PREOPERATIVE WEIGHT LOSS FOR NON-BARIATRIC SURGERY

PREOPERATIVE WEIGHT LOSS FOR PATIENTS WITH OBESITY PRIOR TO NON-BARIATRIC SURGERY

By TYLER MCKECHNIE, MD

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements of the Degree of Master of Science.

McMaster University MASTER OF SCIENCE (2023)

Hamilton, Ontario (Health Research Methodology)

TITLE: Preoperative Weight Loss for Patients Living with Obesity Prior to Non-Bariatric Surgery

AUTHOR: Tyler McKechnie MD (McMaster University)

SUPERVISOR: Dr. Mohit Bhandari MD MSC PhD FRCSC

NUMBER OF PAGES: xii, 47

LAY ABSTRACT

Preoperative weight loss strategies for patients with obesity undergoing major non-bariatric surgery are becoming a necessity given the ubiquitous nature of obesity in our current surgical patient population. The first chapter is a systematic review and meta-analysis evaluating the use of preoperative very low energy diets (VLEDs) prior to non-bariatric surgery for patients with obesity. After screening nearly 800 citations and including 13 studies, this review identified that while currently available evidence is heterogenous, preoperative VLEDs are safe, well tolerated, and effectively induce preoperative weight loss in patients with obesity undergoing non-bariatric surgery for both benign and malignant disease. The second chapter is a population-level retrospective study investigating the impact of a history of bariatric surgery for weight loss on patients undergoing surgery for colorectal cancer. The findings from this study suggested that bariatric surgery prior to surgery for colorectal cancer may be associated with decreased postoperative morbidity and healthcare resource utilization.

ABSTRACT

Background: Improved preoperative weight loss strategies for patients with obesity undergoing major non-bariatric surgery are necessary. As such, this research program focusing on evaluating different preoperative weight loss interventions, namely very low energy diets (VLEDs) and bariatric surgery, for patients with obesity undergoing major non-bariatric surgery was developed.

Methods: The first chapter is a systematic review evaluating the use of preoperative VLEDs reported according to PRISMA. Medline, EMBASE, CENTRAL, and PubMed were systematically searched from inception through to July 2021. Articles were included if they evaluated VLED utilization prior to non-bariatric surgery. Pairwise meta-analyses using inverse variance random effects were performed. The second chapter is a retrospective study investigating the impact of a history of bariatric surgery on patients undergoing surgery for colorectal cancer. Adult patients undergoing resection for colorectal cancer from 2015-2019 were identified from the National Inpatient Sample (NIS). Patients were stratified according to their history of bariatric surgery. Propensity score matching with 4:1 nearest-neighbor matching was performed.

Results: In Chapter 1, 13 studies with 395 patients with obesity receiving VLEDs preoperatively in preparation for non-bariatric surgery were included. Adherence with VLEDs ranged from 94-100%. Mean preoperative weight loss ranged from 3.2-19.2kg. Patients using VLEDs had decreased intraoperative blood loss (MD 305.20mL, 95%CI 208.18-402.23, $p<0.00001$). In Chapter 2, 1,197 patients without prior bariatric surgery and 376 patients with prior bariatric surgery were included. Patients with prior bariatric surgery had an absolute reduction of 6.5% in overall in-hospital postoperative morbidity (19.1% vs. 25.6%, $p<0.0001$) and a $5,256 decrease in hospitalization cost ($70,344 vs. $75,600, $p=0.034$).

Conclusion: These studies support the use of preoperative weight loss techniques for patients with obesity prior to non-bariatric surgery. VLEDs and bariatric surgery have the potential to become cornerstones of pre-habilitation protocols for patients with obesity undergoing elective operations. Further adequately powered prospective study is warranted.

ACKNOWLEDGEMENTS

I would like to thank my thesis supervisor, Dr. Mohit Bhandari, along with the remainder of my thesis committee (Dr. Cagla Eskicioglu, Dr. Sameer Parpia, and Dr. Aristithes Doumouras), for their invaluable support throughout the duration of this graduate degree. I have learned a great deal from each of my committee members and my thesis supervisor pertaining to the conduct of high quality, methodologically sound clinical epidemiological research. I look forward to continuing to learn from them for years to come.

My oral thesis defense would not have been possible without the external review of Dr. Sunil Patel. I am grateful for his input and look forward to collaborating in the future.

I am also extremely grateful to my other co-authors on these papers, Drs. Dennis Hong, Joanna Dionne, Yung Lee, Lily Park, Jay Lee, and Christopher Povolo, without your hard work and collaboration, these projects would not have been possible.

Lastly, I would like to extend a sincere thank you to the Division of General Surgery. The leadership within the Division has provided me the time and resources required to complete this degree, while the remaining staff surgeons and resident physicians have provided tremendous support throughout the completion of this Master of Science program.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
CENTRAL	Cochrane Register of Controlled Trials
CI	Confidence Interval
COS	Core Outcome Sets
CM	Centimeters
GLP-1	Glucagon-like Peptide 1
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCUP	Healthcare Cost and Utilization Project
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IQR	Interquartile Range
Kg	Kilogram(s)
LOS	Length of Stay
M	Meter(s)
MCID	Minimal Clinically Important Difference
MD	Mean Difference
mL	Milliliters
NIS	National Inpatient Sample
OR	Odds Ratio
PICO	Population, Intervention, Comparison, Outcome(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
RR	Risk Ratio
SD	Standard Deviation
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
US	United States
USD	United States Dollar
VLCD	Very Low Calorie Diet
VLED	Very Low Energy Diet
WC	Waist Circumference

DECLARATION OF ACADEMIC ACHIEVEMENT

Tyler McKechnie is primarily responsible for the development of the research question, study design, data analysis, and manuscript preparation. *Chapter 2: Very Low Energy Diets* has been published as a peer-reviewed article in *Surgery* (https://doi.org/10.1016/j.surg.2022.09.006). *Chapter 3: Bariatric Surgery* has been published as a peer-reviewed article in *Surgery* (https://doi.org/10.1016/j.surg.2023.08.011)

CHAPTER 1: INTRODUCTION

1.1 The Obesity Epidemic

Obesity is increasingly prevalent in Western society and across the globe.[1] The economic burden in Canada alone is estimated to have surpassed $100 billion United States Dollars (USD).[2] The healthcare system bears most of this economic burden. More importantly, obesity can adversely impact almost all human physiologic homeostasis. In North America, obesity is defined as a body mass index (BMI) of equal to or greater than 30 kilograms (kg) per meters (m) squared, and these patients with BMIs greater than 30 kg/m^2 are at significantly higher risk of insulin resistance, cardiovascular disease, several types of cancers, and more.[3–5] The prevalence of these conditions, and the downstream consequences, are set to increase along with the rising prevalence of obesity. It is estimated that over half of the North American population will be living with obesity by 2030.[6] With over 10% of Canadian children and adolescents also living with obesity, a number significantly higher than historic values, the obesity epidemic is set to continue for years to come.[7]

1.2 The Impact of Obesity on Surgical Outcomes

It naturally follows that the surgical patient with obesity is unavoidable. Obesity has several deleterious effects on perioperative outcomes. Intraoperatively, patients with obesity are at increased risk of requiring longer operative times, exposing them to the harmful side effects of anesthetic medication, increased intraoperative blood loss, greater perceived technical difficulty by operating surgeons, and increased risk of conversion from a minimally invasive operation to a more invasive operation (i.e., open procedure).[8–10] Postoperatively, the incidence of cardiovascular (1-2% vs. 2-4%), genitourinary (3-10% vs. 6-20%), and wound (3-9% vs. 6-18%) complications are at least doubled compared with patients living without obesity.[11–15] These

increased risks of postoperative complications can in turn contribute to significantly longer postoperative length of stays (LOS) and increased healthcare spending. Long-term oncologic outcomes may also be worsened in patients with obesity undergoing surgery for cancer.[16]

1.3 Preoperative Weight Loss for Patients with Obesity

To pre-emptively mitigate some of these concerns, prescribed preoperative weight loss, often via VLEDs, has become a standard of care for patients with obesity undergoing bariatric surgery (i.e., weight loss surgery).[17] Specifically, patients with obesity often have to complete a six-to-twelve-month medical weight loss program prior to becoming eligible to undergo bariatric surgery for weight loss.[18] These programs can effectively induce significant amounts of preoperative weight loss, which in turn may contribute to decreased postoperative length of stay (LOS) by at least 0.5-1 days, decreased fat content around major intra-abdominal organs by as much as 29% resulting in better visualization and improved ease of the surgery, and reduced overall postoperative morbidity by 33%.[19–22] While these programs are well established and efficacious for patients with obesity undergoing bariatric surgery, equivalent programs for patients with obesity undergoing non-bariatric surgery are scarce and have minimal peer-reviewed evidence supporting their use. Preoperative weight loss strategies for patients with obesity undergoing major non-bariatric surgery are becoming a necessity given the ubiquitous nature of obesity in our current patient population. Interventions such as physical activity, referral to registered dieticians for dietary interventions, VLEDs, glucagon-like peptide 1 (GLP-1) agonists (e.g., Ozempic®), and bariatric surgery must be explored in an effort to optimize patients with obesity prior to elective and semi-elective surgery for benign and malignant diseases alike. As such, this research program focused on evaluating and understanding different preoperative weight loss interventions, namely VLEDs and bariatric surgery, for patients with

obesity undergoing major non-bariatric surgery. The first chapter is a systematic review and meta-analysis evaluating the use of preoperative VLEDs prior to non-bariatric surgery for patients with obesity. The second chapter is a population-level retrospective study investigating the impact of a history of bariatric surgery for weight loss on patients undergoing surgery for colorectal cancer. The efficacy and safety of these interventions for this patient population will be explored with the aim of understanding where they may be useful in clinical practice, as well as understanding whether future randomized prospective work is feasible and warranted in this field. Ultimately, these research projects in addition to future prospective work, will hopefully form the cornerstone for preoperative optimization programs for patients with obesity undergoing non-bariatric surgery.

CHAPTER 2: VERY LOW ENERGY DIETS

2.1 Background

VLEDs or very low-calorie diets (VLCDs) serve as an intensive approach to achieve significant weight loss in a relatively short period of time.[23,24] Individual formulations of each diet vary slightly, however all follow a similar composition. These diets are fortified with protein (i.e., containing 0.8 to 1.5 grams [g] protein/kg of ideal body weight), include all recommended daily micronutrients, yet are limited in their carbohydrate and fat content (i.e., up to 80 g carbohydrate/day and 15 g fat/day) allowing them to induce weight loss while maintaining lean body mass.[25–27] Most VLEDs or 'VLCD-based models', comply with a maximum daily allowance of 1200 calories (most ≤ 800 calories/day) and are normally prescribed for 4-12 weeks in duration, with notable exceptions depending on amount of weight loss desired.[24,25,28–30]

Despite heterogeneity in VLED administration, caloric content, and diet duration, numerous high-quality reviews and meta-analyses provide strong evidence for their safety and efficacy when addressing patients with obesity.[24,26,30,31] As such, VLEDs are now recommended in some clinical practice guidelines for medical weight loss which is refractory to conventional dieting methods.[32–34] Specifically, VLEDs are to be prescribed and supervised by trained personnel for a maximum of 12 weeks, in those who failed conventional weight loss strategies or in whom weight loss needs to be achieved in a short period of time (e.g., for an upcoming bariatric surgery).[35,36] In these groups, VLEDs are associated with significant weight loss in both the short- and long-term, and have been shown to reduce the severity of obesity related comorbidities such as hypertension, type-2 diabetes, and dyslipidemia.[26,31,37] From a surgical perspective, VLEDs are most commonly used for optimizing patients with obesity prior to bariatric surgery for weight loss.[35,36,38] Currently the Canadian Adult Obesity Clinical Practice Guidelines, recommend that bariatric surgery patients "consume very low-calorie meal

supplements in the form of commercially available protein shakes totalling 650–900 kcal/day for two to three weeks prior to surgery".[35] The utilization of VLEDs before bariatric surgery is associated with numerous advantages including significant weight loss prior to surgery, reduction in liver volume, visceral fat reduction, decreased surgeon perceived operating difficulty, decreased LOS, and reduced postoperative complications.[19,20,25,39]

While the preoperative use of VLEDs in bariatric surgery is well established, the evidence and potential benefits of VLEDs prior to other types of surgery remains unclear. A systematic review from 2016 evaluating VLEDs for preoperative weight loss in patients with obesity could only identify two studies which looked at their use in non-bariatric surgery.[25] The review suggested that VLED use in non-bariatric surgery was similar to VLED in bariatric surgery with regards to adherence, weight loss, complications, and blood loss.[25] However, the authors were cautious in suggesting that these results could be generalized to all other types of surgery. Moreover, there was apprehension with regards to the application of VLED in patients with obesity undergoing oncologic resections due to the fear of compounding cancer-induced catabolism.[40] Yet, recent data suggest it can be safely applied to these patients as well as those undergoing elective non-oncologic surgery.[40,41]

2.2 Study Objectives

The primary aim of this systematic review was to evaluate the currently available evidence for the use of VLEDs preoperatively for adult (i.e., over the age of 18 years) patients with obesity undergoing major non-bariatric surgery in terms of efficacy (i.e., weight loss, perioperative outcomes), safety (i.e., adverse events), and adherence to serve as a foundation for further prospective study. The secondary aim of this systematic review was to compare adult patients with obesity undergoing major non-bariatric surgery receiving VLEDs to those not

receiving VLEDs in terms of perioperative outcomes (i.e., operative time, estimated intraoperative blood loss, postoperative morbidity, LOS). The tertiary aim of this systematic review was to appraise previously published data pertaining to the use of preoperative VLEDs in adult patients with obesity undergoing major non-bariatric surgery for oncologic disease in terms of safety (i.e., adverse events). The PICO format for this review was as follows:

Population: Adult patients (i.e., over 18 years of age) with obesity (i.e., BMI greater than 30 kg/m^2) undergoing major non-bariatric surgery.

Intervention: Preoperative VLED with liquid formulation.

Comparison: No preoperative VLED with liquid formulation or no comparison.

Outcomes: VLED efficacy (i.e., weight loss, operative time, estimated intraoperative blood loss, postoperative morbidity, LOS); VLED safety (i.e., adverse events); VLED adherence.

2.3 Study Hypothesis

The *a priori* study hypothesis is that VLEDs used by patients with obesity prior to major non-bariatric oncologic and non-oncologic surgery will be well tolerated (i.e., high percentage of adherence to VLED regimens) and safe (i.e., incidence of VLED-associated adverse events that are low and similar to those reported in studies evaluating VLED use prior to bariatric surgery). To date, there are no high-quality data suggesting that VLEDs impact patients with obesity undergoing non-bariatric surgery differently than patients with obesity undergoing bariatric surgery.[25] Additionally, it is hypothesized that there will be significant between-study heterogeneity identified in the present review.

2.4 Study Design

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix 1). The study protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews *a priori* (CRD42021284333). Local institutional ethics review board approval was not required for this study.

Eligibility Criteria

Articles were eligible for inclusion if they assessed VLED utilization by adult patients with obesity prior to any type of non-bariatric surgery and reported at least one of the following outcomes: preoperative weight change, VLED adherence, VLED safety, operative outcomes, postoperative complications, and/or postoperative LOS following index . These outcomes are defined below in *Outcome Measures.* The VLED must have also included a liquid formulation (e.g., Optifast©, Medimeal©). Studies which evaluated VLEDs prior to bariatric surgery or in the context of medical weight loss programs were excluded. Studies were not discriminated based on type of non-bariatric surgery included. Articles written in all languages were considered for inclusion. Conference abstracts were eligible for inclusion. Randomized control trials (RCTs) and observational studies (i.e., prospective cohorts, retrospective cohorts, and case series) were included. Single-armed, non-comparative studies were eligible for inclusion. Reviews, meta-analyses, abstracts, editorials, letters, opinion pieces, non-peer reviewed research, and other types of studies not reporting primary data were excluded.

Search Strategy

The following databases covering the period from database inception through July 2021 were searched: Medline, EMBASE, Cochrane Register of Controlled Trials (CENTRAL), and PubMed. The search was designed and conducted by a medical research librarian with input from

study investigators. Search terms included “Very-Low Energy Diet”, “Very-Low Calorie Diet”, “Non-Bariatric Surgery”, “Preoperative Weight Loss”, and more (complete search strategy available in Appendices 2-3). The references of studies meeting inclusion criteria as well as previous pertinent systematic reviews were searched manually to ensure that all relevant articles were included. The International Clinical Trials Registry Platform and clinicaltrials.gov were also searched to identify ongoing or unpublished studies (“very low-calorie diets” and “very low energy diets”).

Study Selection

Two reviewers (TM, CP) independently evaluated the systematically searched titles and abstracts using a standardized, pilot-tested form on Covidence©. Discrepancies that occurred at the title and abstract screening phases were resolved by inclusion of the study. Full-text screening ensued with two reviewers (TM, CP). At the full-text screening stage, discrepancies were resolved by consensus between the reviewers. If disagreement persisted, a third reviewer was consulted (CE).

Data Collection

Two reviewers (TM, CP) independently conducted data extraction onto a data collection form design*ed a priori* on Microsoft Excel©. Any discrepancies were resolved by consensus between the reviewers. Extracted data included study characteristics (e.g., author, year of publication, study design, inclusion/exclusion criteria), patient demographics (e.g., age, sex, initial weight/BMI), VLED details (e.g., diet formulation, calories consumed per day, length of dieting period), VLED safety (e.g., tolerability, compliance, adverse events, tissue biopsy, biochemical parameters), operative details (e.g., type of surgery, operative time, blood loss), and postoperative outcomes (e.g., LOS, morbidity, mortality).

Outcome Measures

There are no validated core outcome sets (COS) for preoperative weight loss interventions.[42] Similarly, minimal clinically important difference (MCID) data have not been published for any of the outcomes below. Therefore, the following outcomes were selected *a priori* based on clinical significance and prevalence in the existing literature:

- Preoperative Weight Loss (Efficacy): Recorded as the post-VLED intervention weight subtracted from the pre-VLED intervention weight in kg. This was also recorded as post-VLED intervention BMI subtracted from the pre-VLED intervention BMI in kg/m^2. If change in weight or pre- and post-VLED weights were not reported then this outcome was reported as missing.
- Postoperative Morbidity (Efficacy): Any deviation from the expected postoperative course as reported by each included study. If this was not reported as a pooled outcome in the included study, then the outcome was recorded as missing.
- Operative Time (Efficacy): This will be defined as the time in minutes from the start of the surgical case to the end of the surgical case as recorded in each individual study.
- Estimated Intraoperative Blood Loss (Efficacy): This will be defined as the amount of estimated blood loss in milliliters (mL) during the surgical case as recorded in each individual study.
- Postoperative LOS (Efficacy): This will be defined as the number of days from the index procedure to the time the patient leaves an acute care bed as recorded in each individual study.

- VLED-association Adverse Events (Safety): Any reported morbidity felt to be secondary to the use of the VLED as per each individual study.
- VLED Adherence: The number of doses of VLED taken divided by the number of doses of VLED prescribed.

Details regarding diet protocol such as diet formulation, calories per day, patient monitoring, and length of diet period were recorded to allow for better comparison of these interventions. In addition, if the study included a comparative or control group their demographics, baseline differences, and outcomes were documented to assess efficacy of the intervention as compared to the control.

Risk of Bias Assessment

Risk of bias for observational studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool.[43] Risk of bias for RCTs was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials 2.0.[44] For non-comparative observational studies, the Methodological Index for Non-Randomized Studies (MINORS) tool was used.[45] Two reviewers independently assessed the risk of bias. Discrepancies were discussed amongst the reviewers until consensus was reached. Risk of bias figures were created with RoBvis.[46]

Assessment of Certainty of Evidence

Certainty of evidence for estimates derived from meta-analyses was assessed by Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[47] The GRADE results were collated in a summary of findings table, as recommended by the Cochrane Collaborative. The calculations and organization of results into a summary of findings table was done using the GRADEPro software.[48]

Assessment of Heterogeneity

Baseline study characteristics were assessed to ensure adequate homogeneity between studies in terms of demographics, interventions, and outcomes prior to performing a meta-analysis. Following completion of each meta-analysis, assessment of heterogeneity was completed by visual inspection of the forest plot as well as the inconsistency (I^2) statistic. An I^2 greater than 40% was considered to represent considerable heterogeneity.[49] Heterogeneity was explored through the following *a priori* subgroup analyses: 1) study design (i.e., RCT vs. non-RCT); 2) risk of bias (i.e., high risk of bias vs. low/some risk of bias).

Statistical Analysis

All statistical analyses and meta-analyses were performed on STATA version 15 (StataCorp, College, TX) and Cochrane Review Manager 5.3 (London, United Kingdom). Mean and standard deviation (SD) was estimated for studies that reported median and interquartile range using the method described by Wan *et al.*[50] Missing SD data were calculated according to the prognostic method.[51] A pairwise meta-analysis was performed using an inverse variance random effects model for all meta-analyzed outcomes. A random effects model was selected due to anticipated between study heterogeneity. Pooled effect estimates were obtained by calculating the risk ratio (RR) along with their respective 95% confidence intervals (CI) and mean differences (MD) along with their respective 95% CIs to confirm the effect size estimation for dichotomous and continuous outcomes, respectively. A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time from the inverse variance random effects models to ensure that pooled effect estimates were not driven by a single study. Publication and reporting bias in meta-analyzed outcomes were assessed with funnel plots when data from more

than 10 studies were included in the analysis.[52] A systematic narrative summary was provided for each outcome.

2.5 Study Results

Results of the Search

From 792 citations, 13 studies (four RCTs, three prospective cohorts, four retrospective cohorts, one mixed methods study, and one case series) were included.[28–30,40,53–61] A PRISMA flow diagram of the study selection is illustrated in Figure 1. The reasons for exclusion of the 28 studies excluded at the full-text review stage are recorded in Table 1.

Study Characteristics

Within the 13 included studies, 395 patients (mean age: 56.5 years, 55.8% female) received VLED preoperatively in preparation for non-bariatric surgery. Seven of the included studies compared VLED with a placebo or control diet. Three of the included studies evaluated patients undergoing hepatectomies, two evaluated patients undergoing gastrectomy, two did not specify the operation under investigation, and the following operations were examined in a single study each: hernia repair, laparoscopic cholecystectomy, carotid endarterectomy, total knee replacement, robotic assisted radical prostatectomy, and gynecology resections. One study included patients with BMIs greater than 40 kg/m^2, one study only included patients with BMIs greater than 35 kg/m^2, six studies included patients with BMIs greater than 30 kg/m^2, and one study did not have a BMI cut-off but rather included patients with a waist circumference (WC) of greater than 94 centimeters (cm). Four studies did not report weight-based inclusion criteria. Detailed study characteristics are reported in Table 2.

Intervention Details

The mean duration of preoperative VLED amongst the included studies was 6.6 weeks (range: 0.42-17 weeks). Seven of the included studies included preoperative VLED protocols

less than one month in duration. The most commonly used liquid VLED formulation was Optifast© (five studies), followed by Slim-Fast© (two studies) and Obecure© (two studies). Target daily caloric intake ranged from 450 to 1370. The most restrictive (450 calories per day) was a 1997 study by Pekkarinen *et al.* which evaluated the use of VLED for 7-24 weeks prior to unspecified elective surgery with Modifast©.[30] The most liberal VLED diet was in the most recent study by Maruyama *et al.* in which patients were to consume 1370 calories per day with ObeCure© and solid food for four weeks prior to thoracoscopic and/or laparoscopic esophagectomy or gastrectomy.[61] Adherence with VLED was reported by five studies and ranged from 94% to 100%. All studies reporting adherence had preoperative VLEDs lasting four weeks or less. Further dietary details for each of the included studies are reported in Table 3.

Weight Loss

Ten of the included studies reported weight or BMI change following preoperative VLED. Mean preoperative weight loss ranged from 3.2kg (three-week VLED program with ObeCure©) to 19.2kg (14-week VLED program with Modifast©) and mean preoperative decrease in BMI ranged from 1.2 kg/m^2 (three-week VLED program with ObeCure©) to 7 kg/m^2 (14-week VLED program with Modifast©) in the VLED cohorts. Six of the included studies reported statistically significant reductions in preoperative weight and/or BMI with VLED. Liljensoe *et al*. evaluated an eight-week VLED prior to total knee replacement for osteoarthritis and two patients (5.2%) lost such significant amounts of weight that their knee pain resolved, and their surgery was postponed.[60] Similarly, preoperative weight loss with a 14-week VLED allowed for postponement of four operations due to symptom resolution in the study by Pekkarinen *et al*. (one bladder repair for urinary incontinence, one knee replacement for arthritis, one desmoid tumor resection, and one abdominal aortic aneurysm repair).[30]

Inoue *et al.* sub-classified weight change based on body composition.[40] Following a three-week VLED with ObeCure© in which patients were limited to 15g of carbohydrates per day, they reported significant reductions in total body weight ($p<0.0001$), BMI ($p<0.0001$), body fat mass ($p<0.0001$), and visceral fat mass ($p<0.0001$) without reductions in skeletal muscle mass ($p=0.25$) or subcutaneous fat mass ($p=0.86$).[40] Wilson *et al.* evaluated specific changes in body composition with dual-energy x-ray absorptiometry following a four-week VLED prior to robotic radical prostatectomy and found a preferential loss of fat mass compared to lean body mass.[53] Pre- and post-VLED weight and BMIs for each of the included studies are reported in Table 4.

Perioperative Outcomes

Nine studies reported overall postoperative morbidity. Incidence of postoperative morbidity ranged from 0% (carotid endarterectomy) to 40% (laparoscopic esophagectomy or gastrectomy) for the VLED cohorts. The postoperative complications in the study evaluating esophagectomy and gastrectomy by Maruyama *et al.* included atelectasis and anastomotic leak. Six studies compared overall postoperative morbidity between patients receiving VLED and control diets. Meta-analysis did not demonstrate a difference in postoperative morbidity with the use of VLEDs (RR 1.08, 95% CI 0.70-1.67, $p=0.73$, $I^2=0\%$) (Figure 2). There was no significant interaction noted on study type subgroup analysis ($p=0.69$) nor on risk of bias subgroup analysis ($p=0.82$) (Figures 3A and 3B). Results were unchanged with leave-one-out sensitivity analyses. There were no significant differences in incidence of postoperative morbidity across all individual included studies.

Ten of the included studies reported perioperative outcomes. Specifically, five reported operative time in minutes. Mean operative times across studies in the VLED cohorts ranged from

25 minutes (laparoscopic cholecystectomy) to 577 minutes (laparoscopic esophagectomy or gastrectomy). Three studies compared operative time between patients receiving VLED and control diets. Upon pooling of these comparative data, there was a 13.73-minute reduction in operative time in the VLED group with wide 95% CIs that crossed the line of no effect (95%CI -44.64 to 17.18, p=0.38, I^2=66%) (Figure 4). Subgroup analysis could not be performed due to lack of data. Leave-one-out sensitivity analysis did not significantly alter the findings. Burnand *et al.* demonstrated a significant reduction in operative time in patients with BMIs greater than 30 kg/m^2 undergoing outpatient elective cholecystectomy for symptomatic cholelithiasis with the use of a two-week VLED with Slimfast© (VLED 25 minutes vs. control 31 minutes; p=0.0096).[29] Barth *et al.* and Inoue *et al.* did not find significant differences in operative time between the VLED and non-VLED cohorts in patients undergoing hepatic resection for malignancy and gastrectomy for malignancy, respectively.[40,57]

Four studies reported intraoperative blood loss. Mean blood loss across studies in the VLED cohorts ranged from 95mL (laparoscopic gastrectomy) to 600mL (hepatic resections). Three studies compared intraoperative blood loss between patients receiving and not receiving VLED. Upon pooling of these data, there was a statistically and clinically significant reduction in intraoperative blood loss in the VLED group compared to the control (MD 305.20mL, 95%CI 208.18 to 402.23, p<0.00001, I^2=88%) (Figure 5). Subgroup analysis could not be performed due to lack of data. Leave-one-out sensitivity analysis did not significantly alter the findings. Barth *et al.* randomized 60 patients undergoing partial hepatectomy to receive one week of preoperative VLED with Optifast© or a regular diet and found a significant reduction in intraoperative blood loss in the VLED group (VLED 452mL vs. control 863mL; p=0.021).[57] They also found lower overall volume of intraoperative blood transfusion in the VLED group (VLED 138mL vs. control

322mL; p=0.06).[57] Similarly, an earlier observational study by Reeves *et al.* in 2013 demonstrated a significant reduction in intraoperative blood loss in patients undergoing hepatic resections with a one-week preoperative VLED with Slimfast© (VLED 600mL vs. control 906mL, p=0.02).[54] In a prospective cohort of gastric cancer patients undergoing laparoscopic gastrectomy, Inoue *et al.* also showed a reduction in intraoperative blood loss with a three-week preoperative VLED compared to historical controls (VLED 49mL vs. control 76mL, p=0.043).[40]

Six studies reported postoperative LOS data. Mean LOS in the VLED cohorts ranged from 0.4 days (laparoscopic cholecystectomy) to 21 days (laparoscopic esophagectomy or gastrectomy). Four studies compared LOS between VLED and control cohorts. Meta-analysis found a 0.42-day reduction in LOS in the control group compared to the VLED group (95%CI -0.09 to 0.93, p=0.11, I^2=82%) (Figure 6). Subgroup analyses both by study type and by RoB found significant interactions with both the RCT and Low/Moderate RoB subgroups demonstrating larger MDs in LOS favoring the control group (MD 0.99 days, 95%CI 0.39 to 1.59, p=0.001, I^2=38%) (p-value for interaction=0.002, I^2=90%) (Figure 7). Detailed perioperative outcomes are reported for each of the included studies in Table 5.

Intervention Safety

Seven studies reported safety outcomes related to preoperative VLED use. Safety outcomes were reported heterogeneously and with a wide variety of measures, though VLED-related adverse events were most commonly relied upon for assessing safety of the intervention in the included studies. In four of the studies, patients did not experience any VLED-related adverse events.[30,40,59,61] Doyle *et al.* reported two cases (12.5%) of constipation that were felt to be secondary to VLED use.[55] Similarly, Liljensoe *et al.* did not describe any severe VLED-associated adverse events, and reported a mild adverse event incidence of 31.6% (constipation,

n=4; dry skin, n=3; sleeplessness, n=2; cold sensitivity, n=2; musculoskeletal cramping, n=1).[60] The greatest incidence of VLED-related adverse events, 55.1% (n=43/78) was reported by Griffin *et al.* in a mixed-methods observational study in which they evaluated a 10-week VLED with Optifast© or Optislim© for patients with BMIs greater than 30 kg/m^2 undergoing elective surgery.[28] The most common adverse events included: headache (n=20), nausea (n=7), constipation (n=6), and hypoglycemic events (n=2). Additionally in this study, bloodwork was drawn within the first two weeks of VLED initiation and upon completion, which demonstrated an improved lipid profile and no adverse effect on liver and kidney function.[28] Pekkarinen *et al.* drew bloodwork from participants at weekly intervals during the course of a 14-week preoperative VLED.[30] They noted that leukocytes and lymphocyte levels started to decline by the ninth week of VLED, though there was no statistically significant differences between VLED and control groups.

Oncologic Data

Six of the included studies evaluated patients undergoing oncologic operations.[40,53,54,56,57,61] The most restrictive diet allowed 800 calories per day and the least restrictive diet allowed 1,370 calories per day. Three of the studies utilized Optifast©, two utilized ObeCure©, and one used Slim-Fast©. Adherence rates were identical to those reported by studies evaluating patients undergoing operations for benign disease (94-100%). There were no data to suggest increased postoperative morbidity in oncologic patients receiving preoperative VLED. Barth *et al.* and Inoue *et al.* compared rates of postoperative morbidity between VLED and control groups and found no significant differences.[40,57] Inoue *et al.* also evaluated change in skeletal muscle mass to determine whether preoperative VLED enhanced cancer-induced catabolism and failed to demonstrate a difference in change in skeletal muscle mass in the

preoperative period between the VLED group and the control group.[40] Similarly, Maruyama *et al.* found no change in total protein, albumin, or prealbumin levels pre- and post-VLED for patients undergoing laparoscopic esophagectomy or gastrectomy for cancer.[61] They did however report two cases (40%) of anastomotic leak and noted that further comparative study was warranted to determine causality. Wilson *et al.* found a significant decrease in total lean mass in a cohort of patients undergoing radical robotic assisted prostatectomy for prostate cancer, but without a concomitant increase in postoperative morbidity.[53]

Risk of Bias

Figure 8 presents the risk of bias assessment for each included RCT according to the Cochrane Risk of Bias Tool for Randomized Controlled Trials 2.0. One RCT was at an overall low risk of bias, one had some risk of bias, and two were at high risk of bias. Kip *et al.* assigned all included patients to the treatment arm (n=4) and none to the control arm.[59] In 2019 RCT by Liljensoe *et al.* three patients withdrew from the treatment arm (7.9%).[60] Included RCTs were uniformly at low risk from missing data, outcome measurement, and outcome reporting.

Figure 9 presents the risk of bias assessment for each included comparative observational study according to ROBINS-I. One study was at overall low risk of bias and two were at high risk of bias. Included studies were uniformly at low risk of bias from outcome reporting and patient selection criteria.

Table 6 presents the risk of bias assessment for each included non-comparative observational study according to MINORS. The mean MINORS score across the six non-comparative studies was 8.3 (SD 3.3). Only one study collected data prospectively and none of the studies calculated a sample size *a priori.*

Certainty of Evidence

Figure 10 presents the summary of findings table as per the GRADE assessment of certainty of evidence. The certainty of evidence was very-low for all meta-analyzed outcomes due to high risk of bias of the included studies, high I^2-statistics indicating significant heterogeneity, indirectness resulting from heterogenous patient populations amongst the included studies, and wide 95% CIs crossing the threshold for clinical decision-making.

CHAPTER 3: BARIATRIC SURGERY

3.1 Background

The obesity epidemic continues to propagate worldwide.[62] Presently, there are nearly 100 million individual living with obesity in the United States (U.S.).[6] The proportion of individuals living with obesity is projected to further increase. It is expected that over 50% of the United States population will be obese by 2030.[6] In addition to the obvious public health crisis, these numbers equate to an increasingly obese surgical population. In colorectal surgery, these patients can present unique problems associated with their large volumes of subcutaneous and visceral fat, particularly when operating within the bony confines of the pelvis.[63,64] Unsurprisingly, colorectal surgery in the setting of obesity is associated with increased blood loss, operative time, and surgeon perceived difficulty.[8,64] Postoperative care can be similarly challenging, as patients with obesity have a higher propensity for developing complications such surgical site infections, venous thromboembolism, anastomotic leak, and more.[9,65]

In parallel with the rising prevalence of obesity, we have experienced the advent, development, and proliferation of bariatric surgery as a surgical sub-specialty. Bariatric surgery has quickly become recognized as the most effective and sustainable form of weight loss for patients with obesity.[66] It can improve a number of obesity-related comorbidities, such as type II diabetes, dyslipidemia, nonalcoholic fatty liver disease, and more.[67–69] There are even data supporting overall survival benefit for patients with obesity undergoing bariatric surgery.[70] In addition to improvements in these medical comorbidities, bariatric surgery may also be beneficial for patients undergoing surgery for other indications. Bariatric surgery prior to elective operations such as ventral hernia repair and hysterectomy as a means of inducing preoperative weight loss in patients with obesity may reduce intraoperative difficulty and postoperative complications.[71,72]

A similar study evaluating patients undergoing surgery for colorectal cancer has been performed using the National Inpatient Sample (NIS) (2006-2012).[73] Their data suggested reduced LOS and total inpatient healthcare cost, with equivalent postoperative mortality. They did not evaluate postoperative morbidity.

3.2 Study Objectives

The primary aim of the present study was to utilize a more recent cohort of the NIS (2015-2019) to compare adult patients (i.e., older than 18 years of age) with prior bariatric surgery and patients with BMIs greater than 35 kg/m^2 without prior bariatric surgery undergoing surgery for colorectal cancer in terms of in-hospital postoperative morbidity. The secondary objectives of this population-level database study were to compare adult patients with and without prior bariatric surgery undergoing surgery for colorectal cancer in terms of in-hospital postoperative mortality, system-specific in-hospital postoperative morbidity, discharge disposition, and healthcare resource utilization (i.e., LOS, cost). These data will serve as important background work in designing future research and clinical programs aimed at optimizing patients with obesity undergoing major abdominal surgery. The PICO format for this study was as follows:

Population: Adult patients (i.e., older than 18 years of age) undergoing colectomy and/or proctectomy for colorectal cancer at a NIS associated hospital between October 2015 and December 2019 as identified by International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes.

Exposure: A personal history of bariatric surgery as identified by ICD-10-CM codes.

Comparison: A BMI of 35 kg/m^2 or greater without a personal history of bariatric surgery as identified by ICD-10-CM codes.

Outcome: All of the following outcomes were identified as per ICD-10-CM codes: in-hospital postoperative morbidity (composite of respiratory, cardiovascular, gastrointestinal, genitourinary, and infectious morbidity), in-hospital postoperative mortality, system-specific in-hospital postoperative morbidity (i.e., respiratory, cardiovascular, gastrointestinal, genitourinary, and infectious morbidity), discharge disposition (i.e., home, short-term hospital, skilled nursing facility, home healthcare, other), total LOS in days, and total inpatient cost for index stay in hospital in USD.

3.3 Study Hypothesis

The *a priori* study hypothesis is that patients with a history of bariatric surgery for weight loss undergoing surgery for colorectal cancer will have clinically significant reductions in postoperative morbidity and healthcare resource utilization as compared to matched controls with BMIs greater than 35 kg/m^2 and no personal history of bariatric surgery. In other words, we hypothesize that if patients with obesity undergo bariatric surgery, they will experience fewer postoperative complications following colorectal cancer surgery than patients who do not. This hypothesis is predicated on findings from an earlier study published by Hussan *et al.* in 2017 that evaluated a similar research question using an older cohort of the NIS (2006-2012).[73]

3.4 Study Design

This population-level retrospective cohort study adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (Appendix 4).

Data Source

A retrospective population-based cohort study was performed utilizing October 1st, 2015 to December 31st, 2019 data from the Healthcare Cost and Utilization Project (HCUP) NIS, managed by the Agency for Healthcare Research and Quality (AHRQ). The timeline was chosen

to capture the years that NIS started utilizing ICD-10-CM codes. The NIS is the largest public all-payer inpatient database in the U.S.; it approximates a 20% stratified sample of community hospital discharges, and its included hospitals cover more than 97% of the U.S. population, providing a nationally representative sample of the U.S. patient population and hospital characteristics. The NIS records information on roughly 7 million hospitalizations annually, including weighted data to help make population estimates. Local institutional ethics review board approval was not required for this study.

Cohort Selection

The NIS captures 30 admission diagnoses and 15 admission procedures through the ICD-10-CM codes. Corresponding ICD-10-CM codes were utilized to identify a cohort of adult patients (i.e., older than 18 years of age) admitted with a primary diagnosis of code of colorectal cancer. The study group was further narrowed by identifying only colorectal cancer patients who underwent either colectomy, proctectomy, or proctocolectomy on the given admission. Patients with a BMI of less than 35 kg/m^2 were identified using obesity class identifier codes and excluded from the control group (i.e., no bariatric surgery group). The diagnosis and procedure codes utilized were drawn from previous similar studies.[73,74] See Table 7 for detailed ICD-10-CM codes utilized to identify the cohort for this study.

Patient and Institution Characteristics

The patient characteristics included for analysis were age, sex, race category (i.e., White, Black, Hispanic, Asian or Pacific Islander, and others), BMI class (i.e., $\leq$30 kg/m^2, 30-35 kg/m^2, 35-40 kg/m^2, $\geq$40 kg/m^2), insurance status (i.e., Medicare, Medicaid, Private Insurance, Self-pay, and others), and income quartile. Comorbidities were assessed with the Charlson Comorbidity Index software for ICD-10-CM for each individual patient. The operative approach (i.e.,

minimally invasive, open), specific operation (i.e., colectomy, proctectomy, proctocolectomy), and specific location of the colorectal cancer (i.e., right-sided colon cancer, transverse colon cancer, left-sided colon cancer, other colon cancer, and rectal cancer) were collected. The institution characteristics that included for analysis were teaching status, rural status, region (i.e., Northeast, Midwest, South, West), and bed size (i.e., small, medium, large).

Outcome Measures

The primary outcome was overall in-hospital postoperative morbidity. Postoperative morbidity was identified with ICD-10-CM diagnosis and procedure codes that explicitly identified individual postoperative outcomes. It was defined as a composite of respiratory (i.e., pneumonia, postoperative respiratory failure), cardiovascular (i.e., cerebrovascular accident, myocardial infarction), gastrointestinal (i.e., prolonged postoperative ileus, anastomotic leak, early small bowel obstruction), genitourinary (i.e., acute kidney injury, acute urinary retention, urinary tract infection), and infectious (i.e., surgical site infection, sepsis) morbidity. For postoperative morbidity that was not identifiable by individual ICD-10-CM codes, the AHRQ Patient Safety Indicators were used.

The secondary outcomes included overall in-hospital postoperative mortality, system-specific in-hospital postoperative morbidity, discharge disposition, total LOS, and total in-hospital healthcare cost. System specific complications were collected by grouping postoperative complications into respiratory, cardiovascular, gastrointestinal, genitourinary, and infectious complications using previously described methods.[75] . Discharge disposition was categorized into home, short-term hospital, skilled-nursing facility, home healthcare, and other. Healthcare resource utilization (i.e., LOS, cost) data are recorded in the HCUP NIS. Due to the nature of the

NIS database not having patient identifiers or linkage with other administrative databases, only in-hospital outcomes could be captured and out of hospital outcomes could not be captured.

Statistical Analysis

Patient characteristics are presented as frequencies (%) for categorical variables and means (SD) or medians (interquartile range [IQR]) for parametric and non-parametric continuous variables, respectively. Statistical analyses for categorical and continuous baseline variables were performed using the chi-square test and two sample t-test, respectively. Propensity score matching was performed with a 4:1 matching ratio for patients without prior bariatric surgery and patients with prior bariatric surgery, respectively. Propensity scores were computed by modeling a logistic regression with the dependent variable being the odds of experiencing the exposure of interest (i.e., bariatric surgery) and the independent variables of age, sex, race, Charlson Comorbidity Index, insurance status, income quartile, year of treatment, urgency of colorectal cancer surgery (i.e., elective, emergent), location of colorectal cancer, type of colorectal cancer surgery (i.e., colectomy, proctectomy, proctocolectomy), operative approach (i.e., open, minimally invasive), hospital bed size, hospital location (i.e., urban, rural), and hospital region. Patients were matched with nearest-neighbor greedy matching with calipers set to 0.2.[76] Patients who did not match were excluded from the final analyses. The degree of baseline variable balance was assessed with standardized differences. A high degree of balance was assumed to be achieved with a standardized difference of less than 10%.[77] McNemar's test was used to compare matched dichotomous outcome variables. Paired t-tests and Wilcoxon matched-pairs signed rank test were then used to compare matched parametric and non-parametric continuous outcome variables, respectively. All statistical tests were two-sided with the threshold for significance set at $p<0.05$. Discharge-level weight provided by HCUP was used

to calculate national estimates. All statistical analysis was performed using STATA (StataCorp version 15; College Station, TX).

An *a priori* sample size calculation was performed. Assuming an expected proportion of 30-day postoperative morbidity of 0.30 in the control group, based on previous colorectal cancer surgery literature, and 0.20 in the intervention group, based on a MCID of 33% relative risk reduction, a power of 80%, an alpha of 0.05, and the use of a McNemar's test, a sample size of 293 patients in the intervention arm was required to demonstrate the predicted effect.[8,78,79]

3.5 Study Results

Patient and Hospital Characteristics

Demographic and hospital characteristics of the overall NIS sample and propensity score matched sample of patients undergoing surgery for colorectal cancer stratified according to history of bariatric surgery are reported in Table 8. The overall NIS sample included 4,862 patients without a history of bariatric surgery (mean age: 61.9 [11.6], 54.5% female) and 394 patients with a history of bariatric surgery (mean age: 61.1 [11.1], 69.7% female). Prior to propensity score matching, patients with a history of bariatric surgery were more likely to be female ($p<0.001$), more likely to have private healthcare insurance ($p=0.003$), more likely to receive care in the Western region of the U.S. ($p=0.004$), and had significantly lower BMIs ($p<0.001$).

Following 4:1 propensity score matching, 1,197 patients with a BMI of greater than 35 kg/m^2 and without a history of bariatric surgery (mean age: 61.4 [11.7], 69.4% female) and 376 patients with a history of bariatric surgery (mean age: 61.1 [11.1], 69.9% female) were included. Standardized differences were less than 10% across all baseline patient, treatment, and hospital characteristics, except for BMI, suggesting adequate matching (Table 8). Amongst patients without a history of bariatric surgery, 44.4% had BMIs between 35 and 39.9 kg/m^2 and 55.6%

had BMIs of 40 kg/m^2 or greater. More than half of the cohort of patients with a history of bariatric surgery had a BMI of less than 30 kg/m^2 (58.8%) and 17.8% had a BMI of greater than 40 kg/m^2. The majority of patients had colon cancer (no bariatric surgery: 84.7%, bariatric surgery: 84.7%), were undergoing colectomy (no bariatric surgery: 86.5%, bariatric surgery: 87.0%), and were undergoing elective surgery (no bariatric surgery: 78.9%, bariatric surgery: 78.7%).

Postoperative Morbidity and Mortality

Pairwise comparison of the propensity score matched outcome data demonstrated an absolute reduction of 6.5% in overall in-hospital postoperative morbidity in patients with a history of bariatric surgery (19.1% vs. 25.6%, $p<0.0001$) (Table 9). Analysis of system-specific in-hospital postoperative morbidity demonstrated significant reductions in gastrointestinal morbidity (6.6% vs. 11.6%, $p<0.0001$), genitourinary morbidity (13.8% vs. 15.3%, $p<0.0001$), infectious morbidity (1.3% vs. 3.4%, $p<0.001$), and respiratory morbidity (2.1% vs. 5.5%, $p<0.0001$) in patients with a history of bariatric surgery. Postoperative in-hospital mortality was low in both groups. There was a decrease in postoperative in-hospital mortality in the patients with a history of bariatric surgery (0.5% vs. 1.0%, $p=0.013$).

Discharge Disposition

Most patients were discharged home following their colorectal surgery in both groups (no bariatric surgery: 63.9%, bariatric surgery: 72.9%) (Table 9). Patients with a history of bariatric surgery were significantly more likely to be discharged home after surgery ($p<0.0001$) and were significantly less likely to require home healthcare (7.7% vs. 11.5%, $p<0.0001$) or to be discharged to a skilled-nursing facility (18.1% vs. 23.4%, $p<0.0001$).

Healthcare Resource Utilization

The median total hospitalization costs in the patients without prior bariatric surgery and with prior bariatric surgery were $75,600 USD and $70,344 USD, respectively (Table 10). There was a statistically significant decrease in total hospitalization cost for patients with a history of bariatric surgery (p=0.034).

The median total LOS in the patients without prior bariatric surgery and with prior bariatric surgery were 5 days (IQR 3-8 days) and 5 days (IQR 3-7 days), respectively. Patients with a history of bariatric surgery had a statistically significant decrease in total LOS (p=0.0013).

CHAPTER 4: DISCUSSION

4.1 Very Low Energy Diets Prior to Non-Bariatric Surgery

Preoperative VLEDs have become a mainstay for patients with obesity undergoing bariatric surgery, however their use in major non-bariatric surgery remains relatively novel.[19,25] The systematic review and meta-analysis conducted as part of this Master's thesis identified all peer-reviewed data evaluating the use of preoperative VLEDs for adult patients with obesity undergoing non-bariatric surgery. Overall, 13 studies, four of which were RCTs, were included. Preoperative VLED protocols were highly variable and were used across a variety of operative settings, including hepatectomy, gastrectomy, prostatectomy, hysterectomy, and knee arthroplasty. They were well tolerated with adherence rates ranging from 94% to 100% and demonstrated an acceptable safety profile (i.e., two major adverse events across all studies). Efficacy was confirmed, as all included studies reported preoperative weight loss with VLED. Postoperative morbidity, operative time, and postoperative LOS were not significantly changed with the use of VLEDs. The risk of bias was high amongst most of the included studies.

The obesity epidemic is a well-established phenomenon in Western society.[80,81] As such, we have experienced the emergence of bariatric surgery as a burgeoning surgical sub-specialty in North America. Currently, there are over 250,000 bariatric procedures performed per year in the United States alone.[82] Preoperative care pathways are well defined and two-to-three weeks of VLEDs prior to operations are recommended as part of these by most bariatric guidelines.[34,35] Preoperative VLEDs for bariatric surgery reduce liver volume and visceral fat volume, thus allowing for a corresponding increase in maneuverability during upper gastrointestinal dissection.[20,25,38] The data included in the present review suggest that similar intraoperative benefits may be possible in patients with obesity undergoing non-bariatric surgery. For example, in an RCT evaluating a two-week VLED in patients undergoing elective laparoscopic

cholecystectomy for symptomatic cholelithiasis, blinded surgeons reported significantly increased ease of Triangle of Calot dissection in patients who had received VLED.[29] A qualitative survey conducted as part of the mixed-methods study by Griffin *et al.* evaluating a 10-week preoperative VLED with Optifast© found that over 80% of surgeons felt that preoperative VLED improved the overall ease of their operations, 75% felt that it allowed easier access to target organ, and over 50% felt that its use led to easier laparoscopic access.[28] Interestingly, reductions in operative time and intraoperative blood loss with the use of VLEDs in non-bariatric surgery were more consistently observed than in patients undergoing bariatric surgery.[19,83,84]

Similarly, adherence with preoperative VLEDs in the present study was better than adherence for preoperative VLEDs in bariatric surgery. In RCTs evaluating the use of VLEDs in bariatric surgery, patient reported adherence and tolerability ranges from 80 to 90%.[19,85] In studies relying on measured urinary ketone levels, a more objective measure, adherence is even less.[86] All of the included studies in this systematic review relied upon patient reported adherence. Self-reported adherence ranged from 94 to 100%.[29,40,57,59,61] Given the semi-elective nature of some of the included operations (i.e., surgery for oncologic disease), patients may have been more inclined to adhere to dietary recommendations as compared to patients undergoing purely elective bariatric surgery. Improved adherence could also be explained by the less stringent dietary criteria proposed by some of the included studies.[61] Nonetheless, VLEDs appear feasible across a variety of surgical settings for preoperative weight loss in patients with obesity.

Despite evidence of efficacy and feasibility, apprehension regarding the use of VLEDs in cancer patients has limited their use.[40] Yet, there are data demonstrating a lack of adverse effects on biochemical profiles and lean body mass in these patients. Barth *et al*. reported no difference in coagulation profiles between VLED and non-VLED cohorts undergoing hepatectomy.[57]

Similarly, Griffin *et al.* reported no adverse changes in markers of liver and kidney function in patients undergoing gynecological, orthopedic, and colorectal operations.[28] Inoue *et al.* evaluated patients undergoing gastrectomy for gastric cancer and demonstrated favorable changes in anthropometric measures in response to VLED.[40] Specifically, patients receiving VLED had no change in skeletal muscles mass, which is protective of postoperative morbidity in patients undergoing surgery for cancer.[87] Moreover, 50% of the studies reporting no VLED-related adverse events solely included patients undergoing surgery for cancer.[40,61] Given the currently available data regarding the use of VLEDs in cancer patients, fear of exacerbating cancer-induced catabolism should not deter practitioners from relying on VLEDs as a cornerstone for pre-habilitation of adult surgical patients with obesity undergoing operations for oncologic disease.

Pre-habilitation is a concept that has recently been applied to patients undergoing elective and semi-elective operations.[88,89] It consists of a conglomerate of lifestyle, dietary, exercise, and psychological interventions aimed at mentally and physically preparing patients for surgery.[89] RCTs including patients undergoing colorectal, thoracic, urologic, orthopedic surgery, and more have demonstrated improved functional capacity and quality of life with pre-habilitation.[88,90–92] The majority of pre-habilitation programs have been used in older, frail patients.[93] Despite the evident rise in oncologic patients with obesity, pre-habilitation protocols designed specifically for these patients are lacking. Patients with obesity have significant gains to be made with the use of pre-habilitation, given the high rates of postoperative complications associated with increasing BMI.[65] Studies combining the use of VLEDs, physical activity, and other preoperative interventions aimed at weight loss into a multi-modal pre-habilitation program could improve perioperative care for this increasingly pervasive patient population.

The strengths of the systematic review and meta-analysis that was performed herein include the generalizability of the included data to patients undergoing a wide variety of operative interventions, the comprehensive search strategy, and the rigorous methodology. These data can serve as the foundation for important future research in the rapidly expanding field of pre-habilitation. The limitations include a small number of patients in the included studies, a scarcity of comparative data, reliance on observational data, and heterogeneity of VLED protocols and included operations. There are no validated protocols for preoperative VLED in non-bariatric surgery and thus VLEDs lasted anywhere from three days to 17 weeks, allowed anywhere from 450 to 1400 calories consumed per day, and used a variety of liquid meal replacement formulas. Three studies evaluated patients undergoing hepatectomy and two studies evaluated patients undergoing gastrectomy, but otherwise there was no overlap in operations performed between studies. The pooled data and meta-analyses must be interpreted within the context of this heterogeneity. Overall, given these significant limitations, firm conclusions cannot be drawn from this systematic review and meta-analysis. Further research across a variety of well-defined surgical populations to expand the peer-reviewed literature and allow for meta-analyses of well-designed prospective studies is warranted. Specifically, a large, adequately powered RCT evaluating the impact of preoperative VLEDs prior to non-bariatric surgery on patient important outcome measures is necessary to add clarity this current body of literature.

4.2 Obesity as a Modifiable Risk Factor Prior to Colorectal Cancer Surgery

Obesity is becoming increasingly recognized as one of the major modifiable risk factors for the development of colorectal cancer.[79] For patients requiring operative intervention for their colorectal cancer, obesity is associated with worse intra- and postoperative outcomes.[8,9,94] Bariatric surgery and other means of effective preoperative weight loss may be able to mitigate

perioperative risk.[73] The nationwide database study included as part of this thesis compared clinical outcomes and healthcare resource utilization outcomes between patients with and without prior bariatric surgery undergoing resection for colorectal cancer. After propensity score matching patients with prior bariatric surgery to patients with obesity without prior bariatric surgery, we demonstrated a 25% relative risk reduction and 7% absolute risk reduction in overall in-hospital postoperative morbidity in the bariatric surgery group. Analyses of system-specific in-hospital postoperative morbidity found that patients with prior bariatric surgery had 43% relative risk reduction (5% absolute risk reduction) in gastrointestinal morbidity and 62% relative risk reductions in both respiratory (3% absolute risk reduction) and infectious (2% absolute risk reduction) morbidity. There was no clinically significant difference in median LOS, however patients with prior bariatric surgery had a $5,256 decrease in total cost of admission per patient. Patients with prior bariatric surgery were also more likely to be discharged home as opposed to a skilled nursing facility or to home nursing care.

The findings in the large database study are congruent with previous population-level analyses. Hussan *et al.* analyzed NIS data from 2006 to 2012 comparing patients with and without prior bariatric surgery undergoing colorectal cancer surgery.[73] They found a $5,374 decrease in total cost of admission, a 1.85-day short LOS, and a significantly lower likelihood of requiring post-discharge nursing care (OR 0.65, 95%CI 0.43 to 0.97) in patients with prior bariatric surgery. There was no significant difference between groups in postoperative mortality and they did report postoperative morbidity as an outcome. Thus, our data offer a more nuanced understanding of the expected postoperative course for these patients through a thorough evaluation of a variety of postoperative complications. Moreover, given the statistical methodology in the study by Hussan *et al.*, namely performing a regression analysis on a logistic

regression propensity score model which assumes the intervention and control groups are independent, we feel as though our data add significantly to the body of literature surrounding prior bariatric surgery and perioperative risk for patients undergoing colorectal surgery.[73,95] Interestingly, Hussan *et al.* performed a subgroup analysis only including patients in the bariatric surgery group with a BMI of less than 35kg/m^2 at the time of admission for their colorectal cancer surgery.[73] These data demonstrated even further reductions in perioperative morbidity in the bariatric surgery group, such as iatrogenic intraoperative injury (OR 0.30, 95%CI 0.09-0.95) and postoperative infection (OR 0.39, 95%CI 0.18-0.85), when compared to patients without prior bariatric surgery. This suggests that the predominant mechanism through which bariatric surgery reduces perioperative morbidity in patients undergoing surgery for colorectal cancer is preoperative weight loss. It is important to note, however, that these data do not simply compare patients with and without obesity, but rather evaluate the benefit of preoperative weight loss interventions for patients with obesity. Weight loss prior to surgical intervention is likely beneficial for most patients with obesity, regardless of whether their post-intervention BMI classifies them as obese or not.[18] Therefore, these data may be generalized to preoperative weight loss interventions as a whole, as interventions such as bariatric surgery, VLEDs, and GLP-1 agonists predominantly reduce fat mass, and in particular, visceral fat mass, which is of vital importance for colorectal surgery.[8,22,96,97]

When coupled with the findings in the population level retrospective analysis of the NIS included as part of this thesis, it is reasonable to assume that the significant decreases noted in gastrointestinal, genitourinary, respiratory, infectious, and overall postoperative morbidity are associated with preoperative weight loss as a result of prior bariatric surgery. This is further supported by the majority of patients in the bariatric surgery arm of the present cohort having

BMI of less than 30kg/m^2 at the time of colorectal cancer surgery (58.8%). The possibility for significant confounding must be kept in mind, however, given that the timing of bariatric surgery is unknown given the information available in the NIS database. Nonetheless, the lower BMIs are important because obesity is widely regarded as a risk factor for perioperative complications in colorectal surgery. Intraoperatively, obesity is associated with prolonged operative duration, increased blood loss, and enhanced technical difficulty for operating surgeons.[8,9,64] In particular, visceral adiposity can decrease the ease of maneuverability when operating on the lower gastrointestinal tract.[98] In large, population-level databases, however, surrogates for intraoperative difficulty are relied upon, such as operative time, estimated intraoperative blood loss, and conversions from minimally invasive surgery to laparotomy. These data were not available in the NIS. In the postoperative period, these patients are at increased risk of surgical site infections, wound dehiscence, anastomotic leak, urinary tract infection, and more.[65,99,100] Moreover, obesity presents a significant challenge in terms of postoperative mobilization.[101] Widely regarded as the primary modality through which complications such as prolonged postoperative ileus and atelectasis can be avoided, ambulation following surgery is essential.[102] If obesity precludes ambulation, it not only places patients at heightened risk of the aforementioned complications but may also prolong postoperative LOS and contribute to requiring post-discharge care through skilled-nursing facilities or homecare.[73] These are markers of prolonged and recurrent morbidity and are inevitably associated with increased healthcare spending.[103]

As the prevalence of obesity is likely to continue to rise, strategies aimed at mitigating the risks associated with obesity in the surgical setting are imperative.[80] While the benefits of weight loss secondary to bariatric surgery in these patients were highlighted with the present data, it is unreasonable to rely on bariatric surgery as a preoperative weight loss strategy for

patients with colorectal cancer. Institutions such as Cancer Care Ontario, mandate a 28-day time to treatment for newly diagnosed colorectal cancer.[104] Similar standards exist around the world.[105] Bariatric surgery may, however, be considered as a valuable addition to the preoperative optimization armamentarium for benign diseases that do not confer similar strict treatment timelines. Pertinent further investigation is under way. For the patient with obesity and a newly diagnosed operative colorectal cancer, however, we must develop other approaches to preoperative optimization. One such approach is VLEDs, which were explored in the first study of this Master's thesis. A staple for patients undergoing bariatric surgery, administration of VLEDs with liquid formulations such as Optifast® and Modifast® can effectively induce rapid weight loss.[106] The recent advent and widespread dissemination of GLP-1 agonists, such as Ozempic®, may also offer a potential intervention for achieving rapid preoperative weight loss in surgical patients with obesity.[107,108] Further investigation of these interventions, used both independently and in conjunction with one another, are required in the form of large prospective trials. Moreover, safety data pertaining to the use of these interventions in the setting of neoadjuvant therapy and other adjunctive therapies are required.

The strengths of the population level database study that was performed include the statistical methodological rigor, propensity score matching aimed at reducing the risk of confounding, and the large sample size. The NIS is a robust database and provides a reliable sample that is representative of the U.S. patient population. Yet, there are several limitations. The most notable is the risk of residual confounding. While our statistical approach with propensity score matching controlled for all measured baseline covariates, as demonstrated by the low standardized differences, there are a number of baseline variables that are unmeasured in the NIS database. For example, preoperative nutrition status, current smoking status, enhanced recovery

after surgery protocols, and neoadjuvant therapies are all important variables when evaluating perioperative outcomes and none were measured in the present study.[109–111] Another limitation is the lack of data outside of the index admission. Lack of post-discharge data limits our ability to make conclusions on other important healthcare utilization outcomes such as readmission and reoperation. Furthermore, long-term oncologic outcomes were unable to be assessed, which are highly relevant patient important outcomes. The lack of data prior to admission is a limitation given our propensity score matching methodology. Patients were matched on the likelihood of exposure to bariatric surgery, however the data utilized for matching were collected at the time of their colorectal cancer surgery. As such, we must assume that all of the patient factors that would make them eligible for bariatric surgery in the current database, would have been similar to when bariatric surgery would have been offered. For example, patients with a BMI of greater than 35kg/m^2 in the present study may have had a non-obese BMI (i.e., BMI < 30kg/m^2) several months prior to their admission for colorectal cancer surgery and thus would not have had equal likelihood of receiving the exposure of interest, which should make them ineligible for propensity score matching. Nonetheless, the likelihood of consistent drastic changes in BMI and other important patient factors over the course of months is low, therefore giving confidence in our assumptions for the propensity score model. Given the lack of pre-admission data, we were also unable to determine the temporality between bariatric surgery and colorectal cancer surgery. The magnitude of weight loss can vary based on time from bariatric surgery. This limits the ability to interpret and apply the effect sizes obtained from this study. Similarly, the interpretation of these data must be limited to understanding the benefits of preoperative weight loss for these patients, as opposed to understanding the benefits of preoperative bariatric surgery given the unreasonable expectation of using bariatric surgery as a preoperative weight loss

strategy in the setting of colorectal cancer. Given the observational nature of these data, there is a risk for selection bias such that patients that underwent bariatric surgery were potentially more likely to be able to tolerate the physiologic stress associated with surgery, thus making it more likely to have favorable postoperative outcomes. Lastly, the accuracy of the data may be somewhat limited by the lack of adherence with BMI coding by included institutions. This may result in misclassification bias. Some physicians and institutions do not routinely record BMI data for patient admissions and therefore missing data could impact the accuracy of our findings. Regardless, the sample size in the present study was robust and met our *a priori* sample size calculation threshold, thus improving confidence in the effect estimates.

4.3 Overall: Preoperative Weight Loss Prior to Non-Bariatric Surgery

The studies presented herein provide data supporting the use of preoperative weight loss techniques prior to non-bariatric surgery for patients with obesity. Specifically, the first chapter demonstrated data from a systematic review evaluating the use of preoperative VLEDs in non-bariatric surgery. While currently available evidence is heterogenous, preoperative VLEDs are likely safe and well tolerated. Moreover, they may effectively induce preoperative weight loss in patients with obesity undergoing non-bariatric surgery. They may also improve intraoperative conditions, as evidenced by consistent decreases in intraoperative blood loss with their use. However, the certainty of evidence was very low and the current body of literature pertaining to preoperative VLEDs is weak, highlighting the need for future high-quality prospective work. The second chapter presented the findings of a large retrospective nationwide database propensity-score matched cohort study suggesting that patients with prior bariatric surgery undergoing operations for colorectal cancer may experience clinically significant decreases in overall postoperative morbidity, including gastrointestinal, respiratory, and infectious morbidity, as

compared to patients with obesity without prior bariatric surgery. Furthermore, these patients may have lower total healthcare costs associated with their hospital admission at the time of their colorectal surgery. These data are limited by residual confounding, selection bias, and lack of temporal data. Nonetheless, preoperative optimization of patients with obesity prior to non-bariatric surgery through weight loss interventions may significantly improve perioperative outcomes and decrease healthcare resource utilization associated with this increasingly prevalent patient population. Ultimately, VLEDs and bariatric surgery have the potential to become a cornerstone of pre-habilitation protocols for patients with obesity undergoing elective operations for both benign and malignant disease processes. Further adequately powered prospective study is warranted.

REFERENCES

1. WHO. *Obesity and Overweight*.; 2016. Accessed October 31, 2019. http://www.who.int/mediacentre/factsheets/fs311/ en/2016
2. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic burden of obesity: A systematic literature review. *Int J Environ Res Public Health*. 2017;14(4). doi:10.3390/ijerph14040435
3. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. 2019;92:6-10. doi:10.1016/j.metabol.2018.09.005
4. Bianchini F, Kaaks R, Vainio H. Review Overweight , obesity , and cancer risk. 2002;3(September):565-574.
5. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001. *JAMA*. 2003;289(1):76-79. doi:10.1001/jama.289.1.76
6. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. *New England Journal of Medicine*. 2019;381(25):2440-2450. doi:10.1056/NEJMsa1909301
7. Rodd C, Sharma AK. Recent trends in the prevalence of overweight and obesity among Canadian children. *Can Med Assoc J*. 2016;188(13):E313-E320. doi:10.1503/cmaj.150854
8. McKechnie T, Ramji K, Kruse C, et al. Posterior mesorectal thickness as a predictor of increased operative time in rectal cancer surgery: a retrospective cohort study. *Surg Endosc*. 2022;36(5):3520-3532. doi:10.1007/s00464-021-08674-w
9. Ri M, Aikou S, Seto Y. Obesity as a surgical risk factor. *Ann Gastroenterol Surg*. 2018;2(1):13-21. doi:10.1002/ags3.12049
10. Paajanen H, Käkelä P, Suuronen S, Paajanen J, Juvonen P, Pihlajamäki J. Impact of Obesity and Associated Diseases on Outcome After Laparoscopic Cholecystectomy. *Surg Laparosc Endosc Percutan Tech*. 2012;22(6):509-513. doi:10.1097/SLE.0b013e318270473b
11. Bamgbade OA, Rutter TW, Nafiu OO, Dorje P. Postoperative complications in obese and nonobese patients. *World J Surg*. 2007;31(3):556-560. doi:10.1007/s00268-006-0305-0
12. Doyle SL, Lysaght J, Reynolds J v. Obesity and post-operative complications in patients undergoing non-bariatric surgery. *Obesity Reviews*. 2010;11(12):875-886. doi:10.1111/j.1467-789X.2009.00700.x
13. Phan K, Khuong JN, Xu J, Kanagaratnam A, Yan TD. Obesity and postoperative atrial fibrillation in patients undergoing cardiac surgery: Systematic review and meta-analysis. *Int J Cardiol*. 2016;217:49-57. doi:10.1016/j.ijcard.2016.05.002
14. Brunes M, Johannesson U, Häbel H, Söderberg MW, Ek M. Effects of Obesity on Peri- and Postoperative Outcomes in Patients Undergoing Robotic versus Conventional Hysterectomy. *J Minim Invasive Gynecol*. 2021;28(2):228-236. doi:10.1016/j.jmig.2020.04.038
15. Kazi T, McKechnie T, Lee Y, Sne N, Hong D, Eskicioglu C. The Impact of Obesity on Postoperative Outcomes following Surgery for Colorectal Cancer: Analysis of the National Inpatient Sample 2015-2019. *In Process*. Published online 2023.
16. Toner A, Hamilton M. The long-term effects of postoperative complications. *Curr Opin Crit Care*. 2013;19(4):364-368. doi:10.1097/MCC.0b013e3283632f77

17. Glazer S, Biertho L. Bariatric Surgery: Selection & Preoperative Workup . Canadian Adult Obesity Clinical Practice Guidelines. Published 2020. Accessed October 19, 2022. https://obesitycanada.ca/wp-content/uploads/2020/08/Bariatric-Surgery.pdf
18. Benotti PN, Still CD, Wood C, et al. Preoperative Weight Loss Before Bariatric Surgery. *Archives of Surgery*. 2009;144(12):1150-1155. doi:10.1001/archsurg.2009.209
19. van Nieuwenhove Y, Dambrauskas Z, Campillo-Soto A, et al. Preoperative Very Low-Calorie Diet and Operative Outcome After Laparoscopic Gastric Bypass A Randomized Multicenter Study. *Arch Surg*. 2011;146(11):1300-1305.
20. Hutcheon DA, Hale AL, Ewing JA, et al. Short-Term Preoperative Weight Loss and Postoperative Outcomes in Bariatric Surgery. *J Am Coll Surg*. 2018;226(4):514-524. doi:10.1016/j.jamcollsurg.2017.12.032
21. Alami RS, Morton JM, Schuster R, et al. Is there a benefit to preoperative weight loss in gastric bypass patients? A prospective randomized trial. *Surgery for Obesity and Related Diseases*. 2007;3(2):141-145. doi:10.1016/j.soard.2006.11.006
22. McKechnie T, Lee Y, Doumouras A, Parpia S, Bhandari M, Eskicioglu C. The Impact of Very Low Energy Diets Prior to Bariatric Surgery on Postoperative Morbidity: A Systematic Review and Meta-Analysis. Published online 2023.
23. Delbridge E, Proietto J. State of the science: VLED (Very Low Energy Diet) for obesity. *Asia Pac J Clin Nutr*. 2006;15 Suppl:49-54.
24. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)*. 2006;14(8):1283-1293. doi:10.1038/oby.2006.146
25. Ross LJ, Wallin S, Osland EJ, Memon MA. Commercial Very Low Energy Meal Replacements for Preoperative Weight Loss in Obese Patients: a Systematic Review. *Obes Surg*. 2016;26(6):1343-1351. doi:10.1007/s11695-016-2167-3
26. Mulholland Y, Nicokavoura E, Broom J, Rolland C. Very-low-energy diets and morbidity: a systematic review of longer-term evidence. *British Journal of Nutrition*. 2012;108(5):832-851. doi:10.1017/S0007114512001924
27. Atkinson RL, Dietz WH, Foreyt JP, et al. Very Low-Calorie Diets. *JAMA: The Journal of the American Medical Association*. 1993;270(8):967-974. doi:10.1001/jama.1993.03510080071034
28. Griffin SB, Ross LJ, Burstow MJ, Desbrow B, Palmer MA. Efficacy of a dietitian-led very low calorie diet (VLCD) based model of care to facilitate weight loss for obese patients prior to elective, non-bariatric surgery. *Journal of Human Nutrition and Dietetics*. 2021;34(1):188-198. doi:10.1111/jhn.12819
29. Burnand KM, Lahiri RP, Burr N, Jansen van Rensburg L, Lewis MPN. A randomised, single blinded trial, assessing the effect of a two week preoperative very low calorie diet on laparoscopic cholecystectomy in obese patients. *HPB*. 2016;18(5):456-461. doi:10.1016/j.hpb.2016.01.545
30. Pekkarinen T, Mustajoki P. Use of very low-calorie diet in preoperative weight loss: Efficacy and safety. *Obes Res*. 1997;5(6):595-602. doi:10.1002/j.1550-8528.1997.tb00581.x
31. Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P. Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obesity Reviews*. 2016;17(3):225-234. doi:10.1111/obr.12366

32. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *Can Med Assoc J*. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707
33. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. *Circulation*. 2014;129(25_suppl_2):S102-S138. doi:10.1161/01.cir.0000437739.71477.ee
34. Mechanick JI, Youdim A, Jones DB, et al. Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient—2013 Update: Cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Surgery for Obesity and Related Diseases*. 2013;9(2):159-191. doi:10.1016/j.soard.2012.12.010
35. Garneau P, Glazer S, Jackson T, et al. Guidelines for Canadian bariatric surgical and medical centres: a statement from the Canadian Association of Bariatric Physicians and Surgeons. *Canadian Journal of Surgery*. 2022;65(2):E170-E177. doi:10.1503/cjs.020719
36. Stenberg E, dos Reis Falcão LF, O'Kane M, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations: A 2021 Update. *World J Surg*. 2022;46(4):729-751. doi:10.1007/s00268-021-06394-9
37. Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P. Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obesity Reviews*. 2016;17(3):225-234. doi:10.1111/obr.12366
38. Holderbaum M, Casagrande DS, Sussenbach S, Buss C. Effects of very low calorie diets on liver size and weight loss in the preoperative period of bariatric surgery: a systematic review. *Surgery for Obesity and Related Diseases*. 2018;14(2):237-244. doi:10.1016/j.soard.2017.09.531
39. Naseer F, Shabbir A, Livingstone B, Price R, Syn NL, Flannery O. The Efficacy of Energy-Restricted Diets in Achieving Preoperative Weight Loss for Bariatric Patients: a Systematic Review. *Obes Surg*. 2018;28(11):3678-3690. doi:10.1007/s11695-018-3451-1
40. Inoue K, Yoshiuchi S, Yoshida M, et al. Preoperative weight loss program involving a 20-day very low-calorie diet for obesity before laparoscopic gastrectomy for gastric cancer. *Asian J Endosc Surg*. 2019;12(1):43-50. doi:10.1111/ases.12479
41. Castellana M, Conte E, Cignarelli A, et al. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis. *Rev Endocr Metab Disord*. Published online 2019. doi:10.1007/s11154-019-09514-y
42. NIHR. Core Outcome Measures in Effectiveness Trials. Accessed February 27, 2023. https://www.comet-initiative.org/
43. Sterne J, Hernan M, Reeves B, et al. The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool. *Cochrane Handbook for Systematic Reviews of Interventions*. Published online 2016.
44. Higgins JP, Savovic J, Page MJ, Sterne J. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Cochrane Handbook for Systematic Reviews of Interventions. Published August 22, 2019. Accessed April 29, 2023. https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0

45. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. *ANZ J Surg*. 2003;73(9):712-716. doi:10.1046/j.1445-2197.2003.02748.x
46. robvis (visualization tool). Published 2022. Accessed February 15, 2023. https://www.riskofbias.info/welcome/robvis-visualization-tool
47. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.ad
48. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. Published 2013. Accessed August 29, 2022. https://gdt.gradepro.org/app/handbook/handbook.html
49. Higgins J, Green S. Identifying and measuring heterogeneity. In: *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1. John Wiley & Sons, Inc.; 2011.
50. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135. doi:10.1186/1471-2288-14-135
51. Weir CJ, Butcher I, Assi V, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: A systematic review. *BMC Med Res Methodol*. 2018;18(1). doi:10.1186/s12874-018-0483-0
52. Lan J. The case of the misleading funnel plot. *BMJ*. 2006;333:597-600.
53. Wilson RL, Shannon T, Calton E, et al. Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. *Surg Oncol*. 2020;35:182-188. doi:10.1016/j.suronc.2020.08.006
54. Reeves JG, Suriawinata AA, Ng DP, Holubar SD, Mills JB, Barth RJ. Short-term preoperative diet modification reduces steatosis and blood loss in patients undergoing liver resection. *Surgery*. 2013;154(5):1031-1037. doi:10.1016/j.surg.2013.04.012
55. Doyle A, Adeyi O, Khalili K, et al. Treatment with Optifast reduces hepatic steatosis and increases candidacy rates for living donor liver transplantation. *Liver Transplantation*. 2016;22(9):1295-1300. doi:10.1002/lt.24495
56. Aubrey C, Skeldon M, Chapelsky S, et al. Preoperative weight loss in women with obesity in gynaecologic oncology: A retrospective study. *Clin Obes*. 2021;11(3):e12445. doi:10.1111/cob.12445
57. Barth RJ, Mills JB, Suriawinata AA, et al. Short-term Preoperative Diet Decreases Bleeding After Partial Hepatectomy. *Ann Surg*. 2019;269(1):48-52. doi:10.1097/SLA.0000000000002709
58. Goldberg RF, Parker M, Stauffer JA, et al. Surgeon's requirement for obesity reduction: its influence on weight loss. *Am Surg*. 2012;78(3):325-328.
59. Kip P, Trocha KM, Tao M, et al. Insights From a Short-Term Protein–Calorie Restriction Exploratory Trial in Elective Carotid Endarterectomy Patients. *Vasc Endovascular Surg*. 2019;53(6):470-476. doi:10.1177/1538574419856453
60. Liljensøe A, Laursen JO, Bliddal H, Søballe K, Mechlenburg I. Weight Loss Intervention Before Total Knee Replacement: A 12-Month Randomized Controlled Trial. *Scandinavian Journal of Surgery*. 2021;110(1):3-12. doi:10.1177/1457496919883812
61. Maruyama K, Shimada K, Makino A, Hisamune R, Shirota T, Gomi K. Effective and safe reduction in visceral fat using a formula diet in a short period before highly invasive endoscopic surgery – Case series. *Int J Surg Case Rep*. 2021;83:106026. doi:10.1016/j.ijscr.2021.106026

62. Pi-Sunyer FX. The Obesity Epidemic: Pathophysiology and Consequences of Obesity. *Obes Res*. 2002;10(S12):97S-104S. doi:10.1038/oby.2002.202
63. Bocca G, Mastoridis S, Yeung T, James DRC, Cunningham C. Visceral-to-subcutaneous fat ratio exhibits strongest association with early post-operative outcomes in patients undergoing surgery for advanced rectal cancer. *Int J Colorectal Dis*. 2022;37(8):1893-1900. doi:10.1007/s00384-022-04221-8
64. Yamaoka Y, Yamaguchi T, Kinugasa Y, et al. Mesorectal fat area as a useful predictor of the difficulty of robotic-assisted laparoscopic total mesorectal excision for rectal cancer. *Surg Endosc*. 2019;33(2):557-566. doi:10.1007/s00464-018-6331-9
65. Wahl TS, Patel FC, Goss LE, Chu DI, Grams J, Morris MS. The obese colorectal surgery patient: Surgical site infection and outcomes. *Dis Colon Rectum*. 2018;61(8):938-945. doi:10.1097/DCR.0000000000001085
66. Maciejewski ML, Arterburn DE, van Scoyoc L, et al. Bariatric surgery and long-term durability of weight loss. *JAMA Surg*. 2016;151(11):1046-1055. doi:10.1001/jamasurg.2016.2317
67. Dixon JB, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. *Lancet*. 2012;379:2300-2311. doi:10.1016/S0140
68. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric Surgery: A Systematic Review and Meta-Analysis. *JAMA*. 2004;292(14):1724. doi:10.1001/jama.292.14.1724
69. Lee Y, Doumouras AG, Yu J, et al. Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology*. 2019;17(6):1040-1060.e11. doi:10.1016/j.cgh.2018.10.017
70. Kim J, Eisenberg D, Azagury D, Rogers A, Campos GM. American Society for Metabolic and Bariatric Surgery position statement on long-term survival benefit after metabolic and bariatric surgery. *Surgery for Obesity and Related Diseases*. 2016;12(3):453-459. doi:10.1016/j.soard.2015.11.021
71. Whitley J, Moore KJ, Carey ET, Louie M. The Effect of Bariatric Surgery on Perioperative Complications after Hysterectomy. *J Minim Invasive Gynecol*. 2020;27(6):1363-1369. doi:10.1016/j.jmig.2019.12.011
72. Newcomb WL, Polhill JL, Chen AY, et al. Staged hernia repair preceded by gastric bypass for the treatment of morbidly obese patients with complex ventral hernias. *Hernia*. 2008;12(5):465-469. doi:10.1007/s10029-008-0381-1
73. Hussan H, Stanich PP, Gray DM, et al. Prior Bariatric Surgery Is Linked to Improved Colorectal Cancer Surgery Outcomes and Costs: A Propensity-Matched Analysis. *Obes Surg*. 2017;27(4):1047-1055. doi:10.1007/s11695-016-2421-8
74. Luhn P, Kuk D, Carrigan G, et al. Validation of diagnosis codes to identify side of colon in an electronic health record registry. *BMC Med Res Methodol*. 2019;19(1). doi:10.1186/s12874-019-0824-7
75. Storesund A, Haugen AS, Hjortås M, et al. Accuracy of surgical complication rate estimation using ICD-10 codes. *British Journal of Surgery*. 2019;106(3):236-244. doi:10.1002/bjs.10985
76. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2):150-161. doi:10.1002/pst.433

77. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107. doi:10.1002/sim.3697
78. Alves A. Postoperative Mortality and Morbidity in French Patients Undergoing Colorectal Surgery. *Archives of Surgery*. 2005;140(3):278. doi:10.1001/archsurg.140.3.278
79. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: A meta-analysis of prospective studies. *American Journal of Clinical Nutrition*. 2007;86(3):556-565. doi:10.1093/ajcn/86.3.556
80. Reilly JJ, El-Hamdouchi A, Diouf A, Monyeki A, Somda SA. Determining the worldwide prevalence of obesity. *The Lancet*. 2018;391(10132):1773-1774. doi:10.1016/S0140-6736(18)30794-3
81. Li Z, Bowerman S, Heber D. Health Ramifications of the Obesity Epidemic. *Surgical Clinics of North America*. 2005;85(4):681-701. doi:10.1016/j.suc.2005.04.006
82. English WJ, DeMaria EJ, Hutter MM, et al. American Society for Metabolic and Bariatric Surgery 2018 estimate of metabolic and bariatric procedures performed in the United States. *Surgery for Obesity and Related Diseases*. 2020;16(4):457-463. doi:10.1016/j.soard.2019.12.022
83. Gils Contreras A, Bonada Sanjaume A, Montero Jaime M, et al. Effects of Two Preoperatory Weight Loss Diets on Hepatic Volume, Metabolic Parameters, and Surgical Complications in Morbid Obese Bariatric Surgery Candidates: a Randomized Clinical Trial. *Obes Surg*. 2018;28(12):3756-3768. doi:10.1007/s11695-018-3413-7
84. Chakravartty S, Vivian G, Mullholland N, et al. Preoperative liver shrinking diet for bariatric surgery may impact wound healing: a randomized controlled trial. *Surgery for Obesity and Related Diseases*. 2019;15(1):117-125. doi:10.1016/j.soard.2018.10.001
85. Davenport L, Johari Y, Klejn A, et al. Improving Compliance with Very Low Energy Diets (VLEDs) Prior to Bariatric Surgery—a Randomised Controlled Trial of Two Formulations. *Obes Surg*. 2019;29(9):2750-2757. doi:10.1007/s11695-019-03916-2
86. Faria SL, Faria OP, Cardeal MDA, Ito MK. Effects of a very low calorie diet in the preoperative stage of bariatric surgery: A randomized trial. *Surgery for Obesity and Related Diseases*. 2015;11(1):230-237. doi:10.1016/j.soard.2014.06.007
87. Sakurai K, Kubo N, Tamura T, et al. Adverse Effects of Low Preoperative Skeletal Muscle Mass in Patients Undergoing Gastrectomy for Gastric Cancer. *Ann Surg Oncol*. 2017;24(9):2712-2719. doi:10.1245/s10434-017-5875-6
88. Carli F, Charlebois P, Stein B, et al. Randomized clinical trial of prehabilitation in colorectal surgery. *British Journal of Surgery*. 2010;97(8):1187-1197. doi:10.1002/bjs.7102
89. Carli F, Silver JK, Feldman LS, et al. Surgical Prehabilitation in Patients with Cancer. *Phys Med Rehabil Clin N Am*. 2017;28(1):49-64. doi:10.1016/j.pmr.2016.09.002
90. Ferreira V, Minnella EM, Awasthi R, et al. Multimodal Prehabilitation for Lung Cancer Surgery: A Randomized Controlled Trial. *Ann Thorac Surg*. 2021;112(5):1600-1608. doi:10.1016/j.athoracsur.2020.11.022
91. Minnella EM, Awasthi R, Bousquet-Dion G, et al. Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial. *Eur Urol Focus*. 2021;7(1):132-138. doi:10.1016/j.euf.2019.05.016

92. Santa Mina D, Hilton WJ, Matthew AG, et al. Prehabilitation for radical prostatectomy: A multicentre randomized controlled trial. *Surg Oncol*. 2018;27(2):289-298. doi:10.1016/j.suronc.2018.05.010
93. Baimas-George M, Watson M, Elhage S, Parala-Metz A, Vrochides D, Davis BR. Prehabilitation in Frail Surgical Patients: A Systematic Review. *World J Surg*. 2020;44(11):3668-3678. doi:10.1007/s00268-020-05658-0
94. Gendall KA, Raniga S, Kennedy R, Frizelle FA. The Impact of Obesity on Outcome after Major Colorectal Surgery. *Dis Colon Rectum*. 2007;50(12):2223-2237. doi:10.1007/s10350-007-9051-0
95. Eeren H v., Spreeuwenberg MD, Bartak A, Rooij M de, Busschbach JJV. Estimating Subgroup Effects Using the Propensity Score Method. *Med Care*. 2015;53(4):366-373. doi:10.1097/MLR.0000000000000325
96. Wilding JPH, Batterham RL, Calanna S, et al. Impact of Semaglutide on Body Composition in Adults With Overweight or Obesity: Exploratory Analysis of the STEP 1 Study. *J Endocr Soc*. 2021;5(Supplement_1):A16-A17. doi:10.1210/jendso/bvab048.030
97. Frikke-Schmidt H, O'Rourke RW, Lumeng CN, Sandoval DA, Seeley RJ. Does bariatric surgery improve adipose tissue function? *Obesity Reviews*. 2016;17(9):795-809. doi:10.1111/obr.12429
98. Lascano CA, Kaidar-Person O, Szomstein S, Rosenthal R, Wexner SD. Challenges of laparoscopic colectomy in the obese patient: a review. *The American Journal of Surgery*. 2006;192(3):357-365. doi:10.1016/j.amjsurg.2006.04.011
99. Geiger TM, Muldoon R. Complications following colon rectal surgery in the obese patient. *Clin Colon Rectal Surg*. 2011;24(4):274-282. doi:10.1055/s-0031-1295692
100. Qiu Y, Liu Q, Chen G, et al. Outcome of rectal cancer surgery in obese and nonobese patients: A meta-analysis. *World J Surg Oncol*. 2016;14(1). doi:10.1186/s12957-016-0775-y
101. DeMaria EJ, Carmody BJ. Perioperative Management of Special Populations: Obesity. *Surgical Clinics of North America*. 2005;85(6):1283-1289. doi:10.1016/j.suc.2005.09.002
102. Behm B, Stollman N. Postoperative Ileus: Etiologies and Interventions. *Clinical Gastroenterology and Hepatology*. 2003;1:71-90. doi:10.1053/jcgh.2003.50012
103. Legner VJ, Massarweh NN, Symons RG, McCormick WC, Flum DR. The Significance of Discharge to Skilled Care After Abdominopelvic Surgery in Older Adults. *Ann Surg*. 2009;249(2):250-255. doi:10.1097/SLA.0b013e318195e12f
104. Cancer Care Ontario. *Target Wait Times for Cancer Surgery in Ontario* .; 2016.
105. Molenaar C, Winter D, Slooter G. Contradictory guidelines for colorectal cancer treatment intervals. *Lancet Oncol*. 2021;22(2):167-168.
106. Ard JD, Lewis KH, Rothberg A, et al. Effectiveness of a Total Meal Replacement Program (OPTIFAST Program) on Weight Loss: Results from the OPTIWIN Study. *Obesity*. 2019;27(1):22-29. doi:10.1002/oby.22303
107. Zhong P, Zeng H, Huang M, Fu W, Chen Z. Efficacy and safety of once-weekly semaglutide in adults with overweight or obesity: a meta-analysis. *Endocrine*. 2022;75(3):718-724. doi:10.1007/s12020-021-02945-1
108. Ghusn W, de La Rosa A, Sacoto D, et al. Weight Loss Outcomes Associated with Semaglutide Treatment for Patients with Overweight or Obesity. *JAMA Netw Open*. Published online 2022:E2231982. doi:10.1001/jamanetworkopen.2022.31982

109. Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: A randomised clinical trial. *Lancet*. 2002;359(9301):114-117. doi:10.1016/S0140-6736(02)07369-5
110. Telem DA, Chin EH, Nguyen SQ, Divino CM. *Risk Factors for Anastomotic Leak Following Colorectal Surgery A Case-Control Study*. Vol 145.; 2010.
111. Nakamura T, Sato T, Hayakawa K, et al. Risk factors for perineal wound infection after abdominoperineal resection of advanced lower rectal cancer. *Annals of Medicine and Surgery*. 2017;15:14-18. doi:10.1016/j.amsu.2017.01.024