# The Impact of Roux-en-Y gastric Bypass on Inflammation and Cardiovascular Disease

by

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University of Pittsburgh, 2020

## Abstract

In the United States (US), cardiovascular disease (CVD), which includes several conditions where the heart or blood vessels have decreased functionality, is the cause of 1 in 3 deaths. CVD risk increases with higher degrees of excess adiposity. Bariatric surgery, the most effective treatment for severe obesity, has been associated with a decrease in CVD-related risk factors, but there is a dearth of research evaluating the heterogeneity and sustainability of the effect of bariatric surgery on CVD risk.

This study evaluated a cohort of 1770 US adults who underwent Roux-en-Y gastric bypass (RYGB) surgery (one of two common bariatric surgical procedures) and were followed annually for up to 7 years. Sex-specific 10-year and lifetime predicted CVD risks were calculated among participants with no CVD history (N=1234) using validated scoring algorithms (Framingham-lipid, Framingham-body mass index [BMI], Atherosclerotic [ASCVD]). Mean 10-year and lifetime CVD risks were substantially lower and fewer participants were categorized as having high risk throughout 7 years post-surgery versus pre-surgery, with all scores. However, magnitude of change differed by risk score. Several individual-level factors (male versus female sex, lower versus higher household income, and abnormal versus normal kidney function) were associated with smaller reductions in 10-year/lifetime CVD risks. Participants (N=1180) also experienced substantial mean improvement in C-reactive protein (CRP), a biomarker of CVD risk and non-specific low-grade systemic inflammation, and a reduction from 33% to 3% in elevated CRP (≥1

mg/L) at 7 years versus pre-surgery. Across 7 years of follow-up, the non-fatal CVD event rate per 1000 person-years was 50.4 (95% CI:41.6,61.2) for females and 71.6 (95% CI:53.7,95.5) for males. Standardized mortality ratios (SMRs) for CVD-related mortality indicated a higher mortality rate in the post-RYGB sample compared to the general population.

These findings have direct public health significance by informing the variability and sustainability of CVD risk reductions, including inflammation, associated with RYGB, and determining the post-RYGB CVD event rate. Although RYGB results in substantial CVD risk reduction, CVD-related mortality indicates post-surgical patients are still a high-risk group. This research offers insights into which patients might require additional support beyond RYGB surgery to improve their cardiovascular health.

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## Preface

I would like to acknowledge and thank my mentor and thesis advisor, Dr. Wendy C. King. It has been an absolute honor to learn from her and work with her. I would also like to thank the rest of the members of my dissertation committee, Dr. Emma J.M. Barinas-Mitchell, Dr. Anita P. Courcoulas, Dr. Samar R. El Khoudary and Dr. Abdus S. Wahed, who all provided valuable insights and expertise in multiple areas of this work. Additionally, I would like to thank my previous mentors and supervisors, Dr. Todd Reinhart, Dr. Gerard Campbell, Dr. Deborah L. Chapman and Kathy Gwaley, for their support and encouragement. Finally, this dissertation would not have been possible without the support of my parents, family and friends (special thanks to L.R.S., M.R.S., D.C., and C.C.M who I could always count on to provide kind words and laughter).

# 1.0 Literature Review

## 1.1 Introduction

In 2016, there were more than 1.9 billion adults worldwide who were overweight [Body Mass Index (BMI) greater than or equal to 25] and of these, 650 million with obesity (BMI greater than or equal to 30)[1]. Of the adult population in the United States in 2015, over one-third (39.8%) had obesity and 7.6% had severe obesity (BMI greater than or equal to 40)[2], and these percentages are expected to rise in the next decade[3]. Obesity is associated with type 2 diabetes, certain cancers and an increased risk of cardiovascular disease (CVD)[3]. In the United States, roughly half of the population has at least one major risk factor for CVD[4] with 610,000 deaths attributed to CVD related diseases each year[5].

Bariatric surgery, the most effective treatment for severe obesity[6], has been associated with a decrease in CVD-related risk factors, but there is a dearth of research evaluating the sustainability of CVD-related improvements associated with bariatric surgery[7,8]. Recent reports from the Action for Health in Diabetes (Look AHEAD) Clinical Trial suggest after weight loss CVD biomarkers decrease but then as weight regain begins, the CVD biomarkers begin to increase towards pre-weight loss levels.[9] Also, depending on the amount of initial weight loss, the CVD biomarkers increase may vary by how close they are to pre-weight loss levels after 4 years of follow-up. In those who lose more weight, the CVD biomarkers remain below pre-weight loss levels, yet those who lose less weight have their CVD biomarkers reach pre-weight loss levels regardless of the amount of regain experienced (full or partial)[9]. Thus, understanding how CVD biomarkers may change over the course of all stages of weight loss, including potential weight gain phases after

bariatric surgery is important to understand how large weight loss, even with a certain amount of weight regain, may impact future CVD risk[10].

Some CVD biomarkers are thought to be involved in identifying inflammation. Inflammation and CVD risk are intertwined and CVD biomarkers such as C-reactive protein (CRP) and interleukin-6, have been shown to be associated with increased CVD risk[11]. Since these biomarkers are used to identify inflammation, other outcomes associated with inflammation may be able to be identified through these biomarkers. There is recent evidence that CRP and depression are associated, with those with higher levels of CRP having more depressive symptoms, as well as other inflammatory related diseases, than those with lower levels of CRP[12]. If depression is an inflammatory disease and bariatric surgery can decrease inflammation[13], it is important to understand how inflammation and inflammation related outcomes may change over the course of weight loss and weight regain phases after surgery.

### 1.2 Obesity

Obesity, an accumulation of excessive fat in adipose tissue[14], is associated with higher risk of multiple comorbidities[15]. These comorbidities include cancer (e.g., renal, colon, thyroid, and esophageal), gallstones, osteoarthritis, diabetes mellitus, sleep apnea, and cardiovascular disease[16]. Obesity is also associated with worse physical function, worse mental function, lower quality of life, and a greater risk of all-cause mortality[16]. Within the United States, individuals with obesity have higher medical costs including higher inpatient costs (47%), more outpatient visits (27%), and more prescription medications (80%)[17] compared to individuals without obesity. The total

dollar amount of treatments associated with obesity represents about 21% of the United States' yearly health care costs ($190 to $210 billion)[18].

### 1.2.1 Measurement

There are multiple methods to measure obesity[16,19]. Body mass index (BMI) is the most common method to measure and classify obesity, due to only requiring weight and height, which makes it accessible and inexpensive for use by clinicians and the community[20]. BMI is calculated by dividing an individual's weight in kilograms by their height in meters squared[20]. BMI is correlated with percentage of body fat but is not a direct measure, and thus is considered a surrogate marker for body fatness[19]. BMI is positively correlated with health risks associated with adiposity, including risk for CVD[21]. While BMI has linear and non-linear associations with many health outcomes, indicating a dose-response relationship[22,23], BMI is categorized based on health risk classification, with normal weight defined as 18 to <25 kg/m$^2$, followed by overweight, 25 to <30 kg/m$^2$, and obesity, ≥30kg/ m$^2$. Obesity is broken up into three levels, class 1 to 3[16] (Table 1).

**Table 1. Classification Of Weight Status Based On Body Mass Index[24,25]**

| Classification | BMI (kg/m$^2$) |
|---|---|
| Normal weight | 18 to 24.9 |
| Overweight | 25 to 29.9 |
| Obesity | 30 or more |
| Class 1 | 30 to 34.9 |
| Class 2 | 35 to 39.9 |
| Class 3 (extreme/severe obesity*) | 40 or more |

*Sometimes "severe or morbid obesity" refers to class 3 obesity or class 2 obesity with at least one obesity-related comorbidity[26].

Two more measures of obesity are waist circumference and waist–hip ratio (i.e. the waist circumference divided by the hip circumference). Waist circumference and waist–hip ratio are two

measurements based on considering where the excess fat is distributed. Both of these measures account for the abdominal accumulation of excessive fat in adipose tissue, which has a stronger association with overall morbidity than peripheral or subcutaneous fat accumulation[19]. Also, both have been used in the prediction of CVD risk. Each measurement has cut points which are used to classify cardiometabolic risk for men and women (Table 2). Other, less common methods to measure obesity include air displacement, bioelectrical impedance and skin fold calipers[16,19], with the latter two not recommended for use in adults with severe obesity[27].

**Table 2. Classification Of Cardiometabolic Risk For Men And Women.**

| | Men | Women |
|---|---|---|
| Waist Circumference | | |
| Increased | >94 cm | >80 cm |
| Substantially increased | >102 cm | >88 cm |
| Waist–hip ratio | | |
| Substantially increased | ≥0.90 cm | ≥0.85 cm |

### 1.2.2 Epidemiology

***Prevalence, overall and by sex and race in the United States***

Worldwide, between the years 1980 to 2013, the prevalence of those with overweight and obesity (BMI of 25 or greater) increased 27.5% in adults and 47.1% in children[28]. Within the United States, an analysis of National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2012 revealed that the population of adults with overweight and obesity have outnumbered those with normal weight by a ratio of 2:1[29]. Also, data collected by NHANES between 2013 and 2014 estimated 2 in 3 adults and 1 in 6 children and adolescents are living in the United States with overweight or obesity[24]. Of adults with obesity, 1 in 13 (7.7%) were classified with class 3 obesity[25]. There have been several prediction models used to estimate the increasing rates of obesity. By the year 2030, estimates include nearly 85% of adults with at least

overweight (BMI > 25)[16], 42% with obesity (BMI ≥30) and of the 42% with obesity, 11% severe obesity (BMI > 40)[30].

The all-cause mortality hazard ratio attributed to obesity was 1.18 (95% CI, 1.12–1.25) in a meta-analysis of 2.88 million individuals[31]. However, when stratified by obesity class and compared to normal weight, class 1 was not associated with an increased overall all-cause mortality hazard ratio (0.97; 95% CI, 0.90–1.04), while classes 2 and 3 were associated with an all-cause mortality hazard ratio of 1.34 (95% CI, 1.21–1.47), suggesting a threshold effect[31].

There are differences in levels of obesity between men and women. While there are more men with overweight or obesity compared to women (73.7% vs 66.9%)[24], between 2005 and 2014, the overall prevalence of obesity increased among women, but did not significantly increase for men[24]. Overall, the general differences between men and women indicate women are at a higher risk for obesity and in particular, for the more extreme classes of obesity, compared to men (Table 3)[24].

**Table 3. Obesity Class, 2013–2014 NHANES[24]**

| | All | Men | Women |
|---|---|---|---|
| Overweight or Obesity | 70.2 | 73.7 | 66.9 |
| Overweight | 32.5 | 38.7 | 26.5 |
| Obesity (including extreme obesity) | 37.7 | 35 | 40.4 |
| Extreme obesity | 7.7 | 5.5 | 9.9 |

From the 2013–2014 NHANES survey, reports show obesity differs by race/ethnicity, with non-Hispanic black adults having the highest prevalence (48%), followed by Hispanic adults (43%), non-Hispanic white adults (36%), and non-Hispanic Asian adults (12%)[24]. The highest prevalence of class 3 obesity is in non-Hispanic black adults (12.4%), followed by non-Hispanic white adults (7.6%), and Hispanic adults (7.1%)[24].

***Risk factors for Obesity***

There are multiple factors that play a role in the prevalence of obesity in the United States. Factors linked to excess weight gain and thus obesity include[16]:

- Sex
- Racial disparities
- Genetic predisposition
- Diet
- Physical inactivity and sedentary behaviors
- Medications
- Medical conditions
- Gut bacteria
- Gut hormones (e.g., ghrelin and leptin)[32]
- Factors influencing the list above are issues such as socioeconomic status, environment and individual decisions

### 1.2.3 Treatment For Obesity

Obesity is recommended to be treated through long-term weight reduction[33,34]. As with treating other diseases, there are different degrees of treatment, with some being lower risk than others. In the spectrum of treatment options, some of the most common include diet, exercise, medication and surgery[35].

Treatment of obesity is a two-phase process with a weight loss phase and a weight loss maintenance phase. The weight loss phase is associated with a reduction in adiposity and obesity-related comorbidities[36]. During the weight loss maintenance phase, minimizing weight regain,

which is associated with higher risk of worsening or reoccurrence of comorbidities including diabetes, hypertension, and quality of life[37], is the goal. Thus, together the weight loss and weight maintenance phases are aimed at improving the short-term and long-term resolution of obesity and comorbidities.

***Lifestyle and behavior***

The foundation for the treatment of obesity relies on two components of lifestyle and behavior, diet and exercise modification. Treating obesity through a change in diet is reliant on decreasing the amount of energy intake through a healthy diet that does not impair one's health[35]. The diet component is grounded in reducing the number of calories consumed daily through restriction of the overall number of calories and/or what type of calories. Some diets focus on counting calories, smaller portions or meal replacements to decrease the total amount of energy consumed, while other diets focus on foods that are low in fat, carbohydrates, glycemic, and high in protein[38]. In general, diet strategies result in the net goal of reducing the number of calories consumed in day. While diverse types of diets have comparable weight loss results, the adherence to the chosen diet has been associated with being a better predictor of long-term weight loss success than the type of diet followed[39].

While dietary changes generally have a larger impact on weight loss than adoption of an exercise routine and/or changes to physical activity level, exercise and physical activity are important factors in the weight loss phase of obesity treatment and an important part of weight maintenance[40,41]. One of the ideas behind exercise being more important during the weight maintenance phase is that the adherence to diet decreases as time increases[42]. There are multiple physical activity guidelines for effective weight loss. In general, guidelines aimed at weight control suggest higher levels of activity than those aimed at general health benefits (Table 4).

Contraindication to vigorous physical activity become more likely as obesity level increases, especially in those above BMI 35 kg/m$^2$ [35]. When increasing physical activity through an intervention, it should be noted that the participants do not have a contraindication to the prescribed physical activity. If a contraindication exists, alternatives should be provided, such as starting at low-intensity physical activity and increasing intensity levels over time, breaking up physical activity into smaller, more frequent amounts or offering exercise classes specific to those with the contraindication[43].

**Table 4. Exercise Recommendation Definitions**

| Agency | Population | Benefit | Recommendation |
|---|---|---|---|
| United States Department of Health and Human Services (USDHHS, 2008)[44] | Healthy adults | General health benefits | ≥150 min of aerobic MPA/week (or 75 min of aerobic VPA/week) in bouts ≥10 min, plus strengthening ≥2 d/week |
| American College of Sports Medicine (ACSM, 2009) | Overweight and obese adults | Weight loss<br>Prevention of weight regain | ≥250 min MPA/week (i.e., 36 min/day) |
| Institute of Medicine (IOM, 2002) | Adults | Prevention of weight gain<br>Health benefits | 60 min MPA/day |
| International Association for the Study of Obesity (IASO, 2004)[45,46] | Formerly obese adults | Prevention of weight regain | 60-90 min MPA/day (or lesser amounts of VPA) most days/week |

Table reprinted with permission from King, Bond 2012[43].

Along with focusing on diet and exercise, other factors that impact lifestyle and behavior changes can lead to better weight loss in the short term and sustained weight loss over time. For one, programs to help with any psychological issues including depression or eating disorders should be used to help identify those that may need extra support when employing behavior modification techniques related to increasing physical activity levels[47]. Other factors which may increase healthy behaviors include promotion of individual empowerment through learning to identify triggering events which may lead to uncontrolled eating or other poor lifestyle behaviors

(i.e. alcohol consumption), cognitive changes to decrease prior dysfunctions through patterns, and strategies for how to handle weight regain[35]. Employing social support in groups of patients going through the same changes, or other social structures, may lead to better weight loss maintenance[48].

***Medication***

Weight loss medications currently approved by the US Food and Drug Administration work through appetite suppression or inhibit free fatty acid absorption into the body[49]. Drug therapy has been shown to work most efficiently in conjunction with a lifestyle or behavioral modification intervention and should not be employed as a single intervention for weight loss[49]. Medication for weight loss is indicated for use in those with risk factors or comorbidities associated with obesity (i.e. hypertension or type 2 diabetes) and with a BMI greater than 27 $kg/m^2$ [49]. Medication may also be recommended for those who have less than 5% weight loss after 6 months of behavioral and lifestyle modification and a BMI of at least 30 $kg/m^2$ [19]. These FDA approved drugs have been shown to be associated with clinically meaningful weight loss (≥5%) when compared to placebo after 1 year of treatment[50].

Currently, medications are approved for both short term (i.e. less than 12 weeks) and longer-term use. There are four FDA approved short-term medications (e.g. phentermine, diethylpropion, phendimetrazine and benzphetamine) and three longer-term medications (e.g. orlistat, lorcaserin and phentermine plus topiramate)[50]. While these medications have been proven to be effective in reducing weight in participants, they also are associated with multiple adverse reactions. These side effects include increased heart rate, headaches, dizziness, insomnia and memory or cognitive changes.

Due to these risks, it is recommended that the health benefits be weighed against any potential adverse events when prescribing the medications. It has been noted that those who do not

achieve at least 5% weight loss after 12 weeks of treatment are less likely to reach this threshold by continuing treatment for a longer period[50]. By discontinuing medication in those less likely to succeed reaching clinically meaningful weight loss and recommending alternative treatments, the total number of adverse events associated with continued use of weight loss medications can be decreased[50].

***Bariatric Surgery***

When other interventions have not resulted in significant weight loss, the alternative is a surgical intervention. Current estimates indicate an increasing trend in the number of bariatric surgeries performed in the United States[51]. Bariatric surgical procedures alter the gastrointestinal tract which ultimately leads to acute and sustained weight loss. Currently, surgery is recommended in those with BMI $\geq$ 40, or more than 100 pounds overweight, or BMI $\geq$35 and at least one or more obesity-related co-morbidities[52].

There are three bariatric procedures which account for the vast majority of procedures performed today: Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and laparoscopic adjustable gastric band (LAGB)[53]. RYGB surgery has two parts with the first being the construction of a new gastric pouch of roughly 30 mL in the upper stomach area separating it from the rest of the stomach[53]. The new pouch is significantly smaller than the normal stomach. The second part is to divide the small intestine and connect the bottom end to the newly created small stomach pouch. Finally, the top part of the divided small intestine is connected to the small intestine. RYGB achieves weight loss through both the physical reduction of stomach pouch size, which limits the physical intake of food, malabsorption due to the surgery creating a bypass of regions that would normally absorb calories and nutrients[54] and through changes in the secretion of gastrointestinal hormones which are related to the regulation of appetite and satiety[55]. Along

with weight loss, the change in the gastrointestinal tract impacts metabolic disorders, including the remission of type 2 diabetes[56].

SG removes roughly 80% of the stomach by vertically separating the stomach and leaves a long, yet smaller in proportion, gastric pouch. The new pouch, like the RYGB pouch, holds smaller volume of food, and impacts the stomach's gastrointestinal hormones such as ghrelin which promotes hunger[53].

The LAGB does not alter the stomach through direct surgical intervention, and instead uses an adjustable band. This band is placed around the upper area of the stomach and creates a new, smaller pouch at the top of the stomach area. This new pouch is smaller than the original stomach area and achieves weight loss through limitation of stomach volume[53].

***Prevalence of surgery in the United States***

The number of surgeries in the United States has increased from 158,000 in 2011 to 193,000 in 2014[51]. Also, over this time the relative popularity of bariatric surgical procedures in the United States has changed. In 2011, RYGB was considered the gold-standard of surgery and was the highest performed surgery, with LAGB as the second most common surgery. From 2011 to 2014, both RYGB and LAGB accounted for a smaller proportion of procedures (RYGB 36.7% to 26.8%; LAGB 35.4% to 9.5%) while the proportion of SG increased from 17.8% to 51.7%[51,58]. Now SG is the most common bariatric surgery both in the United States and worldwide. The rise in the popularity of the SG procedure may be attributed to a combination of its perceived efficacy, safety, and technical difficulty. For example, SG has been associated with better weight loss and resolution of comorbidities compared to the LAGB, and SG has a lower risk profile and is more technically simple to perform compared to the RYGB. Late complications of RYGB include risk of internal herniation and marginal ulcerations[59], and LAGB complications include band erosion,

slippage, and gastro-esophageal reflux, while SG does not carry any of these complications[58,60,61]. Although, SG has fewer complications compared to RYGB, RYGB is associated with greater weight loss compared to both SG and LAGB and better or similar improvement in comorbidity outcomes[62-64].

***Safety of bariatric surgery***

The mortality of bariatric surgery has decreased over the past two decades from roughly 0.5-1.0% in the 1990s, to 0.1 to 0.3% in the 2000s[65]. The decreasing rates of mortality and the increase of safety of the surgery has been attributed to the implementation of laparoscopic surgery and training surgeons in the technique. The laparoscopic surgery reduces the morbidity and mortality seen in open bariatric surgery[66]. In addition to switching to a laparoscopic surgery, the American Society for Metabolic and Bariatric Surgery and American College of Surgeons created accreditation systems in 2004 and 2005 and merged in 2012 into the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program. Through the accreditation program, data was collected to help gather resources for the highest care of patients having surgery[67]. After the accreditation program was implemented, the mortality for bariatric surgery was lower in centers with accreditation compared to those that were not[68].

## 1.3 Cardiovascular Disease

CVDs are diseases related to the heart and blood vessels. In CVD, the heart or blood vessels are compromised and have a decrease in functionality, which impacts the blood flow through the body. These complications include damaged or malformed heart muscle or heart values, or disease of the blood vessels supplying the heart, brain or arms and legs of the body.

There are several types of CVDs including coronary heart disease, stroke, and peripheral vascular disease, as well as other conditions (Table 5)[69]. As BMI increases, the risk of CVD increases[31].

### 1.3.1 Obesity And CVD

The mechanism between obesity and CVD is thought to be a function of an increase in CVD risk factors related to increasing BMI[70]. The association between obesity and CVD risk factors includes hypertension, elevated cholesterol levels, high triglycerides, dyslipidemia, and insulin resistance[71]. In addition to risk factors increasing, obesity and CVD also may be influenced by endothelial dysfunction, subclinical inflammation, and lower than average physical and cardiorespiratory fitness which all rise with increasing BMI levels[31,72]. Obesity also impacts cardiovascular structure and function. For example, obesity increases the risk of left ventricular structural abnormalities which may lead to remodeling and LV hypertrophy, left atrial enlargement, and impairment of systolic and diastolic function[72].

**Table 5. Types Of CVD[69].**

| Types of CVD | Description | Clinical manifestations/Symptoms | Risk factors |
|---|---|---|---|
| I. Coronary heart diseases | Ischemic heart disease; most common type | (i) Heart attack<br>(ii) Angina at chronic condition | High BP, high BC, tobacco use, unhealthy diet, physical inactivity, diabetes, advancing age, inherited disposition |
| II. Stroke | Common form of CVD and three categories: (i) Ischemic stroke; (ii) hemorrhagic stroke; (iii) Transient ischemic attack | Brain damage, leading to sudden impairments; weakness often on one side of the body | High BC, tobacco use, unhealthy diet, physical inactivity, diabetes, and advancing age |
| III. Rheumatic heart disease and Rheumatic fever | Inflammation of heart valves and heart muscle caused rheumatic fever (streptococcal bacteria); begins as a sore throat or tonsillitis in children | (i) Shortness of breath, fatigue, irregular heartbeats, chest pain and fainting<br>(ii) Fever, pain and swelling of the joints, nausea, stomach cramps and vomiting | - |
| IV. Congenital heart disease | Malformations of heart of central blood vessel at birth or during gestation (e.g., hole in heart, abnormal valves, and abnormal heart chambers) | Breathlessness or a failure to attain normal growth and development | Maternal alcohol and medication use; maternal infection (e.g., rubella); poor maternal nutrition; close blood relationship between parents consanguinity |
| V. Peripheral vascular disease | Peripheral arterial disease; Two important forms (i) Atherosclerosis (ii) Abdominal aortic aneurysm | - | Long-standing high BP; Marfan syndrome tangential heart disorders, syphilis, and other infectious and inflammatory disorders |
| VI. Deep vein thrombosis and pulmonary embolism | The blood clots in the leg veins, which can dislodge and move to the heart and lungs | - | Surgery, obesity, cancer, recent childbirth, use of contraceptive and hormone replacement therapy, long |

| | | | |
|---|---|---|---|
| | | | periods of immobility and previous episodes of DVT |
| VII. Other cardiovascular diseases | Tumors of the heart, vascular tumors of the brain; disorders of heart muscle (cardiomyopathy); heart valve diseases | - | - |

***Types of CVD***

CVDs can be broken into two groups, CVDs due to atherosclerosis and CVDs not due to atherosclerosis. CVDs due to atherosclerosis include ischemic heart disease or coronary artery disease, cerebrovascular disease, diseases of the aorta and arteries, including hypertension and peripheral vascular disease. Other CVDs not due to atherosclerosis are congenital and rheumatic heart disease, cardiomyopathies, and cardiac arrhythmias[73]. The CVDs due to atherosclerotic disease are the most common[74].

Atherosclerotic disease takes place in the walls of blood vessels over a long period of time starting in childhood and adolescence and manifesting in later adulthood[75]. Fatty material and cholesterol accumulate in the medium and large blood vessel walls. When the blood vessel walls experience high levels of low-density lipoprotein cholesterol (LDL) and other materials, the lining becomes permeable to lymphocytes and monocytes. The immune system cells move to the blood vessel walls and can then move the LDL into blood vessel wall. Through the process, muscle cells move to the blood vessel wall and a fibrous cap forms[76]. Over time this buildup of material, called a plaque, cause the blood vessel to narrow, and the vessels lose the ability to allow sufficient blood flow through the vessel. The lower blood flow through the blood vessels can decrease the amount of oxygen-carrying blood reaching the heart muscle, brain, and arms and legs which results in CVD of those areas (coronary heart disease, cerebrovascular disease, peripheral arterial disease). Over time the plaque fibrous cap thins and can become unstable and may rupture and break loose into the bloodstream and create a thrombus or blood clot. This clot, depending on where it was created, may lead to a heart attack (coronary artery) or stroke (brain blood vessel)[76].

### 1.3.2 Obesity Paradox

While there is evidence supporting the relationship between individuals with overweight/obesity and higher rates of CVD [i.e. coronary heart disease (CHD), hypertension, and heart], there is also support for these individuals to have a better short-term prognosis of lower CVD mortality, all-cause mortality, and rehospitalizations after initial diagnosis of a CVD than normal weight individuals with the same type of CVD[77]. These apparently contradictory results together are known as the obesity paradox. For example, over the course of 3 years it was found that heart failure patients with low BMI had the highest risk of adverse events, including CVD mortality and rehospitalizations compared to overweight patients who had the lowest risk[72]. Another example was recognized in patients with CHD; patients with class 2 and 3 obesities had a better prognosis during the short-term follow-up compared to patients with normal BMI[72]. Potential reasons for the obesity paradox include lower prevalence of smoking, greater metabolic reserve, use of cardiac medications and greater muscle mass and muscular strength, among those with higher versus lower BMI, and other unmeasured confounding factors. While short-term prognosis favors those with higher BMI, longer-term follow-up indicates those with higher BMI were at a higher risk of mortality[72]. Those with CHD and class 2 or class 3 obesity had a higher long-term mortality compared to those with lower levels of BMI[72].

### 1.3.3 Epidemiology

***Prevalence***

**Worldwide**

In 2013, the total number of CVDs were roughly half of all noncommunicable diseases and accounted for 17.3 million deaths (31% of all deaths) across the globe. Estimates are this number will only increase and more than 23.6 million CVD-related deaths are expected by the year 2030.

**United States**

Roughly 92.1 million people in the United States currently have a CVD or suffer from effects of a previous stroke[78]. Additionally, CVDs lead to more deaths than cancer and chronic lower respiratory disease combined. CVDs are the cause of 1 in every 3 deaths or an estimated 801,000 deaths each year[78]. This translates to about 2,200 CVD deaths each day or 1 CVD death every 40 seconds. In 2013, the death rates were higher in males than females (269.8 vs 184.8 per 100,000)[79]. The death rates also varied by race and sex, with the highest rates in non-Hispanic black males, followed by non-Hispanic white males, non-Hispanic black females, Hispanic males, non-Hispanic white females, 356.7, 270.6, 246.6, 197.4, and 183.8, per 100,000 respectively, and the lowest rates in Hispanic females (136.4 per 100,000). About 35% of deaths occurred in those younger than 75, which is younger than the current life expectancy for those living in the United States (79 years)[80]. The leading cause of death by CVD type was coronary heart disease (CHD), followed by stroke, heart failure, high blood pressure, diseases of the arteries, and other forms of CVDs (45.1%, 16.5%, 8.5%, 9.1%, and 3.2%, respectively)[78].

***Decline in CVD-related deaths***

There has been a decline in the death rate from CVDs over the past two decades. The declines from 1990 to 2013 were about 11% in men and 14% in women worldwide[81]. The main explanation for this was a decrease in deaths attributed to ischemic heart disease and stroke[81]. The decrease in deaths from CVD was modeled using the validated IMPACT Coronary Heart Disease Model which attributed a decline in CHD mortality due to more effective treatments for unstable angina, heart failure and myocardial infarction.

***CVD Risk factors***

There are several risk factors related to CVDs and many are modifiable through individual lifestyle and behavior changes. Changes in these risk factors have been associated with CVD prevention and reductions in the risk of CVD related mortality[73].

Risk factors

- Increasing age
- Biological sex
- Tobacco use
- Poor diet
- Physical inactivity
- Harmful use of alcohol
- Being overweight/obese
- High blood pressure/hypertension
- High blood sugar levels/diabetes
- High blood lipids/dyslipidemia
- Low socioeconomic status

- Inherited genetic traits
- Psychological factors (i.e. stress, depression)

Overall, tobacco use, obesity, hypertension, diabetes, and dyslipidemia are believed to be the cause of over half of CVD related deaths[82]. These behavioral and metabolic risk factors often coexist in the same person and act synergistically to increase the individual's total risk of developing acute vascular events such as heart attacks and strokes.

Biological sex may also be an important risk factor for CVD outcomes[83]. There are several differences between males and females including general biological differences as well as environmental, lifestyle and attitudes which may all lead to differences between sexes in CVD risk and CVD outcomes. For example, type 2 diabetes contributes a higher risk of mortality from ischemic heart disease (IHD) in women compared to men (5.00 for women, 1.85 in men)[84]. Furthermore, mental stress (a risk factor for coronary heart disease), microvascular disease, coronary artery spasm, and spontaneous coronary artery dissection are all more prevalent in women than men[83]. Other outside influences which may impact time to CVD outcome diagnosis and medical care for CVD include women presenting symptoms differently compared to men, as well as diagnostic testing for IHD which has a lower specificity in women[83]. There are also differences in incidence of CVD outcomes between men and women. However, these differences vary by age; at younger ages women have lower rates of IHD, acute coronary syndromes, hypertension and heart failure than men, but at older ages women have higher rates of CVD outcomes compared to men[83]. These differences between sexes draws attention for the need for more sex differentiated CVD risk and outcome reporting.

***Economic burden***

In the United States, CVDs cost an estimated $273 billion in direct costs and $444 billion in combined direct and indirect costs each year[85]. The American Heart Association (AHA) estimated that by 2035, close to half (45%) of the population in the United States would suffer from at least one form of CVD. This would increase the cost of CVDs in 2035 to $1.1 trillion in direct and indirect costs ($748.7 billion and $368 billion)[86]. Besides medical costs, CVDs also inhibit daily life and these disabilities limit the ability of individuals to complete tasks at home or at work. These disabilities result in loss of productivity and potential income. The top CVD related disabilities are attributed to heart disease, stroke, and hypertension[86].

### 1.3.4 Treatment Of CVD

While a goal of some interventions is to reduce the risk of developing CVD, once a CVD has been diagnosed, the goal becomes treating an existing CVD to limit poor outcomes. Interventions to treat CVD have been shown to decrease morbidity and mortality associated with CVD[73]. Given that obesity is a preventable independent risk factor for CVD, many of the treatments for CVD are similar to the treatment of obesity.

***Weight reduction***

A reduction of 5 to 10 percent in body weight is recommended as a CVD treatment by the American Heart Association/American College of Cardiology (AHA/ACC) Foundation[34]. Weight reduction may be achieved through a variety of means including diet, exercise, physical activity, medication, and surgery. Weight loss and its relationship to decreases in CVD risks are well documented and suggest with more weight reduction, the better the benefit[87]. Improvements in hypertension, diabetes, and dyslipidemia are just a couple examples of decreasing CVD risks

through weight reduction[34]. Blood pressure decreases between 0.5 to 2.0 mmHg for every 1 kg of weight lost, and women who lost more than 5 kg reduced their risk for diabetes by 50 percent or more. Declines in obesity are associated with decreases in total cholesterol, LDL, and an increase in high density lipoprotein cholesterol (HDL)[34].

***Lifestyle and Behavior modification***

Change in lifestyle begins with stopping poor health habits and adoption of healthy habits. Smoking cessation, limiting alcohol intake, increasing physical activity, and improving diet are all recommended in secondary prevention programs and have been shown to benefit individuals with CVD[73]. Smoking cessation has significant benefits for CVD. The risk of CVD event decreases soon after smoking stops and reaches levels of a nonsmoker within three to five years[73].

***Diet***

Diet can also have a beneficial impact on risk of CVDs. One diet that has been associated with beneficial results and lowering future CVD risk is the Mediterranean diet. The Mediterranean diet is based on increasing fruit, vegetables, whole grains, low-fat dairy products, poultry and fish while decreasing sugar-sweetened beverages and red meats[88]. Patients may also benefit more from a customized and personalized diet plan. These diets may focus on decreasing cholesterol, sodium (no more than 2400 mg per day), sugar or other diet modifications[89].

***Physical activity***

There are multiple cardiovascular benefits associated with physical activity including weight loss, reductions in LDL, decreases in blood pressure, and remission of diabetes[90]. For general health benefits a minimum of at least 150 minutes of moderate-intensity per week is recommended[91] (Table 4). For treatment of CVD through weight loss, the recommendations of 60

minutes of MVPA per day (IOM) or a total of at least 250 minutes of MVPA per week (ACSM) apply (Table 4)[43].

***Other programs***

Cardiac rehabilitation is an outpatient program designed to help assist those after an acute coronary syndrome or revascularization as well as those who suffer from chronic conditions such as angina or peripheral artery disease[92]. The program may include physical activity to help the patient recover from an event. Also, it provides help with lifestyle modification and adherence through patient education. The education aspect is guided by the patient's own ability to understand and is conveyed to the patient at a level they can comprehend and apply the knowledge to their lives[92]. Education on CVDs, therapeutic options, medications and healthier lifestyle choices are meant to optimize care and decrease future CVD events. Providing information to patients to help them recognize their risk factors and how to manage and recognize worsening symptoms is a central aspect to secondary prevention programs.

***Medications***

The use of medications in the secondary prevention of CVDs is significant and beneficial. Depending on the type of CVD, the recommended medication may differ. Medications include statins, aspirin, beta blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers, as well as the influenza vaccine[93].

***Bariatric surgery***

Bariatric surgery is most commonly performed in females with a median age in the 40s, i.e., a low CVD risk group. Due to this initial low CVD risk, it may take decades for a CVD event to occur in this group. Given the lack of substantial long-term (i.e. 10-20 years) data following the bariatric surgery population, the ability to estimate the effect of bariatric surgery on CVD

outcomes is difficult. However, the Swedish Obese Subjects (SOS) study followed participants for over 20 years. In this study the adjusted hazard ratios for the surgery group compared to the control group were 0.67 (95% CI, 0.54-0.83; $P < .001$) for all cardiovascular events and 0.47 (95% CI, 0.29-0.76; $P = .002$) for CVD mortality[94]. The major limitation of the SOS study is that most participants underwent bariatric surgery procedures that are no longer in use or recommended[95]. In a meta-analysis, of 32 studies with a mean follow-up of 4.5 years, the association between surgery and long-term decreases in CVD outcomes was less clear and the authors concluded there remains uncertainty regarding bariatric surgery's overall impact on reducing CVD outcomes[96]. In another example in diabetic patients 5 years after bariatric surgery (Roux-en-Y or Laparoscopic Adjustable Gastric Banding), the composite outcome of coronary artery disease or cerebrovascular events had lower incidence in the surgical group (2.1%) compared to the non-surgical group (4.3%).

Bariatric surgery has been linked to reductions in CVD risk factors and development/progression of CVD. After surgery, the reductions in risk factors generally correspond to the amount of weight loss, with higher reductions in those who lose more[97]. For example, after surgery there is evidence of improvement in cardiac geometry, with level of improvement proportional to amount of weight lost. Left ventricular mass decreases which leads to better left ventricular systolic and diastolic function. Because the degree of weight loss varies by bariatric procedure, reductions in CVD risk factors also tend to differ by procedure. Furthermore, it is hypothesized that at least some bariatric surgical procedures alter gut-secreted hormones that regulate metabolism,[97] with insulin resistance improving just days after RYGB, i.e., prior to significant weight loss. Although an observational study, results from the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) study suggest the impact on CVD risk several years

following surgery may also differ by surgical procedure. For example, prevalence of diabetes remission at 7 years after surgery in the RYGB surgery group was 60.2% (95% CI, 54.7-65.6) while in the LAGB group it was 20.3% (95% CI, 9.7-30.9). In addition to the LABS-2 study, the diabetes remission rate was better in the surgical group compared to the non-surgical group after 15 years in the SOS study (30.4% compared to 6.5%)[98].

## 1.4 CVD Risk

CVD risk scores are useful tools which allow for the identification of individuals at high or intermediate risk of a future CVD outcome. CVD risk scores can be used in a large age range (20 to 79 years) which allows for younger/asymptomatic individuals' risks to be estimated. Incorporating age is a vital component of CVD risk scores due to CVD outcomes occurring later in life. Targeted early prevention of CVD outcomes have been shown to decrease CVD events later in life[99]. By identifying those at the highest risk, clinicians can recommend targeted interventions to lower CVD risk in those who need it the most. For older individuals, or those with limited life expectancy, clinical considerations should dictate the intensity of risk assessment and prevention efforts[100].

### 1.4.1 Measurement

There are short-term and lifetime risk estimations for CVD. The lifetime risk estimation may be less valuable for individuals who have high short-term (10-year) risk, as decisions regarding prevention efforts may be clear[100]. However, an understanding of longer-term risk may

provide a means for encouraging adherence to lifestyle or pharmacological therapies, especially for patients who have low short-term risk or might have difficulty understanding the importance of their short-term risk[100].

In a meta-analysis[101] of CVD risk scores, the authors identified 363 CVD risk scores/prediction models, with a range of predictors, outcomes, and populations for use. However, of the 363 models identified, the authors found that only 70 models were externally validated by independent researchers. In addition, many of these scores/models lacked methodical information and accompanying recommendations for how the scores could be applied in clinical care. Among the externally validated CVD risk scores, there are a few scores that are far more popular and well known than others (Table 6). Each of these risk scores was developed in a specific population and has accompanying population-specific recommendations for use. Most of these scores were not chosen for the current study based on either the recommended population (e.g., China) or requirement of a risk score component (e.g., family history of myocardial infarction) that is unavailable in the current project (Table 6).

The 10-year and lifetime Framingham CVD risk scores and the 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) risk scores are described in detail in section 1.4.2 (Table 7). Both the 10-year and lifetime Framingham risk scores have been shown to have relatively high external validity. There have been 44 validations of the Framingham CVD risk scores across multiple continents (i.e., Asia, Europe, Australia, and North America) encompassing a variety of populations[101,102]. In a meta-analysis of the lifetime Framingham risk score, which included 18 cohorts made up of Caucasian and black men and women, it reflected observed outcomes well[103]. Specifically, those with an optimal risk-factor profile had lower lifetime risks of

CVD outcomes (fatal coronary heart disease or nonfatal myocardial infarction and fatal or nonfatal stroke)[103]. This trend held when stratified by birth cohorts and race[103].

Although the Framingham scores are still widely used today, in 2013 the ASCVD risk scores were recommended by the American College of Cardiology/American Heart Association (ACC/AHA), which included support from the American Association of Cardiovascular and Pulmonary Rehabilitation, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease[100]. Like the Framingham risk scores, the ASCVD 10-year and lifetime scores have been validated in multiple studies in different populations. For example, in one validation study of 18,498 US adults, the predicted CVD risk and the observed CVD outcomes were similar. It was concluded that when used in the validated populations of US Caucasian and black men and women, the ASCVD demonstrated moderate to good discrimination of atherosclerotic CVD risk[104].

**Table 6. Common CVD Risk Scores**

| Name of Risk Score | Recommended Population | Reason for Exclusion |
|---|---|---|
| SCORE CVD death risk score[105,106] | European | Not recommended for use in United States |
| Reynolds Risk Score [107] | Women in the United States | Requires family history of MI |
| QRISK, QRISK2[108,109] | United Kingdom | Not recommended for use in United States |
| PROCAM [110] | Northern European | Not recommended for use in United States |
| MESA risk score[111] | United States | Requires family history of MI |
| JBS3[112] | United Kingdom | Not recommended for use in United States |
| China-PAR risk predictor[113] | Chinese | Not recommended for use in United States |
| PREDICT CVD risk predictor[114] | New Zealand | Not recommended for use in United States |
| 10-year Framingham[115] | United States | Not applicable |
| Framingham Lifetime[116] | United States | Not applicable |
| 10-year ASCVD[100] | United States | Not applicable |
| ASCVD Lifetime[100] | United States | Not applicable |

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; JBS, Joint British Societies; China-PAR, Predication for ASCVD Risk in China.

## Table 7. CVD Risk Score Components And Related Outcomes

| Risk score components | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Gender | Total cholesterol (mg/dL) | HDL cholesterol (mg/dL) | Systolic blood pressure (mmHg) | Blood pressure treatment (yes or no) | Current smoking (yes or no) | Diabetes mellitus (yes or no) | BMI | Race |
| Framingham 2008 | | | | | | | | | | |
| Lipids | x | x | x | x | x | x | x | x | | |
| BMI | x | x | | | x | x | x | x | x | |
| Framingham Lifetime | | | | | | | | | | |
| Lipids | x | x | x | x | x | x | x | x | | |
| BMI | x | x | | | x | x | x | x | x | |
| 10-year and Lifetime ASCVD | x | x | x | x | x | x | x | x | | x |

| CVD Outcomes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CHD death | Nonfatal MI | Coronary insufficiency | Fatal or nonfatal ischemic or hemorrhagic stroke | Transient ischemic attack | Intermittent claudication | Heart failure | Angina pectoris |
| Framingham 2008 | | | | | | | | |
| Lipids | x | x | x | x | x | x | x | x |
| BMI | x | x | x | x | x | x | x | x |
| Framingham Lifetime | | | | | | | | |
| Lipids | x | x | x | x | x | x | x | x |
| BMI | x | x | x | x | x | x | x | x |
| 10-year and Lifetime ASCVD | x | x | | x | | | | |

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; BMI, Body mass index; HDL, high-density lipoproteins; CHD, Coronary heart disease.

**Table 8. CVD Outcomes And Definitions**

| Cardiovascular Disease Outcome | Definition |
|---|---|
| Coronary heart disease (CHD) death | A death attributed to CHD, a disease in which the arteries supplying the heart with blood are impacted by plaque buildup[117]. |
| Nonfatal myocardial infarction | The heart muscle is cut off from the flow of oxygen-rich blood; without restoration of blood, the heart muscle begins to die[118]. |
| Coronary insufficiency | When one or more coronary arteries has insufficient blood flow which can then lead to lethal cardiac arrhythmias in the absence of myocardial necrosis[119]. |
| Fatal or nonfatal ischemic or hemorrhagic stroke | The flow of oxygen-rich blood to the brain is blocked (ischemic) or sudden bleeding in the brain (hemorrhagic). Brain cells can start to die after a few minutes. Blocked blood supply to the brain is most commonly caused by blood clots. High blood pressure and aneurysms can lead to bleeding in the brain[120]. |
| Transient ischemic attack (TIA) | TIA, also known as a "mini-stroke," may occur when a blood clot stops the flow of blood to the brain, but only for a short amount of time. Unlike a stroke, it does not result in permanent brain damage. However, a TIA increases the risk of having a full scale stroke in the future[120]. |
| Intermittent claudication | Intermittent claudication, or simply claudication, is the pain caused by too little blood flow. It is usually felt in the legs during exercise but may also cause pain in the arms. It is a symptom of peripheral artery disease, a circulation problem within the legs and arms[121]. |
| Heart failure | Results when the heart cannot pump enough blood due to lack of force such that not enough blood reaches the body[122]. |
| Angina pectoris | Associated with chest pain or discomfort (pressure or squeezing) in the chest, shoulders, arms, neck, jaw, or back when the heart does not get enough oxygen-rich blood[123]. |

### 1.4.2 Risk Scores

***Framingham 2008 10-year risk score***

The Framingham 2008 risk score was developed based on previous versions of the risk score to meet the need of a risk score to predict general CVD risk in adults[115]. The original risk score was published in 1998 and measured the outcome of CHD, defined as CHD death, nonfatal MI, unstable angina and stable angina. In 2002 the original Framingham risk score was modified through removing diabetes and adding hypertension treatment, smoking, and total cholesterol. The risk score was again modified in 2008 to address the need for an instrument that could identify the risk of a more encompassing composite CVD endpoint (i.e., any major atherosclerotic CVD event) that previous iterations were missing. In addition to the previous outcomes of CHD death, nonfatal MI, and angina, the following outcomes were added: coronary insufficiency, fatal or nonfatal ischemic or hemorrhagic stroke, transient ischemic attack, intermittent claudication and heart failure[115].

The development of the 2008 risk score included people 30 to 74 years of age who were free of prevalent CVD. Two calculations were developed for the Framingham 2008 risk scores. One was based on a cholesterol algorithm and a second based on a BMI algorithm. A study assessing the agreement between the BMI-based and cholesterol-based CVD risk scores[124] determined the average differences between the two risk scores were small (0.6% for men and 0.5% for women). Due to potential limitations with a risk score based on laboratory tests, such as cholesterol, a risk score that relies on measures collected as part of a more routine clinical care (e.g. BMI) may lead to the ability to follow participants through medical records more easily over time without the need for extra laboratory tests to collect information. Another potential benefit of

including BMI in the calculation of CVD risk is it might improve accuracy among an obese population, with varying severity of obesity, due to obesity's direct association with increased risk of CVD outcomes[72]. However, as no CVD risk score has been developed specifically among adults with class 1, 2 and 3 obesity, it is unclear whether a score with BMI versus cholesterol measures would be more accurate among adults with obesity.

The Framingham risk score has been categorized historically into three categories: low (10%), intermediate (10-20%), and high risk (20% or more)[125]. These categories are used not only to identify those at highest risk of CVD outcome, but also for guidance for when to start stain therapy as a preventative measure. The 10-year risk assessment is recommended to be done every four to six years among individuals 40 to 79 without established CVD or diabetes[100,105]. After screening, statin therapy combined with health behavior modification should be considered in those with a Framingham risk score of 20% or greater 10-year CVD event risk; or in those with 10% to 20% CVD risk as well as LDL ≥ 3.5 mmol/L, non-HDL ≥ 4.3 mmol/L, apolipoprotein B ≥ 1.2 g/L; or men ≥ 50 and women ≥ 60 years with 1 additional CVD risk factor (i.e. diabetes, atherosclerosis, chronic kidney disease)[126].

***Framingham lifetime risk score***

In 2006, the Framingham lifetime risk of atherosclerotic CVD was published to meet the need of estimating the impact CVD risk factors on lifetime risk of CVD. The lifetime score was created in the same population as the Framingham 2008 10-year risk score (i.e., individuals from the Framingham Heart Study who were free of prevalent CVD). CVD outcomes were myocardial infarction, coronary insufficiency, angina, stroke, and/or claudication, and like the 10-year risk score, two versions were calculated, one BMI and one laboratory based. The Framingham lifetime risk score has been categorized into two categories: low (<39%) and high risk (≥39% or more)[116].

Additionally, the lifetime score has been used to categorize people into five mutually exclusive risk factor groups: 1) all risk factors are optimal, 2) at least one risk factor is not optimal, 3) at least one risk factor is elevated, 4) one major risk factor is present, and 5) two or more major risk factors are present[127] (Table 9). These groups are then used to identify those at highest risk of CVD outcome with groups 1-3 being low risk and groups 4-5 as high risk. The use of the Framingham lifetime score has been used more for the identification of high-risk individuals and for guidance of behavioral changes rather than guidance for pharmaceutical recommendations.

***ASCVD 10-year and lifetime risk scores***

The ASCVD 10 year and lifetime score were created in 2013 by the ACC and AHA in collaboration with National Heart, Lung, and Blood Institute (NHLBI) and stakeholder and professional organizations to be used to develop guidelines to promote cardiovascular health. The ASCVD was created independently of risk scores already in use, including the Framingham risk score, due to the ACC/AHA belief that these scores had several limitations including non-representation of the current US general population, and poor endpoint definition or justification. Instead, the ASCVD was developed in multiple cohorts from large populations of both Caucasian and African-American patients in the United States with at least 12 years of follow-up. The endpoints chosen were based on clinician and patient relevance and with input from the American Stroke Association. The ASCVD 10-year and lifetime risk scores estimate an individual's risk of first atherosclerotic cardiovascular disease event defined as first occurrence of nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke[100].

Like the Framingham 10-year risk score, the ASCVD 10-year risk score is used to identify those at highest risk of CVD outcomes and who would likely benefit from statin therapy. The

ACC/AHA 2013 ASCVD risk score is categorized as low risk if <7.5 and high risk if ≥7.5%. Those at high risk are advised for initiation of a moderate to high intensity statin[128].

According to the evidence presented by the ACC/AHA guidelines for the use of the ASCVD risk score, the ASCVD lifetime score was not found to have compelling evidence for guiding pharmacologic therapy decisions[100]. Instead, it is recommended by the ACC/AHA that lifetime risk information may be used more appropriately to motivate therapeutic lifestyle change in younger individuals. While it is not recommended for use as a tool for pharmacologic therapy decisions, the ASCVD lifetime risk score has been categorized into two categories: low (<39%) and high risk (≥39% or more) to convey the future risk[129].

***Change in CVD risk score in bariatric surgery population***

There are some suggested contraindications to bariatric surgery, such as severe heart failure, unstable coronary artery disease and portal hypertension[130], which may influence the populations' baseline CVD risk. Thus, those who undergo bariatric surgery may have a slightly lower CVD risk, on average, than those not undergoing surgery at the same BMI and non-CVD related comorbidity levels. These relative contraindications may have an impact on the population undergoing surgery. Yet, overall there is evidence that CVD risk decreases after surgery, including evidence of decreases in CVD risk scores, and could help prevent CVD outcomes.

The basis for this change in risk is likely due to bariatric surgery's impact on several CVD risk factors[97] (e.g. systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol, smoking and diabetes)[131]. Although several CVD risk scores have been applied to studies in bariatric surgery, in general most studies report an overall decrease in CVD risk score at follow-up from presurgery values, independent of the risk score used[132-134]. In a review of CVD risk after surgery by Benraounne et al., the reduction of CVD risk based on the Framingham risk score varied

from a decrease of 2.7% to 4.0%, and the ASCVD score had a decrease of 11.5(+-7.4) to 7.2(+-6.1) after RYGB[135]. There may be a difference between biological sex and CVD risk reduction, with one study reporting a differential reduction in ASCVD risk score after one-year post-surgery (5.42% in males compared to 2.77% in females)[136].

While most studies of bariatric surgery show a decline in CVD risk, the magnitude of reduction seems to differ by factors outside of the conventional risk factors which contribute to the risk score. For example, surgical procedure seems to impact the Framingham risk score reductions. After roughly 12-15 months post-surgery, the Roux-en-Y gastric bypass (RYGB) Framingham absolute risk score reduction was 2.7 to 3.6 from pre-surgery levels in samples of 500 and 95[137,138], LAGB absolute reduction was 3.2 among a sample of 647[134] and 2.2 among a sample of 45 who underwent GS[132]. There is a lack of longer-term follow-up (i.e. many studies only following up to two years). Additional limitations of the literature are small sample sizes, and the study of bariatric surgery procedures which have fallen out of favor[7]. There is also a lack of studies investigating change in CVD risk over time may be impacted by factors not involved in the creation of risk score.

Overall, there is a lack of investigation into the impact of pre-surgery and post-surgery nontraditional CVD risk factors on the change in CVD risk score over time. While the literature may be sparse in the bariatric surgery population, there are examples of independent predictors of CVD risk change outside of the bariatric surgery population. For example, in a population with type 2 diabetes enrolled in a yearlong aerobic and resistance training intervention, improvement in physical fitness significantly predicted improvements in CVD risk factors (CRP and HDL cholesterol)[139] and the UK Prospective Diabetes Study (UKPDS) global CHD 10-year risk score independent of weight loss[139]. Also, while not directly evaluation change in CVD risk score, there

are studies which showed CVD risk score at a single time point differ by factors such as education, income, physical activity and ethnicity[140].

**Table 9. Framingham Lifetime Risk Score Component Categories[103]**

| | Total cholesterol (mg/dL) | Systolic blood pressure (mmHg) | Diastolic blood pressure | Current smoking (yes or no) | Diabetes mellitus (yes or no) |
|---|---|---|---|---|---|
| Optimal | <180 | <120 | /<80 | No | No |
| Not optimal | 180 to 199 | 120 to 139 | 80 to 89 | No | No |
| Elevated | 200 to 239 | 140 to 159 | 90 to 99 | No | No |
| Major | (≥240 | ≥160 | ≥100 | Yes | Yes |

## 1.5 Inflammation

Inflammation is a part of the immune system's response to the presence of harmful agents, such as physical wounds, bacteria or viruses. Damaged tissues signal the body to release chemicals to stimulate the body's inflammatory response. These chemicals begin a cascade of signals in the body to repair damaged tissues[126]. Inflammation can be separated into two categories, acute and chronic. Acute inflammation is defined by its short timeframe, edema, and increased leukocytes[141]. Chronic inflammation involves lymphocytes, macrophages, and proliferation of blood vessels and connective tissues, and has been associated with an increased risk of a multitude of diseases including CVD, diabetes, and certain types of cancer[142].

### 1.5.1 Obesity And Inflammation

Obesity is thought to be associated with chronic inflammation through an upregulation of pro-inflammatory mediators. These mediators are mostly related to the increase in adipose tissue.

As obesity severity increases, adipose tissue not only expands but its endocrine functions are also thought to change the tissue[143]. The expansion and change in adipose tissue result in an increase in the overexpression and secretion of adipocytokines or adipokines[144]. Adipokines include leptin, interleukin (IL-6), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and resistin, all of which are related to the inflammatory response[142]. Furthermore, due to obesity's association with inflammation, biochemical markers have been used to investigate the change in inflammation following the treatment of obesity. Several studies of multiple different weight loss interventions show an association between weight loss and CRP following the intervention. There is also evidence from cross-sectional studies that CRP is positively associated with BMI, waist circumference, and waist-hip ratio[145].

### 1.5.2 C-Reactive Protein

CRP is present in all people. CRP was initially identified as an acute-phase protein with elevated concentrations during a viral infection. More recently, elevated CRP levels have been associated with cardiovascular disease, chronic inflammatory conditions and even some cancers[146].

The CRP molecule is a pentameric protein composed of five noncovalently bonded polypeptide subunits[147,148] and is synthesized and secreted in the body by hepatocytes located in the liver. The most important regulator of CRP secretion is believed to be the cytokine IL-6[148], but tumor necrosis factor and cytokine interleukin (IL)-1 have also been linked to its stimulation and release[149]. When exposed to a stimulus (infection or tissue inflammation), the cytokines activate CRP release into the body and levels of CRP elevate. CRP functions to support the host

defense mechanisms through the activation of the complement system and phagocytic leukocytes[148].

The reaction of the levels of CRP in the event of a stimulus has made it a useful marker to monitor any cell damage that may be taking place in the body. When exposed to infection, CRP can rise rapidly to 1000-fold higher[148] then decline relatively quickly due to the half-life of roughly 18 hours[146]. Yet, when the stimulus for CRP release is thought to be a chronic condition like low grade inflammation, which usually lack outward or clinical signs of inflammation, CRP may remain in a minor but significantly elevated state in the body (above 1 mg/dL but below 10 mg/dL)[150]. These elevations in CRP are slightly above normal levels but lower than levels which would signal an acute infection (≥ 10.0 mg/dl). This has made CRP a useful, but non-specific marker for cell damage and chronic inflammatory conditions[151]. Thus, CRP can be used as a marker to monitor some chronic diseases which all have evidence of being associated with chronic inflammation. These diseases include rheumatoid arthritis, inflammatory bowel disease, and some vasculitis syndromes[151].

***Normal CRP***

In healthy adults, CRP circulates in the body at a concentration within the range of 0.5 to 1 milligrams per deciliter (mg/dL), while in unhealthy people the concentrations are continually elevated above normal levels[148].

There is variability within CRP levels in healthy adults. Studies have looked at biological and outside influences that may explain some of the variability. There is conflicting evidence for the impact of age and sex with some studies reporting no link between CRP and age and sex[151], and others suggesting among healthy adults, men and older individuals have significantly higher levels of CRP than women and younger individuals[148].

In twin studies, it is shown that there is a significant heritable component in CRP values that is independent of age and BMI[147]. Another piece of evidence that CRP levels may have a large genetic component, is that the self-correlation coefficient of CRP measurements repeated years apart is about 0.5 mg/dL[147] demonstrating minor change over time effects within individuals. CRP level does not vary by anemia, polycythemia, protein levels, red blood cell shape and seasonality[147,151].

***Elevated CRP***

A few risk factors for elevated CRP levels that are not due to acute infection have been identified. These factors include trans-fat consumption, obesity, hormone therapy, pregnancy and birth control pills[142]. Medications including cholesterol-lowering statin drugs and anti-inflammatories (such as aspirin, ibuprofen, diclofenac, and naproxen) have been associated with the potential to lower elevated CRP levels to the normal range[142].

Also, the increase in the amount of pro-inflammatory chemicals including IL-6, is thought to play a significant role in the underlying increase in chronic inflammation related to obesity. IL-6 is a cytokine that mediates the inflammatory response through a seine kinase cascade. Roughly a third of IL-6 originates from adipose tissue[142]. Production and secretion of IL-6 is upregulated in the presence of obesity due to the expansion of adipose tissue. Once IL-6 is released into the body, it goes on to stimulate the release of white blood cells and platelets and CRP[142].

### 1.5.3 Measurement

CRP can be measured in fresh or frozen plasma. There are two types of tests used to measure CRP which vary by the level of CRP they can detect. CRP tests which can measure higher amounts of CRP (above 10 mg/dL) are used if detection of infection is the primary goal. A second,

more sensitive CRP test can be used in the absence of infection when the primary goal is to evaluate low-grade systemic inflammation (i.e., levels below 10 mg/dL). These tests are referred to as high-sensitivity assays[152] and include immunonephelometry, immunoturbidimetry, high-sensitivity enzyme-linked immunosorbent assay (ELISA) and resonant acoustic profiling (RAP). When using these high-sensitivity assay techniques, CRP levels are often referred to as high sensitivity C-reactive protein (hsCRP). The assays can detect CRP within a range of 0.01 to 10 mg/L[152].

### 1.5.4 CRP And Health Outcomes

#### *Weight change and CRP*

Inflammation is a complication of obesity and has been associated with both weight gain and weight loss. A theory as to why weight change impacts CRP levels directly is based on the idea that weight change impacts adiposity. The change in adiposity is thought to influence the number of cytokines, importantly IL-6, which regulates CRP production and secretion. With either an increase or decrease in the amount of IL-6, CRP would also change, and the overall amount of inflammation would be impacted[145]. Due to the proposed biological mechanism of CRP's association with obesity, we would assume that as one either loses or gains weight through any mechanism, the decrease or increase in adipose tissue would correlate to a change in CRP. Weight loss interventions and long-term follow-up measuring weight gain have provided some evidence of the impact of weight changes on CRP levels in the body. For example, in both lifestyle and bariatric surgery interventions, weight loss and CRP levels decreased over time. In a lifestyle intervention which employed an increase in physical activity, weight decreased a mean of −6.2 kg (range, −15.0 to 0.0 kg) and CRP levels decreased to mean of −0.9 mg/L (range, −2.3 to 0.5 mg/L)[145]. In surgical interventions, a study reported the weight change was −33.1 kg (range, −44.3

to −23.3 kg) and the change in CRP level was −4.5 mg/L (range, −6.6 to −2.3 mg/L)[145]. These results indicate that larger declines in CRP levels occur as weight loss increases. The change in CRP after surgery is further confirmed in a meta-analysis where a decrease in CRP after multiple different bariatric surgical procedures (e.g. RYGB, LAGB, and vertical banded gastoplasty) was roughly 65%[153].

***CVD***

There is evidence that CRP should not be used as a standalone measurement of CVD risk, but instead used only in addition to the conventional risk factors of CVD. A cross-sectional study of 15,152 cases and 14,820 controls across 52 countries found that the population attributable risk for a myocardial infarction was almost completely accounted for by already known risk factors including smoking, dyslipidemia, hypertension, diabetes mellitus, abdominal obesity, depression and other psychological factors, low levels of physical activity, inadequate fruit and vegetable consumption, and both high and low alcohol consumption[150]. While CRP may not be considered a viable option to assess all CVD outcomes alone, there is a body of literature that has concluded chronic low-grade inflammation, which can be measured with CRP, has an impact on the risk of a CVD event[154-156]. Thus, the American Heart Association/Centers for Disease Control (AHA/CDC) guidelines for global CVD risk assessment define three risk groups by serum CRP levels: <1, 1–3 and >3 mg/l, for low-, moderate-, and high-risk groups, respectively[152] to be used in conjunction with other more traditional CVD risk factors.

While CRP may not be the best way to identify CVD risk alone, it is still important to understand the chronic inflammation being reflected by elevated levels of CRP. There is a lack of information on how changes in CRP over time (and thus inflammation over time) may impact

changes in CVD risk. More information is needed on the potential relationship between change in CRP and potential change in CVD risk over long term follow-up.

### 1.6 Longitudinal Assessment Of Bariatric Surgery-2 (LABS-2) Study

In 2002 the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored Working Group on Research in Bariatric Surgery recognized the need to better understand bariatric surgery procedures and clinically important predictors of outcomes. In response to this recommendation, the Bariatric Surgery Research Consortium was established and included clinical centers and a data coordinating center. Together the centers' focus was on providing information through research on the potential complications from bariatric surgery as well as its impact on obesity[157].

The Longitudinal Assessment of Bariatric Surgery (LABS)-2 is one of several studies that resulted from this consortium. LABS-2 was a prospective cohort study of 2,458 adults who were at least age 18. Participants were recruited between February 2005 and February 2009 and underwent their first bariatric surgery as part of clinical care between April 2006 and April 2009 at one of ten hospitals at six clinical centers throughout the United States: Columbia University Medical Center and Weill-Cornell University Medical Center (New York), University Health Systems of Eastern North Carolina and East Carolina University (North Carolina), Neuropsychiatric Research Institute (North Dakota), Oregon Health and Science University and Legacy Good Samaritan Hospital (Oregon), University of Pittsburgh Medical Center (Pennsylvania), and Virginia Mason Medical Center and University of Washington (Washington). Participants were followed annually for seven years or until January 31, 2015, whichever came

first. The majority of participants were women (78.6%); and white (86.2%). At their pre-surgery assessment, the median age was 46 years (IQR: 37, 54), and median BMI was 45.9 kg/m$^2$ (IQR: 33.0, 94.3)[158] .

A previous analysis of pre-surgery LABS-2 data[116] found that among participants without diabetes or existing CVD prior to surgery (n=2070), over a third (36.5%) had high 10-year CHD predicted risk, and most (76%) participants with low 10-year predicted risk, had high lifetime CVD predicted risk. The study concluded there is a need for long-term monitoring and treatment of elevated CVD risk factors among bariatric surgery patients, to maximize lifetime CVD risk reduction. Additional analyses of LABS-2 data found improvements in the prevalence of comorbidities related to CVD at 7 years post-surgery compared to pre-surgery (i.e. type 2 diabetes [11.6 vs 28.3%], high LDL [14.3 vs 33.3%], hypertension [51.6 vs 67.6%]),[36] as well as associations between weight regain and the progression of diabetes, hyperlipidemia, and hypertension[37]. Additionally, there was a LABS-2 study which reported on change in CRP in both RYGB and LAGB surgery groups[159]. They reported an improvement in CRP in both RYGB and LAGB from pre-surgery to 3 years post-surgery[159]. However, these studies were unable to speak to change in predicted CVD risk, CVD event rate, longer term CRP change or CRP CVD risk score categorization following surgery.

LABS-2 is a study that stands out among other longitudinal studies not only due to its use of a country wide consortium, but also because if its high levels of data collection in participants after several years of follow-up. In a meta-analysis of other bariatric studies, a high number of participants are lost one year after surgery, with as many as 75% of RYGB lost and 50% of LAGB lost to follow-up[160]. In contrast, LABS-2 achieved fairly high levels of retention with weight

measurements collected in over 80% of participants who underwent RYGB or LAGB in years 6 and 7 (87% and 83%, respectively)[36].

***Surgical procedure**:* All analysis will be carried out in LABS-2 participants who underwent RYGB due to 1) the majority of participants in LABS-2 underwent RYGB; 2) RYGB is associated with greater weight loss compared to both SG and LAGB, and better or similar improvement in comorbidity outcomes[62-64], and 3) RYGB is still a fairly common procedure with the second highest usage rates in the United States at 17.8%[161].

***LABS data points to be used**:* LABS-2 participants underwent standardized research assessments at their pre-surgery assessment and at a 6 month and annual follow-up assessments where information was gathered by trained research staff through certified protocols and questionnaires. To reduce site difference in data collection, sites used LABS-provided equipment to collect data. Objective measures of patient status and co-morbidities were used when available. Weight was collected through in-person visits, medical records, or self-report when other measures not available. Laboratory measures including total cholesterol, HDL, LDL, triglycerides, hemoglobin A1C (HbA1c), glucose, high-sensitivity CRP, were assayed at a central laboratory from samples collected by each site. An 8 hour fast was required for LDL, triglycerides, glucose and CRP. Information on the comorbidities was collected through a variety of measures including the use of self-repot, medical records, and physical examination. This information was utilized to report the presence or absence of any LABS-2 defined comorbidity including history of ischemic heart disease, congestive heart failure, hypertension, hyperlipidemia, and dyslipidemia. Sociodemographics were self-reported. Validated questionnaires were used to assess depressive symptoms over the past week were measured with the Beck Depression Inventory (BDI) version 1. Medication and frequency of use was assessed through asking participants to bring their

medication from the past 90 days to each research assessment and complete the LABS-2 Medication Form[162]. For this study, CVD was defined as having a: nonfatal myocardial infarction (MI), stroke, ischemic heart disease, congestive heart failure, angina, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or death attributed to CVD. Mortality was determined using the annual study follow-up and the National Death Index[163] through December 31, 2014. Underlying cause of death was obtained from the National Death Index death certificate data. CVD mortality was defined as diseases of the circulatory system using the World Health Organization (WHO) Global Burden of Disease Study cause list (ICD 10 codes: I00-I99)[164].

## 1.7 Aims

Among adults who underwent RYGB:

1. Report the predicted 10-year and lifetime CVD risk, using 10-year and lifetime Framingham-lipid, Framingham-BMI, ASCVD, as well as the risk score components, by annual assessment through 7 years of follow-up among participants with no history of CVD. Evaluate pre- to post-surgery change in predicted CVD risk (manuscript 1).
    a. Report predicted CVD risk from lowest weight until end of follow-up (i.e., during weight regain) and evaluate change over time.
    b. Compare how different risk scores influence predicted CVD risk.
2. Report non-fatal CVD events and CVD-related mortality by time since RYGB and the event rates (manuscript 1).
    a. Compare event rates during short-mid (<5 years) vs. long-term (5-7 years) follow-up.

    b. Compare post-RYGB CVD-related mortality to the expected mortality in the general population matched for age, sex and race.

3. Determine the pre-surgery factors independently related to pre- to post-surgery change in predicted 10-year and lifetime CVD risk scores, respectively, controlling for pre-surgery CVD risk (manuscript 2).
4. Report the pre-surgery and post-surgery CRP values by annual assessment through 7 years of follow-up. Evaluate pre- to post-surgery change in CRP.
    a. Report CRP trajectory groups based on pre-surgery through end of follow-up and evaluate differences between groups (manuscript 3).
5. Determine if pre- to post-surgery change in CRP is related to pre- to post-surgery change in predicted ASCVD 10-year risk (manuscript 3).

# 2.0 Manuscript 1: Change In Predicted 10-Year And Lifetime Cardiovascular Disease Risk Following Roux-En-Y Gastric Bypass: Results From A 7-Year Multicenter Prospective Cohort Study

## 2.1 Brief Overview

**Objective** To report sex-specific changes in CVD risk following Roux-en-Y gastric bypass surgery (RYGB).

**Background:** Long-term changes in cardiovascular disease (CVD) risk following bariatric surgery are not well characterized.

**Methods:** Between 2006-2009 1770 adults enrolled in a prospective cohort study underwent Roux-en-Y gastric bypass (RYGB) at 1 of 10 U.S. hospitals. Research assessments were conducted pre-surgery and annually post-surgery over 7 years. Sex-specific predicted 10-year and lifetime CVD risk were calculated using the Framingham-lipid, Framingham-body mass index (BMI) and Atherosclerotic (ASCVD) scoring algorithms among participants with no history of CVD. Of 1566 eligible participants, 1234 (75.9%) with CVD risk determination pre- and post-surgery were included (1013 females, 221 males).

**Results**: Based on the Framingham-lipid, the percentage of females with predicted high (>20%) 10-year CVD risk declined from pre-surgery (6.5% [95% CI:6.7-7.5]) to 1 year post-surgery (1.0% [95% CI:0.8-1.2]; p<0.001), then increased 1 to 7 years post-surgery (to 2.8% [95% CI:1.6-3.3]; p=0.003), but was lower 7 years post-surgery versus pre-surgery (p<0.001). Time trends for percentage of high-risk participants and mean CVD risk scores were similar for both sexes and other evaluated CVD risk scores. For example, among males mean lifetime ASCVD

score declined from pre-surgery to 1 year post-surgery, then increased 1 to 7 years post-surgery. However, there was a net decline from pre-surgery ($p<0.001$).

**Conclusion:** Among both females and males, predicted 10-year and lifetime CVD risk was substantially lower 7 years post-RYGB than pre-surgery, suggesting RYGB surgery can lead to sustained improvements in short- and long-term CVD risk.

## 2.2 Introduction

As body mass index (BMI) increases, the risk of developing cardiovascular disease (CVD) also increases[1]. The association is thought to be primarily a function of an increase in CVD risk factors (i.e., hypertension, dyslipidemia, and insulin resistance[2]) related to increasing BMI[3]. Obesity also directly increases risk of CVD by impacting cardiovascular structure and function. For example, obesity increases the risk of left ventricular structural abnormalities which may lead to remodeling and left ventricle hypertrophy, left atrial enlargement, and impairment of systolic and diastolic function[4]. Those with severe obesity (BMI $\geq$ 40 kg/m$^2$) are an especially high risk population for specific types of CVD including coronary artery disease, myocardial infarction and heart arrhythmias, compared to those with less severe obesity[5].

Roux-en-Y gastric bypass (RYGB) surgery, which was the most common modern-day bariatric surgical procedure prior to 2013 and is currently the second most common procedure[6,7], is an effective treatment for severe obesity[8]. Surgical changes to the gastrointestinal tract result in substantial weight loss and impact metabolic disorders including the remission of Type 2 diabetes (T2D)[9]. There is also evidence that CVD risk and CVD-related mortality decline in the first few years following RYGB surgery[10-12]. However, associations between post-surgery weight regain

with worsening of T2D, hyperlipidemia, and hypertension[13], suggest initial improvements in CVD risk may diminish over time. Studies of currently performed bariatric surgical procedures with repeated measures over long-term follow-up are needed to evaluate the sustainability of the reduction in CVD risk[12,14]. Furthermore, given evidence that biological sex may moderate the effect of interventions on CVD risk (i.e., due to general biological differences, as well as differences in environment, lifestyle and attitudes that can affect CVD risk and CVD outcomes)[15,16], there is a need to evaluate sex-specific changes in CVD[17,18].

Since CVD events (e.g. stroke, heart attack, angina) usually occur later in life, risk assessment for future CVD events is critical to monitoring health status[19]. This can be done by evaluating individual risk factors (e.g. systolic pressure, T2D, treatment for hypertension), or with CVD risk scores, which use an array of CVD risk factors to estimate the likelihood of an individual having a CVD event within a specified time frame (i.e. 10-years or lifetime)[20,21].

The primary aim of this study was to report sex-specific changes in CVD risk following RYGB in a large multisite prospective cohort study with long-term follow-up. Changes from pre-surgery to 7 years post-surgery in predicted 10-year and lifetime CVD risk (based on the Framingham Risk Score (FRS)[22] and the Atherosclerotic CVD (ASCVD)[21] risk score), as well as individual CVD risk factors, were evaluated. Secondary aims were to evaluate changes in predicted CVD risk in relation to post-surgery weight regain, as well as to report short- and long-term rates of post-surgery non-fatal CVD events and CVD-related mortality.

## 2.3 Materials And Methods

### *Design and Participants*

The Longitudinal Assessment of Bariatric Surgery (LABS)-2 was a prospective cohort study of 2,458 adults who were at least age 18 at time of enrollment[23]. Participants who underwent their first bariatric surgery between April 2006 and April 2009 were recruited between February 2005 and February 2009 at one of ten hospitals at six clinical centers throughout the United States. Research assessments are described in **Supplementary Appendix 1**.

Participants were eligible for evaluation of the secondary aim of CVD event reporting if they underwent RYGB (N=1770) regardless of CVD status at pre-surgery assessment. Per recommended exclusion criteria[19,21,22], CVD risk scores were not calculated for participants with a history of CVD (n=204. For the primary aim of reporting change in CVD risk after RYGB, all data components to calculate CVD risk scores at the pre-surgery assessment and at least one follow-up assessment were required for participants to be included in the analysis of CVD risk (n=1234 of 1566 without a history of CVD prior to the first post-surgery assessment, 78.7%) (**Supplementary Figure 1**).

### *Measures*

Assessment of sociodemographics, anthropometrics and individual CVD risk score components has been described previously[13] and is provided in **Supplementary Appendix 1**.

***CVD risk scores***

The Framingham and the ASCVD 10-year and lifetime CVD risk scores were calculated using published algorithms[19,21,22]. All four scores utilize age, sex, total cholesterol, systolic blood pressure, blood pressure treatment, smoking status, and T2D and hyperlipidemia treatment. Race is also used in ASCVD scoring algorithms. Both risk scores both predict coronary heart disease (CHD) death, nonfatal myocardial infarction (MI) and stroke, but the Framingham also predicts coronary insufficiency, transient ischemic attack, intermittent claudication, heart failure and angina pectoris. Alternative versions of the Framingham 10-year and lifetime risk scores (hereafter referred to as "Framingham-lipid") replace lipid variables (total cholesterol and hyperlipidemia treatment) with BMI[22] which allows for calculation of risk with less clinical data (hereafter referred to as "Framingham-BMI"). Pre-surgery age was used to calculate risk scores at all assessments to eliminate the effect of aging on change in risk[24]. CVD scores were not calculated for participants following a CVD event[19,21,22].

To describe CVD risk and to help guide statin therapy decisions in the clinical setting, both the Framingham and ASCVD 10-year risk scores are categorized[25,26]. The Framingham 10-year risk categories are defined as: low (score <10%), intermediate (10-20%), and high (>20% or more) 10-year risk[27]. The ASCVD 10-year categories are defined as low (score <7.5%) and high (≥7.5%) 10-year risk[28]. The Framingham 10-year intermediate and high risk categories[29] and the ASCVD high risk category indicate it may be appropriate to initiate statin therapy[30]. Lifetime scores are intended to motivate patients to make lifestyle changes rather than to guide pharmacological interventions[19]. The Framingham-lipid, Framingham-BMI and ASCVD lifetime scores utilize the same cut point to indicate low (<39%) and high (≥39%) lifetime CVD risk.

***CVD events***

A LABS-certified clinical researcher used medical records, physical examination, and patient interviews to determine history of CVD prior to surgery, and CVD events annually post-surgery[23]. CVD-related mortality was determined using the annual study follow-up and the National Death Index[31] through December 31, 2014. For this study, CVD was defined as having a nonfatal myocardial infarction (MI), stroke, ischemic heart disease, congestive heart failure, angina, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or death attributed to CVD. Additional information on CVD assessment and identification of CVD-related mortality is available in **Supplementary Appendix 1**.

To be able to compare the observed CVD-related mortality in the 7 years following RYGB to the CVD-related mortality rate in the general population matched on participants' sex, age and race, and calendar year, sex-, age-, race-, and year-specific crude mortality rates from the U.S. general population for each calendar year from 2006-2014 were downloaded from the death certificate database collected by the Centers for Disease Control and Prevention (CDC) Wonder Underlying Cause of Death[32].

***Statistical analysis***

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). All reported p values are two-sided; p values less than 0.05 are reported to guide interpretation of findings.

All further analyses were stratified by sex. Descriptive statistics were used to summarize participant characteristics. The observed CVD risk scores, as well as individual CVD risk components [i.e., systolic blood pressure/diastolic blood pressure/treatment for hypertension, total cholesterol /treatment for hypercholesterolemia, high-density lipoproteins (HDL-C), T2D and

current cigarette smoking], were reported by time point in relation to surgery through 7 years of follow-up. Both continuous and categorical versions of the risk scores and components are reported. Because the Framingham 10-year intermediate and high risk categories[29] can both be used to initiate statin therapies, these groups were combined for some analyses, while the three category version (i.e., low, intermediate and high) was used to describe the more detailed change in risk score category over time.

Binary mixed models were used for dichotomous CVD risk categories and CVD risk score components, and mixed-effects ordinal logistic regression models were used for three-level Framingham 10-year CVD risk categories. Likewise, linear mixed models were used to estimate the mean of continuous CVD risk scores and CVD risk score components by time point. Mixed models used all available data via maximum likelihood, with a person-level random intercept, and controlled for pre-surgery factors related to missing data (i.e., site, age and pre-surgery smoking status), with time since surgery entered as a discrete fixed effect. Pairwise comparisons were made between pre-surgery and year 1 (to assess short-term change), pre-surgery and 7 years (to assess long-term change), as well as year 1 and 7 years (to assess the durability of the short-term change). P values were adjusted by simulation for multiple comparisons[33]. The modeling was repeated for estimating the distributions of categorical risk groups and the mean of continuous CVD risk scores in relation to weight regain, with time since participants' lowest recorded weight entered as a discrete fixed effect.

Event rates were calculated for non-fatal CVD events and CVD-related mortality by dividing the number of events by the person-years of observation per 1000 person-years, overall and by short (<5 year) and long-term follow-up (≥ 5 years)[34]. The matched mortality rate in the general population was calculated by multiplying the sex-, age-, race-, and year-specific crude

mortality rate per 1,000 from the general population by the number of LABS-2 RYGB participants with each characteristic. Standardized mortality ratios (SMRs) were calculated as the ratio of observed morality rate in the RYGB sample to the calculated mortality rate in the matched-general population. The 95% confidence intervals (CI) for the event rates and the SMRs were constructed using the Poisson distribution.

## 2.4 Results

Within the CVD risk score sample (1013 females, 221 males), the median age of females was 45 years (IQR: 36-53), 84.9% were white, and median BMI was 46.1 kg/m$^2$ (42.2-51.3). Among males, the median age was 47 years (IQR: 38-55), 92.3% were white, and median BMI was 47.4 kg/m$^2$ (IQR: 43.2-53.0). Additional characteristics by sex are reported in **Table 10**.

Data completeness of CVD scores among the sex-specific analysis samples by time period is provided in supplemental material (**Supplementary Table 12**). Across follow-up, 64.1% of potential CVD risk scores were determined among females and 60.9% among males.

***CVD risk.***

**Figure 1** shows the modeled percentages (95% CI) of females and males categorized as intermediate/high or high risk of having a CVD event within 10-years or lifetime based on the Framingham-lipid, Framingham-BMI and ASCVD scores. The estimated percentage of females and males with predicted intermediate/high or high 10-year risk was lower 1 year post-surgery vs pre-surgery (p for all <0.001), then appeared to increase from 1 year to 7 years post-surgery (p for both Framinghams <0.01; for ASCVD females p=0.14, males p=0.08). Still, the percentage with predicted intermediate/high or high 10-year risk was lower at 7 years compared to pre-surgery (p

for all <0.001). Similar to the 10-year results, both Framinghams and ASCVD categorized fewer female and male participants with high lifetime risk at 1 year post-surgery compared to pre-surgery (p for all <0.001**, Figure 1;** values provided in **Supplementary Table 13**). Though the percentage of females and males with high risk increased from 1 year to 7 years post-surgery (p for all ≤0.01 with exception of female Framingham-lipid, p=0.12), the percentage with high risk was lower at 7 years compared to pre-surgery (p for all <0.001). A comparison of the modeled means of the 10-year and lifetime CVD risk scores by time point revealed similar time trends (**Supplementary Table 4, Supplementary Figure 4**).

Although time trends were similar across 10-year and lifetime CVD risk scores for both sexes, the percentage identified as high risk varied by score and sex (e.g., among females, the percentage with high 10-year CVD risk, was highest with the Framingham-BMI and lowest with the ASCVD; the percentage with predicted high lifetime CVD risk was highest with ASCVD and lowest with Framingham-lipid). Likewise, the magnitude of change over time varied by score and sex (e.g., among males, there was a greater absolute and relative decrease in the percentage with predicted high lifetime risk 1 year and 7 years post-surgery based on the Framingham-lipid vs. the Framingham-BMI or ASCVD).

***CVD risk score components***

**Figure 2** shows the modeled values of CVD risk score components (i.e. total cholesterol, HDL-C, systolic blood pressure, blood pressure treatment, smoking prevalence, T2D and BMI) by time in relation to RYGB among females. Although most CVD risk score components were different (i.e. worse) in year 7 compared year 1 (**Figure 2**, values provided in **Supplementary Table 15)**, both year 1 and year 7 values were different (i.e. better) compared pre-surgery (p for all <.01). An exception was smoking, the prevalence of which was higher (i.e., worse) 1 year and

7 years post-surgery vs pre-surgery (p for both <.001). Time comparisons were similar among males compared to females (i.e. worse at year 7 compared to year 1 but better at year 7 compared to pre-surgery) (**Supplementary Figure 6**, **Supplementary Table 15**).

***Changes in CVD risk in relation to weight regain***

From the CVD risk sample of 1234 participants, 1102 (911 females and 191 males; **Supplementary Figure 4**) had CVD risk determination following their lowest recorded weight (median time since surgery=4.4 [IQR=1.6-7.5] years; median follow-up after lowest weight=2.7 [IQR=0.4-6.5] years). The percentage of participants with predicted intermediate/high or high 10-year and lifetime risk increased across time as a linear function of weight regain for both females and males (p for all ≤0.01) except for the ASCVD 10-year, which showed a similar trend in males (p=0.06) but did not appear to increase among females (p=0.92) (**Figure 3**).

***CVD events***

The frequency and the rates of non-fatal CVD events and CVD morality are reported in **Table 11** among all participants who underwent RYGB (N=1770)**;** the frequency of these outcomes by time in relation to RYGB is available in supplemental material (**Supplementary Table 16**). For both females and males, atherosclerotic cardiovascular disease was the most common ICD-10 coded CVD-related mortality (**Supplementary table 17**).

Among females, there were 499 non-fatal CVD events and 8 CVD deaths within 7 years following RYGB, corresponding to a non-fatal event rate of 50.4 (95% CI:41.6-61.2) per 1000 person-years and CVD mortality rate of 0.9 (95% CI:0.5-1.9) per 1000 person-years. The SMR for females was 1.18 (95% CI:0.51, 2.32; p=0.74). The non-fatal event rate was higher during long-term versus short-term follow-up (61.1 [95% CI:48.5-77.0] vs 42.5 [33.8-53.3] per 1000 person-year; p<0.001). The mortality rate appeared higher during the long-term versus short term

follow-up but given the low frequency of the outcome, statistical power to evaluate this comparison was limited (1.2 [95% CI:0.5-3.3] vs 0.8 [95% CI:0.3-2.1] per 1000 person-years; p=0.52).

Among males, there were 179 non-fatal CVD events within 7 years following RYGB, corresponding to an event rate of 71.6 (95% CI:53.7-95.5) per 1000 person-years and CVD mortality rate of 4.3 (95% CI:2.3-8.2) per 1000 person-years. The SMR for males was 1.96 (95% CI:0.89, 3.71; p=0.09). There was not clear evidence that the non-fatal event rates among males differed during long-term versus short-term follow-up (65.4 [95% CI:45.7-93.6] vs 76.3 [95% CI:53.9-108.1] per 1000 person-year; p=0.47). The mortality rate was higher during the long-term versus short term follow-up (8.8 [95% CI:4.2-18.3] vs 1.6 [95% CI:0.4-6.2] per 1000 person-years; p=0.03).

## 2.5 Discussion

Among a large cohort of adults with severe obesity, discounting age, predicted 10-year and lifetime CVD risk was lower throughout 7 years following RYGB surgery versus pre-surgery whether assessed with the Framingham-lipid, the Framingham-BMI or the ASCVD scoring algorithm. This was true whether considering the percentage of participants with elevated risk or the sample's mean risk. Although the magnitude of improvement in CVD risk varied by score and timeframe, improvement was substantially larger 1 through 7 years following RYGB than what is typically achieved from diet, exercise or lifestyle interventions aimed at weight loss or CVD risk reduction in overweight and obese adults[35-37]. For example, 1 year post-RYGB, the percentage of participants with high CVD risk decreased by 84.6% in females and 89.0% in males with the

Framingham-lipid algorithm, or by 73.2% in females and 60.6% in males with the ASCVD algorithm. Seven years post-RYGB these values were still striking, with 57% and 79% decreases in females and males, respectively, with the Framingham-lipid algorithm, or 60.6% and 38.4% decreases in females and males, respectively, with the ASCVD algorithm.

The reductions in overall CVD risk found in this study are supported by previous findings in other bariatric surgery research. For example, a retrospective cohort study with 1724 RYGB participants and 1724 matched non-surgical controls found a reduction in CVD events (e.g. myocardial infarction, congestive heart failure, or stroke) in the surgical group. After 12 years of follow-up number of CVD events was 63 in the RYGB group and 110 in the control group[14]. Results showed that the RYGB group had significant reductions in CVD events compared to the non-surgical control group[14].

Multiple short term (10-year) and long-term (lifetime) CVD risk scores were employed due to the difference between the usage of the scores in clinical care and lack of a consensus on which CVD risk score is best for the bariatric surgery population. The selected CVD risk scores were chosen due to the ability of each score to be used in younger populations in which CVD events are less likely to occur. Additionally, the 2008 Framingham score was chosen due to its prevalence, recognizability, and high external validity. However, the Framingham was developed among only Caucasians, and includes CVD outcomes without proven statin therapy benefit (e.g. heart failure). Thus, the ASCVD risk score, which addresses these limitations and is recommended by the American College of Cardiology/American Heart Association (ACC/AHA)[21], was also used.

While both Framingham scores and the ASCVD score showed similar trends of change in 10-year and lifetime CVD risk over time, the scores differed in the percentage of participants

identified as having high 10-year and lifetime CVD risk. For example, the Framingham-BMI 10-year algorithm categorized more participants as high risk across follow-up compared to the lipid version. This difference in categorization may be due to the high levels of obesity among bariatric surgery patients both before and after surgery, compared to the general population in which the scores were developed. Compared to the ASCVD score, both Framingham scores identified more women and men as having intermediate or high 10-year risk, perhaps because the Framingham predicts more outcomes. Given these risk designations can be used for the initiation of statin therapy, and the lifetime risk scores can be used to motivate patients to make behavioral changes, score selection has important clinical implications. For example, more females and males would be identified as potential candidates for initiation of statins if the Framingham-BMI was used versus the Framingham-lipid, or either Framingham versus the ASCVD.

Similar to a previous study showing select CVD risk factors (i.e. increases in SBP, HDL-C) increased as a function of weight regain[38], the current study demonstrated that the percentage of participants with predicted intermediate/high or high for 10-year and lifetime CVD risk (with the exception of the 10-year ASCVD in women) increased as a function of time since lowest weight. Future work should investigate additional factors that contribute to change in CVD risk over time among adults who undergo bariatric surgery and interventions that may mitigate weight regain and associated CVD risk factor changes.

The non-fatal CVD event rates within the current study revealed females had a higher rate of non-fatal CVD events in the long-term (i.e., 5 or more years) versus short-term (i.e., fewer than 5 years) post-surgery. In contrast, the short- vs. long-term non-fatal CVD event rates were similar among males (and similar to the female long-term rate). There are several reasons why females, but not males, may have lower rates in the short-term. Females may be physically healthier prior

to surgery. Specifically, men undergoing bariatric surgery tend to be older, have higher BMI, and more obesity-related comorbidities compared to women[39]. Additionally, women develop CVD, on average, 7 to 10 years after men. Thus, the higher rate among women 5 years after surgery may be a reflection of aging[40].

Our post-RYGB sample had a SMR higher than 1 (females: 1.18; males: 1.96), indicating a higher mortality rate compared to the general population, adjusted for age, sex and race. This could reflect that despite improvements in weight and comorbidities following surgery, post-surgical patients still have higher levels of obesity and other comorbidities including T2D, respiratory disorders and non-alcoholic fatty liver disease[41]. However, the 95% CI of these SMR included 1. Thus, additional research is needed to determine whether these findings reflect low power to detect a difference or no actual difference.

***Strengths and limitations***

Major strengths of this study were the longer-term follow-up, which allowed for continued measurement of CVD risk through maximum weight loss and several years of weight regain in adults undergoing RYGB, and the large geographically diverse cohort. Additionally, multiple common CVD risk algorithms were compared.

Several limitations should be considered when interpreting the data, including the lack of representation of the gastric sleeve procedure which was uncommon during the study's time period (2006-2009), but has surpassed RYGB as the most common procedure performed in the United States[42]. Also, this study lacked a non-surgical comparison group. Thus, the impact surgery had on reductions in risk, events and mortality cannot be commented on directly. Similarly, because CVD risk was calculated independent of age (i.e. participant age at pre-surgery was used for all CVD risk score calculations), the impact of age on CVD risk is lost. Additionally, our cohort was

86% Caucasian, thus the ability to apply the findings of this study to other populations may not be appropriate. Finally, due to the lack of CVD events in our cohort, there was a lack of statistical power for some short-term versus long-term comparisons and for a precise SMR estimate.

## 2.6 Conclusions

Among a large cohort of adults who underwent RYGB surgery, predicted 10-year and lifetime CVD risk improved after surgery. In general, discounting age, CVD risk declined from pre-surgery to 1 year, then increased between 1 and 7 years post-surgery. However, after 7 years, CVD risk was substantially lower among both females and males compared to pre-surgery. While similar time trends were evident using all three CVD risk scores, the percentage of patients identified as having high 10-year and lifetime CVD risk and the magnitude of change over time, differed by score and sex. These findings help inform sex-specific short and long-term improvements in CVD risk after RYGB surgery and demonstrate that CVD risk score selection has important clinical implications.

## 2.7 Tables and Figures

**Table 10. Characteristics Of Adults Prior To Undergoing Roux-En-Y Gastric Bypass In The Cvd Risk Score Sample And Cvd Event Sample, Stratified By Sex.**

| | CVD risk score sample (N=1234)[a] No. (%)b | | CVD event sample (N=1770) No. (%)[b] | |
|---|---|---|---|---|
| | Female (N=1013) | Male (N=221) | Female (N=1413) | Male (N=357) |
| Age, years | | | | |
| Median (25th -75th %-ile) | 45 (36, 53) | 47 (38, 55) | 45 (36, 53) | 47 (39, 56) |
| Range | 19-70 | 19-75 | 19-73 | 19-75 |
| Race | | | N=1397 | N=354 |
| White | 860 (84.9) | 204 (92.3) | 1177 (84.3) | 317 (89.5) |
| Black | 115 (11.4) | 14 (6.3) | 168 (12.0) | 28 (7.9) |
| Other | 38 (3.8) | 3 (1.4) | 52 (3.7) | 9 (2.5) |
| Ethnicity | | | | N=356 |
| Hispanic | 39 (3.8) | 7 (3.2) | 72 (5.1) | 15 (4.2) |
| Non-Hispanic | 974 (96.2) | 214 (96.8) | 1341 (94.9) | 341 (95.8) |
| Married or living as married[c] | 788/1302 (60.6) | 231/332 (69.6) | 788/1301 (60.6) | 231/332 69.6 |
| Education | N=970 | N=209 | N=1303 | N=332 |
| High school or less | 231 (23.8) | 45 (21.5) | 312 (23.9) | 73 (22.0) |
| Some college | 419 (43.2) | 87 (41.6) | 559 (42.9) | 141 (42.5) |
| College degree | 320 (33.0) | 77 (36.8) | 432 (33.2) | 118 (35.5) |
| Employed for pay[c] | 680/967 (70.3) | 150/206 (72.8) | 894/1298 (68.9) | 231/328 (70.4) |
| Household income, US $ | N=939 | N=205 | N=1263 | N=326 |
| Less than 25,000 | 181 (19.3) | 29 (14.2) | 262 (20.7) | 54 (16.6) |
| 25,000-49,999 | 278 (29.6) | 58 (28.3) | 368 (29.1) | 79 (24.2) |
| 50,000-74,999 | 216 (23.0) | 42 (20.5) | 299 (23.7) | 79 (24.2) |
| 75,000-99,999 | 141 (15.0) | 30 (14.6) | 188 (14.9) | 49 (15.0) |
| >100,000 | 123 (13.1) | 46 (22.4) | 146 (11.6) | 65 (19.9) |

**Table 10 (Continued)**

| | CVD risk score sample | | CVD event sample | |
|---|---|---|---|---|
| Current smoker | 18 (1.8) | 5 (2.3) | 32 (2.3) | 11 (3.1) |
| | N=1011 | | N=1410 | N=356 |
| Body mass index, kg/m$^2$ | | | | |
| Median (25th -75th %-ile) | 46.1 (42.2, 51.3) | 47.4 (43.2, 53.0) | 46.3 (42.1, 51.5) | 47.8 (43.4, 53.3) |
| Range | 34.1-81.0 | 33.7-76.0 | 33.8-81.0 | 33.7-76.0 |
| Hypertension medication[c] | 560 (55.3) | 140 (63.3) | 777/1394 (55.7) | 239/353 (67.7) |
| Hyperlipidemia medication[c] | 266/1007 (26.4) | 75/221 (33.9) | 380/1379 (27.6) | 147/352 (41.8) |
| Total cholesterol (mg/dl) | | | N=1357 | N=344 |
| Median (25th -75th %-ile) | 189.0 (162.0, 215.0) | 175.0 (153.0, 198.0) | 188.0 (162.0, 215.0) | 170.5 (148.0, 197.0) |
| Range | 84.0-384.0 | 96.0-298.0 | 84.0-384.0 | 96.0-469.0 |
| High-density lipoproteins (mg/dl) | | | N=1357 | N=344 |
| Median (25th -75th %-ile) | 44.0 (38.0, 53.0) | 37.0 (32.0, 43.0) | 44.0 (38.0, 52.0) | 36.0 (31.0, 42.0) |
| Range | 21.0-107.0 | 21.0-83.0 | 21.0-107.0 | 15.0-83.0 |
| Low-density lipoprotein (mg/dl) | N=866 | N=192 | N=1160 | N=299 |
| Median (25th -75th %-ile) | 112.0 (89.0, 134.0) | 105.0 (82.0, 124.0) | 112.0 (89.0, 134.0) | 101.0 (78.0, 124.0) |
| Range | 27.0-308.0 | 23.0-223.0 | 27.0-308.0 | 23.0-223.0 |
| Triglycerides (mg/dl) | N=863 | N=192 | N=1155 | N=299 |
| Median (25th -75th %-ile) | 137.0 (101.0, 191.0) | 141.0 (106.0, 199.5) | 138.0 (100.0, 193.0) | 142.0 (107.0, 208.0) |
| Range | 37.0-1584.0 | 43.0-675.0 | 30.0-1584.0 | 43.0-1677.0 |
| Systolic blood pressure (mmHg) | | | N=1383 | N=354 |
| Median (25th -75th %-ile) | 129.0 (120.0, 138.0) | 133.0 (120.0, 142.0) | 128.0 (119.0, 138.0) | 130.0 (120.0, 142.0) |
| Range | 83.0-189.0 | 90.0-186.0 | 83.0-189.0 | 90.0-192.0 |
| Type 2 Diabetes | 314 (31.0) | 90 (40.7) | 455/1385 (32.9) | 160/352 (45.5) |
| Hypertension | 667 (65.8) | 164 (74.2) | 926/1387 (66.8) | 281/353 (79.6) |

Abbreviations: CVD, cardiovascular disease.

[a] Participants free of pre-surgery history of cardiovascular disease and have cardiovascular disease risk score at pre-surgery and at least one follow-up assessment.

[b] Denominator shifts between variables due to missing data. Data are reported as No. (%) unless otherwise indicated.

[c] No./total (%).

**Table 11. CVD Event Rates Following Roux-En-Y Gastric Bypass, Stratified By Sex (N=1770[a]).**

| | Total Events, No. | Total Person-Years | Event rate per 1000 person-year | | | p-value[b] |
|---|---|---|---|---|---|---|
| | | | Overall (≤7 years) | Short-term (<5 years) | Long-term (5-7 years) | |
| **Females** (N=1413)[c] | | | | | | |
| Total non-fatal CVD events | 499 | 9891 | 50.4 (41.6-61.2) | 42.5 (33.8-53.3) | 61.1 (48.5-77.0) | 0.004 |
| Nonfatal myocardial infarction | 37 | 7065 | 5.3 (3.6-7.8) | 4.1 (2.6-6.6) | 7.0 (4.3-11.4) | 0.07 |
| Stroke | 22 | 5182 | 4.2 (2.5-6.9) | 2.7 (1.3- 5.5) | 7.4 (3.9- 13.8) | 0.02 |
| Ischemic heart disease | 206 | 6278 | 33.6 (27.7-40.7) | 30.5 (24.3-38.3) | 37.4 (29.7-47.1) | 0.11 |
| Congestive heart failure | 25 | 5182 | 4.8 (2.8-8.1) | 4.0 (2.1-7.5) | 6.5 (3.3-12.7) | 0.21 |
| Angina | 181 | 6738 | 27.1 (22.1-33.4) | 22.6 (17.5-29.1) | 33.4 (26.2-42.5) | 0.005 |
| Revascularization | 28 | 6749 | 3.9 (2.2-6.7) | 2.0 (1.0-4.3) | 6.3 (3.6-11.1) | 0.001 |
| Percutaneous coronary intervention | 22 | 6749 | 3.3 (1.9-5.8) | 1.3 (0.5-3.2) | 6.0 (3.3-10.9) | 0.002 |
| Coronary artery bypass grafting | 6 | 6748 | 0.9 (0.3-2.1) | 1.0 (0.4-2.7) | 0.6 (0.2-2.6) | 0.50 |
| CVD Mortality | 8 | 8452 | 0.9 (0.5-1.9) | 0.8 (0.3-2.1) | 1.2 (0.5-3.3) | 0.52 |
| **Males** (N=357)[d] | | | | | | |
| Total non-fatal CVD events | 179 | 2499 | 71.6 (53.7-95.5) | 76.3 (53.9-108.1) | 65.4 (45.7-93.6) | 0.47 |
| Nonfatal myocardial infarction | 15 | 1727 | 8.6 (4.9-15.1) | 9.6 (4.9-18.8) | 7.3 (3.0-17.6) | 0.62 |
| Stroke | 10 | 1297 | 6.7 (3.2-14.4) | 5.5 (2.2-13.3) | 9.4 (3.7-23.6) | 0.29 |
| Ischemic heart disease | 63 | 1552 | 39.6 (29.0-54.1) | 46.7 (32.0-68.3) | 31.0 (19.5-49.4) | 0.16 |
| Congestive heart failure | 21 | 1293 | 15.3 (8.7-26.9) | 12.3 (6.0-25.2) | 22.2 (11.6-42.3) | 0.14 |
| Angina | 42 | 1684 | 24.1 (16.0-36.2) | 25.5 (15.3-42.5) | 22.2 (12.7-39.0) | 0.70 |
| Revascularization | 28 | 1682 | 14.6 (9.0-23.6) | 11.5 (5.8-22.7) | 19.2 (10.4-35.4) | 0.24 |
| Percutaneous coronary intervention | 22 | 1682 | 12.6 (7.6-20.9) | 8.7 (4.6-16.5) | 18.3 (9.8-34.1) | 0.057 |
| Coronary artery bypass grafting | 6 | 1680 | 3.3 (1.1-10.0) | 5.0 (1.4-17.6) | 1.2 (0.1-11.3) | 0.28 |
| CVD Mortality | 9 | 2087 | 4.3 (2.3-8.2) | 1.6 (0.4-6.2) | 8.8 (4.2-18.3) | 0.03 |

Abbreviations: CVD, cardiovascular disease; No., number.

[a] Includes participants with pre-surgery history of CVD (n=145).

[b] Comparing short and long term rates.

[c] Number of events for females with a pre-surgery history of CVD (N=82): myocardial infarction:13; stroke: 9; ischemic heart disease: 51; congestive heart failure: 16; angina: 41; revascularization: 16; CVD mortality: 2.

[d] Number of events for males with a pre-surgery history of CVD (N=63): myocardial infarction: 9; stroke: 4; ischemic heart disease: 42; congestive heart failure: 15; angina:27; revascularization: 21; CVD mortality: 3.

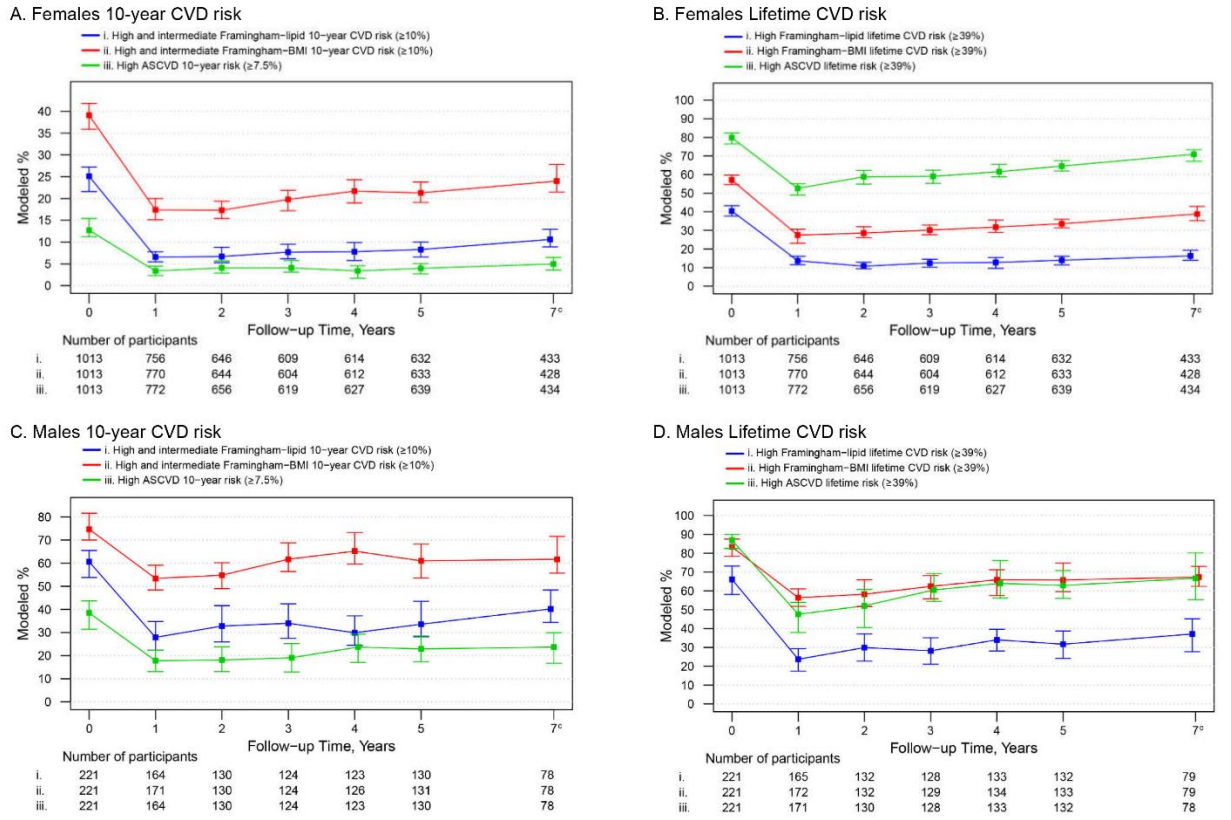



**Figure 1. Modeled[a] Percentage And 95% Confidence Intervals Of Adults Categorized As Intermediate/High[b] Or High CVD Risk By Time In Relation To Roux-En-Y Gastric Bypass, Stratified By Sex.**

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; BMI, Body Mass Index (kn/m$^2$); CVD, cardiovascular disease.

[a] Adjusted for factors related to missing follow-up data (i.e. site, age and current smoking status at pre-surgery). All pairwise comparison tests (for pre-surgery vs 1 year, 1 year vs 7 years and pre-surgery vs 7 years) were significant ($p \leq 0.01$) with the exception of 1 year vs 7 years 10-year ASCVD ($p=0.14$) and lifetime Framingham-lipids ($p=0.12$) in females, and the 10-year ASCVD in males ($p=0.08$).

[b] Because the Framingham intermediate risk category can be used to initiate statin therapy, the Framingham intermediate and high risk groups were combined.

[c] Data collection ended before the 7 year assessment of 316 females and 71 males.

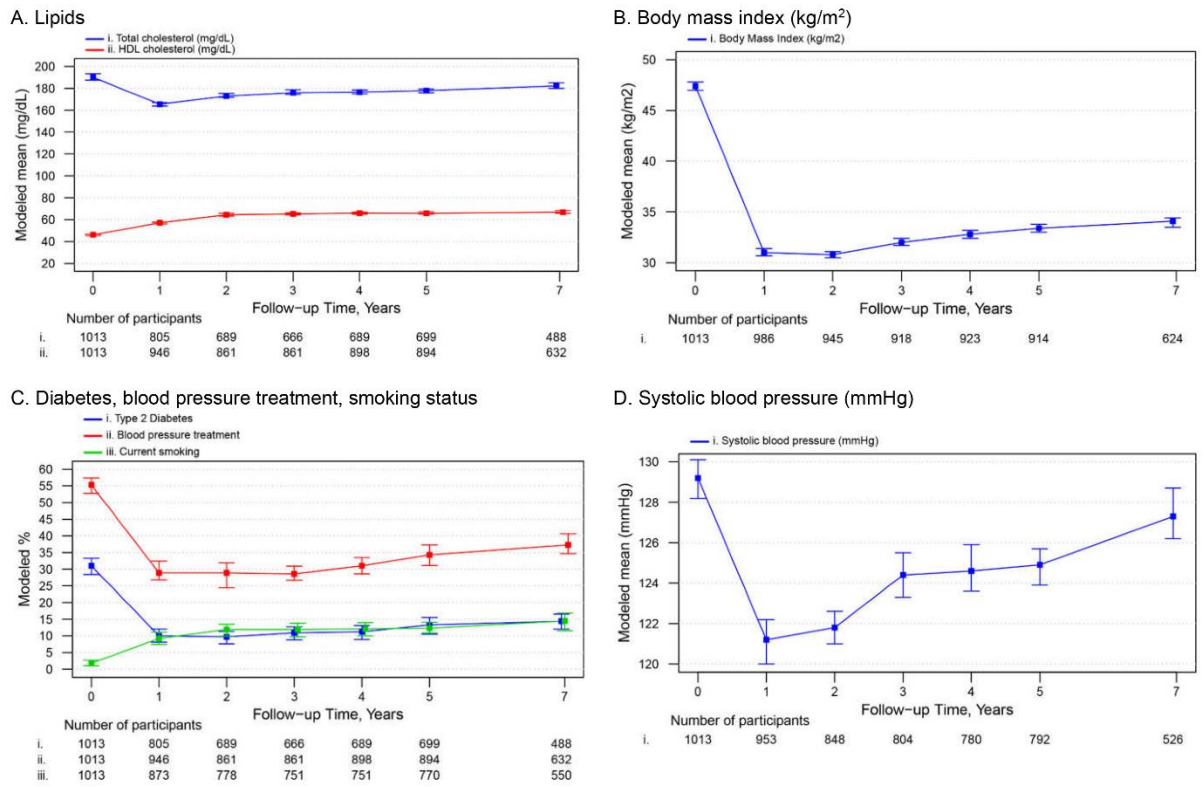



**Figure 2. Modeled[a] Mean Or Percentage And 95% Confidence Intervals Of CVD Risk Components Among Females By Timepoint In Relation To Roux-En-Y Gastric Bypass.**

Abbreviations: HDL, high-densitiy lipoprotein.

[a] Adjusted for factors related to missing (i.e. site, age and current smoking status at pre-surgery) follow-up data. All pairwise comparison tests (for pre-surgery vs 1 year, 1 year vs 7 years and pre-surgery vs 7 years) were significant ($p \leq 0.01$).

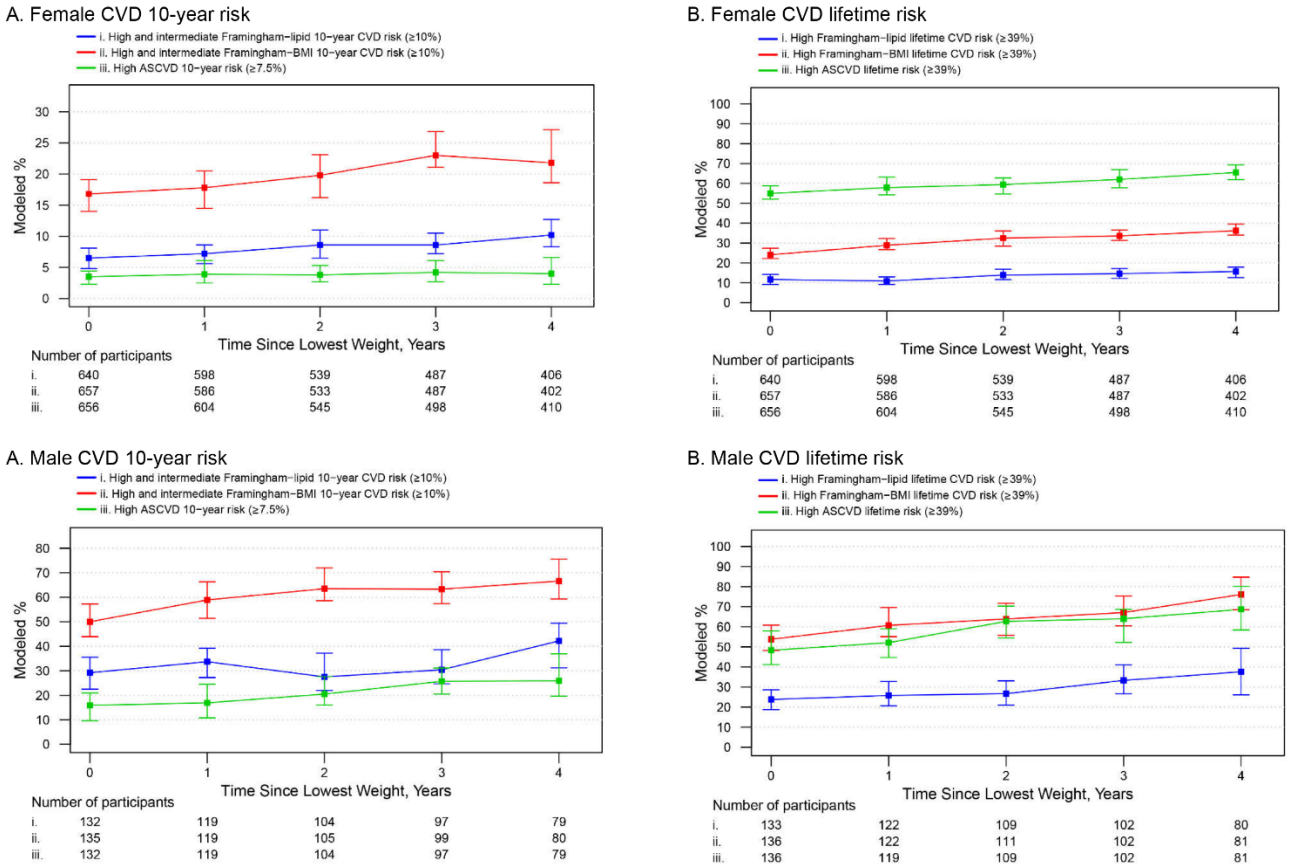



**Figure 3. Modeled[a] Percentage And 95% Confidence Intervals Of Participants Categorized As Intermediate/High[b] CVD Risk By Time Since Lowest Weight, Stratified By Sex.**

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; BMI, Body Mass Index (kn/m$^2$); CVD, cardiovascular disease.

[a] Adjusted for factors related to missing (i.e. site, age and current smoking status at pre-surgery) follow-up data. All pairwise comparison tests (for pre-surgery vs 1 year, 1 year vs 7 years and pre-surgery vs 7 years) were significant ($p \leq 0.01$) with the exception of 1 year vs 7 years.

[b] Because the Framingham intermediate risk category can be used to initiate statin therapy, the Framingham intermediate and high risk groups were combined.

[c] A linear term for time since lowest weight recorded was significant ($p \leq 0.05$) for all CVD scores with the exception of 10-year ASCVD in females (p=0.92) and males (p=0.06).

## 2.8 Supplemental Content

### 2.8.1 Appendix 1. Measures

***Research assessments***

The written informed consent protocol was approved by institutional review boards and was obtained for participants at every clinical center. Research assessments were carried out by trained research staff 30 days before scheduled surgery (pre-surgery assessment) then annually for up to 7 years after surgery until January 31, 2015, after which data collection was discontinued. The research staff followed standard protocols and used study provided equipment to record participant data when possible to reduce site differences in data collection. Research assessments were primarily conducted in-person with options for phone, mail and chart review when in-person assessments were not possible. The 6-year assessment involved minimal data collection which did not allow for determination of CVD risk. All measures were assessed at all other time points, unless otherwise specified.

***Sociodemographics and Anthropometrics***

Sociodemographic variables including sex, age, race, ethnicity, marital status, education, employment (to determine 'work for pay' and 'work night or evening shifts'), and annual household income were assessed on study-specific questionnaires[1]. Height (measured pre-surgery only) and weight were measured using a standardized protocol[2]. Body mass index was calculated as weight in kilograms divided by height in meters squared.

***CVD risk factors***

Current cigarette smoking was self-reported at all assessments. Lipid profile from serum (total cholesterol, high-density lipoproteins [HDL-C], low-density lipoprotein cholesterol [LDL-c], triglycerides) and diabetes (T2D)-related parameters (hemoglobin A1C [HbA1c] and glucose [from serum]) were assayed at a central laboratory. Fasting (at least 8 hours) was required for HDL-C, triglycerides and glucose. Information on medications (e.g. hypertension medication) and comorbidities were collected through a variety of sources including self-report, medical records, and physical examination[3].

***CVD events***

A LABS-certified clinical researcher used medical records, physical examination, and patient interviews to determine history of CVD prior to surgery, and CVD events annually post-surgery[4]. In addition, research staff followed an "events and complications" protocol on or after the year 5 assessment to assess CVD events that occurred since surgery to address any previous missed assessments.

***CVD mortality***

Underlying cause of death was obtained from the National Death Index death certificate data. CVD-related mortality was defined as diseases of the circulatory system using the World Health Organization (WHO) Global Burden of Disease Study cause list (ICD 10 codes: I00-I99)[5].

### 2.8.2 Tables and Figures

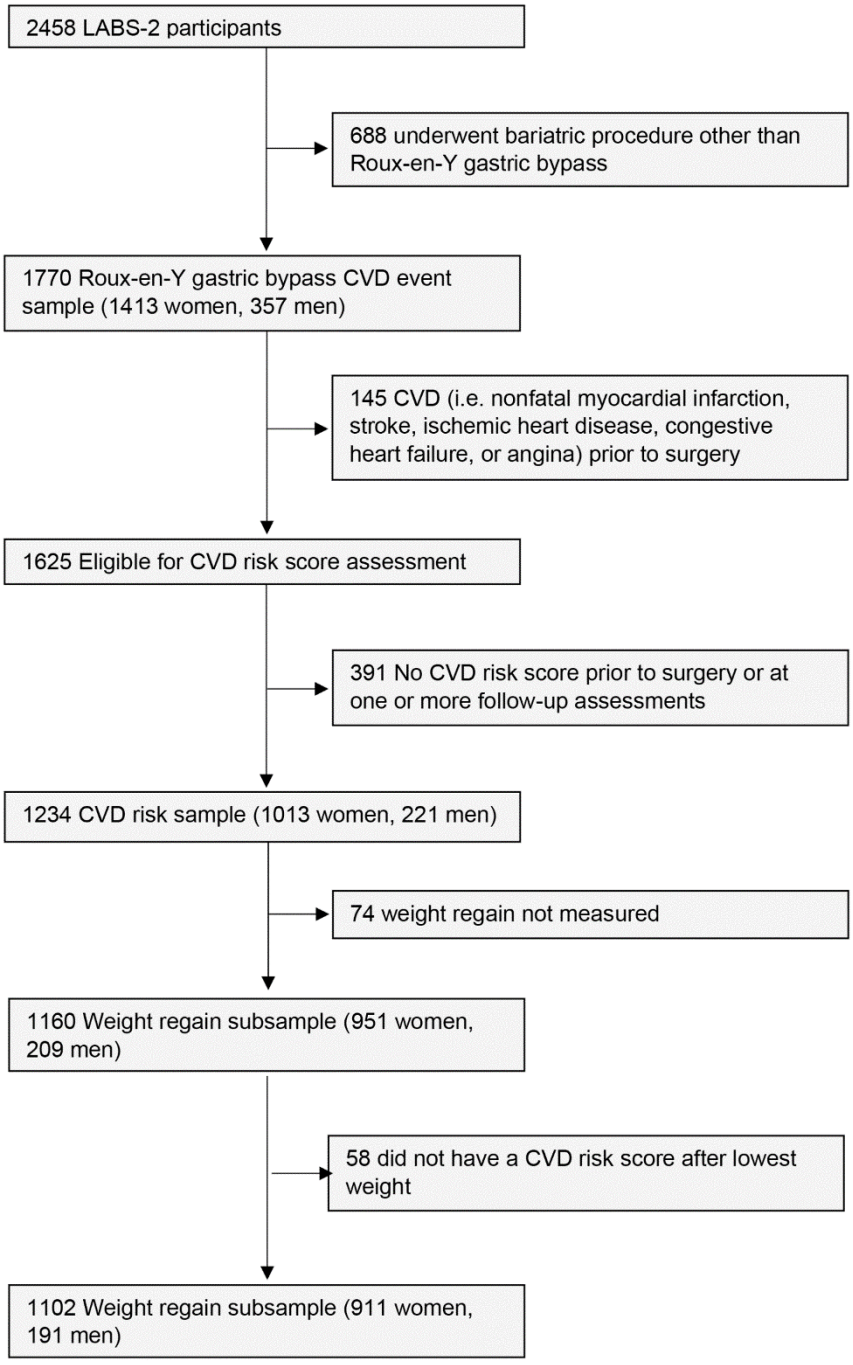



**Figure 4. Participant Flow Chart**

**Table 12. Data Completeness For CVD Risk Scores Among The Analysis Sample (N=1234) By Time In Relation To Roux-En-Y Gastric Bypass, Stratified By Sex.**

| | Pre-surgery | | Post-surgery | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Year 1 | | Year 2 | | Year 3 | | Year 4 | | Year 5 | | Year 7[b] | |
| **Females** | N=1013 | | N=1013 | | N=1011 | | N=1009 | | N=1007 | | N=1000 | | N=675 | |
| 10-year | | | | | | | | | | | | | | |
| Framingham-lipid | 1013 | (100.0) | 751 | (74.1) | 640 | (63.3) | 593 | (58.8) | 596 | (59.2) | 612 | (61.2) | 424 | (62.8) |
| Framingham-BMI | 1013 | (100.0) | 764 | (75.4) | 637 | (63.0) | 588 | (58.3) | 594 | (59.0) | 615 | (61.5) | 423 | (62.7) |
| ASCVD | 1013 | (100.0) | 751 | (74.1) | 640 | (63.3) | 593 | (58.8) | 596 | (59.2) | 612 | (61.2) | 424 | (62.8) |
| Lifetime | | | | | | | | | | | | | | |
| Framingham-lipid | 1013 | (100.0) | 756 | (74.6) | 646 | (63.9) | 609 | (60.4) | 614 | (61.0) | 632 | (63.2) | 433 | (64.1) |
| Framingham-BMI | 1013 | (100.0) | 770 | (76.0) | 644 | (63.7) | 604 | (59.9) | 612 | (60.8) | 633 | (63.3) | 428 | (63.4) |
| ASCVD | 1013 | (100.0) | 772 | (76.2) | 656 | (64.9) | 619 | (61.3) | 627 | (62.3) | 639 | (63.9) | 434 | (64.3) |
| **Males** | N=221 | | N=221 | | N=221 | | N=220 | | N=220 | | N=219 | | N=143 | |
| 10-year | | | | | | | | | | | | | | |
| Framingham-lipid | 221 | (100.0) | 164 | (74.2) | 130 | (58.8) | 124 | (56.4) | 123 | (55.9) | 130 | (59.4) | 78 | (54.5) |
| Framingham-BMI | 221 | (100.0) | 171 | (77.4) | 130 | (58.8) | 124 | (56.4) | 126 | (57.3) | 131 | (59.8) | 78 | (54.5) |
| ASCVD | 221 | (100.0) | 164 | (74.2) | 130 | (58.8) | 124 | (56.4) | 123 | (55.9) | 130 | (59.4) | 78 | (54.5) |
| Lifetime | | | | | | | | | | | | | | |
| Framingham | 221 | (100.0) | 165 | (74.7) | 132 | (59.7) | 128 | (58.2) | 133 | (60.5) | 132 | (60.3) | 79 | (55.2) |
| Framingham BMI | 221 | (100.0) | 172 | (77.8) | 132 | (59.7) | 129 | (58.6) | 134 | (60.9) | 133 | (60.7) | 79 | (55.2) |
| ASCVD | 221 | (100.0) | 171 | (77.4) | 130 | (58.8) | 128 | (58.2) | 133 | (60.5) | 132 | (60.3) | 78 | (54.5) |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; BMI, Body Mass Index (kg/m$^2$); CVD, Cardiovascular disease.

[a] If participants were pregnant Framingham-BMI was not calculated, but the Framingham-lipid was calculated if components were available.

[b] N represents those who were alive at time of assessment and prior to data collection end.

[c] Data collection ended before the 7 year assessment of 316 females and 71 males.

[d] No./total (%).

**Table 13. Modeled[a] Percentages And 95% Confidence Intervals Of Predicted 10-Year And Lifetime CVD Risk Categorizations According To The Framingham And ASCVD Scoring Algorithms By Time In Relation To Roux-En-Y Gastric Bypass, Stratified By Sex.**

| | Model-Based Estimates, % (95% CI) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-surgery | Post-surgery | | | | | | | | |
| Females | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 1 vs 7 |
| **Framingham 10-year** | | | | | | | | | | |
| *Lipids* | | | | | | | | <0.001 | <0.001 | 0.02 |
| Low (<10%) | 74.9 (72.8-76.9) | 93.5 (92.6-93.9) | 93.0 (92.4-93.4) | 92.0 (90.7-92.4) | 92.0 (91.1-92.3) | 91.4 (90.8-92.0) | 89.7 (89.6-90.6) | | | |
| Intermediate (10-20%) | 18.6 (16.4-19.7) | 5.5 (4.9-6.6) | 6.2 (5.6-6.5) | 7.2 (7.0-8.5) | 7.2 (6.2-7.9) | 7.2 (6.7-7.9) | 7.5 (6.1-8.8) | | | |
| High (>20%) | 6.5 (6.7-7.5) | 1.0 (0.8-1.2) | 0.9 (1.0-1.2) | 0.8 (0.6-0.8) | 0.8 (1.0-1.5) | 1.4 (1.3-1.8) | 2.8 (1.6-3.3) | | | |
| Intermediate/High (≥10%) | 25.1 (21.6-27.2) | 6.6 (5.5-7.8) | 6.7 (5.3-8.8) | 7.7 (6.2-9.5) | 7.8 (5.8-9.9) | 8.3 (6.6-10.0) | 10.6 (8.9-12.9) | <0.001 | <0.001 | 0.007 |
| *BMI* | | | | | | | | <0.001 | <0.001 | 0.003 |
| Low (<10%) | 57.8 (35.7-59.1) | 86.3 (37.6-88.3) | 83.9 (24.4-86.1) | 82.3 (30.1-84.9) | 81.3 (43.0-83.9) | 80.5 (51.0-83.1) | 77.6 (38.4-80.3) | | | |
| Intermediate (10-20%) | 16.5 (9.1-23.5) | 7.3 (2.8-14.2) | 6.7 (1.7-14.1) | 9.3 (2.6-15.9) | 10.8 (4.1-19.7) | 9.6 (4.3-16.0) | 10.1 (4.3-17.6) | | | |
| High (>20%) | 25.7 (17.3-53.9) | 6.4 (4.1-59.6) | 9.4 (5.2-74.0) | 8.4 (4.1-66.3) | 7.9 (3.5-52.9) | 9.9 (4.8-44.7) | 12.3 (7.1-56.0) | | | |
| Intermediate/High (≥10%) | 39.1 (35.9-41.8) | 17.4 (15.1-20.0) | 17.3 (15.4-19.4) | 19.8 (17.2-21.9) | 21.7 (19.0-24.3) | 21.3 (19.1-23.8) | 24.0 (21.5-27.8) | <0.001 | <0.001 | <0.001 |
| **ASCVD 10-year** | | | | | | | | <0.001 | <0.001 | 0.14 |
| Low (<7.5%) | 87.3 (85.4-89.6) | 96.6 (95.5-97.8) | 95.9 (93.9-96.9) | 95.9 (94.9-97.2) | 96.6 (95.7-97.6) | 96.0 (94.8-96.8) | 95.0 (93.4-96.6) | | | |
| High (≥7.5%) | 12.7 (11.2-15.4) | 3.4 (2.3-4.5) | 4.1 (2.9-5.7) | 4.1 (3.1-5.8) | 3.4 (1.7-4.6) | 4.0 (2.7-5.1) | 5.0 (3.6-6.5) | | | |
| **Framingham Lifetime** | | | | | | | | | | |
| *Lipids* | | | | | | | | <0.001 | <0.001 | 0.12 |
| Low (<39%) | 59.6 (56.8-63.4) | 86.3 (84.5-88.2) | 89.2 (87.4-91.6) | 87.5 (85.6-89.1) | 87.2 (83.9-89.8) | 86.0 (82.6-88.0) | 83.7 (81.5-85.7) | | | |
| High (≥39%) | 40.4 (37.7-43.3) | 13.7 (11.6-16.1) | 10.8 (9.4-12.9) | 12.5 (10.2-14.5) | 12.8 (9.6-15.4) | 14.0 (11.5-16.1) | 16.3 (14.0-19.3) | | | |

**Table 13 (continued)**

| | Pre-surgery | Post-surgery | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *BMI* | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 1 vs 7 |
| Low (<39%) | 42.9 (40.9-45.8) | 72.6 (70.3-75.3) | 71.5 (68.7-74.7) | 69.9 (66.6-72.4) | 68.3 (64.9-70.9) | 66.5 (63.1-68.7) | 61.2 (58.3-64.5) | | | |
| High (≥39%) | 57.1 (54.6-59.7) | 27.4 (23.1-30.6) | 28.5 (26.1-31.9) | 30.1 (27.6-32.8) | 31.7 (28.9-35.5) | 33.5 (31.3-35.9) | 38.8 (35.2-42.9) | | | |
| **ASCVD Lifetime** | | | | | | | | <0.001 | <0.001 | <0.001 |
| Low (<39%) | 20.1 (17.3-22.5) | 47.4 (44.1-50.7) | 41.2 (37.1-45.7) | 41.0 (36.6-44.1) | 38.5 (34.5-42.1) | 35.5 (32.2-38.4) | 29.1 (25.3-31.6) | | | |
| High (≥39%) | 79.9 (76.5-82.4) | 52.6 (49.0-55.1) | 58.8 (54.9-62.2) | 59 (55.3-62.3) | 61.5 (58.8-65.5) | 64.5 (61.9-67.4) | 70.9 (67.1-73.4) | | | |

| Males | Pre-surgery | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 1 vs 7 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Framingham 10-year** | | | | | | | | | | |
| *Lipids* | | | | | | | | <0.001 | <0.001 | 0.03 |
| Low (<10%) | 38.3 (31.9-42.2) | 80.2 (79.1-88.4) | 74.9 (68.4-83.1) | 71.3 (61.3-79.5) | 77.8 (72.4-88.1) | 74.0 (67.5-83.9) | 66.4 (58.0-77.0) | | | |
| Intermediate (10-20%) | 34.5 (27.5-44.1) | 16.8 (9.6-18.9) | 20.7 (13.0-28.3) | 24.3 (15.0-36.5) | 18.6 (9.2-25.1) | 17.5 (7.8-21.8) | 28.0 (17.5-38.9) | | | |
| High (>20%) | 27.2 (19.9-34.6) | 3.0 (1.2-3.6) | 4.4 (1.6-6.1) | 4.5 (1.7-7.8) | 3.6 (1.2-7.2) | 8.5 (4.9-13.6) | 5.7 (1.3-10.0) | | | |
| Intermediate/High (≥10%) | 60.6 (53.8-65.5) | 27.9 (22.4-34.8) | 32.8 (25.9-41.6) | 34.0 (27.5-42.4) | 29.9 (24.5-37.2) | 33.6 (28.1-43.5) | 40.2 (34.4-48.4) | <0.001 | <0.001 | 0.005 |
| *BMI* | | | | | | | | <0.001 | <0.001 | 0.04 |
| Low (<10%) | 22.3 (17.1-27.4) | 51.5 (45.1-60.0) | 49.5 (44.9-58.3) | 36.5 (29.2-42.8) | 35.1 (28.0-44.5) | 40.0 (32.0-46.2) | 42.2 (32.2-52.3) | | | |
| Intermediate (10-20%) | 19.1 (14.2-23.9) | 27.4 (20.8-31.2) | 30.1 (22.0-35.8) | 34.4 (24.4-43.7) | 42.8 (27.5-54.3) | 29.4 (17.7-38.4) | 21.0 (8.8-29.1) | | | |
| High (>20%) | 58.6 (53.9-67.0) | 21.1 (15.1-25.4) | 20.4 (11.0-28.2) | 29.1 (23.4-36.7) | 22.1 (12.5-35.9) | 30.6 (25.7-41.5) | 36.8 (25.0-50.1) | | | |
| Intermediate/High (≥10%) | 74.7 (70.0-81.6) | 53.4 (48.4-59.1) | 54.8 (49.0-60.2) | 61.7 (56.4-68.8) | 65.2 (59.6-73.2) | 61.0 (53.6-68.2) | 61.7 (55.7-71.6) | <0.001 | <0.001 | 0.04 |

**Table 13 (continued)**

| | Pre-surgery | Post-surgery | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 1 vs 7 |
| **ASCVD 10-year** | | | | | | | | <0.001 | <0.001 | 0.08 |
| Low (<7.5%) | 61.5 (54.2-66.7) | 82.2 (77.6-88.4) | 81.9 (76.2-87.3) | 80.9 (73.5-85.7) | 76.3 (69.0-82.4) | 77.1 (73.3-82.1) | 76.3 (69.3-81.5) | | | |
| High (≥7.5%) | 38.5 (31.4-43.7) | 17.8 (13.1-22.4) | 18.1 (13.1-23.8) | 19.1 (12.9-25.2) | 23.7 (17.0-29.3) | 22.9 (17.4-28.5) | 23.7 (16.7-29.9) | | | |
| **Framingham Lifetime** | | | | | | | | | | |
| *Lipids* | | | | | | | | <0.001 | <0.001 | 0.003 |
| Low (<39%) | 33.9 (26.4-39.5) | 76.3 (71.2-82.0) | 70.1 (64.7-77.0) | 71.8 (65.4-76.4) | 66.0 (58.5-71.4) | 68.3 (58.6-77.2) | 62.9 (55.4-69.4) | | | |
| High (≥39%) | 66.1 (58.1-73.2) | 23.7 (17.4-29.3) | 29.9 (22.7-37.2) | 28.2 (21.1-35.1) | 34.0 (28.1-39.6) | 31.7 (24.2-38.7) | 37.1 (27.7-45.2) | | | |
| *BMI* | | | | | | | | <0.001 | <0.001 | 0.01 |
| Low (<39%) | 16.7 (11.4-21.6) | 43.6 (37.5-48.9) | 41.8 (33.4-49.9) | 37.6 (29.6-45.7) | 34.1 (25.9-38.9) | 34.2 (23.0-38.8) | 32.7 (25.2-39.7) | | | |
| High (≥39%) | 83.3 (78.3-87.5) | 56.4 (51.8-61.1) | 58.2 (51.7-65.9) | 62.4 (55.8-68.1) | 65.9 (57.5-71.2) | 65.8 (59.6-74.8) | 67.3 (62.4-73.0) | | | |
| **ASCVD Lifetime** | | | | | | | | <0.001 | <0.001 | 0.002 |
| Low (<39%) | 13.1 (8.8-21.5) | 52.4 (45.1-60.4) | 47.9 (41.4-60.2) | 39.5 (30.8-47.8) | 36.0 (29.3-45.0) | 37.1 (29.7-45.9) | 33.3 (24.4-44.5) | | | |
| High (≥39%) | 86.9 (82.5-90.0) | 47.6 (37.9-53.9) | 52.1 (40.5-60.8) | 60.5 (54.4-69.2) | 64.0 (56.2-76.1) | 62.9 (56.0-70.8) | 66.7 (55.3-80.1) | | | |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; BMI, Body Mass Index ($kg/m^2$); CVD, Cardiovascular disease.

[a] Adjusted for factors related to missing follow-up data (i.e. site, age and current smoking status at pre-surgery).

**Table 14. Modeled[a] Means And 95% Confidence Intervals Of 10-Year And Lifetime CVD Risk Score According To The Framingham And ASCVD Scoring Algorithms By Time In Relation To Roux-En-Y Gastric Bypass, Stratified By Sex.**

| | Model-Based Estimates, mean (95% CI) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-surgery | Post-surgery | | | | | | | | |
| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 1 vs 7 |
| **Framingham 10-year** | | | | | | | | | | |
| *Lipids* | 7.4 (7.0-7.8) | 3.9 (3.6-4.1) | 3.8 (3.6-4.1) | 4.1 (3.8-4.3) | 4.0 (3.8-4.3) | 4.3 (4.1-4.7) | 4.9 (4.5-5.3) | <0.001 | <0.001 | <0.001 |
| *BMI* | 10.6 (9.8-11.4) | 6.0 (5.6-6.4) | 5.9 (5.5-6.5) | 6.4 (6.0-6.8) | 6.4 (6.0-6.7) | 6.8 (6.4-7.2) | 7.7 (7.2-8.2) | <0.001 | <0.001 | <0.001 |
| **ASCVD 10-year** | 3.6 (3.4-3.9) | 1.9 (1.7-2.0) | 1.8 (1.6-2.0) | 1.9 (1.7-2.1) | 1.8 (1.6-1.9) | 2.0 (1.8-2.1) | 2.2 (1.9-2.5) | <0.001 | <0.001 | 0.002 |
| **Framingham Lifetime** | | | | | | | | | | |
| *Lipids* | 34.0 (32.9-35.1) | 19.9 (18.3-21.0) | 19.3 (18.3-20.3) | 19.7 (18.7-20.7) | 19.7 (18.7-20.6) | 20.7 (19.7-22.3) | 22.5 (21.4-23.6) | <0.001 | <0.001 | <0.001 |
| *BMI* | 47.9 (46.6-49.4) | 28.4 (26.3-29.6) | 28.1 (26.9-29.3) | 29.2 (27.4-30.4) | 30.1 (28.9-31.6) | 31.5 (29.9-32.8) | 34.2 (32.3-35.4) | <0.001 | <0.001 | <0.001 |
| **ASCVD Lifetime** | 39.1 (38.6-39.6) | 29.6 (28.5-30.3) | 31.5 (30.9-32.9) | 32.0 (31.2-32.8) | 32.7 (31.4-33.4) | 33.6 (32.8-34.4) | 35.3 (34.5-36.2) | <0.001 | <0.001 | <0.001 |
| Males Modeled | | | | | | | | P value | P value | P value |
| | Pre-surgery | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | 1 vs pre | 7 vs pre | 1 vs 7 |
| **Framingham 10-year** | | | | | | | | | | |
| *Lipids* | 15.1 (14.0-16.5) | 8.3 (7.2-9.4) | 8.9 (8.1-9.9) | 8.9 (7.9-10.5) | 9.2 (8.2-10.1) | 9.6 (8.7-10.8) | 9.9 (8.1-11.4) | <0.001 | <0.001 | 0.004 |
| *BMI* | 23.8 (21.7-25.6) | 14.1 (12.4-15.3) | 15.1 (13.7-17.0) | 15.7 (14.0-17.5) | 16.0 (14.7-17.7) | 16.5 (15.2-18.2) | 17.7 (16.1-20.1) | <0.001 | <0.001 | <0.001 |
| **ASCVD 10-year** | 7.6 (6.6-8.5) | 4.4 (3.6-5.5) | 4.8 (3.8-6.2) | 4.7 (4.0-5.8) | 4.8 (4.1-5.6) | 5.1 (4.3-6.2) | 5.2 (4.5-6.1) | <0.001 | <0.001 | 0.01 |
| **Framingham Lifetime** | | | | | | | | | | |
| *Lipids* | 48.6 (46.1-51.6) | 29.2 (26.6-31.4) | 30.4 (27.8-33.2) | 30.9 (29.0-33.9) | 31.8 (28.0-33.9) | 32.8 (30.3-35.9) | 33.8 (30.8-36.5) | <0.001 | <0.001 | <0.001 |
| *BMI* | 67.5 (63.8-70.1) | 45.0 (42.5-48.1) | 45.8 (42.9-49.3) | 47.2 (43.9-50.6) | 49.4 (47.1-52.8) | 50.3 (48.0-52.9) | 52.7 (49.5-55.4) | <0.001 | <0.001 | <0.001 |
| **ASCVD Lifetime** | 53.2 (51.8-55.4) | 37.2 (34.6-40.2) | 39.5 (37.1-42.4) | 41.5 (39.4-44.1) | 43.8 (40.4-46.6) | 42.5 (39.9-45.0) | 44.3 (40.8-48.2) | <0.001 | <0.001 | <0.001 |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; BMI, Body Mass Index ($kg/m^2$); CVD, Cardiovascular disease.

[a] Adjusted for factors related to missing follow-up data (i.e. site, age and current smoking status at pre-surgery).

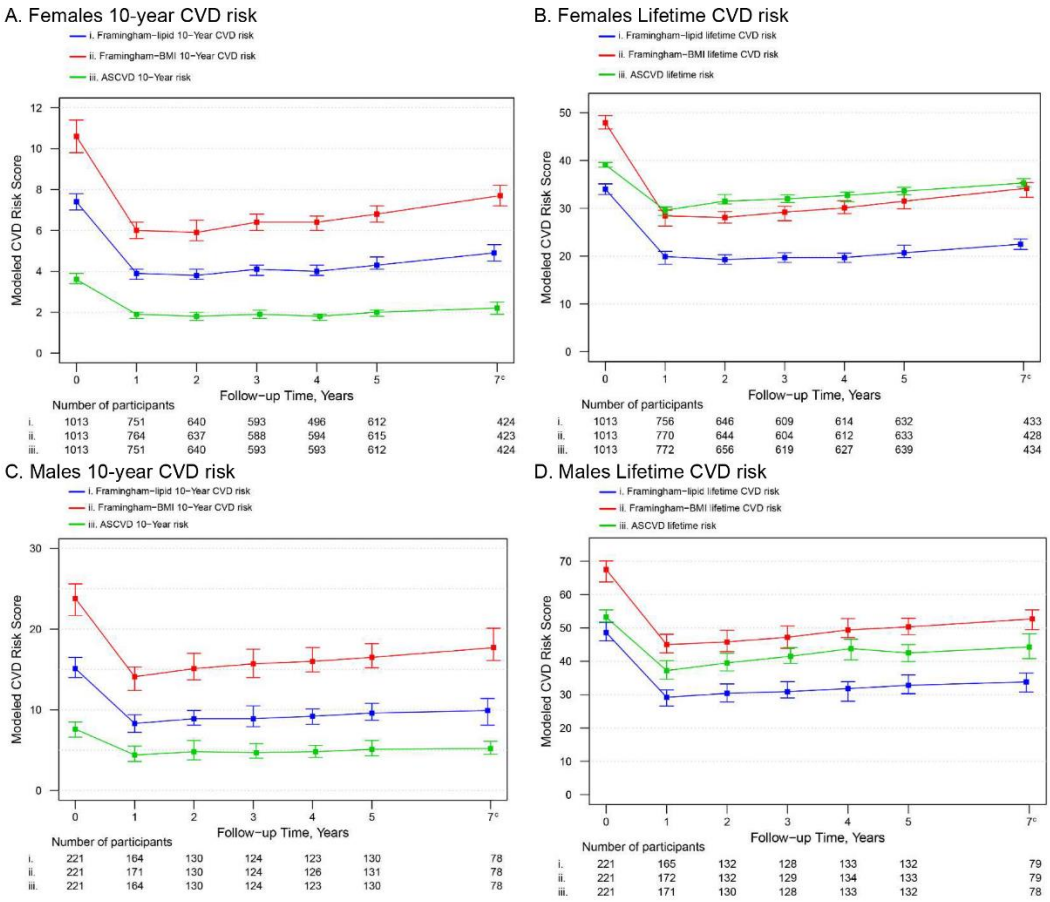



**Figure 5. Modeled[a] Means And 95% Confidence Intervals Of 10-Year And Lifetime CVD Risk Scores According To The Framingham And ASCVD Scoring Algorithms By Time In Relation To Roux-En-Y Gastric Bypass, Stratified By Sex[b].**

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; BMI, Body Mass Index (kg/m$^2$); CVD, Cardiovascular disease.

[a] Adjusted for factors related to missing (i.e. site, age and current smoking status at pre-surgery) follow-up data.

[b] Data collection ended before the 7 year assessment of 316 females and 71 males.

[c] Pairwise comparison tests were all significant ($p \leq 0.01$ for pre-surgery vs 1 year, 1 year vs 7 years and pre-surgery vs 7 years)

**Table 15. Modeled[a] Mean Or Percentage And 95% Confidence Interval Of CVD Risk Components By Timepoint In Relation To Roux-En-Y Gastric Bypass, Stratified By Sex.**

| | Model-Based Estimates, mean (95% CI)[b] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-surgery | Post-surgery | | | | | | | | |
| Females | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 7 vs 1 |
| Total cholesterol (mg/dL) | 190.1 (187.4-193.3) | 165.4 (163.8-166.8) | 172.9 (171.6-175.4) | 176.0 (174.6-178.8) | 176.6 (175.0-178.6) | 178.0 (176.0-179.4) | 182.3 (180.1-185.1) | <0.001 | <0.001 | <0.001 |
| HDL cholesterol (mg/dL) | 46.1 (45.4-46.6) | 57.2 (56.2-57.8) | 64.3 (63.2-65.6) | 65.1 (64.2-66.0) | 65.8 (64.8-66.6) | 65.6 (64.9-67.0) | 66.7 (65.7-68.1) | <0.001 | <0.001 | <0.001 |
| Systolic blood pressure (mmHg) | 129.2 (128.2-130.1) | 121.2 (120.0-122.2) | 121.8 (121.0-122.6) | 124.4 (123.3-125.5) | 124.6 (123.6-125.9) | 124.9 (123.9-125.7) | 127.3 (126.2-128.7) | <0.001 | 0.009 | <0.001 |
| Blood pressure treatment[c] | | | | | | | | <0.001 | <0.001 | <0.001 |
| Yes | 55.3 (52.8-57.4) | 28.9 (26.8-32.4) | 28.9 (24.4-31.9) | 28.6 (26.7-30.9) | 31.0 (28.6-33.5) | 34.3 (31.1-37.3) | 37.3 (34.7-40.6) | | | |
| Current smoking[c] | | | | | | | | <0.001 | <0.001 | <0.001 |
| Yes | 1.8 (1.0-2.7) | 9.2 (7.4-11.1) | 11.9 (9.9-13.5) | 11.9 (9.7-13.8) | 12.1 (10.0-14.0) | 12.3 (10.8-14.1) | 14.5 (11.5-16.8) | | | |
| Type 2 Diabetes[c] | | | | | | | | <0.001 | <0.001 | 0.001 |
| Yes | 31.0 (28.4-33.3) | 10.0 (8.1-12.0) | 9.7 (7.6-11.3) | 10.9 (8.8-12.7) | 11.2 (8.9-13.1) | 13.3 (10.5-15.5) | 14.4 (12.0-16.5) | | | |
| BMI ($kg/m^2$) | 47.4 (47.0-47.8) | 31.0 (30.7-31.4) | 30.8 (30.5-31.1) | 32.0 (31.7-32.4) | 32.8 (32.4-33.2) | 33.4 (33.0-33.8) | 34.1 (33.5-34.4) | <0.001 | <0.001 | <0.001 |
| Hyperlipidemia Treatment[c] | | | | | | | | <0.001 | <0.001 | 0.52 |
| Yes | 26.3 (24.1-28.2) | 11.4 (9.4-13.5) | 11.4 (9.9-12.9) | 11.2 (9.7-13.2) | 12.6 (10.6-14.4) | 12.3 (10.1-14.7) | 12.2 (10.3-15.3) | | | |
| Males | Pre-surgery | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 1 vs 7 |
| Total cholesterol (mg/dL) | 176.7 (172.8-182.2) | 153.4 (149.4-156.9) | 160.3 (156.2-164.8) | 162.2 (158.6-165.9) | 161.1 (156.5-166.3) | 163.5 (157.7-167.0) | 165.6 (162.5-169.7) | <0.001 | <0.001 | <0.001 |
| HDL cholesterol (mg/dL) | 38.3 (37.0-39.4) | 49.0 (46.9-50.9) | 53.1 (50.7-55.7) | 53.9 (50.8-55.5) | 52.0 (50.5-54.5) | 52.6 (50.2-54.8) | 55.1 (52.6-57.4) | <0.001 | <0.001 | <0.001 |
| Systolic blood pressure (mmHg) | 131.3 (128.6-132.8) | 124.6 (122.9-126.7) | 128.4 (126.5-131.3) | 130.9 (129.1-133.5) | 130.3 (128.3-132.5) | 131.5 (130.1-133.6) | 134.5 (132.3-137.3) | <0.001 | .04 | <0.001 |

**Table 15 (continued)**

| | Pre-surgery | Post-surgery | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 | P value 1 vs pre | P value 7 vs pre | P value 7 vs 1 |
| Blood pressure treatment[b] | | | | | | | | <0.001 | <0.001 | 0.005 |
| Yes | 63.3 (59.0-70.0) | 29.6 (24.2-34.6) | 29.4 (22.7-36.3) | 35.4 (28.7-40.4) | 36.8 (30.8-43.3) | 39.0 (33.6-47.5) | 41.2 (33.7-48.6) | | | |
| Current smoking[c] | | | | | | | | 0.02 | 0.002 | 0.33 |
| Yes | 2.3 (0.4-4.0) | 6.6 (3.0-9.9) | 8.5 (4.5-11.7) | 9.7 (5.3-12.6) | 6.8 (3.9-10.4) | 8.0 (4.3-12.0) | 9.3 (5.7-14.1) | | | |
| Type 2 Diabetes[c] | | | | | | | | <0.001 | <0.001 | 0.21 |
| Yes | 40.7 (35.1-48.2) | 11.8 (8.3-14.7) | 12.6 (8.6-16.6) | 12.2 (7.4-18.5) | 15.9 (11.6-21.3) | 16.2 (11.4-22.4) | 16.0 (11.6-20.3) | | | |
| BMI ($kg/m^2$) | 48.5 (47.7-49.2) | 32.6 (32.0-33.3) | 32.8 (32.1-33.5) | 33.8 (33.0-34.6) | 34.9 (34.2-35.4) | 34.9 (34.2-35.9) | 35.7 (34.8-36.4) | <0.001 | <0.001 | <0.001 |
| Hyperlipidemia Treatment[c] | | | | | | | | <0.001 | <0.001 | 0.15 |
| Yes | 33.9 (29.3-39.1) | 10.9 (8.1-14.3) | 10.1 (7.1-13.2) | 11.1 (7.4-15.5) | 11.4 (7.3-15.4) | 13.0 (8.2-17.0) | 15.4 (9.8-21.1) | | | |

Abbreviations: BMI, Body Mass Index ($kg/m^2$); CI, confidence interval; HDL, high-density lipoprotein.

[a] Adjusted for factors related to missing follow-up data (i.e. site, age and current smoking status at pre-surgery).

[b] unless otherwise indicated

[c] % (95% CI)

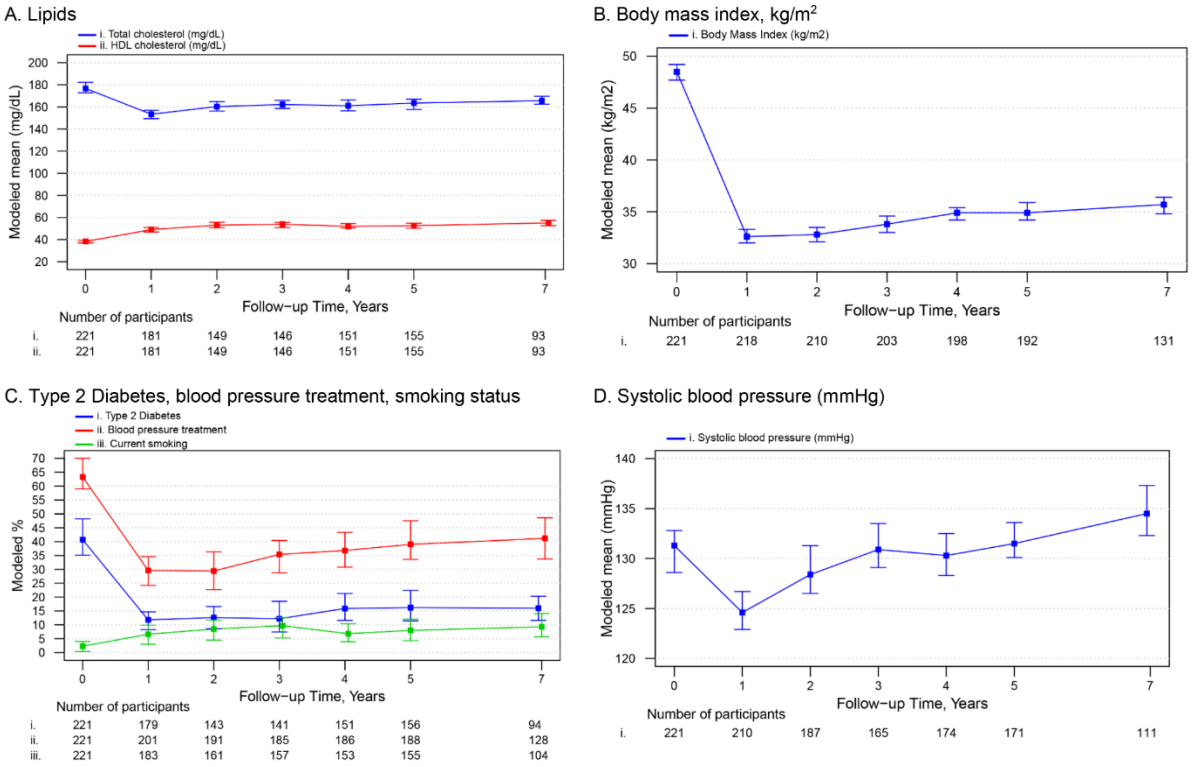



**Figure 6. Modeled Mean Or Percentage And 95% Confidence Interval Of CVD Risk Components By Timepoint In Relation To Roux-En-Y Gastric Bypass In Males.**

**Table 16. Observed CVD Events By Year Since Roux-En-Y Gastric Bypass Surgery (N=1770), Stratified By Sex.**

| | Year 1 | | Year 2 | | Year 3 | | Year 4 | | Year 5 | | Year 6 | | Year 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Females (N=1413)[a]** | | | | | | | | | | | | | | |
| Nonfatal myocardial infarction | 5/1067 | (0.5) | 2/997 | (0.2) | 5/1029 | (0.5) | 5/1070 | (0.5) | 9/1068 | (0.8) | 7/1083 | (0.7) | 4/751 | (0.5) |
| Stroke | 2/1018 | (0.2) | 0/774 | (0.0) | 3/820 | (0.4) | 5/897 | (0.6) | 5/978 | (0.5) | 2 | NA | 5/693 | (0.7) |
| Ischemic heart disease | 11/885 | (1.2) | 21/747 | (2.8) | 37/860 | (4.3) | 34/964 | (3.5) | 43/1024 | (4.2) | 43/1084 | (4.0) | 17/714 | (2.4) |
| Congestive heart failure | 1/1019 | (0.1) | 4/777 | (0.5) | 4/820 | (0.5) | 6/896 | (0.7) | 6/977 | (0.6) | NA | NA | 4/693 | (0.6) |
| Angina | 6/1023 | (0.6) | 16/841 | (1.9) | 34/938 | (3.6) | 30/1026 | (2.9) | 40/1079 | (3.7) | 40/1084 | (3.7) | 15/747 | (2.0) |
| Revascularization | 2/1023 | (0.2) | 4/841 | (0.4) | 2/935 | (0.2) | 1/1029 | (0.1) | 6/1088 | (0.6) | 8/1084 | (0.7) | 5/750 | (0.7) |
| Percutaneous coronary intervention | 2/1023 | (0.2) | 1/841 | (0.1) | 1/935 | (0.1) | 1/1029 | (0.1) | 6/1087 | (0.6) | 8/1084 | (0.7) | 3/750 | (0.4) |
| Coronary artery bypass grafting | 0/1023 | (0.0) | 3/840 | (0.4) | 1/935 | (0.1) | 0/1028 | (0.0) | 0/1088 | (0.0) | 0/1084 | (0.0) | 2/750 | (0.3) |
| CVD mortality | 3/1344 | (0.2) | 0/1299 | (0.0) | 1/1276 | (0.1) | 0/1258 | (0.0) | 2/1221 | (0.2) | 1/1229 | (0.1) | 1/825 | (0.1) |
| **Males (N=357)[a]** | | | | | | | | | | | | | | |
| Nonfatal myocardial infarction | 0/269 | (0.0) | 4/244 | (1.6) | 5/252 | (2.0) | 1/266 | (0.4) | 3/262 | (1.2) | 2/270 | (0.7) | 0/164 | (0.0) |
| Stroke | 0/265 | (0.0) | 2/195 | (1.0) | 1/206 | (0.5) | 2/229 | (0.9) | 0/244 | (0.0) | 4 | NA | 1/154 | (0.7) |
| Ischemic heart disease | 9/225 | (4.0) | 11/187 | (5.9) | 13/210 | (6.2) | 9/249 | (3.6) | 9/251 | (3.6) | 9/270 | (3.3) | 3/160 | (1.9) |
| Congestive heart failure | 6/265 | (2.3) | 1/195 | (0.5) | 4/205 | (2.0) | 1/230 | (0.4) | 4/244 | (1.6) | NA | NA | 5/154 | (3.3) |
| Angina | 5/267 | (1.9) | 7/214 | (3.3) | 6/229 | (2.6) | 8/264 | (3.0) | 5/270 | (1.9) | 8/270 | (3.0) | 3/170 | (1.8) |
| Revascularization | 7/267 | (2.6) | 2/213 | (0.9) | 3/227 | (1.3) | 2/263 | (0.8) | 5/272 | (1.8) | 7/270 | (2.6) | 2/170 | (1.2) |
| Percutaneous coronary intervention | 4/267 | (1.5) | 1/213 | (0.5) | 2/227 | (0.9) | 2/263 | (0.8) | 5/272 | (1.8) | 6/270 | (2.2) | 2/170 | (1.2) |
| Coronary artery bypass grafting | 3/267 | (1.1) | 1/213 | (0.5) | 1/226 | (0.4) | 0/262 | (0.0) | 0/272 | (0.0) | 1/270 | (0.4) | 0/170 | (0.0) |
| CVD mortality | 2/342 | (0.6) | 0/324 | (0.0) | 0/318 | (0.0) | 0/306 | (0.0) | 0/302 | (0.0) | 1/297 | (0.3) | 6/198 | (3.0) |

Abbreviations: CVD, Cardiovascular disease.

[a] Denominators differ due to differences in reporting and forms used to report events.

**Table 17. Cardiovascular Disease Mortality By IDC-10 Codes Following RYGB, Stratified By Sex.**

| Cardiovascular disease | Number of deaths | Females (N=1413) | Males (N=357) |
|---|---|---|---|
| Mitral valve disease, unspecified | 1 | 1 | 0 |
| Hypertensive heart disease without (congestive) heart failure | 1 | 1 [a] | 0 |
| Acute myocardial infarction, unspecified | 1 | 0 | 1 |
| Chronic ischemic heart disease | 1 | 0 | 1 |
| Atherosclerotic cardiovascular disease | 5 | 2 | 3[a] |
| Pulmonary embolism without mention of acute cor pulmonale | 1 | 0 | 1 |
| Endocarditis, valve unspecified | 2 | 1 | 1 |
| Other hypertrophic cardiomyopathy | 1 | 1 [a] | 0 |
| Cardiac arrest, unspecified | 1 | 1 | 0 |
| Cardiomegaly | 1 | 0 | 1 [a] |
| Phlebitis and thrombophlebitis of other deep vessels of lower extremities | 1 | 1 | 0 |
| Stroke, not specified as hemorrhage or infarction | 1 | 0 | 1 [a] |

[a] 5 participants had history of cardiovascular disease at pre-surgery (1 of the 3 males with atherosclerotic cardiovascular disease).

# 3.0 Manuscript 2: Predictors Of Change In Cardiovascular Disease Risk And Cardiovascular Disease Events Following Gastric Bypass: A 7-Year Prospective Multi-Center Study

## 3.1 Brief Overview

**Objective:** To identify predictors of change in cardiovascular disease (CVD) risk and cardiovascular events following Roux-en-Y gastric bypass surgery (RYGB).

**Background:** Change in short-term (i.e. 10-year) and Lifetime CVD risk following RYGB has significant heterogeneity.

**Methods:** Between 2006-2009, 1625 adults without a history of CVD enrolled in a prospective cohort study and underwent RYGB at 1 of 10 U.S. hospitals. Participants were followed annually for a maximum of 7 years. Associations between pre-surgery characteristics (anthropometric, sociodemographic, physical and mental health, alcohol/drug use, eating behaviors) and 1) pre- to post-surgery change in 10 year and Lifetime Atherosclerotic CVD (ASCVD) risk scores, respectively, and 2) having a CVD event (nonfatal myocardial infarction, stroke, ischemic heart disease, congestive heart failure, angina, percutaneous coronary intervention, coronary artery bypass grafting or CVD-attributed death) as repeated measures (years 1-7) were evaluated.

**Results**: Pre-surgery factors independently associated with decreases in both 10-year and Lifetime risk scores 1-7 years post-RYGB were higher CVD risk score, female sex, higher household income, and normal kidney function. Additionally, Black race and having diabetes were independently associated with decreases in 10-year risk, while not having diabetes and a higher

(better) composite mental health score were independently related to decreases in Lifetime risk. A lower (worse) pre-surgery composite physical health score was associated with a higher CVD event risk (RR=1.68, per 10 points).

**Conclusion**: This study identified multiple pre-surgery factors that characterize patients who may have more cardiovascular benefit from RYGB, and patients who might require additional support to improve their cardiovascular health.

## 3.2 Introduction

Within the United States (US), cardiovascular disease (CVD) is the cause of 1 in every 3 deaths, or an estimated 801,000 deaths each year[78]. Obesity increases risk of CVD through elevations in blood pressure, dyslipidemia, diabetes and inflammation, which are all related to increased CVD events[165]. Obesity also directly increases risk of CVD by impacting cardiovascular structure and function[166].

Bariatric surgery, the most effective treatment for severe obesity, results in sustainable long-term weight loss[167]. There is also some evidence that bariatric surgery leads to a reduction in CVD events[168]. For example, in a retrospective matched cohort study of patients with diabetes who underwent bariatric surgery (n=2,287) and their matched nonsurgical controls (n=11,435), after 8 years of follow-up, the surgical group (Roux-en-Y gastric bypass [RYGB], sleeve gastrectomy, Laparoscopic Adjustable Gastric Banding [LAGB] or duodenal switch) had lower incidence in the composite outcome, major adverse cardiovascular events, in the surgical group [30.8% (95% CI, 27.6%-34.0%)] compared to the nonsurgical group [47.7% (95% CI, 46.1%-49.2%)] ($P < .001$)[168]. Additionally, bariatric surgery is associated with a reduction in short-term (i.e. 10-year) and

Lifetime CVD risk as measured by CVD risk scores, but there is significant heterogeneity of treatment effect, with some patients achieving large risk reductions while others experience little change or even an increase in risk [138,169,170]. There is evidence from other populations that certain sociodemographics, comorbidities, physical fitness, depressive symptoms, substance use[171-175] and other patient-level factors are associated with CVD risk[176], but an examination of pre-surgical factors that might predict change in CVD risk or CVD events following bariatric surgery is lacking.

The aim of this study was to identify pre-surgery predictors of change in CVD risk and CVD events following RYGB, one of the two most common bariatric surgical procedures in the US[177]. Identifying patient-level factors related to surgically-induced change in CVD risk may help determine which patients are most likely to experience CVD risk reduction from surgical treatment of obesity versus those who would likely require further intervention (e.g., education and counseling during clinical follow-up) to improve their CVD risk profile. Likewise, identifying patient-level factors related to CVD event risk following surgery may help inform which patients require a higher level of surveillance and in-depth cardiac care post-surgery. This study builds on previous work in a large geographically diverse sample of adults who underwent RYGB surgery. The previous study found that, on average and independent of aging, 10-year and Lifetime CVD risk, as assessed by the Atherosclerotic CVD (ASCVD) 10-year and Lifetime risk scores[170], was substantially lower 1 year after surgery, compared to pre-surgery, then increased 1 to 7 years post-surgery. However, there was a net decline from pre-surgery throughout 7 years of follow-up.

## 3.3 Methods

### *Design and Participants*

The Longitudinal Assessment of Bariatric Surgery (LABS)-2 was a prospective cohort study of 2,458 adults who were at least age 18. Participants were recruited between February 2005 and February 2009 and underwent their first bariatric surgery as part of clinical care between April 2006 and April 2009 at one of ten hospitals at six clinical centers throughout the US. Written informed consent was obtained from participants and the institutional review boards at every center approved the protocol.

Standardized research assessments were conducted independent of clinical care by trained research staff within 30 days prior to scheduled surgery then annually for up to 7 years through the study end date (January 31, 2015). To reduce site difference in data collection, sites used LABS-provided equipment to collect data when possible. Research assessments were conducted in person except for a brief telephone or mail assessment at 6-months and 6-years[178], which did not include many of the variables needed to calculate CVD risk.

This report is limited to LABS-2 participants who underwent RYGB (N=1770), as it accounted for the majority (72.0%) of surgical procedures in the cohort and remains a common procedure, with usage rates of 26.8% to 36.7% in the current bariatric surgery setting[177]. Additionally, participants with a pre-surgery history of CVD were excluded (N=145), leaving 1625 participants. The sample was further reduced to 1234 participants for the evaluation of factors related to change in CVD risk score, as 391 participants were missing follow-up ASCVD risk score data (**Supplementary Figure 7).**

### *Measures*

#### *CVD risk*

The Atherosclerotic CVD (ASCVD) 10-year and Lifetime ASCVD risk scores were used to assess CVD risk due to endorsement by the American College of Cardiology/American Heart Association (ACC/AHA)[100], popularity and historical use in clinical care[115]. The ASCVD 10-year and Lifetime risk scores are validated to predict the risk of experiencing the composite outcome of coronary heart disease (CHD) death, nonfatal myocardial infarction (MI) or stroke in Caucasian and African American populations[101]. The ASCVD risk scores are calculated from age, gender, race, total cholesterol, systolic blood pressure, blood pressure treatment, current smoking, diabetes, and hyperlipidemia treatment[100]. Pre-surgery age was used to calculate ASCVD risk scores at all annual assessments to eliminate the effect of aging on change in risk[179]. Per scoring recommendations, ASCVD risk scores were not calculated following a CVD event[115]. Change in ASCVD risk was calculated at each annual follow-up assessment as the post-surgery value minus the pre-surgery value, such that a negative number indicates a decrease in risk and a positive number indicates an increase in risk.

#### *Categorization of CVD risk*

To describe CVD risk and to help guide statin therapy decisions in the clinical setting, the ASCVD 10-year risk score is categorized[180] as low (score <7.5%) and high (≥7.5%) 10-year risk[181]. The high-risk category indicates it may be appropriate to initiate statin therapy[182]. To convey future CVD risk the ASCVD Lifetime risk score is categorized into two categories: low (<39%) and high risk (≥39%)[183].

***CVD events***

CVD events were defined as having a nonfatal myocardial infarction (MI), stroke, ischemic heart disease, congestive heart failure, angina, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or death attributed to CVD. CVD events were identified by a LABS-certified clinical researcher with medical records, physical examination, and patient interviews to determine history of CVD prior to surgery and annually post-surgery (i.e., yes/no in the past year)[184].

***Characteristics and behaviors potentially related to change in CVD risk or CVD outcomes.***

Assessment of anthropometrics, sociodemographics, comorbidities, physical function, mental health, substance use and eating behaviors in the LABS-2 study has been previously reported[178,184]. Pre-surgery factors evaluated in this report are listed in **Table 18** and variable descriptions are provided in supplemental material (**Supplementary Appendix A**).

***Statistical analysis***

Descriptive statistics were used to summarize participant characteristics and to report pre- to post-surgery change in ASCVD risk scores by post-surgery assessment. Frequencies and percentages are reported for categorical data. Medians, 25th and 75th percentiles are reported for continuous data.

Mixed models were fit via maximum likelihood to assess the association between pre-surgery factors, listed by domain in **Table 18**, and repeatedly measured CVD outcomes (i.e., risk scores and events), with time since surgery (continuous) as fixed effects and a person-level random intercept. Pre-surgery factors previously reported to be associated with missing CVD outcome data (i.e., site, age and past year smoking status[185]) were also entered into all model as fixed effects. More specifically, first a series of basic multivariable linear mixed models were used to assess

associations between each pre-surgery factor and change in 10-year ASCVD risk score (continuous). Given the strong impact CVD risk has on subsequent change in CVD risk, these basic models were also adjusted for the pre-surgery 10-year ASCVD score. To identify independent associations, factors identified at $P<.20$ within each basic model were evaluated in a single model. Variables with $P>.10$ were removed using backwards elimination until all variables in the final model had $P\leq.10$. Regression coefficients (*βeta*) and 95% confidence intervals (CI) are reported; a negative *βeta* indicates a reduction (i.e., improvement) in 10-year ASCVD risk score. This methodology was repeated for the Lifetime score.

As a secondary analysis, among participants with high Lifetime CVD risk pre-surgery (ASCVD Lifetime risk score ≥39%), Poisson mixed models with robust error variance[186] were used to estimate and test the significance of associations between pre-surgery factors and the repeated outcome measure, post-surgery Lifetime ASCVD risk classification (high, indicating no change, or low, indicating a reduction). The same model building strategy was applied. Relative risks (RR) and 95% CI are reported; a RR >1 indicates an increased chance of improvement (i.e., changing from high to low risk Lifetime risk). The low frequency of participants with high 10-year CVD risk pre-surgery (ASCVD 10-year risk score ≥7.5%)[170] precluded a similar analysis for 10-year CVD risk.

Next, a series of Poisson mixed models with robust error variance[186] were used to assess associations between pre-surgery factors (except ASCVD Lifetime risk score), and the repeated past-year composite CVD events measure (yes/no at each annual assessment). Data was not censored following an initial CVD event, as participants could have CVD events in multiple follow-up years. RR (>1 indicates an increased risk of a CVD event) and 95% CI are reported.

Finally, due to the large weight loss typically experienced with RYGB[187] and the association between weight status and risk of CVD[188], the association of percent weight loss from pre-surgery, as a time-dependent covariate, and each CVD outcome was modeled, controlling for factors in the respective final pre-surgery model. Interactions between pre-surgery factors and time were assessed in all models.

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). All reported *P* values are two-sided; *P* values were used to guide interpretation of findings[189].

## 3.4 Results

### *Participant characteristics*

Participants in the CVD event sample (N=1625) were mostly female (82%), White (85%), non-smokers at time of surgery (97.5%), and without diabetes (67.1%). Median age was 44 (IQR: 36-53) years, and median BMI was 27 kg/m$^2$ (IQR: 23-32). Characteristics among the ASCVD risk score subsample (N=1234) were similar. A complete table of pre-surgery characteristics among both samples is available in the supplemental material (**Supplementary Table 22**). Median follow-up time for the ASCVD risk score subsample was 6.0 years and for the CVD events sample was 6.1 years. Change in CVD risk is reported in **Supplementary Appendix B**. Across follow-up, 230 of 1625 participants had a total of 426 CVD events (n=414 non-fatal; n=12 fatal), a rate of 37.5 (95%CI: 27.3, 51.7) events per 1000 person-years.

***Pre-surgery factors related to change in CVD risk***

**Table 19** shows the basic models of pre-surgery characteristics that entered the final models for change in 10-year or Lifetime ASCVD risk score, respectively. There were no significant interactions with time. Additional basic model results are provided in supplemental material (**Supplementary Table 23**). **Table 19** also shows the final pre-surgery models based on the model building strategy outlined in the methods section (i.e. pre-surgery characteristics with *P* ≤.10 were retained).

***10-year CVD risk***

Pre-surgery factors independently associated with a mean decrease (improvement) in 10-year ASCVD risk score in the final model were: higher 10-year ASCVD risk score [*βeta*= -0.45 (95% CI: -0.48, -0.42) per 1 unit], female sex [versus male: *βeta*= -0.80 (95% CI: -1.15, -0.44)], Black race [versus White: *βeta* = -0.67 (95% CI: -1.14, -0.19)], higher household income level [e.g., greater than $75,000 versus less than $25,000: β= -0.70 (95% CI: -1.08, -0.31)], normal kidney function [versus abnormal: *βeta*= -0.94 (95% CI: -1.44, -0.45)], and having diabetes [versus not having: *βeta*= -0.58 (95% CI: -0.89, -0.28)]. Not having past-year psychiatric counseling (potentially indicating better mental health) [versus having: *βeta*= -0.27 (95% CI: -0.57, 0.03)] was also associated with a mean decrease at *P*≤.10 (**Table 19**).

***Lifetime CVD risk***

Pre-surgery factors independently associated with a mean decrease (improvement) in Lifetime ASCVD risk score in the final model were: higher Lifetime ASCVD risk score [*βeta*= -0.55 (95% CI: -0.62, -0.48)], female sex [versus male: *βeta*= -2.19 (95% CI: -3.95, -0.42)], higher household income level [e.g., greater than $75,000 versus less than $25,000: *βeta*= -3.13 (95% CI: -4.94, -1.33)], normal kidney function [versus abnormal: *βeta*= -2.44 (95% CI: -4.73, -0.14)], not

having diabetes [versus having: *βeta*= -2.19 (95% CI: -3.82, -0.57)] and a higher Short Form (SF)-36 Mental Component Summary (MCS) score (indicating better mental health) [*βeta*= -0.72 (95% CI: - 1.29, -0.14) per 10 points (**Table 19**).

***Models of high to low Lifetime CVD risk***

Factors associated with improvement in Lifetime ASCVD risk classification (from high pre-surgery to low post-surgery) in basic models were female sex [versus male: RR=1.09 (95% CI: 1.03, 1.15)] and not having diabetes [versus having: RR=1.05 (95% CI: 1.01, 1.09) (**Supplementary Table 24**). In the final model, only female sex (versus male) was retained.

***Pre-surgery factors associated with CVD events***

Pre-surgery 10-year ASCVD risk score was not significantly associated with the composite past-year CVD event outcome, even in the basic model (RR=1.04, 95% CI, 0.98, 1.11; p=.21), while lower SF-36 Physical Component Summary (PCS) score (indicating worse physical health) [RR: 1.68 (95% CI: 1.22, 2.31), per 10 points lower], the inability to complete a Long Distance (400 meter) Corridor Walk [RR: 1.73 (95% CI: 0.79, 3.76)] and past-year psychiatric counseling (potentially indicating worse mental health) [versus not having counseling; RR: 1.84 (95% CI: 0.81, 4.18)] were (**Table 20**). Only the SF-36 PCS score, *P*= 0.002, was retained in the final model. Additional basic model results are provided in supplemental material (**Supplementary Table 25**).

***Percent weight loss and CVD risk***

When added to the final pre-surgery models shown in **Table 19**, greater percent weight loss was independently associated with a mean decrease (improvement) in 10-year ASCVD score [*βeta*= -0.13 (95% CI: -0.17, -0.09, *P*<.001) per 5%] and Lifetime ASCVD risk score [*βeta*= -0.81 (95% CI: -1.06, -0.57, *P*<.001) per 5%], respectively. In contrast, percent weight loss from pre-surgery was not independently associated with moving from high to low Lifetime ASCVD risk

(RR=0.99, 95% CI: (0.98, 1.02), *P*=0.22) or an increased risk of having a CVD event (RR=0.99, 95% CI: 0.88, 1.10, *P*=0.81).

## 3.5 Discussion

Among adults who underwent RYGB from a large geographically diverse US cohort, we identified multiple pre-surgery factors independently associated with greater improvement in the 10-year and Lifetime ASCVD risk scores, which included higher CVD risk, female sex, higher household income, normal kidney function. Additionally, Black race and having diabetes were related to greater improvement in the 10-year ASCVD risk score, while not having diabetes and having a higher SF-36 MCS score (i.e., better mental health) were related to greater improvement in the Lifetime ASCVD risk score.

In previous LABS-2 studies of the RYGB cohort, sex was not independently associated with weight loss[190] or weight regain[191]. However, compared to men, women had a greater mean improvement in both the in 10-year and Lifetime ASCVD risk scores, independent of the corresponding pre-surgery ASCVD risk value. A hypothesis for this finding is a differential effect of surgery on hormone levels in men versus women, which impact CVD risk. It has been reported that obese premenopausal women (which account for 67% of females in this cohort pre-surgery) have significantly lower levels of estrogen compared to non-obese women[192]; it thus follows that as weight decreases, estrogen levels may increase. Increased estrogen has been linked to higher levels of high-density lipoproteins, lower levels of low-density lipoproteins and an overall lower incidence of CVD prior to menopause in women[193]. Thus, the greater CVD risk improvement in

women versus men found in this study may be indicative of improvement in hormone levels among women which are reflected in improvement in CVD risk.

Blacks in the US, have a higher prevalence of hypertension, stroke, heart failure, and peripheral artery disease, as well as an overall earlier age of onset of CVD, compared to Whites[194]. Thus, Black versus White race being associated with greater mean improvement in 10-year risk is a particularly interesting finding. A history of differential access to medical care likely accounts for some of the racial disparities in CVD risk. The identification and treatment of CVD risk factors such as obesity and high blood pressure (which can be achieved through bariatric surgery) has been proposed as a step to reduce the disparate rates of CVD in the US. Thus, perhaps among patients who are able to access and undergo interventions associated with improvements in CVD health, Blacks have more substantial improvement than Whites. This study's Black sample may be different compared to the general US' Black population in terms of overall medical access, insurance coverage, socioeconomic status and other environmental exposures, all of which may have influenced the improvement of ASCVD risk in the Black sample compared to the White sample in this study[195].

Consistent with literature linking socioeconomic status factors to overall health and CVD risk, pre-surgery household income was associated with an improvement in CVD risk[196]. Both individual and environmental factors associated with higher levels of income may contribute to improvement in CVD risk[197]. For example, annual income may be related to an individual's general environment (i.e. home located in less polluted area) as well as their ability to access healthier food choices (i.e., fresh produce and fruit).

Those with normal versus abnormal kidney function pre-surgery had better improvement in CVD risk. This finding is supported by evidence of CVD being the leading cause of morbidity

and mortality among patients with kidney disease even after adjustment for other CVD risk factors (i.e. diabetes and hypertension)[198]. One possible explanation is that as kidney function worsens, glomerular filtration rate declines, which is linked to an increase in the calcification of vascular, subintima and media of large vessel calcification, all associated with an increase in CVD mortality[198].

A perplexing finding was the mean improvement in 10-year risk but a worsening in Lifetime risk post-surgery in those with versus without diabetes pre-surgery. The 10-year risk result likely reflects the fact that remission of diabetes after surgery is common[199], and the scoring algorithm results in a lower risk score for no diabetes. A reason for the discrepant association with diabetes between the 10-year and Lifetime risk scores may be due to the age of the study sample (median age was 44 years), as there is evidence among adults with diabetes that those below versus above the age of 40 have a lower risk of developing CVD over 10 years, but a higher Lifetime risk of CVD[200].

Poor mental health has been associated with an increased risk of CVD[201]. Furthermore, it has been suggested that a lower mental health score may indicate a higher risk for an unhealthy lifestyle (i.e. unhealthy diet, cigarette smoking, lack of physical activity with higher levels of sedentary behavior) and non-adherence to regimens (i.e. medication and diet), which may lead to an increase in CVD risk over time[202-204]. Thus, it is not surprising that a higher SF-36 MCS score (indicating better mental health) pre-surgery was associated with a greater mean improvement in Lifetime ASCVD risk score. There was also indication that pre-surgery psychiatric counseling, perhaps a surrogate measure for poor mental health status, may be associated with less mean improvement in 10-year risk.

Not surprisingly, worse physical health pre-surgery, as measured by the SF-36 PCS score (which considers physical function, role physical, bodily pain and general health perception), was related to a higher risk of having a CVD event across 7 years of follow-up. A similar finding was reported in postmenopausal women (age range: 50 to 79) who participated in the Women's Health Initiative (WHI) clinical trials[205]; after adjustment for potential confounders, WHI participants with lower (worse) SF-36 PCS scores had greater risk of CVD incidence and CVD-specific death[205]. In contrast, neither pre-surgery ASCVD 10-year risk score nor weight loss were predictive of CVD events. The lack of these associations may be due to the limited number of CVD events (likely reflecting participants age[206], e.g., median pre-surgery age was 44), as well as the lack of additional follow-up time.

Major strengths of this study include the comprehensive pre-surgery and post-surgery assessments and longer-term follow-up (up to 7 years). The extensive evaluations allowed for continued measurement of CVD risk, as well as multiple individual level factors in adults undergoing RYGB in a large geographically diverse US cohort. Additionally, unlike previous studies within the bariatric surgery literature where 10-year or Lifetime CVD risk and CVD risk factors were only reported as being higher or lower after surgery[207-209], this study identified factors associated with magnitude of change in CVD risk. More specifically, this is one of the first studies to identify multiple individual level factors associated with change in CVD 10-year and Lifetime risk in the bariatric surgery population.

There are several limitations in this study worth noting, including the lack of representation of the gastric sleeve procedure which was uncommon during the study's time period (2006-2009), but has now surpassed RYGB as the most common procedure performed in the US[178]. Additionally, while there were significant relationships between pre-surgery factors and

improvement in 10-year ASCVD risk, the clinical importance of these factors is difficult to estimate due to the relatively small effect sizes in the model. As we previously reported[170], the 10-year and Lifetime ASCVD risk change gets smaller as time from surgery increases (i.e. less CVD benefit from surgery), However, the lack of significance of interaction terms between pre-surgery factors and time indicated the pre-surgery factors identified as beneficial in this study had consistent associations with outcomes across 7 years.

## 3.6 Conclusions

This study identified multiple factors that may help identify patients prior to bariatric surgery whose CVD risk would be helped the most from a bariatric surgical intervention (e.g., those with high CVD risk, females, those who identify as Black race in the US), as well patients who might require different or additional support after surgery (e.g., those with low income or abnormal kidney function, poor mental health), such as education, counseling (e.g., more scheduled follow-up appointments after surgery), and CVD-risk targeted medication (e.g., lipid lowering or hypertensive medication) to improve their cardiovascular health.

## 3.7 Tables and Figures

**Table 18. Pre-Surgery Factors[a], By Domain, Evaluated As Predictors Of Pre- To Post-Surgery Change In 10 Year And Lifetime CVD Risk, Respectively, And Post-Surgery CVD Event**

| **Control variables (forced in all models)** | |
|---|---|
| ASCVD 10-year or Lifetime risk score | |
| Site[b] | |
| Age[b] | |
| Past year smoking[b] | |
| **Factors considered in the full model if p<0.20 in basic model** | |
| **Anthropometrics[210]** | **Mental health[211]** |
| Body mass index | Beck Depression Inventory-1 score, past week[212] |
| Body mass index at age 18 | SF-36 Mental Component Summary score, past 4 weeks[213] |
| **Sociodemographics[171]** | Psychiatric counseling, past year[214] |
| Sex | Psychiatric medication, past 3 months |
| Race | **Interpersonal Support[211]** |
| Ethnicity | Interpersonal Support Evaluation List score, current |
| Marital status | **Substance use, past year[174]** |
| Education | Symptoms of alcohol problems |
| Work for pay | Frequency of drinking alcohol |
| Annual household income | Marijuana use |
| **Comorbidities** | Illegal drug use |
| Asthma[215,216] | **Eating behaviors to control weight, past 6 months[174]** |
| Sleep apnea[217] | Decreased fat intake |
| Abnormal kidney function[218] | Ate fewer high carbohydrate foods |
| Diabetes[219] | Increased fruits and vegetables |
| **Women's Health[c]** | |
| Polycystic ovary syndrome[220] | |
| Menopause[221] | |
| **Physical function[173,222,223]** | |
| Severe walking limitation | |
| SF-36 Physical Component Summary score, past 4 weeks | |
| Long Distance Corridor Walk | |
| Ability to complete | |
| Completion time | |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; SF-36; Short Form 36-Item Health Survey. [a] A description of each variable is provided in supplemental material. Variables represented current status at the time of the pre-surgery assessment unless otherwise noted.
[b] Related to missing CVD risk scores across follow-up.
[c] Only determined in women

**Table 19. Associations Between Pre-Surgery Factors And Change In 10-Year And Lifetime ASCVD Risk Scores, Respectively, 1-7 Years Since Roux-En-Y Gastric Bypass.**

| | | Change in 10-year ASCVD risk | | | | Change in Lifetime ASCVD risk | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Basic models[a] | *P* | Final model[b] N=1132 | *P* | Basic models[a] | *P* | Final model[b] N=1119 | *P* |
| | n | *Beta* (95%CI) | | *Beta* (95%CI) | | *Beta* (95%CI) | | *Beta* (95%CI) | |
| Pre-surgery ASCVD risk, per 1 unit higher | 1234 | -0.46 (-0.48, -0.43) | <.001 | -0.45 (-0.48, -0.42) | <.001 | -0.46 (-0.51, -0.41) | <.001 | -0.55 (-0.62, -0.48) | <.001 |
| **Sociodemographics** | | | | | | | | | |
| Sex (ref=Male) | 1013 | | <.001 | | <.001 | | 0.15 | | 0.02 |
| Female | 221 | -0.76 (-1.10, -0.42) | | -0.80 (-1.15, -0.44) | | -1.22 (-2.90, 0.46) | | -2.19 (-3.95, -0.42) | |
| Race (ref=White) | 1064 | | 0.007 | | 0.007 | | 0.09 | | 0.06 |
| Black | 129 | -0.66 (-1.10, -0.21) | | -0.67 (-1.15, -0.20) | | 1.09 (-0.95, 3.13) | | 0.91 (-1.31, 3.13) | |
| Other | 41 | 0.39 (-0.30, 1.08) | | 0.48 (-0.23, 1.19) | | 3.24 (0.05, 6.43) | | 3.81 (0.52, 7.10) | |
| Annual household income (ref= Less than $25,000) | 340 | | 0.003 | | 0.003 | | <.001 | | 0.003 |
| $25,000-$49,000 | 336 | -0.52 (-0.91, -0.14) | | -0.46 (-0.84, -0.08) | | -1.16 (-2.91, 0.59) | | -0.87 (-2.66, 0.92) | |
| $50,000-$74,999 | 258 | -0.64 (-1.04, -0.23) | | -0.63 (-1.03, -0.23) | | -2.18 (-4.03, -0.34) | | -1.57 (-3.46, 0.32) | |
| Greater than $75,000 | 210 | -0.68 (-1.06, -0.30) | | -0.70 (-1.08, -0.31) | | -3.72 (-5.47, -1.97) | | -3.13 (-4.94, -1.33) | |
| **Comorbidities** | | | | | | | | | |
| Abnormal kidney function (ref=Yes) | 1132 | | 0.005 | | <.001 | | 0.003 | | 0.04 |
| No | 101 | -0.67 (-1.13, -0.20) | | -0.94 (-1.44, -0.45) | | -3.26 (-5.38, -1.13) | | -2.44 (-4.73, -0.14) | |
| Diabetes status (ref=Yes) | 830 | | <.001 | | <.001 | | 0.005 | | 0.008 |
| No | 404 | 0.57 (0.28, 0.87) | | 0.58 (0.28, 0.89) | | -2.15 (-3.67, -0.64) | | -2.19 (-3.82, -0.57) | |
| **Mental health** | | | | | | | | | |
| SF-36 MCS score, per 10 points higher (better) | 1154 | 0.01 (-0.12, 0.13) | 0.91 | | | -0.79 (-1.36, -0.22) | 0.006 | -0.72 (-1.29, -0.14) | 0.01 |
| Psychiatric counseling (ref=Yes) | 891 | | 0.07 | | 0.08 | | 0.82 | | |
| No | 277 | -0.28 (-0.58, 0.02) | | -0.27 (-0.57, 0.03) | | -0.16 (-1.55, 1.23) | | | |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; SF-36 MCS, Short Form Health Survey-36 Mental Component Summary.

[a] Basic model: adjusted only for pre-surgery factors related to missing follow-up data (site, age and past-year smoking), pre-surgery 10-year or lifetime ASCVD risk and time since surgery. A negative *beta* indicates a decrease in risk.

[b] Final model: A single model with all the listed variables (chosen through variable selection) as covariates along with the factors in the Basic model.

**Table 20. Associations Between Pre-Surgery Factors And CVD Events 1-7 Years Since Roux-En-Y Gastric Bypass (N=1625).**

| | | CVD event | | | |
|---|---|---|---|---|---|
| | | **Basic models**[a] | ***P*** | **Final model**[b] **N=1625** | ***P*** |
| | **n** | **RR (95%CI)** | | **RR (95%CI)** | |
| **Physical function** | | | | | |
| SF-36 PCS score, per 10 points lower (worse) | 1472 | 1.68 (1.22, 2.31) | 0.002 | 1.68 (1.22, 2.31) | 0.002 |
| Long Distance Corridor Walk | | | | | |
| Inability to complete (ref=No) | 1082 | | 0.17 | | |
| Yes | 438 | 1.73 (0.79, 3.76) | | | |
| **Mental health** | | | | | |
| Psychiatric counseling (ref=No) | 1138 | | 0.15 | | |
| Yes | 350 | 1.84 (0.81, 4.18) | | | |

Abbreviations: SF-36 PCS, Short Form Health Survey-36 Physical Component Summary score.

[a] Basic model: adjusted only for pre-surgery factors related to missing follow-up data (site, age and past-year smoking) and time since surgery. A relative risk (RR) above 1.0 indicates improvement in CVD risk (from high to low risk category).

[b] Final model: Only one variable was retained via variable selection. Thus, the estimates are identical to the basic model.

## 3.8 Supplemental Content

### 3.8.1 Appendix A. Variable Descriptions

All variables were assessed on study-specific questionnaires[224] as current status within 30 days prior to surgery unless otherwise noted.

**Sociodemographics and anthropometric measurements[171,225]:** Sociodemographic variables including age, sex, race, ethnicity and annual household income, were self-reported. Due to the low frequency of some races (i.e., Asian, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander), race was collapsed from several categories into three categories: white/Caucasian, black/African-American and 'other'. For those who did not elect to report race, race was set to missing. Ethnicity was categorized as Hispanic or non-Hispanic, regardless of race. Physical measurements (i.e. height, weight and blood pressure) were collected through standardized protocols by trained personnel. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI at age 18 was derived from a self-administered a weight history questionnaire[226].

**CVD risk factors:** Past-year cigarette smoking was assessed pre-surgery. Additionally, current **c**igarette smoking was self-reported at all assessments. Lipid profile (total cholesterol, high-density lipoproteins, low-density lipoprotein cholesterol and triglycerides) and diabetes-related parameters (hemoglobin A1C and glucose) from serum were assayed at a central laboratory. Fasting (at least 8 hours) was required for high-density lipoproteins, triglycerides and glucose. Information on medications (e.g. hypertension medication and hyperlipidemia treatment)

and comorbidities were collected through a variety of sources including self-report, medical records and physical examination[3].

**Comorbid conditions:** Asthma[227], sleep apnea[217], abnormal kidney function[228], and diabetes status[229] were assessed through self-administered questionnaires, medical record reviews, patient interviews, physical examination and laboratory assays[224].

**Women's health variables:** Polycystic ovary syndrome[230] and menopause[231] were assessed using medical records and a self-administered reproductive questionnaire[224]. Polycystic ovary syndrome and menopause status were evaluated among women only in the basic models. If these conditions entered a full model, a three-level variable was considered: male, female no, female yes.

**Physical function:** Severe walking limitation was defined as the self-reported inability to walk 200 feet without assistance[232]. The Medical Outcomes Short-Form Health Survey (SF- 36) is a 36-item generic measure of functional health[172], with a timeframe of the past 4 weeks. The SF-36 yields eight scale scores and two summary scores. This study used the Physical Component Summary (PCS) score. Norm-based methods were used to transform the score to a mean of 50 and standard deviations of 10 in the general U.S. population; a lower score indicates worse functional health[233].The long-distance corridor walk (400 m)[232] was conducted as an objective measure of exercise capacity and was timed (in seconds). The ability to complete the long-distance corridor walk was assessed for those who elected to attempt the long-distance corridor walk[226].

**Mental health[234]:** Symptoms of depression over the past week were assessed using the Beck Depression Inventory, version 1 (BDI-1), scaled from 0 to 63, with a higher score indicating greater severity of depression[235]. Mental health was also measured using the SF-36 norm-based Mental Component Summary (MCS) score; a lower score indicates worse mental health[233].

Counseling and/or hospital admissions for psychiatric or emotional problems in the past 12 months were self-reported. Psychiatric medication for any psychiatric or emotional problem was self-reported.

**Interpersonal Support**[234]**:** Current perceived social support was measured using the 12-item Interpersonal Support Evaluation List (ISEL-12); a higher score (range 0-12) indicates greater support availability[236].

**Substance use:** Past-year frequency of drinking alcohol and symptoms of alcohol problems[237] were measured with the Alcohol Use Disorders Identification Test (AUDIT). Past-year illegal drug use[238] was self-reported with the question, "In the past 12 months, other than as prescribed by a physician, have you used the following: opiates, amphetamines, hallucinogens, inhalants, marijuana, cocaine, phencyclidine". Additional names of each substance were provided. Participants responded "no" or "yes" to each substance. A "yes" response to any substance other than opioid use was used to determine illegal drug use. Opioid use was excluded due to difficulties in differentiating between prescribed and non-prescribed use[239].

**Weight control practices**[174]**:** Weight control practices in the past 6 months were assessed via self-administered questionnaires. Participants were identified as engaging in a given weight control practice (e.g., counting fat grams) if they reported doing so each week in the past 6 months[224].

**Change in weight:** The percent weight change from pre-surgery was calculated as post-surgery weight minus pre-surgery weight divided by pre-surgery weight multiplied by 100, such that a negative number indicates weight loss[240].

### 3.8.2 Appendix B. Change In CVD Risk.

**Figure 7** shows observed median and IQR of change in 10-year and Lifetime ASCVD risk scores, respectively, from pre-surgery to each post-surgery assessment through 7 years. The observed change in 10-year ASCVD risk score revealed heterogeneity in effect at each assessment throughout follow-up (e.g., 25$^{th}$, 75th %-ile of change in 10-year ASCVD risk score at year 1: -2.6, -0.4, respectively and year 7: -2.3, -0.2, respectively) (**Table 21**). This heterogeneity is also reflected in the observed change in Lifetime ASCVD risk score (e.g., 25$^{th}$, 75th %-ile change in Lifetime ASCVD risk score at year 1: -19, 0 and year 7: -11, 0). The percentage of participants who changed from high Lifetime CVD risk pre-surgery to low risk post-surgery was 40% at 1-year post-surgery and declined to 21% at 7 years post-surgery (**Table 21**).

### 3.8.3 Tables And Figures

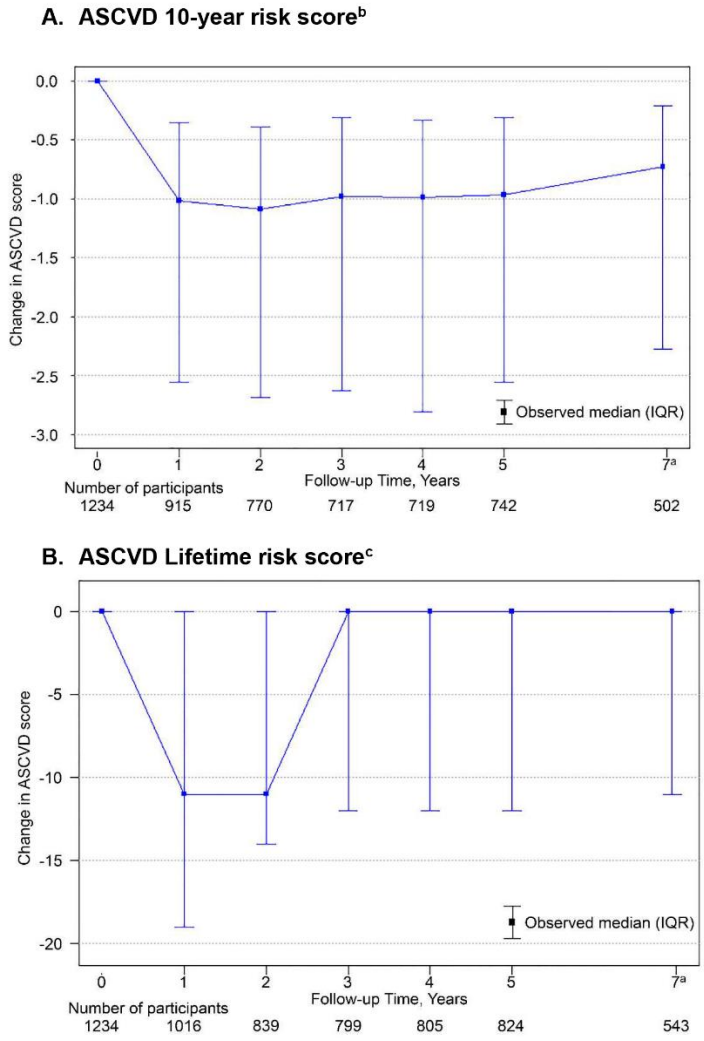



**Figure 7. Observed Pre- To Post-Surgery Change In ASCVD Risk Scores From Pre-Surgery By Time Since Roux-En-Y Gastric Bypass (N=1234).**

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease.
[a] Data collection ended before the 7-year assessment of 387 participants.
[b] A negative value indicates a decrease in 10-year CVD risk. At the pre-surgery assessment the median 10-year ASCVD score was 2.3 (25$^{th}$ to 75%-ile: 1.0 to 5.3; range: 0.1, 55.3)
[c] A negative value indicates a decrease in lifetime CVD risk. At the pre-surgery assessment the median lifetime ASCVD score was 39.0 (25$^{th}$ to 75%-ile: 39.0 to 50.0; range: 5.0, 69.0). The median and third quartile were both 0 for years 3 through 7.

**Table 21. Observed Pre- To Post-Surgery Change In ASCVD Risk Scores By Time Since Roux-En-Y Gastric**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7[a] |
|---|---|---|---|---|---|---|
| **10-year ASCVD score**[b] (N=1234) | n=915 | n=770 | n=717 | n=719 | n=742 | n=502 |
| Median (25th -75th %-ile) | -1.0 (-2.6, -0.4) | -1.1 (-2.7, -0.4) | -1.0 (-2.6, -0.3) | -1.0 (-2.8, -0.3) | -1.0 (-2.6, -0.3) | -0.7 (-2.3, -0.2) |
| Range | (-23.6, 15.0) | (-22.6, 9.7) | (-26.0, 24.2) | (-24.4, 15.1) | (-19.0, 9.9) | (-26.5, 10.2) |
| **Lifetime ASCVD score**[c] (N=1234) | n=1016 | n=839 | n=799 | n=805 | n=824 | n=543 |
| Median (25th -75th %-ile) | -11 (-19, 0) | -11 (-14, 0) | 0 (-12, 0) | 0 (-12, 0) | 0 (-12, 0) | 0 (-11, 0) |
| Range | (-64, 45) | (-64, 31) | (-64, 31) | (-64, 42) | (-64, 45) | (-64, 45) |
| **Lifetime ASCVD improvement** (N=1001)[d] | n=821 | n=678 | n=639 | n=654 | n=672 | n=431 |
| High to low risk | 325 (39.6) | 224 (33.0) | 198 (31.0) | 188 (28.8) | 184 (27.4) | 93 (21.6) |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease.

[a] Data collection ended before the 7-year assessment of 387 participants.

[b] A negative score indicates a decrease in 10-year CVD risk. At the pre-surgery assessment the median 10-year ASCVD score was 2.3 ($25^{th}$ to 75%-ile: 1.0 to 5.3; range: 0.1, 55.3).

[c] A negative score indicates a decrease in Lifetime CVD risk. At the pre-surgery assessment the median Lifetime ASCVD score was 39 ($25^{th}$ to 75%-ile: 39 to 50; range: 5, 69).

[d] Only those who were identified as high Lifetime risk pre-surgery (≥39%) were evaluated for improvement

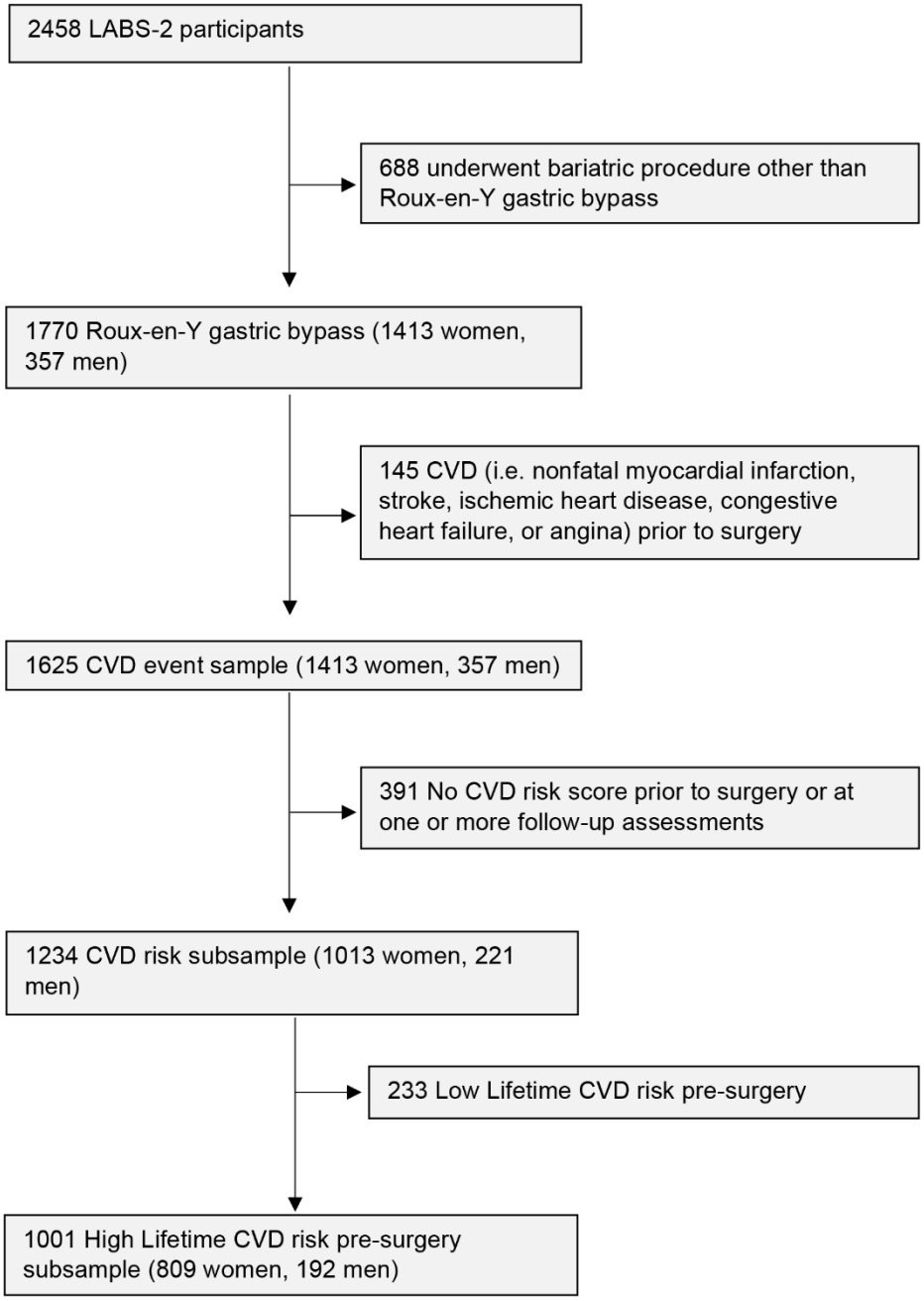



**Figure 8. Participant Flow**

**Table 22. Pre-Surgery Characteristics Of CVD Event Sample And CVD Risk Subsample**

| | CVD event sample n=1625 | CVD risk subsample n=1234 |
|---|---|---|
| **Control variables** | | |
| Age, years | | |
| Median(25th:75th) | 44 (36 : 53) | 44 (37 : 54) |
| Range | 19 : 75 | 19 : 75 |
| Smoked in the past year, n (%) | | |
| Yes | 40 (2.5%) | 23 (1.9%) |
| ASCVD 10-year risk score | n=1488 | |
| Median(25th:75th) | 2.3 (1.0 : 5.3) | 2.3 (1.0 : 5.6) |
| Range | 0.0 : 55.3 | 0.0 : 51.4 |
| ASCVD Lifetime risk score | n=1587 | |
| Median(25th:75th) | 39 (39 : 50) | 39 (39 : 50) |
| Range | 5 : 69 | 5 : 69 |
| **Anthropometrics** | | |
| Body mass index, $kg/m^2$ | | |
| Median(25th:75th) | 46.6 (42.5 : 51.9) | 46.3 (42.4 : 51.5) |
| Range | 33.7 : 81.0 | 33.7 : 81.0 |
| Body mass index at age 18, $kg/m^2$ | n=1011 | n=785 |
| Median(25th:75th) | 26.6 (22.5 : 31.6) | 26.6 (22.5 : 31.2) |
| Range | 14.5 : 69.9 | 14.5 : 69.9 |
| **Sociodemographics** | | |
| Sex, n (%) | | |
| Female | 1331 (81.9%) | 1013 (82.1%) |
| Race, n (%) | n=1607 | |
| White | 1372 (85.4%) | 1064 (86.2%) |
| Black | 180 (11.2%) | 129 (10.5%) |
| Other | 55 (3.4%) | 41 (3.3%) |
| Ethnicity, n (%) | n=1624 | |
| Hispanic | 79 (4.9%) | 46 (3.7%) |
| Married or living as married, n (%) | n=1500 | n=1178 |
| Yes | 928 (61.9%) | 739 (62.7%) |

**Table 22 (continued)**

| | CVD event sample | CVD risk subsample |
|---|---|---|
| Education, n (%) | n=1501 | n=1179 |
| High School or less | 348 (23.2%) | 276 (23.4%) |
| Some college/post High School education | 651 (43.4%) | 506 (42.9%) |
| College degree or higher | 502 (33.4%) | 397 (33.7%) |
| Employed for pay, n (%) | n=1493 | n=1173 |
| Yes | 1055 (70.7%) | 830 (70.8%) |
| Annual household income, n (%) | n=1458 | n=1144 |
| Less than $25,000 | 283 (19.4%) | 210 (18.4%) |
| $25,000-$49,000 | 415 (28.5%) | 336 (29.4%) |
| $50,000-$74,999 | 343 (23.5%) | 258 (22.6%) |
| Greater than $75,000 | 417 (28.6%) | 340 (29.7%) |
| **Comorbidities** | | |
| Asthma, n (%) | n=1588 | n=1225 |
| Yes | 398 (25.1%) | 316 (25.8%) |
| Sleep apnea, n (%) | n=1624 | |
| Yes | 814 (50.1%) | 626 (50.7%) |
| Abnormal kidney function, n (%) | n=1560 | n=1233 |
| Yes | 121 (7.8%) | 101 (8.2%) |
| Diabetes, n (%) | n=1594 | |
| Yes | 525 (32.9%) | 404 (32.7%) |
| **Women's Health** | | |
| Polycystic ovarian syndrome | | |
| Yes | 159 (9.8%) | 126 (10.2%) |
| Menopausal (women only) | n=995 | n=797 |
| Yes | 328 (33.0%) | 282 (35.4%) |
| Physical function | | |
| Severe walking limitation, n (%) | n=1470 | n=1131 |
| Yes | 96 (6.5%) | 65 (5.7%) |
| SF-36 Physical Component Summary score | n=1472 | n=1154 |
| Median(25th:75th) | 36.4 (27.7 : 44.7) | 36.6 (27.8 : 45.0) |
| Range | 8.5 : 65.7 | 8.9 : 65.7 |

**Table 22 (continued)**

| | CVD event sample | CVD risk subsample |
|---|---|---|
| Long Distance Corridor Walk | n=1520 | n=1171 |
| Ability to complete walk | 438 (28.8%) | 320 (27.3%) |
| Long Distance Corridor Walk completion time, seconds | n=1081 | n=850 |
| Median(25th:75th) | 372.9 (336.7 : 414.2) | 371.7 (337.2 : 414.0) |
| Range | 202.0 : 802.9 | 261.0 : 802.9 |
| **Mental health** | | |
| Beck Depression Inventory-1 score | n=1518 | n=1163 |
| Median(25th:75th) | 6.0 (3.0 : 11.0) | 6.0 (3.0 : 11.0) |
| Range | 0.0 : 44.0 | 0.0 : 37.0 |
| SF-36 Mental Component Summary score | n=1472 | n=1154 |
| Median(25th:75th) | 51.6 (42.6 : 57.3) | 51.6 (42.5 : 57.2) |
| Range | 16.8 : 75.9 | 17.9 : 75.9 |
| Psychiatric counseling, n (%) | n=1488 | n=1168 |
| Yes | 350 (23.5%) | 277 (23.7%) |
| Currently on psychiatric medications, n (%) | n=1494 | n=1173 |
| Yes | 552 (36.9%) | 430 (36.7%) |
| **Interpersonal Support** | | |
| ISEL support score | n=1493 | n=1175 |
| Median(25th:75th) | 44.0 (38.0 : 47.0) | 44.0 (38.0 : 47.0) |
| Range | 12.0 : 48.0 | 12.0 : 48.0 |
| **Substance use** | | |
| Symptoms of alcohol problems, n (%) | n=1492 | n=1172 |
| Yes | 100 (6.7%) | 81 (6.9%) |
| Frequency of drinking alcohol, n (%) | n=1497 | n=1175 |
| Never | 638 (42.6%) | 486 (41.4%) |
| Monthly or less | 552 (36.9%) | 442 (37.6%) |
| Two to four times a month | 220 (14.7%) | 168 (14.3%) |
| Two to three times a week | 59 (3.9%) | 52 (4.4%) |
| Four or more times a week | 28 (1.9%) | 27 (2.3%) |
| Marijuana, n (%) | n=1491 | n=1172 |
| Yes | 61 (4.1%) | 43 (3.7%) |

**Table 22 (continued)**

| | CVD event sample | CVD risk subsample |
|---|---|---|
| Illegal drug use, n (%) | n=1489 | n=1170 |
| Yes | 67 (4.5%) | 48 (4.1%) |
| Eating behaviors to control weight | | |
| Decreased fat intake, n (%) | n=1450 | n=1138 |
| Yes | 192 (13.2%) | 160 (14.1%) |
| Ate fewer high carbohydrate foods, n (%) | n=1442 | n=1129 |
| Yes | 191 (13.2%) | 158 (14.0%) |
| Increased fruits and vegetables, n (%) | n=1425 | n=1117 |
| Yes | 248 (17.4%) | 206 (18.4%) |

Abbreviations: SF-36, Short Form 36-Item Health Survey; ISEL, Interpersonal Support Evaluation List.

**Table 23. Basic Models Testing Associations[a] Between Pre-Surgery Factors And Change In ASCVD Risk Scores 1-7 Years Following Roux-En-Y Gastric Bypass (N=1234).**

| | N | Change in 10-year ASCVD risk *Beta*[a] (95%CI) | *P* value | Change in Lifetime ASCVD risk *Beta*[a] (95%CI) | *P* value |
|---|---|---|---|---|---|
| **Control variables** | | | | | |
| Age, years | 1234 | 0.04 (0.02, 0.05) | <.001 | 0.17 (0.12, 0.23) | <.001 |
| Smoked in the past year, n (%) | 1234 | -1.88 (-2.81, -0.95) | <.001 | 4.19 (-0.04, 8.42) | 0.052 |
| ASCVD 10-year risk score | 1234 | -0.46 (-0.48, -0.43) | <.001 | - | |
| ASCVD Lifetime risk score | 1234 | - | | -0.46 (-0.51, -0.41) | <.001 |
| **Anthropometrics** | | | | | |
| Body mass index, per 5 points higher | 1234 | 0.04 (-0.05, 0.13) | 0.43 | 0.43 (0.02, 0.84) | 0.04 |
| Body mass index at age 18, per 5 points higher | 785 | 0.01 (-0.11, 0.13) | 0.88 | 0.10 (-0.49, 0.69) | 0.74 |
| **Sociodemographics** | | | | | |
| Sex (ref=Male) | 1013 | | <.001 | | 0.15 |
| Female | 221 | -0.76 (-1.10, -0.42) | | -1.22 (-2.90, 0.46) | |
| Race (ref=White) | 1064 | | 0.007 | | 0.09 |
| Black | 129 | -0.66 (-1.1, -0.21) | | 1.09 (-0.95, 3.13) | |
| Other | 41 | 0.39 (-0.3, 1.08) | | 3.24 (0.05, 6.43) | |
| Ethnicity (ref=Not Hispanic) | 1188 | | 0.97 | | 0.56 |
| Hispanic | 46 | -0.02 (-0.74, 0.71) | | 1.00 (-2.36, 4.37) | |
| Marital status (ref=No) | 439 | | 0.54 | | 0.42 |
| Yes | 739 | -0.08 (-0.35, 0.18) | | -0.50 (-1.73, 0.72) | |
| Education (ref= College degree or higher) | 397 | | 0.10 | | 0.02 |
| High school or less | 276 | 0.36 (0.01, 0.70) | | 2.01 (0.45, 3.58) | |
| Some college/post High school education | 506 | 0.04 (-0.25, 0.34) | | 1.58 (0.25, 2.91) | |
| Work for pay (ref=No) | 343 | | 0.02 | | 0.002 |
| Yes | 830 | 0.34 (0.06, 0.63) | | 2.06 (0.75, 3.37) | |
| Annual household income (ref= Less than $25,000) | 340 | | 0.003 | | <.001 |
| $25,000-$49,000 | 336 | -0.52 (-0.91, -0.14) | | -1.16 (-2.91, 0.59) | |
| $50,000-$74,999 | 258 | -0.64 (-1.04, -0.23) | | -2.18 (-4.03, -0.34) | |
| Greater than $75,000 | 210 | -0.68 (-1.06, -0.30) | | -3.72 (-5.47, -1.97) | |
| **Comorbidities** | | | | | |
| Asthma (ref=No) | 909 | | 0.96 | | 0.80 |
| Yes | 316 | 0.01 (-0.28, 0.29) | | -0.17 (-1.49, 1.15) | |
| Sleep apnea (ref=No) | 608 | | 0.84 | | 0.24 |
| Yes | 626 | 0.03 (-0.24, 0.30) | | 0.76 (-0.49, 2.01) | |

**Table 23 (continued)**

| | N | Change in 10-year ASCVD risk *Beta*[a] (95%CI) | *P* value | Change in Lifetime ASCVD risk *Beta*[a] (95%CI) | *P* value |
|---|---|---|---|---|---|
| Abnormal kidney function (ref=Yes) | 1132 | | 0.005 | | 0.003 |
| No | 101 | -0.67 (-1.13, -0.20) | | -3.26 (-5.38, -1.13) | |
| Diabetes (ref=Yes) | 830 | | <.001 | | 0.005 |
| No | 404 | 0.57 (0.28, 0.87) | | -2.15 (-3.67, -0.64) | |
| Polycystic ovary syndrome (ref=No/not applicable)[b] | 887 | | 0.09 | | 0.94 |
| Yes | 126 | -0.31 (-0.67, 0.05) | | -0.07 (-1.87, 1.74) | |
| Menopause (ref=No) | 731 | | 0.24 | | 0.43 |
| Yes | 282 | 0.33 (-0.12, 0.77) | | -0.84 (-2.95, 1.27) | |
| **Physical function** | | | | | |
| Severe walking limitation (ref=No) | 1066 | | 0.17 | | 0.07 |
| Yes | 65 | 0.41 (-0.18, 1.01) | | 2.47 (-0.21, 5.15) | |
| SF-36 Physical Component Summary score, per 10 points lower (worse) | 1154 | -0.02 (-0.15, 0.10) | 0.70 | 0.17 (-0.41, 0.75) | 0.57 |
| Long Distance Corridor Walk | | | | | |
| Inability to complete (ref=No) | 320 | | 0.98 | | 0.008 |
| Yes | 851 | 0.004 (-0.31, 0.32) | | 1.96 (0.51, 3.42) | |
| Completion time, per 10 second lower | 850 | -0.02 (-0.04, 0.001) | 0.07 | -0.03 (-0.15, 0.08) | 0.58 |
| **Mental health** | | | | | |
| Beck Depression Inventory-1 score, per 10 points higher (worse) | 1163 | -0.01 (-0.19, 0.19) | 0.99 | 0.70 (-0.23, 1.62) | 0.14 |
| SF-36 Mental Component Summary score, per 10 points higher (better) | 1154 | 0.01 (-0.12, 0.13) | 0.91 | -0.79 (-1.36, -0.22) | 0.006 |
| Psychiatric counseling (ref=Yes) | 891 | | 0.07 | | 0.82 |
| No | 277 | -0.28 (-0.58, 0.02) | | -0.16 (-1.55, 1.23) | |
| Psychiatric medication (ref=No) | 743 | | 0.70 | | 0.60 |
| Yes | 430 | -0.05 (-0.32, 0.22) | | 0.33 (-0.89, 1.56) | |
| **Interpersonal Support** | | | | | |
| ISEL score, per 10 points lower (worse) | 1175 | -0.07 (-0.27, 0.14) | 0.52 | 0.31 (-0.62, 1.25) | 0.51 |
| **Substance use** | | | | | |
| Symptoms of alcohol problems (ref=No) | 1091 | | 0.50 | | 0.85 |
| Yes | 81 | -0.17 (-0.68, 0.33) | | -0.22 (-2.54, 2.10) | |

**Table 23 (continued)**

| | N | Change in 10-year ASCVD risk *Beta*[a] (95%CI) | *P* value | Change in Lifetime ASCVD risk *Beta*[a] (95%CI) | *P* value |
|---|---|---|---|---|---|
| Frequency of drinking alcohol, per 1 additional drink (Ref=Never) | 1647 | | 0.96 | | 0.93 |
| Monthly or less | 1633 | 0.02 (-0.28, 0.32) | | -0.01 (-1.55, 1.52) | |
| Two to four times a month | 580 | -0.13 (-0.54, 0.27) | | -0.02 (-2.10, 2.07) | |
| Two to three times a week | 193 | 0.05 (-0.58, 0.69) | | 0.57 (-2.72, 3.86) | |
| Four or more times a week | 108 | -0.08 (-0.95, 0.78) | | 1.89 (-2.55, 6.33) | |
| Marijuana use (ref=No) | 1129 | | 0.40 | | 0.53 |
| Yes | 43 | 0.29 (-0.39, 0.98) | | 1.01 (-2.12, 4.14) | |
| Illegal drug use (ref=No) | 1122 | | 0.47 | | 0.66 |
| Yes | 48 | 0.24 (-0.41, 0.89) | | 0.68 (-2.3, 3.66) | |
| **Eating behaviors to control weight** | | | | | |
| Decreased fat intake (ref=Yes) | 978 | | 0.97 | | 0.26 |
| No | 106 | 0.01 (-0.36, 0.37) | | -0.99 (-2.72, 0.73) | |
| Ate fewer high carbohydrate foods (ref= Yes) | 971 | | 0.78 | | 0.39 |
| No | 158 | -0.05 (-0.43, 0.32) | | -0.78 (-2.53, 0.98) | |
| Increased fruits and vegetables (ref= Yes) | 911 | | 0.86 | | 0.11 |
| No | 206 | 0.03 (-0.31, 0.36) | | -1.27 (-2.82, 0.28) | |

Abbreviations: SF-36, Short Form 36-Item Health Survey; ISEL, Interpersonal Support Evaluation List.

[a] All models adjusted for pre-surgery 10-year or Lifetime ASCVD risk, respectively, pre-surgery factors related to missing follow-up data (site, age and past-year smoking status) and time since surgery. A negative *Beta* indicates a decrease in CVD risk.

[b] Evaluated among women only in the basic model. Considered in the full multivariable model with the following categories: men, women no to polycystic ovary syndrome, woman yes to polycystic ovary syndrome.

**Table 24. Basic Models Testing Associations[a] Between Pre-Surgery Factors And Change From High To Low Lifetime ASCVD Risk 1-7 Years Since Roux-En-Y Gastric Bypass (N=1001).**

| | Improvement in Lifetime ASCVD risk category (high to low) | | |
|---|---|---|---|
| | **n** | **Basic models[a]** | ***P* value** |
| | | **RR (95%CI)** | |
| **Control variables** | | | |
| Age, years | 1001 | 1.001 (1.00, 1.01) | 0.01 |
| Smoked in the past year, n (%) | 1001 | 1.06 (0.95, 1.18) | 0.27 |
| ASCVD Lifetime risk score | 1001 | 1.001 (1.00, 1.01) | 0.051 |
| **Anthropometrics** | | | |
| Body mass index, per 5 points higher | 1001 | 1.002 (0.99, 1.01) | 0.72 |
| Body mass index at age 18, per 5 points higher | 637 | 0.99 (0.98, 1.02) | 0.98 |
| **Sociodemographics** | | | |
| Sex (ref=Male) | 809 | | 0.006 |
| Female | 192 | 1.09 (1.03, 1.15) | |
| Race (ref=White) | 854 | | 0.74 |
| Black | 111 | 1.01 (0.95, 1.08) | |
| Other | 36 | 1.03 (0.94, 1.13) | |
| Ethnicity (ref=Not Hispanic) | 967 | | 0.82 |
| Hispanic | 34 | 0.99 (0.88, 1.11) | |
| Marital status (ref=No) | 356 | | 0.98 |
| Yes | 602 | 0.99 (0.96, 1.04) | |
| Education (ref=College degree or higher) | 315 | | 0.91 |
| High school or less | 243 | 1.01 (0.96, 1.05) | |
| Some college/post High School education | 402 | 1.01 (0.97, 1.05) | |
| Work for pay (ref=No) | 298 | | 0.35 |
| Yes | 655 | 0.98 (0.94, 1.02) | |
| Annual household income (ref= Less than $25,000) | 276 | | 0.82 |
| $25,000-$49,000 | 185 | 0.99 (0.94, 1.04) | |
| $50,000-$74,999 | 270 | 0.99 (0.94, 1.05) | |
| Greater than $75,000 | 198 | 0.98 (0.93, 1.03) | |
| **Comorbidities** | | | |
| Asthma (ref=No) | 730 | | 0.75 |
| Yes | 262 | 1.01 (0.97, 1.05) | |
| Sleep apnea (ref=No) | 469 | | 0.76 |
| Yes | 532 | 0.99 (0.96, 1.03) | |
| Abnormal kidney function (ref=Yes) | 903 | | 0.27 |
| No | 97 | 1.03 (0.98, 1.09) | |
| Diabetes (ref=Yes) | 597 | | 0.04 |
| No | 404 | 1.05 (1.00, 1.09) | |
| Polycystic ovary syndrome (ref=No/not applicable) | 707 | | 0.73 |
| Yes | 102 | -0.01 (-0.09, 0.06) | |
| Menopause (ref=No) | 541 | | 0.68 |
| Yes | 268 | 1.01 (0.95, 1.08) | |

**Table 24 (continued)**

| | n | Basic models[a] | *P* value |
|---|---|---|---|
| **Physical function** | | | |
| Severe walking limitation (ref=No) | 858 | | 0.57 |
| Yes | 61 | 1.02 (0.95, 1.10) | |
| SF-36 Physical Component Summary score, per 10 points lower (worse) | 937 | 1.00 (0.99-1.02) | 0.67 |
| Long Distance Corridor Walk | | | |
| Inability to complete (ref=No) | 659 | | 0.32 |
| Yes | 287 | 1.02 (0.98, 1.07) | |
| Long Distance Corridor Walk completion time, per 10 second lower | 658 | 0.99 (0.99, 1.002) | 0.49 |
| **Mental health** | | | |
| Beck Depression Inventory-1 score, per 10 points higher (worse) | 937 | 1.01 (0.98, 1.04) | 0.44 |
| SF-36 Mental Component Summary score, per 10 points high (better) | 937 | 1.00 (0.99, 1.01) | 0.55 |
| Psychiatric counseling (ref=Yes) | 727 | | 0.76 |
| No | 222 | 0.99 (0.95, 1.04) | |
| Psychiatric medication (ref=No) | 587 | | 0.45 |
| Yes | 366 | 1.01 (0.98, 1.05) | |
| **Interpersonal Support** | | | |
| Interpersonal Support Evaluation List | | | |
| Overall score, per 10 points lower (worse) | 955 | 1.00 (0.97, 1.03) | 0.97 |
| **Substance use** | | | |
| Symptoms of alcohol problems (ref=No) | 894 | | 0.66 |
| Yes | 57 | 1.02 (0.94, 1.09) | |
| Frequency of drinking alcohol, per 1 additional drink (Ref=Never) | 1647 | | 0.96 |
| Monthly or less | 1633 | 0.99 (0.96, 1.04) | |
| Two to four times a month | 580 | 0.98 (0.92, 1.04) | |
| Two to three times a week | 193 | 1.01 (0.92, 1.09) | |
| Four or more times a week | 108 | 0.99 (0.89, 1.11) | |
| Marijuana use (ref=No) | 920 | | 0.93 |
| Yes | 32 | 0.99 (0.90, 1.10) | |
| Illegal drug use (ref=No) | 915 | | 0.99 |
| Yes | 36 | 0.99 (0.91, 1.10) | |
| **Eating behaviors to control weight** | | | |
| Decreased fat intake (ref=No) | 792 | | 0.57 |
| Yes | 129 | 1.02 (0.96, 1.07) | |
| Ate fewer high carbohydrate foods (ref=No) | 778 | | 0.59 |
| Yes | 137 | 1.01 (0.96, 1.07) | |
| Increased fruits and vegetables (ref=No) | 729 | | 0.37 |
| Yes | 176 | 1.02 (0.98, 1.07) | |

Abbreviations: SF-36, Short Form 36-Item Health Survey; ISEL, Interpersonal Support Evaluation List.
[a] All models adjusted for pre-surgery factors related to missing follow-up data (site, age and past-year smoking status) and time since surgery. A relative risk (RR) above 1.0 indicates improvement in CVD risk (from high to low risk category).

**Table 25. Basic Models Testing Associations Between Pre-Surgery Factors And CVD Events 1-7 Years Since Roux-En-Y Gastric Bypass (N=1625).**

| | n | CVD event<br>Basic models[a]<br>RR (95%CI) | *P* value |
|---|---|---|---|
| **Control variables** | | | |
| Age, years | 1625 | 1.02 (0.98, 1.06) | 0.36 |
| Smoked in the past year, n (%) | 1625 | 2.18 (0.27, 17.46) | 0.46 |
| ASCVD 10-year risk score | 1625 | 1.04 (0.98, 1.11) | 0.21 |
| **Anthropometrics** | | | |
| Body mass index, per 5 points higher | 1625 | 1.08 (0.88, 1.34) | 0.46 |
| Body mass index at age 18, per 5 points higher | 1011 | 0.93 (0.66, 1.29) | 0.64 |
| **Sociodemographics** | | | |
| Sex (ref=Male) | 1331 | | 0.78 |
| Female | 294 | 0.88 (0.37, 2.12) | |
| Race (ref=White) | 1372 | | 0.44 |
| Black | 180 | 1.76 (0.61, 5.02) | |
| Other | 55 | 1.94 (0.39, 9.57) | |
| Ethnicity (ref=Not Hispanic) | 1545 | | 0.62 |
| Hispanic | 79 | 0.63 (0.10, 3.95) | |
| Marital status (ref=No) | 572 | | 0.82 |
| Yes | 928 | 1.09 (0.51, 2.34) | |
| Education (ref=College degree or higher) | 502 | | 0.65 |
| High school or less | 348 | 1.34 (0.48, 3.73) | |
| Some college/post high school education | 651 | 1.52 (0.63, 3.66) | |
| Work for pay (ref=No) | 438 | | 0.26 |
| Yes | 1055 | 0.64 (0.29, 1.40) | |
| Annual household income (ref= Less than $25,000) | 283 | | 0.26 |
| $25,000-$49,000 | 415 | 0.51 (0.19, 1.36) | |
| $50,000-$74,999 | 343 | 0.45 (0.16, 1.28) | |
| Greater than $75,000 | 417 | 0.39 (0.14, 1.09) | |
| **Comorbidities** | | | |
| Asthma (ref=No) | 1190 | | 0.29 |
| Yes | 398 | 1.51 (0.70, 3.22) | |
| Sleep apnea (ref=No) | 810 | | 0.23 |
| Yes | 814 | 1.57 (0.75, 3.31) | |
| Abnormal kidney function (ref=Yes) | 1439 | | 0.38 |
| No | 121 | 1.90 (0.45, 8.05) | |
| Diabetes (ref=Yes) | 1069 | | 0.25 |
| No | 525 | 0.65 (0.32, 1.34) | |
| **Women's Health** | | | |
| Polycystic ovary syndrome (ref=No/not applicable) | 887 | | 0.34 |
| Yes | 126 | 0.01 (-0.01, 0.02) | |
| Menopause (ref=No) | 731 | | 0.68 |
| Yes | 282 | 1.01 (0.95-1.08) | |
| **Physical function** | | | |
| Severe walking limitation (ref=No) | 1374 | | 0.24 |
| Yes | 96 | 2.49 (0.47, 8.34) | |
| SF-36 Physical Component Summary score, per 10 points lower (worse) | 1472 | 1.68 (1.22, 2.31) | 0.002 |

**Table 25 (continued)**

| | n | RR (95%CI) | *P* value |
|---|---|---|---|
| Long Distance Corridor Walk | | | |
| Inability to complete (ref=No) | 1082 | | 0.17 |
| Yes | 438 | 1.73 (0.79, 3.76) | |
| Long Distance Corridor Walk completion time, per 10 seconds lower | 1081 | 1.00 (0.94, 1.07) | 0.94 |
| **Mental health** | | | |
| Beck Depression Inventory-1 score, per 10 points higher (worse) | 1518 | 1.22 (0.69, 2.18) | 0.50 |
| SF-36 Mental Component Summary score, per 10 points higher (better) | 1472 | 0.86 (0.61, 1.21) | 0.37 |
| Psychiatric counseling (ref=Yes) | 1138 | | 0.15 |
| No | 350 | 0.55 (0.24, 1.24) | |
| Psychiatric medication (ref=No) | 942 | | 0.47 |
| Yes | 552 | 1.33 (0.62, 2.84) | |
| **Interpersonal Support** | | | |
| ISEL score, per 10 points lower (worse) | 1493 | 1.14 (0.69, 1.89) | 0.61 |
| **Substance use** | | | |
| Symptoms of alcohol problems (ref=No) | 1392 | | 0.59 |
| Yes | 100 | 0.57 (0.08, 4.34) | |
| Frequency of drinking alcohol, per 1 additional drink (Ref=Never) | 1497 | | 0.85 |
| Monthly or less | | 0.68 (0.29, 1.60) | |
| Two to four times a month | | 0.67 (0.19, 2.34) | |
| Two to three times a week | | 0.89 (0.13, 6.21) | |
| Four or more times a week | | 0.10 (0.01, 57.29) | |
| Marijuana use (ref=No) | 1430 | | 0.74 |
| Yes | 61 | 1.38 (0.20, 9.32) | |
| Illegal drug use (ref=No) | 1422 | | 0.82 |
| Yes | 67 | 1.25 (0.19, 8.26) | |
| **Eating behaviors to control weight** | | | |
| Decreased fat intake (ref=No) | 1258 | | 0.62 |
| Yes | 192 | 1.31 (0.45, 3.82) | |
| Ate fewer high carbohydrate foods (ref=No) | 1251 | | 0.24 |
| Yes | 191 | 1.83 (0.67, 4.97) | |
| Increased fruits and vegetables (ref=No) | 1177 | | 0.91 |
| Yes | 248 | 1.06 (0.39, 2.91) | |

Abbreviations: ASCVD, Atherosclerotic cardiovascular disease; SF-26, Short Form 36-Item Health Survey; ISEL, Interpersonal Support Evaluation List.

[a] Additionally adjusted for pre-surgery factors related to missing follow-up data (site, age and past-year smoking) and time since surgery.

# 4.0 Manuscript 3: Change In C-Reactive Protein Following Roux-En-Y Gastric Bypass Through 7 Years Of Follow-Up

## 4.1 Brief Overview

**Background:** C-reactive protein (CRP) is a biomarker of inflammation and cardiovascular disease risk. Long-term change in CRP is not well characterized in the context of Roux-en-Y gastric bypass (RYGB).

**Methods:** Between 2006-2009, 1770 adults enrolled in a US multi-center prospective cohort study (Longitudinal Assessment of Bariatric Surgery) underwent RYGB. Research assessments were conducted pre-surgery and annually post-surgery up to 7 years. This study included those who had CRP assessed pre-surgery and at one or more follow up assessments (n=1180).

**Results**: Pre-surgery, participants' median age was 46 years and median body mass index (BMI) was 46 kg/m$^2$; 80% were female. At pre-surgery, mean (95% CI) CRP (mg/L) was the highest of all time points (1.01 [0.95-1.08]); it then decreased to a nadir of 0.18 (0.15-0.22) at 2 years post-surgery ($P$<0.001 versus pre-surgery). CRP was higher (worsened) at 7 years (0.26 [0.22, 0.29) compared to 2 years post-surgery, but remained lower at 7 years compared to pre-surgery. Additionally, only 3.2% (95% CI, 1.6-4.8) of participants had elevated CRP 7 years post-surgery versus 32.9% (95% CI, 30.2-35.3) pre-surgery ($P$<0.001). Several pre-surgery factors were associated with following a less favorable CRP (mg/L) trajectory over time including higher pre-surgery CRP, higher BMI, smoking and diabetes.

**Conclusions:** The vast majority of adults who underwent RYGB experienced a sustained improvement in CRP throughout 7 years of follow-up, with non-elevated values. However, those with higher pre-surgery CRP and BMI, diabetes, and who smoke may benefit from additional testing and closer monitoring to assure non-elevated inflammation after surgery.

## 4.2 Introduction

Overweight and obesity, which affect two-thirds of US adults, is associated with chronic inflammation[29]. The mechanism is thought to be through the expansion and change in adipose tissue that accompanies weight gain, which causes an upregulation of proinflammatory cytokines (i.e. interleukins-1 and -6)[241]. This over expression of proinflammatory cytokines results in an increase in the secretion of inflammation markers such as C-reactive protein (CRP). While short-term inflammation (e.g., elevated CRP, defined as >1 mg/dL)[242] usually lacks outward or clinical signs, chronic low-grade inflammation, as is typical with obesity, is indicative of sustained activation of the innate immune system and has been linked to negative health outcomes, including increased risk of cardiovascular disease (CVD)[243-248]. Thus, CRP is often regarded as a biomarker for CVD risk [6,245,247]. The American Heart Association recommends CRP be used in the clinical setting in conjunction with other CVD indicators for CVD risk and treatment[248,249]. To indicate the different levels of CVD risk, CRP is categorized into low (i.e., non-elevated), moderate (1.0 mg/L-3.0 mg/L) and high (>3.0 mg/L)[250].

Bariatric surgery is an effective treatment for severe obesity[6] and has been shown to reduce chronic inflammation (as measured by CRP levels) as soon as 3 months and for up to 3 years after surgery[159,251]. However, there is a lack of data to inform our understanding of the magnitude,

heterogeneity and durability of change in inflammation, and its long-term effects after surgery. Additionally, prior studies of bariatric surgery have not evaluated CRP by CVD risk categories. Thus, the aim of this study was to evaluate CRP changes during longer-term follow-up after surgery in a large geographically diverse sample. This study was limited to adults undergoing Roux-en-Y gastric bypass (RYGB) surgery, reflecting the timeframe of study enrollment (2006-2009).

## 4.3 Methods

### *Design and Participants*

The Longitudinal Assessment of Bariatric Surgery (LABS)-2 was a prospective cohort study of 2,458 adults who were at least age 18. Participants were recruited between February 2005 and February 2009 and underwent their first bariatric surgery as part of clinical care between April 2006 and April 2009 at one of ten hospitals at six clinical centers throughout the United States. Written informed consent was obtained from participants and at every center the institutional review boards approved the protocol.

Selection of surgical procedure was based on patient and surgeon preference and independent of the research study. Reflecting the timeframe of study enrollment, most participants (N=1770) underwent RYGB. Standardized research assessments were conducted independent of clinical care by trained research staff within 30 days prior to scheduled surgery, at 6 months following surgery then annually for up to 7 years through the study end date (January 31, 2015). Research assessments were conducted in person except for a brief telephone or mail assessment at 6-months and 6-years, which did not include CRP measurement. To reduce site difference in data

collection, sites used LABS-provided equipment to collect data when possible. Research assessments were conducted in person except for a brief telephone or mail assessment at 6-months and 6-years[36]. This report includes participants who underwent RYGB and had CRP assessed pre-surgery and at one or more follow up assessments (N=1180 of 1770).

***Measures***

**CRP**[246]. Values were determined from samples collected by each site following a required 8 hour fast and assayed at a central laboratory. Clinical cut points of CRP were used to categorize CRP as elevated (≥1.0 mg/L), as well as low risk of CVD (less than 1.0 mg/L), moderate risk of CVD (1.0 mg/L to 3.0 mg/L) and high risk of CVD (more than 3.0 mg/L)[252]. Additionally, CRP values above 10.0 mg/L, indicative of autoimmune disease flare-ups, cancer, pneumonia or other significant infection16, were identified.

**Anthropometric measurements:** Measurement of weight and height followed standardized protocols by trained personnel[253]. Body mass index (BMI), was calculated as weight in kilograms divided by height in meters squared.

**Sociodemographics:** Sex, age, race, ethnicity, marital status, education, employment (work for pay, and work night or evening shifts), and annual income were self-reported on study-specific questionnaires[254].

**CVD risk score:** The ASCVD 10-year risk score was calculated using published algorithms[100]. The score utilizes age, sex, race, total cholesterol, systolic blood pressure, blood pressure treatment, smoking status, and diabetes and hyperlipidemia treatment. The risk score predicts coronary heart disease (CHD) death, nonfatal myocardial infarction (MI) and stroke in the next 10 years. Pre-surgery age was used to calculate risk scores at all assessments to eliminate the effect of aging on change in risk[255].

***Statistical analysis***

Descriptive statistics were used to summarize participant characteristics. Frequencies and percentages are reported for categorical data. Medians, 25th and 75th percentiles are reported for continuous data. The Pearson chi square test and the Fisher's Exact test for categorical variables, the Cochran-Armitage test for ordinal variables, and the Wilcoxon rank sum test for continuous variables were used to assess differences in distributions of pre-surgery characteristics of LABS-2 participants in the analysis sample to those who were excluded due to missing data (i.e., underwent RYGB and missing CRP at pre-surgery or all follow-up assessments). The observed CRP and CRP CVD risk categories (<1.0 mg/L, 1.0-3.0 mg/L, and >3.0 mg/L) were reported by time point in relation to surgery through 7 years of follow-up.

Mixed models used all available data via maximum likelihood, with a person-level random intercept, and controlled for pre-surgery factors related to missing data (i.e., site, age and smoking status), with time since surgery entered as a discrete fixed effect. A linear mixed model (LMM) with gamma distribution was used to estimate mean CRP (mg/L), as a repeated measure at pre-surgery and in years 1-5 and 7, with 95% confidence intervals (CI). Likewise, a mixed-effects binomial regression model and ordinal logistic regression model was used to estimate the percentages of the two-level and three-level CRP CVD risk categories, respectively, with 95% CI. Pairwise comparisons were made between pre-surgery and year 2, which was identified as the year with the nadir mean CRP value (to assess short-term change), pre-surgery and 7 years (to assess long-term change), and 2 and 7 years (to assess the durability of the short-term change). P values were adjusted by simulation for multiple comparisons[256].

Growth mixture models with time since surgery were used to estimate CRP (mg/L) trajectories over time and to group participants with similar modeled trajectories. The time scale

was anchored to pre-surgery with a maximum time post-surgery of 7.5 years. The model with the lowest Bayesian information criterion (BIC) was considered the best fitting model[257]. The modeled group trajectories of CRP were plotted. Descriptive statistics were used to summarize pre-surgery participant characteristics by trajectory group. Associations between participant pre-surgery characteristics and trajectory group membership were evaluated with the Chi-square or Fisher's Exact test for categorical variables, the Cochran-Armitage test for ordinal variables, and the Wilcoxon rank sum test for continuous variables.

A LMM was used to estimate and test significance of the association between change in CRP (mg/L) (repeated measure, years 1-5 and 7) and change in ASCVD 10-year risk score from pre-surgery across follow-up (repeated measure, 1-5 and 7 years). Additionally, a LMM was used to estimate and test the significance of associations between categorical change in CRP (mg/L) (no change, or a reduction) and ASCVD 10-year risk score.

All reported P values are two-sided; P values less than 0.05 were considered to be statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## 4.4 Results

There were few measured differences between the CRP sample and LABS-2 participants who underwent RYGB but were excluded from this report due to lack of CRP (**Table 26**). However, the CRP sample (N=1180) was older (median 46 versus 44 years; p=0.008), more White (87.3% versus 81.4%) and less Black (9.1% versus 15.5%; *P* <.001) compared to the excluded group (N=590).

**Figure 9A** shows the box plots of the observed median, interquartile range (IQR) and min and max (outlier values suppressed) of CRP (mg/L) at pre-surgery through 7 years of follow-up after RYGB. Two participants (0.2%) had pre-surgery CRP values above 10 (12.9 and 10.3) mg/L. No participants had CRP values above 10 post-surgery. At pre-surgery, CRP was the highest with the most variability of all time points (median: 0.73 mg/L [IQR: 0.40, 1.37]). **Figure 9B** shows the observed sample distribution of low, moderate and high CRP categorization across 7 years of follow-up. Again, this figure shows the higher amount in variability at pre-surgery compared to post-surgery. At pre-surgery 67% of participants had low, 30% had moderate and 3% had high CRP. At 2 years post-surgery, 98% of participants had low CRP, 2% had moderate, and less than 1% had high CRP. By 7 years, 97% of participants still had low CRP.

Modeled means with 95% CI of CRP (mg/L) are shown in **Figure 10A** and reported in supplemental material (**Table 27**); all three time point comparisons were significantly different (2 years and 7 years post-surgery versus pre-surgery; 2 years post-surgery versus 7 years post-surgery; $P<.001$ for all). At pre-surgery, CRP was the highest (mean: 1.01 [95% CI: 0.95, 1.08 mg/L]). After surgery CRP decreased to its nadir value at 2 years (mean: 0.18 [95% CI: 0.15, 0.22 mg/L]) and then increased at 7 years compared to 2 years post-surgery, but remained lower at 7 years compared to pre-surgery (mean: 0.26 [95% CI: 0.22, 0.29 mg/L]) (**Figure 10A; Table 27**). Modeled CRP category distributions are also reported in supplemental material (**Table 27**). Only 3.2% (95% CI, 1.6-4.8) of participants had elevated CRP 7 years post-surgery versus 32.9% (95% CI, 30.2-35.3) pre-surgery ($P<0.001$).

***CRP trajectories***

To further explore change in CRP over longer-term follow-up, 7-year trajectories of CRP were examined. Only two groups were identified, with the vast majority (93.5%) in a single group (group 1; **Figure 10B**). Thus, the group 1 trajectory looked similar to the overall sample mean. That is, group 1 was characterized by a large improvement (decrease) in CRP from a mean of 0.9 mg/L pre-surgery to 0.1 mg/L 2-years post-surgery, with stable CRP values from 2-7 years. Group 2 also had a large improvement (decrease) in CRP from a mean of 1.7 mg/L pre-surgery to 0.8 mg/L 2-years post-surgery. However, group 2 did not have the same stability following year 2, rather CRP worsened (increased), ending with a mean value of 1.3 mg/L at year 7. (**Figure 10B**).

Pre-surgery characteristics by trajectory group are reported in supplemental material (**Table 28**). In addition to differing in pre-surgery CRP values with group 2 having higher CRP (1.4 versus 0.7 mg/L), BMI was higher (median 48.7 $kg/m^2$ versus 46.2 $kg/m^2$), more participants smoked (7.8% versus 1.8%) and more participants had diabetes (44.7% versus 33.3%) in group 2 versus group 1

***Association between change in CRP and change in ASCVD 10-year risk score***

There was not a statistically significant association between change in CRP (mg/L) and change in ASCVD 10-year risk score (Beta: 0.05 (95% CI: -0.09, 0.18); P=0.48). However, there was a statistically significant association between change in categorical CRP (comparing improvement to no change) and change in ASCVD 10-year risk score where negative values indicated an improvement in CVD risk (Beta: -1.13 (95% CI: -1.17, -1.08); P<0.001) (**Table 29**).

## 4.5 Discussion

This large cohort of adults with severe obesity who underwent RYGB experienced sustained improvement in CRP from pre-surgery through 7 years of follow-up. This improvement was evident when assessed on a continuous scale or categorized by CVD risk thresholds (low, moderate, high). At the pre-surgery assessment, one-third of participants had elevated CRP levels (≥1 mg/L), whereas at 7 years post-surgery only 3% did, indicating a large, uniform, sustained and rather substantial shift from elevated CRP to low levels of CRP. Although generally CRP improvement persisted throughout 7 years of follow-up, we were able to identify a small group of participants who had a less favorable CRP trajectory. This group experienced a worsening in CRP after 2 years post-surgery which continued through 7 years post-surgery.

There are some short-term studies on CRP in the bariatric surgery literature which also reported improvement in CRP[159,258]. For example, in a study of 43 participants undergoing RYGB or sleeve gastrectomy, CRP declined significantly ($P$<.001) from presurgery (median 0.39 [IQR: 0.24, 0.69] to 6 months [median: 0.09 (0.05, 0.23]) after surgery. Additionally, a previous LABS-2 study reported an improvement in CRP in both RYGB and laparoscopic adjustable gastric Banding (LAGB) participants from pre-surgery to 3 years post-surgery[159]. While both of these studies reported on CRP over time, the lack of longer-term follow-up limited the ability to evaluate if the improvement in CRP was sustained. This is especially important since there are examples from the bariatric literature of worsening in outcomes in the longer-term follow-up. For example, other studies of the LABS-2 RYGB cohort have, reported an increase in diabetes and hypertension prevalence between 3 to 7 years post-surgery[178], as well as an increase in non-fatal CVD event rates in women (80% of this sample) between 5 and 7 years post-surgery[170]. Additionally, they did

not evaluate CRP as a categorical measure, which is how it is commonly used as a biomarker in the clinical setting to assess CVD risk.

While the overall trend of CRP was sustained improvement after surgery, we were able to identify a small group of participants who did not have as favorable of a CRP trajectory. There were multiple pre-surgery factors which were different between these two groups. The group with the less favorable CRP trajectory had higher CRP (mg/L), higher BMI kg/m$^2$, was more likely to smoke and have diabetes pre-surgery. These pre-surgery factors may be useful in identifying patients who could be at risk of poor CVD health outcomes due to inflammation's association with poor CVD outcomes. Thus, patients with these pre-surgery factors may need additional inflammation (i.e. CRP) monitoring. Additionally, while we did not identify a statistically significant association between change in CRP, evaluated on a continuous scale, and change in ASCVD 10-year risk score, we did find an association between change in CRP status and ASCVD 10-year risk score. Specifically, we identified that those who changed from elevated to low CRP were more likely to also improve their ASCVD 10-year risk score.

Although CRP has been an independent predictor of adverse cardiovascular events (i.e, myocardial infarction, ischemic stroke, and sudden cardiac death) in multiple large prospective studies of the general population[259], our study only detected a weak association between change in CRP status and change in the ASCVD 10-year risk score, and no association with change in CRP when evaluated on a continuous scale. Thus, our findings support the use of CRP in the clinical setting in conjunction with other indicators of CVD risk. In particular, CRP may be appropriate for inclusion in a new CVD risk score, along with other established CVD risk factors (age, sex, race, total cholesterol, systolic blood pressure, blood pressure treatment, smoking status, and diabetes and hyperlipidemia treatment).

Major strengths of this study were the longer-term follow-up, which allowed for continued and accurate measurements of CRP levels from pre-surgery through 7 years post-surgery in adults undergoing RYGB, and the large geographically diverse cohort. Several limitations should be considered when interpreting the data, including the exclusive use of the RYGB surgical group. While RYGB was the most common modern-day bariatric surgical procedure prior to 2013, it is currently the second most common procedure[51,58]. The lack of representation of the gastric sleeve procedure limits this study in terms of applicability to the current bariatric surgical population[260]. Additionally, other markers of inflammation, such as cystatin C, a cysteine protease inhibitor, were not included in the LABS-2 study across follow-up. As with other LABS-2 reports of outcomes requiring a fasting blood draw, a sizeable portion the RYGB cohort was excluded from the analysis due to missing data. For the most part, excluded versus included LABS-2 participants who underwent RYGB were similar. However, those who were excluded for missing data were slightly younger and a higher percentage were Black. Race distribution did not differ by CRP trajectory group membership, but age at time of surgery did. All analysis controlled for age.

## 4.6 Conclusions

Although one-third of pre-surgery RYGB patients had elevated CRP pre-surgery, the vast majority (97%), had values in the normal range post-surgery throughout 7 years of follow-up. We were able to identify a subgroup of participants with less favorable CRP trajectory. In this group the participants who had higher pre-surgery levels of CRP, high pre-surgery BMI, currently smoke and have diabetes may be more susceptible to post-surgery worsening in inflammation after nadir CRP. Thus, if CRP begins to increase from nadir values post-surgery, the results of this study

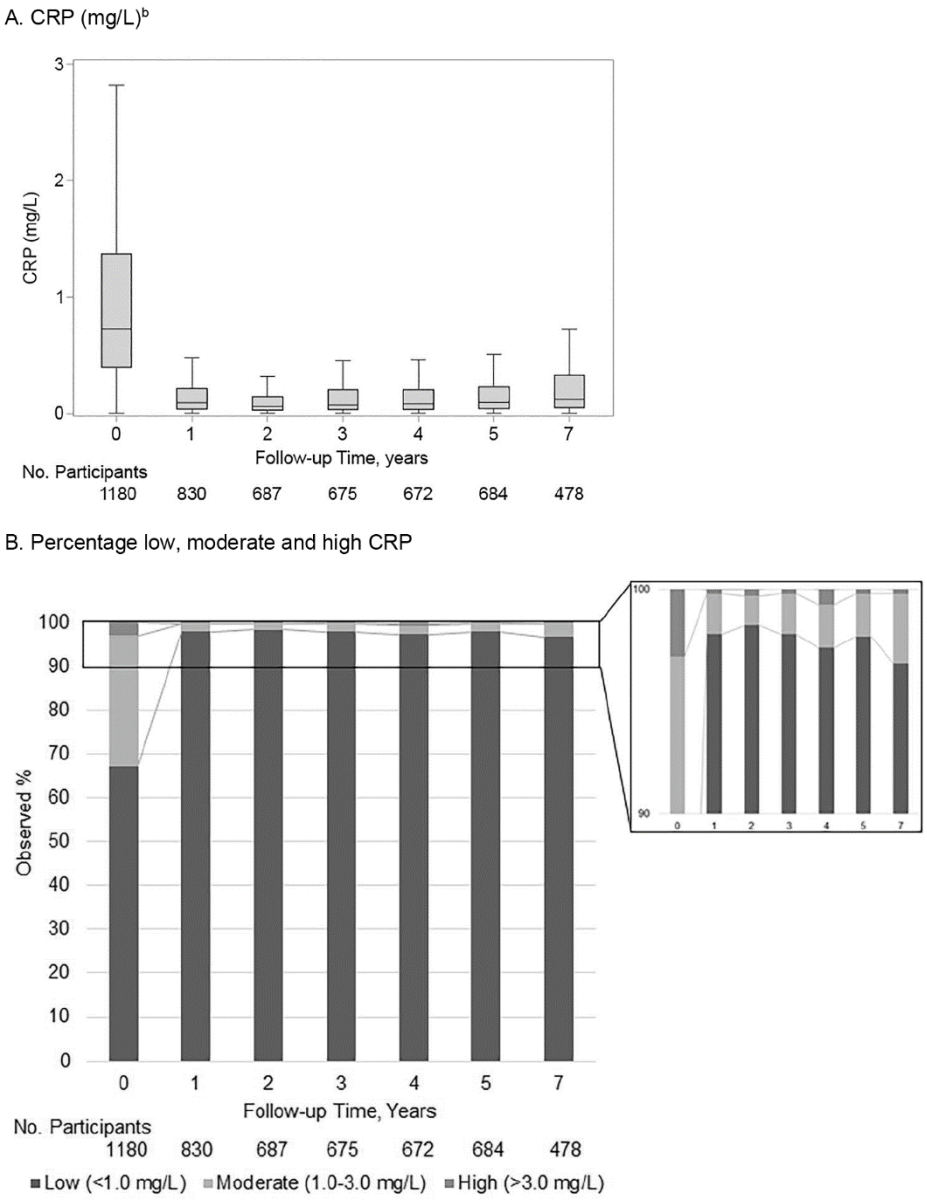
suggests that additional testing and closer monitoring of the patient may be warranted to ensure the most beneficial outcomes of inflammation and associated CVD outcomes post-surgery.

## 4.7 Tables and Figures

**Table 26. Characteristics Of Adults Prior To Undergoing Roux-En-Y Gastric Bypass Included Versus Excluded From The C-Reactive Protein (CRP) Sample.**

| | CRP sample[a] (N=1180[b]) No. (%)[c] | Excluded (N=590[b]) No. (%)[c] | *P* |
|---|---|---|---|
| Age, years | | | 0.008 |
| Median (25th:75th %-ile) | 46 (37: 54) | 44 (36: 52) | |
| Range | 19: 75 | 19: 70 | |
| Sex | | | 0.71 |
| Male | 241 (20.4) | 116 (19.7) | |
| Female | 939 (79.6) | 474 (80.3) | |
| Race | n=1169 | n=582 | <0.001 |
| White | 1020 (87.3) | 474 (81.4) | |
| Black | 106 (9.1) | 90 (15.5) | |
| Other | 43 (3.7) | 18 (3.1) | |
| Ethnicity | | n=589 | 0.48 |
| Hispanic | 55 (4.7) | 32 (5.4) | |
| Non-Hispanic | 1125 (95.3) | 557 (94.6) | |
| Married or living as married[d] | 684/1108 (61.7) | 335/525 (63.8) | 0.42 |
| Education | n=1109 | n=526 | 0.68 |
| High school or less | 257 (23.2) | 128 (24.3) | |
| Some college | 489 (44.1) | 211 (40.1) | |
| College degree | 363 (32.7) | 187 (35.6) | |
| Household income, US $ | n=1083 | n=506 | 0.42 |
| Less than 25,000 | 213 (19.7) | 103 (20.4) | |
| 25,000-49,999 | 305 (28.2) | 142 (28.1) | |
| 50,000-74,999 | 250 (23.1) | 128 (25.3) | |
| 75,000-99,999 | 166 (15.3) | 71 (14.0) | |
| >100,000 | 149 (13.8) | 62 (12.3) | |
| Employed for pay[d] | 762/1103 (69.1) | 363/523 (69.4) | 0.90 |
| Smoke currently[d] | 26/1180 (2.2) | 17/590 (2.9) | 0.38 |
| Smoke currently or within 1 year of surgery[d] | 159/1176 (13.5) | 95/590 (16.1) | 0.14 |
| Body mass index, kg/m$^2$ | | | 0.44 |
| Median (25th: 75th %-ile) | 46.4 (42.4: 51.9) | 47.0 (42.4: 52.0) | |
| Range | 33.7: 81.0 | 33.9: 77.2 | |
| Hyperlipidemia[c] | 431/1160 (37.2) | 194/378 (51.3) | 0.70 |
| Type 2 diabetes[c] | 398/1168 (34.1) | 217/569 (38.1) | 0.10 |
| Hypertension[d] | 812/1164 (69.8) | 395/576 (68.6) | 0.61 |
| C-reactive protein (mg/L) | n=1180 | n=272 | 0.14 |
| Median (25th: 75th %-ile) | 0.7 (0.4: 1.4) | 0.8 (0.4: 1.5) | |
| Range | 0.0: 12.9 | 0.0: 9.2 | |

[a] Participants have CRP measurement at pre-surgery and at least one follow-up assessment.
[b] Denominator shifts between variables due to missing data.
[c] Data are reported as No. (%) unless otherwise indicated.
[d] No./total (%).




[a] Time point 0 is the pre-surgery assessment.
[b] Maximum extreme values (defined as Q3 + 1.5*(Q3-Q1)) were suppressed.

**Figure 9. C-Reactive Protein (CRP) Over Time Sincea Roux-En-Y Gastric Bypass (N=1180).**

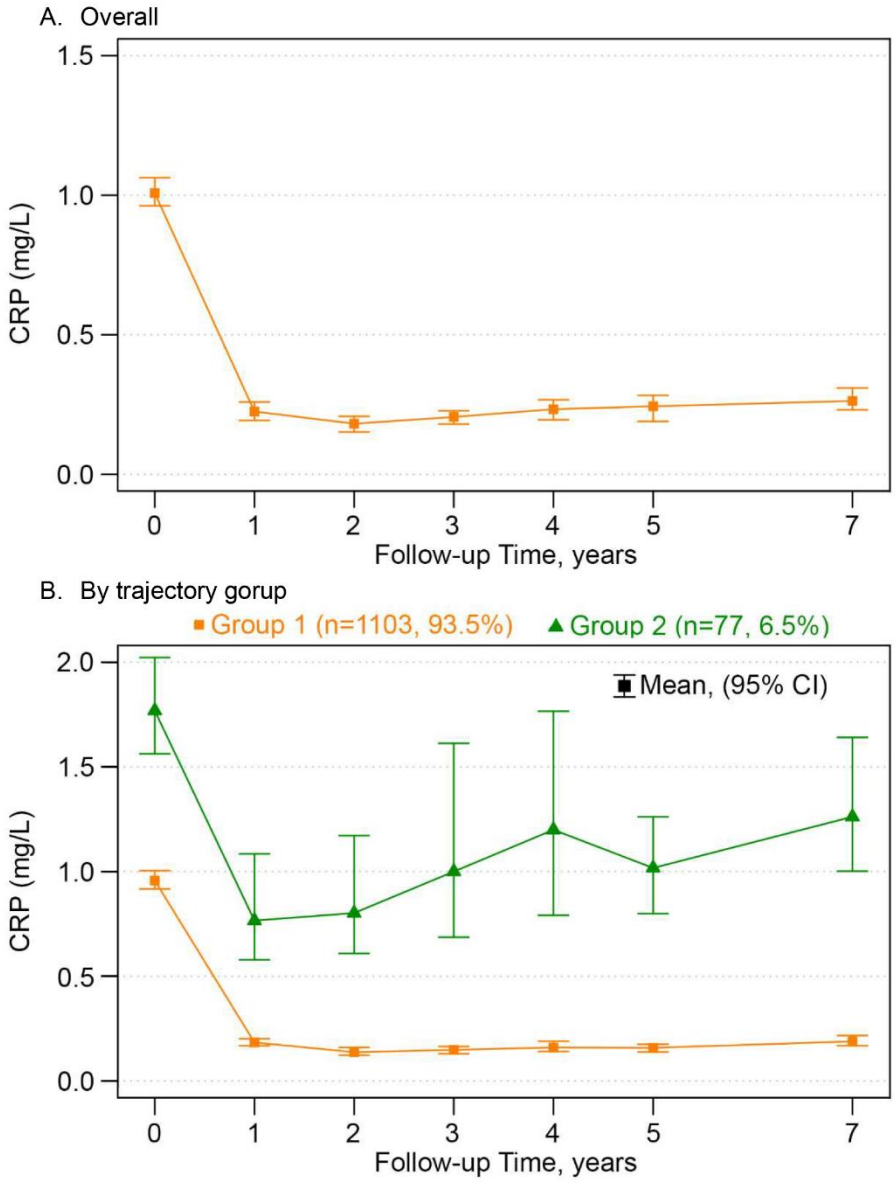



**Figure 10. Modeled C-Reactive Protein (CRP Mg/L) By Time In Relation To Roux-En-Y Gastric Bypass[ab].**

[a] Time point 0 is pre-surgery assessment.
[b] Lines indicate modeled mean CRP with adjustment for factors measured at the pre-surgery assessment related to missing follow-up data (i.e., site, age and smoking status).

## 4.8 Supplemental Content

### 4.8.1 Tables And Figures

**Table 27. C-Reactive Protein (CRP) By Time In Relation To Roux-En-Y Gastric Bypass.**

| | Pre-surgery | Post-surgery | | | | | |
|---|---|---|---|---|---|---|---|
| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 |
| **C-reactive protein** | n=1180 | n=830 | n=687 | n=675 | n=672 | n=684 | n=478 |
| *Observed* | | | | | | | |
| CRP (mg/L) | | | | | | | |
| Median | 0.73 | 0.09 | 0.06 | 0.07 | 0.08 | 0.10 | 0.13 |
| ($25^{th}$, 75th%-ile) | (0.40, 1.37) | (0.04, 0.22) | (0.03, 0.15) | (0.04, 0.21) | (0.04, 0.21) | (0.04, 0.23) | (0.05, 0.33) |
| CRP CVD risk categories, mg/L, n (%) | | | | | | | |
| Low, <1.0 | 793 (67.2) | 816 (98.0) | 680 (98.4) | 672 (98.0) | 663 (97.4) | 682 (97.9) | 475 (96.7) |
| Moderate, 1.0-3.0 | 351 (29.8) | 15 (1.8) | 9 (1.3) | 12 (1.8) | 13 (1.9) | 13 (1.9) | 15 (3.1) |
| High, >3.0 | 36 (3.1) | 2 (0.2) | 2 (0.3) | 2 (0.3) | 5 (0.7) | 2 (0.3) | 1 (0.2) |
| *Modeled* [a] | | | | | | | |
| CRP (mg/L) | | | | | | | |
| Mean [b] | 1.01 | 0.22 | 0.18 | 0.21 | 0.23 | 0.24 | 0.26 |
| (95% CI) | (0.95, 1.08) | (0.21, 0.25) | (0.15, 0.22) | (0.17, 0.24) | (0.19, 0.29) | (0.18, 0.28) | (0.22, 0.29) |
| CRP CVD risk categories, mg/L [b] (%, 95% CI) | | | | | | | |
| Low, <1.0 | 69.1 | 98.6 | 98.8 | 98.5 | 98.0 | 98.6 | 97.9 |
| | (66.2, 73.3) | (93.3, 99.6) | (92.8, 99.6) | (94.0, 99.4) | (93.7, 99.2) | (93.2, 99.3) | (89.4, 99.1) |
| Moderate, 1.0-3.0 | 27.7 | 1.2 | 0.9 | 1.2 | 1.2 | 1.1 | 1.9 |
| | (24.0, 30.8) | (0.3, 6.3) | (0.2, 6.9) | (0.3, 5.9) | (0.5, 5.5) | (0.4, 6.4) | (0.6, 9.5) |
| High, >3.0 | 3.1 | 0.2 | 0.3 | 0.3 | 0.7 | 0.3 | 0.2 |
| | (2.2, 4.8) | (0.1, 0.9) | (0.1, 0.7) | (0.1, 0.6) | (0.3, 1.9) | (0.1, 0.6) | (0.2, 0.8) |
| CRP risk categories [b] (%, 95% CI) | | | | | | | |
| Low, <1.0 mg/L | 67.1 | 97.9 | 98.3 | 97.8 | 97.3 | 97.8 | 96.8 |
| | (63.8, 69.6) | (96.7, 98.7) | (97.3, 99.1) | (96.6, 98.9) | (96.5, 98.3) | (96.9, 98.8) | (95.5, 98.2) |
| Elevated, ≥1.0 mg/L | 32.9 | 2.1 | 1.7 | 2.2 | 2.7 | 2.2 | 3.2 |
| | (30.2, 35.3) | (1.2, 2.8) | (0.8, 2.9) | (1.2, 3.4) | (1.7, 3.4) | (1.4, 3.1) | (1.6, 4.8) |

Abbreviations: CRP, C-reactive protein.

[a] Adjusted for factors related to missing follow-up data (i.e. site, age and current smoking status pre-surgery).

[b] Values at year 2 and year 7 are significantly different (p for both<.001) than pre-surgery. Values at year 2 versus year 7 are significantly different (p<.001).

**Table 28. C-Reactive Protein (CRP) By Trajectory Group.**

| | Decline group n=1103[b] No. (%)[c] | Incline group n=77[b] No. (%)[c] | *P* |
|---|---|---|---|
| Age, years | | | 0.96 |
| Median (25th: 75th %-ile) | 46 (37: 55) | 46 (37: 54) | |
| Range | 19: 75 | 24: 64 | |
| Sex | | | 0.83 |
| Male | 226 (20.5%) | 15 (19.5%) | |
| Female | 877 (79.5%) | 62 (80.5%) | |
| Race | n=1094 | n=75 | 0.13 |
| White | 957 (87.5%) | 63 (84.0%) | |
| Black | 95 (8.7%) | 11 (14.7%) | |
| Other | 42 (3.8%) | 1 (1.3%) | |
| Ethnicity | | | 0.37 |
| Hispanic | 53 (4.8%) | 2 (2.6%) | |
| Non-Hispanic | 1050 (95.2%) | 75 (97.4%) | |
| Married or living as married[d] | 648/1042 (62.2%) | 36/66 (54.5%) | 0.22 |
| Education | n=1042 | n=67 | 0.92 |
| High school or less | 241 (23.1%) | 16 (23.9%) | |
| Some college | 461 (44.2%) | 28 (41.8%) | |
| College degree | 340 (32.6%) | 23 (34.3%) | |
| Household income, US $ | n=1017 | n=66 | 0.56 |
| Less than 25,000 | 196 (19.3%) | 17 (25.8%) | |
| 25,000-49,999 | 293 (28.8%) | 12 (18.2%) | |
| 50,000-74,999 | 232 (22.8%) | 18 (27.3%) | |
| 75,000-99,999 | 152 (14.9%) | 14 (21.2%) | |
| >100,000 | 144 (14.2%) | 5 (7.6%) | |
| Employed for pay[d] | 716/1037 (69.0%) | 46/66 (69.7%) | 0.91 |
| Smoke currently[d] | 20/1103 (1.8%) | 6/77 (7.8%) | 0.001 |
| Smoke currently or within 1 year of surgery[d] | 146/1103 (13.2%) | 13/73 (17.8%) | 0.27 |
| Body mass index, kg/m$^2$ | n=1103 | n=77 | 0.016 |
| Median (25th: 75th %-ile) | 46.2 (42.4: 51.6) | 48.7 (43.7: 53.9) | |
| Range | 33.7: 81.0 | 35.7: 72.5 | |
| Hyperlipdemia[d] | 399/1085 (36.8%) | 32/75 (42.7%) | 0.31 |
| Type 2 Diabetes[d] | 364/1092 (33.3%) | 34/76 (44.7%) | 0.043 |
| Hypertension[d] | 760/1087 (69.9%) | 52/77 (67.5%) | 0.66 |
| CRP (mg/L) | n=1103 | n=77 | <0.001 |
| Median (25th: 75th %-ile) | 0.7 (0.4: 1.3) | 1.4 (0.6: 2.6) | |
| Range | 0.0: 12.9 | 0.0: 10.3 | |

Abbreviations: BDI, Beck depression index.

[a] Participants have CRP measurement at pre-surgery and at least one follow-up assessment.

[b] Denominator shifts between variables due to missing data.

[c] Data are reported as No. (%) unless otherwise indicated.

[d] No./total (%).

**Table 29. Associations Between Change In ASCVD 10-Year Risk Score And Change In Categorical CRP, 1-7 Years Since Roux-En-Y Gastric Bypass[a]**

| | **Change in ASCVD 10-year risk score[b] N= 1098 *Beta* (95%CI)** | ***P*** |
|---|---|---|
| Change in CRP (ref=no change/low to elevated) | | |
| Elevated to low | -1.13 (-1.17, -1.08) | <.001 |
| Body mass index, kg/m2 per 5 unit decrease | -0.02 (-0.04, -0.01) | 0.001 |
| Smoke currently (ref=No) | | |
| Yes | 0.21 (0.05, 0.37) | 0.01 |
| Type 2 diabetes (ref=No) | | |
| Yes | 0.06 (0.02, 0.11) | 0.007 |

[a] Negative values indicate a decrease (improvement) from pre-surgery.
[b] Adjusted for factors related to missing follow-up data (pre-surgery age, past-year smoking status, site), and time since surgery.

## 4.9 Additional Analyses

### 4.9.1 CRP And Depressive Symptoms

#### 4.9.1.1 Introduction

Bariatric surgery is an effective treatment for severe obesity[6] and has been shown to reduce chronic inflammation (as measured by CRP levels) as soon as 3 months and for up to 3 years after surgery[159,251]. Additionally, there is evidence from a meta-analysis of the bariatric surgery literature, that after surgery there are improvements in the prevalence, as well as the severity of depression[261]. Specifically, while there is research evaluating associations between inflammatory markers and depressive symptoms in the general population, there is a dearth of research evaluating if a reduction in inflammation impacts depressive symptoms overtime in the bariatric surgery population. Thus, the aim of this analysis was to evaluate the association between pre- to post-surgery change in CRP and depressive symptoms. This study was limited to adults undergoing Roux-en-Y gastric bypass (RYGB) surgery, reflecting the timeframe of study enrollment (2006-2009).

#### 4.9.1.2 Measures Specific To This Analysis

*Depression*. Symptoms of depression over the past week were assessed using the Beck Depression Inventory, version 1 (BDI-1)[212]. In bariatric surgery, the BDI is one of the most widely used instruments in the assessment of mental health[262]. The BDI is a 21 item test which is scored from 0 to 63 with each item ranging from 0 to 9 (minimal symptoms) to 10 to 63 (mild to severe

symptoms) with higher scores indicating greater severity of depression[212]. Within this study, the BDI score was amended due to the advice many participants received prior to surgery to lose weight: no points were assigned to those who endorsed they purposefully tried to lose weight for the one BDI item that assesses weight loss[263]. Depression treatment was defined as self-reported depression medication or counseling/hospital admissions for depression in the past 12 months assessed with the LABS-2 Psychiatric and Emotional Test Survey[214].

#### 4.9.1.3 Statistical Analysis

The Pearson chi square test and the Wilcoxon rank sum test were used, as appropriate, to assess differences in distributions of pre-surgery depressive symptoms of LABS-2 participants in the analysis sample to those who were excluded due to missing data (i.e., underwent RYGB and missing CRP at pre-surgery or all follow-up assessments). Mixed models used all available data via maximum likelihood, with a person-level random intercept, and controlled for pre-surgery factors related to missing data (i.e., site, age and smoking status), with time since surgery entered as a discrete fixed effect. A linear mixed model (LMM) was used to estimate and test significance of the association between change in CRP (mg/L) from pre-surgery and the change in BDI score from pre-surgery across follow-up (repeated measures, 1-5 and 7 years). A second model included further adjustment for potential confounders of pre-surgery depressive symptoms[264] (static), sex[265] (static), anti-depressant treatment (repeated measure)[266] and percentage of weight change (time-varying)[267]. Given the inclusion of participants without depressive symptoms could weaken the association (i.e., no ability to have a reduction in depressive symptoms despite changes in CRP), the LMMs were repeated in those with at least mild depressive symptoms pre-surgery.

#### 4.9.1.4 Results

Depressive symptomology was similar between the CRP sample and LABS-2 participants who underwent RYGB but were excluded from this report due to lack of CRP (**Table 1**). BDI score by time in relation to Roux-en-Y gastric bypass is reported in **Table 2**. At pre-surgery, 30.9% of participants reported at least mild depression symptoms versus 10.0-22.8% in years 1-7 post-surgery.

Change in CRP (mg/L) from pre-surgery was not associated with change in BDI score across follow-up in the basic ($P$=0.64) or adjusted ($P$=0.70) models (**Table 3**). This was also true when the analysis was repeated among the subsample with at least mild depressive symptoms (n=339; all $P$>.41) (**Table 3**). Among participants with at least mild depressive symptoms (N=339), very few (range: 3.4% (n=5) to 1.2% (n=3) per year) had moderate/high CRP post-surgery (**Table 2**). This low frequency precluded evaluating if change in CRP categorization was associated with change in BDI score.

#### 4.9.1.5 Discussion

There is limited evidence evaluating if elevated systemic inflammation (measured as a continuous variable) contributes to depression. However, in a retrospective cohort study of 1494 adult women (median age: 47 years; mean BMI: 26.6 kg/m$^2$) without depression at initial assessment, there was a 44% increase in risk for major depressive disorder for every standard deviation increase in log transformed CRP[268]. Additionally, in a study of 73,131 people (mean age range: 53-61; majority female: 53-58%) which analyzed both cross-sectional, as well as prospective cohorts, those with higher CRP levels had an increased risk for antidepressant use and hospitalization for depression[269]. Yet in our study we did not find a significant relationship between pre- to post-surgery change in inflammation, as measured by continuous CRP, and change in

depressive symptoms, as measured by the BDI. One reason for this lack of association may be the almost universal improvement from moderate/high CRP at pre-surgery to low CRP post-surgery. For example, of those with mild/moderate depression pre-surgery, 37% had elevated CRP at pre-surgery, but only 1-3% had elevated CRP across follow-up. With a generally uniform response in improvement in CRP to low levels, and without an adequate number of participants with mod/high CRP post-surgery, the relationship between CRP and BDI would be difficult to measure. In particular, this scenario led to a lack of statistical power to carry out modeling between improvement in CRP categorization (e.g., elevated to low) and change in depressive symptoms. Thus, it may not be possible to evaluate the association between surgery induced changes in CRP and depressive symptoms in the bariatric surgery population without an extremely large sample.

### 4.9.1.6 Tables and Figures

**Table 30. Depressive Symptoms Of Adults Prior To Undergoing Roux-En-Y Gastric Bypass Included Versus Excluded From The C-Reactive Protein (CRP) Sample.**

| | CRP sample[a] (N=1180[b]) No. (%)[c] | Excluded (N=590[b]) No. (%)[c] | *P* |
|---|---|---|---|
| Depression treatment/ counseling/hospitalization[d] | 425/1084 (39.2) | 201/517 (38.9) | 0.90 |
| Depression medication[d] | 383/1089 (35.2) | 174/519 (33.5) | 0.52 |
| BDI score | n=1106 | n=543 | 0.97 |
| Median (25th: 75th %-ile) | 6 (3: 11) | 6 (3: 11) | |
| Range | 0: 44 | 0: 37 | |
| BDI depression symptomatology | n=1106 | n=543 | 0.81 |
| No/minimal (0-9) | 764 (69.1) | 372 (68.5) | |
| Mild and above (10-63) | 342 (30.9) | 171 (31.5) | |

Abbreviations: BDI, Beck depression index; CRP, C-reactive protein.
[a] Participants have CRP measurement at pre-surgery and at least one follow-up assessment.
[b] Denominator shifts between variables due to missing data.
[c] Data are reported as No. (%) unless otherwise indicated.
[d] No./total (%).

**Table 31. Depression Symptomatology And C-Reactive Protein (CRP) Among Participants With Mild Or Above Depressive Symptoms Pre-Surgery By Time In Relation To Roux-En-Y Gastric Bypass**

| | Pre-surgery | Post-surgery | | | | | |
|---|---|---|---|---|---|---|---|
| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 7 |
| **All participants[a]** | **n=1098** | **n=918** | **n=802** | **n=762** | **n=745** | **n=762** | **n=589** |
| Depression symptomatology[b] | | | | | | | |
| No/minimal (0-9) | 759 (69.1) | 826 (90.0) | 686 (85.5) | 635 (83.3) | 588 (78.9) | 599 (78.6) | 455 (77.3) |
| Mild (10-18) | 263 (24.0) | 66 (7.2) | 76 (9.5) | 91 (11.9) | 107 (14.4) | 111 (14.6) | 99 (16.8) |
| Moderate (19-29) | 65 (5.9) | 21 (2.3) | 31 (3.9) | 31 (4.1) | 42 (5.6) | 41 (5.4) | 30 (5.1) |
| Severe (30-63) | 11 (1.0) | 5 (0.5) | 9 (1.1) | 5 (0.7) | 8 (1.1) | 11 (1.4) | 5 (0.9) |
| **Mild-severe depressive symptom subsample (N=339)** | | | | | | | |
| CRP CVD risk, (n, %) | n=339 | n=242 | n=184 | n=178 | n=187 | n=187 | n=146 |
| Low, <1.0 mg/L | 214 (63.1) | 239 (98.8) | 180 (97.8) | 174 (97.8) | 183 (97.9) | 184 (98.4) | 141 (96.6) |
| Moderate/high, ≥1.0 mg/L | 125 (36.9) | 3 (1.2) | 4 (2.2) | 4 (2.3) | 4 (2.1) | 3 (1.6) | 5 (3.4) |

[a] Participants with CRP and Beck Depression Inventory (BDI) at pre-surgery and at least one post-surgery assessment.
[b] Based on the BDI Score.

**Table 32. Associations Between Change In C-Reactive Protein (CRP) And Change In Beck Depression Inventory (BDI)[a], 1-7 Years Since Roux-En-Y Gastric Bypass.**

| | All participants[b] | | | | Participants with mild-severe depressive symptoms pre-surgery[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | **Change in BDI Basic Model[c] N= 1098 *Beta* (95%CI)** | *P* | **Change in BDI Fully Adjusted Model[d] N= 1067 *Beta* (95%CI)** | *P* | **Change in BDI Basic Model[c] N= 339 *Beta* (95%CI)** | *P* | **Change in BDI Fully Adjusted Model[d] N= 328 *Beta* (95%CI)** | *P* |
| Individual improvement (decrease) in CRP (mg/L) from pre-surgery per 1 unit | -0.07 (-0.37, 0.23) | 0.64 | 0.06 (-0.23, 0.35) | 0.70 | 0.14 (-0.57, 0.84) | 0.71 | 0.29 (-0.40, 0.99) | 0.41 |

[a] Negative values indicate a decrease (improvement) from pre-surgery.
[b] Participants with BDI and CRP at pre-surgery and at least one post-surgery assessment.
[c] Adjusted for factors related to missing follow-up data (pre-surgery age, past-year smoking status, site), and time since surgery.
[d] Also adjusted for pre-surgery depression symptoms, sex, percent weight change and depression treatment (time-varying).

# 5.0 Public Health Impact

In the United States (US), cardiovascular disease (CVD), which includes several conditions where the heart or blood vessels have decreased functionality, is the cause of 1 in 3 deaths. CVD risk increases with higher degrees of excess adiposity. Adults with severe obesity (BMI ≥40 $kg/m^2$), who make up approximately 9.2% of US adults, are an especially high-risk population for specific types of CVD including coronary artery disease, myocardial infarction and heart arrhythmias, compared to those with less severe obesity[5,270]. The most effective intervention to treat severe obesity is bariatric surgery[8]. Bariatric surgical procedures alter the gastrointestinal tract resulting in acute and sustained weight loss. Currently, surgery is recommended in those with BMI ≥ 40 $kg/m^2$, or more than 100 pounds overweight, or BMI ≥35 $kg/m^2$ and at least one or more obesity-related co-morbidities[52]. In addition to weight loss, there is evidence that CVD risk, CVD-related mortality and inflammation markers (i.e. CRP) decline in the first few years following bariatric surgery[94,96,159,251,271]. However, there is a dearth of information regarding the CVD event rate and the magnitude, variability and durability of change in CVD risk after surgery, as well as a lack of information about individual-level characteristics which may influence the degree of surgery-induced improvement in CVD risk.

The Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) was used to help inform the literature on change in CVD risk and inflammation and CVD event rate in the bariatric surgery population. LABS-2 was a prospective cohort study of 1770 adults who underwent Roux-en-Y gastric bypass (RYGB) and were at least age 18 years of age. During the timeframe of study enrollment (2006-2009) RYGB surgery was considered the gold-standard of surgery and is currently the second most common procedure[6,7]. This research set out to use the LABS-2 RYGB

cohort to add a deeper understanding of the change in CVD risk after RYGB, including identifying predictors of change to be able to identify those who may need more clinical guidance to achieve the best CVD improvement after surgery. Additionally, we wanted to report non-fatal CVD events and CVD-related mortality by time since RYGB and compare post-surgery CVD-related mortality to the general population.

We employed three common short term (10-year) and long-term (lifetime) CVD risk scores due to the usage of the scores in clinical care and lack of a consensus on which CVD risk score is best for the bariatric surgery population. Additionally, the selected CVD risk scores were chosen due to the appropriateness of utilizing each score in younger populations in which CVD events are less likely to occur. We found that, discounting age, predicted 10-year and lifetime CVD risk was lower throughout 7 years following RYGB surgery versus pre-surgery whether assessed with the Framingham-lipid, the Framingham-BMI or the Atherosclerotic Cardiovascular Disease (ASCVD) scoring algorithm. Although the magnitude of improvement in CVD risk varied by score and timeframe, improvement was substantially larger 1 through 7 years following RYGB than what is typically achieved from diet, exercise or lifestyle interventions aimed at weight loss or CVD risk reduction in overweight and obese adults[35-37]. For example, 7 years post-surgery only 5.0% were classified as having high 10-year ASCVD risk versus 12.7% pre-surgery based on the 10-year ASCVD score.

Although the net improvement of CVD risk from pre-surgery was striking when assessed by any of the CVD risk algorithms, the scores differed in the percentage of participants identified as having high 10-year and lifetime CVD risk across all timepoints. For example, compared to the ASCVD score, both Framingham scores identified more women and men as having intermediate or high 10-year risk, perhaps because the Framingham predicts more outcomes. Given these 10-

year CVD risk designations can be used for the initiation of statin therapy, and the lifetime CVD risk scores can be used to motivate patients to make behavioral changes, score selection has important clinical implications. In particular, more females and males would be identified as potential candidates for initiation of statins if the Framingham-BMI was used versus the Framingham-lipid, or either Framingham versus the ASCVD. The need for clinical guidelines on which CVD risk score should be used in this population is warranted and future research should focus on identifying the best risk score for this population.

In addition to CVD risk scores, another way to measure CVD risk is through the use of biomarkers for inflammation. A popular biomarker that has been used to assess CVD risk is CRP. In the LABS-2 cohort, those who underwent RYGB experienced a mean decrease in CRP from their pre-surgery levels through 7 years of follow-up. The improvement in CRP from pre-surgery to post-surgery was evident when assessed on a continuous scale or categorized by CVD risk thresholds (low, moderate, high). At the pre-surgery assessment, 67% of participants had low risk CRP levels (<1 mg/L); at 7 years post-surgery this percentage improved to 97%, which demonstrates both the clinical significance and the durability of CRP improvement over longer-term follow-up after surgery. Trajectory group analysis indicated that participants tended to fall into one of two patterns of CRP over time. Group 1, which included the majority of participants (93.5%), experienced a large improvement in the first-year post-surgery, which remained fairly stable across 7 years of follow-up. However, in group 2 (6.5%), which had higher pre-surgery CRP values, followed a less favorable trajectory after their initial improvement and at 2 years post-surgery began to experience a worsening (incline) in CRP, such that the net improvement by year 7 was smaller compared to group 1. Thus, if CRP begins to increase from nadir values post-surgery, the results of this study suggests that additional testing and closer monitoring of the patient

may be warranted to ensure the most beneficial outcomes of inflammation and associated CVD health post-surgery.

Given the variability in CVD risk response to RYGB, we carried out analysis to identify pre-surgery factors associated with improvement in CVD risk. We were able to identify several pre-surgery factors independently associated with greater improvement in the 10-year and Lifetime ASCVD risk scores, which included higher CVD risk at pre-surgery, male sex, White race, lower household income, abnormal kidney function, lower scores of mental health (as measured by SF-36 MCS)/psychiatric counseling in the past 6 months and better physical health (as measured by SF-36 PCS). Thus, when clinicians are screening individuals for surgery it may be valuable to recommend additional follow-up or guidance to those who may need additional support and medical intervention in the longer-term follow-up after surgery. By targeting those who may benefit from prolonged support after surgery, CVD outcomes may be prevented.

A history of differential access to medical care likely accounts for some of the racial disparities in CVD risk in the US. The identification and treatment of CVD risk factors such as obesity and high blood pressure (which can be achieved through bariatric surgery) has been proposed as a step to reduce the disparate rates of CVD in the US. Thus, Black versus White race being associated with greater mean improvement in 10-year risk is a particularly interesting finding of this study. Perhaps this finding reflects that among patients who can access and undergo interventions associated with improvements in CVD health, Blacks have, on average, more substantial improvement than Whites, due to their previous differential access to medical care.

In addition to assessing change in CVD risk as measured by scoring algorithms that take individual risk factors into account, or specific markers, such as CRP, we determined sex-specific non-fatal CVD event rates. The non-fatal CVD event rates within the current study revealed

females had a higher rate of non-fatal CVD events in the long-term (i.e., 5 or more years) versus short-term (i.e., fewer than 5 years) post-surgery. In contrast, the short- versus long-term non-fatal CVD event rates were similar among males (and similar to the female long-term rate). There are several potential explanations for these findings. Females may be physically healthier prior to surgery. Specifically, men undergoing bariatric surgery tend to be older, have higher BMI, and more obesity-related comorbidities compared to women[39]. Additionally, women develop CVD, on average, 7 to 10 years after men. Thus, the higher non-fatal CVD event rate among women 5 years after surgery may be a reflection of aging[40].

We also calculated standardized mortality ratios (SMRs) (ratio of observed mortality rate in the RYGB sample to the calculated mortality rate in the matched-general population) for CVD-related mortality (defined by ICD-10 codes). The post-RYGB sample had a SMR higher than 1 (females: 1.18; males: 1.96), indicating a higher mortality rate compared to the general population, adjusted for age, sex and race. This could reflect that despite improvements in weight and comorbidities following surgery, post-surgical patients still have higher levels of obesity and other comorbidities including T2D, respiratory disorders and non-alcoholic fatty liver disease[41]. However, the 95% confidence intervals of these SMR included 1, likely reflecting the low frequency of CVD-related deaths in the RYGB sample. Thus, additional research is needed to determine whether these findings reflect low power to detect a difference or no actual difference.

Overall, this work contributes to the understanding of CVD risk and pre-surgery factors related to change in CVD risk after RYGB. The reported changes in CVD risk after RYGB as measured by CVD risk scores and the inflammation biomarker, CRP, demonstrate the ability of RYGB surgery to substantially improve CVD health, on average, over the longer-term, while also highlighting differences in response to surgery. This work also suggests that although

RYGB appears to result in substantial CVD risk reduction, post-surgical patients may still experience higher CVD-related mortality than the general population. Individual-level factors related to the degree of change in CVD risk following bariatric surgery can be used in the clinical setting to target groups who may benefit from additional CVD screening, education on healthy CVD lifestyle and potentially medical intervention, which have the potential to improve CVD health in a particularly vulnerable population.

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