The Effect of Weight Reduction Interventions on Health-Related Quality of Life Among Overweight/Obese Individuals

by

Chantele Elissa Mitchell-Miland

BS, Xavier University, 2001

MPH, Tulane University School of Public Health and Tropical Medicine, 2003

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This dissertation was presented

by

Chantele Mitchell-Miland

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and approved by

Tiffany Gary-Webb, PhD, MHS, Associate Professor, Departments of Epidemiology and Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh

Wendy C King, PhD, Associate Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Andrea Kriska, PhD, MS, Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Bonny Rockette-Wagner, PhD, Assistant Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Ada O Youk, PhD, Associate Professor, Departments of Biostatistics, Epidemiology, and Clinical & Translational Studies, Graduate School of Public Health, University of Pittsburgh

Dissertation Advisor: Thomas J Songer, PhD, Assistant Professor, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

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Chantele Mitchell-Miland, PhD

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INTRODUCTION: Health related quality of life (HRQoL) has been shown to improve after participation in two effective lifestyle interventions to treat overweight/obesity, a Lifestyle Intervention (increased physical activity and weight loss – and bariatric surgery (surgically altering the stomach and/or intestines). It is unknown if HRQoL (measured by Euroqol 5 dimension – EQ5D) is maintained over long periods of time or if HRQoL also improves when the lifestyle intervention movement goal focuses on sedentary behavior reduction.

METHODS: This dissertation first examined how HRQoL (EQ5D index and EQVAS – visual analog scale) improved among participants enrolled in a 12-month DPP-based community lifestyle intervention program of lifestyle change vs. change in sedentary behavior. at 6 months, and among each intervention group prepost (6 and 12 months). Second, this paper evaluated changes in HRQoL among a cohort of participants enrolled in the Longitudinal Assessment of Bariatric Study (LABS-2). One assessment evaluated changes in HRQoL among who underwent the Roux-En-Y Gastric Bypass or Laparoscopic Band Gastric Bypass up to 5 years postsurgery. Another assessment evaluated HRQoL measurement among 2 instruments presurgery and 1-year postsurgery (EQ5D and Short-Form 6 dimension – SF6D derived from the SF36).

RESULTS: Components of HRQoL improved significantly in both the lifestyle and sedentary intervention groups compared to the delayed control group at 6 months and prepost at 6 months and 12 months. Among LABS-2 participants, improvements in HRQoL were sustained over 5 years in both types of surgery groups. Results also demonstrated that changes in HRQoL differed by instrument (EQ5D or SF6D) where the EQ5D had more ceiling effects (responses at the highest point of the instrument).

PUBLIC HEALTH SIGNIFICANCE: Participation in community lifestyle interventions with a sedentary behavior goal improved HRQoL providing an alternate effective intervention strategy for those who can’t or won’t engage in moderate physical activity and improvements in HRQoL were sustained up to 5 years after bariatric surgery. The EQ5D and SF6D provided different assessments of HRQoL among bariatric patients which may impact systematic reviews and interpretations of how bariatric surgery affects quality of life.

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Preface

There are many people to thank for this momentous accomplishment including my entire doctoral committee for helping me reach this stage in my academic career. Dr. Thomas Songer, my advisor and committee chair, has been a steady source of support and guidance throughout my studies. A special thank you to Drs. Wendy King and Andrea Kriska for not only serving as committee members but also permitting me to use their data for this dissertation. And to all of my committee members including Drs. Tiffany Gary-Webb, Ada Youk, and Bonny Rockette-Wagner each for their expertise, pep talks, guidance, and massive amounts of time spent both on meeting with me and on reading documents. This ‘thank you’ extends also to of my informal mentors, like Mario Browne and Drs. Dara Mendez, and Marnie Bertolet for their invaluable support.

My friends and family have been my “everything” throughout this process. They have celebrated with me, picked me up when I’ve fallen, and have stood steady throughout this adventure. Thank you to my mother and father, my children, David and Ramon, for providing any type of support I needed and being flexible even when it meant that I was not available. While there are too many friends to list, I wanted acknowledge the tireless support of my friends Benjamin Congedo, Rachel Samuels, Dr. Jon Walker, and Dr. Tia Brown, who kept me grounded throughout. Lastly, yet very importantly, I would like to thank Patrick Kendall - one of my biggest cheerleaders, and Dr. Monique Kelly - a graduate of Pitt Public Health Epidemiology, both of whom helped me prepare for all 3 exams.

Growing up, first in the middle-class white suburbs and later in poverty-stricken black neighborhoods, statistics played a huge role as I tried to figure out who I was – not quite white, not quite black, but yet still a black girl. Statistics had an impact on how I felt about myself, my perceived opportunities for success, and what race meant. As I reflect on my journey from then

to now, I’m grateful for the support Pitt Public Health has provided in molding me into the Epidemiologist I am.

1.0 Introduction

The effects of overweight and obesity are numerous and constitute one of the most prominent public health concerns today, especially as prevalence rates continue to rise [1]. Complications from obesity and related diseases, such as Type 2 Diabetes Mellitus (T2DM), pose a significant burden on the healthcare system, as well as lower health related quality of life (HRQoL). This dissertation document will: (a) provide supporting evidence that overweight and obesity is a major public health problem, (b) present an overview of the literature on how overweight and obesity interventions have developed over time and are part of the current treatment guidelines for individuals either with and without T2DM, (c) discuss the importance and complexity of studying HRQoL for overweight and obesity interventions, (d) discuss current gaps in the literature, and (e) will present 3 aims, in manuscript format, that address the gaps. The aims of this dissertation target 2 interventions for overweight and obesity and the related changes in HRQoL for each.

1.1 Obesity – A significant public health problem

1.1.1 Definition and Epidemiology of Obesity in the US

Obesity is widespread in the US population and carries morbidity and increased risk of mortality [1]. According to the National Center for Health Statistics (NCHS), obesity affected 39.8% or 93.3 million adults and 18.5% of youth in the US from 2015-2016 [1] and continues to rise. Combined 2013-2014 NCHS statistics for overweight and obesity show almost three fourths of the US adult population, or 70.2%, are overweight or obese, with 32.5% being overweight alone [2].

Of public health significance is the high prevalence of obesity, its continuing increase, and the many adverse health comorbidities that often occur. Figure 1-1 illustrates time trends in overweight, obesity, and extreme obesity using age-adjusted and sex stratified data from the National Health and Nutrition Examination Survey (NHANES) [2]. The figure shows that the prevalence of overweight has remained relatively stable over time, while the prevalence of obesity has risen substantially; so much so that the prevalence has nearly tripled from 1960 to 2014 for both men and women. This trend is present among youth as well [3]. Obesity is associated with numerous comorbidities, such as T2DM, dyslipidemia, hypertension, obstructive sleep apnea, cancer, steatohepatitis, gastroesophageal reflux, arthritis, polycystic ovary syndrome, and infertility, that can cause significant impairment to those affected [4].

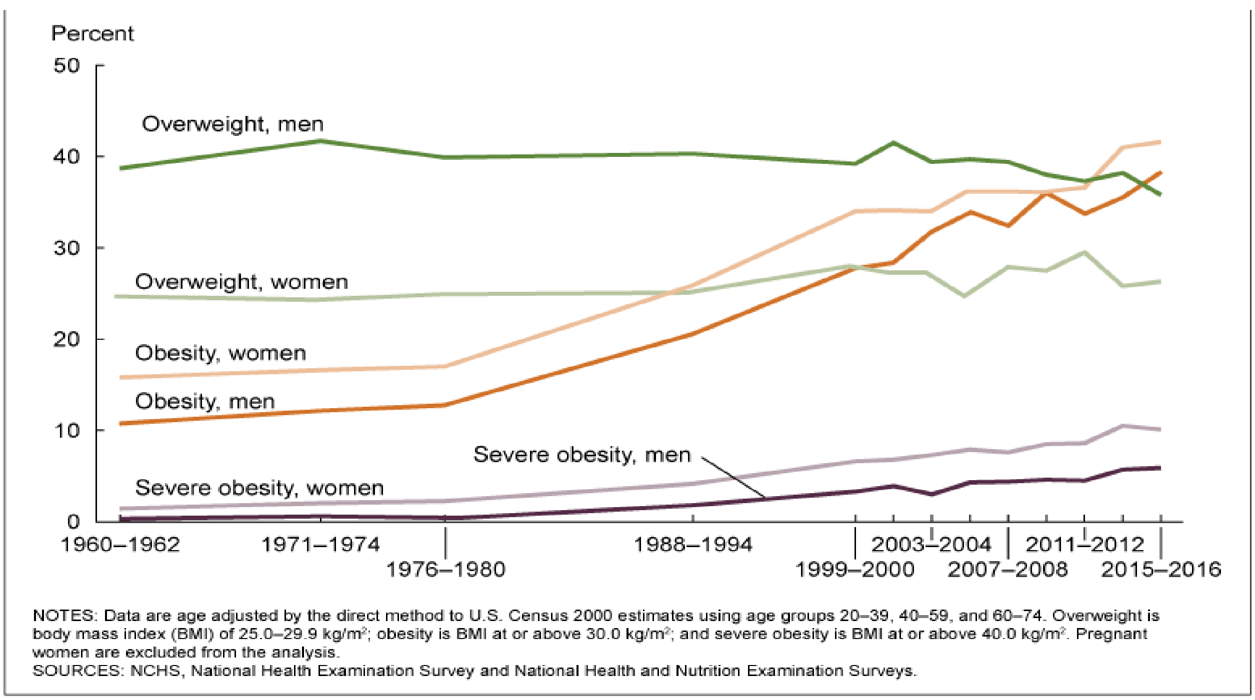

Figure 1-1: Trends in adult overweight, obesity, and extreme obesity among men and women aged 20-74: United States, 1960-1962 through 2013-2016

Body Mass Index (BMI) is the metric most often used to identify presence of excess weight and is an indicator of obesity [5]. BMI is calculated by considering weight for height in an individual and is expressed as weight (in kg) divided by height squared (in meters). Table 1-1 outlines the current standard definitions for excess weight used in practice [5].

Table 1-1: BMI (kg/m2) by weight class

Weight category	BMI
Underweight	≤ 18.49
Normal weight	18.5 – 24.9
Overweight	25.0 - 29.9
Obesity - Class I	30.0 - 34.9
Obesity - Class II	35.0 - 39.9
Obesity - Class III*	≥ 40.0
* Also referred to as extreme, severe, and morbid obesity [6]	

BMI is often used because it is a simple, noninvasive, and inexpensive screening tool to assess the level of excess weight on an individual [7]. Several studies have shown that excess weight, classified by BMI cutoffs (Table 1-1), are related to risk of adverse health effects, including death [8-10]. However, all excess weight is not equal. Excess weight may be due to fat deposits, greater muscle or bone mass [8]. Excess weight due to greater muscle or bone mass is not associated with the same risk as excess weight due to fat [8]. Furthermore, several considerations must be made when assessing risk due to excess fat. Age, gender, sexual maturity, height, and fat distribution are all important considerations for understanding and interpreting BMI regarding risk of adverse health effects [8]. Thus, other measures are often used along with BMI to improve assessment morbidity and mortality risk.

BMI indices are often used in conjunction with measures of body fat distribution, such as waist circumference or waist to hip ratio to assess adverse health effects [4]. Measures of waist circumference help to detect the presence of visceral fat, fat that is carried in the abdominal region, located behind the abdominal muscles and surrounding the organs [11]. Visceral fat is more predictive of adverse health effects than fat carried otherwise [11-13]. Similar to the BMI, the World Health Organization (WHO) has developed cutoffs for waist circumference to serve as guidelines for increased risk of adverse health effects [14]. A waist circumference of 94 centimeters or more in men or 80 centimeters or more in women have been associated with increased risk of T2DM, hypertension and cardiovascular disease (CVD) [14].

Appropriate BMI cutoffs continue to be evaluated to improve its ability to assess risk [15]. While some researchers question whether BMI should continue to be the initial screening tool for obesity [7], many are dedicated to improve assessment. There are now recommendations for lower cutoffs by the American Diabetes Association (ADA) [16]. Individuals of Asian descent have been the focus of lowering cutoffs because they often have higher risk of T2DM at lower BMI cutoffs as compared to those of European descent [15, 17]. While there are not formal recommendations to change the guidelines for other populations, research has indicated that the current guidelines may not be sufficient, such as for African Americans [18]. More accurate measures of visceral fat and obesity, such as the dual energy X-ray absorptiometry (DEXA) scan, computerized tomography, and magnetic resonance imaging are available, but are more costly and intrusive, and thus are not used as widely [7, 8].

1.1.2 Causes of Obesity

Obesity is a chronic condition that has multiple causes and can develop at any point in life [19]. Genetics, socio-economic, psychosocial, and biological factors, along with behavioral and lifestyle factors associated with unbalanced energy intake and energy expenditure are the most commonly cited causes for obesity [20]. The rapid rise in obesity is primarily credited to unbalanced energy intake (excessive or inadequate food consumption) coupled with insufficient energy expenditure (physical inactivity and high amounts of sedentary behavior) [19, 21]. Energy intake and energy expenditure are modifiable risk factors for increased weight and fat accumulation, thus obesity is often preventable [22, 23]. Several factors are known to contribute to behavioral and lifestyle factors associated with the development of obesity.

Physical and social environmental factors, such as available food sources and learned social behaviors, can have a significant influence on how individual behavioral and lifestyle factors develop [19]. For example, children living in low income households and those with parents or family members that are overweight and/or obese, are more likely to be overweight or obese themselves [19]. The learned behaviors contributing to obesity in childhood often continue into adulthood. Neighborhood factors, such as lack of availability of grocery stores or fresh fruits and vegetables, lack of safe places to exercise or be social, sidewalks in disrepair, and low community support can contribute to increased risk [19, 24]. Psychosocial and mental illness, such as depression, can also contribute to poor diet, physical inactivity, and increased sedentary behavior [19]. Neighborhood factors can have a bidirectional relationship with psychosocial and mental illness such that each contribute to the development and perpetuation of each other [19].

Indirect factors of income, education, age, race, and sex are also important to consider in the development of overweight and obesity [25]. Age is a factor for obesity that cannot be changed but remains one of the most important indicators of obesity risk among the US population [25]. According to the Centers for Disease Control (CDC) and Prevention 2011-2014 report, adults aged 40-59 have the highest prevalence (40.2%) of obesity out of all age categories overall and for both men and women (38.3% and 42.1%, respectively) [25]. Regardless of age, women have a higher observed prevalence of obesity compared to men (38.3% vs 34.3%, respectively) [25], most likely because women are more likely to carry fat in the abdominal region [8]. Non-Hispanic blacks and Hispanics have a higher prevalence of obesity compared to non-Hispanic whites and Non-Hispanic Asians (48.1%, 42.5%, 34.5%, 11.7%, respectively) [25]. While there is some research that suggests that minorities may have heightened risk for obesity and other comorbidities due to genetics [26], most research suggests that other factors, such as socioeconomic status, may help explain differences by race better than using race alone [27].

Income and education level are important factors because they have impacts on the ability to afford a greater selection of foods, to secure better employment opportunities which affects housing and ability to maintain a healthy lifestyle, to develop greater health literacy, and to have more opportunities to engage in physical activity [23].

1.1.3 Consequences of Obesity

The consequences of overweight and obesity are important public health concerns, not only because of the magnitude of people that are affected but also because of the detrimental effects that they have on the individual. Individuals with class I or II (group 1) or class II or above obesity (group 2) have 14% and 25% more physician visits and 34% and 74% more inpatient days compared to normal weight individuals [28]. Individuals with class I obesity or greater had 38% more primary care visits and 48% more inpatient days compared to normal weight individuals [29]. Overweight and obese individuals may also suffer from musculoskeletal comorbidities, such as osteoarthritis, a chronic form of arthritis and the leading cause of chronic disability among older adults, body pain due to the presence of excess weight [30], poorer mental health outcomes, reduced quality of life [21]. Overweight and obesity are major risk factors for T2DM, heart disease, stroke, and cancer [21].

T2DM is an important consequence of overweight and obesity and begins with chronic insulin resistance [31]. While all mechanisms for insulin resistance are not understood, high amounts of visceral fat [32, 33], highly processed carbohydrates [34-36], and low physical activity [37, 38] are associated with insulin resistance. When insulin resistance occurs, cell insulin receptors that allow the insulin to bind to the cell so that glucose can enter and be metabolized in the cell do not work properly, resulting in higher amounts of glucose in the blood [39]. The body attempts to maintain homeostasis by increasing insulin production via cells in the pancreas, however, over time, the body can no longer keep up [40]. As the body becomes more inefficient at balancing glucose levels, the risk for impaired glucose tolerance, and T2DM increases [40].

An impaired glucose tolerance (IGT) test confirms that an individual is at higher risk of developing T2DM [40]. IGT occurs when blood sugars are higher than normal, but not high enough to be classified as T2DM [31]. In the presence of insulin resistance, patients can experience symptoms of frequent urination, increased thirst and/or hunger, dry mouth, blurred vision, fatigue and nausea [41]. Other symptoms may include weight gain or weight loss, or poor wound healing [41]. Prolonged exposure to high blood glucose results in permanent damage to cells and often eventually the diagnosis of T2DM [40]. Common complications of T2DM include skin infections, eye complications (glaucoma, cataracts, retinopathy, and other eye problems), kidney function changes (ketoacidosis or nephropathy), gastroparesis and neuropathy (nerve damage, usually to extreme extremities), and cardiovascular disease, the leading cause of death in the US [42]. Figure 1-2 shows a visual depiction of complications associated with obesity including T2DM [43].

T2DM related deaths were ranked 7th among the 15 leading causes of death in the US according to 2016 CDC statistics [44], however, T2DM may be underreported as a cause of death due to uncounted cases where it is an underlying cause [45]. Attempts have been made to assess the true impact of T2DM on the population. Stokes et al was able to estimate T2DM population attributable fractions (PAF) for cohorts aged 30-84 [46]. Using 1997-2009 data from the National Health Interview Survey (NHIS) and 1999-2010 from NHANES, cohorts were followed through to 2011 and included cases where T2DM was listed as the primary and underlying cause of death. The estimated PAF was between 11.5% - 11.8% among all individuals and 19.4% among obese individuals, indicating that the impact of T2DM on mortality may be underestimated [46].

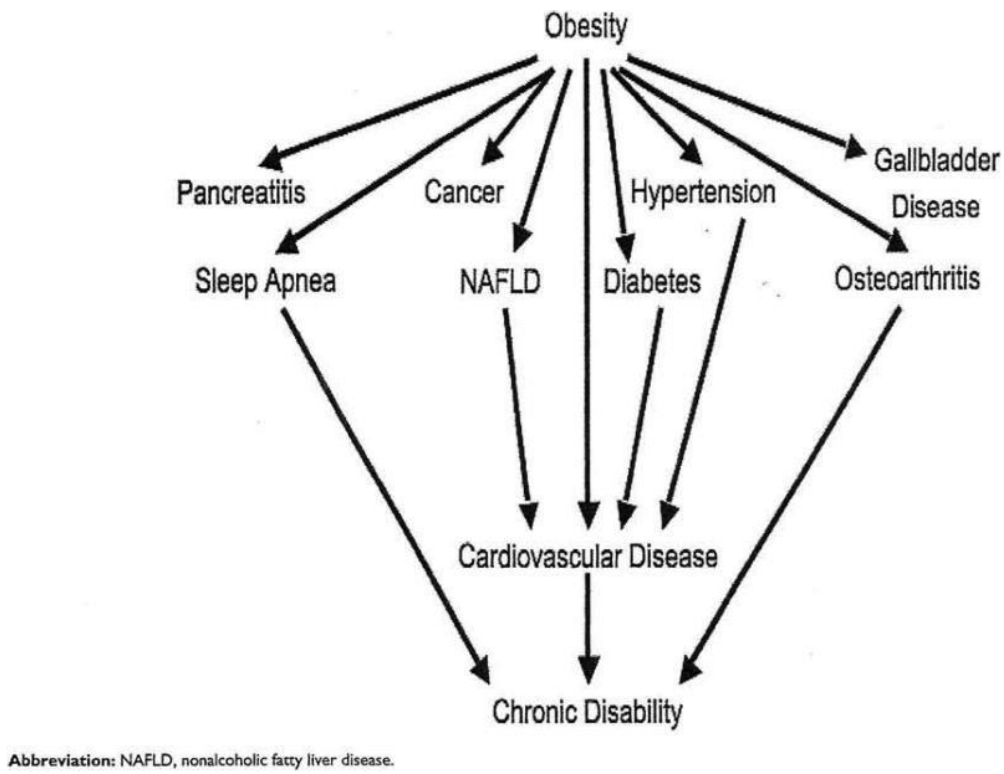

Figure 1-2: Complications of Obesity

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Economically, overweight and obesity cost society $147 billion per year; approximately $1429 more per individual with obesity as compared to a normal weight individual, according to estimates from NCHS 2015-2016 [25]. Analysis of a nationally representative sample of the population found that obese adults aged 18-65 incur a 36% increase in medical expenditure compared to normal weight individuals [23].

2.0 Research on the Treatment of Obesity With and Without T2DM

Obesity and obesity related health problems are largely preventable. Projections based on current data indicate that obesity will continue to be a major health concern in 2030 if immediate and significant measures are not taken to reduce obesity and its health effects [47]. Obesity and T2DM, as a consequence of obesity, have several points of intervention. Primary prevention targets individuals with obesity and other risk factors, such as family history, where individuals have not shown any symptoms of T2DM and have normal blood glucose tests [48, 49]. Secondary prevention interventions target the early stages of T2DM among obese individuals [31]. Tertiary prevention strategies target the use of therapies to prevent or delay the more serious health consequences of T2DM among obese individuals [49]. Weight reduction coupled with increased physical activity is a strategy at any level of prevention [50]. Given the role that excessive weight plays on comorbidity, the more an individual approaches normal weight, the better the outcomes [50]. Research exploring methods to intervene on overweight and obesity has led to improved health outcomes and changed standards of care.

2.1 Lifestyle Intervention (LI) as a treatment modality for obesity

As people have become heavier, researchers and clinicians have sought to understand how and why the increase is occurring. The increase in obesity has occurred incrementally and has largely been attributed to behavioral habits where energy intake is not balanced with energy expenditure [51]. Lifestyle Interventions (LI), characterized by interventions to promote behavioral changes to diet and physical activity levels, have been explored at length over the years as a non-invasive approach to improve health outcomes for individuals who are overweight or obese [52].

The first component of behavior change is to reduce energy intake by eating in "moderation" and being more selective about the types of foods that are being consumed [52]. Studies evaluating the impact of lifestyle change have examined differing models of diet modification to change energy intake and achieve weight loss [53-55]. For some studies "moderation" has meant a prescribed caloric intake with encouraged restrictions or decreases in the consumption of certain foods, such as those with high fat, and/or high sugar [54, 55]. Others supply meals [56].

The second component of behavior change, energy expenditure, involves changes to physical activity. Most lifestyle intervention programs include a target physical activity level to reach [55]. For example, in the Diabetes Prevention Program (DPP), participants were encouraged to attain and maintain a minimum of 150 minutes of moderate intensity activity per week [52, 57]. Other studies have used a prescribed exercise regimen, such as walking a certain amount per day or week [58, 59].

Usually, a combination of diet modification and increased physical activity is able to achieve modest weight loss (≥ 5%) using a behavior modification curriculum employing techniques like motivational interviewing, self-monitoring, and individualized short and long-term goals [52, 55]. Some studies have also used compensation as an added incentive for reaching goals [56]. LI regimens may be tailored toward a population and may include targeted reductions in other high-risk behaviors, such as cigarette smoking, alcohol use, adiposity measures, and sedentary behavior [52, 60-68].

2.1.1 Lifestyle Intervention (LI) as a prevention modality of T2DM

LI, used as a prevention method for T2DM, has been studied in many populations. The Malmo feasibility study [69], conducted from 1974-1985, followed 4 groups (2 intervention groups and 2 control) in Malmo, Sweden and evaluated the effectiveness of LI on T2DM and IGT in male individuals compared to IGT and normal glucose controls who did not want to participate in the intervention. Thus, there was no randomization in the Malmo study. Improvement in glucose tolerance was observed in 75.8% of treatment participants compared to a deterioration of glucose tolerance among 67.1% control participants where 28.6% developed T2DM [52].

The China Da Qing Diabetes Prevention Study (CDQDPS) [70], conducted from 1986-1992, was the first study to randomize individuals by clinic to diet, exercise, or diet+exercise compared to a control group. After 6 years of follow up there was a 31%, 46%, and 42% risk reduction of T2DM among the diet, exercise, and diet+exercise groups, respectively, compared to control [52].

The Finnish Diabetes Prevention Study [71], conducted from 1993-1998, evaluated 523 subjects who were randomly assigned to a control group or a diet and exercise intervention group. During the first year, there was a 4.7 reduction in BMI among intervention participants compared to 0.9 in the control. After 3.2 and 7 years of follow-up, there was a 58% and 43% risk reduction in T2DM in the intervention group compared to control, respectively [52].

The Diabetes Prevention Program (DPP), conducted from 1996-2001, was a randomized clinical trial designed to test the effectiveness of LI (diet modification and increased physical activity) compared to a placebo and a drug intervention (metformin and originally troglitazone) in 27 centers throughout the US [57]. The LI group used a cognitive behavior therapy (CBT) based curriculum to achieve behavior change goals. The first goal was to accomplish diet modification by a reduction in calories and fat intake and the second goal was to achieve a minimum weekly physical activity level of 150 minutes per week of moderate intensity activity. Achievement of the behavior change goals increased the likelihood that the participant would meet the weight loss goal of losing 7 percent of the original body weight [57].

DPP subjects that received LI or metformin had a 58% (95% Confidence Interval (CI) = 48%-66%) or 31% (95% CI = 17%-43%) reduced risk of T2DM after 2.8 years of follow-up, respectively, compared to placebo [57]. The study results were so profound that the study was stopped early and participants in the placebo group were invited to participate in LI. At 10-years of follow-up, the LI group continued to maintain a 34% risk reduction of T2DM compared to the metformin and placebo groups despite the fact that reductions in body weight were not maintained [72].

The results from the DPP study reframed treatment guidelines for treating overweight and obesity and supported the effectiveness of LI to prevent T2DM for the following reasons. First, DPP was the first study to compare lifestyle intervention to a medication treatment comparison group. Secondly, DPP included participants as young as their 20's at baseline and multiple racial and ethnic groups representing 45% of the study population, increasing generalizability. Thirdly, DPP was conducted at 27 centers throughout the United States among over 3000 participants. Overall, this study was one of the first to provide highly generalizable empirical evidence for the prevention of T2DM through weight loss [57].

2.1.2 Translations of the DPP and Group Lifestyle Balance (GLB)

Since the landmark results of the DPP, new studies have focused on translating the curriculum and program of the DPP to wide ranges of populations. One of these approaches is the Group Lifestyle Balance (GLB), which will be highlighted in this dissertation research. GLB was developed as a translation of the DPP lifestyle intervention program into primary care and community settings using a group-based rather than the one-on-one based curriculum used in the DPP. Seidel et al published results from the first GLB translational effort in 2008 demonstrating that 46.4% and 26.1% of participants lost ≥ 5% or ≥ 7%, respectively, of their pre-intervention weight after 12 weeks of intervention [73]. At the six-month follow-up, 87.5% and 66.7% had an observed ≥ 5% and ≥ 7% weight loss, respectively [73]. These results established that the change in delivery method for the intervention did not alter the success of the program.

Kramer et al later developed a model for prevention training and program delivery [74]. Several members who originally developed the DPP lifestyle intervention at the University of Pittsburgh, modified the existing program to the GLB – a group rather than an individual delivery method. Other modifications included focusing on healthy foods rather than the food pyramid, having an initial emphasis on fat intake and calories, pedometer introduced during core sessions use of inexpensive food samples and incentives, 2-day training and support by the Diabetes Prevention Support Center (DPSC). The program was not randomized and was evaluated in two phases (Phase 1: 2005-2006 and Phase 2: 2007-2009). Measures were collected at baseline and post-intervention at 6 months and 12 months for Phase 2. Nondiabetic individuals with a BMI ≥ 25 kg/m2 and the metabolic syndrome or prediabetes participated (N=93). Over 50% of the sample (52.2%) of the sample reached a 5% weight loss.

The GLB, by way of the DPSC at the University of Pittsburgh (https://www.diabetesprevention.pitt.edu/), is now based on a tailored curriculum that adjusts to changing guidelines for diet and physical activity and varying populations –Latinos [75], individuals with traumatic brain injury [76, 77], a peer based intervention for individuals with serious mental illness [78], and others [73, 79, 80]. The GLBMoves study, a National Institutes of Health (NIH) funded translation of GLB, modifies the existing lifestyle intervention to include a sedentary behavior reduction component in addition to original intervention that focuses on increasing and maintaining moderate vigorous physical activity goals. Data from GLBMoves will be used in this dissertation research.

2.1.3 Modification as a Treatment Modality for Obesity in Persons with T2DM

The success of previous LI interventions to decrease weight and improve health outcomes among individuals without T2DM encouraged researchers to explore LI among overweight and obese individuals with T2DM [81]. The Look AHEAD (Action for Health in Diabetes) was the first large randomized trial to evaluate the effectiveness of lifestyle intervention on cardiovascular disease (CVD) risk. Look AHEAD included 5145 overweight or obese men and women with T2DM in 16 centers in the US. Researchers developed the rationale for this study in response to the promising results of reduced CVD, and reduced risk of CVD, measured by reduction of plague build up in blood vessels and the heart, among individuals at risk for T2DM that used LI in the DPP [81]. To evaluate CVD in Look AHEAD, participants were randomized to Intensive Lifestyle Intervention (ILI) or Diabetes Support and Education (DSE) [82]. At baseline, participants from both arms of the study had a mean BMI of 36.0±5.9 kg/m^2 and achieved a mean weight loss of 4.7±0.2% at year eight of the study. The study was stopped after 9.6 years of follow-up, earlier than anticipated, because CVD risk was not different between the ILI and DSE groups due to a very low CVD rate in both groups [82, 83]. It is hypothesized that the CVD event was low for four reasons, [1] physicians were well aware of study guidelines and may have provided better treatment to study participants, [2] participants enrolled in the study were generally health conscious and were allowed to participate in other programs to improve their health, [3] study eligibility criteria only included participants that had a maximal exercise test, meaning their CVD risk was lower than someone with a poorer exercise test, and [4] only 14% of participants had a history of heart disease meaning participants were likely to be healthier [84].

While the main aim to reduce CVD events were not satisfied by statistical findings, ILI was still found to be beneficial among Look AHEAD participants. ILI participants experienced improved CVD risk factors, cardiorespiratory fitness, glycemic control, diabetes remission, blood pressure, HDL cholesterol, low-grade inflammation, plasminogen activator inhibitor, hepatic steatosis, physical function, obstructive sleep apnea, depression, erectile dysfunction, urinary incontinence in women, health-related quality of life, and spouse weight loss and decreased use of diabetes drugs, medication use and cost [85]. Thus, ILI was shown to be an important factor in improving health even among those with T2DM compared to control.

2.2 Medicinal Therapies for Obesity Treatment With and Without T2DM

LI is the preferred method for achieving weight loss, however, pharmacotherapy treatments may be used to treat obesity and/or to reduce the risk of T2DM for those at high risk or treat T2DM [86, 87]. Specific guidelines for treatment of overweight and obesity with pharmacotherapy is covered in section 3.3.2.

2.3 Bariatric Surgery

Bariatric surgery was first identified as a plausible approach to weight loss in 1954 by Kremlin et al, after he noticed impaired fat absorption in dogs following the resection of the small intestine [88]. His observation established the foundation of bariatric surgery and its ability to affect absorption regardless of the number of calories consumed. Since its inception, bariatric surgery has continued to be modified and was eventually introduced as a method of weight loss for humans.

According to the American Society for Metabolic and Bariatric Surgery, the first bariatric surgeries on humans were conducted on obese patients in the 1950s at the University of Minnesota [89]. Methods to enhance weight loss and reduce complications are continuing to be developed [90-94]. Several procedures have been developed with different methods to adjust the stomach size, the rate of absorption, the hormones that affect appetite and satiety, and/or a combination of both.

Bariatric surgery procedures have changed based on evidence regarding their effectiveness, safety, and surgical requirements. Bariatric surgery has shown promising results for treating obesity in those with and without T2DM and can assist those undergoing the procedure to lose upwards of 30% of their preoperative weight [95, 96]. While in general, bariatric surgery results in superior weight loss and related comorbidity improvement compared to LI [97], bariatric surgery is the most invasive weight loss intervention. In some individuals, complications can occur both resulting from the actual surgery and from long-term maintenance complications. In the most extreme cases death can occur from the surgery [98].

To date, the four surgeries that are most commonly performed in the United States are the vertical sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), and duodenal switch. Vertical sleeve gastrectomy enhances weight loss by vertically reducing the stomach size to about 25% of the original size. While the stomach function is largely unaltered, the smaller size of the stomach promotes satiety sooner and the decrease in ghrelin production, a hunger relating peptide protein, results in less feelings of hunger and less food consumption [99, 100]. During the RYGB procedure a small pouch of the stomach is cut to and attached to the lower portion of the small intestine that has been divided into two portions [101]. The top portion of the small intestine is rerouted to the lower portions of the intestines where the stomach acids and digestive enzymes can eventually mix with the food which promotes satiety, suppresses hunger, and can reverse T2DM [101, 102]. LAGB is the least invasive procedure in which an adjustable band is placed around the upper portion of the stomach. The band is adjusted gradually over time to achieve the desired opening. Food is digested normally and weight loss is promoted by feelings of fullness due to a smaller stomach [101]. The duodenal switch is a two-part procedure where the stomach is reduced by way of the sleeve gastrectomy, part one, and a large portion of the small intestine is bypassed through rerouting of the intestines, part two. During the second part of the procedure, nearly three-fourths of the small intestine is bypassed by the food stream. Thus the food does not mix with the bile and pancreatic enzymes until very far down in the small intestines changing the absorption of calories, protein, fat, nutrients and vitamins [101].

In 2004, Buchwald et al conducted a systematic review and meta-analysis of 134 studies that included a sum of 17,851 patients (72.6% of patients being women) [103]. The mean BMI prior to surgery was 46.9 kg/m^2 with a range of 32.3 to 68.8 kg/m2. Studies included 5 randomized controlled trials, 28 nonrandomized controlled trials or series with a comparison group, and 101 uncontrolled case series. Most patients were nonsmokers (69.5%) and only 4.4% had previous bariatric surgery. The most frequent comorbidities were hypercholesteremia (40.2%), dyslipidemia (35.6%), and hypertension (35.4%). Only 15.3% of the sample had T2DM and 25.8% had glucose tolerance impairment. The overall percentage of excess weight loss was 61.2% for 10,172 individuals after at least 2 years of follow-up. BMI mean weight loss was 14.2 in 8232 patients and a decrease in absolute weight of 39.7 kg in 7588 patients. Note: Numbers do not add up to 10,172. Time of follow-up was reported using a dichotomized measure for time - ≤ 2 years or > 2 years. When tested, weight loss did not differ significantly between the ≤ 2 years or > 2 years follow-up time groups. Results of excess weight loss, fasting glucose, fasting insulin, and T2DM are presented in Table 2-1. Excess weight loss, a standard measure of weight loss in bariatric surgery, is calculated as (weight loss/excess weight) * 100, where excess weight=total preoperative weight – ideal weight [103]. Participants were able to achieve reduced glucose, and in most cases, were able to achieve remission of T2DM. Results did differ by surgical procedure, where the biliopancreatic diversion or duodenal switch had the best observed results. However, due to safety issues the Biliopancreatic diversion is rarely performed today [104, 105]. Similar results have been found in other reviews, even in those that have been updated [97, 106, 107].

Table 2-1: Results of Bariatric Surgery for Buchwald et al Systematic Review by Surgery Type [103]

Outcome Measure	Excess weight loss	Fasting Glucose, mmol/L	Fasting Insulin pmol/L	T2DM		
				Remission	Remission or improved	New or Worse cases
Total	-61.2%	-0.86	-114.6	76.8%	86.0%	0.7%
Gastric banding	-47.5%	-0.71	-77.1	47.9%	80.6%	0.2%
Gastric bypass	-61.6%	-1.43	-118.3	83.7%	93.2%	0.5%
Gastroplasty	-68.2%	-0.56	-122.9	71.6%	90.8%	6.7%
Biliopancreatic diversion with or without duodenal switch	-70.1%	-0.67	-132.5	98.9%	76.7%	0
• Values adjusted for timepoint						

The sleeve gastrectomy, not covered in the Buchwald review, is now the most used procedure for bariatric surgery in the US [108]. Carlos Hoyuela presented results of a prospective study of 145 patients who underwent the laparoscopic sleeve gastrectomy patients from 2006 whose follow-up data were presented for up to five years [109]. The mean presurgery BMI of patients was 41.5 (SD = 7.9) and mean follow-up time was 32.7 (SD = 28.5). During the follow-up period, no mortality was observed and the total 30-day complication rate was 5.1%. For late complications, 24 (15.3%) had symptomatic gastroesophageal reflux, 1 (0.6%) needed laparoscopic repair for a hiatal hernia, 1 (06%) had a gastric stricture, and 7 (4.4%) had symptomatic cholelithiasis. Excess weight loss was 82.0% at 1-year post surgery and 60.3% at five years. These data are consistent with other published study results [110-122].

Bariatric surgery has been used as both a means to prevent T2DM and as a “treatment” in persons with T2DM. Long et al [123], conducted a prospective, longitudinal study to observe individuals with IGT and severe obesity (>45 kg excess body weight; 109 who underwent gastric bypass and 27 who did not) who had 2 years of follow-up information. The rate of conversion to

T2DM was 0.15 cases per 100 person-years in the bariatric group and 4.72 in the comparison group.

Furthermore, remission rates of T2DM are high with bariatric surgery. The combined remission rate in Chang et al was 92% (85%-97%) among randomized controlled trials (RCT) (n=8) and 86% (79%-92%) for observational studies (n=43) [123]. By surgery type, remission was highest among those who underwent gastric bypass (95% among RCT and 93% for observational studies), followed by sleeve gastrectomy (86% among observational studies) and lowest for the adjustable gastric band (74% among RCT and 68% among observational studies). Hoyuela had a similar observed remission rate for those who underwent sleeve gastrectomy at 75% [109]. Using a metaanalytic mean, Buchwald et al found that 1417 of 1846 patients (76.8%, 95% CI = 70.7% - 82.69%) had total remission while 414 of 485 (85.4%, 95% CI = 78.4%-93.7%) experienced resolution (remission) or improvement as reported in the study after at least 2 years post-surgery [103]. Similar to Chang et al, remission rates were highest by complexity of the surgery. Those undergoing the biliopancreatic diversion or duodenal switch had the highest remission rates (97.9%) while those who underwent the gastric banding procedure had the lowest remission rates (47.38%) [103].

Complications can often occur with bariatric surgery. Chang et al found the complication rate after surgery ranged from 10% to17% among all surgical procedures [106]. Surgical complications include bleeding, stomal stenosis, leak, vomiting, reflux, gastrointestinal symptoms, and nutritional and electrolyte abnormalities among others. Complications are more common for gastric bypass (22%), above the average, whereas complications from adjustable gastric banding and sleeve gastrectomy are lower (13% complications) [106].

Enhanced recovery after surgery (ERAS) are multimodal perioperative care pathways that are designed to achieve early recovery and reduce the profound stress response [124]. A review of studies using the ERAS protocol compared to those not using ERAS found differences in length of hospital stays, overall morbidity, minor complications, major complications, and hospital readmissions [125]. ERAS include preoperative counseling, optimization of nutrition, standardized analgesic and anesthetic regimens and early mobilization [126]. Length of hospital stay was statistically significantly shorter by 2.39 days compared to non-ERAS studies, however, there were no other statistically significant differences for other outcomes – overall morbidity, minor complications, major complications, or hospital readmissions [125].

In 2002, The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; www.clinicaltrials.gov) issued a Request for Applications to research the safety and effectiveness of bariatric surgery in response to the increasing prevalence of overweight and obesity in the US, the increasing number of performed bariatric surgeries, and the goal to find effective therapies that helped individuals lose weight that was sustained over time [127]. The Request for Applications was also aimed at understanding how weight loss impacts comorbidities and mortality over time. In response, a group of researchers in six clinical sites throughout the US and a data coordinating center at the University of Pittsburgh proposed a project that was approved for funding in September 2003. The project was entitled the Longitudinal Assessment for Bariatric Surgery or LABS and involved a series of observational studies designed to study the safety and efficacy of bariatric surgery labeled as LABS-1, LABS-2, and LABS-3 [128].

All LABS studies included adults that were 18 years or older seeking their first bariatric procedure at a participating center [128]. Each of the studies in LABS investigated a different component of bariatric surgery. The purpose of LABS-1 was to evaluate the short-term safety of bariatric surgery within 30 days [129]. Data were collected to observe adverse outcomes such as death and percutaneous or operative reintervention. LABS-2 was designed to evaluate the relationship of patient and surgical characteristics to longer term safety and efficacy of bariatric surgery [129]. Data were collected prior to surgery, 30 days and 6 months after surgery, and then yearly up to 7 years post-surgery. LABS-3 diabetes and LABS-3 psychosocial are subsets of the LABS-2 study participants. Both studies were designed to examine mechanisms of T2DM resolution and psychopathology and eating pathology, respectively. Obesity-related diseases were also explored [129].

Data from the LABS consortium have resulted in over 70 publications. LABS-1 followed 4776 patients undergoing first time or “primary” bariatric procedures [98]. The mean age was 44.5 and median BMI was 46.5 kg/m^2 with 21.2% being men. Most patients (71.4%) had a Roux-en-Y (RYGB) the majority of which were performed with a laparoscopically procedure (87.2%), 21.5% had the laparoscopic banding procedure, and (3.5%) had another procedure. Less than 5% of patients (4.1%) had a major adverse outcome within 30 days of surgery [127]. Mortality rates were highest among those who underwent the open RYGB procedure (2%). No deaths occurred among those with the band procedure. While deaths that occurred during the follow-up might be related to the procedure, those who underwent RYGB were also sicker preceding surgery. Participants with higher BMI’s, BMI ≥ 75 kg/m^2, had a 61% higher risk of complications compared to those with lower BMI’s, BMI ≤ 53 kg/m^2.

LABS-2 included 2458 participants, most of whom were women (78.6%) [130]. Women were younger than men (45 vs. 48) and mostly white 86.2% with 10.5% being black. Race, employment, and income were statistically different by gender. Mean BMI was 45.7 kg/m^2 for females and 46.9 kg/m^2 for males. Most patients had an RYGB procedure (70.7%) – 62.6% with a laparoscopic procedure and 8.1% with the open procedure – followed by 24.8% with the banding procedure and 4.5% with another procedure. A third of all participants, 33.4%, had T2DM at baseline with males having a higher prevalence of T2DM (45.9%) compared to females (30.0%). Most participants did not report depressive symptoms and if depressive symptoms were present, the severity was mild to moderate. Data from a similar LABS-2 report showed that 35.3% of participants reported antidepressant medication use [131].

Multiple LABS-2 reports have explored weight loss over time [95, 97, 132, 133], changes in depressive symptoms [131], sexual dysfunction [134], HRQoL [135], and multiple other outcomes. In one of the follow-up reports, seven-year follow-up data was presented. LABS 2 had observed great improvements in weight loss that were largely sustained over time as shown in Figure 2-1 [133]. Over half of the participants (58.9%) with T2DM that underwent the RYGB procedure experienced diabetes remission, while 24% of those who underwent the banding procedure experienced remission at year 7. For the RYGB procedure, the rate of death was 5.32 per 1000 person-years (95% CI = 1.72,12.39) totaling to 59 deaths over the course of the 7-year follow-up period. Three occurred in the first 30 days and 56 occurred more than 30 days post-surgery. Fourteen participants had to have subsequent bariatric procedures. For the laparoscopic banding procedure (LAGB) procedure, the rate of death was 3.92 per 1000 person-years (95% CI = 1.07, 10.05) totaling to 15 deaths occurred over the course of the 7-year follow-up. All deaths occurred more than 30 days post-surgery. In contrast to RYGB, there were 160 subsequent bariatric surgery procedures for those that underwent LAGB.

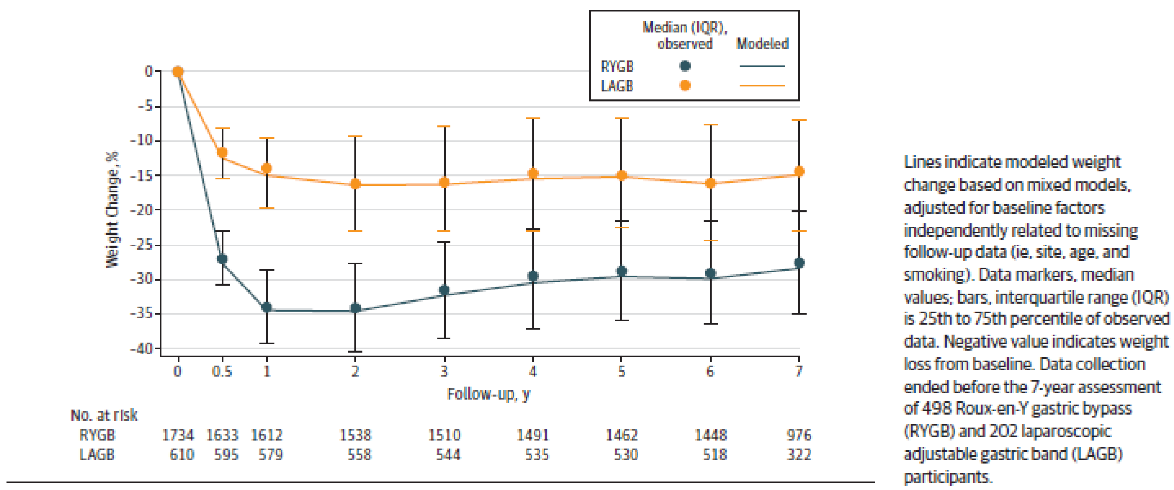


Figure 2-1: Observed and modeled percent weight change by time point

Reproduced with permission from Seven-Year weight trajectories and health outcomes in the longitudinal assessment of bariatric surgery (LABS) Study. 2018. JAMA Surg, 153(5): p. 427-434.

3.0 Clinical and Practical Guidelines for the Treatment of Obesity

Research presented in the preceding sections has led to the development of clinical and practical guidelines designed to provide a flexible treatment plan that for individuals at different levels of readiness to change (RTC). Many individuals seek guidance for weight loss outside of their health care provider's office, such as from commercial agencies. Flow charts, such as the one on the following page (Figure 3-1) [50], provide a tool to health care professionals to aid in the complex decision making treatment process made with patients regardless of where their weight loss treatment is initiated.

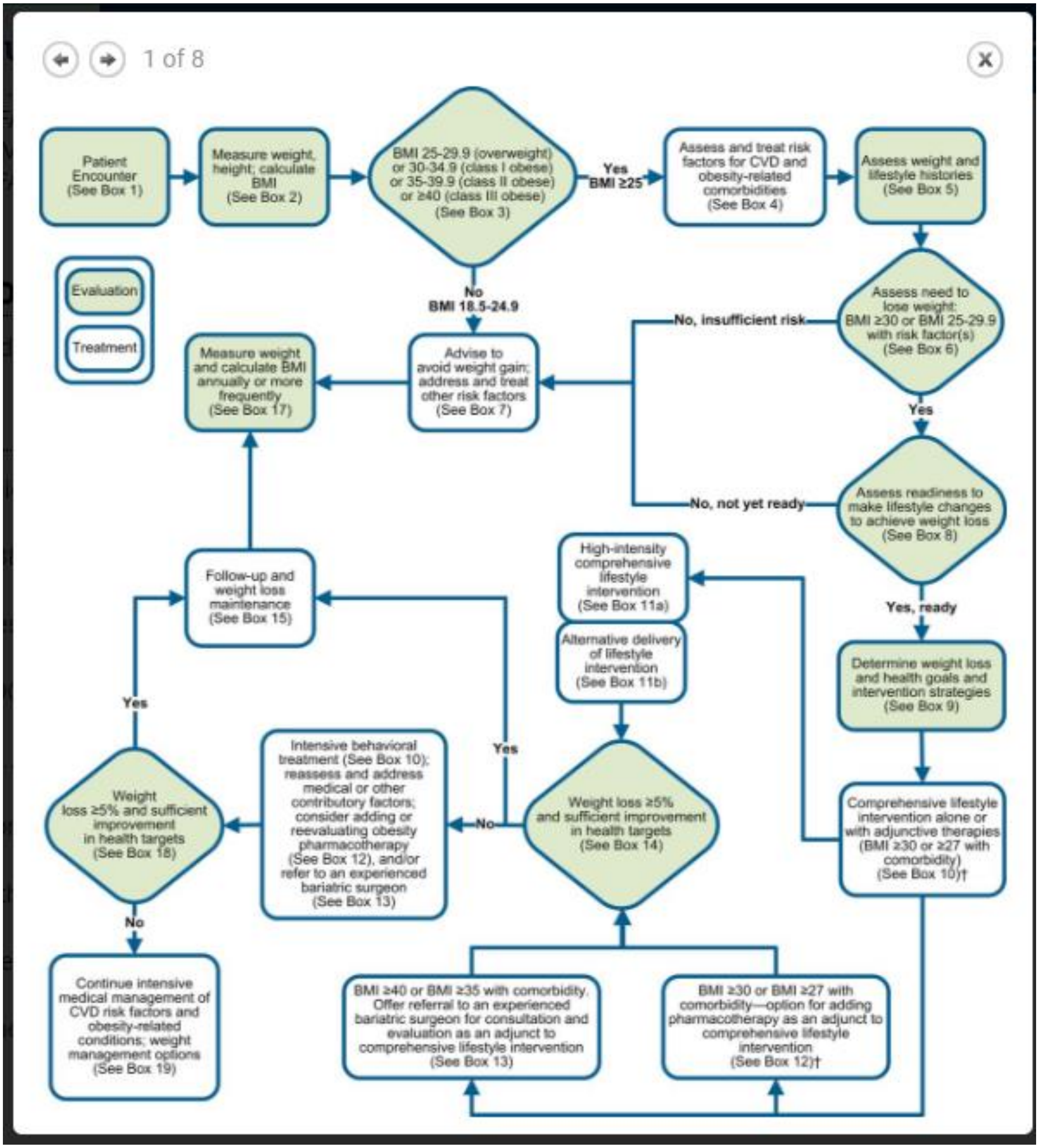


Figure 3-1: Clinical Guidelines for obesity care

Reproduced from Jensen, M.D., et al., 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation, 2014. **129**(25 Suppl 2): p. S102-38.

For each of the boxes in Figure 3-1, there is an explanation of the interaction or the decision-making process. Shapes and shaded boxes indicate whether a treatment evaluation or a treatment plan should be considered. In this diagram, shaded green boxes mark evaluation points versus the white boxes that indicate points of treatment. The NIH developed a practical guide for the identification, evaluation, and treatment of overweight and obesity in adults with a similar diagram [136].

Following the guidelines, beginning from when a patient examination occurs, a health care provider will assess whether a patient is overweight or obese by BMI only, at first. The health care provider will then assess increased risk for comorbidity by using waist circumference measurements and other risk factors that may indicate that more aggressive treatment may be needed [136]. Risk factors include established coronary heart disease, other atherosclerotic diseases, T2DM, and sleep apnea. Three or more of the following risk factors constitute a high absolute risk or significant increased risk of mortality: hypertension, cigarette smoking, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose, family history of early cardiovascular disease, and age (male ≥ 45 years, female ≥ 55 years) [136]. Once the risk profile has been assessed and considered, the health care provider will move forward with treatment plan considerations.

While not covered extensively in this review, readiness to change (RTC) for losing weight is an extremely important component of consultation between the health care provider and patient [136, 137]. There are several different measures that can be used to assess RTC. RTC assessments help identify reasons and motivation for weight loss, previous attempts at weight loss, available support from family, understanding the risks and benefits of available treatments, attitudes toward physical activity, time availability, and potential barriers including financial limitations [136]. Assessing RTC can strengthen rapport between the health care provider and patient and improve health intervention outcomes by facilitated conversation and informed decision making [137].

Considering RTC as an important component of the decision-making process, health care providers can use a flow chart, such as Figure 3-1, to assess the best course of treatment that is also in the best interest of the patient. After assessing RTC, typically the next course of action is to use the first line treatment, LI, to either stabilize weight gain, if the patient is not ready to begin a LI weight loss plan, or to discuss an LI plan to lose weight. Risk factor assessment is an important part of this decision-making process [50]. LI is an important starting point because it will be used throughout the treatment process regardless of other therapies that are initiated.

3.1 Lifestyle Intervention

As the health care provider and patient move toward the planning and implementation process of LI, there are several things to consider prior to the creation of a treatment plan. First and foremost, it is imperative that the decisions made during the plan creation process are joint decisions between the health care provider and the patient. As a plan is created, the health care provider guides the patient through the decision-making process by considering RTC, risk factors and the patient's BMI category [50].

Existing comorbidities and risk factors along with BMI and waist circumference determine the suggested plans of action for LI treatment plans. For BMI's in the overweight (25-29.9 kg/m^2) category, the presence of comorbidities factor into considering treatment [136]. For those at the lower thresholds of the overweight category, weight maintenance may be an agreed upon strategy of improving health, with a focus on behavior change to improve food choices and achieving physical activity goals, rather than a more aggressive weight loss plan [136].

For those in the higher risk categories, that is either who are obese or overweight with several comorbidities, a weight loss treatment plan using LI may be created. For those patients that agree and are ready to make these changes, it is suggested that patients lose 10% of their baseline weight at a rate of 1 to 2 pounds per week [136]. It is important that calories are reduced only to the level necessary to lose weight slowly and progressively. Extreme weight loss in short periods of time is often not sustainable and does not promote long-term health improvements nor effective behavior change.

As discussed previously, LI plans are created by making changes to diet, physical activity and behavior. Generally, the calorie guidelines are 1000 to 1200 kcal/day for women and 1200 to 1600 kcal/day for men [136]. For physical activity, moderate levels for 20 minutes per day on 3 to 5 days per week are recommended. Reduction in sedentary time is also recommended. Behavior change is addressed when the health care provider and patient discuss how the patient will accomplish these goals. This occurs by developing a plan with short term and long-term goals that is tailored to the patient's resources, RTC, and ability to participate in each component of the LI plan. At this point in the planning process the health care provider and patient will discuss potential barriers to accomplishing their goals and how they will address them. For example, a patient might identify that it is harder to stick to their diet when they eat at restaurants. The health care provider and patient can then come up with a plan on how to address this barrier. Short term and long-term goals will be accomplished by frequent contact between the health care provider and the patient, self-monitoring, and the establishment of a reward system. Through frequent monitoring the health care provider and patient can identify further barriers as well as successes and tailor the plan accordingly to continue progressing to the goals. [50, 136]

Once the weight loss goal is achieved, new goals will be established to continue with behavior change so that the weight is maintained. Often, patients achieve weight loss but are not able to sustain it. New recommendations for weight maintenance have been proposed so that the health care provider and patient relationship can continue for the support of weight maintenance. During this process, BMI, waist circumference, comorbidities and risk factors will continue to be monitored to assess if the current treatment plan is effective or if new modifications need to be made. This process may also be conducted prior to weight loss in instances where the patient is not ready to fully commit to an LI treatment plan. During this time, the health care provider will work with the patient to achieve weight maintenance and may try to implement goals in preparedness of a more aggressive LI treatment plan. Typically, it is ideal to see how much behavior change, through LI dietary and physical activity changes, can be accomplished before other methods of weight loss are introduced, however, at any time during the process, the health care provider and patient can discuss medications or surgery for weight loss based on the patient's eligibility for other interventions. [50, 136]

3.2 Pharmaceutical Therapy

Health care providers are often encouraged to work with individuals for at least 6 months with LI, presuming that there are not any immediate health needs that are contraindicated for using LI alone [136]. The goal of pharmaceutical therapy is to help patients achieve between 5-10% weight loss [138]. Like LI, medications also have recommendations for use based on the presence of risk factors and comorbidities along with BMI classification. Typically, medications are not indicated for use among individuals at lower ranges of the overweight category. However, among those with greater BMI's in the overweight category (27.0-29.9 kg/m^2) treatment with medication is recommended in the presence of comorbidities and indicated for anyone in the class I obese category or greater (≥ 30 kg/m^2). Medication use is suggested only after careful consideration of other therapies and of possible adjustments to LI treatment plans. [50, 136]

LI is always preferred over medication as it has been shown to be more effective in studies, provides a longer-term method to achieve weight loss sustainment and has fewer side effects and risks [50, 72]. In cases where patients have lost weight and are having trouble with weight maintenance, medication may be suggested. Currently, the two drugs that are approved for weight loss are Sibutramine (Meridia) and Orlistat (Xenical). All patients do not respond to pharmacotherapy. Studies have shown that response to pharmacotherapy in the initial phases of use often continues and does not otherwise [139]. In addition to using medications for weight maintenance, these medications may be used when LI does not seem to be effective for weight loss. Medications should only be considered and used as part of the comprehensive treatment plan to reduce weight which includes LI [50, 136].

Weight loss pharmacotherapy has several side effects that often are contraindications for use. Sibutramine's most common adverse effects are increased blood pressure and pulse [140], while Orlistat decreases absorption of fat-soluble vitamins, causes soft stools and can cause anal leakage. Sibutramine is contraindicated for individuals with high blood pressure, congenital health defects, congestive heart failure, arrhythmias, or history of stroke. Prior to prescribing medications, the health care provider will carefully evaluate the risk to benefit ratio with the patient and should carefully monitor side effects and adverse effects of the medication along with whether the medication is assisting the patient in reaching their weight loss goals. Medications should be discontinued if they are not providing any health benefits for the patient, if there are serious side effects, or if side effects outweigh the benefit of the medication. Patients with high risk factors for mortality and or with greater obesity may be good candidates for surgery. [50, 136]

Treatment of T2DM includes LI, oral hypoglycemic agents (OHA; oral agents that reduce high blood sugar) or insulin or combinations. The primary treatment goals are to reduce weight [141] and hyperglycemia to a general target level of ≤ 7% A1c levels and/or an FPG of < 126 mg/dL (7.0 mmol/L) [141, 142]. (HbA1c is a 2 to 3 month average of blood glucose levels whereas, FPG is the blood glucose level after a patient has been fasting for a specific period of time [143].) In cases where a patient is morbidly obese or might benefit from weight loss, metformin, a medical therapy, may be introduced as it has indications for that. Typically, metformin, a biguanide, is introduced as the first line treatment for T2DM patients. Other OHA's, by drug class, are sulfonylureas [142, 144], meglinitides [142, 144-146], thiazolidinediones [142, 144], dipeptidyl peptidase 4 (DPP-4) inhibitors [144, 147], and sodium-glucose co-transporter-2 SGLT2. In addition to OHA's, insulin may be introduced to treat T2DM. Like OHA's there are several types of insulins - rapid-acting, short-acting, intermediate-acting, long-acting, and pre-mixed [148]. The need for larger amounts insulin use is often a sign of more significant disease progression [149]. Insulin use is often associated with weight gain [150]. Many treatments for T2DM do not assist with weight loss which can be an issue when treating overweight and obesity among patients with T2DM [151].

3.3 Bariatric Surgery

Bariatric surgery involves a surgical procedure whereby the stomach is cut, stabled or banded to be a smaller size with or without surgical alterations to the large and small intestines [107]. Most procedures can be classified by whether they involve gastric banding, gastric bypass, gastroplasty, or biliopancreatic diversion alone, or with duodenal switch [107]. Current surgical guidelines advocate for an individualized method where the procedure selected is based on desired therapeutic goals [152]. Laparoscopically performed procedures are endorsed over open procedures due to quicker recovery and fewer complications [152]. Endoscopic procedures are now available for banding. Contraindications for bariatric surgery (substance use, poorly controlled psychiatric illness, and bulimia nervosa) are often determined on a case by case basis and may directly relate to the specific procedure that is being considered [152].

Guidelines for bariatric surgery are only indicated for those with BMI's in the obese categories. Those with class I obesity (30.0-34.9 kg/m^2) are recommended for surgery in the presence of T2DM or metabolic syndrome [152].

General guidelines for bariatric surgery are as follows [152],

- BMI ≥ 40 kg/m^2 without coexisting medical problems where bariatric surgery does not pose excessive risk
- BMI ≥ 35 kg/m^2 with 1 or more severe obesity related comorbidity (T2DM, hypertension, hyperlipidemia, obstructive sleep apnea, obesity-hypoventilation syndrome, Pickwickian syndrome, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous statis disease, sever urinary incontinence, debilitating arthritis, or considerably impaired HRQoL)
- BMI ≥ 30 kg/m^2 with T2DM or metabolic syndrome
- Guidelines do not recommend bariatric surgery for glycemic control alone, lipid lowering alone, or cardiovascular disease risk reduction alone irrespective of BMI criteria.

The selection of a bariatric surgery procedure involves an individualized and comprehensive assessment of comorbidities, comprehensive medical history, psychosocial history, physical examination and lab testing, a justification for the medical necessity of the procedure, a thorough discussion with the patient about risks and benefits along with an assessment of financial and insurance information. In addition to individual level factors, technology and evidenced based practice play a role in bariatric selection. Table 3-1, below, shows how the frequency of bariatric surgeries have changed from 2011 – 2017 [108]. Patients are also encouraged to lose weight prior to the surgery as it has been shown to be associated with improved outcomes post-surgery [152]. A thorough preoperative assessment is completed with the patient to ensure that all lab levels are stable enough to conduct the surgery. [152]

Table 3-1: Estimates of the Number of Bariatric Surgical Procedure Performed from 2011-2017

Estimate of Bariatric Surgery Numbers, 2011-2017

Published June 2018

	2011	2012	2013	2014	2015	2016	2017
Total	**158,000**	**173,000**	**179,000**	**193,000**	**196,000**	**216,000**	**228,000**
Sleeve	17.80%	33.00%	42.10%	51.70%	53.61%	58.11%	**59.39%**
RYGB	36.70%	37.50%	34.20%	26.80%	23.02%	18.69%	**17.80%**
Band	35.40%	20.20%	14.00%	9.50%	5.68%	3.39%	**2.77%**
BPD-DS	0.90%	1.00%	1.00%	0.40%	0.60%	0.57%	**0.70%**
Revision	6.00%	6.00%	6.00%	11.50%	13.55%	13.95%	**14.14%**
Other	3.20%	2.30%	2.70%	0.10%	3.19%	2.63%	**2.46%**
Balloons	–	–	–	–	0.36%	2.66%	**2.75%**

The ASMBS total bariatric procedure numbers are based on the best estimation from available data (BOLD,ACS/MBSAQIP, National Inpatient Sample Data and outpatient estimations).

Reproduced from American Society for Metabolic and Bariatric Surgery. *Estimate of bariatric surgery numbers, 2011-2017*. 2018 [cited 2018 September 12, 2018]; Available from: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers.

Pre-surgery assessments and medication adjustments ensure that the surgery goes as optimally as possible. Post-surgery follow-ups assess adherence to behavioral recommendations post-surgery, evaluation of medication use which might interfere with weight loss, development of maladaptive eating behaviors, psychological complications, and radiographic or endoscopic evaluation to assess pouch enlargement, anastomotic dilation, formation of a gastrogastric fistula for RYGB patients or inadequate band restriction for LAGB patients [152]. Frequency of follow-up is often dependent on the procedure and complications as well as comorbidities. Revision of the surgery may be needed if there are severe complications. [152]

3.4 Summary of Clinical Guidelines

In summary, LI is an important method of weight loss regardless of whether medications or surgery are considered or used. Treatment plans should always include informed decision making that fosters a partnership between the health care provider and patient. In addition to improved health outcomes, the health care provider should also consider what procedures will be sustainable for the patient and will help improve their HRQoL which will be discussed in more detail in the next section.

4.0 Health Related Quality of Life

Health related quality of life (HRQoL) represents a multidimensional concept of health. Quality of life measures generally address health from the perspective of physical, mental, and social well-being [153]. As technological advances have been made in healthcare to prolong the lives of individuals with illness and disease, considerations for impacts of treatments should include more than just the length of life and physical health. In the last four years, HRQoL has become a means for health care providers to assess the individual perception of health at different stages of wellness and disease, including after the introduction of a new therapy, surgery, etc. [154].

On the surface, HRQoL is easy to understand as a concept. However, measuring HRQoL in a meaningful way can be quite complicated. To begin to understand aspects of measurement and how these are addressed, the fundamental components of validity and reliability will be discussed followed by current types of generic measures used to measure HRQoL.

4.1 HRQoL Reliability and Validity

Reliability, as a concept, identifies the degree to which an instrument identifies values in a stable and consistent fashion [155]. Reliability is measured by the magnitude that multiple replications, represented by a group or individual, are correlated with one another. The higher the correlation, the more consistent the measure is. Internal consistency is most often reported with a suggested range of 0.50-0.70 for groups and 0.85-0.95 for individuals [155]. Kappa coefficients, the proportion of responses in agreement, can also be used to assess reliability [155]. There are different suggested cutoffs, but generally coefficients that are < to 0.40 are considered poor, 0.40 – 0.60 acceptable, and ≥ 0.60 good with improvement in agreement as values increase [155].

Validity is a more difficult concept to measure. Validity represents the degree to which the measure does what it is intended to do, and is often interpreted with respect to the accuracy of a measure [156]. An instrument cannot be valid without also being reliable [156]. There are three types of validity: content-related, construct-related, and criterion-related [156]. Content validity is a prerequisite for other validity and represents the degree to which the items represent the content domain [156]. For HRQoL measures, questions should be sufficient and adequately represent the patient population [157]. Construct validity focuses on the behavior of the measure, that is, "Do respondents' answers reflect what they are intended to?" Construct validity is evaluated using convergent and discriminant validity. Convergent validity refers to how well similar questions correlate with each other whereas discriminant validity verifies that questions that are opposite of each other or are different do not have high correlations. Procedures using specific statistical approaches can test to evaluate construct validity [157]. Criterion validity is nested under content and construct validity and evaluates the validity of an instrument compared to a gold standard [157].

One of the most important components of validity is the ability to measure changes over time, which is important for HRQoL. The goal is often to detect the smallest meaningful change. The minimally important difference (MID), defined as the smallest change at which a provider may consider changing management of care based on functioning, has been created to assess change [158]. MIDs are important but can be controversial based on the lack of consensus on the appropriate estimation method to use [159-162].

Generally, there are 2 main approaches for estimating MID – distribution-based or anchor-based. Distribution based estimation depends on the spread of the data around the mean whereas anchor-based estimation uses an anchor, an independent and verified measure of change, to assess minimal changes in HRQoL. Anchor based estimation is considered more precise due to higher criterion validity [159, 163], however, because there is no consensus on the best anchor, there can be disagreement and variability around the estimated values [160, 162]. To address this issue, multiple anchors are recommended in the estimation process [160, 162]. Other methods that use an anchor-based like estimation have been developed, such as estimation based on the multiattribute health classification system, where scores are based on preference weights (defined in section 3.5.2.2, page 38), which is a variation of the anchor based estimation approach [164]. Lastly, MIDs differ based on the specific disease or health condition and the population assessed, oftentimes at the country level, just as validation of and scores for HRQoL do. MIDs are specific to the HRQoL measure which differ by category.

4.2 Categories of HRQoL

HRQoL measures fall into two basic categories – generic and disease specific. Generic measures of HRQoL are designed to assess HRQoL across a range of populations and across many diseases and health conditions. Specific measures of HRQoL are designed to assess HRQoL related to a specific disease or condition [155]. These measures are important when trying to understand the burden of a specific disease or condition. Unlike generic HRQoL measures, HRQoL for disease specific measures only apply to that particular disease and cannot be used across different types of diseases [157].

4.2.1 Generic HRQoL Measures – Health Profile Subtype

Generic HRQoL measures, based upon health profile instruments use a series of domains or dimensions (e.g. physical, mental, emotional, social) to measure HRQoL [155]. Each domain is scored, and these individual scores inform how an individual, or a group, is performing in that designated area. Domain scores can also be combined into summary scores to provide information about how a patient is performing in a general area such as general physical health. The SF36 is a widely used health profile instrument.

4.2.1.1 Short Form 36 (SF36)

The 36-item Short Form Health Survey (SF36) was developed in the United States in the late 1980's from the results of the RAND Medical Outcomes Study that studied patients with chronic conditions in relation to quality of life [165]. The SF36 is a standardized instrument widely used as a measure of health outcome. The SF36 measure eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health [165]. Scores for the 36 questions are transformed to a 0-100 scale where higher scores, represent better HRQoL. Two component scores, the physical component score (PCS), and mental component score (MCS), can be calculated to summarize the physical and emotional quality of life. Methods have been developed to meaningfully evaluate the summary scores using a correlated structure [166]. The mean US SF36 physical and mental component scores have been estimated to be 49.22 and 53.78 respectively from a sample of 3,844 adults in the National Health Measurement Study [167]. PCS and MCS scores were standardized using a representative sample of the 1998 US general population, so that the mean score equals 50 and the standard deviation equals 10. Higher scores indicate more positive PCS and MCS status [165]. The SF6D is a preference based generic measure of HRQoL that is derived from the SF36 and will be discussed in the next section.

4.2.2 Generic HRQoL measures – Preference Based Subtype

In contrast to health profile scores, preference-based measures provide a single score, with a range from 0-1 to indicate, on a continuum, an individual's HRQoL; where 0 represents death and 1 represents perfect health [168]. Preference based measures were originally developed by economists to assess if the benefits of a treatment were justified based on the costs. That is, will this new treatment provide a better quality of life to the patient compared to their current health state and other existing treatments and is the improvement justifiable to the cost? Economists developed a value called the quality-adjusted life year (QALY), to answer their questions [168]. QALY's are calculated by multiplying a preference weight by the duration (time interval) of a specific health state.

In order to calculate QALY, health states first had to be defined and divided into measurable units [168, 169]. Health states were defined by examining the natural history of disease and were divided into predefined units by using identifiable measures [168], such as, Hemoglobin A1C levels and presence of symptoms for T2DM. It must be appreciated that health states are not always easy to define or divide. For some diseases or conditions, there are multiple causes, or the true etiology is not understood enough to develop specific cutoff points. This remains a consideration when understanding and using QALY [168].

Preference weights, sometimes referred to as <u>utility weights</u> or <u>preference utility weights</u>, reflect the desirability for a specific health state and is the second value needed to calculate QALYs [168]. These weights can be estimated from the literature or can be estimated using direct, indirect, or estimation or mapping methods using regression approaches [164, 168, 170] . Preference weights that are found in the literature are used when direct or indirect methods are not available [168, 170]. Caution is recommended in using information from the literature to elicit and estimate utility weights from multiple sources as the methods of valuation often differ by study [168].

Direct methods to identify utility weights include time trade off (TTO), Standard Gamble (SG), or Visual Analog Scale (VAS) procedures. These methods generally ask respondents to score preferences in the form of probabilities between death and perfect health [168]. The SG method ask respondents to gamble between perfect health (p) and death (1-p). For example, an individual might be asked to respond to the following prompt: “Imagine that your health could be improved to full health from your current condition, however, you will have to assume a certain risk of death. What probability of death would you be willing to assume to have full health?” Given the current question, a person with obesity and prediabetes might accept a 95% chance of perfect health and a 5% chance of death. Thus, the preference score would be .95. The assumption with this method is that in order to achieve perfect health, persons with poorer health will accept a higher risk of death, i.e. a lower probability of perfect health, than persons in better health [168].

For the TTO method, respondents are asked to decide how much time in perfect health they would be willing to trade to escape their current health state [168]. For example, an individual might be asked to respond to the following: “Imagine that you are told that you have 10 years left to live. As you are told this, you are also told that you can choose to live in your current health state for the entire ten years, or you can give up some life years to live in perfect health. Indicate with a cross on this line, how many years you would be willing to give up.” Continuing with the hypothetical example, an individual with obesity with prediabetes may be willing to trade 2 life years to live in full or perfect health. The assumption made using this technique is that 8 years in perfect health is equal to 10 years living with obesity and prediabetes. To calculate how many years an individual values living in their current health state, the time selected living in perfect health is divided by the duration of the period and scaled 0-1 [168]. For the hypothetical example above, the individual would value living with obesity and prediabetes 8/10 or 0.8 compared to full health (1.0). Using this method, people in poorer health are assumed to trade more time in perfect health life to escape their current health.

Though complicated, SG and TTO are preferred to indirect methods and are rooted in utility theory – one of their biggest strengths [168]. While the theory behind each test stands, the actual test can be administered in different ways. For example, a person can be asked to imagine a health state, rather than using their own. Also, therapies or treatments can be offered in relation to achieving perfect health, which may add context to an individual’s decision-making process.

One disadvantage of these methods is that they may only capture a respondent's familiarity or apprehension with taking risk rather than their value of life. Direct methods can be complex to administer and are thought to be unethical when asking people to consider their deaths especially if they are frail or near the end of their lives. In addition, persons with certain health conditions may not have enough difference in their scores to be able to detect change or may need very large samples to have adequate variance [168].

The VAS procedure represents an alternative to these methods [168] . With the VAS method, respondents are given a scale of 0 – 100, with higher scores indicating better health, and asked to rate their current health on that day [168, 171]. While this scale avoids some of the problems from the TTO and SG, Drummond and Brazier do not recommend using this scale alone, as it is prone to measurement bias [172, 173]. Respondents may avoid the extremes, 0 or 100, and may gravitate toward where they think their health should be, but not what they are really experiencing.

Multiattribute Health Status Classification System (MAHSCS) methods are indirect methods in which researchers use a public sample to estimate preference weights for multiple health states using one of the direct methods. These preference weights are then integrated into a scoring algorithm. While MAHSCS methods have less random error than direct methods, they might not have enough participants with a specific health condition to adequately describe it. The most commonly used MAHSCS methods are the Quality of Well-Being scale (QWB) [174], Health Utilities Index (HUI) [175], the SF6D [176, 177], and the Euroqol – 5 dimension (EQ5D) [171]. Each measure uses a different direct method to estimate preference weights. Scores for MAHSCS often differ by country or other factors. Because the MAHSCS uses a standardized system of creating health states, QALY's are calculated by multiplying utility weight by the period of time in years [178]. The Euroqol and SF6D are described in more detail below.

Ceiling and floor effects can be an issue for both health profile and preference based subtypes of generic HRQoL measures [179]. Ceiling and floor effects occur when an uncharacteristically large number of respondents answer toward one extreme end of the survey - full health for ceiling effects or poor health for floor effects. These effects refer to a limited ability of the measure to differentiate between good health or poor health states, respectively [168]. The presence of ceiling or floor effects may represent a general lack of sensitivity within the measure for a particular population [180]. Floor and ceiling effects are observable descriptively by examining the distribution of answers. Data skewed to the left or right may be an indication of ceiling or floor effects, respectively. While there is no consensus on the cut off for either of these effects, different methods have been created to aid more accurate detection [181] and to control for them in analysis [179]. Once these effects have been identified, data transformation or specialized data analysis techniques are used to account for the effect.

4.2.2.1 Euroqol 5 Dimension (EQ5D)

The Euroqol – 5 dimension 3 Long (EQ5D) was introduced in 1990 by a group of researchers in Europe and measures HRQoL across 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [171]. The EQ5D has been administered in a variety of populations [182-184] and the measure responds similarly to other widely used HRQoL instruments [182, 184, 185]. Respondents are asked one question in each dimension. Answer options for each dimension have a range of 1 to 3 (“no”, “some”, or “extreme”); with lower scores indicating better health. Preference weights for the EQ5D were originally developed from the UK general population. However, recently scores have been developed using populations from Belgium, Denmark, Finland, Germany, Japan, New Zealand, Slovenia, Spain, the US, and Zimbabwe (Figure 4).

An EQ5D index score for the United States, available at www.euroqol.org, has been developed with a range of -0.11-1.0, where higher scores indicate better HRQoL and negative scores indicate a perception of health that is worse than death [183]. The mean U.S. EQ5D index value of 0.87 has been estimated to represent a non-institutionalized adult using data from a sample of approximately 53,600 individuals [183]. Figure 4-1 (found at www.euroqol.org) shows how EQ5D scores differ by health state, the presence and severity of impairment among each of the 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; listed in order), and by country preference weights; not all 243 unique health states are shown. Table 4-1 shows the health states in the order they occur in Figure 4-1 and aids in comparing the level of impairment to the index score by country. The EQ5D is known to have a ceiling effect in which it is difficult to differentiate differences in better health outcomes, but is not known to have floor effects – difficulty differentiating differences in worse health outcomes [181, 182, 186]. The EQ5D can be administered by self, proxy, or by phone.

Table 4-1: Health States and Associated Impairment (Corresponds with Figure 4-1)

Health State	Mobility	Self-Care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression
11111	None	None	None	None	None
21111	Some	None	None	None	None
12111	None	Some	None	None	None
11121	None	None	None	Some	None
11112	None	None	None	None	Some
11122	None	None	None	Some	Some
21232	Some	None	Some	Extreme	Some
32211	Extreme	Some	Some	None	None
22323	Some	Some	Extreme	Some	Extreme
22233	Some	Some	Some	Extreme	Extreme
33321	Extreme	Extreme	Extreme	Some	None
33333	Extreme	Extreme	Extreme	Extreme	Extreme

The EQVAS assesses perceived health state using a continuum of 0 “worst imaginable health state” to 100 “best imaginable health state”. Higher scores indicate better health. Using a sample of 13,600 non-institutionalized U.S. adults, the mean EQVAS score was estimated as 79.2 [183]. Minimally important (clinically relevant) changes were estimated to be 0.03 for the EQ5D index score and 10 for the EQVAS score [164].

4.2.2.2 Short Form 6 Dimension (SF6D)

The Short Form Health Survey 6 Dimension (SF6D) was derived by Brazier et al [176, 177] in the late 1990's, by reducing the eight dimensions of the SF36 to a one score preference-based measure. The six dimensions that were included are physical functioning, role limitations, social functioning, pain, mental health, and vitality. The US valuation of the SF6D was developed in the past five years (2013), and has not been used as frequently as the SF36 [187]. Preference weights for the SF6D were first estimated using the standard gamble (SG) method from a general population of 611 UK residents, and the scale has been found to have good reliability and validity [182, 188]. In 2013, a study, published by Craig et al, estimated US preference weights using a modified SG method that is more robust to floor effects [187]. To date few studies have used US preference weights to obtain SF6D scores. Unlike the EQ5D, the SF6D using the UK preference weights and unmodified SG, has been found to have floor effects but not ceiling effects [181, 182, 186].

4.2.3 Obesity Specific HRQoL Measures

Disease specific measures, unlike generic measures, are designed to assess how symptoms and issues related to the disease of interest have an impact on HRQoL. One of the greatest advantages of disease specific measures is the increased content validity increasing the sensitivity to measure differences and changes [189]. Disadvantages are that they cannot be used to compare HRQoL across different diseases and QALY's cannot be calculated from them. Obesity specific HRQoL fit into this class of disease specific measures. Obesity specific HRQoL measures can hone in on the complex and multifactorial components of obesity and can assess HRQoL in relation to these components. Some of the most commonly used obesity specific HRQoL measures are listed in Table 4-2.

Table 4-2: Most Commonly Used Obesity Specific HRQoL measures

Measures	*Description*
Impact of Weight on Quality of Life (IWQOL)	A 31-item scale that consists of a total score and a score for 5 domains: physical function, self-esteem, sexual life, public distress, and work [190].
The Obesity Problems Scale (OP)	A module of eight questions developed to assess how bothered one is about their obesity. Higher scores indicate greater psychosocial dysfunction [191].
Weight Distress	A modified version of the Medical Outcomes Study distress scale where questions are reworded to be specific to weight. The total score ranges from 3 to 36, lower scores indicate less distress [192].
Health State Preference in Persons with Obesity Scale (HSP)	An obesity-specific health state classification system that assesses the characteristics of physical attractiveness, social functioning, health distress and emotions in the context of the respondent's weight [192].

4.2.4 Summary of HRQoL

HRQoL is a useful but complicated way of measuring an individual's perception of health momentarily and over time. Generic and disease specific measures of HRQoL have specific advantages and disadvantages of use and it is up to the health care provider or researcher to determine what aspects of measurement are most important to them. HRQoL measures may differ by population, situation and disease. Next, obesity will be discussed in relation to HRQoL.

5.0 Obesity's Impact on HRQoL

Illnesses or disease states typically lower HRQoL (compared to a non-illness state) and interventions typically increase HRQoL to higher levels than prior to treatment [154]. The impact of overweight and obesity on HRQoL are no exception. Obesity and associated comorbidities - prediabetes and T2DM – are related to lower HRQoL than normal weight individuals [193-197] and lower HRQoL is also associated with T2DM [196, 197], as well as low levels of physical activity [198, 199], and sedentary behavior [200]. Some of the most common HRQoL measures that are used to evaluate obesity are the SF36 and obesity specific measures. Table 6 shows most of the common measures used to evaluate HRQoL and obesity and T2DM along with a description of each measure [201].

Table 5-1: Most Commonly used HRQoL Measures among Obese and T2DM Individuals

Generic	Obesity	T2DM	
SF36	X	X	Assesses 8 dimensions of physical, social, and mental health. The physical component summary (PCS) is a physical summary score and the mental component summary (MCS) a mental summary score of the items in the SF36. PCS and MCS scores were standardized using a representative sample of the 1998 US general population, so that the mean score equals 50 and the standard deviation equals 10. Higher scores indicate more positive PCS and MCS status. [165]
SF20		X	6 subscales: physical, role, and social functioning; mental health; pain; health perceptions; summed items within scales; transformed to 0-100 scale where 100 is best A generic measure with 6 subscales: physical, role, and social functioning; mental health; pain; health perceptions; summed items within scales; transformed to 0-100 scale where 100 is best.
The 15-D	X		A generic, 15-dimensional measure of HRQoL (physical, social, and mental domains) that can be used as a single index score measure [202]. Item responses were aggregated to a total score ranging between 0-1, where a higher total score indicates a more positive 15-D status.
Current Health Scale	X		Measure comes from the General Health Rating Index [203]. This scale includes 9 general statements on perceived health. Item responses are aggregated to a total score ranging between 0 and 100, where a higher score indicates more positive perceived health status.
The Nottingham Health Profile II (NHPII)	X	X	Generic measure that measures areas of task performance most affected by health [204]. It contains 7 statements that refer to the effects of health problems on occupation, ability to perform domestic tasks, hobbies, personal relationships, sex life, social life, and holidays. Item responses are aggregated to a total score ranging between 7 and 21, where a lower score indicates a more positive NHPII status.
Sickness Impact Profile (SIP)		X	A generic measure with 136 statements: physical and psychosocial dimensions and independent categories; scores for overall SIP, 12 categories, and 2 dimensions
Dartmouth COOP/WONCA Chart		X	A generic measure with 6 domains assessed by single items on a 5-point scale: physical activities, feelings, daily activities, social activities, change in health, and overall health; a pictograph represents the options
Quality of Well-Being Scale (QWB)		X	Generic measure with 3 functional scales (mobility, physical activity, social activity), 36 symptom/problem complexes (later reduced to 25); QWB index adjusted by preference weights obtained from random samples of general population
EuroQol (EQ5D)	X	X	Generic measure with 5 dimensions with 3 levels of responses: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression; single index, 5 domain scores; used in valuation of health states
Well-Being Questionnaire (WBQ)		X	A generic measure with 18 items measuring psychological well-being are scored on a 4-point Likert Scale for an overall general well-being scale and 3 subscales: depression, anxiety, and positive well-being.
World Health Organization Quality of Life Questionnaire (WHOQoL)		X	A generic measure where 100 items are scored on a 5-point Likert scale; overall quality of life and 6 domains: physical health; psychological state; level of independence; social relationships; environment; spirituality, religion and personal beliefs; higher results indicate better HRQoL
Note: Table created from Table 1 in Andersen review [201] and Table 1 from Luscombe review [205].			

5.1 Obesity and HRQoL

While overweight and obesity have been shown to decrease HRQoL, a limitation of the research has been isolating the effects of overweight and obesity from its co-occurring comorbidities [198, 206]. To address this issue, Jia et al used Medical Expenditure Panel Survey, a representative sample of the US non-institutionalized civilian population, to assess HRQoL by BMI while controlling for age, sex, race, income, current smoking, physical activity, and disease (asthma, hypertension, diabetes, heart disease, stroke, and emphysema) [198]. The sample included 13,646 subjects and used the SF12 and EQ5D (UK preference weights) to assess HRQoL. The percentage of the sample in each BMI class was 2.1 for underweight, 39.7 for normal weight, 35.1 for overweight, 15.0 for class I, and 8.2 for class II. The mean sample values for the PCS-12, MCS-12, EQ5D index, and EQVAS scores were 49.4 (SE=0.13), 51.2 (SE=0.11), 0.823 (SE=0.0031), and 79.2 (SE=0.22) respectively. The mean scores for each measure are very close to the population averages – 49.22 for the PCS-12, 53.78 for the MCS-12 [167], 0.87 for the EQ5D index and 79.2 for the EQVAS [183].

Multivariable analysis (Table 5-2) indicates that as weight increases physical functioning HRQoL decreased greater than mental functioning as observed by the PCS-12 and MCS-12, which has been observed by other researchers [194, 206-210]. For example, at class II obesity, the difference for PCS-12 is -4.00 compared to -1.07 for the MCS-12 [198]. Differences in the EQ5D index score for the class II obesity result in nearly a year of life lost, given a ten-year period. For the EQVAS, as weight increased, the overall perception of health decreased.

Table 5-2: Multivariate Linear Regression Analysis for Jia et al

Obesity Class	PCS-12		MCS-12		EQ5D index		EQVAS	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Underweight	-0.87	0.227	-1.60	0.0317	-0.029	0.0879	-3.75	0.0109
Normal Weight (ref)	0.00	.	0.00	.	0.00	.	0.00	.
Overweight	-0.73	0.001	-0.24	0.3345	-0.013	0.0115	-0.52	0.1931
Class I Obesity	-1.86	<0.0001	-0.08	0.82	-0.033	<0.0001	-3.23	<0.0001
Class II Obesity	-4.00	<0.0001	-1.07	0.0303	-0.073	<0.0001	-4.84	<0.0001
* model controls for age, sex, race, income, current smoking, physical activity, and disease (asthma, hypertension, diabetes, heart disease, stroke, and emphysema)								

Even though it is accepted that obesity results in lower HRQoL, there can be great variability in scores, by measure, including different preference weights associated with each measure, and population. Figure 6 illustrates this [211]. For example, for the EQ5D index scores for the UK and US preference weights seem to be relatively similar for overweight, albeit the standard error is wider for the UK preference weight. However, the preference weights for obesity differ more by the preference weight used than those for overweight indicating that different populations (US vs UK) perceive impairments from obesity differently for the EQ5D. Variability is an accepted component of HRQoL, if it is not due to limitations of the actual measure.

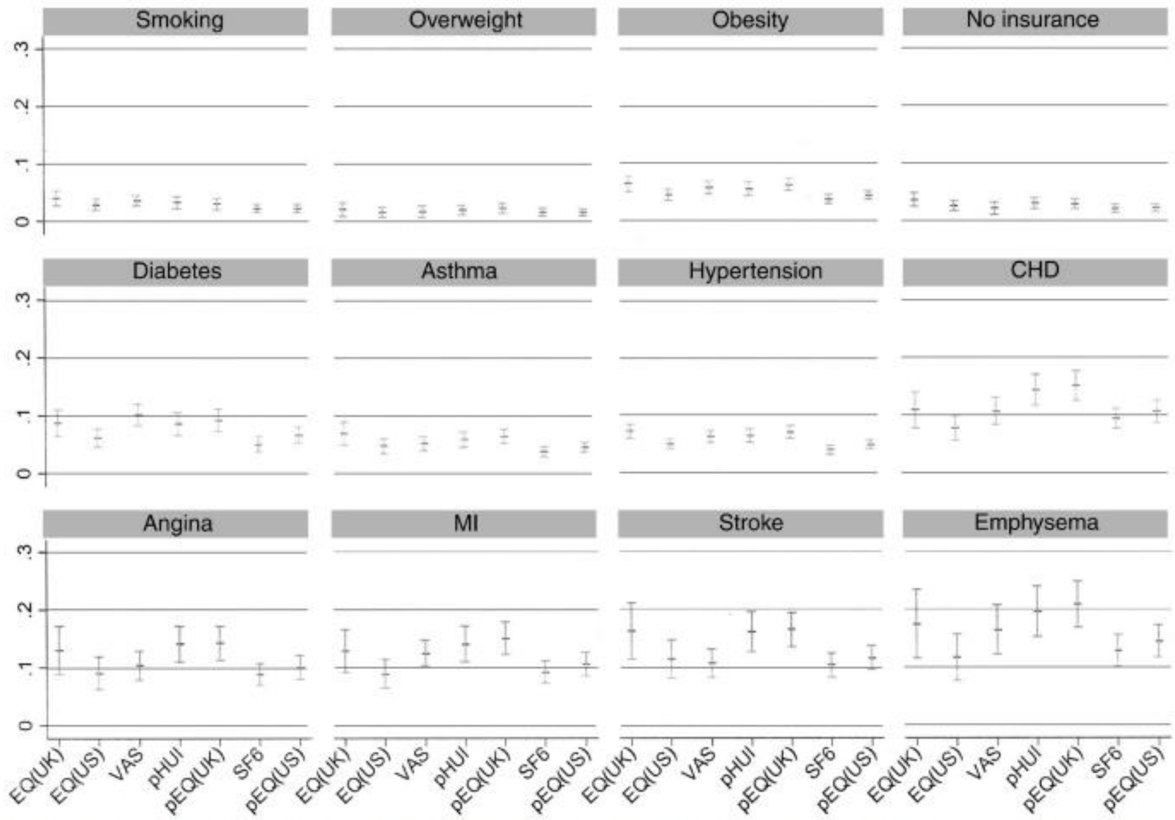


FIGURE 1. Each graph shows the parameter estimate and 95% CI for the disutility associated with each problem on 7 preference scores adjusted for sociodemographics. The y-axis is size of disutility in HRQL units.

Figure 5-1: Differences in Preference Based Scores by Preference Weight and Diseasee

Reproduced with permission from Relative disutilities of 47 risk factors and conditions assessed with seven preference-based health status measures in a national U.S. sample: toward consistency in cost-effectiveness analyses. Franks, P., J. Hanmer, and D.G. Fryback, Med Care, 2006. **44**(5): p. 478-85 https://journals.lww.com/lww-medicalcare/Abstract/2006/05000/Relative_Disutilities_of_47_Risk_Factors_and.13.aspx.

5.2 Prediabetes and HRQoL

Prediabetes is a health condition that is often accompanied with other comorbidities. Many studies evaluate prediabetes in the context of an intervention program, rather than by itself. The DPP presented 4-year outcomes post LI intervention (mean follow-up of 3.2 years) [212]. As a reminder, the DPP was a nationwide study aimed at delaying or preventing the onset of T2DM that recruited participants with prediabetes and/or metabolic syndrome. The goal of the study was to achieve and maintain modest weight reduction by treatment through LI (dietary changes and increase in physical activity (150 min/wk of moderate intensity activity)) or through the use of metformin [54]. Results indicated that the physical function and general health domains of the SF36 scores improved for the LI group at year 1, followed by a decline through years 2 to 4 (Figure 6). Improvements were greater for LI compared to the metformin group for the SF6D (0.0084 vs 0.0019) and the PCS (1.57 vs 0.15). Weight loss and insulin secretion and insulin resistance were mediators for changes in HRQoL after controlling for demographic factors and baseline weight and physical activities for the SF6D, physical component, body pain, and vitality domains of the SF36. Two other studies using LI are discussed in the “Gaps in the literature” section.

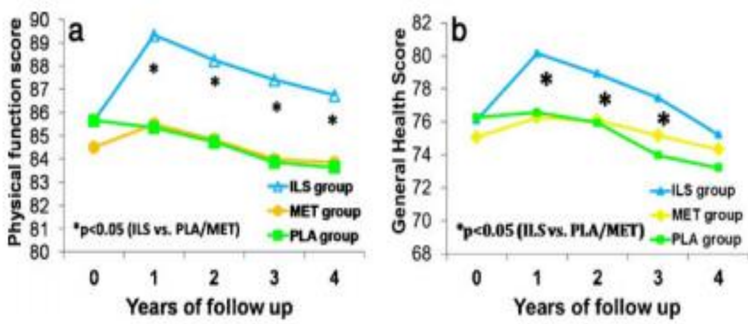


Figure 1. Changes in physical function (1a) and general health (1b) scores across treatment groups. ILS, intensive lifestyle; PLB, Placebo; MET, Metformin. Data available in study participants decreased overtime from baseline (n=3206) to year 1 (n=3143), year 2 (n=2988), year 3 (n=2941), and year 4 (n=1859).

Figure 5-2: SF36 changes in physical function and general health scores for DPP study through year 4

5.3 T2DM and HRQoL

Once an individual has developed T2DM, their HRQoL usually declines substantially (Figure 6). Generally, increased age and/or increased Hemoglobin A1c's, an average score of blood sugar, are associated with decreased HRQoL scores [213]. Additionally, as comorbidities and complications of T2DM increase, impairment in HRQoL increases as well. Surprisingly, all comorbidities do not cause the same impairment. For example, retinopathy has less observed impairment than neuropathy [213]. The expected range of scores for T2DM were taken from 40 publications which may speak to some of the great variation in scores. Overall, PCS were more impaired than MCS scores (Table 8).

Table 5-3: SF36 PCS-36 and MCS-36 score ranges for T2DM from 40 studies [214]

	PCS	MCS
T2DM	27-49	39-63

5.4 Bariatric Surgery and HRQoL

Bariatric surgery has been one the most promising interventions for obesity for weight loss and improvements in HRQoL. The time at which the HRQoL measure is administered is a challenge in assessing HRQoL for bariatric surgery. Many studies do not administer HRQoL surveys longitudinally [215]. For example, Khandalava et al [215] administered the SF36 to 350 patients who had undergone bariatric surgery to find predictors associated with HRQoL post-surgery (Table 7). Both the PCS-36 and MCS-36 were lower than the population average for this study. The multivariable analysis of predictors on HRQoL indicated a negative association between age at time of surgery, pre-surgical BMI and duration since surgery.

Another small study by Kolotkin et al [216] evaluated changes in the SF36 over a 6 year period using a longitudinal design. The aim of the study was to evaluate SF36 scores for 323 patients who received a gastric bypass compared two obese groups not undergoing surgical weight loss. Table 9 shows the values for the gastric bypass group only. At baseline, scores are well below the population norms for both the PCS and slightly below for the MCS. Over the six-year follow-up the PCS has greater observed improvement, approaching the population norms. These findings for greater improvement in the PCS than the MCS are consistent with results from the "Obesity and HRQoL" section. Weight loss was significantly correlated with improvements in the PCS, although not sustained over time [216].

Table 5-4: SF36 PCS-36 and MCS-36 for threee different bariatric surgery studies

	Follow-up Time	Study Type	Timepoint	PCS-36	MCS-36
Khandalava [215]	7.3 yrs.	Cross-Sectional	Post-surgery	46.4	47.8
Kolotkin [216]	6 yrs.	Longitudinal	Baseline	32.5	43.8
			Baseline – 6yrs	+11.3	+3.8
			2yrs – 6yrs	-2.3	-1.7
Belle [130]	N/A	Longitudinal	Baseline	51.6	36.5
King [135]	3 years	Longitudinal	Baseline	39.9	NA
			3 years	44.8	NA
* All scores have been standardized to have a mean of 50 and a standard deviation of 10					

The LABS-2 study, whose population is a focus of this dissertation, also evaluated HRQoL using the SF36. As a larger nationally representative study, the MCS-36 and PCS-36 (51.6 and 36.5, respectively) [130] scores were much higher at baseline than the previously reviewed studies. The mental health scores were comparable to the national average of 50, however, the physical health scores were more than 10 points, or 1 standard deviation lower, than the national average indicating impairment. Scores for women were slightly lower for both the MCS and PCS but were not statistically different compared to men. LABS-2 also used the obesity specific measure, IWQoL-Lite, to assess HRQoL at baseline. IWQoL scores were statistically different for the total scores, work, physical functioning, sexual life and self-esteem for women compared to men, where women had lower scores. Scores were not statistically significant by sex for public distress and physical functioning. Results from the bariatric study review demonstrate how variable the values can be over time based on population and when the survey is administered.

Taking a different approach to evaluating HRQoL, King et al reported changes in the pain and physical functioning domains of the SF36 from baseline to up to the first 3 years following bariatric surgery for 2458 LABS-2 participants [135]. From baseline to 1-year post-surgery, mean SF36 scores improved by 7.4 points for the bodily pain domain and 12.7 for the physical function domain. Scores decreased from year 1 for the next 2 follow-up years. Specifically, the physical function domain score improved to a mean of 49.2 at year 1 from the baseline mean of 36.5, but then decreased to means of 48.8 and 47.8 at years 2 and 3, respectively, even though leg pain reporting continued to improve through the 3 years.

Khandalava et al [215] administered the SF36 post-surgery only to 350 patients who had undergone bariatric surgery to find predictors associated with HRQoL post-surgery (Table 5-4). Both the PCS-36 and MCS-36 were lower than the population average for this study. The multivariable analysis of predictors on HRQoL indicated a negative association between age at time of surgery, pre-surgical BMI and duration since surgery.

5.5 Summary of HRQoL in obesity and T2DM

HRQoL obesity and related interventions are primarily measured using the SF36 and obesity specific measures. Adults with obesity and T2DM typically have lower HRQoL compared to normal weight adults and sex differences exist. Weight loss and presence of comorbidity have impacts on changes in HRQoL. Preference-based measures are being used more than previously used to assess HRQoL, however, as discussed in the HRQoL section, the preference weight used can have an impact on the value produced.

6.0 Gaps in the literature

In summary, overweight and obesity is a major public health problem that is rising in prevalence and poses severe health consequences. There are several effective interventions to treat obesity that have shown improvements in HRQoL. Preference-based generic measures of HRQoL, which may be ideal for economic comparisons of treatment, require more research to understand how different preference weights impact changes in HRQoL. US preference weights have been developed for 2 of the most widely used preference-based measures but have not been used extensively in obesity and obesity reduction research.

A recent literature search found that only 8 studies evaluating obesity, prediabetes, T2DM and/or treatments relating to these conditions (medication, lifestyle intervention, or bariatric surgery) have used the US preference weights for the EQ5D among the US population. Of the 8 studies, 1 study evaluated the association between obesity and HRQoL [217], 1 study evaluated changes in the EQ5D index among prediabetic, overweight participants comparing LI and delayed intervention [218], 1 study evaluated changes in the EQ5D index in association with BMI after laparoscopic gastric band surgery [219], 4 studies evaluated HRQoL among patients with T2DM [220-223], and 1 study used a national data sample to compare differences in preference based measures among 47 risk factors and conditions including obesity, overweight and T2DM (Figure 6) [211]. Baseline unadjusted EQ5D indexes using US preference weights for 6 of the 8 studies are presented in Table 10 because indexes were not given by weight class or T2DM status for 2 of the studies. The table shows that even though there is variation in index values for each risk factor or condition, generally, scores decrease as the risk factor or health condition becomes more severe.

As seen in Table 10, among studies that evaluate EQ5D index changes over time, decreases in risk factors, i.e. weight loss, have observed improvements in HRQoL. Eaglehouse et al [218], observed greater weight loss among the LI intervention group compared to delayed control resulting in greater improvements in EQ5D indexes after 6 months. Age and having a baseline EQ5D indexes below average were statistically significantly associated with the improvement. At five years of follow-up, Grandy et al [220], found that patients with T2DM had greater declines in EQ5D index and EQVAS scores compared to those without T2DM. Differences were statistically significantly related to age, gender and marginally associated with changes in BMI. Lin et al [219], found that greater decreases in BMI after bariatric surgery were associated with higher EQ5D indexes. Values were higher for all categories because assessments were taken post-surgery. Marrett et al [221], found that hypoglycemia, and weight gain were associated with lower EQ5D indexes among T2DM patients using antihyperglycemic medications.

Table 6-1: Baseline Unadjusted and Changes in EQ5D Indexes by Study and Health Condtions

	Bentley[217]	Eaglehouse[218]	Grandy[220]	Lin[219]	Stevens[222]	Zhang[223]
Study Type	Obesity	LI (Prediabetes)	T2DM	Gastric Band	T2DM	T2DM
Normal	0.89	--	--	0.94	--	0.82
Overweight	0.87	--	0.838	0.92	--	0.83
Overweight/Prediabetic		0.90 +0.01 (int)$^{+}$ 0.92 – 0.01 (cont)$^{\wedge}$	--	--	--	--
Obese	0.83	--	--	--	--	--
Class I	--	--	--	0.89	--	0.81
Class II	--	--	--	0.84	--	0.75
Class III	--	--	--	0.82	--	--
Morbid I	--	--	--	0.80	--	--
Morbid II	--	--	--	0.70	--	--
T2DM	--	--	0.798	--	0.67	0.80

$^{+}$ int = intervention
$^{\wedge}$ cont = control

No prior studies have presented data among these disease states (i.e. obesity and T2DM) using the US preference weights for the SF6D and no studies on bariatric surgery have evaluated HRQoL using the EQ5D and the SF6D concurrently in the same population. This proposed project provides an opportunity to fill these gaps in the literature by evaluating changes in the EQ5D index for 2 studies that use interventions to decrease obesity and reduce T2DM risk factors. Furthermore, the proposed project will add to the literature by evaluating changes in the EQ5D index and SF6D index for both measures in the bariatric surgery – a novel approach to understanding preference based HRQoL changes for obesity reduction in the US population.

7.0 Dissertation Aims

To address these gaps in the literature, the following research aims were assessed:

7.1 Dissertation Aim 1: Change in EQ5D in GLBMoves Study

Research Question: What is the effect of sedentary behavior reduction (within a lifestyle intervention) on changes in HRQoL amongst US individuals with prediabetes and/or metabolic syndrome.

Aim 1. To determine if two interventions; (a) a sedentary behavior reduction intervention combined with lifestyle modification and (b) a lifestyle modification intervention, evaluated separately, are effective in improving HRQoL (measured by EQ5D index and EQVAS) among a diverse group of older adults at risk for T2D compared to a control group.

Hypothesis: It is hypothesized that participants randomized to the sedentary intervention will have a statistically significant improvement in HRQoL compared to a control group at 6 months. It is hypothesized that participants randomized to lifestyle modification alone will have a statistically significant improvement in HRQoL compared to a control group at 6 months.

Aim 2. To assess if two interventions; (a) a sedentary behavior reduction intervention combined with lifestyle modification and (b) a physical activity lifestyle modification intervention, evaluated separately, are effective in improving HRQoL among a diverse group of older adults at risk for T2D prepost at 6 months.

Hypothesis: It is hypothesized that participants with greater reduction in sedentary behavior (pre-post 6 months) and/or increased physical activity, stratified by intervention arm, will achieve statistically significant improvement in HRQoL as measured by the EQ5D survey after 6 months compared to those without.

7.2 Dissertation Aim 2: Yearly Changes (up to 5 years) in HRQoL compared to presurgery by EQ5D for LABS-2 Participants

Research Question: Is postsurgery improvement in HRQoL maintained over 5 years post-surgery?

Aim 1: To evaluate yearly postsurgery changes in HRQoL (EQ5D index and EQVAS) compared to presurgery HRQoL by type of bariatric procedure.

Hypothesis: Health-related quality of life changes, will have sustained improvement from presurgery up to 5 years of follow-up.

Aim 2: To descriptively estimate quality-adjusted life years gained, using QALYs, up to five years among individuals receiving bariatric surgery.

Aim 3: To assess predictors and factors related to changes in QALYs after surgery.

7.3 Dissertation Aim 3: Changes in HRQoL (as measured by EQ5D and SF6D) in LABS-2 Study

Research Question: Do post-surgery HRQoL index scores measured by two different preference-based instruments (the EQ5D index and the SF6D index) differ in a population of severely obese individuals receiving bariatric surgery in the LABS-2 study.

Aim 1: To compare the correlations between quality of life scores for the baseline values of EQ5D index and SF6D index, by each measure, at baseline and 1 year pre-post, among a cohort of participants receiving bariatric surgery in the LABS-2 study.

Hypothesis: HRQoL index scores for each measure at baseline before surgery will be highly correlated ($r \geq 0.85$).

Aim 2: To evaluate ceiling effects for baseline presurgery values of EQ5D index and SF6D index, among a cohort of participants receiving bariatric surgery in the LABS-2 study.

Hypothesis: Ceiling effects will be more abundant for the EQ5D index compared to the SF6D index, whereas, floor effects will be more abundant for the SF6D compared to the EQ5D index.

Aim 3: To explore if EQ5D and SF6D index score changes one-year postsurgery survey are related to percent weight change.

8.0 Paper 1: Impact of a Community-Based Sedentary Behavior Reducing Lifestyle Intervention on Participant Reported Quality of Life

8.1 Abstract

Introduction: Health related Quality of life (HRQoL) improves after participation in a community-based lifestyle intervention that includes, along with weight loss, the goal of increasing physical activity levels. It is unknown whether HRQoL will also improve due to a lifestyle intervention in which the movement goal focuses instead on sedentary behavior reduction, an important risk factor for type 2 diabetes and cardiovascular health.

Purpose: HRQoL changes were examined among overweight participants randomized to receive an effective DPP-based community lifestyle intervention (DPP-GLB) with increasing MVPA as one of its goals (GLB-MOD) or one in which MVPA was replaced with sedentary time reduction (GLB-SED), compared to a delayed control group at 6 months. Six and 12-month prepost improvements in HRQoL relate to participating in these two interventions were also investigated.

Methods: Participants (N=277) enrolled in a 12-month 22-session intervention program completed the Euroqol 5 dimension (EQ5D index and EQVAS) at baseline, 6, and 12 months. Linear mixed models were used to evaluate change by randomization arm and prepost changes at 6 and 12 months.

Results: At 6 months, mean EQ5D index increased by +0.04 (p=0.02) in GLB-SED and mean EQVAS increased by +4.39 (p=0.047) in GLB_MOD compared to the delayed control arm. There was a significant prepost improvement in the EQVAS in both intervention arms and in the EQ5D index for the GLB_SED arm at 6 and 12 months.

Discussion: Participation in community lifestyle interventions with a sedentary behavior goal appeared to improve certain aspects of HRQoL providing an alternate effective intervention strategy for those who can't or won't engage in MVPA.

8.2 Introduction

Overweight/obesity and insufficient physical activity are independently associated with higher rates of prediabetes, Type 2 Diabetes Mellitus (T2DM), heart disease, and lower life expectancy [57, 224-230]. Lifestyle interventions have been found to be successful at lowering the risk of adverse health outcomes among overweight individuals by assisting individuals in reaching recommended physical activity levels and losing weight [53-55, 231, 232]. The Diabetes Prevention Program (DPP) [57] and community translations of the DPP, such as the Group Lifestyle Balance (GLB) program [73], have been found to be effective for weight loss and increasing moderate intensity or greater physical activity (MVPA) levels to 150 minutes/week [73, 79, 80].

Not only has participation in lifestyle intervention programs been successful in increasing MVPA, weight loss and decreasing risk of morbidity, such as T2DM, but they also improve health related quality of life (HRQoL) [212, 233-237]. HRQoL is a multidimensional concept of health that includes dimensions of physical, mental, and social well-being [153]. A 2016 study by Eaglehouse and colleagues showed that those receiving the DPP-GLB 12-month in-person lifestyle intervention, showed to be effective at increasing MVPA and reducing body weight, had greater improvements in HRQoL using the Euroqol 5 dimension (EQ5D) instrument at 6 months compared to those in the delayed-start control group [218]. This was one of the first DPP-translation studies to demonstrate improvements in HRQoL following intervention [238].

Lifestyle intervention programs have traditionally focused on increasing MVPA and weight loss. However, more recently, replacing sedentary behavior reduction with MVPA has also been shown to be important. This is because time spent sedentary has been shown to be an independent factor associated with increased risk of type 2 diabetes and cardiovascular disease [136]. Sedentary behaviors are any low energy expenditure behaviors performed while sitting or lying down [239]. Because sedentary time may remain unchanged even when MVPA is increased interventions are needed that specifically target sedentary behavior reduction both independent of and in addition to improving MVPA [240, 241]. High levels of sedentary behavior have also been shown to be associated with lower self-reported HRQoL as measured by the Short Form 36 [200].

To evaluate how intervention on sedentary behavior impacts weight loss, the DPP-GLB curriculum has been modified to include an initial movement goal to decrease sedentary time prior to adding a goal to increase MVPA (GLB-SED). This change was initiated to encourage greater reductions in sedentary behaviors and to provide a more gradual increase in movement for those individuals who may initially find it difficult to increase their MVPA. We are currently not aware of any other DPP-based translation efforts that have added a sedentary reduction goal and it is currently unknown whether this intervention will have a similar effect on HRQoL as the original DPP-GLB curriculum.

The purpose of the current study is to first evaluate HRQoL changes among overweight participants with prediabetes or metabolic syndrome who were randomized to receive the original DPP-GLB intervention with a modified intervention on sedentary time reduction and weight loss (GLB-SED) compared to the delayed control at 6 months, which has not been done previously. Next, HRQoL change was evaluated with the goal of increasing MVPA and weight loss (GLB-MOD) compared to the delayed control at 6 months. This will be the first time the impact of sedentary time reduction on HRQoL will be examined within an effective community-based lifestyle intervention effort. We will then investigate whether 6-month and 12-month prepost improvements in HRQoL relate to achieving recommended PA levels or achieving relevant reductions in sedentary behavior and weight loss.

8.3 Methods

8.3.1 Research Design

This investigation examined data from the NIH-funded Physical Activity and Sedentary Behavior Change Project (*i.e.,* GLB Moves, Principal Investigator: Dr. A. Kriska), which implemented DPP-based Centers for Disease Control and Prevention (CDC) recognized programs in five community centers in Allegheny County, Pennsylvania. Recruitment was conducted from January 2015 to the end of 2018. Participants were randomized to one of three arms: DPP-GLB:(1) the DPP-based CDC recognized Group Lifestyle Intervention (GLB) with physical activity and weight loss goals (2) GLB-SED: a modified version of the GLB with sedentary reduction and weight loss goals (3) a delayed-control arm. The delayed-control group allowed for a control comparison group and mimicked real life where resources may limit the availability of programming resulting in a delayed delivery for some participants. After 6-months, these waitlisted participants were randomly assigned to one of the intervention arms (1:1) and received a yearlong lifestyle intervention identical to the that received by those who began immediately.

Recruitment procedures included presentations at potential community centers, flyers and poster, advertisements in community center newsletters, and targeted direct mailing to zip codes around the various community centers. The eligibility criteria included individuals with a BMI ≥ 24kg/m^2 (≥ 22 kg/m^2 for Asians), who were 40 years or older with prediabetes (American Diabetes Association) and/or the metabolic syndrome (National Cholesterol Education Program ATP-III criteria). There were no physical activity or sedentary behavior study entry criteria. For this report, participants were excluded from analysis if they were missing the EQ5D at the baseline or 6-month follow-up timepoints.

8.3.2 Lifestyle Intervention

A detailed description of the standard DPP-GLB lifestyle intervention curriculum used for the DPP-GLB arm in the GLB Moves study has been previously reported [55, 74] and is freely available online at www.diabetesprevention.pitt.edu. The intervention followed the basic structure of past DPP-based CDC recognized lifestyle interventions which included a 12-month in-person, group-based program with a total of 16 core sessions and 6 maintenance sessions taught by a trained lifestyle coach. The first 6 months of core sessions was designed to deliver 12 weekly sessions followed by 4 bi-weekly sessions. The last 6 months, months 7-12 [242], consisted of 6 monthly maintenance sessions. The main goals of the DPP-GLB lifestyle intervention arm were to encourage participants to achieve and maintain MVPA levels to at least 150 minutes per week of moderate intensity physical activity (similar to a brisk walk) and to achieve and maintain a 7% weight loss by a steady safe and consistent progression. All lifestyle coaches completed a standardized 2-day training workshop provided by the Diabetes Prevention Support Center and recognized by the CDC [74]. Group sessions were held at community centers where participants received session handouts, self-monitoring logs, and a pedometer.

The GLB-SED intervention curriculum was adapted to direct participants to decrease the time that they are sitting in a day rather than to increase MVPA as is the case in the current GLB-MOD and DPP programs. Participants were gradually asked to decrease their sitting time until they eliminated 30-minute sitting bouts in a day with non-sitting activity. Participants were initially asked to monitor the number of 10-minute bouts of TV/computer/video watching or other sitting behaviors that they replaced with any non-sitting activity they choose as well as the number of short breaks they took from sitting by getting in the standing position. These “taking breaks from sitting” (TABS) were encouraged at least five times a day and were recorded by the participant. Participants were then encouraged to work up to a “super TAB”, or 30 minutes of sedentary time replaced by non-sitting activity, sequentially from 1 to 3 times per day resulting in an encouraged 5 TABS and 3 super TABS per day.

8.3.3 Study Measures

All study measures were collected by trained personnel at the community site using standardized measures. Study data were collected at baseline and at 6- and 12-months following randomization. Baseline data included the collection of self-reported age, race, gender, and family history of T2DM (non-modifiable risk factors). Participants in the delayed arm repeated baseline measures at the 6-month assessment to capture changes in the wait control period prior to being randomized to an intervention group. Participants received a $25 gift card for clinical assessment completed but did not receive compensation for intervention sessions.

8.3.4 Health Related Quality of Life

The EQ5D-3L is a valid and standard instrument that measures 5 dimensions of HRQoL - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [171]. Answer options for each dimension range from 1 to 3 (“no”, “some”, or “extreme”), with lower scores indicating better health. An index score, hence referred to as the EQ5D score, is calculated by applying preference weights based on the US population to each of the 5 dimensions [183]. Preference weights for the EQ5D are generated from the Time Trade Off (TTO) method to consider the population preference for the health of each of the 3125 health states, ranging from full health to death [243]. The index score can range from -0.11 – 1.0, where higher scores indicate better perceived health [183]. A negative score indicates a perception of health that is worse than death [183].

The Visual Analog Scale (EQVAS) allows respondents to rate their overall health status on a specific day from 0-100, where higher scores indicate better health. The EQVAS can provide a more comprehensive assessment of HRQoL when used with EQ5D score as it measures a slightly different component of HRQoL [172, 173]. Mean estimated scores from a sample of 13,600 non-institutionalized U.S. adults in 2008 were 0.87 and 79.2 for the EQ5D score and EQVAS, respectively [183]. Minimally important (clinically meaningful) changes were estimated to be 0.03 for the EQ5D index and 10 for the EQVAS score [164].

8.3.5 Weight, Physical Activity and Sedentary Behavior

Participants were weighed at the beginning of each assessment visit without shoes on a digital scale. The Modifiable Activity Questionnaire (MAQ) was administered by research staff to capture detailed estimates of physical activity performed in the past month and was calculated from frequency and duration of 40 common recreational activities [244]. Values of energy expenditure in metabolic task equivalent (MET) units were then assigned to each activity using the online compendium of physical activity and values of activity were expressed in METhrs/week[245] – 150 min MVPA/week is equivalent to 7.5 MET hrs per week. Leisure sedentary behavior was assessed as time spent watching television using a single item question “How much time (per day) do you spend sitting watching TV”. The MAQ has been validated for measuring leisure MVPA and sedentary time. [246-248].

Binary indicators (yes or no) were created to designate if participants had achieved at least 7.5 Metabolic Equivalent (MET) hrs per week and had decreased their TV watching by 30 minutes per day.

8.3.6 Statistical Analysis

Baseline characteristics were presented using frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. Pearson's correlation coefficient was used to assess the test-retest reliability for the wait-control arm (n = 95) for EQVAS (r=0.59) and Index (r = 0.49).

Comparisons for improvements in each continuous repeated measure of HRQoL (EQ5D index and EQVAS) for the delayed intervention group and GLB-MOD and GLB-SED treatment arms were conducted using linear mixed models using all available data, assuming an unstructured covariance matrix with a random intercept, random effects for person and site and time (baseline, 6 months), randomization arm, and time x randomization arm interaction entered as a discrete fixed effect. Chi-square tests were used to assess the number of participants who had improvement from baseline to 6 months in the EQ5D index or the EQVAS.

Change in each continuous HRQoL measure (EQ5D index and EQVAS) as the outcome by intervention group (GLB-MOD or GLB-SED) were estimated using separate paired t-tests pre and post 6 and 12 month values. Associations between each continuous HRQOL measure (EQ5D index and EQVAS) as the outcome and a decrease of ≥30 minutes of TV watching per day (0=no, 1=yes) and increase of ≥7.5 MET-hours per week (0=no, 1=yes) were estimated in separate linear mixed models, with each factor of interest (decrease in TV watching and increase in MET hours), time, and factor x visit interaction entered as fixed effects and person entered as a random effect by intervention group (GLB-MOD or GLB-SED). Decrease in TV watching was used as a static variable because it could not be measured at baseline, the values at 6 months or 12 months were used for both the baseline and follow-up value. Similar models were constructed to examine the associations between these factors at baseline and 12 months. All models assumed an unstructured covariance matrix.

Associations between change in each continuous HRQoL measure (EQ5D index and EQVAS) and nonmodifiable risk factors (age (continuous), race, gender, and family history of diabetes (all dichotomous)) were estimated using separate linear mixed models for each independent variable at 6 and 12 months by intervention group (GLB-MOD or GLB-SED). Models including all of the independent variables were also fit to assess the change in HRQoL associated with each nonmodifiable risk factor variable (age, race, gender, family history of diabetes) after adjusting for the others. All models included visit, factor (≥30 minutes of TV watching per day (0=no, 1=yes) and increase of ≥7.5 MET-hours per week (0=no, 1=yes)), and factor x visit interaction as fixed effects, and person entered as a random effect. All models assumed an unstructured covariance matrix.

8.4 Results

Participant recruitment numbers from informed consent to the analysis sample is provided in Supplemental Figure 8-1. The GLB-Moves project enrolled a total of 308 participants. Of those, 277 (90%) participants had HRQoL values at both the baseline and 6-month follow-up timepoints. White race was associated with meeting eligibility criteria for this report (83.39% eligible versus 64.52% not eligible; p=0.02) while Asian race was associated with not being eligible (0.72% eligible versus 6.45% not eligible; p=0.05 – Table 8-4: Supplemental table 1).

Demographic and clinical characteristics of all arms were similar at baseline and are reported in Table 8-1. In total, 83.4% of participants were non-Hispanic whites, 79.5% of participants were female, 53.8% of participants reported a family history of T2DM, and 87.4% reported attending college or greater. The mean baseline age was 63.3 (standard deviation [SD] = 8 .9) years, the mean baseline weight was 96.1 (SD = 19.8) kg, and the mean baseline BMI was 35.58 ± 6.53 kg/m^2.

Participants reported a mean EQVAS of 73.33 (SD = 17.46) among all randomization groups and 0.86 (SD = 0.12) for the EQ5D index, which were both slightly below the national average (EQVAS = 79.2; EQ5D index = 0.87). A total of 97 participants (34.4%) reported "no problems" for all 5 questions in the questionnaire (eq index value of 1.00).

8.4.1 Comparisons between the intervention arms and 6-month delayed control

Improvement in HRQoL was evaluated by randomization assignment. After 6-months of lifestyle intervention, both intervention groups had greater improvements in one of the two components of HRQOL compared to the 6-month delayed control (control). Improvements in HRQoL reached statistical significance in the EQ5D index for the GLB-SED arm and in the EQVAS for the GLB-MOD arm (Table 8-2). The estimated mean change in EQ5D index compared to the control was $\beta=+0.01$ (standard error [SE]=0.03; $p=0.46$) and $\beta=+0.04$ (SE=0.03; $p=0.02$) for the GLB-MOD and GLB-SED arms, respectively. For the singular EQVAS question the estimated mean difference in change was $\beta=+4.39$ (SE=2.41; $p=0.047$) and +2.88 (SE=2.23; $p=0.20$) for the GLB-MOD and GLB-SED arms, respectively, compared to control. Comparing the changes of the combined intervention groups to control resulted in a +0.02 (SE=0.01; $p=0.08$) greater improvement in the EQ5D index and a +3.66 (SE=1.91; $p=0.056$) greater improvement in the EQVAS. HRQoL improvement among individuals with a baseline EQ5D index or EQVAS below the national average was assessed for each intervention group at 6-months compared to the delayed control group and did not reached statistical significance, but trended toward improvement for both the EQ5D index (GLB-MOD: $\beta=+0.0003$, SE=0.02, $p=0.99$; GLB-SED: $\beta=+0.03$, SE=0.02; $p=0.16$) and the EQVAS (GLB-MOD: $\beta=+6.19$, SE=3.28, $p=0.06$; GLB-SED: $\beta=+3.25$, SE=3.22; $p=0.31$).

8.4.2 Prepost change in HRQoL by intervention group

Significant changes in HRQoL, out to 12 months post-intervention, were reported for participants randomized to both the GLB-MOD and GLB-SED intervention arms. Shown in Figure 8-1, mean improvements in the EQVAS for the GLB-MOD arm were +5.87 (SE=1.17; $p<0.0001$) and +4.88 (SE=1.23; $p=0.0001$) at 6 and 12 months, respectively. Similar mean improvements in the EQVAS were reported for the GLB-SED arm at 6 and 12 months; +5.75 (SE=1.29; $p<0.0001$) and +4.90 (SE=1.38; $p=0.0006$), respectively. Additionally, mean improvements for the EQ5D index in the GLB-SED arm were +0.03 (SE=0.01; $p=0.006$) and +0.04 (SE=0.01; $p=0.006$) at 6 and 12 months, respectively. There were no significant improvements in the EQ5D index for the GLB-MOD arm.

Similarly, statistically significant HRQoL improvements, out to 12 months, among individuals that had an EQ5D index or EQVAS below the national average were reported for participants randomized both to the GLB-MOD and GLB-SED intervention arms. Mean improvements in the EQVAS for the GLB-MOD arm at 6 and 12 months were +11.64 (SE=1.79; $p<0.0001$) and +10.30 (SE=1.87; $p<0.0001$), respectively. Mean improvements were similar for the GLB-SED arm at 6 and 12 months were +11.26 (SE=1.84; $p<0.0001$) and +12.03 (SE=1.56; $p<0.0001$), respectively. Mean improvement at 12 months was +0.04 (SE=0.008; $p<0.0001$). Similar mean improvement in the EQ5D index for the GLB-SED arm at 6 and 12 months were +0.05 (SE=0.01; $p<0.0001$) and +0.07 (SE=0.01; $p<0.0001$), respectively. There were no significant improvements in the EQ5D index for the GLB-MOD arm at 6 months (β =+0.02, SE=0.01, $p=0.15$).

8.4.3 Prepost change in MVPA and sedentary time predictors of HRQoL change by intervention group

Prepost changes in meeting program goals, defined as increased MVPA (≥7.5 MET-hours per week) and reduced sedentary time (≥30 minutes of TV watching per day), as predictors of HRQoL changes, were evaluated at 6-months and 12-months, respectively, for both intervention groups separately (GLB-MOD and GLB-SED). Results of linear mixed regression models indicate, that within the GLB-SED arm, increased MVPA was significantly related to prepost EQ5D index decline at 12 months and decreased sedentary time was significantly related to prepost EQVAS improvements at 6 months in both the univariate and fully adjusted models (Table 8-3). Increased MVPA was associated with stable estimated mean declines in the EQ5D index of β=-0.06 (SE=0.02; p=0.01) and β=-0.06 (SE=0.02; p=0.02) in univariate and fully adjusted models, respectively. Decreased sedentary time was associated with estimated mean improvements in the EQVAS of β=+5.84 (SE=2.54; p=0.02) and β=+6.24 (SE=2.57; p=0.02) in univariate and fully adjusted models, respectively.

8.5 Discussion

This study is the first to report changes in HRQoL among overweight adults at high risk for Type 2 Diabetes and cardiovascular disease that were randomized to a DPP-based community lifestyle intervention in which the primary movement goal involved sedentary behavior reduction rather than increasing physical activity levels. Specifically, compared to delayed intervention controls, the participants randomized to the sedentary reduction intervention arm exhibited greater improvements that were clinically meaningful in HRQoL in the EQ5D index, but not the EQVAS at 6 months. In contrast, participants randomized to the MVPA intervention arm exhibited greater improvement in the EQVAS that were not clinically meaningful and statistically significant change in the EQ5D index. Participants randomized to the traditional DPP-GLB intervention that included a moderate (or greater) activity goal exhibited greater improvement in the EQVAS at both the 6 and 12 month time points, a single measure of perceived current health, when compared to controls. There were also statistically significant prepost changes in the EQVAS for both the MVPA and sedentary behavior reduction intervention at 6 months and 12 months (respectively) and in the EQ5D index among sedentary behavior reduction participants.

In our previously published DPP-GLB lifestyle intervention study on changes in HRQoL by Eaglehouse, participants had demonstrated improvements in both the EQ5D index and EQVAS HRQoL measures compared to controls at 6 months [218]. Participants in our previous study were younger (recruitment age started at 18 years versus 40 years in this study), less likely to be female, more likely to have a college degree, and weighed less. They also had lower median self-reported MVPA and mean EQVAS, but higher mean EQ5D index scores and more participants reporting "no" problems (versus some or extreme problems) at baseline compared to participants included in this study. While changes in the EQVAS among participants in the GLB-MOD arm compared to control in both studies reached statistical significance, participants in our previous study had more improvement in the EQVAS +6.55, compared to this study, +4.39. Results among individuals having scores below the national average at baseline showed substantial improvement at 6 months and 12 months prepost for both the EQ5D index and EQVAS among both intervention arms, GLB-MOD and GLB-SED, except for the GLB-MOD at 6 months.

Overall, participants had less improvement in this study, compared to previous results with studies using similar interventions. There are several possible reasons for these differences. Due to the increase of sedentary behavior over the age of 40 years of age, our recruitment age for these participants was slightly older than some other studies. The results found in this study are characteristic of improvement in HRQoL when individuals are older and may have more difficulty improving functional issues without additional support [249] compared to participant populations with a lower recruitment age. There were also several demographic differences between this sample and other previously published study cohorts which could have led to lower baseline HRQoL levels [250]. For example, the participants in this study were more likely to be non-white compared to our previously published HRQoL study. Non-white individuals typically have lower HRQoL compared to white individuals that relate to factors beyond the effects of excess body weight and physical inactivity [250]. These factors may limit the ability of the intervention to impact on HrQoL.

This study is an important addition to the literature because it is the first study we are aware of to evaluated HRQoL among participants receiving a lifestyle intervention with a movement goal of reducing sedentary behaviors. Additional strengths of this study include the large sample size for a community translation effort and the longitudinal study design that included a control group. The participant retention rate for the study was high at 86%. Session attendance was also very high. Out of 16 possible core sessions in the first six months, participants averaged 15 out of 16 and 5 out of 6 of the post core sessions in the last six months. Also, this study had a more diverse sample in terms of race, and education compared to previously published studies which allowed for a more in depth comparison of factors related to HRQoL change.

There were also some limitations. Even though the sample was more diverse, there were not enough individuals of non-white race to explore race without combining all non-white individuals into one category and non-whites were more likely to be excluded due to missing data. Such factors could include additional personal baseline factors, environmental/neighborhood factors, and intervention related factors. Future studies should seek to collect additional information that could better examine additional intervention factors related to changes in HRQoL.

Overall, these study results indicate that there were improvements in HRQoL, although not among both EQ5D instruments. Of note the each instrument measures HRQoL in a different way. The EQ5D index uses a composite score of common dimensions among individuals whereas the EQVAS is a single measure of how an individual’s overall health state. Each measure has its own merit and advantage with measuring HRQoL and neither should not be discounted. Analysis indicate, even when not statistically significant, that trends are toward improvement among both treatment arms. In the instances this is not the case among the total sample, it is among individuals who had baseline values below the national average. These trends and associations are particularly because the DPP-based lifestyle intervention programs are often used as first-line treatment to reduce morbidity and mortality among overweight and obese individuals with prediabetes and/or metabolic syndrome and are reimbursed by Centers for Medicare and Medicaid Services nationwide. Individual's all over the nation, who won't or can't increase their activity levels, now can have access to care that reduces their morbidity risk and improves their HRQoL.

8.6 Tables and Figures

Table 8-1: Baseline characteristics of included study sample by Randomization Assignment

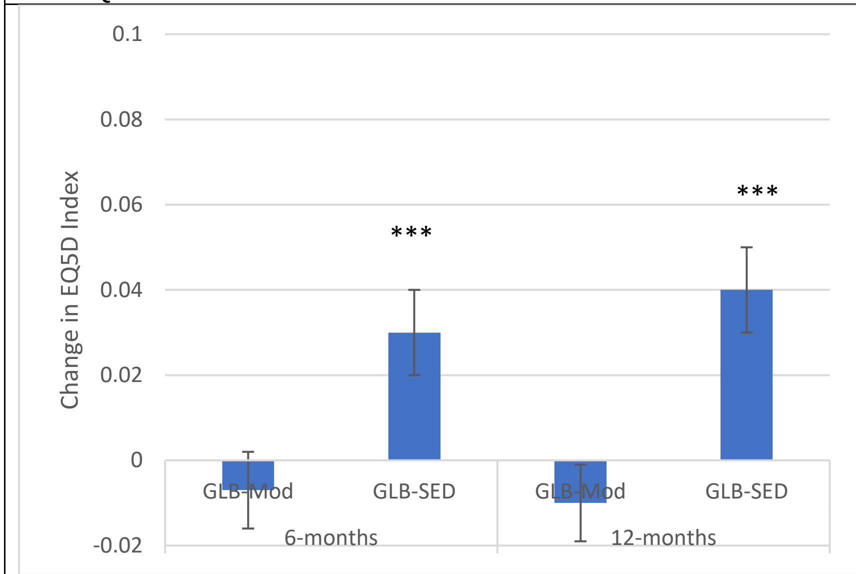
	All n = 277	Delayed n = 95	GLB-MOD n = 94	GLB-SED n = 88
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age (years)	62.32 ± 8.89	61.79 ± 9.56	63.79 ± 8.28	61.87 ± 8.80
Weight (KG)	96.14 ± 19.83	95.41 ± 19.28	97.09 ± 21.35	95.92 ± 18.90
BMI kg/m^2	35.58 ± 6.53	35.33 ± 6.30	35.78 ± 7.07	35.63 ± 6.22
Gait Speed	1.07 ± 0.23	1.07 ± 0.25	1.05 ± 0.21	1.09 ± 0.22
Total MET activity	11.33 ± 12.33	9.35 ± 9.48	13.67 ± 15.23	10.96 ± 11.26
TV Watching Hours	3.18 ± 2.09	3.16 ± 2.00	3.30 ± 2.28	3.08 ± 1.97
EQ5D Index	0.87 ± 0.12	0.87 ± 0.11	0.89 ± 0.10	0.84 ± 0.14
EQVAS	73.21 ± 17.46	71.33 ± 18.22	75.65 ± 15.80	72.63 ± 18.20
	N (%)	**N (%)**	**N (%)**	**N (%)**
Race				
White	229 (83.58)	80 (85.11)	81 (86.17)	68 (79.07)
Not White	45 (16.42)	14 (14.89)	13 (13.83)	18 (20.93)
Gender (Female)	220 (79.42)	75 (78.95)	77 (81.91)	68 (77.27)
Education				
8^{th} grade or less	1 (0.36)	0	1 (1.06)	0
Some high school	5 (1.81)	3 (3.16)	0	2 (2.27)
High school or GED	29 (10.47)	12 (12.63)	8 (8.51)	9 (10.23)
Some college or technical school	98 (35.38)	33 (34.74)	40 (42.55)	25 (28.41)
College graduate	82 (29.60)	27 (28.42)	25 (26.60)	30 (34.09)
Graduate degree	62 (22.38)	20 (21.05)	20 (21.28)	22 (25.00)
Family History of Diabetes	149 (53.79)	61 (64.21)	45 (47.87)	43 (48.86)
Met MVPA goal	142 (51.26)	44 (46.32)	53 (56.38)	45 (51.14)
TV Hours ≥ 2 hours/day	215/276 (77.90)	71/94 (75.53)	75 (79.79)	69 (78.41)

Significance set at P<0.05
Abbreviations: EQ5D index = EuroQol 5 Dimension index; EQVAS = EuroQol Visual Analog Scale; GLB-MOD = MVPA intervention arm; GLB-SED = sedentary behavior reduction arm; MET = Metabolic Equivalent; MVPA = moderate+ intensity physical activity

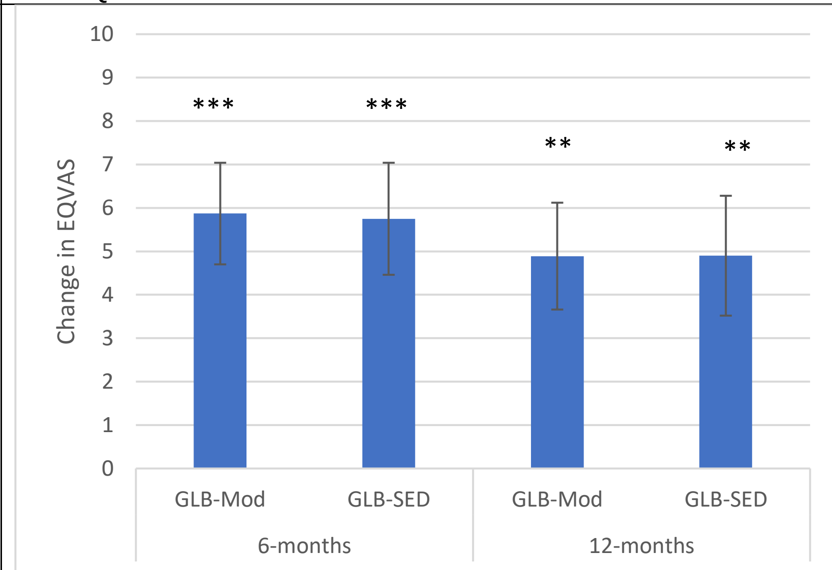
Table 8-2: Changes in the EQ5D index and EQVAS from Baseline to 6 months (N = 277)

	Baseline	6-months	Mean Difference	Modeled Difference (SE)	p-value
EQ5D index					
Delayed	0.83 (0.81-1.00)	0.83 (0.80-1.00)	-0.03 (0.12)	Ref	Ref
GLB-MOD	0.83 (0.82-1.00)	0.83 (0.81-1.00)	-0.02 (0.11)	+0.01 (0.03)	0.46
GLB-SED	0.83 (0.80-1.00)	0.83 (0.81-1.00)	0.008 (0.10)	+0.04 (0.03)	0.02
EQVAS					
Delayed	71.00 (60.00-88.00)	75.00 (65.00-85.00)	1.26 (16.38)	Ref	Ref
GLB-MOD	77.50 (70.00-90.00)	85.00 (75.00-90.00)	5.64 (13.51)	+4.39 (3.38)	0.047
GLB-SED	75.00 (69.50-86.50)	80.00 (70.00-90.00)	4.14 (15.24)	+2.88 (3.44)	0.20
Significance set at P<0.05 **Abbreviations:** EQ5D index = EuroQol 5 Dimension index; EQVAS = EuroQol Visual Analog Scale; GLB-MOD = MVPA intervention arm; GLB-SED = sedentary behavior reduction arm					

1A: EQ5D index



1B: EQVAS



Bars represent Standard Error
* P<0.05
** P<0.001
** P<0.0001
Abbreviations: GLB-MOD = MVPA intervention arm; GLB-SED = sedentary behavior reduction arm; EQ5D index = EuroQol 5 Dimension index; EQVAS = EuroQol Visual Analog Scale

Figure 8-1: Prepost changes at 6 and 12 months for the EQ5D index and EQVAS stratified by Intervention Arm (6 months: N = 268; 12 months: N = 243)

Table 8-3: Reduction in TV Hours and Total MET Hours associated with prepost changes in EQ5D index and EQVAS at 6 and 12 months stratified by intervention arm (6 months: N = 268; 12 months: N = 243)

	GLB-MOD				GLB-SED			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Variable	Main*Time β (SE)	p-value	Main*Time β (SE)	p-value	Main*Time β (SE)	p-value	Main*Time β (SE)	p-value
EQ5D Index 6 months								
TV watching decrease by 30 min (ref=no)	0.0003 (0.02)	0.99	-0.004 (0.02)	0.83	0.03 (0.02)	0.17	0.03 (0.02)	0.18
MET Hours ≥ 7.5 MET hrs (ref=no)	0.002 (0.02)	0.92	0.002 (0.02)	0.93	0.02 (0.02)	0.30	0.03 (0.02)	0.23
EQ5D Index 12 months								
TV watching decrease by 30 min (ref=no)	0.02 (0.02)	0.32	0.02 (0.02)	0.41	-0.009 (0.02)	0.68	-0.009 (0.02)	0.65
MET Hours ≥ 7.5 MET hrs (ref=no)	0.005 (0.02)	0.80	0.009 (0.02)	0.67	-0.06 (0.02)	**0.01**	-0.06 (0.02)	**0.02**
EQVAS 6 months								
TV watching decrease by 30 min (ref=no)	0.90 (2.45)	0.72	0.48 (2.45)	0.84	5.84 (2.54)	**0.02**	6.24 (2.57)	**0.02**
MET Hours ≥ 7.5 MET hrs (ref=no)	1.87 (2.93)	0.53	1.87 (2.96)	0.53	3.56 (3.20)	0.27	4.45 (3.17)	0.16
EQVAS 12 months								
TV watching decrease by 30 min (ref=no)	3.50 (2.52)	0.17	3.22 (2.52)	0.20	1.70 (2.78)	0.54	1.63 (2.75)	0.55
MET Hours ≥ 7.5 MET hrs (ref=no)	-3.48 (2.75)	0.21	-3.52 (2.77)	0.21	5.22 (3.19)	0.10	5.22 (3.19)	0.10

*Adjusted models included TV Hours decrease by 30 min, MET Hours ≥ 7.5 MET hrs, Weight Loss 5%, time x TV Hours decrease by 30 min, time x MET Hours ≥ 7.5 MET hrs, and time x Weight Loss 5%,
Significance set at P<0.05
Abbreviations: GLB-MOD = MVPA intervention arm; GLB-SED = sedentary behavior reduction arm; EQ5D index = EuroQol 5 Dimension index; EQVAS = EuroQol Visual Analog Scale; MET = Metabolic Equivalent

8.7 Addendum

Table 8-4: Supplemental Table 1: GLB participants included versus not included in HRQoL analysis

	All N = 308+	Included* N = 277+	Not Included N = 31+	P
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (years)	62.34 ± 9.10	62.32 ± 8.89	62.57 ± 10.98	0.74
Baseline Weight (KG)	96.08 ± 19.78	96.14 ± 19.83	95.42 ± 19.53	0.99
Gait Speed (m/s)	1.07 ± 0.22	1.07 ± 0.23	1.07 ± 0.21	0.79
Total MET activity – Baseline	11.22 ± 12.09	11.33 ± 12.33	10.20 ± 9.87	0.10
TV Watching Hours – Baseline	3.20 ± 2.11	3.18 ± 2.09	3.40 ± 2.35	0.73
EQ5D index – Baseline	0.86 ± 0.12	0.87 ± 0.12	0.78 ±0.05	0.02
EQVAS – Baseline	73.33 ± 17.46	73.21 ± 17.46	80.20 ± 17.89	0.26
	N (%)	**N (%)**	**N (%)**	
White	251 (81.49)	231 (83.39)	20 (64.52)	0.02
Black	51 (16.56)	42 (15.16)	9 (29.03)	0.05
American Indian	2 (0.65)	2 (0.72)	0	1.0
Asian	4 (1.31)	2 (0.72)	2 (6.45)	0.05
Pacific Islander	0	0	0	--
Other	2 (0.65)	2 (0.72)	0	1.0
Race not given	0	0	0	--
Latino/Hispanic	5 (1.81)	5 (1.62)	0	1.0
Gender (Female)	244 (79.22)	220 (79.42)	24 (77.42)	0.82
Education				0.14
8th grade or less	1 (0.32)	1 (0.36)	0	
Some high school	5 (1.62)	5 (1.81)	0	
High school or GED	29 (9.42)	29 (10.47)	0	
Some college or technical school	115 (37.34)	98 (35.38)	17 (54.84)	
College graduate	88 (28.57)	82 (29.60)	6 (19.35)	
Graduate degree	70 (22.73)	62 (22.38)	8 (25.81)	
Family History of Diabetes	165 (53.57)	149 (53.79)	16 (51.61)	0.82

* Eligible pts had both the EQ5D score and the EQVAS at the baseline and 6-month timepoints
+ Denominator for each variable unless specified otherwise due to missing data
- Continuous variables were analyzed using the Wilcoxon Rank Sum test for a conservative estimate
- Categorical variable were analyzed using the Fisher's exact test

Abbreviations: EQ5D index = Euroqol 5 Dimension index; EQVAS = Euroqol Visual Analog Scale; MET = Metabolic equivalent; SD = Standard Deviation

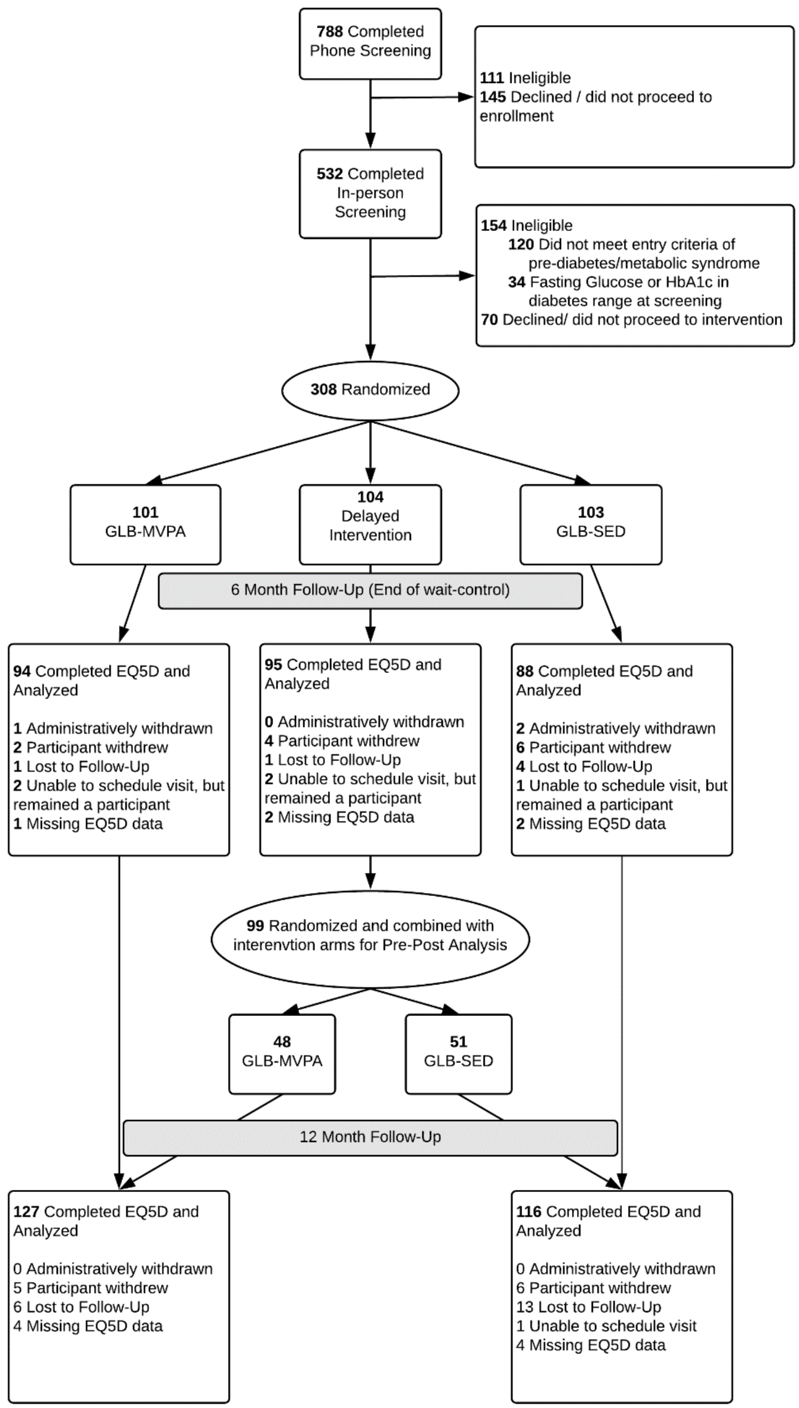


Figure 8-2: Supplemental Figure 1: Flow of GLB-MOVES study participants from consent through 12 month follow-up

9.0 Paper 2: 5-year Changes in Health Related Quality of Life and Quality of Life Years (QALY's) among adults Pre and Post Bariatric Surgery

9.1 Abstract

Introduction: Bariatric surgery has had positive reported effects on health-related quality of life (HRQoL), although, few longitudinal reports have examined long-term effects using the EuroqoL-5 Dimension (EQ5D) in a US population. This report evaluates changes, up to 5 years, versus presurgery, among individuals enrolled in the Longitudinal Assessment of Bariatric Surgery (LABS-2) study.

Methods: LABS-2 participants who had a Roux-en Y (RYGB) or Laparoscopic Band (LAGB) procedure and completed an EQ5D-3L assessment presurgery and one or more annual assessments in years 1-5 were included. Longitudinal mixed models evaluated EQ5D (index and visual analog scale (EQVAS)) changes between presurgery and yearly follow-up, and tested associations between pre-surgery factors and weight loss with changes in quality-adjusted life years (QALY; time in perfect health), through 5 years postsurgery.

Results: Of the 377 eligible participants, 86.7% had complete data at year-1, 77.5% at year-2, 71.1% at year-3, 66.6% at year-4, and 70.0% at year-5. EQ5D index (range: -0.11–1.0) and EQVAS (range: 0-100) 5 year mean improvements from presurgery were 0.06 and 15.6, respectively, for the RYGB group (n=263), and 0.04 and 5.9, respectively, for the LAGB group (n=114; p<0.01 for all). Mean QALY gains from pre-surgery over 5 years were 0.35 and 0.25 or RYGB and LAGB, respectively. In the full model with demographics, pre-surgery body mass index, surgical procedure, and percent weight loss; presurgery BMI (per 10 units; Beta=0.09; p=0.007) and percent weight loss (per 5%; Beta=0.05; p<0.0001) were statistically significantly (p<.05) related to change in QALY.

Conclusions: Sustained improvements in HRQoL were found up to 5 years after bariatric surgery.

9.2 Introduction

Individuals with severe obesity, a BMI ≥ 35 kg/m^2, have increased morbidity and mortality risks, impaired health related quality of life (HRQoL) (i.e., perceived disability, ability to function at a basic level, and perception of well-being) [193-197], and incur more health care costs, on average, compared with individuals with a normal range BMI (18.5 kg/m^2 - 24.9 kg/m^2) [251, 252]. The economic burden of obesity is incurred in healthcare, as well as losses in productivity and economic growth as a result of lost work days, lower productivity at work, permanent disability, and increased mortality risk [253], which all have implications on reduced HRQoL. Understanding how HRQoL is impacted after intervention on obesity can provide insight to improvements in individual health and function.

HRQoL, a patient reported outcome , includes several domains of health to assess the multiple dimensions of physical, mental, social, and emotional functioning [254]. The Euroquol 5 dimension (EQ5D) [171] is a widely used measure that is easy to administer and has been validated in multiple populations [183]. The EQ5D measures HRQoL by assessing how much disability is incurred in relation to full health and can be used to calculate quality-adjusted life years (QALY) [171], a descriptive composite measure of length of life gained and the related patient's assessment of their HRQoL in that lifespan [255].

Bariatric surgery has been found to be effective for weight loss, reduction of comorbidity and mortality risk, and improvement of HRQoL, among individuals with severe obesity [97, 103, 106, 107]. While the durability of improvements in weight and comorbidities has been studied extensively [95-98, 128, 129, 132-135, 256-260] , there is a dearth of longitudinal research evaluating how HRQoL is impacted > 1 year after bariatric surgery in a US population [261]. A 2016 meta-analysis [262] concluded that, compared to adults who do not have surgery, adults who undergo bariatric surgery have improvements in HRQoL ≥ 5 years. While the results are encouraging, only two of the six included studies in this meta-analysis collected data prospectively

– one clinical trial and one cohort study – the other four studies were cross-sectional. Furthermore, neither of these two prospective studies evaluated HRQoL with the EQ5D.

The Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study was a large US multi-center prospective cohort study, designed to evaluate the relationship of patient and surgical characteristics to longer term safety and efficacy of bariatric surgery [129], which administered the EQ5D pre- and annually post-surgery. Reflecting the timing of recruitment (2006-2009), participants primarily received Roux-en-Y gastric bypass (RYGB) or laparoscopic gastric banding (LAGB) procedure. The aims of this report were to measure changes in HRQoL between presurgery and yearly postsurgery follow-ups through 5 years, as measured by the EQ5D, and to identify factors associated with pre- to post-surgery changes in the QALY among LABS-2 study participants who received the RYGB or the LAGB procedures.

9.3 Methods

9.3.1 Parent Study and Analytic Sample

LABS-2 study participants underwent an initial bariatric surgical procedure between March 14, 2006, and April 24, 2009, at 1 of 10 hospitals at 6 US clinical centers [130]. The institutional review boards (IRB) at each center and the data coordinating center approved the protocol and all participants provided written informed consent. The study is registered at ClincalTrials.gov (NCT00465829).

Research assessments were conducted by trained research personnel within 30 days prior to scheduled surgery and annually following surgery. All measures, unless otherwise noted, were administered, at the presurgery and annual postsurgery assessments. The EQ5D was added to the study protocol post initiation on a rolling basis between July 10, 2008 and October

30, 2008 at all sites. To be included in this report, participants had to have completed the EQ5D at the presurgery assessment and at least one follow-up assessment, at which they were not pregnant within the past six months, over the first 5-years of follow-up (August 2014).

9.3.2 Measures

9.3.2.1 Dependent Variables

The EQ5D-3L (3 Long) measures 5 dimensions of HRQoL - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [171]. Answer options for each dimension range from 1 to 3 (“no”, “some”, or “extreme”), with lower scores indicating better health. The index score, hence referred to as the EQ5D index, is calculated by applying preference weights based on the US population to each of the 5 dimensions [183]. Preference weights for the EQ5D are generated using the Time Trade Off (TTO) method and determine the population preference of the 3125 health states, ranging from full health to death [243]. The index score ranges from -0.11 – 1.0, where higher scores indicate better perceived health and negative scores indicate a perception of health that is worse than death [183].

QALY is a metric used to evaluate changes in disease burden relief that includes two components of change, the degree of change (measured by the EQ5D index) and the duration of change. To assess improvement from surgery, measured in QALY, the EQ5D index at each follow-up was subtracted from the presurgery score and multiplied by time since surgery. For example, the 5-year QALY score = (additional utility value [5-year EQ5D index - presurgery EQ5D index]) * 5. QALY’s provide an estimate of the amount of time that an individual is in perfect health. That is, if an individual is evaluated for a 1-year period and has an additional utility value of 1 then they have gained 1 QALY or a full year at perfect health compared to presurgery. However, if an individual is evaluated for 1 year and has an additional utility value of 0.5 then they have gained 0.5 QALYs or half a year in perfect health compared to presurgery.

The Euroqol also includes a Visual Analog Scale (EQVAS), which allows respondents to rate their overall health status on a specific day from 0-100, where higher values indicate better health. The EQVAS is often included together with the EQ5D index to provide a more comprehensive assessment of HRQoL [172, 173]. The mean estimated EQ5D index and EQVAS from a sample of 13,600 non-institutionalized U.S. adults in 2008 were 0.87 and 79.2, respectively [183]. Minimally important (clinically meaningful) changes were estimated to be 0.03 for the EQ5D index and 10 for the EQVAS [164].

9.3.2.2 Independent Variables

Sociodemographic

Sociodemographic variables (age, race, sex, education and employment) were self-reported. Due to low frequencies, race and education categories were collapsed to create binary variables (black, American Indian, Pacific Islander and multi-race versus white, and up to high school diploma or equivalent versus some college or greater, respectively).

Anthropometric and Comorbidity Specific

A standardized protocol was used to collect height pre-surgery and weight at each assessment [130, 133], which were used to calculate BMI; weight in kg divided by height in meters squared. Percent weight loss at follow-up was calculated as: 100*(presurgery weight minus current weight at follow-up)]/presurgery weight. Thus, a positive number indicates weight loss. Hypertension was defined as having systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg from a single measurement, or currently taking an antihypertensive medication [130]. Dyslipidemia was defined as either lipoprotein (LDL) ≥ 160 mg/dL, high density lipoprotein (HDL) < 40 mg/dL, fasting triglycerides ≥ 200 mg/dL, or currently taking a lipid lowering medication [130]. Diabetes was defined as either taking diabetes medication or having HbA1c of at least 6.5% or, if HbA1c was unavailable, an 8-hour fasting glucose of at least 126 mg/dL [130, 263].

Mental Health Functioning

Depressive symptoms over the past week were assessed using the Beck Depression Inventory (BDI) version 1. Higher scores (range 0-63) indicate greater severity of depressive symptoms. Given that bariatric patients are generally trying to lose weight, the BDI question to evaluate weight loss (e.g., "I have lost more than 5 pounds.") as a depressive symptom was omitted from calculation of the BDI score if participants endorsed that they were purposefully trying to lose weight by eating less [130]. Daily psychiatric medication usage was also used to assess mental health functioning, as it is related to presence of symptoms or mental disorders and may interfere with weight loss [264].

9.3.3 Statistical Analysis

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). All reported p-values were 2-sided; p-values were used to guide the interpretation of results [265]. To address known differences in outcomes by surgical procedure, all analysis was stratified by surgical procedure unless otherwise stated.

To assess selection bias, presurgery characteristics were compared for those who met inclusion criteria versus those who were eligible for EQ5D assessment (i.e., had surgery after the EQ5D was added to the LABS-2 study protocol) but excluded due to missing EQ5D data, using the Pearson's chi-square test or the Fisher Exact test, as appropriate, for categorical variables, the Cochran Armitage Test for ordinal variables, and the Wilcoxon rank-sum test for continuous variables. The same tests were used to evaluate potential differences in presurgery characteristics by non-randomized surgical procedure.

Data of women who were pregnant within the past six months of their assessment were censored (i.e., omitted from analysis) because of known fluctuations in weight and other issues, such as post-partum depression, which may impact the sense of well-being [266, 267] . Longitudinal analyses were performed with linear mixed models using all available data assuming the unstructured covariance matrix with a person-level random intercept, and time entered as a discrete fixed effect, with control for site and pre-surgery dyslipidemia status, which were associated with missing EQ5D data at follow-up. First, modeling was used to estimate values and test pairwise differences in the EQ5D index and EQVAS between presurgery and each follow-up assessment. Stability following surgery (i.e., from year-1 to year-5) was evaluated by testing a linear and quadratic time effect. Next modeling was used to assess if change in QALY at each follow-up was different from zero. For both analyses p-values were adjusted for multiple comparisons (alpha = 0.05/5 = 0.01) [268]. Modeled means and 95% confidence intervals (CI), and adjusted p-values are reported.

A series of multivariable linear mixed models were used to evaluate factors associated with change from presurgery in QALY as a repeated measure, among the full sample (RYGB + LAGB). First, to evaluate pre-surgery predictors and surgical procedure, basic models uniquely tested, age [215, 269], sex [269], race [215, 269], education [215, 269], employment status [215, 269] and BMI [215, 269] at time of surgery, and, surgical procedure [270], and a multivariable model tested all factors simultaneously. Next, to evaluate the effect of weight loss, weight loss was tested in a basic model and added to the multivariable model with pre-surgery factors and surgical procedure. Beta coefficients, 95% Confidence Intervals, and p-values are reported.

9.4 Results

Sample Selection and Selection Bias

Participant flow from informed consent to the analysis sample is provided in Figure 1. Out of the 562 participants who had access to the EQ5D and underwent the RYGB or LAGB, 185 (32.9%) participants were excluded from this report due to insufficient EQ5D data. Among the 377 included participants, follow-up data was available for 327 (86.7%) at year 1, 292 (77.5%) at year 2, 268 (71.1%) at year 3, 251 (66.6%) at year 4, and 264 (70.0%) at year 5.

Excluded versus included participants were similar with respect to most pre-surgery characteristics (Table 9-3. Supplemental Table 1). However, excluded versus included RYGB participants had a median BMI of 47.9 (IQR=43.5-53.0) kg/m^2 versus 46.0 (IQR=41.5-50.6) kg/m^2, respectively (p =0.03) and weight followed a similar pattern. For LAGB, fewer excluded versus included participants had education past a high school diploma (64.9% versus 81.6%; p=0.03).

Presurgery Sample Characteristics

Sample characteristics overall and by surgical procedure are presented in Table 9-1. Overall, the median age was 47 (IQR=37-56) and most participants were female (77.5%), underwent the RYGB procedure (70.0%), were white (82.7%), were employed (67.0%), and had at least some college or greater education (77.7%). Over half of the participants had hypertension (71.0%) and dyslipidemia (68.8%), while 33.3% of participants had diabetes and 44.2% reported using psychiatric medications. Median BDI score was 5.0 (IQR=2.0-9.0), which is in the subclinical range. RYGB and LAGB were similar with respect to most pre-surgery characteristics. However, median weight and BMI were higher among the RYGB versus LAGB surgery group (e.g., 129.5 kg and 46.0 kg/m^2 versus 120.5kg and 43.8 kg/m^2, respectively; p<0.01 for both).

EQ5D index by yearly follow-up compared to presurgery

RYGB

The presurgery modeled mean for the EQ5D index was 0.75 (95% CI=0.72-0.78). EQ5D index means at year 1, 2, 3, 4 and 5 were 0.85 (95% CI=0.81-0.88), 0.86 (95% CI=0.83-0.90), 0.84 (95% CI=0.80-0.87), 0.83 (95% CI=0.80-0.87), and 0.81 (95% CI=0.78-0.85), respectively; all pairwise comparisons to presugery were significant at $p<0.0001$ (Figure 9-2: panel A). However, there was a linear time effect from 1 to 5 years ($p<0.01$) indicating a decline in the EQ5D index across follow-up.

LAGB

The presurgery modeled mean for the EQ5D index was 0.77 (95% CI = 0.73-0.81). EQ5D index at year 1, 2, 3, 4 and 5 were 0.81 (95% CI=0.77-0.86; pairwise $p<0.01$), 0.81 (95% CI=0.83-0.90; pairwise $p=0.01$), 0.84 (95% CI=0.80-0.87; pairwise $p=0.01$), 0.83 (95% CI=0.80-0.87; pairwise $p<0.01$), and 0.81 (95% CI=0.78-0.85; pairwise $p=0.04$), respectively (Figure 9-2: panel B). There was no indication of a time effect from year 1 to year 5 ($p=0.16$) indicating that the magnitude of improvement was stable over follow-up.

<u>EQVAS by yearly follow-up compared to presurgery</u>

RYGB

The modeled presurgery mean for the EQVAS was 57.91 (95% CI = 54.49-61.32). EQVAS at year 1, 2, 3, 4 and 5 were 80.63 (95% CI=79.98-84.28), 79.51 (95% CI=75.75-83.27), 76.98 (95% CI=73.31-80.66), 76.35 (95% CI=72.62-80.09), and 73.49 (95% CI=69.79-77.18), respectively; all pairwise comparisons to presugery were significant at $p<0.0001$ (Figure 9-2; panel A). However, there was a linear time effect from 1 to 5 years ($p<0.0001$), indicating a decline in EQVAS across follow-up.

LAGB

For LAGB, presurgery modeled means for the EQVAS was 62.11 (95% CI=57.94-66.38). EQVAS at year 1, 2, 3, 4 and 5 were 73.53 (95% CI=69.16-77.91), 71.39 (95% CI=66.77-76.0), 71.56 (95% CI=66.97-76.15), 72.10 (95% CI=67.34-76.86), and 68.03 (95% CI=63.20-72.85), respectively; all pairwise comparisons to presugery were significant at p<0.0001 (Figure 9-2; panel B). However, there was a linear time effect from 1 to 5 years (p<0.01) indicating a decline across follow-up.

QALY

The modeled mean for the presurgery EQ5D index for the RYGB group was 0.75. The modeled mean QALY gains (i.e., gains in perfect health) at year 1, 2, 3, 4 and 5 were +0.13 (95% CI=0.03-0.23), +0.27 (95% CI=0.16-0.38), +0.30 (95% CI=0.20-0.41), +0.39 (95% CI=0.28-0.49), and +0.35 (95% CI=0.25-0.45) (Figure 9-3; panel A). In the LAGB group the modeled mean for presurgery EQ5D index was 0.77. Modeled mean QALY gains at year 1, 2, 3, 4, and 5 were +0.04 (95% CI=-0.07-0.14), +0.09 (95% CI=-0.02-0.20), +0.14 (95% CI=0.03-0.25), +0.25 (95% CI=0.14-0.37), and +0.28 (95% CI=0.17-0.39) (Figure 9-3; panel B). Median changes in percent weight change and QALY's, by procedure, are presented in Table 9-4: Supplemental Table 2.

Basic and Multivariable QALY Change Models

Basic models indicated that undergoing the RYGB versus LAGB procedure was associated with a mean gain in QALY of 0.09 (95%CI=0.002-0.17) and being a male versus female was potentially associated with a similar gain (β=0.08, 95%CI=-0.007-0.17), while other pre-surgery factors did not predict gain in QALY (Table 9-2). The basic model for percent weight loss was associated with gains in QALY (β=0.05, 95%CI=0.03-0.07). Presurgery BMI was associated with gains in QALY (β=0.07, 95%CI=0.01-0.14) after adjustment for percent weight loss. All associations were weaker (p>0.05) in the pre-surgery multivariable model (e.g., (β=0.07, 95%CI=-0.01-0.16, for RYGB versus LAGB) except for presurgery BMI (β=0.09, 95%CI=0.02-0.15) and percent weight loss (β=0.05, 95%CI=0.03-0.07).

9.5 Discussion

This report shows that patients who received either the RYGB or LAGB procedure had sustained improvements in HRQoL over 5 years, compared to pre-surgery, as measured by both the EQ5D index and EQVAS. The improvement in HRQoL in the RYGB group was stable up to 2 years after surgery and linearly decreased from year 2-5, whereas change for the LAGB group was stable from 1 to year 5. On average, over the 5-year period, individuals who underwent the RYGB procedure had a cumulative gain of 0.35 QALY of a year and the LAGB group had a cumulative gain of 0.25 QALY. With adjustment for potential confounders (e.g. pre-surgery BMI), undergoing the RYGB versus LAGB procedure was associated with greater mean gain of 0.09 QALY's. While being male versus female was potentially associated with a similar size gain (0.08). No other variables evaluated in this study (age, race, education, presurgery BMI, or percent weight loss) were associated with gains in QALY in basic and multivariable models.

Improvements over time for HRQoL, up to 3 years postsurgery [271], among bariatric patients using the EQ5D-3L have previously been reported [219, 269, 272-282], although not all of them detected statistically significant improvements over time [272, 275, 276]. The most common follow-up period is one year [261]. Meta-analysis results from a 2020 study evaluating improvements after bariatric surgery found that the pooled mean EQ5D index at presurgery, 1 year, 2 years, and 3 years were 0.73 (0.69-0.77), 0.87 (0.86-0.880), 0.84 (0.82-0.87), and 0.84 (0.82-0.86), respectively [261]. Participant characteristics of data included in meta-analysis varied by presence of morbidity, country of participants, and procedures performed. Generally, participants were mostly female similar to this report but slightly younger, however, results of the meta-analysis were similar the RYGB group 0.75, 0.85, 0.86, 0.84, at presurgery, 1 year, 2 years, and 3 years respectively, in this report. The LAGB group had a slightly higher presurgery EQ5D index of 0.77, but smaller increases post-surgery with 0.81, 0.81, and 0.84 at years 1 through 3. Similar to previous reports, the EQ5D index had a slight downward trend from the second to the fifth year postoperatively, but remained higher than presurgery [283], however this trend was only observed among RYGB patients and this is the first time it has been reported using the EQ5D.

Among 10 studies that evaluated HRQoL among bariatric patients, the mean presurgery scores for the EQVAS vary widely, ranging from 27.0-90.0 presurgery [269, 271, 272, 274, 276, 277, 281, 282, 284, 285]. McEwen et al reported mean presurgery EQVAS values for the US population by sex, 34.0 for women and 27.0 for men, the combined mean was approximately 33.3 [282]. Prospectively assessed EQVAS 1-year post-surgery was also reported by sex, 55 for women and 68 for men, the combined mean was approximately 56.3. Our LABS-2 report is the first to report EQVAS values for up to five years. Compared to the McEwen paper, the modeled mean values were higher in this report for presurgery EQVAS values (57.91 for the RYGB and 62.11 for the LAGB) and one-year postsurgery EQVAS values were (80.63 and 73.53, respectively).

QALY's have been used for the past 50 years to estimate the long-term impact of HRQoL on life expectancy [178]. Most studies evaluating factors related to change focus on the EQ5D index rather than QALY's because QALY's are usually associated with cost-effectiveness analysis and derived using simulation models [286]. However, QALY's are an informative summary measure of cumulative improvement, and assessment of related factors can provide insight into who benefits most from QALY's [287]. Only one other study, McEwen et al [282], evaluated QALY's using empirical data from the EQ5D index in the US population and US preference weights. One hundred twenty-two patients were included; 65% underwent RYGB and 34% LAGB, although the analysis did not adjust for surgery procedure. The mean presurgery EQ5D index was 0.73 for women and 0.82 for men, similar to values in our LABS-2 RGYB (0.75) and LAGB

(0.77) samples. There was a 0.15 QALY gain for women and 0.08 for men after 1-year postsurgery, which would be approximately a 0.12 gain among both groups, similar for the QALY gain for RYGB group (0.11) at one year, meaning that at one year, participants gained 11% of a year at perfect health. This LABS-2 report showed that there was a clinically meaningful gain as presurgery BMI increases 0.09 after adjusting for percent weight loss 0.09 indicating that individuals who weighed more at presurgery were more likely to lose more weight. There was also larger QALY gain for those who underwent the RYGB had a larger QALY gain (0.09) compared to those who underwent LAGB over a five year period. While these results did not remain statistically significant in the multivariable models, further exploration into other factors related to selection of surgery procedure may provide more insight into this relationship. Previous research has shown greater improvements in HRQoL with RYGB procedures compared to LAGB [288]. Research has indicated that women's HRQoL values can be lower than men's when other comorbidities are present [289].

While this report adds valuable information to the literature by showing the HRQoL improvements, using the EQ5D index (with domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and EQVAS, remain over five years, the findings may be affected by limitations that should be considered when interpreting results. First, 32.9% of the sample was excluded due to insufficient data. Selection bias analysis indicates that those who were excluded from versus included in the analysis who underwent the RYGB were more likely to be heavier and have more depressive symptoms, while those excluded versus included who underwent the LAGB procedure were less educated. However, excluded versus included participants were similar with respect to gender, race, and comorbidities (hypertension, dyslipidemia, Type 2 Diabetes, use of psychiatric medications, and BDI scores). Also, the sample had little racial variability. These differences may have impacts in the generalizability of this research. Secondly, there were several participants among the analysis sample who had missing data at follow-up. To address this, all analyses adjusted for factors associated with missing follow-up and used all available data. Thirdly, because all possible factors were not adjusted for in the multivariable models, there is potentially residual confounding.

In conclusion, bariatric surgery improves HRQoL over time and improvements, compared to presurgery, are sustained up to 5 years as evidenced by this study. This finding is important both as prevalence of severe obesity continues to rise and as treatments continue to be developed. While improvement in HRQoL appeared to be larger following RYGB versus LAGB, surgical procedure was not significantly associated with gain in QALY after adjustment for demographics or baseline BMI. Additionally, these factors and weight loss were not independently associated with gain in QALY, demonstrating the challenge in predicting an individual's chance of improvement after bariatric surgery. Of public health significance, in the treatment of obesity, is understanding how individual's lives are affected, of which HRQoL is an essential component, and whether there are sustained improvements.

9.6 Tables and Figures

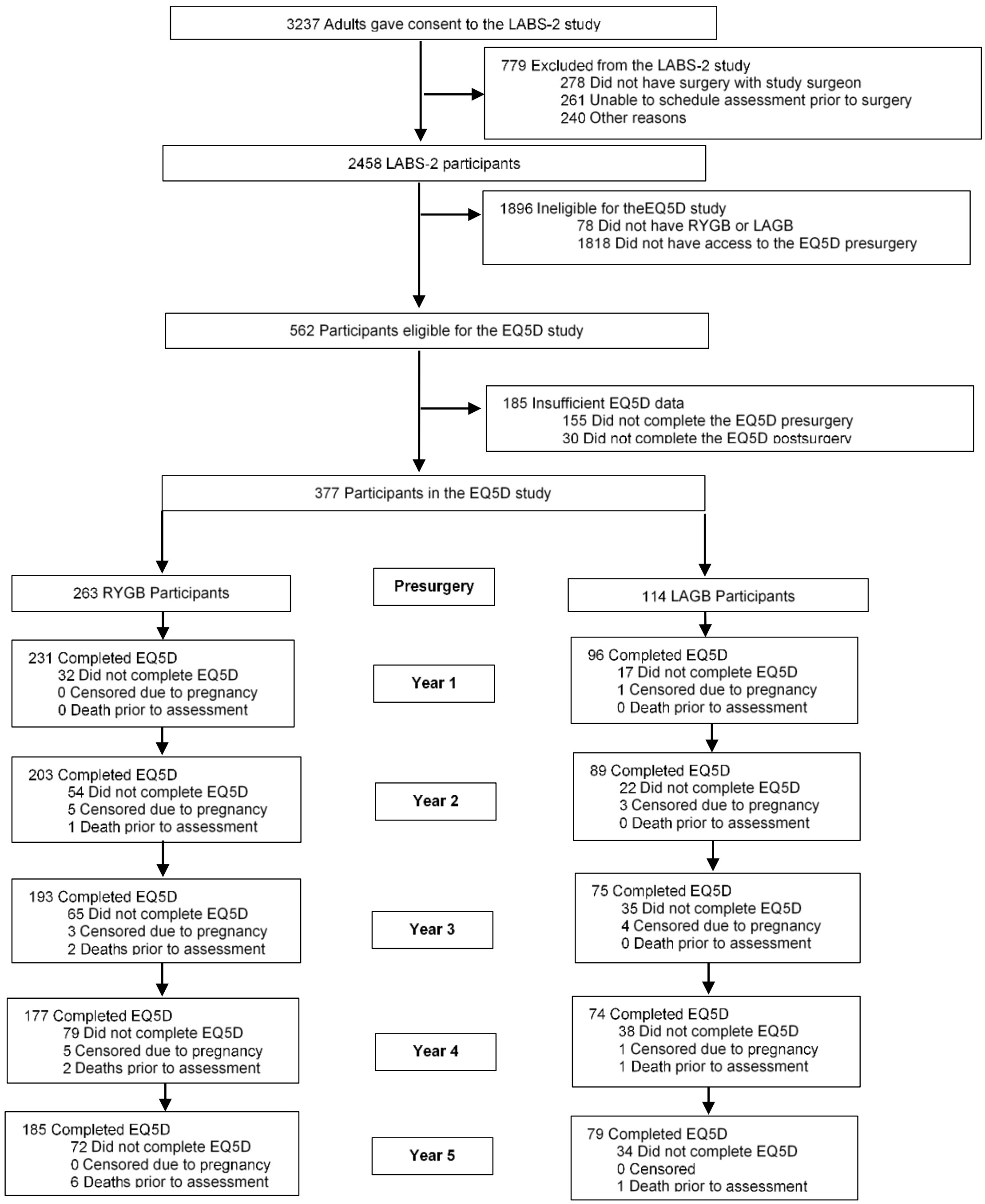
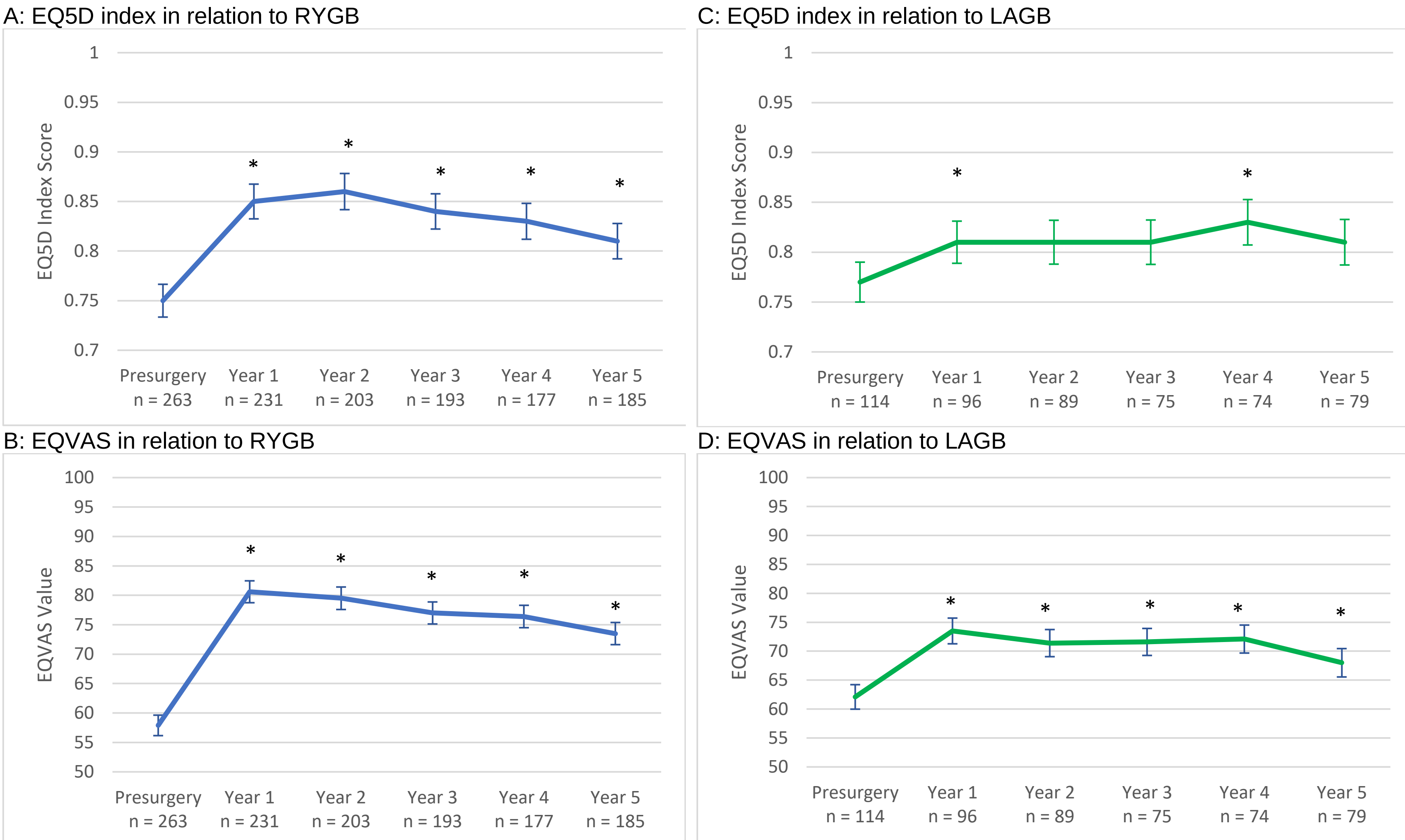


Figure 9-1: Flow of EQ5D study participants from consent through 4-year follow-up

Table 9-1: Presurgery Characteristics of Study Sample Overall and by Surgical Procedure

	Total (N=377) n (%)	RYGB (N=263) n (%)	LAGB (N=114) n (%)	p-value
Demographics				
Age				0.57
Median (IQR)	47 (37-56)	47 (37-55)	49 (37-56)	
Range	19-72	19-70	19-72	
Male (vs female)	510 (22.6)	342 (21.7)	168 (24.6)	0.54
White race (vs black)	306 (82.7)	210 (82.0)	96 (84.2)	0.61
>HS (vs ≤ HS)	293 (77.7)	200 (76.0)	93 (81.6)	0.24
Employed (vs not employed)	252 (67.0)	179 (68.3)	73 (64.0)	0.42
BMI (kg/m^2)				<0.01
Median (IQR)	45.1 (41.1-49.8)	46.0 (41.5-50.6)	43.8 (40.4-46.5)	
Range	33.8-74.9	33.9-74.9	33.8-70.0	
Weight (kg)				<0.01
Median (IQR)	126.8 (113.2-142.3)	129.5 (113.6-146.4)	120.5 (110.9-135.5)	
Range	75.0-240.0	75.0-240.0	85.0-227.7	
Hypertension	262 (71.0)	192 (73.9)	70 (64.2)	0.06
Dyslipidemia	218 (68.8)	154 (69.4)	64 (67.4)	0.72
Diabetes	122 (33.4)	90 (35.2)	32 (29.4)	0.28
Psychiatric medication use	164 (44.2)	115 (44.6)	49 (43.4)	
BDI score				0.88
Median (IQR)	5.0 (2.0-9.0)	5.0 (2.0-9.0)	5.5 (3.0-10.0)	
Range	0-36.0	0-36.0	0-25.0	
Abbreviations: BDI = Beck Depression Inventory; BMI = Body Mass Index; HS = High School; LAGB = Laparoscopic adjustable gastric band; RYGB = Roux-en-Y gastric bypass				



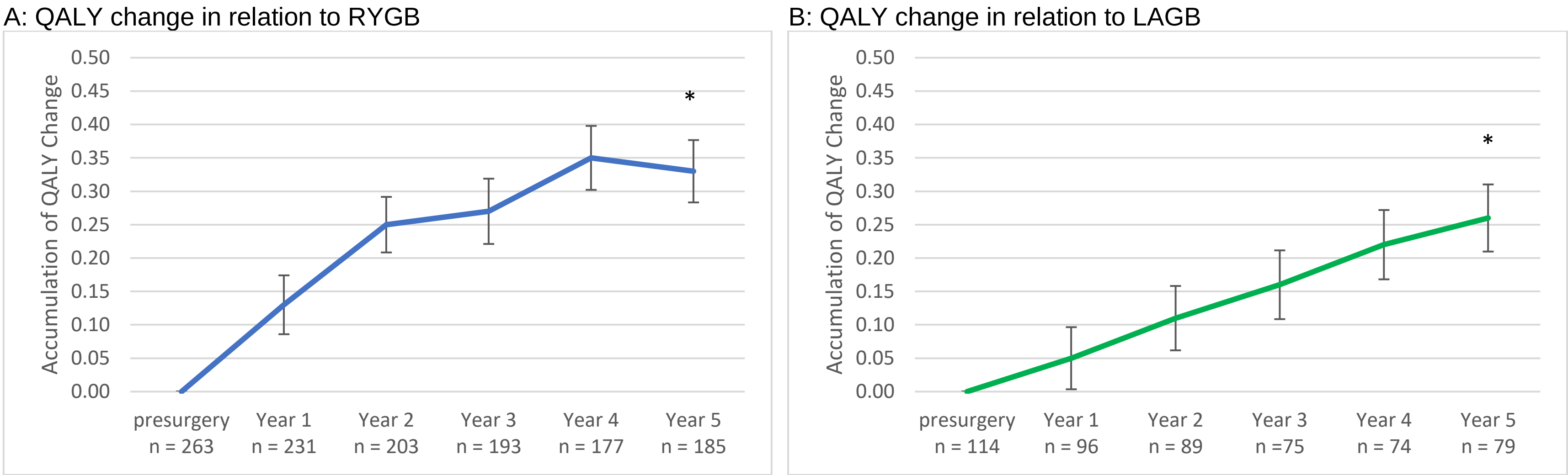
- EQ5D and EQVAS adjusted for factors related to missing follow-up data (site and dyslipidemia)

*Significance of pairwise comparisons of each follow-up time point compared to presurgery were evaluated at p<0.01 (adjusted for multiple comparisons).

Abbreviations: EQ5D index = Euroqol 5 Dimension index; EQVAS = Euroqol Visual Analog Scale; LAGB = Laparoscopic adjustable gastric band; RYGB = Roux-en-Y gastric band

Figure 9-2: EQ5D index and EQVAS over time from presurgery to 5 year follow-up, stratified by surgical procedure*

(A) Among RYGB participants, there was a linear time effect (p<0.01) indicating a decline in the EQ5D index from 1 to 5 years, however scores remained higher than presurgery. (B) For the LAGB participants, there was no time effect (p=0.16; linear) indicating that the improvement in the EQ5D index was stable over time where all scores, year 1 to year 5, remained higher than presurgery scores. (C) For RYGB participants, there was a linear time effect (p<0.0001), indicating a decline in EQVAS at year 5 from the initial improvement at year 1, but the EQVAS remained higher than presurgery. (D) For LAGB participants, there was a linear time effect (p<0.01) indicating a decline in the EQVAS at year 5 from the initial improvement at year 1, but the EQVAS remained higher than presurgery.



- QALY (quality adjusted life years) adjusted for factors related to missing follow-up data (site and dyslipidemia)
* Significance of pairwise comparisons of each follow-up time point compared to presurgery were evaluated at p<0.01 (adjusted for multiple comparisons).
Abbreviations: LAGB = Laparoscopic adjustable gastric band; RYGB = Roux-en-Y gastric bypass

Figure 9-3: QALY over time from presurgery to 5 year follow-up, stratified by surgical procedure*

Table 9-2: Basic and Multivariable Models of Group Effects in Pre- to Post-Surgery Change in QALYs Following Bariatric Surgery

	Basic Models (N=377)		**Pre-surgery Multivariable Model (N=316)**		**Multivariable Model with Weight Loss(N=316)**	
	Beta 95% CI	p-value	Adj. Beta 95% CI	p-value	Adj. Beta 95% CI	p-value
Presurgery Factors						
Age (per 10 years)	0.01 (-0.02-0.04)	0.52	0.02 (-0.02-0.05)	0.33	0.01 (-0.02-0.05)	0.44
Male (ref=[female])	0.08 (-0.007-0.17)	0.07	0.08 (-0.003-0.17)	0.15	0.06 (-0.03-0.15)	0.18
White race (ref=[black])	0.02 (-0.08-0.12)	0.70	0.02 (-0.08-0.13)	0.66	0.008 (-0.10-0.11)	0.88
>High School (ref[≤ HS])	-0.01 (-0.10-0.07)	0.76	-0.02 (-0.11-0.07)	0.59	-0.01 (-0.11-0.05)	0.49
Employed (ref=[not employed])	-0.06 (-0.14-0.02)	0.16	-0.04 (-0.12-0.03)	0.27	-0.03 (-0.11-0.05)	0.49
BMI kg/m^2 (per 10 kg/m^2)	-0.02 (-0.07-0.03)	0.38	**0.07 (0.001-0.14)**	**0.02**	**0.09 (0.02-0.15)**	**0.007**
Surgical Procedure						
RYGB (ref=[LAGB])	**0.09 (0.002-0.17)**	**0.04**	0.004 (-0.09-0.10)	0.94	-0.006 (-0.10-0.09)	0.90
Percent weight loss, per 5%	**NA**		**0.03 (0.01-0.05)**	**0.0001**	**0.05 (0.03-0.07)**	**<0.0001**

All models adjusted for pre-surgery factors related to missing follow-up (site, dyslipidemia status)
Abbreviations: BMI = Body Mass Index; HS = High School; LAGB = Laparoscopic adjustable gastric band; NA = Not Applicable; RYGB = Roux-en-Y gastric band

9.7 Addendum

Table 9-3: Supplemental Table 1: Comparison of LABS-2 participants eligible for the EQ5D study sample who met inclusion criteria vs were excluded due to missing data, stratified by surgical procedure

	RYGB; N=393*			LAGB; N=169*		
Continuous Variables	Excluded (N = 130) n (%)	Included (N = 263) n (%)	p-value	Excluded (N=55) n (%)	Included (N=114) n (%)	p-value
Age (years)						
Median (IQR)	49 (39-56)	47 (37-55)	0.22	48 (39-56)	49.0 (37-56)	0.92
Range	20-73	19-70		27-72	19-72	
Male (vs female)	104/130 (80.0)	206 (78.3)	0.70	45 (81.8)	86 (75.4)	0.35
White race (vs black)	111/129 (86.1)	210/256 (82.0)	0.32	47/54 (87.0)	96 (84.2)	0.63
>HS (vs ≤ HS)	85.4	76.1	0.06	64.9	81.6	0.03
Employed (vs not employed)	58/91 (63.7)	179/262 (68.3)	0.42	25/39 (64.1)	73 (64.0)	0.99
BMI (kg/m²)						
Median (IQR)	47.9 (43.5-53.0)	46.0 (41.5-50.6)	0.008	44.9 (40.2-49.2)	43.8 (40.4-46.5)	0.41
Range	35.5-77.2	33.9-74.9		33.0-64.3	33.8-70.0	
Weight						
Median (IQR)	135.0 (119.1-155.9)	129.5 (113.6-146.4)	0.03	118.6 (106.4-139.5)	120.5 (110.9-135.5)	0.60
Range	94.5-227.3	75-240		92.3-186.4	85-227.7	
Hypertension	89/121 (75.6)	192/260 (73.9)	0.95	32/49 (65.3)	70/109 (64.2)	0.90
Dyslipidemia	61/91 (67.0)	114/182 (62.6)	0.48	19/34 (55.9)	49/771 (59.7)	0.70
Diabetes	44/106 (41.5)	90/256 (35.2)	0.25	13/45 (28.9)	32/109 (29.4)	0.95
Psychiatric Meds	52/109 (47.7)	90/256 (44.6)	0.58	17/43 (39.5)	32/109 (43.4)	0.67
BDI	n=115	n=262		n=51	n=114	
Median (IQR)	7.0 (3.0-13.0)	5.0 (2.0-9.0)	0.051	6.0 (2.0-10.0)	5.5 (3.0-10.0)	0.95
Range	0-28.0	0-36.0		0-32.0	0-25.0	

*Denominator for each variable unless specified otherwise due to missing data
Abbreviations: LAGB = Laparoscopic adjustable gastric band; RYGB = Roux-en-Y gastric band

Table 9-4: Supplemental Table 2: Postsurgery Changes from Presurgery by follow-up, stratified by surgical procedure

	Postsurgery Follow-up Timepoints				
	1 year	2 year	3 year	4 year	5 year
RYGB	**n=231** **n (%)**	**n=203** **n (%)**	**n=193** **n (%)**	**n=177** **n (%)**	**n=185** **n (%)**
Percent Weight Change					
Median (IQR)	33.1 (28.2-38.7)	33.8 (27.3-39.9)	30.1 (23.9-37.5)	28.5 (21.2-35.9)	28.2 (21.1-35.2)
Range	8.0-52.8	9.8-53.3	6.7-52.8	7.1-55.0	4.9-49.0
QALY Change					
Median (IQR)	0.1 (0.01-0.2)	0.2 (0-0.4)	0.1 (0-0.5)	0.2 (0-0.7)	0.2 (0-0.8)
Range	-0.4-0.5	-0.7-1.2	-1.5-1.8	-1.5-2.1	-2.8-2.7
LAGB	**n=96** **n (%)**	**n=89** **n (%)**	**n=75** **n (%)**	**n=74** **n (%)**	**n=79** **n (%)**
Percent Weight Change					
Median (IQR)	13.4 (9.4-20.4)	13.7 (8.8-21.2)	12.7 (6.5-21.0)	14.5 (7.0-22.6)	14.0 (3.3-22.3)
Range	-8.0-35.9	-11.8-43.2	-12.5-40.6	-13.2-49.6	-19.6-54.8
QALY Change					
Median (IQR)	0.1 (0-0.2)	0.1 (0-0.3)	0.1 (0-0.5)	0.2 (0-0.7)	0.1 (-0.1-0.9)
Range	-0.5-0.5	-0.8-1.1	-1.0-1.7	-2.0-2.0	-1.6-2.5

10.0 Paper 3: Comparing the EQ5D and the SF6D Assessments of Health Related Quality of Life among Longitudinal Assessment of Bariatric Surgery (LABS-2) Participants pre and 1-year Post Surgery

10.1 Abstract

Introduction: The EuroQol 5 dimension (EQ5D) and Short Form 6 dimension (SF6D; derived from the Short Form 36) are instruments which employ different methods of (range = 0 [death] – 1 [perfect health])

Methods: Adults who completed both the EQ5D and SF36 prior to and 1-year following Roux-en Y (RYGB) and Laparoscopic adjustable gastric band (LAGB) surgery (n=308) were examined to identify overall scores at both time points and change in the EQ5D and SF6D indexes in this 1-year period, respectively. Pearson's correlation between the two HRQoL indexes were calculated with presurgery, postsurgery and change values. Central tendency and variability measures of each index were described. Ceiling effects were evaluated by identifying those who reported perfect health (1) on all dimensions. Median and interquartile ranges (IQR) of change in the EQ5D and SF6D index, respectively, by category of percent weight change, by 10-unit categories, were calculated.

Results: Correlations for the EQ5D and SF6D indexes were 0.67 (p<0.0001) presurgery, and 0.46 (p<0.0001) and 0.36 (p<0.0001) prepost surgery for the RYGB and LAGB groups, respectively. The EQ5D index contained more outliers, skewness, and a higher peak (median=0.78; IQR=0.71-0.83; skew= -1.32; kurtosis=2.62) pre-surgery compared to the SF6D index (median=0.68; IQR=0.59-0.78; skew= -0.23; kurtosis= -0.21). Prepost surgery changes for the RYGB and LAGB groups were similar for both indexes. Ceiling effects in the EQ5D index ranged from 9-18% presurgery to 13-40% postsurgery; whereas SF6D index ceiling effects were <2% postsurgery only. EQ5D and SF6D index changes generally increased as weight loss increased.

Discussion: While the EQ5D and SF6D index were highly correlated before and after surgery, the prepost change correlation was lower. The EQ5D had more ceiling effects and outliers compared to the

SF6D and therefore did not provide as complete an assessment of HRQoL in this cohort of bariatric patients. However, all benefits and limitations for each instrument should be considered prior to selection of the most appropriate HRQoL measurement.

10.2 Introduction

Health-Related Quality of Life (HRQoL) is a multidimensional construct of health that most commonly addresses the physical, mental, and social dimensions of health. At this time, several instruments exist to assess HRQoL [1]. Serial measurements of HRQoL among the same individual can be used to assess how HRQoL changes over time. In particular, clinicians can evaluate how an individual's HRQoL improves or declines in response to an intervention or in the presence of illness.

Based upon their respective measurement methods, HRQoL instruments can differ in how they apply value to physical, mental, and social health levels. Preference based instruments of HRQoL combine and weight dimension scores into an index of overall health on a 0-1 range scale, where 0 indicates death and 1 indicates perfect health. Preference weighting adjusts for the desirability of a specified health condition compared to perfect health or death and can have an impact on the actual range of a particular instrument based on how a population values health and disability for each dimension [168].Past research has shown that different preference-based HRQoL instruments can produce different scores among multiple populations [181, 290, 291] for the same individual.

Differences in index health scores between instruments are often due to the differing properties of the instruments involved; including number of dimensions assessed, number of answer options, and the method used to generate the preference weight [168]. The Euroqol 5 Dimension (EQ5D-3L), one of the most widely used preference based HRQoL instruments, examines five dimensions with three answer options per dimension, and uses the time trade off (TTO) method to calculate preference weights. [243]. The Short form 6-dimension (SF6D), another more recent, preference-based instrument, derived from the Short Form 36 Health Survey (SF36) [176, 177], examines 6 dimensions, with 4-6 derived answer options per dimension, and uses the Standard Gamble (SG) method to place a value on health. [177, 182].

Bariatric surgery has been found to be effective for weight loss, reduction of comorbidity and mortality risk, and improvement of HRQoL, among individuals with severe obesity [97, 103, 106, 107]. As obesity levels increase, the use of bariatric surgery will increase [292], and assessments of HRQoL will continue to be used to assess HRQoL and cost effectiveness in this population. It is important, therefore, to examine how quality of life scores may or may not vary by type of instrument used among bariatric surgery patients [168]. Comparisons of the effects of different HRQoL instruments on presurgery values, ceiling effects, and pre to postsurgery change among bariatric surgery recipients are needed. Ceiling effects exist when participant scores cluster at the top of a scale, making it impossible to discern differences between people who are not having any impairment from individuals who are doing well but are not in perfect health [293].

A prior investigation, by Sauerland et al, included several HRQoL indexes, including EQ5D and SF6D, among pre and postsurgery bariatric surgery patients in Europe [273]. While this report compares these indexes, it does not compare them to each other but rather to the Moorhead-Ardelt II Questionnaire only, which is being validated in four different languages. Furthermore, the EQ5D and SF6D indexes used UK preference weights, which have been shown to be different from US preference weights [211]. A recent meta-analysis, which included data from Sauerland et al, evaluated differences between the EQ5D and SF6D. Results indicated that the mean EQ5D index was higher presurgery and 1-year postsurgery compared to the SF6D. While these results did provide a glimpse into differences in the EQ5D and SF6D indexes among bariatric surgery patients, there remains a paucity of research about how these instruments function in the US population [290].

This report will fill a gap in the bariatric literature to address how the EQ5D and SF6D instruments compare when measuring HRQoL among bariatric surgery participants in a large multi-center trial. Having a better understanding of how the EQ5D and SF6D instruments quantify HRQoL among persons receiving bariatric surgery will enhance future evaluations of health in this population.

10.3 Methods

10.3.1 Participants

This report examined the performance of the EQ5D and SF6D instruments among persons receiving bariatric surgery who participated in the Longitudinal Assessment of Bariatric Surgery (LABS-2) Study. The LABS-2 study was a large US multi-center prospective cohort study, designed to evaluate the relationship of participant and surgical characteristics to longer term safety and efficacy of bariatric surgery [129]. The LABS-2 study enrolled 2458 adults who underwent an initial bariatric surgical procedure as standard clinical care between March 14, 2006, and April 24, 2009, at 1 of 10 hospitals at 6 US clinical centers [130]. The institutional review boards (IRB) at each center and the data coordinating center approved the protocol and all participants provided written informed consent.

Research assessments were conducted by trained research personnel within 30 days prior to scheduled surgery and annually following surgery. The SF36, from which the SF6D is derived, was available at study initiation; the EQ5D was added to the study protocol after study initiation on a rolling basis based on clinical centers' IRB approval between July 10, 2008. and October 30, 2008. All other measures, unless otherwise noted, were administered, at the presurgery and annual post-surgery assessments. This report uses data from pre-surgery and 1-year post surgery for subjects who completed the EQ5D and the SF36 measures at both time points.

10.3.2 HRQoL Instruments

The EQ5D-3L (3 Long) measures 5 dimensions of HRQoL - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [171]. Answer options for each dimension range from 1 to 3 (“no”, “some”, or “extreme”), with lower scores indicating better health. The index health score, hence referred to as the EQ5D index, is calculated by applying preference weights based on the US population to each of the 5 dimensions [183]. As noted in the introduction, preference weights for the EQ5D are generated using the TTO method, and determine the population preference of the 3125 potential health states generated from the EQ5D, ranging from full health to death [243]. The index can range from -0.11 to 1.0, where 0 indicates death, 1.0 indicates perfect health and negative scores indicate a perception of health that is worse than death [183]. Change in the index was calculated as 1-year value minus pre-surgery value. The EQ5D also includes a Visual Analog Scale (EQVAS), which allows respondents to rate their overall health status on a specific day from 0-100, where higher values indicate better health. The EQVAS is often included together with the EQ5D index to provide a more comprehensive assessment of HRQoL. However the EQVAS was only used to identify ceiling effects in this report [172, 173].

The Short Form 6 Dimension (SF6D) was derived by Brazier et al [176, 177] by reducing the eight dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health: all range from 0-100 with 100 indicating perfect health) [294] of the SF36 to a one score preference-based measure based on six of the original eight dimensions - physical functioning (6 response levels), role limitations (4), social functioning (5), pain (6), mental health (5), and vitality (5). The SF6D index is calculated by applying preference weights based on the US population generated using the Standard Gamble (SG) method, resulting in 18,000 potential health states, ranging from full health to death [187] using the Brazier revised scoring program using sf6d_sf36v1_US_mod algorithm [295]. The index ranges from 0.29 to 1.0 [177, 185]. Change in the index was calculated as 1-year value minus pre-surgery value.

10.3.3 Sociodemographic Variables

Sociodemographic variables (age, race, sex, education and employment) were self-reported. Due to low frequencies, race and education categories were collapsed to create binary variables (black, Asian, American Indian, Pacific Islander and multi-race versus white, and up to high school diploma or equivalent versus some college or greater, respectively).

10.3.4 Anthropometric and Comorbidity Specific Variables

A standardized protocol was used to collect height pre-surgery and weight at each assessment [130, 133], which were used to calculate BMI; weight in kg/ height in meters squared. Percent weight change at the 1-year follow-up was calculated as: 100*(pre-surgery weight minus post-surgery weight)]/pre-surgery weight. Thus, a negative number indicates weight gained. Hypertension was defined as having systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg from a single measurement, or taking an antihypertensive medication when evaluated [130]. Dyslipidemia was defined as either lipoprotein (LDL) ≥ 160 mg/dL, high density lipoprotein (HDL) < 40 mg/dL, fasting triglycerides ≥200 mg/dL, or currently taking a lipid lowering medication [130]. Diabetes was defined as either taking diabetes medication or having HbA1c of at least 6.5% or, if HbA1c was unavailable, an 8-hour fasting glucose of at least 126 mg/dL [130, 263].

Depressive symptoms over the past week were assessed using the Beck Depression Inventory (BDI) version 1. Higher scores (range 0-63) indicate greater severity of depressive symptoms. Given that bariatric patients are generally trying to lose weight, the BDI question to evaluate weight loss (e.g., "I have lost more than 5 pounds.") as a depressive symptom was omitted from calculation of the BDI score if participants endorsed that they were purposefully trying to lose weight by eating less [130]. Daily psychiatric medication usage was also used to assess mental health functioning, as it is related to presence of symptoms or mental disorders and may interfere with weight loss [264].

10.3.5 Statistical Analysis

First, selection bias was assessed by comparing pre-surgery characteristics for those who met inclusion criteria (had access to and completed the EQ5D, EQVAS, and all questions needed to be calculated the SF6D and general health scale on the SF36 pre-surgery and 1 year post-surgery; N=308) vs those who were eligible but excluded due to missing data (N=271), using the Pearson's chi-square test or the Fisher Exact test, as appropriate, for categorical variables, the Cochran Armitage Test for ordinal variables, and the Wilcoxon rank-sum test for continuous variables. The same tests were used to evaluate potential differences in presurgery characteristics among the included sample, by the RYGB and LAGB procedures, which accounted for 66.6% and 29.9% of participants, respectively. Pre-surgery analyses were conducted among the total sample. Post-surgery and change analyses were stratified by surgical procedure.

Agreement. To assess agreement between the two scales, Pearson correlation coefficients were calculated with presurgery and prepost change values. Measures of central tendency (mean and median) and variability (standard deviation, interquartile range, kurtosis, and skewness) of the EQ5D and SF6D indexes were compared with pre-surgery, post-surgery and changes values. In addition, the W statistic and p-value from the Shapiro-Wilk test were used, however, due to the conservative nature of the test, normality was assessed in consideration of all available data.

Ceiling effects. Ceiling effects were explored by time point among individuals who had a 1.0 (perfect health) on either index or who had 1 on all dimensions for either the EQ5D or SF6D instrument. Ceiling effects analysis was conducted using two different methods; 1. Using indexes and 2. Using dimension responses. To assess ceiling effects among indexes, frequencies and percentages of those with an index of 1.0 on the EQ5D or the SF6D were calculated. Next, frequencies and percentages were generated to identify how many individuals, among those who had a 1.0 index on either the EQ5D or the SF6D, also had an EQVAS value or a SF36 general health scale value (for the SF6D only), respectively, that fell below 90 (cutoff one) or below 95 (cutoff two). Ninety and 95 cutoffs were chosen because a 10-unit change on the EQVAS [164] or a 5-unit change on the SF36 general health scale [296] represent a clinically meaningful change and might aid in differentiating those who were more likely to have perfect health from those who did not. The EQVAS was used as a comparator for both the SF6D and the EQ5D indexes because the SF36 general health scale is not completed independently from the SF6D whereas the EQVAS is for the EQ5D. This is a novel approach to assess ceiling effects, however, the EQVAS has been used in a previous assessment of ceiling effects[181]. Specifically, Bharmal and Thomas described demographic and morbidity characteristics of individuals who had an EQ5D index 1 by whether the individual's EQVAS value fell below or above the EQVAS mean [181]. For ceiling effect comparisons using the dimension values, respondents who reported no limitations on all five of the EQ5D dimensions (EQ5D=11111) were identified and their responses were assessed using the SF6D descriptive system. This step was omitted for the SF6D because all EQ5D dimensions were 1 when all SF6D derived dimensions were 1. This approach to evaluating ceiling effects was previously used by Bharmal and Thomas [181].

Validity. Lastly, the EQ5D and SF6D indices were evaluated in relation to weight loss. Medians and interquartile ranges of indexes were calculated by 10-unit percent weight change category.

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). All reported p-values were 2-sided; p-values were used to guide the interpretation of results [265].

10.4 Results

10.4.1 Pre-surgery Sample Characteristics

Among the 579 who had the opportunity to complete the EQ5D questionnaire, 308 (53.20%) met the inclusion criteria (shown in Table 10-5. supplemental table 1). BMI was significantly lower (median: 45.21 kg/m^2 versus 46.62 kg/m^2; p=0.03) and the SF6D index was significantly higher (median: 0.68 versus 0.64; p=0.01), for those included versus not included, respectively, however differences were small. Presurgery sample characteristics among those included in this report are presented in Table 10-1. Briefly, the median age was 47 (IQR = 37-56) and participants were mostly female (77%), white (84.21%), and employed (66.56%).

10.4.2 Instrument Agreement

Correlations for the EQ5D and SF6D indexes were strong presurgery (r=0.67; p<0.0001) and moderate prepost surgery (RYGB: r=0.46; p<0.0001; LAGB: r=0.36; p<0.0001), and indicated that as the EQ5D index increases, so does the SF6D. Correlations for the EQVAS and SF36

General Health scale were moderate pre ($r=0.56$; $p<0.0001$) and weak prepost surgery (RYGB: $r=0.35$; $p<0.0001$; LAGB: $r=0.36$; $p=0.0004$).

10.4.3 Distributions of EQ5D and SF6D indexes

Pre-surgery

Frequency distributions in the total sample presurgery the EQ5D and SF6D indexes are presented in Figure 10-1; Panel A. Results of the Shapiro-Wilk test for the EQ5D and SF6D indexes are $W=0.85$ ($p<0.0001$) and $W=0.98$ ($p=0.0006$), respectively ($W \geq 0.9$ approximates normal distribution in consideration of other data). The mean and standard deviation was slightly higher for the EQ5D (Mean = 0.75; SD =0.17) compared to the SF6D (Mean = 0.68; SD = 0.12) with a 0.07 mean difference between the 2 measures. The EQ5D index contained more outliers and greater left skewness, and peak (Median = 0.78; IQR = 0.71-0.83; skew = -1.32; kurtosis = 2.62) compared to the SF6D index (Median = 0.68; IQR = 0.59-0.78; skew = -0.23; kurtosis = -0.21). Using all data taken together, the EQ5D index was found to not be normally distributed while the SF6D index was.

10.4.4 PrePost Change in RYGB and LAGB Surgical Procedures

Figures 1b and 1c show distributions of prepost change in the EQ5D or SF6D indexes among those who had the RYGB or LAGB procedure, respectively. The Shapiro-Wilk test W statistic for the EQ5D index and SF6D index are $W=0.94$ ($p<0.0001$) and $W=0.99$ ($p=0.68$), respectively for those who had the RYGB procedure (Figure 10-1 Panel B). Mean prepost change for the EQ5D index (mean =0.11; SD = 0.15) and the SF6D index (mean =0.11; SD = 0.11) were similar. The median and spread were slightly higher for the EQ5D index (median = 0.09; IQR = 0.01-0.18) compared to the SF6D (median = 0.11; IQR = 0.04-0.18). The EQ5D was less left skewed but had a higher peak (skew = -0.05; kurtosis = 1.62) compared to the SF6D (skew = -0.17; kurtosis = -0.02). Statistics and histograms indicate that prepost changes for the EQ5D and SF6D index are normally distributed (Figure 10-1; Panel B).

For the LAGB procedure (Figure 10-1 Panel C), the Shapiro-Wilk test W statistic for the EQ5D and SF6D indexes are W=0.94 (p=0.001) and W=0.93 (p<0.0001). Mean prepost changes are similar for the EQ5D (mean =0.07; SD = 0.18) and the SF6D (mean = 0.06; SD = 0.11). The median and spread (IQR) for the EQ5D index 0.05 (IQR = 0-0.17) and SF6D index 0.05 (IQR = 0-0.11) were also similar. The EQ5D was skewed left and had a slightly larger peak (skew = -0.46; kurtosis = 1.17) while the SF6D was skewed right (skew = 1.03; kurtosis = 1.03). Statistics and histograms indicate that prepost changes for the EQ5D and SF6D index are normally distributed (Figure 10-1 Panel C).

10.4.5 Ceiling Effects by index score

Pre-surgery

At presurgery, responses indicating perfect health (index = 1.0) were observed for the EQ5D index only. A total of 34 (11.04%) met criteria for ceiling effects with the EQVAS cutoff of 90, and 36 (11.69%) with the cutoff of 95. The EQVAS mean 70.59 (SD = 15.48), median 74 (IQR = 65-80) and range 20 – 95 for those with an EQ5D index of 1.0.

10.4.6 Prepost Change in RYGB and LAGB surgical procedures

RYGB

For pre-surgery values, 20 (9.76%) participants out of 205 had an EQ5D index of 1.0 with 18 (8.78%) having EQVAS values that were under the 90 EQVAS cutoff and all 20 (9.76%) being under the 95 EQVAS cutoff. The EQVAS mean was 69.10 (SD = 18.44), median was of 75 (IQR

= 57.5-82.5) and range was 20 – 90 for all those who had an EQ5D index of 1.0. At postsurgery, the number of participants reporting an EQ5D index of 1.0 increased to 84 (40.98%) out of 205. In these subjects, 37 (18.05%) had EQVAS values under the 90 EQVAS cutoff and 59 (28.78%) under 95. The postsurgery EQVAS mean was 88.38 (SD = 7.78), median was 90 (IQR = 82-95), and range was 70 – 100. There were a total of 19 (9.27%) participants out of 205 who had an EQ5D index of 1.0 at both pre and postsurgery time points, with 17 (8.29%) having EQVAS values below 90 and 19 with values below 95. An SF6D index of 1.0 was reported at postsurgery only among 2 (0.98%) participants out of 205. One participant had an EQVAS value below 90 and two (0.98%) below 95. The SF36 general health scale mean 90 (SD = 10), median 90 (IQR = 89-100) and range 80 – 100 were lower than the EQVAS mean 96.33 (SD = 6.35), median 100 (IQR = 89-100), and range 89 – 100.

LAGB

Ceiling effects were present for the EQ5D only. At presurgery, 17 (18.48%) participants out of 92 reported an EQ5D index of 1.0 with 16 (17.39%) participants having an EQVAS of 90 or 95. The EQVAS mean was 72.35 (SD = 11.37) and median of 73 (IQR = 65-80) with a range of 50 – 95. At postsurgery the number of participants who had an EQ5D index of 1.0 increased to 38 (41.30%) out of 92 participants with 24 (26.09%) participants having an EQVAS below 90 and 31 (33.70%) below 90. The EQVAS mean was 84.84 (SD = 9.53), median 85 (IQR = 80-90), and range 50 – 100. A total of 12 (13.04%) participants out of 92 had an EQ5D index of 1.0 at both pre and postsurgery timepoints with 11 (11.96%) having an EQVAS below 90 and 12 (13.04%) below 95.

10.4.7 Ceiling Effects by Dimension

Table 10-3 provides the distribution of SF6D responses for individuals who indicated no limitation on each EQ5D dimension. Agreement with the SF6D of no limitations was below 50%

in the physical function, pain, mental health, and vitality dimensions. This was evident at presurgery, and pre and postsurgery by type of surgery (RYGB, or LAGB), except for where agreement was 59.5% for the physical function dimension post-RYGB. The highest agreement with the SF6D was observed for the role limitation and social functioning dimensions, where percent agreement was at or over 70%, except for the LAGB presurgery timepoint where agreement was 52.9%.

10.4.8 EQ5D and SF6D index changes by percent weight loss (Validity)

Prepost Change in RYGB and LAGB surgical procedures

For the RYGB and LAGB procedures, generally, prepost improvements were higher for EQ5D index compared to the SF6D index, however, HRQoL improved as weight loss increased for both instruments. For the RYGB procedure, greatest improvement in the EQ5D index (median = 0.16; IQR = 0.04-0.22) occurred among participants who achieved ≤-40% weight change. In contrast, greatest improvement in the SF6D index (median = 0.13; IQR = 0.04-0.17) improvement capped among participants who achieved between -30% to -39.99% weight loss and decreased (median=0.10; IQR = 0.04-0.20) among those with ≤-40% weight loss. For the LAGB procedure, greatest improvement in both the EQ5D (median = 0.20; IQR = 0.17-0.40) and SF6D (median = 0.13; IQR = 0.10-0.20) indexes occurred among participants who achieved between -30% to -39.99% weight loss from their presurgery weight. Of note, EQ5D prepost improvement was lowest among participants who achieved >-10% weight loss compared to (median = 0.01; IQR = -0.16-0.17) participants who experienced no weight loss (median = 0.03; IQR = -0.07-0.19).

10.5 Discussion

This report describes how the EQ5D and SF6D instruments function in relation to assessing HRQoL in persons receiving bariatric surgery. The correlations for the EQ5D and SF6D indexes were strong presurgery, but correlations of prepost changes were weak to moderate. Additionally, the EQ5D was more left skewed presurgery compared to the SF6D, which was most likely due to the higher presence of ceiling effects. The ceiling effects were particularly relevant with measuring change between presurgery and prepost change, both in the indexes and dimensions. The EQ5D and SF6D identified similar trends of change by percent weight change – as percent weight change increased, the amount of change between prepost scores increased, however, the actual prepost change for the EQ5D compared to the SF6D was not the same between the two instruments. For the same percent weight change category, the prepost change in the SF6D was higher than the prepost change in the EQ5D, except for the lowest or highest weight change category.

To date, there is no consistent or gold standard approach to exploring ceiling effects within the EQ5D or SF6D index systems [181, 291]. Prior methods include comparing EQ5D index or dimension results to the SF6D index or derived dimension results within the same sample of individuals [181, 291]. While that method aids in understanding how the two scales differ on indicators of perfect health, it does not aid in a better understanding of how to differentiate between individuals where the instrument is efficient at assessing perfect health compared to times when it is not. Thus, this report uses a novel approach to explore ceiling effects, comparing the EQ5D and SF6D indexes to the EQVAS and SF36 general health scale score which offers that level of guidance. Results indicated that ceiling effects, defined by when the index was 1.0 and the EQVAS value was below the cutoff of 90 or 95, occurred with greater frequency with the EQ5D index at presurgery and postsurgery, and only with the SF6D index for the RYGB postsurgery group. Results also indicated that ceiling effects increased for the EQ5D index, from pre to postsurgery timepoints for both the RYGB and LAGB surgical groups.

The LAGB surgical group had a greater percentage of individuals with ceiling effects postsurgery than the RYGB group. This might imply that those in the RYGB had more true improvement than those in the LAGB group because individuals who receive the LAGB procedure are often not as ill and have less room for improvement. Finally, the proportion of those who reported perfect EQ5D index at both the pre and post timepoints and did not meet the 90 or 95 EQVAS cutoff was higher in the LAGB group compared to the RYGB group which further supports the previous statement. These results are similar with previous research results where there are greater improvements in HRQoL among individuals who received the RYGB procedure compared to LAGB [288].

While there is a paucity of research on ceiling effects among individuals with obesity and who have received bariatric surgery, two previous studies have identified that the EQ5D is more likely to have ceiling effects compared the SF6D [181, 291]. Results on ceiling effects, results from this report were comparable to other reports that have shown similar trends between EQ5D and SF6D indexes among individuals with obesity by class of obesity (or percent weight change in this report) [297]. That is, in Sach et al's reporting on the EQ5D and SF6D index differences by BMI group (underweight, normal, pre-obese, obese 1, obese 2, obese 3, and obese 1-3), generally, the SF6D index was higher than the EQ5D index, but there were fluctuations that deviated from this observation among lower and higher weight change classes. While, percent weight change in the year following bariatric surgery was evaluated in this report rather than BMI at a single time point in Sach's, we saw similar fluctuations by percent weight change. Even with these fluctuations, our results indicate that HRQoL improves after bariatric surgery [290].

Also, of importance, was the functioning of each measure in relation to percent weight change. The EQ5D and SF6D estimated differences in HRQoL similarly for all categories of percent weight change except for those who gained weight, a very small group. That is, for those who did not gain weight, the EQ5D scores were higher than the SF6D scores, but each score increased or decreased similarly by percent weight change category [298-301]. However, when individuals gained weight post-surgery, the SF6D prepost change was higher than the EQ5D which has been previously documented in the literature where poorer health states tend to have higher scores on the SF6D compared to the EQ5D [298-301].

While the purpose of this report is to evaluate the instrument's performance in response to bariatric surgery, it is important to consider the implications that our findings have on instrument selection. Results from this report may seemingly indicate that the SF6D is a better choice over the EQ5D. Even though results from the SF6D analysis captured a more comprehensive measure of HRQoL, it is important to remember that the SF36 was not developed to be a preference-based measure [176, 177] which may present its own limitations. This is evident when evaluating the range of the SF6D (0.29-1.0) meaning that individuals in poorer health, will not be able to indicate lack of function past a certain level creating a floor effect that may be difficult to detect or discern.

When considering instrument selection, there are two very important considerations. The first is that ceiling effects were present with the EQ5D index. This does not mean that clinicians and health professionals should no longer use the EQ5D as the EQ5D is easy to use and presents very low burden for patients, but rather, that the EQ5D is prone to ceiling effects. Using the appropriate analysis methods or a novel approach similar to the one used in this report may aid in being able to discern who is truly in perfect health and who is not.

A second implication regarding instrument selection has to do with prepost differences between the two instruments. When overall prepost differences were compared for each instrument by surgical procedure there was little difference between the score differences. However, when the prepost differences were stratified by percent weight change, the magnitude of the differences increased by instrument within each category of weight loss. These differences may have impacts on how effective the intervention is deemed to be. The paucity in previous research may have implications on cost-effectiveness analysis indicating that one instrument might show greater improvement or cost savings compared to another within the same population.

This report has several strengths. This report uses longitudinal data and evaluates pre-surgery data and data by surgery group. Evaluating data in this way allows a comprehensive comparison of the instruments. This report also evaluates distributions and ceiling effects by time point and over time (prepost change) for each instrument. Previous reports have not examined instrument performance at this level of detail. Examinations of distributions provide information about approximation to normal distribution and can give insight into possible ceiling effects. Lastly, this report provides a stratified comparison of instrument change by percent weight change, which can be more informative with regard to differences in prepost HRQoL changes by changes in weight than a cross sectional evaluation of indexes by BMI.

This report also has limitations. There are debates on how to evaluate ceiling effect. The approaches used in this report cannot may not be superior over other methods that have been previously used. All comparisons between instruments were made descriptively. Other comparisons such as mapping and other statistical measures would possibly provide useful information. Modeling techniques might provide insight into what factors contribute to the noted changes. This report also only evaluates short-term changes (pre- to 1-year postsurgery).

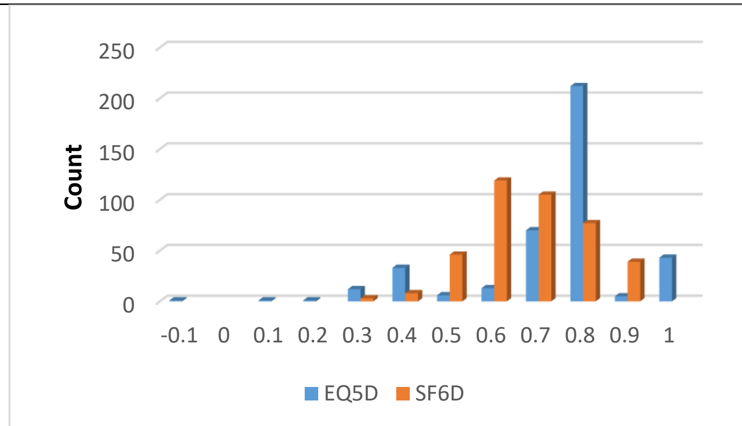
In conclusion, this report provides important and timely information regarding the EQ5D and the SF6D HRQoL instruments as they relate to bariatric surgery. This is the first report that examines these differences using US preference weights. The SF6D appeared to provide a less biased assessment of HRQoL change than the EQ5D all benefits and limitations for each instrument should be considered prior to selection of the most appropriate HRQoL measurement. While further research is needed to understand how these instruments perform over longer periods of time, this report provides clinicians and health professionals with valuable information to aid in their selection of an instrument, to know the limitations of the instrument and possible ways to deal with the limitations.

10.6 Tables and Figures

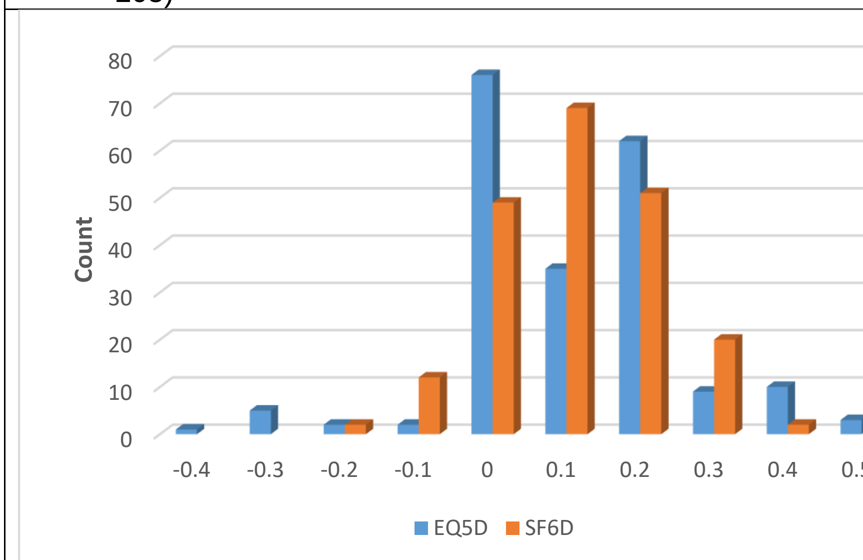
Table 10-1: Presurgery Characteristics of Study Sample and RYGB and LAGB subsamples

	Total (N = 308) n (%)	RYGB (N = 205) n (%)	LAGB (N = 92) n (%)
Demographics			
Age			
Median(IQR)	47.00 (37.00-55.50)	47.00 (37.00-55.00)	48.50 (37.50-55.50)
Range	19.00-72.00	19.00-70.00	22.00-72.00
Sex (Female), n (%)	237 (76.95)	158 (77.07)	71 (77.17)
Race (White) , n (%)	256 (84.21)	169 (84.08)	79 (85.87)
Education (Some college or greater)	242 (78.57)	158 (77.07)	78 (84.78)
Employed (yes)	205 (66.56)	137 (66.83)	63 (68.48)
BMI			
Median(IQR)	45.21 (41.19-50.15)	45.98 (41.52-50.59)	43.64 (40.37-46.24)
Range	33.89-74.88	33.89-74.88	35.37-57.36
Weight (kg)			
Median(IQR)	127.27 (113.64-143.64)	130.91 (115.45-149.54)	120.45 (112.05-133.18)
Range	75.00-240.00	75.00-240.00	87.73-179.09
Hypertension (yes), n (%)	212 (70.67)	150 (74.26)	54 (62.07)
Dyslipidemia (yes), n (%)	136 (60.99)	90 (60.81)	38 (58.46)
Diabetes (yes), n (%)	96 (32.21)	68 (34.00)	23 (26.44)
Psychiatric Medication (yes), n (%)	135 (44.55)	90 (44.78)	38 (41.76)
Depressive Symptoms			
Median(IQR)	5.00 (2.00-10.00)	5.00 (2.00-9.00)	6.00 (3.00-10.00)
Range	0-36.00	0-36.00	0-25.00
Abbreviations: BMI = Body Mass Index; IQR = Interquartile Range			

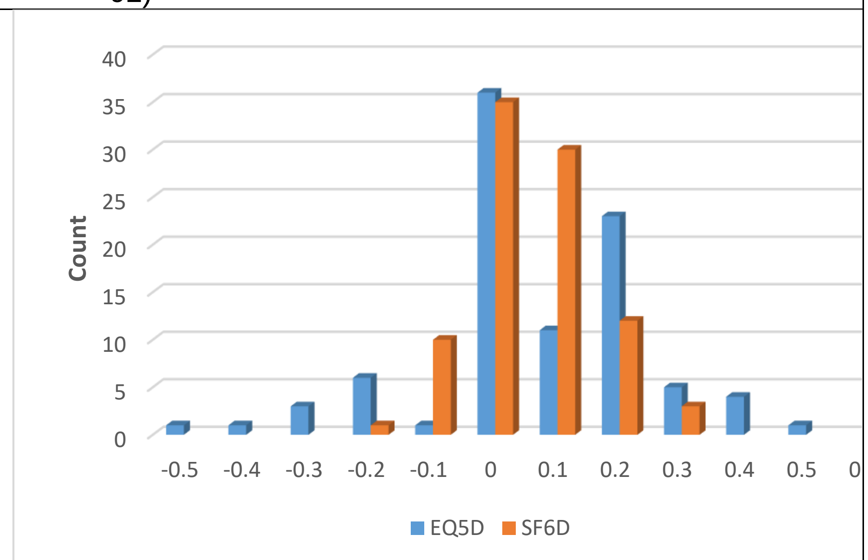
A. Total Presurgery (N = 308)



B. RYGB Pre and Post Surgery Change Differences (N = 205)



C. LAGB Pre and Post Surgery Change Differences (N = 92)



Abbreviations: EQ5D = EuroQol 5 Dimension; LAGB = Laparoscopic Banding Gastric Bypass; RYGB = Roux-en Y Gastric Bypass; SF6D = Short Form 6 Dimension

Figure 10-1: Distributions of EQ5D and SF6D indexes presurgery and prepost change by surgery group

Table 10-2: Ceiling Effects at Presurgery in the total sample, and Pre, Post, and both Pre&Postsurgery by surgical procedure

	Presurgery Presurgery (N = 308) N (%)	RYGB Presurgery (N = 205) N (%)	RYGB Postsugery (N = 205) N (%)	RYGB Pre&Postsurgery (N = 205) N (%)	LAGB Presurgery (N = 92) N (%)	LAGB Postsurgery (N = 92) N (%)	LAGB Pre&Posturgery (N = 92) N (%)
EQ5D							
Index = 1.0	37 (12.01)	20 (9.76)	84 (40.98)	19 (9.27)	17 (18.48)	38 (41.30)	12 (13.04)
Index = 1 and EQVAS < 90	34 (11.04)	18 (8.78)	37 (18.05)	17 (8.29)	16 (17.39)	24 (26.09)	11 (11.96)
Index = 1 and EQVAS < 95	36 (11.69)	20 (9.76)	59 (28.78)	19 (9.27)	16 (17.39)	31 (33.70)	12 (13.04)
SF6D							
Index = 1.0	0	0	3 (1.46)	0	0	0	0
Index = 1 and GenHlth < 90	--	--	2 (0.98)	--	--	--	--
Index = 1 and GenHlth < 95	--	--	2 (0.98)	--	--	--	--
Index = 1 and EQVAS < 90	--	--	2 (0.98)	--	--	--	--
Index = 1 and EQVAS < 95	--	--	1 (0.49)	--	--	--	--

Abbreviations: EQ5D index = EuroQol 5 Dimension index; EQVAS = EuroQol Visual Analog Scale; GenHlth = General Health Scale (SF36); LAGB = Laparoscopic Banding Gastric Bypass; RYGB = Roux-en Y Gastric Bypass; SF6D = Short Form 6 Dimension

Table 10-3: SF6D dimension distribution of responses for those who reported EQ5D=11111 (perfect health across all dimensions)

	Presurgery						Postsurgery					
Level	**Physical Functioning**	**Role Limitation**	**Social Functioning**	**Pain**	**Mental Health**	**Vitality**	**Physical Functioning**	**Role Limitation**	**Social Functioning**	**Pain**	**Mental Health**	**Vitality**
	All Presurgery (N = 37)											
1	21.6	83.8	70.3	27.0	29.7	29.7	--	--	--	--	--	--
2	56.8	5.4	29.7	46.0	51.4	48.7	--	--	--	--	--	--
3	18.9	8.1	0	18.9	16.2	13.5	--	--	--	--	--	--
4	2.7	2.7	0	2.7	2.7	8.1	--	--	--	--	--	--
5	0	--	0	0	0	0	--	--	--	--	--	--
6	0	--	--	0	--	--	--	--	--	--	--	--
	RYGB (N = 20)						RYGB (N = 84)					
1	25.0	75.0	85.0	20.0	35.0	40.0	59.5	89.3	92.9	42.9	45.2	20.2
2	55.0	10.0	15.0	55.0	60.0	45.0	36.9	2.4	3.6	36.9	41.7	63.1
3	15.0	15.0	0	20.0	5.0	15.0	3.6	7.1	1.2	15.5	10.7	15.5
4	5.0	0	0	5.0	0	0	0	1.2	1.2	4.8	2.4	1.2
5	0	--	0	0	0	0	0	--	1.2	0	0	0
6	0	--	--	0	--	--	0	--	--	0	--	--
	LAGB (N = 17)						LAGB (N = 38)					
1	17.7	94.1	52.9	35.3	23.5	17.7	47.4	86.8	84.2	42.1	39.5	5.3
2	58.8	5.9	47.1	35.3	41.2	52.9	50.0	2.6	13.2	50.0	42.1	44.7
3	23.5	0	0	29.4	29.4	29.4	2.6	10.5	2.6	7.9	15.8	36.8
4	0	0	0	0	5.9	0	0	0	0	0	2.6	10.5
5	0	--	0	0	0	0	0	--	0	0	0	2.6
6	0	--	--	0	--	--	0	--	--	0	--	--

Abbreviations: EQ5D index = EuroQol 5 Dimension index; LAGB = Laparoscopic Banding Gastric Bypass; RYGB = Roux-en Y Gastric Bypass; SF6D = Short Form 6 Dimension

Table 10-4: EQ5D and SF6D Indexes by Percent weight change: Presurgery and Prepost by Surgery Type

Percent weight change	**≥0% n=3**	**0>-10% n=23**	**-10%-19.99% n=44**	**-20%-29.99% n=94**	**-30%-39.99% n=96**	**≤-40% n=43**
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
EQ5D – all presurgery	0.40 (0.38-0.81)	0.82 (0.71-0.84)	0.81 (0.73-0.86)	0.78 (0.69-0.83)	0.78 (0.71-0.83)	0.78 (0.71-0.83)
SF6D – all presurgery	0.61 (0.56-0.74)	0.63 (0.58-0.81)	0.75 (0.66-0.84)	0.68 (0.58-0.75)	0.67 (0.60-0.76)	0.64 (0.56-0.73)
RYGB (N)	0	0	6	65	89	41
EQ5D Presurgery	--	--	0.83 (0.78-1)	0.78 (0.71-0.83)	0.78 (0.71-0.83)	0.78 (0.71-0.83)
EQ5D Postsurgery	--	--	1 (0.80-1)	0.83 (0.76-1)	0.84 (0.82-1)	0.84 (0.83-1)
EQ5D Change	--	**--**	**0.02 (0-0.15)**	**0.07 (0-0.17)**	**0.09 (0.02-0.18)**	**0.16 (0.04-0.22)**
SF6D Presurgery	--	--	0.85 (0.68-0.85)	0.67 (0.58-0.75)	0.68 (0.62-0.76)	0.65 (0.56-0.73)
SF6D Postsurgery	--	--	0.85 (0.81-0.85)	0.81 (0.67-0.85)	0.82 (0.75-0.85)	0.81 (0.64-0.88)
SF6D Change	--	**--**	**-0.003 (-0.02-0.01)**	**0.11 (0.02-0.17)**	**0.13 (0.04-0.17)**	**0.10 (0.04-0.20)**
LAGB (N)	3	23	38	24	3	0
EQ5D Presurgery	0.40 (0.38-0.81)	0.82 (0.71-0.84)	0.81 (0.71-0.84)	0.80 (0.71-0.84)	0.80 (0.43-0.83)	--
EQ5D Postsurgery	0.43 (0.31-1)	0.83 (0.71-1)	0.83 (0.80-1)	1 (0.83-1)	1 (0.83-1)	--
EQ5D Change	**0.03 (-0.07-0.19)**	**0.01 (-0.16-0.17)**	**0.02 (0-0.17)**	**0.11 (0-0.19)**	**0.20 (0.17-0.40)**	--
SF6D Presurgery	0.61 (0.56-0.74)	0.63 (0.58-0.81)	0.73 (0.65-0.81)	0.69 (0.63-0.80)	0.64 (0.55-0.75)	--
SF6D Postsurgery	0.58 (0.52-0.79)	0.75 (0.59-0.85)	0.80 (0.67-0.85)	0.84 (0.79-0.89)	0.77 (0.75-0.85)	--
SF6D Change	**0.02 (-0.09-0.05)**	**0.02 (0-0.12)**	**0.05 (0-0.08)**	**0.08 (0.05-0.17)**	**0.13 (0.10-0.20)**	--

Abbreviations: EQ5D index = EuroQol 5 Dimension index; LAGB = Laparoscopic Banding Gastric Bypass; RYGB = Roux-en Y Gastric Bypass; SF6D = Short Form 6 Dimension

10.7 Addendum

Table 10-5: Supplemental Table 1: Comparison of LABS-2 participants eligible for the EQ5D study sample who met inclusion criteria vs were excluded due to missing data

	Included* (N = 308) n (%)	Not Included (N = 271) n (%)	p-value
Demographics			
Age			0.66
Median(IQR)	47.00 (37.00-55.50)	48.00 (38.00-56.00)	
Range	19.00-72.00	19.00-73.00	
Sex (Female), n (%)	237 (76.95)	215 (79.34)	0.49
Race (White), n (%)	256/304 (84.21)	219/264 (82.95)	0.69
Education (Some college or greater)	242 (78.57)	160/210 (76.19)	0.52
Employed (yes)	205 (66.56)	137/213 (64.32)	0.60
BMI			0.03
Median(IQR)	45.21 (41.19-50.15)	46.62 (41.80-51.50)	
Range	33.89-74.88	32.96-77.22	
Weight (kg)			0.22
Median(IQR)	127.27 (113.64-143.64)	130.45 (113.18-149.09)	
Range	75.00-240.00	83.18-227.73	
Hypertension (yes) , n (%)	212/300 (70.67)	182/254 (71.65)	0.80
Dyslipidemia (yes) , n (%)	136/223 (60.99)	114/174 (65.52)	0.35
Diabetes (yes) , n (%)	96/298 (32.21)	90/232 (38.79)	0.12
Psychiatric Medication (yes), n (%)	135/303 (44.55)	107/234 (45.73)	0.79
Depressive Symptoms			0.09
Median(IQR)	5.00 (2.00-10.00)	6.00 (3.00-11.00)	
Range	0-36.00	0-32.00	
EQ5D			0.11
Median(IQR)	0.78 (0.71-0.83)	0.78 (0.69-0.82)	
Range	-0.04-1.00	0.13-1.00	
EQVAS			0.72
Median(IQR)	60.00 (40.00-75.00)	60.00 (45.00-70.00)	
Range	10.00-100.00	30.00-100.00	
SF6D			0.01
Median(IQR)	0.68 (0.59-0.78)	0.64 (0.57-0.73)	
Range	0.30-0.93	0.38-0.93	
General Health (SF36)			0.50
Median(IQR)	52.50 (35.00-70.00)	50.00 (35.00-65.00)	
Range	0-100.00	5.00-95.00	

* Had access to and completed the EQ5D, EQVAS, and all questions needed to be calculated the SF6D and general health scale on the SF36 pre-surgery and 1 year post-surgery
Abbreviations: BMI = Body Mass Index; EQ5D index = EuroQol 5 Dimension index; EQVAS = EuroQol Visual Analog Scale; LAGB = Laparoscopic Banding Gastric Bypass; RYGB = Roux-en Y Gastric Bypass; SF6D = Short Form 6 Dimension

Table 10-6: Supplemental Table 2: Dimension Value with Descriptions for EQ5D and SF6D

EQ5D	**SF6D**
Dimension Value: Description	Dimension Value: Description
Dimension: Mobility	*Dimension: Physical Functioning*
1: I have no problems in walking about 2: I have some problems in walking about 3: I am confined to bed	1: Your health does not limit you in vigorous activities 2: Your health limits you a little in vigorous activities 3: Your health limits you a little in moderate activities 4: Your health limits you a lot in moderate activities 5: Your health limits you a little in bathing and dressing 6: Your health limits you a lot in bathing and dressing
Dimension: Self-Care	*Dimension: Role Limitation*
1: I have no problems with self-care 2: I have some problems washing or dressing myself 3: I am unable to wash or dress myself	1: You have no problems with your work or other regular daily activities as a result of your physical health or any emotional problems 2: You are limited in the kind of work or other activities as a result of your physical health 3: You accomplish less than you would like as a result of emotional problems 4: You are limited in the kind of work or other activities as a result of your physical health and accomplish less than you would like as a result of emotional problems
Dimension: Pain/Discomfort	*Dimension: Pain*
1: I have no pain or discomfort 2: I have moderate pain or discomfort 3: I have extreme pain or discomfort	1: You have no pain 2: You have pain but it does not interfere with your normal work 3: You have pain that interferes with your normal work a little bit 4: You have pain that interferes with your normal work moderately 5: You have pain that interferes with your normal work quite a bit 6: You have pain that interferes with your normal work extremely
Dimension: Anxiety/Depression	*Dimension: Mental Health*
1: I am not anxious or depressed 2: I am moderately anxious or depressed 3: I am extremely anxious or depressed	1: You feel tense or downhearted and low none of the time 2: You feel tense or downhearted and low a little of the time 3: You feel tense or downhearted and low some of the time 4: You feel tense or downhearted and low most of the time 5: You feel tense or downhearted and low all of the time

Dimension: Usual Activities	*Dimension: Vitality*	*Dimension: Social Functioning*
Dimension Value: Description	Dimension Value: Description	Dimension Value: Description
1: I have no problems with performing my usual activities 2: I have some problems with performing my usual activities 3: I am unable to perform my usual activities	1: You have a lot of energy all of the time 2: You have a lot of energy most of the time 3: You have a lot of energy some of the time 4: You have a lot of energy a little of the time 5: You have a lot of energy none of the time	1: Your health limits your social activities none of the time 2: Your health limits your social activities a little of the time 3: Your health limits your social activities some of the time 4: Your health limits your social activities most of the time 5: Your health limits your social activities all of the time

11.0 Discussion

11.1 Summary

This dissertation's purpose was to fill in gaps in the literature regarding changes in HRQoL following current interventions (lifestyle intervention and bariatric surgery) on overweight and obesity. The first investigation (Paper 1) demonstrated that HRQoL (EQ5D index and EQVAS) improves among overweight and prediabetic participants after a DPP-translated 22-session intervention on sedentary behavior, which had not previously been studied, both compared to the 6-month delayed control group at 6 months and prepost at 6 months and 12 months following intervention. Prepost improvements in HRQoL increased (EQ5D index) or were maintained (EQVAS) from 6 to 12 months post intervention. Of note, these improvements were not found consistently among both instruments. The second investigation (Paper 2) demonstrated that improvements in HRQoL (EQ5D index and EQVAS) are maintained up to five years postsurgery compared to presurgery among participants that received the Roux-En-Y (RYGB) or Laparoscopic banding (LAGB) gastric bypass surgery. This is the first report to describe longitudinal changes in HRQoL past three years postsurgery using the EQ5D and EQVAS. Subsequently, results indicate that participants gained time in perfect health following bariatric surgery that increased over the five-year period. Lastly, the third investigation (Paper 3) demonstrated that the EQ5D index and SF6D index instruments measure HRQoL differently among the same population of bariatric surgery patients presurgery and 1-year post-surgery. Results indicated that the EQ5D index was more likely to have ceiling effects presurgery and post-surgery, which had an impact on the instrument's ability to measure change over time.

11.2 Strengths and Limitations

There were several strengths to this research which improves the validity and generalizability of the findings. The exploration of HRQoL changes using data from both lifestyle intervention and bariatric surgery, two of the most commonly used interventions to address overweight and obesity, was a significant strength. While this approach parallels guidelines for obesity care and morbidity risk reduction (first line intervention being lifestyle intervention followed by recommendation for bariatric surgery when indicated), it also explores novel approaches such as lifestyle intervention on sedentary behavior. This approach presents a more comprehensive assessment of how HRQoL changes in relation to care for obesity.

As an additional step toward a thorough exploration of HRQoL change as it relates to obesity care, this dissertation included a comparative evaluation of two HRQoL instruments with summary scores, EQ5D and SF6D. Findings from this investigation indicated that two similar measures do not produce the same results in measured HRQoL at the same assessment time point or with change from presurgery to 1-year postsurgery among bariatric surgery patients. These findings provide important information regarding instrument selection and meaningful approaches to address survey limitations.

While this dissertation has many strengths, it also has some limitations. One of them is that, there while both samples for GLB-MOVES and LABS-2 had diverse samples, there was not a large enough sample to evaluate differences by important factors, such as race, income, and gender. Additionally, for participants that received bariatric surgery, there were not enough participants who received the sleeve gastrectomy, the bariatric surgery procedure performed at the highest frequency, to stratify by, such as had been done for the RYGB and LAGB procedures. Lastly, within the GLB-MOVES study, only the EQ5D had been administered to participants and thus, the instrument comparison could not be performed for the lifestyle intervention study.

Because change in HRQoL was generally lower in the GLB-MOVES study compared to LABS-2, it is possible that comparisons between the two instruments would likely be different.

11.3 Public Health Findings

In totality the results of this dissertation provide significant contributions to public health. Overweight and obesity, caused by multiple factors, continue to present significant health burden (T2DM, dyslipidemia, hypertension, obstructive sleep apnea, cancer, steatohepatitis, gastroesophageal reflux, arthritis, polycystic ovary syndrome, and infertility [302, 303]) to those suffering from it and the health care system that supports them [19]. Overweight and obesity are even significant risk factors for severe illness and death with emerging illness such as COVID-19 [304]. Importantly, obesity affects approximately 40% of the US adult population and is continuing to rise.

Lifestyle intervention and bariatric surgery have been established as two of the most effective interventions for obesity that both reduce weight, improve morbidity risk for type 2 diabetes and cardiovascular disease, and improve HRQoL [50]. Of interest for any intervention is that they improve individual's lives in as many ways as possible. As the science on obesity care moves forward, it is important to show that this truth remains. This study shows, using novel approaches, sedentary behavior reduction in lifestyle intervention and evaluating long-term HRQoL changes in bariatric surgery, that HRQoL improvements are sustained after treatment for obesity. This means that individual's overall standard of life is improved after treatments used in this dissertation for obesity.

11.4 Future Directions

While this dissertation, filled many gaps in the literature and has moved the field of obesity care forward, it's important to build off of this research. Future directions for this research should include larger samples of diverse populations to examine how differences may be associated with changes in HRQoL after intervention on obesity, for example race. Also, research studies often include participants who are willing and able to make change which does not reflect the general US population. Examining HRQoL changes among people at varying readiness to change and with varying resources to make change, such as individuals who live in food deserts or who don't have health insurance (mainly for individuals otherwise eligible for bariatric surgery).

Additionally, it's important to evaluate how HRQoL as measured by the EQ5D and/or SF6D may change among individuals who receive sleeve gastrectomy compared to other more prevalent forms. It is also important to understand how different preference based HRQoL measures, such as the EQ5D compared to other measures, measure HRQoL changes with regard to lifestyle intervention. Moreover, other instruments should be compared, contrasted, and evaluated for ways to approximate areas where limitations are present. These efforts will present a more comprehensive assessment of how treatment for obesity can both lengthen individuals lives and improve their functioning.

Appendix A

Acronym	Definition
A1c	Hemoglobin A1c
ADA	American Diabetes Association
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CI	Confidence Interval
CVD	Cardiovascular Disease
DEXA	dual-energy X-ray absorptiometry
DPP	Diabetes Prevention Program
DSE	Diabetes Support and Education
EQ5D	Euroqol 5 Dimension
ERAS	Enhanced Recovery After Surgery
FPG	Fasting Plasma Glucose
GLB	Group Lifestyle Balance
GLB-MOD	Group Lifestyle Balance - MVPA intervention arm
GLB-SED	Group Lifestyle Balance - Sedentary behavior reduction arm
HRQoL	Health Related Quality of Life
HUI	Health Utilities Index
IGT	Impaired Glucose Test
ILI	Intensive Lifestyle Intervention
LABS-2	Longitudinal Assessment of Bariatric Surgery
LAGB	Laparoscopic adjustable gastric banding
LI	Lifestyle Intervention
MAHSCS	Multiattribute Health Status Classification System
MCS	Mental Component Score
MCS-12	Mental Component Score for the SF-12
MET	Metabolic Equivalent
MID	Minimally Important Difference
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
OHA	Oral Hypoglycemic agents
PCS	Physical Component Score
PCS-12	Physical Component Score for the SF-12
QWB	Quality of Well-Being Scale
RTC	Readiness to Change
RYGB	Roux-en-Y
SF36	Short Form 36
SF6D	Short Form 6 Dimension
SG	Standard Gamble
T2DM	Type 2 Diabetes Mellitus
TTO	Time Trade Off

VAS	Visual Analog Scale
WHO	World Health Organization

Appendix B

IMAGES

Image has been redacted for copyright purposes. See citation for image source.

Figure 4-1: EQ5D index scores by health states and country. Source: www.euroqol.org

Bibliography

1. Hales, C.M., et al., *Prevalence of Obesity Among Adults and Youth: United States, 2015-2016.* NCHS Data Brief, 2017(288): p. 1-8.
2. Fryar, C.D., M.D. Carroll, and C.L. Ogden, *Prevalence of overweight, obesity, and extreme obesity among adults aged 20 and over: United States, 1960 - 1962 through 2011 - 2014.* 2016, National Center for Health Statistics Data, Health E-Stats.
3. Trust for America's Health and the Robert Wood Johnson Foundation, *Obesity rates and trends overview*. 2004-2018.
4. Haslam, D.W. and W.P. James, *Obesity.* Lancet, 2005. **366**(9492): p. 1197-209.
5. WHO, *Physical Status: The use and interpretation of anthropometry: Report of a World Health Organization (WHO) Expert Committee.* 1995, World Health Organization.
6. Jarolimova, J., J. Tagoni, and T.A. Stern, *Obesity: its epidemiology, comorbidities, and management.* Prim Care Companion CNS Disord, 2013. **15**(5).
7. Gonzalez, M.C., M. Correia, and S.B. Heymsfield, *A requiem for BMI in the clinical setting.* Curr Opin Clin Nutr Metab Care, 2017. **20**(5): p. 314-321.
8. Centers for Disease Control and Prevention. *Body mass index: Considerations for practitioners*. Accessed 3/27/2018]; Available from: https://www.cdc.gov/obesity/downloads/bmiforpactitioners.pdf.
9. Jackson, A.S., et al., *The effect of sex, age and race on estimating percentage body fat from body mass index: The Heritage Family Study.* Int J Obes Relat Metab Disord, 2002. **26**(6): p. 789-96.
10. James, W.P., *What are the health risks? The medical consequences of obesity and its health risks.* Exp Clin Endocrinol Diabetes, 1998. **106 Suppl 2**: p. 1-6.
11. Canoy, D., *Distribution of body fat and risk of coronary heart disease in men and women.* Curr Opin Cardiol, 2008. **23**(6): p. 591-8.
12. Folsom, A.R., et al., *Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study.* Arch Intern Med, 2000. **160**(14): p. 2117-28.
13. Vazquez, G., et al., *Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis.* Epidemiol Rev, 2007. **29**: p. 115-28.
14. WHO, *Waist Circumference and Waist-Hip Ratio Report of a WHO Expert Consultation*. 2008: Geneva, Switzerland.
15. Humphreys, S., *The unethical use of BMI in contemporary general practice.* Br J Gen Pract, 2010. **60**(578): p. 696-7.
16. Misra, A., *Ethnic-Specific Criteria for Classification of Body Mass Index: A Perspective for Asian Indians and American Diabetes Association Position Statement.* Diabetes Technol Ther, 2015. **17**(9): p. 667-71.
17. W. H. O. Expert Consultation, *Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.* Lancet, 2004. **363**(9403): p. 157-63.
18. Gallagher, D., et al., *How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups?* Am J Epidemiol, 1996. **143**(3): p. 228-39.

19. Egger, G. and J. Dixon, *Beyond obesity and lifestyle: a review of 21st century chronic disease determinants.* Biomed Res Int, 2014. **2014**: p. 731685.
20. Centers for Disease Control and Prevention, *Adult obesity causes & consequences*. 2017.
21. Williams, E.P., et al., *Overweight and Obesity: Prevalence, Consequences, and Causes of a Growing Public Health Problem.* Curr Obes Rep, 2015. **4**(3): p. 363-70.
22. Chang, L. and J. Neu, *Early factors leading to later obesity: interactions of the microbiome, epigenome, and nutrition.* Curr Probl Pediatr Adolesc Health Care, 2015. **45**(5): p. 134-42.
23. Finkelstein, E.A., C.J. Ruhm, and K.M. Kosa, *Economic causes and consequences of obesity.* Annu Rev Public Health, 2005. **26**: p. 239-57.
24. Arroyo-Johnson, C. and K.D. Mincey, *Obesity Epidemiology Worldwide.* Gastroenterol Clin North Am, 2016. **45**(4): p. 571-579.
25. Ogden, C.L., et al., *Prevalence of Obesity Among Adults and Youth: United States, 2011-2014.* NCHS Data Brief, 2015(219): p. 1-8.
26. Chen, G., et al., *Genome-wide analysis identifies an african-specific variant in SEMA4D associated with body mass index.* Obesity (Silver Spring), 2017. **25**(4): p. 794-800.
27. Lincoln, K.D., C.M. Abdou, and D. Lloyd, *Race and socioeconomic differences in obesity and depression among Black and non-Hispanic White Americans.* J Health Care Poor Underserved, 2014. **25**(1): p. 257-75.
28. Quesenberry, C.P., Jr., B. Caan, and A. Jacobson, *Obesity, health services use, and health care costs among members of a health maintenance organization.* Arch Intern Med, 1998. **158**(5): p. 466-72.
29. Thompson, D., et al., *Body mass index and future healthcare costs: a retrospective cohort study.* Obes Res, 2001. **9**(3): p. 210-8.
30. Anandacoomarasamy, A., et al., *The impact of obesity on the musculoskeletal system.* Int J Obes (Lond), 2008. **32**(2): p. 211-22.
31. Ferrannini, E., *Definition of intervention points in prediabetes.* Lancet Diabetes Endocrinol, 2014. **2**(8): p. 667-75.
32. Griffin, M.E., et al., *Free fatty acid-induced insulin resistance is associated with activation of protein kinase C theta and alterations in the insulin signaling cascade.* Diabetes, 1999. **48**(6): p. 1270-4.
33. Yu, C., et al., *Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle.* J Biol Chem, 2002. **277**(52): p. 50230-6.
34. Akram, M. and A. Hamid, *Mini review on fructose metabolism.* Obes Res Clin Pract, 2013. **7**(2): p. e89-e94.
35. Stanhope, K.L., et al., *Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans.* J Clin Invest, 2009. **119**(5): p. 1322-34.
36. Zuniga, Y.L., et al., *Rice and noodle consumption is associated with insulin resistance and hyperglycaemia in an Asian population.* Br J Nutr, 2014. **111**(6): p. 1118-28.
37. Hawley, J.A., *Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance.* Diabetes Metab Res Rev, 2004. **20**(5): p. 383-93.
38. Hawley, J.A. and S.J. Lessard, *Exercise training-induced improvements in insulin action.* Acta Physiol (Oxf), 2008. **192**(1): p. 127-35.
39. Tchernof, A. and J.P. Despres, *Pathophysiology of human visceral obesity: an update.* Physiol Rev, 2013. **93**(1): p. 359-404.

40. Weir, G.C. and S. Bonner-Weir, *Five stages of evolving beta-cell dysfunction during progression to diabetes.* Diabetes, 2004. **53 Suppl 3**: p. S16-21.
41. American Diabetes Association, *Diagnosis and classification of diabetes mellitus.* Diabetes Care, 2010. **33 Suppl 1**: p. S62-9.
42. Schorr, A.B., *Complications of type 2 diabetes mellitus: a brief overview.* J Am Osteopath Assoc, 1999. **99**(12 Suppl): p. S10-4.
43. Pi-Sunyer, X., *The medical risks of obesity.* Postgrad Med, 2009. **121**(6): p. 21-33.
44. Xu, J., et al., *Deaths: Final Data for 2016.* Natl Vital Stat Rep, 2018. **67**(5): p. 1-76.
45. American Diabetes Association. *Statistics about diabetes*. 1995-2017; Available from: http://www.diabetes.org/diabetes-basics/statistics/?referrer=https://www.google.com/.
46. Stokes, A. and S.H. Preston, *Deaths Attributable to Diabetes in the United States: Comparison of Data Sources and Estimation Approaches.* PLoS One, 2017. **12**(1): p. e0170219.
47. Finkelstein, E.A., et al., *Obesity and severe obesity forecasts through 2030.* Am J Prev Med, 2012. **42**(6): p. 563-70.
48. Eckel, R.H., et al., *Obesity and type 2 diabetes: what can be unified and what needs to be individualized?* J Clin Endocrinol Metab, 2011. **96**(6): p. 1654-63.
49. Dornhorst, A. and P.K. Merrin, *Primary, secondary and tertiary prevention of non-insulin-dependent diabetes.* Postgrad Med J, 1994. **70**(826): p. 529-35.
50. Jensen, M.D., et al., *2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society.* Circulation, 2014. **129**(25 Suppl 2): p. S102-38.
51. Mitchell, N.S., et al., *Obesity: overview of an epidemic.* Psychiatr Clin North Am, 2011. **34**(4): p. 717-32.
52. Tuomilehto, J., P. Schwarz, and J. Lindstrom, *Long-term benefits from lifestyle interventions for type 2 diabetes prevention: time to expand the efforts.* Diabetes Care, 2011. **34 Suppl 2**: p. S210-4.
53. Chirinos, D.A., et al., *Lifestyle modification and weight reduction among low-income patients with the metabolic syndrome: the CHARMS randomized controlled trial.* J Behav Med, 2016. **39**(3): p. 483-92.
54. Diabetes Prevention Program Research, G., *The Diabetes Prevention Program (DPP): description of lifestyle intervention.* Diabetes Care, 2002. **25**(12): p. 2165-71.
55. Venditti, E.M. and M.K. Kramer, *Necessary components for lifestyle modification interventions to reduce diabetes risk.* Curr Diab Rep, 2012. **12**(2): p. 138-46.
56. Galani, C. and H. Schneider, *Prevention and treatment of obesity with lifestyle interventions: review and meta-analysis.* Int J Public Health, 2007. **52**(6): p. 348-59.
57. Knowler, W.C., et al., *Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin.* N Engl J Med, 2002. **346**(6): p. 393-403.
58. Gusi, N., et al., *Cost-utility of a walking programme for moderately depressed, obese, or overweight elderly women in primary care: a randomised controlled trial.* BMC Public Health, 2008. **8**: p. 231.
59. Qiu, S., et al., *Impact of walking on glycemic control and other cardiovascular risk factors in type 2 diabetes: a meta-analysis.* PLoS One, 2014. **9**(10): p. e109767.
60. Allen, P., et al., *Impact of periodic follow-up testing among urban American Indian women with impaired fasting glucose.* Prev Chronic Dis, 2008. **5**(3): p. A76.

61. Davis-Smith, Y.M., et al., *Implementing a diabetes prevention program in a rural African-American church.* J Natl Med Assoc, 2007. **99**(4): p. 440-6.
62. Jiang, L., et al., *Translating the Diabetes Prevention Program into American Indian and Alaska Native communities: results from the Special Diabetes Program for Indians Diabetes Prevention demonstration project.* Diabetes Care, 2013. **36**(7): p. 2027-34.
63. Mann, D.M., J. Palmisano, and J.J. Lin, *A pilot randomized trial of technology-assisted goal setting to improve physical activity among primary care patients with prediabetes.* Prev Med Rep, 2016. **4**: p. 107-12.
64. O'Brien, M.J., et al., *The feasibility, acceptability, and preliminary effectiveness of a Promotora-Led Diabetes Prevention Program (PL-DPP) in Latinas: a pilot study.* Diabetes Educ, 2015. **41**(4): p. 485-94.
65. Parikh, P., et al., *Results of a pilot diabetes prevention intervention in East Harlem, New York City: Project HEED.* Am J Public Health, 2010. **100 Suppl 1**: p. S232-9.
66. Ruggiero, L., S. Oros, and Y.K. Choi, *Community-based translation of the diabetes prevention program's lifestyle intervention in an underserved Latino population.* Diabetes Educ, 2011. **37**(4): p. 564-72.
67. Van Name, M.A., et al., *Effective Translation of an Intensive Lifestyle Intervention for Hispanic Women With Prediabetes in a Community Health Center Setting.* Diabetes Care, 2016. **39**(4): p. 525-31.
68. Yeh, M.C., et al., *Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City.* Diabet Med, 2016. **33**(4): p. 547-51.
69. Eriksson, K.F. and F. Lindgarde, *Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study.* Diabetologia, 1991. **34**(12): p. 891-8.
70. Li, G., et al., *The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study.* Lancet, 2008. **371**(9626): p. 1783-9.
71. Eriksson, J., et al., *Prevention of Type II diabetes in subjects with impaired glucose tolerance: the Diabetes Prevention Study (DPS) in Finland. Study design and 1-year interim report on the feasibility of the lifestyle intervention programme.* Diabetologia, 1999. **42**(7): p. 793-801.
72. Diabetes Prevention Program Research, G., et al., *10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study.* Lancet, 2009. **374**(9702): p. 1677-86.
73. Seidel, M.C., et al., *Translating the Diabetes Prevention Program into an urban medically underserved community: a nonrandomized prospective intervention study.* Diabetes Care, 2008. **31**(4): p. 684-9.
74. Kramer, M.K., et al., *Translating the Diabetes Prevention Program: a comprehensive model for prevention training and program delivery.* Am J Prev Med, 2009. **37**(6): p. 505-11.
75. Rosas, L.G., et al., *Evaluation of a culturally-adapted lifestyle intervention to treat elevated cardiometabolic risk of Latino adults in primary care (Vida Sana): A randomized controlled trial.* Contemp Clin Trials, 2016. **48**: p. 30-40.
76. Driver, S., M. Reynolds, and K. Kramer, *Modifying an evidence-based lifestyle programme for individuals with traumatic brain injury.* Brain Inj, 2017. **31**(12): p. 1612-1616.

77. Driver, S., et al., *Impact of a Community-Based Healthy Lifestyle Program on Individuals With Traumatic Brain Injury.* J Head Trauma Rehabil, 2018.
78. O'Hara, K., A. Stefancic, and L.J. Cabassa, *Developing a peer-based healthy lifestyle program for people with serious mental illness in supportive housing.* Transl Behav Med, 2017. **7**(4): p. 793-803.
79. Williams, L.B., et al., *Design of a cluster-randomized controlled trial of a diabetes prevention program within African-American churches: The Fit Body and Soul study.* Contemp Clin Trials, 2013. **34**(2): p. 336-47.
80. Whittemore, R., et al., *Translating the diabetes prevention program to primary care: a pilot study.* Nurs Res, 2009. **58**(1): p. 2-12.
81. National Institute of Diabetes and Digestive and Kidney Disease. *Look AHEAD: Action for health in Diabetes*. December 20, 2018]; Available from: https://repository.niddk.nih.gov/studies/look-ahead/.
82. Look Ahead Research Group, *Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study.* Obesity (Silver Spring), 2014. **22**(1): p. 5-13.
83. Gregg, E.W. and R. Wing, *Looking again at the Look AHEAD study.* Lancet Diabetes Endocrinol, 2017. **5**(10): p. 763-764.
84. Pi-Sunyer, X., *The Look AHEAD Trial: A Review and Discussion Of Its Outcomes.* Curr Nutr Rep, 2014. **3**(4): p. 387-391.
85. Annuzzi, G., et al., *The results of Look AHEAD do not row against the implementation of lifestyle changes in patients with type 2 diabetes.* Nutr Metab Cardiovasc Dis, 2014. **24**(1): p. 4-9.
86. Allbasic, E., E. Ramic, and A. Allc, *Prevention of diabetes in family medicine.* Materia Socio Medica, 2013. **25**(2): p. 80-82.
87. American Diabetes Association, *5. Glycemic Targets.* Diabetes Care, 2016. **39 Suppl 1**: p. S39-46.
88. Kremen, A.J., J.H. Linner, and C.H. Nelson, *An experimental evaluation of the nutritional importance of proximal and distal small intestine.* Ann Surg, 1954. **140**(3): p. 439-48.
89. American Society for Metabolic and Bariatric Surgery. *Story of Obesity Surgery*. 2004; Available from: https://asmbs.org/resources/story-of-obesity-surgery.
90. Jorgensen, S., M. Olesen, and E. Gudman-Hoyer, *A review of 20 years of jejunoileal bypass.* Scand J Gastroenterol, 1997. **32**(4): p. 334-9.
91. Griffen, W.O., Jr., V.L. Young, and C.C. Stevenson, *A prospective comparison of gastric and jejunoileal bypass procedures for morbid obesity.* Ann Surg, 1977. **186**(4): p. 500-9.
92. Alden, J.F., *Gastric and jejunoileal bypass. A comparison in the treatment of morbid obesity.* Arch Surg, 1977. **112**(7): p. 799-806.
93. Halverson, J.D., et al., *Jejunoileal bypass. Late metabolic sequelae and weight gain.* Am J Surg, 1980. **140**(3): p. 347-50.
94. Lowell, J.A., et al., *Liver transplantation after jejunoileal bypass for morbid obesity.* J Am Coll Surg, 1997. **185**(2): p. 123-7.
95. Courcoulas, A.P., et al., *Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity.* JAMA, 2013. **310**(22): p. 2416-25.
96. Courcoulas, A.P., et al., *Long-term outcomes of bariatric surgery: a National Institutes of Health symposium.* JAMA Surg, 2014. **149**(12): p. 1323-9.

97. Courcoulas, A.P., et al., *Three-Year Outcomes of Bariatric Surgery vs Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment: A Randomized Clinical Trial.* JAMA Surg, 2015. **150**(10): p. 931-40.
98. Longitudinal Assessment of Bariatric Surgery, C., et al., *Perioperative safety in the longitudinal assessment of bariatric surgery.* N Engl J Med, 2009. **361**(5): p. 445-54.
99. Cohen, R., et al., *Ghrelin levels and sleeve gastrectomy in super-super-obesity.* Obes Surg, 2005. **15**(10): p. 1501-2.
100. Langer, F.B., et al., *Sleeve gastrectomy and gastric banding: effects on plasma ghrelin levels.* Obes Surg, 2005. **15**(7): p. 1024-9.
101. The Regents of the University of California. *Laparoscopic Gastric Bypass*. 2016; Available from: http://bariatric.surgery.ucsf.edu/conditions--procedures/laparoscopic-gastric-bypass.aspx.
102. Karamanakos, S.N., et al., *Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study.* Ann Surg, 2008. **247**(3): p. 401-7.
103. Buchwald, H., et al., *Bariatric surgery: a systematic review and meta-analysis.* JAMA, 2004. **292**(14): p. 1724-37.
104. Rezvani, M., et al., *Is laparoscopic single-stage biliopancreatic diversion with duodenal switch safe in super morbidly obese patients?* Surgery for Obesity and Related Diseases, 2014. **10**(3): p. 427-430.
105. Werling, M., et al., *Biliopancreatic Diversion is associated with greater increases in energy expenditure than Roux-en-Y Gastric Bypass.* PloS one, 2018. **13**(4): p. e0194538.
106. Chang, S.H., et al., *The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012.* JAMA Surg, 2014. **149**(3): p. 275-87.
107. Franco, J.V., et al., *A review of studies comparing three laparoscopic procedures in bariatric surgery: sleeve gastrectomy, Roux-en-Y gastric bypass and adjustable gastric banding.* Obes Surg, 2011. **21**(9): p. 1458-68.
108. American Society for Metabolic and Bariatric Surgery. *Estimate of bariatric surgery numbers, 2011-2017*. 2018 [cited 2018 September 12, 2018]; Available from: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers.
109. Hoyuela, C., *Five-year outcomes of laparoscopic sleeve gastrectomy as a primary procedure for morbid obesity: A prospective study.* World J Gastrointest Surg, 2017. **9**(4): p. 109-117.
110. Bohdjalian, A., et al., *Sleeve gastrectomy as sole and definitive bariatric procedure: 5-year results for weight loss and ghrelin.* Obes Surg, 2010. **20**(5): p. 535-40.
111. Himpens, J., J. Dobbeleir, and G. Peeters, *Long-term results of laparoscopic sleeve gastrectomy for obesity.* Ann Surg, 2010. **252**(2): p. 319-24.
112. D'Hondt, M., et al., *Laparoscopic sleeve gastrectomy as a single-stage procedure for the treatment of morbid obesity and the resulting quality of life, resolution of comorbidities, food tolerance, and 6-year weight loss.* Surg Endosc, 2011. **25**(8): p. 2498-504.
113. Braghetto, I., et al., *Is laparoscopic sleeve gastrectomy an acceptable primary bariatric procedure in obese patients? Early and 5-year postoperative results.* Surg Laparosc Endosc Percutan Tech, 2012. **22**(6): p. 479-86.
114. Sarela, A.I., et al., *Long-term follow-up after laparoscopic sleeve gastrectomy: 8-9-year results.* Surg Obes Relat Dis, 2012. **8**(6): p. 679-84.

115. Rawlins, L., et al., *Sleeve gastrectomy: 5-year outcomes of a single institution.* Surg Obes Relat Dis, 2013. **9**(1): p. 21-5.
116. Sieber, P., et al., *Five-year results of laparoscopic sleeve gastrectomy.* Surg Obes Relat Dis, 2014. **10**(2): p. 243-9.
117. Boza, C., et al., *Long-term outcomes of laparoscopic sleeve gastrectomy as a primary bariatric procedure.* Surg Obes Relat Dis, 2014. **10**(6): p. 1129-33.
118. Liu, S.Y., et al., *Long-term Results on Weight Loss and Diabetes Remission after Laparoscopic Sleeve Gastrectomy for A Morbidly Obese Chinese Population.* Obes Surg, 2015. **25**(10): p. 1901-8.
119. Lemanu, D.P., et al., *Five-year results after laparoscopic sleeve gastrectomy: a prospective study.* Surg Obes Relat Dis, 2015. **11**(3): p. 518-24.
120. Pok, E.H., et al., *Laparoscopic sleeve gastrectomy in Asia: Long term outcome and revisional surgery.* Asian J Surg, 2016. **39**(1): p. 21-8.
121. Alexandrou, A., et al., *Laparoscopic sleeve gastrectomy for morbid obesity: 5-year results.* Am J Surg, 2015. **209**(2): p. 230-4.
122. Perrone, F., et al., *Gender Influence on Long-Term Weight Loss and Comorbidities After Laparoscopic Sleeve Gastrectomy and Roux-en-Y Gastric Bypass: a Prospective Study With a 5-Year Follow-up.* Obes Surg, 2016. **26**(2): p. 276-81.
123. Long, S.D., et al., *Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes. A longitudinal interventional study.* Diabetes Care, 1994. **17**(5): p. 372-5.
124. Melnyk, M., et al., *Enhanced recovery after surgery (ERAS) protocols: Time to change practice?* Can Urol Assoc J, 2011. **5**(5): p. 342-8.
125. Malczak, P., et al., *Enhanced Recovery after Bariatric Surgery: Systematic Review and Meta-Analysis.* Obes Surg, 2017. **27**(1): p. 226-235.
126. Wilmore, D.W. and H. Kehlet, *Management of patients in fast track surgery.* BMJ, 2001. **322**(7284): p. 473-6.
127. National Institute of Diabetes and Digestive and Kidney Disease. *Longitudinal assessment of bariatric surgery (LABS)*. 2020 [cited 2020 December 9, 2020]; Available from: https://repository.niddk.nih.gov/studies/labs/.
128. Purnell, J.Q., et al., *Type 2 Diabetes Remission Rates After Laparoscopic Gastric Bypass and Gastric Banding: Results of the Longitudinal Assessment of Bariatric Surgery Study.* Diabetes Care, 2016. **39**(7): p. 1101-7.
129. Belle, S.H., et al., *Safety and efficacy of bariatric surgery: Longitudinal Assessment of Bariatric Surgery.* Surg Obes Relat Dis, 2007. **3**(2): p. 116-26.
130. Belle, S.H., et al., *Baseline characteristics of participants in the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study.* Surg Obes Relat Dis, 2013. **9**(6): p. 926-35.
131. Mitchell, J.E., et al., *Course of depressive symptoms and treatment in the longitudinal assessment of bariatric surgery (LABS-2) study.* Obesity (Silver Spring), 2014. **22**(8): p. 1799-806.
132. Courcoulas, A.P., et al., *Preoperative factors and 3-year weight change in the Longitudinal Assessment of Bariatric Surgery (LABS) consortium.* Surg Obes Relat Dis, 2015. **11**(5): p. 1109-18.
133. Courcoulas, A.P., et al., *Seven-Year Weight Trajectories and Health Outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) Study*. JAMA Surg, 2018. **153**(5): p. 427-434.

134. Sarwer, D.B., et al., *Sexual functioning and sex hormones in persons with extreme obesity and seeking surgical and nonsurgical weight loss.* Surg Obes Relat Dis, 2013. **9**(6): p. 997-1007.
135. King, W.C., et al., *Change in Pain and Physical Function Following Bariatric Surgery for Severe Obesity.* JAMA, 2016. **315**(13): p. 1362-71.
136. National Heart Lung and Blood Institute, *The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. 2000.
137. Ceccarini, M., et al., *Assessing motivation and readiness to change for weight management and control: an in-depth evaluation of three sets of instruments.* Front Psychol, 2015. **6**: p. 511.
138. Curry, S.A., *Obesity Epidemic: Pharmaceutical Weight Loss.* R I Med J (2013), 2017. **100**(2): p. 18-20.
139. Guy-Grand, B., et al., *International trial of long-term dexfenfluramine in obesity.* Lancet, 1989. **2**(8672): p. 1142-5.
140. Bray, G.A., et al., *A double-blind randomized placebo-controlled trial of sibutramine.* Obes Res, 1996. **4**(3): p. 263-70.
141. American Diabetes Association, *6. Obesity Management for the Treatment of Type 2 Diabetes.* Diabetes Care, 2016. **39 Suppl 1**: p. S47-51.
142. Luna, B. and M.N. Feinglos, *Oral agents in the management of type 2 diabetes mellitus.* Am Fam Physician, 2001. **63**(9): p. 1747-56.
143. American Diabetes Association, *2. Classification and Diagnosis of Diabetes.* Diabetes Care, 2016. **39 Suppl 1**: p. S13-22.
144. Quianzon, C.C. and I.E. Cheikh, *History of current non-insulin medications for diabetes mellitus.* J Community Hosp Intern Med Perspect, 2012. **2**(3).
145. Viollet, B., et al., *Cellular and molecular mechanisms of metformin: an overview.* Clin Sci (Lond), 2012. **122**(6): p. 253-70.
146. Black, C., et al., *Meglitinide analogues for type 2 diabetes mellitus.* Cochrane Database Syst Rev, 2007(2): p. CD004654.
147. Dicker, D., *DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors.* Diabetes Care, 2011. **34 Suppl 2**: p. S276-8.
148. Wallia, A. and M.E. Molitch, *Insulin therapy for type 2 diabetes mellitus.* JAMA, 2014. **311**(22): p. 2315-25.
149. DeWitt, D.E. and I.B. Hirsch, *Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review.* JAMA, 2003. **289**(17): p. 2254-64.
150. Russell-Jones, D. and R. Khan, *Insulin-associated weight gain in diabetes--causes, effects and coping strategies.* Diabetes Obes Metab, 2007. **9**(6): p. 799-812.
151. Inzucchi, S.E., *Oral antihyperglycemic therapy for type 2 diabetes: scientific review.* JAMA, 2002. **287**(3): p. 360-72.
152. Mechanick, J.I., et al., *Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery.* Endocr Pract, 2013. **19**(2): p. 337-72.
153. Armstrong, D. and D. Caldwell, *Origins of the concept of quality of life in health care: A rhetorical solution to a political problem.* Social Theory & Health, 2004. **2**: p. 361-371.

154. Stanton, A.L., T.A. Revenson, and H. Tennen, *Health psychology: psychological adjustment to chronic disease.* Annu Rev Psychol, 2007. **58**: p. 565-92.
155. Coons, S.J., et al., *A comparative review of generic quality-of-life instruments.* Pharmacoeconomics, 2000. **17**(1): p. 13-35.
156. Zamanzadeh, V., et al., *Design and Implementation Content Validity Study: Development of an instrument for measuring Patient-Centered Communication.* J Caring Sci, 2015. **4**(2): p. 165-78.
157. Hays, R.D., R. Anderson, and D. Revicki, *Psychometric considerations in evaluating health-related quality of life measures.* Qual Life Res, 1993. **2**(6): p. 441-9.
158. Schunemann, H.J. and G.H. Guyatt, *Commentary--goodbye M(C)ID! Hello MID, where do you come from?* Health Serv Res, 2005. **40**(2): p. 593-7.
159. Guyatt, G.H., et al., *Methods to explain the clinical significance of health status measures.* Mayo Clin Proc, 2002. **77**(4): p. 371-83.
160. Hays, R.D., S.S. Farivar, and H. Liu, *Approaches and recommendations for estimating minimally important differences for health-related quality of life measures.* COPD, 2005. **2**(1): p. 63-7.
161. Wyrwich, K.W., et al., *Estimating clinically significant differences in quality of life outcomes.* Qual Life Res, 2005. **14**(2): p. 285-95.
162. Revicki, D., et al., *Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes.* J Clin Epidemiol, 2008. **61**(2): p. 102-9.
163. King, M.T., *A point of minimal important difference (MID): a critique of terminology and methods.* Expert Rev Pharmacoecon Outcomes Res, 2011. **11**(2): p. 171-84.
164. Luo, N., J. Johnson, and S.J. Coons, *Using instrument-defined health state transitions to estimate minimally important differences for four preference-based health-related quality of life instruments.* Med Care, 2010. **48**(4): p. 365-71.
165. Ware, J., et al., *SF-36 Health Survey: Manual and Interpretation Guide*. 1993, The Health Institute, New England Medical Center: Boston.
166. Farivar, S.S., W.E. Cunningham, and R.D. Hays, *Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V.I.* Health Qual Life Outcomes, 2007. **5**: p. 54.
167. Maglinte, G.A., R.D. Hays, and R.M. Kaplan, *US general population norms for telephone administration of the SF-36v2.* J Clin Epidemiol, 2012. **65**(5): p. 497-502.
168. Sinnott, P., V. Joyce, and P. Barnett, *Preference Measurement in Economic Analysis. Guidebook*. 2007, Menlo Park CA: VA Palo Alto, Health Economics Resource Center.
169. Gold, M., et al., *Cost-Effectiveness in health and medicine*. 1996, New York: Oxford University Press.
170. Sullivan, P.W., W.F. Lawrence, and V. Ghushchyan, *A national catalog of preference-based scores for chronic conditions in the United States.* Med Care, 2005. **43**(7): p. 736-49.
171. Shaw, J.W., J.A. Johnson, and S.J. Coons, *US valuation of the EQ-5D health states: development and testing of the D1 valuation model.* Med Care, 2005. **43**(3): p. 203-20.
172. Brazier, J., *Current state of the art in preference-based measures of health and avenues for further research. The University of Sheffield School of Health and Related Research, Health Economics and Decision Science Discussion Paper Series.* 2005, Sheffield, University of Sheffield.

173. Drummond, M., et al., *Methods for the economic evaluation of health care programmes*. 2005, Oxford: Oxford University Press.
174. Kaplan, R.M. and J.P. Andersen, *The general health policy model: An integrated approach*, in *Quality of life and pharmacoeconomics in clinical trials. 2nd edition*, B. Spilker, Editor. 1996, Lippincott-Raven: Philadephia (PA). p. 309-22.
175. Fanshel, S. and J.W. Bush, *A health status index and its application to health services outcomes.* Operations Research, 1970. **18**: p. 1021-66.
176. Brazier, J., et al., *Deriving a preference-based single index from the UK SF-36 Health Survey*. J Clin Epidemiol, 1998. **51**(11): p. 1115-28.
177. Brazier, J., J. Roberts, and M. Deverill, *The estimation of a preference-based measure of health from the SF-36.* J Health Econ, 2002. **21**(2): p. 271-92.
178. Prieto, L. and J.A. Sacristan, *Problems and solutions in calculating quality-adjusted life years (QALYs).* Health Qual Life Outcomes, 2003. **1**: p. 80.
179. Huang, I.C., et al., *Addressing ceiling effects in health status measures: a comparison of techniques applied to measures for people with HIV disease.* Health Serv Res, 2008. **43**(1 Pt 1): p. 327-39.
180. Feeny, D., et al., *A primer for systematic reviewers on the measurement of functional status and health-related quality of life in older adults.* 2013, Agency for Healthcare Research and Quality: Rockville, MD.
181. Bharmal, M. and J. Thomas, 3rd, *Comparing the EQ-5D and the SF-6D descriptive systems to assess their ceiling effects in the US general population.* Value Health, 2006. **9**(4): p. 262-71.
182. Brazier, J., et al., *A comparison of the EQ-5D and SF-6D across seven patient groups.* Health Econ, 2004. **13**(9): p. 873-84.
183. Jia, H. and E.I. Lubetkin, *Estimating EuroQol EQ-5D scores from Population Healthy Days data.* Med Decis Making, 2008. **28**(4): p. 491-9.
184. Johnsen, L.G., et al., *Comparison of the SF6D, the EQ5D, and the oswestry disability index in patients with chronic low back pain and degenerative disc disease.* BMC Musculoskelet Disord, 2013. **14**: p. 148.
185. Walters, S.J. and J.E. Brazier, *Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D.* Qual Life Res, 2005. **14**(6): p. 1523-32.
186. Tsuchiya, A., J. Brazier, and J. Roberts, *Comparison of valuation methods used to generate the EQ-5D and the SF-6D value sets.* J Health Econ, 2006. **25**(2): p. 334-46.
187. Craig, B.M., et al., *US valuation of the SF-6D.* Med Decis Making, 2013. **33**(6): p. 793-803.
188. Petrou, S. and C. Hockley, *An investigation into the empirical validity of the EQ-5D and SF-6D based on hypothetical preferences in a general population.* Health Econ, 2005. **14**(11): p. 1169-89.
189. Tayyem, R., et al., *Analysis of health-related quality-of-life instruments measuring the impact of bariatric surgery: systematic review of the instruments used and their content validity.* Patient, 2011. **4**(2): p. 73-87.
190. Kolotkin, R.L. and R.D. Crosby, *Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-lite) in a community sample.* Qual Life Res, 2002. **11**(2): p. 157-71.

191. Karlsson, J., et al., *Psychosocial functioning in the obese before and after weight reduction: construct validity and responsiveness of the Obesity-related Problems scale.* Int J Obes Relat Metab Disord, 2003. **27**(5): p. 617-30.
192. Mathias, S.D., et al., *Assessing health-related quality-of-life and health state preference in persons with obesity: a validation study.* Qual Life Res, 1997. **6**(4): p. 311-22.
193. Kolotkin, R.L., K. Meter, and G.R. Williams, *Quality of life and obesity.* Obes Rev, 2001. **2**(4): p. 219-29.
194. Doll, H.A., S.E. Petersen, and S.L. Stewart-Brown, *Obesity and physical and emotional well-being: associations between body mass index, chronic illness, and the physical and mental components of the SF-36 questionnaire.* Obes Res, 2000. **8**(2): p. 160-70.
195. Sullivan, M., et al., *Swedish obese subjects (SOS)--an intervention study of obesity. Baseline evaluation of health and psychosocial functioning in the first 1743 subjects examined.* Int J Obes Relat Metab Disord, 1993. **17**(9): p. 503-12.
196. Goldney, R.D., et al., *Diabetes, depression, and quality of life: a population study.* Diabetes Care, 2004. **27**(5): p. 1066-70.
197. Manuel, D.G. and S.E. Schultz, *Health-related quality of life and health-adjusted life expectancy of people with diabetes in Ontario, Canada, 1996-1997.* Diabetes Care, 2004. **27**(2): p. 407-14.
198. Jia, H. and E.I. Lubetkin, *The impact of obesity on health-related quality-of-life in the general adult US population.* J Public Health (Oxf), 2005. **27**(2): p. 156-64.
199. Mokdad, A.H., et al., *Actual causes of death in the United States, 2000.* JAMA, 2004. **291**(10): p. 1238-45.
200. Balboa-Castillo, T., et al., *Longitudinal association of physical activity and sedentary behavior during leisure time with health-related quality of life in community-dwelling older adults.* Health Qual Life Outcomes, 2011. **9**: p. 47.
201. Andersen, J.R., et al., *Health-related quality of life after bariatric surgery: a systematic review of prospective long-term studies.* Surg Obes Relat Dis, 2015. **11**(2): p. 466-73.
202. Sintonen, H., *The 15D instrument of health-related quality of life: properties and applications.* Ann Med, 2001. **33**: p. 328-36.
203. Davies, A., et al., *Adult health status and patient satisfaction measures used in RAND's health insurance experiment*. 1998: Santa Monica.
204. Hunt, S., J. McEwen, and S.P. McKenna, *Measuring health status: a new tool for clinicians and epidemiologists.* J R Coll Gen Pract, 1985. **35**: p. 185-8.
205. Luscombe, F.A., *Health-related quality of life measurement in type 2 diabetes.* Value Health, 2000. **3 Suppl 1**: p. 15-28.
206. Fontaine, K.R. and I. Barofsky, *Obesity and health-related quality of life.* Obes Rev, 2001. **2**(3): p. 173-82.
207. Ford, E.S., et al., *Self-reported body mass index and health-related quality of life: findings from the Behavioral Risk Factor Surveillance System.* Obes Res, 2001. **9**(1): p. 21-31.
208. Sturm, R. and K.B. Wells, *Does obesity contribute as much to morbidity as poverty or smoking?* Public Health, 2001. **115**(3): p. 229-35.
209. Larsson, U., J. Karlsson, and M. Sullivan, *Impact of overweight and obesity on health-related quality of life--a Swedish population study.* Int J Obes Relat Metab Disord, 2002. **26**(3): p. 417-24.

210. Moriarty, D.G., M.M. Zack, and R. Kobau, *The Centers for Disease Control and Prevention's Healthy Days Measures - population tracking of perceived physical and mental health over time.* Health Qual Life Outcomes, 2003. **1**: p. 37.
211. Franks, P., J. Hanmer, and D.G. Fryback, *Relative disutilities of 47 risk factors and conditions assessed with seven preference-based health status measures in a national U.S. sample: toward consistency in cost-effectiveness analyses.* Med Care, 2006. **44**(5): p. 478-85.
212. Florez, H., et al., *Impact of lifestyle intervention and metformin on health-related quality of life: the diabetes prevention program randomized trial.* J Gen Intern Med, 2012. **27**(12): p. 1594-601.
213. Trikkalinou, A., A.K. Papazafiropoulou, and A. Melidonis, *Type 2 diabetes and quality of life.* World J Diabetes, 2017. **8**(4): p. 120-129.
214. Mills, T., et al., *Quality of life in glaucoma and three other chronic diseases: a systematic literature review.* Drugs Aging, 2009. **26**(11): p. 933-50.
215. Khandalavala, B.N., et al., *Predictors of Health-Related Quality of Life After Bariatric Surgery.* Obes Surg, 2015. **25**(12): p. 2302-5.
216. Kolotkin, R.L., et al., *Six-year changes in health-related quality of life in gastric bypass patients versus obese comparison groups.* Surg Obes Relat Dis, 2012. **8**(5): p. 625-33.
217. Bentley, T.G., et al., *Race and gender associations between obesity and nine health-related quality-of-life measures.* Qual Life Res, 2011. **20**(5): p. 665-74.
218. Eaglehouse, Y.L., et al., *Impact of a community-based lifestyle intervention program on health-related quality of life.* Qual Life Res, 2016. **25**(8): p. 1903-12.
219. Lin, V.W., et al., *Association between health-related quality of life and body mass after adjustable gastric banding: a nonlinear approach.* Value Health, 2013. **16**(5): p. 823-9.
220. Grandy, S., K.M. Fox, and S.S. Group, *Change in health status (EQ-5D) over 5 years among individuals with and without type 2 diabetes mellitus in the SHIELD longitudinal study.* Health Qual Life Outcomes, 2012. **10**: p. 99.
221. Marrett, E., et al., *Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain.* Diabetes Obes Metab, 2009. **11**(12): p. 1138-44.
222. Stevens, G.D., et al., *Primary care medical home experience and health-related quality of life among adult medicaid patients with type 2 diabetes.* J Gen Intern Med, 2015. **30**(2): p. 161-8.
223. Zhang, P., et al., *Health utility scores for people with type 2 diabetes in U.S. managed care health plans: results from Translating Research Into Action for Diabetes (TRIAD).* Diabetes Care, 2012. **35**(11): p. 2250-6.
224. Davey Smith, G., et al., *Incidence of type 2 diabetes in the randomized multiple risk factor intervention trial.* Ann Intern Med, 2005. **142**(5): p. 313-22.
225. Lindstrom, J., et al., *The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity.* Diabetes Care, 2003. **26**(12): p. 3230-6.
226. Ramachandran, A., et al., *The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1).* Diabetologia, 2006. **49**(2): p. 289-97.
227. Roumen, C., E.E. Blaak, and E. Corpeleijn, *Lifestyle intervention for prevention of diabetes: determinants of success for future implementation.* Nutr Rev, 2009. **67**(3): p. 132-46.

228. Lindahl, B., et al., *A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: pronounced short-term impact but long-term adherence problems.* Scand J Public Health, 2009. **37**(4): p. 434-42.
229. Kosaka, K., M. Noda, and T. Kuzuya, *Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males.* Diabetes Res Clin Pract, 2005. **67**(2): p. 152-62.
230. Pan, X.R., et al., *Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study.* Diabetes Care, 1997. **20**(4): p. 537-44.
231. 2018 Physical Activity Guidelines Advisory Committee, *Physical activity guidelines advisory committee scientific report*. 2018, U.S. Department of Health and Human Services: Washington, DC.
232. Tuomilehto, J., et al., *Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.* N Engl J Med, 2001. **344**(18): p. 1343-50.
233. Nilsen, V., et al., *Predictors of health-related quality of life changes after lifestyle intervention in persons at risk of type 2 diabetes mellitus.* Qual Life Res, 2014. **23**(9): p. 2585-93.
234. Yadav, R., et al., *Effect of a short-term yoga-based lifestyle intervention on health-related quality of life in overweight and obese subjects.* The Journal of Alternative and Complementary Medicine, 2016. **22**(6): p. 443-449.
235. Karlsen, T.I., et al., *Health related quality of life after gastric bypass or intensive lifestyle intervention: a controlled clinical study.* Health and quality of life outcomes, 2013. **11**(1): p. 17.
236. Block, G., et al., *Development of Alive!(A Lifestyle Intervention Via Email), and its effect on health-related quality of life, presenteeism, and other behavioral outcomes: randomized controlled trial.* Journal of medical Internet research, 2008. **10**(4): p. e43.
237. Wolf, A.M., et al., *Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study*. Diabetes care, 2004. **27**(7): p. 1570-1576.
238. Corso, P.S., et al., *Cost Effectiveness of a Weight Management Program Implemented in the Worksite: Translation of Fuel Your Life.* J Occup Environ Med, 2018. **60**(8): p. 683-687.
239. Tremblay, M.S., et al., *Physiological and health implications of a sedentary lifestyle.* Appl Physiol Nutr Metab, 2010. **35**(6): p. 725-40.
240. Owen, N., et al., *Too much sitting: the population health science of sedentary behavior.* Exerc Sport Sci Rev, 2010. **38**(3): p. 105-13.
241. Owen, N., et al., *Adults' sedentary behavior determinants and interventions.* Am J Prev Med, 2011. **41**(2): p. 189-96.
242. Centers for Disease Control and Prevention Diabetes Prevention Program, *Standards and operating procedures*.
243. Rabin, R. and F. de Charro, *EQ-5D: a measure of health status from the EuroQol Group.* Ann Med, 2001. **33**(5): p. 337-43.
244. Kriska, A.M., et al., *Physical activity in individuals at risk for diabetes: Diabetes Prevention Program.* Med Sci Sports Exerc, 2006. **38**(5): p. 826-32.
245. Ainsworth, B.E., et al., *Compendium of physical activities: an update of activity codes and MET intensities.* Med Sci Sports Exerc, 2000. **32**(9 Suppl): p. S498-504.

246. Rockette-Wagner, B., et al., *The impact of lifestyle intervention on sedentary time in individuals at high risk of diabetes.* Diabetologia, 2015. **58**(6): p. 1198-202.
247. Jacobi, D., et al., *Relationships of self-reported physical activity domains with accelerometry recordings in French adults.* Eur J Epidemiol, 2009. **24**(4): p. 171-9.
248. Pettee Gabriel, K., et al., *Reliability and convergent validity of the past-week Modifiable Activity Questionnaire.* Public health nutr, 2011. **14**(3): p. 435-42.
249. Thompson, W.W., et al., *Health-related quality of life among older adults with and without functional limitations.* Am J Public Health, 2012. **102**(3): p. 496-502.
250. Craig, B.M., et al., *Demographic differences in health preferences in the United States.* Med Care, 2014. **52**(4): p. 307-13.
251. Hassan, Y., et al., *Lifestyle interventions for weight loss in adults with severe obesity: a systematic review.* Clin Obes, 2016. **6**(6): p. 395-403.
252. Sturm, R. and A. Hattori, *Morbid obesity rates continue to rise rapidly in the United States.* Int J Obes (Lond), 2013. **37**(6): p. 889-91.
253. Tremmel, M., et al., *Economic Burden of Obesity: A Systematic Literature Review.* Int J Environ Res Public Health, 2017. **14**(4).
254. Cieza, A. and G. Stucki, *Content comparison of health-related quality of life (HRQOL) instruments based on the international classification of functioning, disability and health (ICF).* Qual Life Res, 2005. **14**(5): p. 1225-37.
255. Owens, D.K., *Interpretation of cost-effectiveness analyses.* J Gen Intern Med, 1998. **13**(10): p. 716-7.
256. Ahmed, B., et al., *Long-term weight change and health outcomes for sleeve gastrectomy (SG) and matched Roux-en-Y gastric bypass (RYGB) participants in the Longitudinal Assessment of Bariatric Surgery (LABS) study.* Surgery, 2018. **164**(4): p. 774-783.
257. King, W.C., et al., *Objective assessment of changes in physical activity and sedentary behavior: Pre- through 3 years post-bariatric surgery.* Obesity (Silver Spring), 2015. **23**(6): p. 1143-50.
258. King, W.C., et al., *Prevalence of alcohol use disorders before and after bariatric surgery.* JAMA, 2012. **307**(23): p. 2516-25.
259. King, W.C., et al., *Comparison of the Performance of Common Measures of Weight Regain After Bariatric Surgery for Association With Clinical Outcomes.* JAMA, 2018. **320**(15): p. 1560-1569.
260. Subak, L.L., et al., *Urinary Incontinence Before and After Bariatric Surgery.* JAMA Intern Med, 2015. **175**(8): p. 1378-87.
261. Xia, Q., et al., *Health state utilities for economic evaluation of bariatric surgery: A comprehensive systematic review and meta-analysis.* Obes Rev, 2020. **21**(8): p. e13028.
262. Driscoll, S., et al., *Long-term health-related quality of life in bariatric surgery patients: A systematic review and meta-analysis.* Obesity (Silver Spring), 2016. **24**(1): p. 60-70.
263. International Expert, C., *International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes.* Diabetes Care, 2009. **32**(7): p. 1327-34.
264. Shrivastava, A. and M.E. Johnston, *Weight-gain in psychiatric treatment: risks, implications, and strategies for prevention and management.* Mens Sana Monogr, 2010. **8**(1): p. 53-68.
265. Wasserstein, R. and N. Lazar, *The ASA Statement on p-Values: Context, Process, and Purpose.* The American Statistician, 2016. **70**(2): p. 129-133.
266. Rossner, S., *Weight gain in pregnancy.* Hum Reprod, 1997. **12 Suppl 1**: p. 110-5.

267. Sumithran, P., et al., *How common is substantial weight gain after pregnancy?* Obes Res Clin Pract, 2018. **12**(2): p. 139-145.
268. Edwards, D. and J.J. Berry, *The efficiency of simulation-based multiple comparisons.* Biometrics, 1987. **43**(4): p. 913-28.
269. Oh, S.H., et al., *The improvement of quality of life in patients treated with bariatric surgery in Korea.* J Korean Surg Soc, 2013. **84**(3): p. 131-9.
270. Strain, G.W., et al., *The effects of weight loss after bariatric surgery on health-related quality of life and depression.* Nutr Diabetes, 2014. **4**: p. e132.
271. Ribaric, G., et al., *3-year real-world outcomes with the Swedish adjustable gastric band in France.* Obes Surg, 2013. **23**(2): p. 184-96.
272. Date, R.S., et al., *Is selection bias toward super obese patients in the rationing of metabolic surgery justified?--A pilot study from the United Kingdom.* Surg Obes Relat Dis, 2013. **9**(6): p. 981-6.
273. Sauerland, S., et al., *Validity of the Czech, German, Italian, and Spanish version of the Moorehead-Ardelt II questionnaire in patients with morbid obesity.* Obes Facts, 2009. **2 Suppl 1**: p. 57-62.
274. Sendi, P., et al., *Health-related quality of life in patients with class II and class III obesity.* Obes Surg, 2005. **15**(7): p. 1070-6.
275. Andenaes, R., et al., *Changes in health-related quality of life in people with morbid obesity attending a learning and mastery course. A longitudinal study with 12-months follow-up.* Health Qual Life Outcomes, 2012. **10**: p. 95.
276. Campbell, J.A., et al., *An Exploratory Study of Long-Term Publicly Waitlisted Bariatric Surgery Patients' Quality of Life Before and 1 Year After Bariatric Surgery, and Considerations for Healthcare Planners.* Pharmacoecon Open, 2018. **2**(1): p. 63-76.
277. Campbell, J.A., et al., *A Head-to-Head Comparison of the EQ-5D-5L and AQoL-8D Multi-Attribute Utility Instruments in Patients Who Have Previously Undergone Bariatric Surgery.* Patient, 2016. **9**(4): p. 311-22.
278. Lee, Y.J., et al., *Validation of the Korean version Moorehead-Ardelt quality of life questionnaire II.* Ann Surg Treat Res, 2014. **87**(5): p. 265-72.
279. Mar, J., et al., *Two-year changes in generic and obesity-specific quality of life after gastric bypass.* Eat Weight Disord, 2013. **18**(3): p. 305-10.
280. Biter, L.U., et al., *Quality of Life 1 Year After Laparoscopic Sleeve Gastrectomy Versus Laparoscopic Roux-en-Y Gastric Bypass: a Randomized Controlled Trial Focusing on Gastroesophageal Reflux Disease.* Obes Surg, 2017. **27**(10): p. 2557-2565.
281. Fermont, J.M., et al., *The EQ-5D-5L is a valid approach to measure health related quality of life in patients undergoing bariatric surgery.* PLoS One, 2017. **12**(12): p. e0189190.
282. McEwen, L.N., et al., *The cost, quality of life impact, and cost-utility of bariatric surgery in a managed care population.* Obes Surg, 2010. **20**(7): p. 919-28.
283. Rausa, E., et al., *Quality of Life and Gastrointestinal Symptoms Following Laparoscopic Roux-en-Y Gastric Bypass and Laparoscopic Sleeve Gastrectomy: a Systematic Review.* Obes Surg, 2019. **29**(4): p. 1397-1402.
284. de Quadros, L.G., et al., *Endoscopic Argon Plasma Coagulation vs. Multidisciplinary Evaluation in the Management of Weight Regain After Gastric Bypass Surgery: a Randomized Controlled Trial with SHAM Group.* Obes Surg, 2020. **30**(5): p. 1904-1916.

285. Twells, L.K., et al., *Morbidity and health-related quality of life of patients accessing laparoscopic sleeve gastrectomy: a single-centre cross-sectional study in one province of Canada.* BMC Obes, 2017. **4**: p. 40.
286. Salem, L., et al., *Cost-effectiveness analysis of laparoscopic gastric bypass, adjustable gastric banding, and nonoperative weight loss interventions.* Surg Obes Relat Dis, 2008. **4**(1): p. 26-32.
287. Whitehead, S.J. and S. Ali, *Health outcomes in economic evaluation: the QALY and utilities.* Br Med Bull, 2010. **96**: p. 5-21.
288. Campos, G.M., et al., *Better weight loss, resolution of diabetes, and quality of life for laparoscopic gastric bypass vs banding: results of a 2-cohort pair-matched study.* Arch Surg, 2011. **146**(2): p. 149-55.
289. Kolotkin, R.L., et al., *Health and health-related quality of life: differences between men and women who seek gastric bypass surgery.* Surg Obes Relat Dis, 2008. **4**(5): p. 651-8; discussion 658-9.
290. Sauerland, S., et al., *Mapping utility scores from a disease-specific quality-of-life measure in bariatric surgery patients.* Value Health, 2009. **12**(2): p. 364-70.
291. van Stel, H.F. and E. Buskens, *Comparison of the SF-6D and the EQ-5D in patients with coronary heart disease.* Health Qual Life Outcomes, 2006. **4**: p. 20.
292. Pierce, J., et al., *Bariatric surgery in the balance: a paradigm shift in general surgery.* Surg Obes Relat Dis, 2010. **6**(3 Supplement): p. S10.
293. Garin, O., *Ceiling Effect*, in *Encyclopedia of Quality of Life and Well-Being Research*, A.C. Michalos, Editor. 2014, Springer Netherlands: Dordrecht. p. 631-633.
294. Lins, L. and F.M. Carvalho, *SF-36 total score as a single measure of health-related quality of life: Scoping review.* SAGE Open Med, 2016. **4**: p. 2050312116671725.
295. Brazier, J.E., D. Rowen, and J. Hanmer, *Revised SF-6D scoring programmes: a summary of improvements.* PRO newsletter, 2008. **40**(Fall issue): p. 14-15.
296. Wyrwich, K.W., et al., *A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease.* Health Serv Res, 2005. **40**(2): p. 577-91.
297. Sach, T.H., et al., *The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D.* Int J Obes (Lond), 2007. **31**(1): p. 189-96.
298. Longworth, L. and S. Bryan, *An empirical comparison of EQ-5D and SF-6D in liver transplant patients.* Health Econ, 2003. **12**(12): p. 1061-7.
299. Marra, C.A., et al., *A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis.* Soc Sci Med, 2005. **60**(7): p. 1571-82.
300. Szende, A., et al., *Psychometric and utility-based measures of health status of asthmatic patients with different disease control level.* Pharmacoeconomics, 2004. **22**(8): p. 537-47.
301. Bryan, S. and L. Longworth, *Measuring health-related utility: why the disparity between EQ-5D and SF-6D?* Eur J Health Econ, 2005. **6**(3): p. 253-60.
302. World Health Organization. *Obesity and Overweight Fact Sheet*. 2013; Available from: http://www.who.int/dietphysicalactivity/media/en/gsfs_obesity.pdf
303. World Health Organization, *Global strategy on diet, physical activity and health p. 2*. 2003.
304. Dietz, W. and C. Santos-Burgoa, *Obesity and its Implications for COVID-19 Mortality.* Obesity, 2020. **28**(6): p. 1005-1005.