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Prehabilitation for Enhanced Recovery After Colorectal Surgery

Gillis, Chelsia

UNIVERSITY OF CALGARY

Prehabilitation for Enhanced Recovery After Colorectal Surgery

by

Chelsia Gillis

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Abstract

Background: Postoperative morbidity is largely the product of the preoperative condition of the patient, the quality of surgical care provided, and the degree of surgical stress elicited. Enhanced Recovery After Surgery (ERAS) minimizes surgical stress with standardized evidence-based perioperative care; yet the ERAS care elements focus mainly on the intra-and postoperative periods, which may not sufficiently enhance recovery if *preoperative* patient-related factors have not been modified before surgery. Prehabilitation programs aim to enhance recovery by targeting the preoperative condition of the patient.

Methods: This dissertation includes four manuscripts that broadly contribute to the evidence that supports the hypothesis that the patient's preoperative status modifies outcomes in colorectal surgery.

Results: First, intermediately frail and frail patients with poor functional walking capacity before surgery suffer more postoperative complications than patients with better functional walking capacity. Second, nutrition prehabilitation, with and without exercise, reduces mean length of hospital stay by two days. Third, patient interviews suggest that patients support the idea of using prehabilitation to enhance their preoperative condition. Finally, the last manuscript offers methodological suggestions to measure and analyze external variables as a means of advancing the prehabilitation literature and further enhancing patient outcomes.

Conclusion: The findings of this doctoral dissertation add to the growing body of evidence that the process of surgical *recovery begins before surgery*. Prehabilitation interventions can be applied to support better postoperative recoveries.

Keywords: Prehabilitation, pre-surgery, Enhanced Recovery After Surgery, ERAS, colorectal surgery

Preface

This doctoral dissertation comprises four manuscripts, one of which has been published, and the other three have been submitted/are ready for submission. Each of the co-authors have provided permission for the manuscripts to be included in this dissertation.

Chapter 3: Gillis C, Fenton TR, Gramlich L, Sajobi TT, Culos-Reed S.N, Bousquet-Dion G, Elsherbini N, Minnella E, Awasthi R, Liberman AS, Boutros M, Carli F. Prehabilitated intermediately frail and frail patients who cannot attain a 400m six-minute walking distance before colorectal surgery suffer more postoperative complication. (Accepted by *Journal of Nutrition Health & Aging* on May 25th, 2020)

Chapter 4: Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed S.N, Sajobi TT, Fenton TR. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: A systematic review and meta-analysis. *Gastroenterology*. 2018 Aug;155(2):391-410.e4

Chapter 5: Gillis C, Gill M, Gramlich L, Culos-Reed S.N, Nelson G, Ljungqvist O, Carli F, Fenton TR. Prehabilitation: A useful extension of Enhanced Recovery After Surgery protocols for patients. (Submitted to *Clinical Nutrition* on May 26th, 2020).

Chapter 6: Gillis C, Carli F, Gramlich L, Culos-Reed S.N, Sajobi TT, Fiest K, Fenton TR. An evaluation of third variable effects to understand who, when, why, and how patients benefit from surgical prehabilitation. (Ready for submission).

Chelsia Gillis was involved in the conception and design of the studies. Chelsia was responsible for the acquisition of the data for the meta-analysis and conducted all of the patient interviews. Chelsia was also responsible for conducting the statistical and qualitative analyses, interpreting the data, and drafting these four manuscripts. Tanis Fenton provided overall supervision to Chelsia in conducting these studies and contributed to study conception, interpretation of data and critical revisions to the manuscripts. Leah Gramlich co-supervised Chelsia and contributed to study conception, interpretation of findings, and provided critical input to the manuscripts. Nicole Culos-Reed and Tolulope Sajobi were involved in the study conception and design, provided interpretation and critical revision of manuscripts. Dr. Sajobi additionally provided statistical analysis support. All other listed co-authors contributed to the interpretation of the findings and provided critical input to the revision of the manuscripts. Additionally, Francesco Carli supplied the data for the frailty (chapter 3) and epidemiology (chapter 6) manuscripts. Katherine Buhler was involved in the data acquisition and analysis for the meta-analysis (chapter 4). Marlyn Gill was involved in the qualitative analysis (chapter 5). All authors read and approved the final manuscripts.

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Lastly, I would like to thank my family and friends who have always supported me and my demanding schedule with love and patience. I want to thank my parents, Janet & Greg Gillis, who taught me the value of hard work. I want to specifically dedicate this PhD work to my wonderful sister, Amanda Gillis, who is always looking for ways to support me, and my incredible husband, Ciaran Keane, who makes everything in life more fun.

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List of Abbreviations

6MWT: Six-minute walk test

6MWD: Six-minute walking distance

ASA: American Society of Anesthesiologists

ATP: Adenosine triphosphate

BMI: Body mass index

CI: Confidence interval

CHAMPS: Community Healthy Activities Model Program for Seniors

ERAS: Enhanced Recovery After Surgery

ERP: Enhanced Recovery Pathway

EWGSOP: European Working Group on Sarcopenia in Older People

FFM: Fat-free mass

g: Grams

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

HADS: Hospital Anxiety and Depression Scale

HRQL: Health-related quality of life

IBW: Ideal body weight

IQR: Interquartile range

kg: Kilograms

LOS: Length of hospital stay

m: Meters

mL: Millilitres

MICD: Minimal important clinical difference

min: Minute

O_2: Oxygen

ONS: Oral nutrition supplement

OR: Odds Ratio

PG-SGA: Patient-Generated Subjective Global Assessment

PaCER: Patient and Community Engagement Research

POD: Postoperative day

PRISMA: Preferred Reporting of Systematic Reviews and Meta-Analyses

RCT: Randomized controlled trail

RR: Risk ratio

SD: standard deviation

SEM: Standard error of the mean

SF-36: 36-Item Short Form Survey

WMD: Weighted mean difference

X: Independent variable

Y: Dependent variable Y

Z: Extraneous or third variable

Chapter 1: INTRODUCTION

Postoperative morbidity and mortality are largely the product of the preoperative condition of the patient, the quality of surgical care provided, and the degree of surgical stress elicited [1-3]. This doctoral research introduction will review each of these components, starting with describing the surgical stress response to provide the reader with the necessary context to appraise the potential contribution of preoperative interventions, including *prehabilitation*, to modern surgical practice and recovery.

1.1 Surgical stress

Surgical injury incites a physiological response, known as the surgical stress response. Afferent nerves and cytokines generated from the site of injury activate the hypothalamic–pituitary–adrenal axis and sympathetic nervous system producing integrated endocrine, hemodynamic, and immune responses to re-establish the body's dynamic steady-state[4]. The endocrine response alters metabolism to support energy production and synthesis of inflammatory proteins (e.g., fibrinogen, a positive acute phase protein involved in wound healing), and manifests clinically as hyperglycemia (elevated blood glucose) and catabolism (body protein breakdown)[5, 6]. The hemodynamic response maintains plasma volume, cardiovascular homeostasis, and supports an elevated oxygen demand; clinically, this response might be observed as hypertension (high blood pressure), tachycardia (elevated heart rate), urinary retention, and edema (swelling related to fluid retention). The immune response involves local and systemic inflammatory responses, mediated by a complex interplay of both pro- and anti-inflammatory cytokines, with the aim of reducing tissue damage, eliminating infections, and initiating the healing process[7].

The physiological response to surgery is believed to be an innate survival mechanism designed to re-establish homeostasis (i.e., body structure and function) as early as possible after injury; however, an inadequate, exaggerated, or prolonged stress response can lead to adverse outcomes[8]. In general, the magnitude of the stress response is believed to complement the severity of injury[9]. An open surgical approach would, therefore, elicit greater stress than a minimally invasive laparoscopic surgical approach, and a longer operating time would provoke greater stress than a shorter operating time[10, 11]. Depending on the extent of injury, surgical stress can generate a hypermetabolic response as high as 60% above basal[12]. Body protein, including skeletal, respiratory, and gut tissue, are sacrificed (catabolized) to meet elevated energy and protein synthetic needs. Cuthbertson[13] recognized the catabolism of injury in 1932 when he discovered that one month after an orthopedic-related trauma, patients continued to suffer from a negative nitrogen balance (1g of nitrogen represents 6.25g of protein). Hill et al., quantified the catabolic cost of injury in the early 1990s, identifying that two weeks post-uncomplicated gastrointestinal surgery patients lost 3kg of total body mass, which included 6% of the body's protein. The authors observed that recuperation of the body mass lost had occurred at three months after surgery *only* in the patients without any preoperative deficits (e.g., weight loss); the patients with preoperative deficits convalesced over a six-month long period [14].

Today, even with advanced surgical care, patients lose a significant amount of body protein from surgery[15]. Acute catabolic periods (e.g., induced by surgery, illness, bedrest) are believed to be responsible for what is referred to as a "catabolic crisis", in which episodes of catabolism are compounded, contributing to the development of sarcopenia (depleted muscle mass), frailty (vulnerability to stressors), and eventually a loss of independence[16]. Older adults are particularly vulnerable to acute periods of catabolism because they are less likely to regain the quantity and/or quality of body protein lost [17, 18]. It is thus unsurprising that modern perioperative interventions aim to moderate the surgical stress response to minimize the negative effects produced, including catabolism, while maintaining the natural purpose of the stress response, which is to return the body to a state of “normal” structure and function (i.e., homeostasis)[19].

1.2 Quality of surgical care

Traditional surgical care includes unnecessary elements that amplify the surgical stress response[20]. That is, some traditional elements generate more stress than is required to achieve homeostasis. Fasting the night before surgery is one such example. Fasting was first introduced in the 19th century when a man died from pulmonary aspiration after the initiation of chloroform anesthesia[21]. Overnight fasting acts as a stressor, exaggerating the body’s efforts to return to homeostasis and augmenting the catabolic response to surgery[22]. International standards for anesthesia[23, 24] now endorse the consumption of food for up to 6 hours and clear liquids for up to 2 hours before elective surgery. Yet many institutions continue to implement traditional fasting practices[25].

The Enhanced Recovery After Surgery (ERAS) Study Group was formed in 2001 by a group of academic surgeons in Europe with the aim of establishing a best-practice care pathway for elective colonic surgery that would decrease variability in care and improve patient outcomes[26]. This group aimed to replace unnecessary traditional surgical care elements with evidence-based elements that attenuate the negative aspects of the surgical stress response. Today, the ERAS® Care System includes: the ERAS® evidence-based protocol, the ERAS® Implementation Program, and the ERAS® Interactive Audit System for several surgical specialties (e.g., colorectal[27] and gynecology[28]).

The ERAS protocols consist of multimodal, multidisciplinary elements that are carried out in the perioperative period (i.e., around the time of surgery). The ERAS elements, such as the use of minimally invasive surgical techniques, are targeted at minimizing the stress response to surgery to maintain homeostasis[26], so that the patient avoids serious catabolism and consequent losses of body protein[29], strength[30], and function[31, 32]. As an example, postoperative insulin resistance is a typical consequence of the surgical stress response that has been observed to persist for weeks after uncomplicated surgery[6, 31]. Presence of insulin resistance (the incapacity of insulin to facilitate the uptake of glucose into cells) induces several postoperative challenges related to the disruption of normal metabolism, including hyperglycemia and exaggerated catabolism (since amino acids are directed toward fuel pathways rather than anabolic pathways)[6]. Many of the ERAS elements, therefore, are aimed at directly or indirectly affecting the action of insulin. Collectively, these elements (e.g., avoiding fasting, treatment with oral carbohydrate loading, minimally invasive surgery, early postoperative mobilization, and pain control with epidural or spinal analgesia as appropriate) promote insulin sensitivity and enhance nutrient utilization so that body protein is spared[31].

An early meta-analysis of six randomized controlled trials (RCT) of ERAS vs. traditional care in colorectal surgery identified that the ERAS protocol did not compromise patient safety as defined by length of stay, postoperative complications and 30-day hospital readmission[33]. The safety and efficacy of using ERAS protocols in colorectal surgery have since been replicated in single centers worldwide[34, 35], in multinational multicenter trials[36], and in several other meta-analyses of RCTs[37, 38]. In fact, ERAS care for colorectal surgery has consistently demonstrated improvements in recovery, resulting in reduced length of stay[39-41], complications[39-41], and costs[41, 42]. Although studies in colorectal surgery continue to dominate the ERAS literature, a recent meta-analysis of 39 studies (n=6511; 14 studies were RCTs) in major abdominal surgery patients (excluding colorectal) found that ERAS care decreases length of hospital stay by 2.5 days (95% confidence interval, CI: 1.8-3.2 days, $P < 0.001$) and is protective against complications (odds ratio, OR: 0.70, 95% CI: 0.56-0.86, $P = 0.001$)[39] when compared to traditional care.

By standardizing perioperative care with evidence-based protocols that also reduce physiological stress and attenuate perturbations in metabolism (e.g., minimize catabolism), ERAS improves surgical outcomes [39, 43]. Yet, the ERAS elements focus mainly on the intra-and postoperative periods, which may not be sufficient if *preoperative* patient-related factors, such as malnutrition, have not been modified before surgery.

1.3 Preoperative condition of the patient

Despite the implementation of ERAS care, complications post-colorectal surgery remain as high as 45%[40] and most patients do not return to their baseline level of function even 8 weeks after surgery[44]. These poor patient outcomes might be the result of unchecked preoperative patient-related factors. Individual patient characteristics can influence the natural response to surgical injury, such that the response is impaired, exaggerated, or prolonged, and thus more likely to produce adverse outcomes[8]. The following section will detail how the preoperative condition of the patient influences postoperative outcomes.

1.3.1 Cardiopulmonary reserve and exercise capacity

Major surgery increases oxygen consumption by as much as 50%[45] to meet a heightened global oxygen demand, including the elevated post-surgical metabolic needs of the liver and muscle[46]. The cardiorespiratory system must function to meet this additional oxygen demand, and the inability to increase cardiac output to meet systemic oxygen requirements is thought to be the cause of a range of serious postoperative complications, including myocardial infarction[47-51]. A compromised systemic blood supply is linked to surgical site infections (immune proteins, such as neutrophils, are part of primary defense and must migrate to the wound)[52], and the failure to oxygenate gut tissues is a hypothesized culprit in the development of anastomotic leakages post-colorectal surgery[53]. It is for this reason that the assessment of adequate cardiorespiratory performance has long been used to identify high risk patients requiring modified perioperative management[54].

Cardiopulmonary exercise testing provides an objective measure of cardiorespiratory performance under conditions of stress (i.e., exercise capacity) through the measurement of oxygen uptake at increasing levels of physical work [51]. Poor exercise performance/capacity (also referred to as exercise intolerance or the inability to perform physical exercise as expected[55]) can be the result of inadequate cardiac reserve, myocardial ischemia, age or disease-related deconditioning, and/or poor pulmonary reserve[56]. Before surgery, poor exercise capacity is suggestive of a future inability to increase cardiac output to meet elevated post-surgical demands[57]. As an example, Gerson et al.,[58] found that the inability to perform 2 minutes of bicycle exercise to raise the heart rate above 99 beats/min (i.e., exercise intolerance) before elective noncardiac surgery independently predicted perioperative complications. Furthermore, Older et al.,[57] used cardiopulmonary exercise testing to identify surgical risk in elderly patients with poor exercise capacity before abdominal surgery. Specifically, the authors measured oxygen uptake at the point during exercise where aerobic metabolism alone was no longer sufficient and anaerobic metabolism begins to predominate (i.e., the anaerobic threshold, which generally reflects physical fitness[46]). The authors identified that 30% of patients tested had an exercise anaerobic threshold of <11ml oxygen/kg/min and these patients had a high mortality rate of 18%, while the patients with an anaerobic threshold >=11ml/kg/min before surgery had a mortality rate of just 0.8%[57]. The patients with a low anaerobic threshold demonstrated poor ability of their cardiorespiratory system to deliver oxygen under stress both before and after surgery[46, 57].

Cardiorespiratory performance contributes to a *physiologic capacity* – defined as the capacity for organs and biological systems to function under stress[59]. A minimum physiological threshold is required to independently carryout daily tasks (i.e., activities of daily living) and to perform physical exercise[60 61]. For a patient with poor preoperative exercise capacity, the physiological challenge of surgery can easily surpass their physiological threshold and compromise functional independence. In fact, the development of functional impairments and iatrogenic disability -- referred to as “hospitalization associated disability”[62] – are not uncommon occurrences in older adults who have had surgery[63] or require hospitalization[64]. The preoperative condition of the patient (i.e., low physiologic capacity; elaborated further in section 1.3.2), the surgical stress elicited, and the post-surgical immobility typically associated with traditional surgical care and hospitalization[64] all contribute to this phenomenon[65]. Assessment of cardiorespiratory performance is thus an important preoperative consideration to identify those who are at risk of surgical complications as well as those who are at risk of postoperative functional decline.

Altogether, without adequate cardiorespiratory capacity to sustain the physiological response to stress, a patient might not be able to compensate for the added demands of surgery and could experience poor surgical outcomes as a result. Exercise capacity thus represents a margin of safety that is not only protective against the development of postoperative complications but also provides protection against the development of functional impairments (Figure 1). Values of exercise capacity derived from cardiopulmonary exercise testing[66] have been demonstrated to predict all-cause postoperative mortality[67], prolonged hospital stay[68], and survival after major surgery[69, 70]. Comparably, preoperative functional impairment [71] or slow walking speed before elective colorectal[44, 72], cardiac [73], and non-cardiac major surgery[74] have been found to associate with higher postoperative morbidity and prolonged recovery of baseline function[71, 75, 76].

Figure 1: Cardiopulmonary reserve & exercise capacity

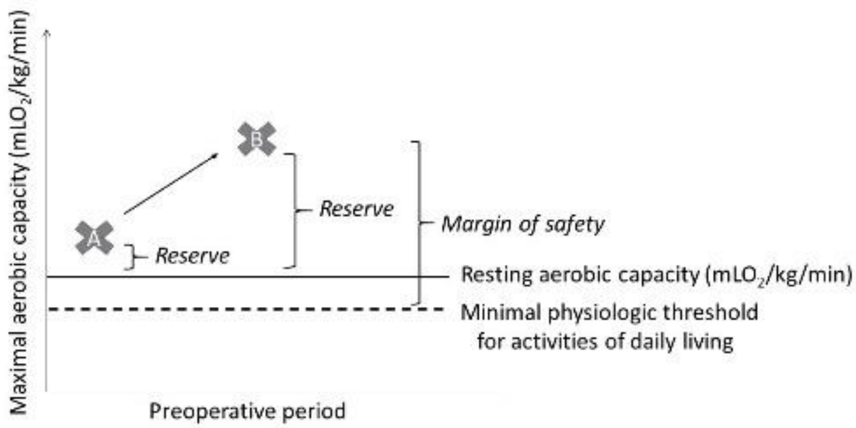

Figure legend: Hypothetical patients (patient A and B) participate in cardiopulmonary exercise testing before surgery. Patient A exhibits poor exercise capacity, has little cardiorespiratory reserve (resting – maximal), and is perilously close to the minimal physiologic threshold required for functional independence. For this patient, a decompensating event as simple as bedrest post-surgery could threaten functional independence. Patient B has excellent exercise capacity and cardiorespiratory reserve, contributing to a margin of safety that would likely permit this patient to withstand surgical stress without compromising functional independence. Ideally, patient A would improve their cardiorespiratory status before surgery, similar to patient B, and thus be a better candidate for surgery who is more likely to experience an uneventful postoperative course (described further in section 1.4: Prehabilitation & functional capacity).

1.3.2 Energy reserve and metabolic capacity

The physiological response to surgical injury incites the catabolism of energy reserves (glycogen, body protein, and fat mass) to sustain energy production and to provide substrates for the inflammatory and healing processes involved in convalescence (e.g., synthesis of acute phase proteins)[6]. A patient with poor energy reserves before surgery, as a result of malnutrition and/or sarcopenia, is at risk of deteriorating their already compromised reserves to support this stress-induced mobilization of substrates[77]. Additionally, poor energy reserves contribute to a *low physiologic reserve* (as seen in frailty) and this physiological deficit influences a patient's ability to mount a "typical" stress response to cope with the surgical stress elicited [78]. As such, the physiologic response to surgery can negatively affect patients with low preoperative reserves and is also affected (i.e., modulated) by the patients' reserve status.

A patient with adequate *physiologic reserve* is believed to have the *physiologic capacity* to endure stress and return to normal structure and function (i.e. homeostasis) within a relatively short period of recovery. At the cellular level this might be represented as excess metabolic capacity[79]. That is, the ability to readily exceed normal basal metabolic function when needed to meet heightened metabolic demands. Decline or exhaustion (e.g., from disease, illness, and/or age) of the excess capacity of metabolic pathways (e.g., glucose utilization in muscle cells, including oxidation of glucose to produce adenosine triphosphate, ATP [80]) and biochemical structures (e.g., mitochondria, an organelle in which cellular respiration takes place to produce ATP[81]) might contribute to diminished physiologic reserve, and thus the physiologic capacity of organs and biological systems to function under stress[79].

Importantly, while we might refer to body protein as a "reserve", this is not strictly correct. Stored glucose (glycogen) and excess body fat represent true energy reserves. Body protein, however, including somatic and visceral proteins, serve a specific function[82]. Catabolism of body protein thus limits function[82, 83]. A patient with depleted body protein presents to surgery with compromised physiologic capabilities (i.e., body function), which may impede their ability to cope with the surgical stress response (i.e., physiologic dysfunction). Additionally, patients with depleted body protein have less "reserve" to sacrifice to the cause of injury without serious concomitant losses in function[18, 84, 85]. As a result, patients with sarcopenia, for instance, might be more susceptible to the negative consequences of postoperative catabolism, which include physiological losses and functioning of skeletal, respiratory and gut tissues[83, 85, 86]. Clinically, theses losses are represented as reduced muscular function[87], impaired ability to cough post-surgery (increasing susceptibility to respiratory infections[88]) and impaired gut mucosal barrier (increasing susceptibility to infections[89]). Exacerbation of physiologic dysfunction[84], mediated by compounding stressful events such as surgery[17, 18], may be an underlying mechanism contributing to the poor survival observed with sarcopenic patients[77 90]. A powerful example of such was presented by Martin et al., in which the authors identified that in a cohort of 1473 lung and gastrointestinal cancer patients exhibiting weight loss, low muscle mass, and low muscle density (an indicator of poor muscle quality) the median overall survival at the end of study was just 8.4 months, compared with 28.4 months in the cohort of patients who had none of these characteristics[90].

Another patient group that presents to surgery with poor physiologic reserve and function are patients with malnutrition. Nutrition deprivation depletes energy reserves (i.e., body fat and protein), and a chronically deficient supply of nutrients deprives the body of the essential substrates required to fuel normal metabolic function[91]. In order to survive, the body adapts, making cellular and hormonal adjustments, including reduction of the basal metabolic rate[86], which, collectively, reduces function but slows deterioration[8, 92]. Severely malnourished children with an infection, for instance, often do not express overt signs of infection, including fever[8]. In surgery, the impaired physiological effects associated with malnutrition are represented as a blunted inflammatory response to injury[8, 93] and immune incompetence[94]. This dysfunctional response is noteworthy because adequate inflammatory and immune responses are required for wound healing[95] and for protection against infection[96]. Yet, activation of the necessary inflammatory and immune responses to defeat infection and restore normal structure and function (i.e., homeostasis) is “metabolically expensive”, such as synthesis of acute phase proteins involved in wound healing, and the malnourished patient is “metabolically poor”. A failure to establish homeostasis in response to stress, as a result of decreased physiological reserve and function, might contribute to the observed vulnerability of malnourished patients to experience adverse events following surgery [78, 97], including greater odds of developing a complication from surgery[98-102], more frequent readmissions to hospital after surgery [99, 103-105], longer hospital stays [98, 99, 102-104], and greater risk of mortality [99, 104, 106, 107].

Deficient energy reserves and reduced metabolic capacity, as seen in malnutrition and sarcopenia, culminate in the form of frailty. While there is no accepted definition of frailty, the definition provided by Campbell is comprehensive, “a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure. As a consequence, the frail person is at increased risk of disability and death from minor external stresses”[108, 109]. Frail patients are believed to have reduced physiological reserve, and thus reduced physiological capabilities *across multiple organ systems*, which ultimately reduces the natural complexity of their biologic systems[110]. A stress response necessitates dynamic coordinated actions and adaptation within and across several complex physiological systems to restore homeostasis. As a result, the compensatory mechanisms attempting to establish homeostasis in a frail patient might fail. A frail patient, for instance, might respond to injury with impaired action (limited in strength, rapidity, range) to fight infection or impaired ability to maintain tissue perfusion within acceptable limits[78]. Equally possible, a reduction in physiological complexity might manifest as a prolonged or exaggerated stress response due to dysregulated signaling pathways involved in homeostatic control[110]. Any preoperative condition that produces a dysfunctional stress response, and hence the impaired ability to restore homeostasis, has the potential to enhance postoperative morbidity. In fact, several studies have identified that frailty is an independent risk factor for serious postoperative complications[111-113], mortality[111, 113], prolonged length of hospital stay[111], and institutional discharge[112, 114].

Altogether, a patient with adequate physiologic reserve and physiologic capacity can draw upon these reserves during times of stress, which should enable adequate functioning of organs and biologic systems to restore homeostasis. As an example, an older adult with adequate *reserve* and excess metabolic *capacity* can *function* to generate ATP for muscle contraction in response to the physiologic stress of lifting groceries. In contrast, a patient with low physiologic reserve might not be able to extend metabolic capacity to cope with the metabolic challenge of a stressor. As an example, a sarcopenic cancer patient with atrophied cardiac muscle[115] (i.e., reserve) has reduced cardiomyocytes for production of ATP (i.e., reserve capacity), which might impact the contractile function needed to maintain tissue perfusion in response to the workload of surgical stress[116]. Physiologic reserve capacity is thus believed to represent a margin of safety that protects the patient from deteriorating beyond the threshold of physiologic integrity that maintains functional independence in response to a physiological challenge.

In summary, preoperative patient characteristics manifest differential capacities to respond to stress and to recover from injury. A patient’s physiologic reserve is believed to moderate the response to injury and influence recovery. The relationship between physiologic reserve and surgical stress is represented in Figure 2.

Figure 2: Physiologic reserve & surgical stress

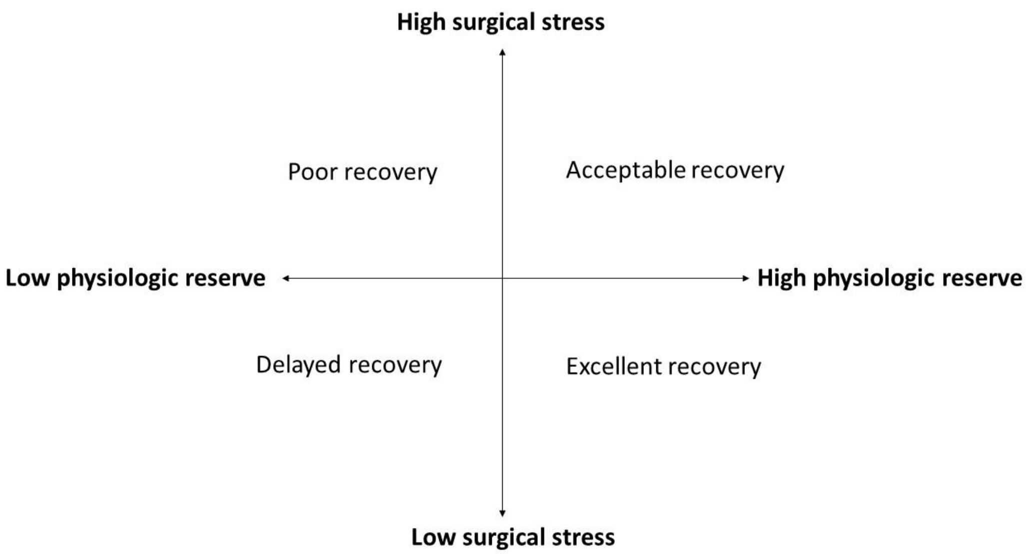

Figure legend: A patient with adequate preoperative physiologic reserve who has surgery under ERAS care, which minimizes surgical stress, would be expected to experience an excellent recovery. If this same patient with adequate preoperative physiologic reserve has surgery using a traditional model of care, which is not focused on minimizing surgical stress, the patient would still be expected to experience an acceptable recovery. However, a patient with low physiologic reserve might exhibit an impaired response to surgical stress (e.g., a malnourished patient might have insufficient reserve to support the inflammatory response necessary for healing) and/or reach the threshold of decompensation earlier than patients with an adequate reserve (e.g., insufficient cardiorespiratory reserve to sustain oxygen delivery at the required level to meet postoperative metabolic demands), leading to a poor or delayed recovery.

1.4 Prehabilitation and functional capacity

The physiological response generated by surgical injury is a predictable impending burden awaiting surgical patients. Prehabilitation programs aim to prepare patients physically and emotionally to withstand the stress of surgery[117]. Although prehabilitation programs vary[118], the focus of this review is on multimodal prehabilitation programs, including nutrition, exercise, and psychological strategies, that aim to enhance functional capacity before surgery to facilitate earlier return of functional capacity post-surgery[117]. Maintaining function is considered the most important target by both clinicians[119] and patients[120]. The following section provides evidence that supports the use of preoperative interventions to modify physiologic reserve, enhance functional capacity, and mitigate poor surgical outcomes.

Functional capacity is the ability to perform and cope with activities of daily living, which requires an integrated effort of the cardiovascular, pulmonary, and skeletal muscular systems[121]. Unimpaired functional capacity necessitates a minimal physiologic reserve[60], which is influenced by exercise[122], nutritional[123], and cognitive/psychological[124] reserve statuses, in a reciprocal-type relationship. As an example, cognitive reserve (i.e., mental “fitness”) contributes to an overall integrated physiologic reserve, which influences functional capacity, and in turn, enhances cognitive reserve[125, 126]. Put simply, functional capacity is affected by mental wellness, and also contributes to mental wellbeing[127-131]. Therefore, the definition of functional capacity is all encompassing and recognizes the interconnectedness among physical, psychological, and nutritional (metabolic) statuses.

The exercise component of multimodal prehabilitation aims to enhance physiologic reserve and functional capacity of the cardiorespiratory (i.e., exercise capacity) and musculoskeletal (i.e., strength, body composition) systems[132]. Habitual physical activity and exercise are well known to preserve physiologic reserve[133] as well as to build functional capacity[134, 135]. Several prospective studies have identified that exercise-training can be carried out successfully in the waiting period before surgery to improve functional capacity[136, 137]. In a small nonrandomized study of patients with advanced rectal cancer, a six-week structured exercise training program significantly improved exercise capacity (oxygen uptake at the lactate threshold, indicative of the same point represented by the anaerobic threshold and is a reflection of physical fitness), measured with cardiopulmonary exercise testing, post-neoadjuvant therapy and prior to surgery[137]. Additionally, several meta-analyses have identified positive outcomes when exercise interventions were applied as part of a multimodal intervention before surgery[43, 138]. A recent meta-analysis of 8 RCTs among 422 major abdominal surgery patients found that preoperative interventions that included physical exercise produced a protective effect against postoperative morbidity (OR 0.52; 0.30 to 0.88; P = 0.01), and, in particular, pulmonary complications (OR 0.37; 0.20 to 0.67; P = 0.001), compared to standard care[138].

In addition, exercise improves metabolic flexibility, defined as the ability to adapt metabolism (e.g., substrate use and storage) in response to substrate availability and requirements[139]. Exercise-training improves exercise performance, in part, through enhanced capacity of skeletal muscle to oxidize both fatty acids and glucose to fuel performance (i.e., metabolic flexibility)[140]. Before surgery, a disturbed glucose metabolism that raises blood glucose concentration abnormally, such as insulin resistance, is prevalent in patients without a prior history of diabetes[141-143] and is representative of a metabolically inflexible state. Possession of a metabolically flexible state is likely to support superior surgical outcomes because of the ability to respond to stress with an adaptive metabolic response that efficiently maintains energy homeostasis without serious consequent losses of body protein. In fact, a stable isotope study identified that whole body protein catabolism on the second day after colorectal cancer surgery was 50% greater in diabetic compared to non-diabetic patients[144]. Preoperative glycemia and insulin resistance are associated with serious postoperative complications[143, 145, 146] and 30-day mortality[147].

The nutrition component of multimodal prehabilitation primarily serves to prevent and treat malnutrition[148]. Preoperative identification and treatment of malnutrition have long been known to improve surgical outcomes[85, 86]. A meta-analysis of 15 RCTs, including 3831 malnourished patients undergoing a variety of surgical procedures, identified that perioperative nutritional support was significantly effective at decreasing the incidence of complications and reducing length of hospital stay by approximately two days [149]. Given that surgical patients have plenty of "opportunity" to develop malnutrition throughout the perioperative period [150], pre-emptive nutrition strategies may also be of value. As an example, cancer patients without any obvious signs of malnutrition randomized to 14 days of preoperative oral nutrition supplementation, versus standard of care, suffered significantly fewer minor and serious complications[151]. Interestingly, as the patients awaited surgery, a decline in both serum albumin and total lymphocyte count was observed in the control but not in the intervention group[151]. These findings suggest that nutritional support can exert a positive effect, in part, through maintenance of physiologic function. Several prospective studies corroborate these results[152, 153]. An older study conducted in elderly patients who had been hospitalized for at least three weeks and were then randomized to receive nutrition supplementation or to remain on hospital food alone identified that the intervention group experienced better immunological competence (as measured by skin reactivity to intracutaneous injection of three antigens at 8 and 26 weeks compared to baseline, and higher immunological competence compared to the control at 26 weeks)[152]. In a study of malnourished patients with and without inflammatory bowel disease, mitochondrial complex I (the first complex of the electron transport chain) activity measured in peripheral blood mononuclear cells (immune cells: lymphocytes, dendric cells and monocytes) was lower in the malnourished subjects (independent of disease) as compared to the age-matched healthy controls[153]. Providing nutritional support (enteral, parenteral, oral nutrition supplements) for one-week increased complex I activity significantly in the malnourished patients[153] and activity returned to normal after 1 month of nutrition support[154].

The secondary aim of multimodal nutrition prehabilitation is to augment exercise gains (exercise capacity, body composition, strength) to enhance physiologic reserve and functional capacity[148]. Provision of key anabolic nutrients, including dietary protein, support anabolic gains[155]. Dietary protein supplies amino acids, which serve as the building blocks for body protein (i.e., “reserve”)[156]. Although there is evidence of reduced anabolic capacity in advanced cancer patients, a substantive dose of amino acids has been found to overcome anabolic failure and stimulate protein anabolism in this group[155, 157, 158]. In fact, a strong positive linear relationship between net protein anabolism and the amount of essential amino acids available in systemic circulation has been observed both in patients with advanced cancer and healthy age-matched controls, independent of muscle mass loss, recent weight loss, and disease status[159]. While dietary protein supplies amino acids (i.e., substrate), several micronutrients (vitamins, minerals) are essential components of energy and protein metabolism. Pyridoxine (vitamin B6), for instance, is a coenzyme involved in nitrogen transfer between amino acids and thus plays a role in protein building and breakdown[156]. A micronutrient deficiency could potentially inhibit anabolic potential of the dietary protein consumed and thus serves as an additional rationale for nutrition provision.

The psychological component of prehabilitation interventions aim to support behavior change (i.e., reinforce exercise and nutrition interventions) and promote mental “fitness” before surgery[160] . Preoperative anxiety, depression, fear and psychological stress are associated with worse surgical outcomes, including length of hospital stay[160, 161]. A possible explanation for the poor clinical outcomes observed in this group might be that anxious patients have been found to require more anesthesia than less distressed patients[162, 163], which could augment anesthesia-related side effects, including nausea[161], that delay hospital discharge. A meta-analysis of prospective preoperative psychological interventions, including relaxation techniques, guided imagery, stress management, and psychotherapeutic interventions, in 605 cancer patients implemented 1-2 weeks before surgery, identified that patient-reported outcomes before and after surgery were enhanced with psychological prehabilitation[164]. A recent Cochrane review of randomized controlled trials of adult participants undergoing elective surgery (n=10,302) reported there was evidence (low quality) that psychological preparation techniques (including provision of procedural information, behavioral instruction, and cognitive interventions) were associated with lower postoperative pain, length of stay and negative affect (such as anxiety, depression, mental health) compared with controls[165].

Importantly, while several meta-analyses[166, 167] and randomized trials[168, 169] on uni-[167] and multimodal[169] prehabilitation have reported both clinical and functional benefits, few studies have identified clinical benefits with the use of prehabilitation in an ERAS setting[170]. Given that ERAS care attenuates surgical stress and independently improves clinical outcomes (see section 1.2), it might not be possible to further enhance clinical outcomes with prehabilitation. For instance, the median length of stay post-colorectal cancer surgery in a prehabilitation vs. rehabilitation trial at a site with high compliance to the ERAS elements[171] was 4 days for both groups[168]. It is unlikely that the median length of stay can be reduced much further after colorectal surgery. Ample evidence, however, suggests that prehabilitated patients exhibit *surgical resilience* under ERAS care[15, 44, 168, 172]. Surgical resilience can be defined as the time it takes to return to homeostasis following surgery[173]. A retrospective analysis of pooled individual patient data from prehabilitation trials in colorectal cancer surgery identified that ERAS patients who participated in multimodal prehabilitation preserved their lean body mass at both 4 and 8 weeks after surgery, compared to the ERAS patients who received rehabilitation[15]. This is an anabolic benefit that has not been observed at other sites employing ERAS care without prehabilitaiton[29]. A study following the outcomes of an institutional change in surgical practice from traditional to ERAS care, observed that patients following ERAS maintained lean body mass 8 days after surgery compared with patients receiving traditional surgical care, but did not maintain these gains at 28 days after surgery[29]. Additionally, a prospective study in colorectal cancer patients indicated that twice as many prehabilitated patients recovered their functional walking capacity, as defined by six-minute walk test (a practical measure of functional capacity), at 8 weeks after surgery, compared with the patients who received ERAS care alone[44]. These findings suggest that prehabilitated patients are more resilient, with a superior return to normal body structure and function, even within the context of modern surgical care practices of ERAS (Figure 3).

Figure 3: Enhanced surgical care trajectory

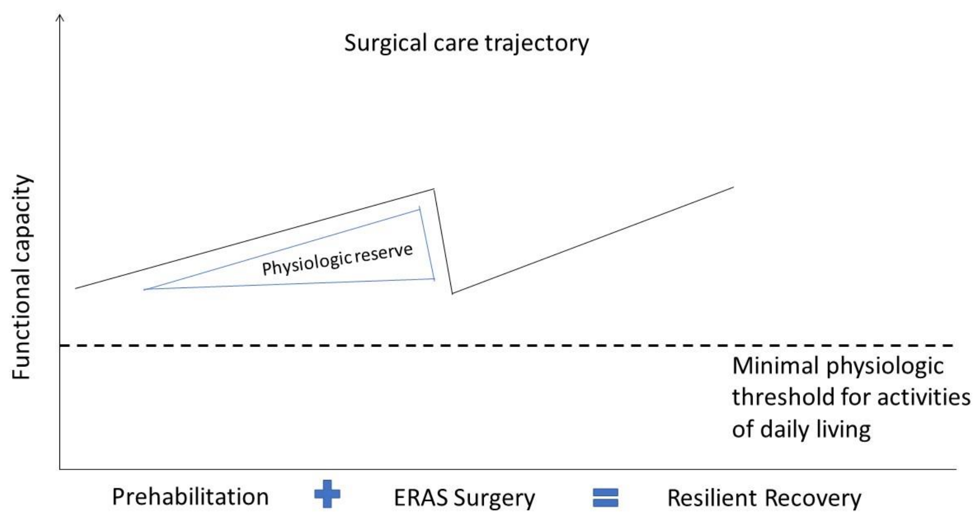

Figure legend: Prehabilitation aims to fortify physiologic reserve and enhance functional capacity before surgery. Enhanced Recovery After Surgery (ERAS) minimizes the physiological response generated by surgical injury. Together, these two programs promote a holistic surgical recovery through attainment of surgical resilience: an earlier return to pre-surgery body structure and function.

This doctoral research introduction presented the biological rationale, theory, and evidence to describe how the preoperative condition of the patient contributes to postoperative morbidity. Any preoperative condition that prevents a patient from tolerating the physiological stress of surgery (e.g., poor cardiopulmonary reserve, sarcopenia), impairs the stress response (e.g., malnutrition, frailty), and/or augments the catabolic response to stress (e.g., insulin resistance) are risk factors for poor surgical outcomes. Prehabilitation programs aim to modify these conditions to promote optimal surgical recovery.

1.5 Colorectal surgery

This doctoral research pertains to colorectal surgery. Colorectal surgeries involve resections of the colon and/or rectum and comprise the largest subspecialty of general surgery. In Alberta, approximately half of the colorectal surgeries performed are related to cancer and the other half comprise non-cancer surgeries, including the treatment of inflammatory bowel disease (IBD)[174]. Colorectal cancer is currently the third most diagnosed cancer in Canada[175]. Colorectal cancer is the second leading cause of death from cancer in men and the third leading cause of death from cancer in women in Canada. It is estimated that 1 in 32 men and 1 in 37 women will die from colorectal cancer[175]. The prognostic and predictive factors for colorectal cancer include the following: cancer stage, surgical margins, cancer cells in lymph and blood vessels, carcinoembryonic antigen, bowel obstruction or perforation, colorectal cancer grade, type of tumor, microsatellite instability, KRAS and BRAF gene mutations[175]. The prevalence of IBD in Canada equates to approximately 1 in every 150 Canadians[176]. The prognostic factors for IBD are not well defined and the disease course is highly variable[177].

Chapter 2: RESEARCH OBJECTIVE

Based on review and synthesis of the evidence, the following global hypothesis is proposed to describe the underlying process by which individual patient-related factors influence surgical outcomes: the patient's preoperative status modifies surgical outcomes through mediation of the surgical stress response (Figure 4).

Figure 4: Perioperative interventions modify surgical outcomes through mediation of the surgical stress response

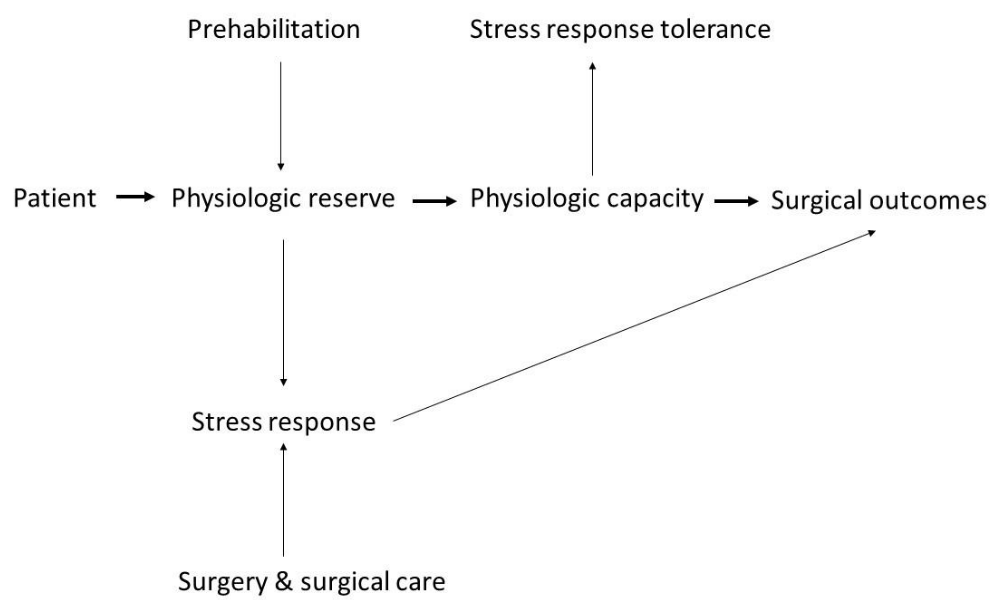

Figure legend: Patients present to surgery with unique *physiologic reserves* and *physiologic capacities*. A patient's physiologic reserve can alter (i.e., mediate) surgical stress: a patient with adequate physiologic reserve will likely generate a typical surgical stress response, while a patient with inadequate physiologic reserve is likely to generate an impaired stress response (overexpressed or underexpressed responses to injury). A patient with malnutrition, for instance, may generate an impaired inflammatory response, making them more susceptible to infection.

The surgery and quality of *surgical care* provided (e.g., Enhanced Recovery After Surgery) is an additional mediator of the surgical stress response. The degree of surgical stress elicited influences surgical outcomes and timing of recovery. However, whether the magnitude of surgical stress elicited is “critical” is dependent, in part, on the patient and their physiologic capacity. That is, the physiological response to surgical injury may surpass the patient’s threshold of tolerance (i.e., exceed physiologic reserve capacity), leading to further injury. As an example, a patient with sarcopenia (depleted body protein) would have a lower threshold for what would be considered a “critical” catabolic response, in which the stress-induced degradation of body protein further depletes their compromised reserve to the point of threatening functional independence. The preoperative condition of the patient (physiologic reserve and capacity) is thus a moderator of surgical outcomes through mediation of surgical stress. *Prehabilitation* aims to enhance recovery by targeting the preoperative condition of the patient.

Overall research objective

This doctoral research will broadly contribute to the body of evidence that either supports or refutes the hypothesis that the patient’s preoperative status modifies surgical outcomes.

Specific research objectives

This doctoral research will address the following four specific research objectives for patients undergoing *colorectal surgery*:

1. analyze the impact of preoperative frailty on clinical and functional outcomes.
2. evaluate the impact of preoperative nutrition repletion on clinical and functional outcomes.
3. describe the preoperative priorities and needs of patients.
4. create a tutorial that applies epidemiological principles to preoperative research design so that future research can be designed to answer important preoperative questions, including who benefits most from preoperative interventions.

Chapter 3: Prehabilitated intermediately frail and frail patients who cannot attain a 400m six-minute walking distance before colorectal surgery suffer more postoperative complications

Chelsia Gillis[1], Tanis R Fenton[1,2], Leah Gramlich[3], Tolulope T Sajobi[1,4], S. Nicole Culos-Reed[5], Guillaume Bousquet-Dion[6], Noha Elsherbini[7], Enrico M Minnella[6], Rashami Awasthi[6], A Sender Liberman[8], Marylise Boutros[9], Franco Carli[6]

[1]Cumming School of Medicine, Department of Community Health Sciences, University of Calgary; [2]Nutrition Services, Alberta Health Services; [3]Department of Medicine, University of Alberta; Edmonton; [4]O'Brien Institute for Public Health, University of Calgary; [5]Faculty of Kinesiology and Department of Oncology, Cumming School of Medicine, University of Calgary; Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services; [6]Department of Anesthesia, McGill University Health Center, Montreal, Quebec; [7]Faculty of Medicine, McGill University; [8]Department of Surgery, McGill University Health Center, Montreal, Quebec; [9]Department of Surgery, Jewish General Hospital, Montreal, Quebec.

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Abstract

Objectives: Recent efforts to prehabilitate intermediately frail and frail elective colorectal cancer patients did not influence clinical or functional outcomes. Despite four weeks of multimodal prehabilitation most patients were unable to achieve a six-minute walking distance (6MWD) of 400m (a prognostic cut-point used in other patient populations) before surgery. The objective of the present study was to describe the subset of prehabilitated patients that could not attain a minimum 400m 6MWD before surgery.

Design: Secondary analysis of a randomized controlled trial.

Setting: Patients participated in multimodal prehabilitation at home and in-hospital for approximately four weeks before surgery.

Participants: Intermediately frail and frail (Fried frailty criteria ≥2) colorectal cancer patients (n=55).

Measurements: Primary outcome was incidence of postoperative complications within 30 days of hospital discharge.

Results: Sixty percent of the patients who participated in prehabilitation did not reach a minimum walking distance of 400m in six minutes before surgery. Compared to the group that attained ≥400m 6MWD (n=19), the <400m group (n=28) were older, had higher percent body fat, lower physical function, lower self-reported physical activity, higher American Society of Anesthesiologists' (ASA) classification, and twice as many were in critical need of a nutrition intervention at baseline. No group differences were observed regarding frailty status (P=0.775). Sixty-one percent of the <400m 6MWD group experienced at least one complication within 30 days of surgery compared to 21% in the ≥400m group (P=0.009).

Conclusion: Several preoperative characteristics were identified in the <400m 6MWD group that could be useful in screening and targeting future prehabilitative treatments. Future trials should investigate use of a 400m standard for the 6MWD as a minimal treatment target for prehabilitation.

Introduction

Functional decline and the subsequent need for extended medical care affect an important proportion of the aging population. While advanced age is not synonymous with frailty, older adults are more likely to be frail, and thus, vulnerable to adverse health outcomes [178,179]. It is estimated that over one million Canadians are frail and five times as many caregivers are caring for an older adult with a chronic illness, disability, or age-related condition[180]. Moreover, 46% of the annual healthcare budget in Canada is spent on people over 65 years of age, although this group accounts for only 16% of the population[180]. The burden of frailty is expected to steadily grow, making frailty an important challenge for our healthcare system[181].

Frail patients are vulnerable to stressors; even minor illnesses among this population can lead to substantive declines in health[182]. Surgery is, therefore, an exceptional challenge for the frail patient. Surgical injury elicits a stress response that incites physiological adaptions[6] that call for adequate stamina to maintain raised cardiac output, cope with fluid shifts, and endure the metabolic demands of surgery[183]. Frail older patients have limited physiologic reserve to support the impending surgical stress response, making them particularly susceptible to the negative effects of surgery, including postoperative complications and prolonged hospital stay[184-186]. Identifying ways to enhance physiologic reserve and function before surgery as well as sustain function after surgery could benefit the vulnerable frail population. There is, however, limited evidence to support specific interventions that improve the outcomes of frail older adults[187] or frail surgical patients [188-191].

Recently, Carli et al.,[170] attempted to improve outcomes among intermediately frail and frail patients undergoing colorectal cancer resection using a prehabilitation intervention before surgery. Multimodal prehabilitation aims to enhance physiologic reserve and function in anticipation of the detrimental effects of surgery to facilitate post-surgical recovery of function[168,192]. Yet, unexpectedly, the multimodal prehabilitation program, integrated within the Enhanced Recovery After Surgery (ERAS) pathway, did not influence either the clinical or functional postoperative outcomes of the frail patients studied. Given that this prehabilitation program was modeled after a previously successful program in patients who were *not* identified as frail[193], the unexpected finding could be the result of an inability to deliver sufficient anabolic stimuli, or due to a lack of response to stimuli, for this specific frail patient group. Corroborating this rationale is that 70% of the patients in the prehabilitation arm entered the study with a baseline 6-minute walk distance (6MWD) below 400m, a prognostic cut-point used in other patient populations[194, 195], and the mean 6MWD for this group remained below 400m during the preoperative period despite the prehabilitation intervention[170].

As the prehabilitation intervention is resource intensive, targeting at-risk populations would be an attractive strategy to increase its efficiency and improve outcomes. The primary objective of this secondary analysis was to describe the patient characteristics of this sub-sample of intermediately frail and frail colorectal cancer patients that could not attain a minimum 400m 6MWD before surgery despite receiving prehabilitation. The secondary objective was to evaluate the clinical, functional, and patient outcomes of this group.

Methods

The methods and results of the original trial have been reported previously[170]. In brief, consecutive patients over 65-years of age scheduled for non-metastatic colorectal cancer surgery were considered for inclusion and screened for frailty using the validated Fried frailty criteria[196].

The Fried frailty criteria are based on a phenotypic assessment of unintentional weight loss, weakness, exhaustion, slow gait, and low physical activity. Patients with 1 or 2 criteria are deemed *intermediately frail* and those with 3 or more criteria are considered *frail*[112]. Intermediately frail and frail patients with Fried frailty criteria $\geq$2 were enrolled from two sites within the McGill University Health Center: Montreal General Hospital and at the Jewish General Hospital. All patients were treated within a perioperative care pathway according to the ERAS guidelines.[197]

Enrolled patients completed baseline functional assessments and were then randomly assigned 1:1 to receive either a four-week prehabilitation program or a four-week rehabilitation program[170]. Outcome assessors, surgeons, and surgical ward staff were blinded to group assignment. The present secondary analysis pertains *only* to the prehabilitation arm of the original trial.

The prehabilitation intervention was multimodal, including nutrition, exercise, and psychological components. The interventions were personalised and prescribed by a kinesiologist, a dietitian and a psychology-trained nurse. The exercise intervention included a weekly supervised training session with a trained kinesiologist at the hospital. During these sessions, patients performed: (1) 30 minutes of moderate aerobic exercise on a recumbent stepper (NuStep Inc., Ann Arbor, MI), (2) 25 minutes of resistance exercises using an elastic band/body weight, and (3) 5 minutes of stretching. Patients were also prescribed a personalized home-based program of aerobic activities (total of 30 minutes as moderate intensity aerobic activity) and resistance training (elastic band routine 3 times per week) according to guidelines of the American College of Sports Medicine[198]. The nutrition intervention was prescribed based on a comprehensive nutrition assessment, including the Patient-Generated Subjective Global Assessment (PG-SGA) [199], and focused on balanced eating, barriers to adequate food intake (e.g., nutrition-impact symptoms), and meeting protein requirements estimated at 1.5g/kg as per the European Society for Clinical Nutrition and Metabolism (ESPEN) in cancer patients[16, 200].

Protein supplements (Immunocal®; Immunotec Inc., Vaudreuil, Canada) were offered in a quantity that matched the identified deficit in habitual dietary protein intake. The psychological component included personalized coping strategies as well as deep breathing exercises to be performed at home three times per week.

The primary outcome of the original trial was the incidence of postoperative complications within 30 days, assessed using the Comprehensive Complications Index (CCI), which is calculated as the sum of all complications, weighted for their severity, based on median reference values from patients and physicians[201, 202]. Length of primary hospital stay was also collected.

Physical status measurements were assessed at baseline and before surgery (on the last workday prior to surgery). Functional walking capacity was captured as six-minute walking distance (6MWD), as measured by the six-minute walking test (6MWT), and was performed as previously described[170]. This test is a valid measure of recovery in colorectal surgery[76, 203]. The minimal clinical important difference has been estimated at 19m for comparisons between groups[204]. Low performance was defined using the European Working Group on Sarcopenia in Older People (EWGSOP) guidelines[205] as a gait speed of <=0.8 meters/second. Low strength was categorized using the EWGSOP guidelines as handgrip <27 kg for males and <16 kg for females. Fat-free mass (FFM) was determined using a multi-frequency bioelectrical impedance analysis (BioSpace InBody 320), and measurements were performed following standardized procedures according to the manufacturer. Reduced FFM was understood as a fat free mass index (FFMI, FFM/m^2) of <17 kg/m^2 for males and <15 kg/m^2 for females[206].

Patient reported outcome measures were assessed at baseline and pre-surgery and included a generic measure of health-related quality of life (HRQL) [36-Item Short Form Survey (SF-36)[207]], a measure of anxiety and depression [Hospital Anxiety and Depression Scale (HADS)[208]] and self-reported physical activity [Community Healthy Activities Model Program for Seniors questionnaire (CHAMPS)[209]].

Statistical analysis

Using data from only the prehabilitation arm of the original trial[170], patients were divided into those who accomplished at least 400m in six minutes (i.e., 6MWD at ≥ 400m) and <400m at their preoperative assessment (after four weeks of prehabilitation). This cut point was selected because it is below the normal range of 6MWD values reported for healthy subjects (normal range from 400-700m)[210], and because the inability to complete 400m in community dwelling elderly is associated with higher risk of mortality, incident cardiovascular disease, and disability[194]. Furthermore, the inability to complete 400m has been found to have prognostic value in several patient populations[195, 211], and has been used as a cut-point for preoperative optimization before colorectal cancer surgery[212].

Baseline patient characteristics and clinical outcomes were compared in patients who achieved <400m and ≥400m 6MWD at their preoperative assessment after prehabilitation. Data were visually assessed for normality using histograms. Between group comparisons were assessed with parametric (independent t-test) or non-parametric (Wilcoxon-Mann Whitney) tests as appropriate. Categorical data were evaluated using Chi-square tests unless cells were <5 in which case Fisher's Exact tests were used. Within group differences were assessed using paired t-test or Wilcoxon signed rank tests, as appropriate. The magnitude of clinical significance for between group differences ($P<0.05$) was quantified using Cohen's effect size (0.2 is considered small, 0.5 is medium, and 0.8 is large[213]). The incidence of at least one complication within 30 days of discharge was further assessed using multivariable logistic regression analysis to account for differences in baseline variables in <400 and ≥400m groups, based on literature review[214], that could be independent predictors of postoperative complications. All analyses were based on available data without imputation of missing values and performed using Stata 14.1 (2015, StataCorp).

Results

A total of 55 intermediately frail and frail colorectal cancer patients were included in this secondary analysis of prehabilitation. Eight patients did not complete the 6MWT pre-surgery (8/55=15%). Sixty percent (n=28/47) of the sample did not attain a minimum 400m 6MWD in the preoperative period (i.e., the <400m group) despite participating in approximately four weeks of prehabilitation [median (interquartile range, IQR): 40 (28-51) days] (Table 1).

Baseline patient characteristics

The patients unable to achieve a minimum 400m 6MWD at their preoperative assessment (after prehabilitation) were significantly older (mean $\pm$ standard deviation, SD: 80 $\pm$ 8 vs. 74 $\pm$ 7 years old, P=0.01), had significantly more body fat [median (IQR): 37(30-43) vs. 31(22-3)]%, P=0.02] and reported less total physical activity energy expenditure [median(IQR): 22(7-80) vs. 56(36-133) kcal/kg/week, P=0.03] at baseline, compared to the patient group that were able to attain a minimum 6MWD of 400m (Table 1). There was a greater proportion of patients with an American Society of Anesthesiologists' (ASA) classification of III or higher (82 vs. 47%, P=0.01) in the <400m group. No between group differences were observed in cancer stage (P=0.455) or surgical procedure (P=0.814). While a statistically significant difference in the use of a laparoscopic approach was not found (P=0.207), 32% of the <400m group underwent surgery with an open procedure compared to 16% in the $\geq$400m group. Additionally, twice as many patients in the <400m group were probably malnourished and in need of a critical nutrition intervention (PG-SGA $\geq$9; 57 vs. 26%, P=0.04). The physical status measures, with the exception of handgrip, were better in the $\geq$400m group at baseline. No between group differences were observed in the Fried frailty criteria ($\geq$3 vs. <3 criteria, P=0.775; 2 to 5 criteria, P=0.09).

Table 1: Patient characteristics and baseline values of intermediately frail and frail colorectal cancer patients who participated in prehabilitation; Data are stratified by patients who achieved a minimum 400m six-minute walking distance versus those who achieved less than 400m at their preoperative assessment (after four weeks of prehabilitation).

	Prehabilitated cohort (n=55)	**<400m 6MWD (n=28)**	**≥400m 6MWD (n=19)**	**P-value***
Patient characteristics				
Age, years, mean SD	77 (7)	80 (8)	74 (7)	0.013
65-74, years, n(%)	23 (42)	9 (32)	10 (53)	0.228
75-84 years, n(%)	22 (40)	10 (36)	8 (42)	0.228
>85, years, n(%)	10 (18)	9 (32)	1 (5)	0.034
Male sex, n(%)	29 (53)	15(54)	7(37)	0.314
ASA Classification III or higher, n(%)	36 (66)	23 (82)	9 (47)	0.012
Weight, kg, median [IQR]	67 [61-82]	67 [57-82]	69 [63-87]	0.386
Fat free mass, kg, median [IQR]	45 [40-53]	45 [40-52]	48 [42-56]	0.474
Fat free mass index, kg/m^2, median [IQR]	17.6 [15.9-19.1]	17.7 [15.9-19.6]	18.1 [16.6-19.0]	0.862
Reduced fat free mass index, n(%)	15 (27)	7 (25)	5 (26)	0.976
Body fat, %, median [IQR]	34 [26-39]	37 [30-43]	31[22-36]	0.018
Body mass Index (BMI), kg/m^2, median [IQR]	24.9 [23.0-30.1]	26.1 [24-31.4]	24.6[21.7-27]	0.156
BMI classifications, n(%)				0.404
Underweight, BMI <18.5 kg/m^2	2 (4)	0	1 (5)	
Normal weight, BMI >=18.5 to 24.9 kg/m^2	26 (47)	11 (39)	10 (53)	
Overweight, BMI >=25 to 29.9 kg/m^2,	26 (47)	7 (25)	4 (21)	
Obese, BMI >=30 kg/m^2, n(%)	14 (25)	10 (36)	4 (21)	
Patient-Generated Subjective Global Assessment >=9, indicative of critical need for nutrition intervention, n(%)	23 (42)	16 (57)	5 (26)	0.037
Missing data	1 (2)			
Physical status				
Self-reported physical activity, total, kcal/kg/week, median [IQR]	36 [11-80]	22 [7-80]	56 [36-133]	0.029
Self-reported physical activity, light, kcal/kg/week, median [IQR]	21 [9-51]	16 [5-50]	38[15-56]	0.093
Self-reported physical activity, moderate, kcal/kg/week, median [IQR]	4 [0-20]	2 [0-7]	19 [4-32]	0.002
Sit to stand, seconds, mean (SD)	9 (4)	8 (3)	11(4)	0.043
6MWD, meters, median [IQR]	360 [254-405]	282 [170-354]	398 [384-423]	<0.001
% predicted, median [IQR]	58 [44-67]	46[27-58]	61[57-72]	<0.001
<400m, n(%)	40 (73)	28 (100)	10 (53)	<0.001
Low performance, n(%)	18 (33)	16 (57)	1 (5)	<0.001
Grip strength, kg, median [IQR]	20.0 [16.5-29.6]	19.3 [15.6-24.9]	20.0 [16.5-30.0]	0.274
Low strength, n%	21 (38)	13 (46)	7 (37)	0.514
Fried frailty criteria, n(%)				0.090
2 criteria	25 (45)	12 (43)	9 (47)	
3 criteria	16 (29)	6 (21)	6 (32)	

4 criteria 5 criteria	7 (13) 7 (13)	3 (11) 7 (25)	4 (21) 0	
Frail, Fried frailty criteria >=3	30 (54.5)	16 (57)	10 (53)	0.775
Metabolic status				
C-reactive protein, mg/L, median [IQR]	6.2 [1.9 to 22.9]	9.4[5.2-25.4]	4.3[1.3-22.9]	0.175
Albumin, g/L, mean (SD)	39.1 (4.7)	37.7 (4.7)	40.2 (4.5)	0.087
Modified Glasgow Prognostic Score, n(%) mGPS0 mGPS 1 mGPS 2 Missing data	31 (56) 12 (22) 7 (13) 5 (9)	13 (46) 8 (29) 4 (14) 3 (11)	11 (58) 4 (21) 3 (16) 1 (5)	0.911
HbA1C, %, mean (SD)	6.2 (0.9)	6.2(0.7)	6.5(1.1)	0.231
Hemoglobin, g/L, mean (SD)	117 (20)	111 (20)	120 (19)	0.144
Clinical characteristics				
AJCC, n(%) 0 1 2 3 4	 10 (18) 8 (15) 15 (27) 19 (35) 3 (5)	 3 (11) 6 (21) 7 (25) 10 (36) 2 (7)	 6 (31.5) 2 (10.5) 3 (16) 7 (37) 1 (5)	0.455
Neoadjuvant therapy, n(%)	11 (20)	4 (14)	5 (26)	0.453
Surgical procedure, n(%) Ileocecal resection Right hemicolectomy Left hemicolectomy Subtotal/Total colectomy Anterior/sigmoid resection Low anterior resection Abdominoperineal resection Transverse colectomy Other bowel surgery	 2 (4) 23 (42) 5 (9) 2 (4) 6 (11) 10 (18) 4 (7) 1 (2) 2 (4)	 0 13 (46) 1 (4) 2 (7) 3 (11) 4 (14) 3 (11) 1 (4) 1 (4)	 1 (5) 7 (37) 2 (11) 0 3 (16) 4 (21) 1 (5) 0 1 (5)	0.814
Laparoscopic approach, n(%)	42 (76)	19 (68)	16 (84)	0.207
Creation of new stoma, n(%)	15 (27)	7 (25)	6 (32)	0.621
Study characteristics				
Duration of prehabilitation intervention, days, median [IQR]	40 [28-51]	41[31-49]	40[35-66]	0.184
Self-reported compliance, median [IQR]	92 [68-100]	94[73-100]	94[71-99]	0.677

6MWD is six-minute walking distance; ASA, American Society of Anesthesiologists' classification; HbA1C, glycated hemoglobin; AJCC, American Joint Committee on Cancer. *P-Value for <400 m and >=400m

Patient-reported outcomes at the preoperative assessment

Regarding HRQL, at baseline, only the physical function scale was different between the two study groups, with the > 400m group reporting significantly better physical function (P=0.01) (Table 2). After prehabilitation, patients in the >400m group continued to report better physical function (P <0.001) than the <400m group, but additionally reported significantly better role physical (P=0.047), general health (P=0.009), and social function (P=0.031), which translated into greater total mental (P=0.003), physical (P=0.017), and overall quality of life (P=0.005) than that reported in the <400m group. While there were no statistically significant group differences in anxiety or depression at baseline, after prehabilitation the >400m group had a lower score for depression (P=0.047). Moreover, the >400m group reported an improvement from baseline in pain (P=0.029) and total physical score (P=0.047) after prehabilitation. No preoperative improvements in HRQL were reported in the <400m group. Of note, at the preoperative assessment there were missing data for four patients (4/28, 14%) in the <400 group and missing data for one patient in the > 400 group (1/19, 5%).

Table 2: Health-related quality of life at baseline and pre-surgery for intermediately frail and frail colorectal cancer patients who participated in prehabilitation; Data are stratified by patients who achieved a minimum 400m six-minute walking distance versus those who achieved less than 400m at their preoperative assessment (after four weeks of prehabilitation).

	Prehabilitated cohort (n=55)	<400m 6WMD (n=28)	>400m 6MWD (n=19)	P-Value*
36-Item Short Form Survey (SF-36)				
Physical function, median [IQR]				
Baseline	50 [30-75]	40[3-60]	75[35-85]	0.010
Pre-surgery	55 [35-70]	43[31-65]	70[50-85]	<0.001
Role physical, median [IQR]				
Baseline	0[0-88]	0[0-75]	25[0-100]	0.349
Pre-surgery	50[0-100]	25[0-53]	63[0-100]	0.047
Bodily Pain, median [IQR]				

Baseline	52[41-84]	52[41-100]	72[51-74]	0.450
Pre-surgery	74[52-100]	74[41-100]	79[62-100] [a]	0.436
General health, mean (SD)				
Baseline	57(38)	58(48)	61(26)	0.788
Pre-surgery	60(21)	53(21)	70(17)	0.009
Vitality, mean (SD)				
Baseline	45(21)	44(21)	50(24)	0.314
Pre-surgery	56(21)	52(21)	60(20)	0.230
Social function, median [IQR]				
Baseline	63[38-88]	50[38-75]	75[50-88]	0.221
Pre-surgery	63[50-88]	63[38-78]	88[50-88]	0.031
Role emotional, median [IQR]				
Baseline	33[0-100]	33[0-100]	50[0-100]	0.543
Pre-surgery	84[0-100]	33[0-100]	100[0-100]	0.143
Mental health, mean (SD)				
Baseline	66(18)	67(18)	66(19)	0.829
Pre-surgery	66(21)	67(19)	65(23)	0.812
Total Physical, mean (SD)				
Baseline	49(21)	47(18)	56(23)	0.174
Pre-surgery	57(19)	50(15)	67(20) [a]	0.003
Total Mental, mean (SD)				
Baseline	54(23)	54(23)	58(24)	0.615
Pre-surgery	59(21)	53(20)	67(20)	0.017
SF-36 Total, mean (SD)				
Baseline	51(22)	50(21)	57(24)	0.252
Pre-surgery	59(19)	52(14)	68(21)	0.005
Hospital anxiety and depression scale (HADS)				
Anxiety, median (SD)				
Baseline	6 [4-8]	6 [3-8]	6 [5-8]	0.477
Pre-surgery	6 [4-8]	6 [4-9]	5 [4-8]	0.670
Depression, median (SD)				

Baseline	5 [3-8]	6 [4-7]	3 [1-9]	0.054
Pre-surgery	4 [2-6]	6 [3-7]	2 [1-5]	0.047

6MWD is six-minute walking distance; *P-Value for <400 m and >=400m; [a] P<0.05 compared to baseline

Physical status outcomes at the preoperative assessment

The median 6MWD for the group that achieved <400m after prehabilitation was 297m (IQR: 317-344m), while the median for the group that achieved ≥400m after prehabilitation was 440m (IQR: 432-466m). All preoperative measures of physical function were significantly better in the ≥400m group compared to the <400m group (Table 3), except for handgrip strength which was not statistically different between groups after prehabilitation. Eighty-nine percent of the ≥400m group improved their 6MWD before surgery to a clinically meaningful extent (i.e., change ≥19m), compared to only 39% in the <400m group (P<0.001). At the preoperative assessment, there were no differences between groups regarding total self-reported physical activity [median (IQR): 47 (18-103) vs 44 (28-141) kcal/kg/week; P=0.392]; upon stratification of physical activity intensity, however, the ≥400m group reported more energy expended from moderate physical activity [median (IQR): 11 (3-18) vs 17 (9-42) kcal/kg/week; P=0.03] and the magnitude of difference in moderate activities between groups was large (effect size: 0.8, 95% CI: 0.2-1.4).

Table 3: Preoperative measures of physical status and clinical outcomes for intermediately frail and frail colorectal cancer patients who participated in prehabilitation; Data are stratified by patients who achieved a minimum 400m six-minute walking distance versus those who achieved less than 400m at their preoperative assessment (after four weeks of prehabilitation).

	Prehabilitated cohort (n=55)	<400m 6MWD (n=28)	≥400m 6MWD (n=19)	P-value*	Effect size** (95% CI)
6MWD, meters, median [IQR]	366 [270-438]	297 [217-344]	440 [432-466]	<0.001	2.41 (1.64 to 3.17)
Missing data	8 (14.5)	0	0		
Preoperative improvement in 6MWD, ≥19m, n(%)	27 (49)	10 (36)	17 (89)	<0.001	
Sit to stand, seconds, mean (SD)	11 (4)	10 (4)	14 (3)	<0.001	1.27

Missing data	11 (20)	3 (11)	0		(0.61 to 1.92)
Handgrip, kg, median [IQR] Missing data	22 [18-28] 9 (16)	21[17-27] 1 (4)	26[20-36] 0	0.203	
Self-reported physical activity, kcal/kg/week, total, median [IQR] Missing data	44[24-126] 11(20)	47[18-103] 3 (11)	44[28-141] 0	0.392	
Self-reported physical activity, kcal/kg/week, light activities, median [IQR]	24 [9-58]	26 [8-60]	20 [11-55]	0.661	
Self-reported physical activity, kcal/kg/week, moderate activities, median [IQR]	13 [7-25]	11 [3-18]	17 [9-42]	0.028	0.78 (0.15 to 1.39)
Length of primary hospital stay, days, median [IQR]	4 [3-8]	6[3-11]	3[3-5]	0.020	-0.53 (-1.12 to 0.06)
At least one complication within 30 days, n(%)	25 (46)	17 (61)	4 (21)	0.009	
Comprehensive complication index at 30 days post-discharge, median [IQR]	0 [0-12]	8.7 [0-24.2]	0 [0-0]	0.008	-0.63 (-1.23 to -0.03)

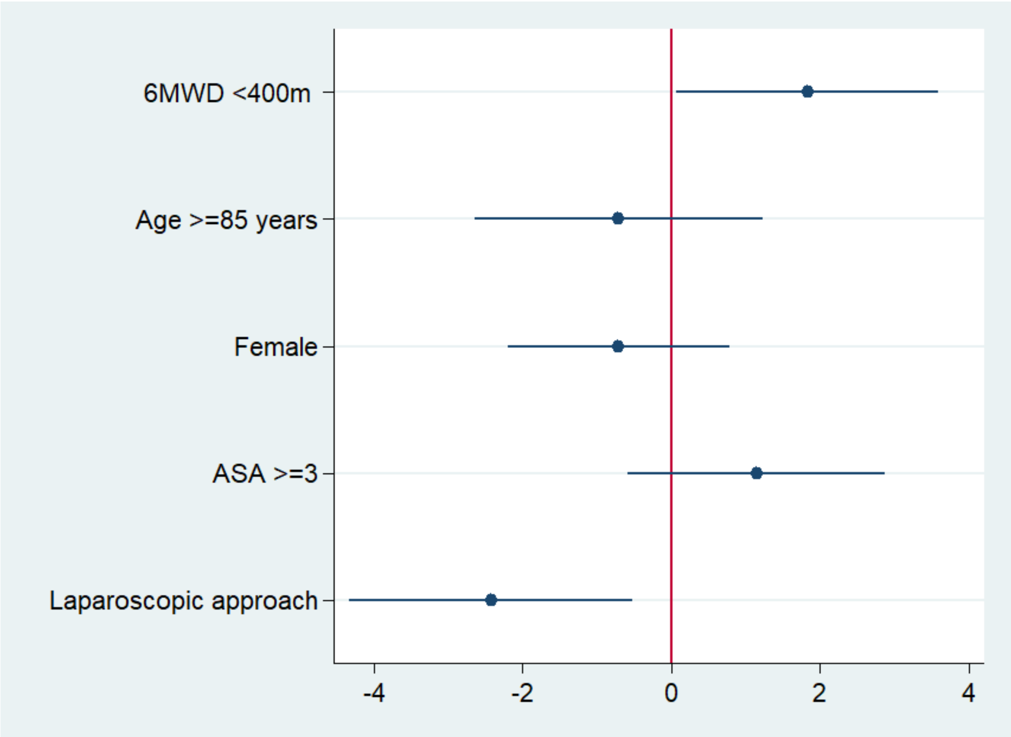
6MWD is six-minute walking distance; *P-Value for <400 m and >=400m; ** Effect sizes derived using means.

Clinical outcomes

The patients unable to attain a minimum 400m 6MWD after prehabilitation stayed in hospital significantly longer [median (IQR): 6 (3-11) vs 3 (3-5) days; P=0.020], compared to the patients that could attain this distance preoperatively (Table 3).

Moreover, a greater proportion of the <400m group (61 vs 21%, P=0.009) suffered at least one complication within 30 days post-discharge. In fact, the patients that did not accomplish a minimum distance of 400m in six minutes before surgery were 6.2 times more likely to suffer a postoperative complication (Odds ratio: 6.2, 95%CI: 1.1 to 36.1; P=0.041; Coefficient, standard error: 1.8, 0.9) after controlling for age, sex, ASA classification greater than III, and surgical approach (Figure 5).

Figure 5: Forest plot displaying multivariate logistic regression model of the variables that predict postoperative complications in intermediately frail and frail colorectal cancer patients (Coefficients, standard error)



Discussion

This descriptive study revealed that the majority (i.e., 60%) of intermediately frail and frail prehabilitated colorectal cancer patients were unable to attain a minimum 400m 6MWD before surgery. The odds of developing a postoperative complication within 30 days of surgery were six times greater in this patient group. Furthermore, while HRQL were similar between the <400m and ≥400m groups at baseline, at the preoperative assessment (after approximately four weeks of prehabilitation), the ≥400m group reported lower depression and higher physical, mental, and overall quality of life compared to the <400m group. The ≥400m group also reported an improvement in pain and in total physical score compared to their baseline assessment. These findings suggest that the patients who did not achieve ≥400m 6MWD, did not reap the same patient-oriented benefits (i.e., better patient-reported outcomes) from prehabilitation as the patients who were able to achieve a >400m 6MWD preoperatively. Interestingly, there was no difference in total self-reported physical activity energy expenditure between groups at the preoperative assessment, however, the >400m group reported engaging in more *moderate* physical activity at this timepoint. This greater investment in moderate activities likely contributed to more than twice as many patients in the >400m group attaining a clinically meaningful improvement in their functional walking capacity before surgery.

There is no universal definition or single method of quantifying frailty. Currently, there are two distinct approaches to understanding frailty, the Fried frailty phenotype, which defines frailty as a syndrome marked by energy dysregulation and physical limitations, and the Frailty Index, which defines frailty as a state of accumulated deficits across multiple systems[178]. The prehabilitation study by Carli et al.,[170] was the first to use the Fried frailty approach to enroll intermediately frail and frail patients and target prehabilitative efforts to this vulnerable patient sub-group[112]. Yet, the authors did not find that prehabilitation reduced postoperative complications or enhanced functional recovery in intermediately frail and frail patients undergoing elective colorectal cancer resection, compared to rehabilitation[170]. This unexpected finding might be explained by use of the Fried frailty criteria itself, which might not be specific nor accurate at identifying patients that will be responsive to multimodal surgical prehabilitation. In support of this idea, our results suggest that prehabilitated patients who were unable to attain a 400m distance before surgery experienced a worse surgical recovery, including a prolonged hospital stay and greater risk of postoperative complications within 30 days, compared to the patients that could attain this distance preoperatively. However, the frailty status (i.e., stages of frailty, based on the Fried criteria) was not different between the <400m and >400m groups. Future trials might consider screening for and treating specific individualized risk factors for surgery, such as poor walking capacity as identified using the 6MWD score of <400m[212], since it appeared to better identify patients at higher risk of postoperative morbidity.

In fact, several individual patient characteristics were different between the <400m and ≥400m groups, and these characteristics could be useful in screening and targeting prehabilitative treatments. At baseline, the <400m group were older, had higher percent body fat, lower physical function, lower self-reported physical activity energy expenditure, greater ASA classification and the majority were in critical need of a nutrition intervention. Most of these patient characteristics are known risk factors for adverse surgical outcomes[215-217], and some are modifiable before surgery. As an example, patients at risk of malnutrition are at greater risk of developing postoperative complications[215], which can be mitigated with preoperative nutrition therapy[16, 151, 166]. Future prehabilitation trials might thus consider screening patients into prehabilitation based on these individualized, potentially modifiable characteristics, and designing personalized prehabilitation interventions to target these specific characteristics, rather than providing the same multimodal program to all patients regardless of their individual baseline risk factors.

Sixty percent of these intermediately frail and frail prehabilitated patients were unable to improve their 6MWD to a minimum of 400m. The inability to complete a 400m distance is predictive of mobility disability in older adults[194], and a slower 6MWD has been found to be predictive of postoperative morbidity in elective colorectal surgery patients[218]. Similarly, Sinclair et al.,[74] identified that a non-cardiac patient walking <427m in six minutes before surgery is at high risk of morbidity, based on their evaluation that a 6MWD <427m was correlated with an anaerobic threshold of <11ml oxygen/kg/min (the anaerobic threshold with the largest evidence base representing high perioperative risk). Our present findings support the prognostic value of a preoperative 6MWD <400m: 61% of the <400m patient group experienced at least one complication within 30 days of surgery compared to 21% in the ≥400m group. Furthermore, the odds of developing a postoperative complication was 6 times more likely in the <400m group compared to the ≥400m group after controlling for other potential predictors. Future trials that are adequately powered should investigate use of a 400m 6MWD as a minimal treatment target for prehabilitation in colorectal surgery.

Optimal strategies to modulate frailty within the limited timeframe before surgery are unknown[190]. Our findings suggest that time spent doing moderate intensity, rather than total, physical activity before surgery may play an important role in improving the physical status and clinical outcomes of intermediately frail and frail patients. We identified that although the *total* physical activity energy expenditure was not different between the <400m and ≥400m groups at the preoperative assessment, *moderate* physical activity was significantly greater in the ≥400m group. Godin et al., recently identified that to achieve a minimally important difference in frailty, an equivalent amount of sedentary time needs to be replaced with physical activity. Based on their results, to reduce risk of mortality by 50%, mildly frail individuals would need to engage in 18 minutes per day of moderate-vigorous activity or 204 minutes of light activity[219]. Taken together, the greater moderate physical activity in the ≥400m group might be the important difference that explains the relative improvements noted in their physical function outcomes, as compared to the <400m group, and thus might be an important treatment target for future trials.

Our findings should be interpreted in light of a few limitations. First, considerable 6MWD values at the pre-surgery assessment were missing (15%), as a result of missing follow-up appointments. It is likely that the fittest patients, most compliant patients, and/or those patients with the most support (i.e., someone to drive them to appointments) were among the patients who participated in the pre-surgery follow up assessments. If this possible selection bias were the case, our findings would underestimate the negative impact that a poor preoperative 6MWD has on postoperative outcomes. Second, our small sample size impacted the precision of our findings as demonstrated by wide confidence intervals. Because our sample was small, our findings should be cautiously considered as exploratory. Further research is needed to investigate these findings in larger, adequately powered studies. Third, the Fried frailty assessment was not performed again pre-surgery to assess the impact of prehabilitation on frailty. Given that a diagnosis of frailty with the Fried criteria includes an assessment of several domains, not just walking capacity, repeating the frailty assessment would have been useful to understand whether the prehabilitation intervention had an impact on frailty itself.

Conclusion

We observed that intermediately frail and frail elective colorectal surgery patients who could not attain ≥400m 6MWD before surgery with our prehabilitation program experienced greater postoperative morbidity within the first 30 days of surgery. The Fried frailty criteria did not significantly differ between the <400m and ≥400m groups, suggesting that 6MWD might better identify patients with higher risk of adverse outcomes. Future trials should investigate the 400m 6MWD as a minimal treatment target for prehabilitation. The patients belonging to the <400m group were older, had higher percent body fat, were less physically fit, were nutritionally compromised, and engaged in less physical activity at baseline. Future trials should also investigate whether or not these individual patient characteristics (e.g., poor physical function and nutritional status) are more appropriate than the Fried frailty criteria for screening patients into prehabilitation.

Chapter summary

The findings of this study support the hypothesis that the patient's preoperative status modifies surgical outcomes. In a small cohort of intermediately frail and frail colorectal cancer patients who participated in multimodal prehabilitation, the incidence of postoperative complications within the first 30 days of surgery were significantly greater in patients who could not attain a minimum 400m six-minute walking distance (poor functional walking capacity), compared to the patients who achieved at least 400m in six minutes (better functional walking capacity). In fact, the odds of developing a complication were six times greater in the patients with poor functional walking capacity, than the patients with better functional capacity, even after controlling for other potential predictors of postoperative complications (age, sex, an anesthesiology classification greater than III and the surgical approach). Notably, all patients were treated with ERAS care. Of interest, the Fried frailty criteria (e.g., intermediately frail vs. frail and the total number of frailty criteria) was not statistically different between the patient groups exhibiting poor and better functional walking capacity.

Although the conclusions of the study are limited by the small sample size, the results suggest that the following findings should be confirmed in subsequent adequately powered studies:

- a minimal functional walking capacity is required to withstand the surgical stress response in an ERAS care setting.
- screening patients into prehabilitation based on individual characteristics that predict adverse outcomes, including poor functional walking capacity, that are also modifiable within the timeframe before surgery, is likely to be of more value than screening for frailty.
- a six-minute walk test of 400m could be a useful therapeutic target for future prehabilitation programs.

Chapter 4: Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: A systematic review and meta-analysis

Chelsia Gillis [1], Katherine Buhler [1], Lauren Bresee [2,3], Francesco Carli [4], Leah Gramlich [5], S.Nicole Culos-Reed [6], Tolulope T Sajobi [1, 3], Tanis R Fenton [1,7]

[1]Cumming School of Medicine, Department of Community Health Sciences, University of Calgary;[2]Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario; [3]O'Brien Institute for Public Health, University of Calgary; [4] Department of Anesthesia, McGill University Health Center, Montreal, Quebec; [5] Department of Medicine, University of Alberta, Edmonton; [6] Faculty of Kinesiology and Department of Oncology, Cumming School of Medicine, University of Calgary; Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services; [7] Nutrition Services, Alberta Health Services.

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Abstract

Background & Aims: Although there have been meta-analyses of the effects of exercise prehabilitation on patients undergoing colorectal surgery, little is known about the effects of nutrition-only (oral nutritional supplements with and without counseling) and multi-modal (oral nutritional supplements with and without counseling and with exercise) prehabilitation on clinical outcomes and patient function after surgery. We performed a systemic review and meta-analysis to determine the individual and combined effects of nutrition-only and multi-modal prehabilitation, compared with no prehabilitation (control), on outcomes of patients undergoing colorectal resection.

Methods: We searched MEDLINE, EMBASE, CINAHL, CENTRAL, and ProQuest for cohort and randomized controlled studies of adults awaiting colorectal surgery who received at least 7 days of nutrition prehabilitation with and without exercise. We performed a random effects meta-analysis to estimate the pooled risk ratio for categorical data and the weighted mean difference for continuous variables. The primary outcome was length of hospital stay; the secondary outcome was recovery of functional capacity, based on results of a 6-minute walk test.

Results: We identified 9 studies (5 randomized controlled studies and 4 cohort studies) comprising 914 patients undergoing colorectal surgery (438 received prehabilitation and 476 served as controls). Receipt of any prehabilitation significantly reduced days spent in hospital compared with controls (weighted mean difference of length of hospital stay, –2.2 days; 95% CI, –3.5 days to –0.9 days). Only 3 studies reported functional outcomes but could not be pooled due to methodological heterogeneity. In the individual studies, multimodal prehabilitation significantly improved results of the 6-minute walk test at both 4 and 8 weeks after surgery compared with standard enhanced recovery pathway care, and at 8 weeks compared with standard enhanced recovery pathway care with added rehabilitation. The 4 observational studies had a high risk of bias.

Conclusions: In a systematic review and meta-analysis, we found that nutritional prehabilitation alone, or when combined with an exercise program, significantly reduced length of hospital stay by 2 days in patients undergoing colorectal surgery. There is some evidence that multimodal prehabilitation accelerated the return to pre-surgery functional capacity.

Introduction

Prehabilitation is an intervention that capitalizes on the waiting period before surgery with preoperative strategies designed to optimize the patient's physical condition to promote an earlier postoperative recovery[117]. A limitation in the interpretation of the available prehabilitation literature is the absence of a well-defined and standardized definition. Our group currently defines colorectal prehabilitation as a trimodal intervention consisting of the following components: 1) personalized nutrition counselling and protein supplementation; 2) individualized aerobic and total body resistance exercise; and, 3) anxiety reduction and relaxation strategies[117, 168]. Although there is no consensus on the optimal duration of prehabilitation, previous studies have identified four weeks as sufficient time to modify behaviour to improve physical function before colorectal surgery[136], and four weeks is within the operative timeframe suggested by the Canadian Oncological Society[220].

At least two randomized controlled trials (RCT)[168, 169] support the use of multimodal prehabilitation, involving multiple complementary interventions, as a means of promoting an earlier return of physical function post-abdominal surgery. Yet, to date, available systematic reviews and meta-analyses on prehabilitation have focused on exercise-only interventions and have produced conflicting results[167, 221-223]. As examples, Lemanu et al.,[221] identified that exercise prehabilitation does not provide any clinical benefit to surgical patients in a variety of settings, while a review by Moran et al.,[222] concluded that exercise prehabilitation improves surgical complication rates post-abdominal surgery.

The existing systematic reviews[167, 221-223] have described the impact of *exercise* prehabilitation on surgical outcomes and may have produced conflicting results for two reasons: 1) Limited power: the meta-analyses had limited power as they mostly included smaller studies (sample size ranging from 10 - 279 participants per study) with diverse endpoints, and; 2) Heterogeneous populations: the reviews compiled research of heterogeneous populations, including all types of surgeries, various levels of exercise/nutritional statuses, different interventions, and unknown or varied results of patient compliance, combined into one message for ‘prehabilitation’.

None of the reviews specified a multimodal component, and the limited research to date suggests that preoperative exercise alone may be insufficient to improve surgical outcomes[224]. Nutrition is a key aspect of prehabilitation that works in synergy with the exercise intervention[225]. Several stable isotope investigations have suggested that exercise with insufficient protein provision will not support optimal gains in muscle accretion[226, 227]. A subgroup analysis of exercise prehabilitation in the systematic review by Moran et al.,[222] corroborates this: when the authors removed a multimodal study (1 of 9 RCTs) from their analysis, the impact of exercise prehabilitation on postoperative morbidity was no longer statistically significant[224].

The purpose of this systematic review of RCTs and prospective cohort studies is to determine the individual and combined impact of nutrition-only prehabilitation and multimodal prehabilitation (nutrition with exercise) on clinical and functional outcomes in adults undergoing colorectal resection surgery. Recovery from surgery is a complex process. Our review is focused on short-term measures of recovery from surgery, including length of primary hospital stay (considered a benchmark of fitness permitting discharge to home[228]), and a longer-term patient-oriented measure of recovery, functional capacity[229,].

Methods

We performed a systematic literature search and meta-analysis according to the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) recommendations. The protocol was registered with PROSPERO (CRD42016053887).

The primary research objective was to determine whether nutrition-only prehabilitation and multimodal prehabilitation improved length of hospital stay (LOS) post-colorectal surgery, compared to a control that did not receive prehabilitation. The secondary objective was to determine whether these interventions facilitated earlier recovery of functional capacity.

Search strategy

The last update of the search was performed on March 7, 2017 and included MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Registry of Controlled Trials (CENTRAL), and ProQuest databases. A grey literature search of published abstracts and conference proceedings from the Canadian Nutrition Society, American Society of Parenteral and Enteral Nutrition, and Enhanced Recovery After Surgery (ERAS) meetings in the last four years was also conducted. The search of online databases included all languages and three search term categories: type of surgery, type of intervention, and timing of the intervention (Appendix A).

Inclusion & exclusion criteria

The initial screening of all identified abstracts was performed independently by two reviewers (CG and KB). Articles were considered for full-text review if inclusion criteria were met: an original prospective cohort or RCT study on the use of nutrition-only prehabilitation or multimodal prehabilitation in adults aged 18 years and older awaiting colorectal resection surgery, compared to a control. Given that prehabilitation is a new intervention, we did not limit our search to RCTs, and stratified the analyses accordingly. Nutrition prehabilitation was defined as any non-invasive nutrition intervention, such as the use of oral nutrition supplements (ONS) with or without dietary counselling, that altered macronutrient (carbohydrate, protein, fat) intake for a minimum of 7 days before surgery. A prehabilitation duration of 7 days or greater was considered minimally adequate based on current surgical care guidelines, which recommend a minimum of 7 days of preoperative nutrition support if malnutrition is present[230]. Multimodal prehabilitation was defined as any intervention that met the above criteria for nutrition and also included aerobic and total body resistance exercise. Any studies that met these criteria were considered for full-text review. Studies that included invasive preoperative nutrition support requiring hospitalization, including parenteral and/or enteral nutrition, were excluded. Studies that included carbohydrate loading-only or specialized immunonutrition products (nutrition supplements enriched with various pharmaconutrients such as arginine, glutamine, omega-3-fatty acids, nucleotides, and antioxidants) were also excluded to enhance homogeneity. The reference list of all identified full-text papers, and any relevant review articles identified during the abstract screen were searched for additional studies. Disagreements were addressed by discussion and consensus.

Assessment of study quality

A component based analysis of the key components of the Cochrane Risk of Bias tool was conducted to assess study quality based on recommendations by Egger[231, 232] and the Cochrane collaboration[233].These recommendations are based on a growing understanding that assessment of study quality using scales can lead to conflicting results depending on the scale used [234, 235]. Therefore, clinical trials in our study were evaluated for quality based on factors that have been found to exaggerate study effect size [236-239], including concealment of randomization, blinding of outcome assessment, and the inclusion of well described attrition[232]. All three factors were considered separately. Similarly, the cohort studies were assessed for blinding of outcome assessment, sufficient duration to assess outcome, and whether the analysis controlled for potential confounders[231]. All three factors were considered separately. CG and KB independently reviewed studies for risk of bias, and inter-rater agreement was assessed.

Data extraction

Study characteristics were independently extracted, by CG and KB, including study design, location of the study, sample size, and whether the study was conducted under Enhanced Recovery Pathway (ERP)[35] vs. traditional surgical care. The following baseline characteristics were recorded if the data were available: patient age, gender, number of patients with cancer and/or malnutrition, type of surgery performed, and the preoperative physical condition of the patients. Intervention characteristics, including nutrition and/or exercise prescription, type of ONS, duration of intervention, intervention compliance, and estimated supplemental energy and protein intakes were collected to evaluate the methodological heterogeneity of the studies. If data were missing, the first author of the identified paper was contacted.

The primary outcome, LOS, was recorded in mean days, beginning the day of surgery until discharge from hospital. If mean data were not available, it was calculated from the raw data (if available), or an approximation of the mean was calculated from the median and range[240]. Functional recovery was considered a return to baseline functional walking capacity, as assessed by the validated six-minute walk test (6MWT) within 20 meters, at four and eight weeks post-surgery[203]. If the information was available, postoperative complications were recorded as total complications, total number of patients with a complication, and total patients with major complications during primary hospital admission and 30 days postoperatively.

Statistical Analysis

All identified studies were included in forest plots for the planned analyses. Nutrition-only and multimodal prehabilitation interventions were assessed separately and together. Recognizing that nutrition-only prehabilitation and multimodal prehabilitation are two distinct interventions, the heterogeneity and effect sizes between the nutrition-only and multimodal prehabilitation groups were examined to determine whether these two interventions could be pooled[241]. Nutrition-only prehabilitation studies and multimodal prehabilitation studies were pooled only if the effect estimates were similar and the 95% confidence intervals overlapped.

Random-effects meta-analyses were used to estimate the pooled risk ratio (RR) for categorical data and the weighted mean difference (WMD) for continuous variables in order to compare the surgical outcomes of patients following prehabilitation vs. control. The data were fitted with a random effects model, in which the underlying assumption was that multiple true effects could exist[242]. This type of model was appropriate because it accounted for multiple true effects from a variety of prehabilitation interventions and diverse study populations, including patents with cancer and other bowel diseases, as well as varied nutritional statuses. Heterogeneity was assessed using the I^2 value and the Q statistic[242, 243]. Heterogeneity was explored and effect modification was evaluated through stratification by study design, study quality, surgical care, and intervention prescription. Publication bias was assessed using Egger's test[242]. All analyses were performed with Stata 14.1. Statistical significance was assessed at α less than 0.05.

Results

Search results

A search of MEDLINE, EMBASE, CENTRAL, CINAHL, and ProQuest resulted in 665 unique articles (Figure 6). The grey literature search did not produce any studies that met all inclusion criteria. After abstract screening, 72 articles were identified for full-text review. An additional 10 articles were identified through hand searching relevant reference lists, yielding a total of 82 articles for full text review. Seventy-three articles were subsequently excluded because the patient population (n=4), intervention (n=41), comparator group (n=10), study design (n=9), or outcomes (n=9) did not meet the inclusion criteria. Between-rater agreement for full-text review was 86.1% (Kappa=0.60). Differences between researchers were discussed before coming to a consensus.

Figure 6: PRISMA Flow Diagram

Five RCTs[168, 244-247] and four prospective cohort studies[44, 248-250] satisfied the inclusion criteria, for a total of 9 studies included for analysis. One included study published in Russian (Khrykov et al[250]) was translated. Two of the studies (MacFie et al [246] & Smedley et al [247]) included two separate and relevant intervention groups, resulting in a total of 11 comparison groups for analysis.

Baseline characteristics

The studies, published between the years 2000 and 2016, included a total of 914 patients undergoing colorectal surgery (intervention: 438, control: 476) (Tables 4 and 5). Most studies employed nutrition-only prehabilitation interventions (6/9 studies) [244-248, 250] and were completed under a traditional care hospital setting (5/9 studies)[245-248, 250] . All three of the multimodal prehabilitation studies were conducted under ERP care[44, 168, 249], whereas only one nutrition-only prehabilitation study took place in an ERP setting[244]. The mean age of participants ranged from 55-69 years, with the exceptions of Chia et al[249] and Khrykov et al[250] who only enrolled patients over the age of 65 years. Six studies enrolled cancer patients exclusively[44, 168, 244, 245, 248, 250]. One study focused on surgery of the colon only [250] and one study on gastrointestinal surgery with 83-92% of cases being colorectal[246]. Two studies did not provide specific details on the proportion of colon vs rectal surgeries performed [247, 248]. The remaining studies were compromised of 37-69% rectal surgeries (5/9 studies)[44, 168, 244, 245, 249]. All of the surgeries were elective, with the exception Chia et al [249], in which 78 and 81% of the patients had elective surgery in the control and intervention groups, respectively. Malnutrition was assessed in most of the studies (6/9 studies)[244-248, 250] with a variety of tools, and nutritional risk was diagnosed in 33-75% of participants.

Table 4: Study characteristics

Author	Location	Study design	Study groups	Surgical care	Sample size
Nutrition Prehabilitation					
MacFie, 2000	Europe, United Kingdom	Unblinded RCT, single center	Group 1: >10 days preop ONS vs. standard of care Group 2: >10 day days preop ONS + > 7 days of postop ONS vs. standard of care	Traditional care	Intervention 1: 24 Intervention 2: 24 Control: 25
Smedley, 2004	Europe, United Kingdom	RCT, multicenter	Group 1: >7 days preop vs. standard of care Group 2: >7 days preop + 4 weeks post-discharge ONS vs. standard of care	Traditional care	Intervention 1: 41 Intervention 2: 32 Control: 44
Burden, 2011	Europe, United Kingdom	Unblinded RCT, pragmatic trial, multicenter	>10 days preop ONS & dietary advice vs. dietary advice alone	Traditional care	Intervention: 54 Control: 62
Khrykov, 2014	Europe, Russia	Prospective cohort, single center (control data collected retrospectively)	Elderly patients received 10-14 days preop ONS and postop early enteral tube feeding + ONS vs. postop parenteral nutrition and progression to ONS.	Traditional care	Intervention: 52 Control: 75
Gillis, 2016	Canada, Montreal	Double-blinded RCT, single center	4 weeks preop + 4 weeks postop ONS & dietary counselling vs. dietary counselling & placebo	Enhanced Recovery After Surgery	Intervention: 22 Control: 21
Maňásek, 2016	Europe, Czech Republic	Prospective cohort, multicenter (control data collected retrospectively)	>10 days preop and > 2 weeks postop ONS vs. standard of care	Traditional care	Intervention: 52 Control: 105
Multimodal prehabilitation					

Li, 2013	Canada, Montreal	Prospective cohort, single center	4 weeks preop and 8 weeks postop nutrition, exercise and anxiety reduction vs. standard ERAS care	Enhanced Recovery After Surgery	Intervention: 42 Control: 45
Gillis, 2014	Canada, Montreal	Single-blinded RCT, single center	4 weeks preop and 8 weeks postop exercise, nutrition, and anxiety reduction vs. 8 weeks rehabilitation (identical intervention)	Enhanced Recovery After Surgery	Intervention: 38 Control: 39
Chia, 2016	Asia, Singapore	Prospective cohort, single center	Elderly patients received 2 weeks preop and 2-6 weeks postop nutrition and exercise vs. standard of care.	Enhanced Recovery Program	Intervention: 57 Control: 60

RCT, randomized controlled trial; ONS, oral nutrition supplement; preop, the preoperative period before surgery; postop, the postoperative period after surgery; ERAS, Enhanced Recovery After Surgery

Table 5: Baseline sample characteristics

Author	Age	Male, n (%)	Cancer, n (%)	Type of surgery performed, n (%)	Preoperative malnutrition, n (%)	Preoperative physical condition
Nutrition Prehabilitation						
MacFie, 2000 (Group 1)	Mean (range) I: 68 (23–84) C:64 (42–85)	I:15 (63) C:12 (48)	"The majority of patients underwent surgery for colorectal malignancy" pg. 724	Elective major gastrointestinal surgery I: Colorectal[a,b]: 20(83) Gastrointestinal: 3(13) Hepatobiliary: 1(4) C: Colorectal[a,b]: 21(84) Gastrointestinal: 3(12) Hepatobiliary: 1(4)	Recalled pre-illness weight loss in previous 6 months >5% I: 11(46) C:10(40)	Grip strength, kg Mean (range) I: 27 (4–48) C: 27 (8–48)
MacFie, 2000 (Group 2)	Mean (range) I: 63 (41–86) C:64 (42–85)	I: 11 (46) C:12 (48)	"The majority of patients underwent surgery for colorectal malignancy" pg. 724	Elective major gastrointestinal surgery I: Colorectal[a,b]: 22(92) Gastrointestinal: 1(4) Hepatobiliary: 1(4) C: Colorectal[a,b]: 21(84) Gastrointestinal: 3(12) Hepatobiliary: 1(4)	Recalled pre-illness weight loss in previous 6 months >5% I: 14(58) C:10(40)	Grip strength, kg Mean (range) I: 29 (10–55) C: 27 (8–48)

Smedley, 2004 (Group 1)	Mean (range) I:61 (23–84) C:63 (25–88)	I: 33 (80) C:28 (64)	I: 31(76) C: 35(80)	Elective moderate to major lower gastrointestinal surgery. Data for operation performed not shown.	At risk of malnutrition according to age, BMI, and history of weight loss I: 16(39) C: 17(39)	Grip strength, kPa Mean (SD) I:74 (23) C:72 (21)
Smedley, 2004 (Group 2)	Mean (range) I:55 (26–81) C:63 (25–88)	I: 19 (59) C:28 (64)	I: 21(66) C:35(80)	Elective moderate to major lower gastrointestinal surgery. Data for operation performed not shown.	At risk of malnutrition according to age, BMI, and history of weight loss I: 14(44) C: 17(39)	Grip strength, kPa Mean (SD) I:75 (21) C:72 (21)
Burden, 2011	Mean (SD) I: 65 (14) C:65 (3)	I: 34 (63) C: 38 (61)	I:54(100) C: 62(100)	Elective curative surgery for colorectal cancer I: Colon[a]: 20(37) Rectum[b]: 29(54) Other[c]: 4(7) Missing[d]: 1(2) C: Colon[a]: 16(26) Rectum[b]: 39(63) Other[c]: 5(8) Missing[d]: 2(3)	Subjective Global Assessment rating C&B I: 30(56) C:23 (37)	Grip strength, kg Mean (SD) I: 27 (10) C: 28 (10)
Khrykov, 2014	Mean(SD) Whole sample 74(7.2)	NA	I: 52(100) C:75(100)	Elective surgery for colon cancer Colon: 127 Rectum: 0	"Prognostic index of hypertrophy" calculated using albumin and arm circumference I: 21(40) below normal C: NA	NA
Gillis, 2016	Mean (SD) I: 68(12) C:69(9)	I: 13 (59) C: 15 (71)	I: 22(100) C:21(100)	Elective resection of nonmetastatic colorectal cancer I: Colon[a]:9 (41) Rectum[b]:9 (41) Missing[d]: 4 (18) C: Colon[a]:9 (43) Rectum[b]:11 (52) Missing[d]: 1 (5)	Patient-Generated Subjective Global Assessment C&B I: 9(41) C:7(33)	Grip strength left hand, kg, Mean (SD) I: 31 (11) C: 30 (9) 6MWT, meters, mean (SD) I: 424 (133) C: 441 (90)
Maňásek, 2016	Mean(SD) I: 64(9.9) C:NA	NA	I: 52(100) C: NA	Colorectal cancer patients without distant metastasis, undergoing surgery	Working Group of Nutritional Care in Oncology Czech Society (PSNPO) screening protocol. The total score	NA

					consisted of a sum of four risk factors – weight loss, BMI, food intake and a risk diagnosis. Reported at risk or malnourished I: 39 (75) C: NA	
Multimodal Prehabilitation						
Li, 2013	Mean(SD) I:67(11) C:66(12)	I: 22(54) C: 29(64)	I: 42(100) C:45(100)	Elective surgery for primary colorectal cancer I: Colon[a]: 19 (45) Rectum[b]: 23(55) C: Colon[a]:14 (31) Rectum[b]:31 (69)	NA	6MWT, meters, mean (SD) I: 422 (87) (baseline) 464 (92) (preop) C: 402 (57) (preop)
Gillis, 2014	Mean(SD) I: 66 (14) C:66 (9)	I:21(55) C:27(69)	I:38 (100) C: 39 (100)	Curative, elective resection of nonmetastatic colorectal cancer I: Colon[a]: 24 (63) Rectum[b]: 14 (37) C: Colon[a]:23 (59) Rectum[b]:16 (41)	NA	Grip strength left hand, kg, Mean (SD) I: 29 (11) C: 32 (9) 6MWT, meters, mean (SD) I: 421 (120) C: 425 (84)
Chia, 2016	Median(range) I:79 (65–93) C: 81 (75–97)	NA	NA	Major colorectal resection (78-81% elective surgery in the control and intervention group, respectively) I: Colon[a]: 36(63) Rectum[b]: 21(37) C: Colon[a]: 30(50) Rectum[b]: 30(50)	NA	Frailty according to Fried classification: I: 15(26) C: 15(25)

"I" refers to intervention group (prehabilitation); "C" refers to the control group; 6MWT is six-minute walk test; SD is standard deviation; BMI is body mass index.

[a] includes right and left hemicolectomy, sigmoid resection, transverse colectomy

[b] includes anterior resection, low anterior resection, abdominoperineal resection, proctocolectomy and total colectomy

[c] total pelvic clearance, laparotomy

[d] missing data according to reported sample size

Intervention characteristics

Most studies (6/9) employed a standard of care control group, while one study used a rehabilitation control group[168], and two studies used dietary advice as a control group[244, 245]. ONS was administered as the nutrition intervention in all studies (although the nutrition intervention in the study by Chia et al [249] was not well defined) (Table 6). The interventions were individualized to patient needs in most studies (5/9 studies)[44, 168, 244, 249, 250]; three studies provided standardized ONS recommendations to all patients [245, 246, 248] and one study encouraged ad libitum ONS intake[247]. While four studies[44, 168, 249,39] did not provide enough information to estimate actual energy and protein intakes, mean preoperative daily intake from ONS was determined for the remainder of studies: energy intake from ONS ranged from 88-542 kcal and protein intake ranged from 18-22g. The shortest mean duration of any prehabilitation intervention was reported to be 14.5 days[247]; three studies did not report the actual duration of the intervention, but based on study inclusion criteria, the prehabilitation intervention lasted > 7 days (Manasek et al [248] 10 days; Khrykov et al [250] 10-14 days; Chia et al [249] 14 days). The mean duration of prehabilitation reported in the nutrition-only studies ranged from 14.5 to 37.6 days. The median duration (mean was not reported) of prehabilitation reported in the multimodal studies ranged from 24.5-33.0 days. All three multimodal studies included aerobic and resistance training[44, 168, 249], which were carried out at home, with the exception of Chia et al[249], in which patients with a Charlson Comorbidity Index >3 received a personalized exercise training program at a day center in a community hospital. Compliance to the prehabilitation intervention prescription could be determined for all studies except two [247, 250], and ranged from 65-94%. The nutrition-only interventions reported a higher mean compliance (range, 75-94%) than the multimodal interventions (range, 65-80%).

Table 6: Description of intervention

Author	Type of oral nutrition supplement	Prescription	Duration of preoperative intervention, days	Preoperative supplemental energy intake (kcal)	Preoperative supplemental protein intake (g)	Compliance to preoperative intervention (%)	Control group
Nutrition Prehabilitation							
MacFie, 2000 (Group 1)	Fortisip (Nutricia) and Fortijuice (Nutricia) as an alternative	*Before surgery*: Encouraged to consume 400ml ONS/ day. Patients were instructed to drink the supplement in addition to, and not in place of, their normal diet	Mean(range) 15.0 (5–59) preop	Reported mean (SEM) 536(22)	Estimated mean 21.4[a]	89.3[b]	No intervention
MacFie, 2000 (Group 2)	Fortisip (Nutricia) and Fortijuice (Nutricia) as an alternative	*Before surgery:* Encouraged to consume 400ml ONS/ day. Patients were instructed to drink the supplement in addition to, and not in place of, their normal diet *After surgery:* A minimum of 7 day supplements were administered in the postoperative period + normal diet. ONS was started as soon as oral fluids were permitted and in the majority of patients this was on POD1. Although patients were instructed to take 400ml/day, they were told to consume an amount that what was tolerable.	Mean(range) 15.0 (5–59)	Reported mean (SEM) 484(33)	Estimated mean 19.4[a]	80.7[b]	No intervention
Smedley, 2004 (Group 1)	Fortisip (Nutricia)	*Before surgery*: Ad libitum ONS between meals. Encouraged in small frequent doses.	Mean(range) 15.1 (7–61)	Reported mean (SD) 542(268)	Estimated mean 21.7[a]	NA	No intervention
Smedley, 2004 (Group 2)	Fortisip (Nutricia)	*Before surgery:* Ad libitum ONS between meals. Encouraged in small frequent doses. *After surgery:* ONS commenced on the first day that the patient was able to take free fluids or a light diet after operation (between 4.7 - 5.8 days after surgery) and ended 4 weeks after discharge from hospital.	Mean(range) 14.5 (7–36)	Reported mean (SD) 536(231)	Estimated mean 21.4[a]	NA	No intervention
Burden, 2011	Fortisip (Nutricia) and Fortijuice	*Before surgery*: A total of 400ml ONS/day to be consumed between meals. Dietary advice consisted of increasing energy and protein from food based on an information leaflet.	Mean (SD, range) 37.6 (43, 10-252)	Estimated mean 450[c]	Estimated mean 18[c]	Reported 36 patients managed 100% of the	Preoperative dietary advice

	(Nutricia) as an alternative					intervention, 8 managed 50%, and 6 managed <25% of the intervention, data missing for 4. Therefore, we estimated overall group mean compliance to be 75%	
Khrykov, 2014	ProSure (Abbott Nutrition)	*Before surgery:* If preoperative dietary intake was determined to meet $\geq$ 75% daily recommended needs, patients received 2 packages ONS (480ml/d). If dietary intake was assessed at <75% daily recommended needs, patients received 3 packages ONS (720ml/d), with the goal of meeting 25kcal/kg and 1.5g protein/kg for 10-14 days before surgery. *After surgery:* In the intervention group, enteral nutrition was initiated for 24 hrs. Patients were then encouraged to consume a post-surgical diet with ONS, progressing the volume slowly. Dietary energy needs were met by the 4th POD until discharge. Patients were also encouraged to mobilize in hospital on POD2 onwards.	NA	2 packages of ProSure[d] =610 3 packages of ProSure=915	2 packages of ProSure[d]=32 3 packages of ProSure=48	NA	No intervention before surgery. After surgery, parenteral nutrition, which progressed to diet and ONS on return of gut function (day 3-4 after surgery)
Gillis, 2016	Immunocal (Immunotec)	*Before surgery:* ONS intake based on individual needs to meet a minimum daily protein intake of 1.2g/kg IBW/day. Individualized nutrition care plans focused on meeting energy and protein requirements with appropriate food choices, management of diarrhea and constipation, blood glucose control, optimization of body composition and nutrient intake by using practical suggestions based on actual food intake. *After surgery:* Identical intervention for 8 weeks.	Median(IQR) 33.5 (23- 49)	Estimated mean 88[e]	Reported mean (SD) 19.8 (7.8)	Reported mean (95%CI) 93.7(86 to 100)	Preoperative dietary advice and placebo

Maňásek, 2016	Nutridrink Protein (Nutricia)	*Before surgery*: A total of 400ml ONS/day to be consumed between meals for at least 10 days before. *After surgery:* A total of 400ml ONS/day to be consumed between meals for two weeks after surgery.	NA	Estimated mean 357[f]	Reported mean(SD) 21.4(4.9)	Reported 36 patients followed the instructions 100%, 13 patients followed 50%, and 3 took ONS irregularly. Therefore, we estimated overall group mean compliance to be 82%	No intervention/ standard diet
Multimodal Prehabilitation							
Li, 2014	Vitalus whey protein isolate INPRO90 (Nutrition Inc.)	*Before surgery:* ONS provided based on individual needs to meet a minimum daily protein intake of 1.2g/kg IBW/day. One or two modifiable dietary behaviours were identified. Exercise: Home-based program with a minimum of 30 min aerobic 3x/week and resistance 3x/week until fatigue Anxiety: A 90-min visit with a trained psychologist focusing on providing anxiety reduction techniques such as relaxation exercises and breathing exercises. Patients received a compact disc of these exercises for home practice. *After surgery:* Identical intervention for 8 weeks post-discharge.	Median (range) 33.0 (21–46)	NA	NA	Reported 45 % full compliance and 70% exercised twice per week during the prehabilitation period; Therefore, we estimated overall group mean compliance to be 65%	No intervention
Gillis, 2014	Immunocal (Immunotec)	*Before surgery:* ONS intake based on individual needs to meet a minimum daily protein intake of 1.2g/kg IBW/d. Individualized nutritional care plans focused on management of diarrhea, constipation, blood glucose control if necessary, optimization of body composition, and appropriate balance of food choices by providing practical suggestions based on actual food intake.	Median(IQR) 24.5 (20-35)	NA	NA	Reported overall group mean compliance 78% during the prehabilitation period	Rehabilitation (identical to prehabilitation intervention, but began after surgery)

		Exercise: Home-based program with a minimum of 20 min aerobic 3x/week and resistance minimum of 20 min 3x/week Anxiety: 60-min visit with a trained psychologist who provided techniques aimed at reducing anxiety, such as relaxation exercises based on imagery and visualization, together with breathing exercises. Patients were provided with a compact disc to perform these exercises at home two to three times per week. *After surgery:* Identical intervention for 8 weeks post-discharge.					
Chia, 2016	Not specified	*Before surgery:* Patients with a Charlson Comorbidity Index >3 received 2 weeks of prehabilitation at a day center in a community hospital. Patients with an index < 3 were required to complete the prehabilitation program at home. The prehabilitation targets were set by the team (nurse, dietitian, physiotherapist) and included cardiovascular and muscle strengthening, and "attention to nutrition" pg. 44. The target for nutrition was to meet 100% of needs via dietary intake within 5-7 days of prehabilitation initiation. *After surgery:* Patients engaged in rehabilitation for 6 weeks. Patients with a Charlson Comorbidity Index >3 received inpatient care at a rehabilitation center for 2-6 weeks, whereas those with a score < 3 followed a home-based rehabilitation program post-discharge.	NA	NA	NA	Reported set targets met in 80% of patients both pre- and postoperatively	Standard of care, which included a transdisciplinary geriatric surgery service.

"I" refers to intervention group (prehabilitation); "C" refers to the control group; ONS, oral nutrition supplement; IBW, Ideal body weight; POD, postoperative day; SD, standard deviation IQR, interquartile range; SEM, standard error of the mean

[a] calculated protein intake was based on reported mean energy intake according to: http://www.nutricia.ie/products/view/fortisip; [b] calculated preoperative compliance was based on the reported mean intake in comparison to prescribed intake; [c] calculated protein and energy intake was based on reported mean compliance according to: http://www.nutricia.ie/products/view/fortisip; [d] obtained from http://www.abbottnutrition.ie/products/product/prosure; [e] calculated energy intake was based on reported mean protein intake according to: http://www.immunotec.com/IRL/Public/en/USA/ShowItemDetails.wcp?Item=00010000; [f] calculated energy intake was based on reported mean protein intake according to: http://nutriciaoncology.pl/produkty/nutridrink-protein/

Outcomes

Length of hospital stay

All studies reported LOS (Table 7, Figure 7); although a measure of data variance could not be obtained for one study, with two comparison groups (MacFie et al [246]), and therefore this study could not be included in the meta-analysis. The mean hospital LOS days varied in the prehabilitation groups from 4.9 to 33 days and varied in the control groups from 5.4 to 33 days. In the nutrition-only studies, mean LOS for the prehabilitation groups varied from 7.8 to 33.0 days, and in the multimodal studies, mean LOS for the prehabilitation groups ranged from 4.9 to 8.4 days. Meta-analysis of LOS revealed that the effect estimates and confidence intervals for the nutrition-only and multimodal prehabilitation studies were similar (WMD of LOS, nutrition-only prehabilitation: -2.8, 95%CI: -4.0 to -1.5, I^2: 42,3%; multimodal prehabilitation: -1.4, 95% CI: -3.4 to 0.6, I^2: 47.7%), indicating that these interventions could be pooled. The subsequent stratifications for LOS follow the principle that the nutrition-only and multimodal prehabilitation interventions could be pooled. Thus, the pooled analyses assess the impact of *any* prehabilitation (nutrition-only and multimodal prehabilitation) on LOS.

Table 7: Description of results

Author	Length of hospital stay	Return to functional capacity at 4 weeks, n (%)	Return to functional capacity at 8 weeks, n (%)	Postoperative complications, n (%)
Nutrition Prehabilitation				
MacFie, 2000 (Group 1)	Mean(SD) I: 12.0 (NA) C: 13.0 (NA)	NA	NA	Total no. complications according to definitions as defined by Copeland et al during primary hospital stay I:7(29) C:3(12)
MacFie, 2000 (Group 2)	Mean(SD) I: 11.0 (NA) C: 13.0 (NA)	NA	NA	Total no. complications according to definitions as defined by Copeland et al during primary hospital stay I:6(25); C:3(12)
Smedley, 2004 (Group 1)	Mean(SD) I: 12.8 (4.5) C: 14.1 (6.6)	NA	NA	Total no. complications according to Buzby definition (unclear whether this is for primary hospital stay) I: 20(49); mean no. per patient:0.41 C: 34(77); mean no. per patient:0.68
Smedley, 2004 (Group 2)	Mean(SD) I: 11.7 (5.1) C: 14.1 (6.6)	NA	NA	Total no. complications according to Buzby definition (unclear whether this is for primary hospital stay) I: 15(47); mean no. per patient:0.31 C: 34(77); mean no. per patient:0.68
Burden, 2011	Median I: 13.5 C:14.0 Range for cohort (5-99) Calculated mean(SD)[a] I:33.1 (23.5) C:33.3 (23.5)	NA	NA	Patients with one or more complications using Buzby definition during primary hospital stay I:24(44) C:26(42)
Khrykov, 2014	Mean(SD) Intensive care: I: 1.9 (2.3)	NA	NA	Any complication within 30 days after surgery (unspecified criterion) I: 2(4)

	C:4.5 (3.2) Total length of stay: I: 20.2 (2.1) C:24.4 (3.5)			C: 4(5)
Gillis, 2016	Median(IQR) I: 5.0 (3-13) C:4.0 (3-10) Mean(SD)[b] I: 7.8 (6.7) C:8.4 (9.1)	6MWT within 20m of baseline value I: 8(36) C:8(38)	NA	Patients with at least one complication within 30 days after surgery, according to Clavien-Dindo classification I: 8 (36) C: 9 (43) Patients with at least one complication graded Clavien-Dindo>3 within 30 days I: 2(9) C:2(10)
Maňásek, 2016	Mean (SD) I: 9.4 (5.0) C:12.0 (6.4)	NA	NA	Wound and anastomosis dehiscence and infectious complications within 2–4 weeks after surgery. Postoperative complications (%): Wound: ~5.8 (I) vs. 12.4% (C) Anastomosis: ~1.9 (I) vs. 8.2%(C) Infectious: ~5.8 (I) vs 11.9%(C)
Multimodal Prehabilitation				
Li, 2014	Median (IQR) I:4.0 (3–6) C:4.0 (3–6) Mean(SD)[b] I:5.5 (4.6) C: 5.4 (4.0)	6MWT within 20m of baseline value I: 24(57) C:13(29)	6MWT within 20m of baseline value I:34(81) C:18(40)	Patients with at least one complication during primary hospital stay, according to Clavien-Dindo classification I:15(36) C: 20(44) Patients with at least one complication graded Clavien–Dindo > 3 during primary hospital stay I:2(5) C:1(2)
Gillis, 2014	Median (IQR) I:4.0 (3–5) C:4.0 (3–7) Mean(SD)[b] I:4.9 (4.0) C:7.6 (10.6)	6MWT within 20m of baseline value I: 18(47) C:17(44)	6MWT within 20m of baseline value I: 32(84) C:24(62)	Patients with at least one complication graded Clavien–Dindo > 3 during primary hospital stay[b] I: 1(3) C: 4(10)

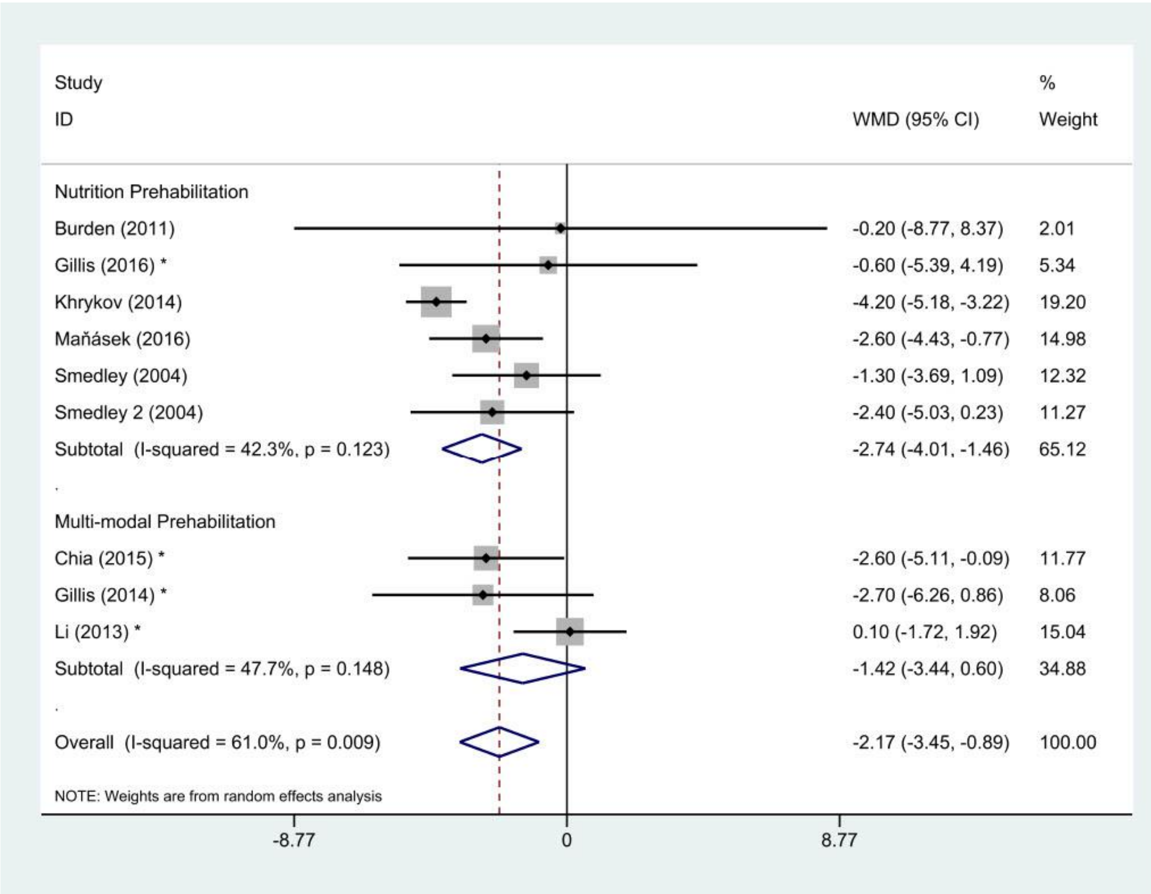
				Patients with at least one complication within 30 days of surgery, according to Clavien-Dindo classification I:12(32) C:17(44)
Chia, 2016	Mean (range) I:8.4 (3–23) C:11.0 (3–37) Calculated SD[a] I:5.0 C:8.5	NA	Modified Barthel Index at 6 weeks after surgery: I: 56(98) C: 56 (93)	Patients with at least one complication graded Clavien–Dindo > 3 during primary hospital stay I:3(5) C:5 (8)

"I" refers to intervention group (prehabilitation); "C" refers to the control group; 6MWT, six-minute walk test; preop, period before surgery; postop, postoperative period after surgery. SD, standard deviation; IQR, interquartile range

[a] calculated using formula as per Hozo et al (reference 31)

[b] calculated from raw data

Figure 7: Nutrition-only prehabilitation and multimodal prehabilitation on length of hospital stay post-colorectal surgery



* Denotes studies employing Enhanced Recovery Pathway (ERP)

Any prehabilitation produced an overall significant WMD of -2.2 hospital days (95%CI: -3.5 to -0.9 days) with moderate statistical heterogeneity (I^2:61%, p=0.009) (Figure 7). The results therefore indicate that receipt of any prehabilitation significantly reduced hospital stay by 2 days. Examined separately, only the nutrition-only prehabilitation intervention had a significant impact on LOS. Nearly all of the nutrition-only studies were conducted in a traditional care setting with only one small nutrition-only prehabilitation study (n=22) being conducted in an ERP setting. It should also be noted that there were comparably fewer multimodal prehabilitation studies contributing to this outcome (i.e., 8 nutrition study groups, n=301 vs. 3 multimodal study groups, n=137) and that all multimodal prehabilitation studies employed ERP care (proven to reduce LOS[35]).

Exploring heterogeneity in length of hospital stay

Stratification by traditional and ERP surgical care revealed that any prehabilitation significantly reduced LOS under traditional care by almost 3 days (WMD of LOS: -2.9 days, 95%CI: -4.2 to -1.6 days, I^2:45,7%), but the effect of prehabilitation did not reach statistical significance under ERP care (WMD of LOS: -1.2 days, 95%CI: -2.8 to 0.4 days, I^2:22,3%) (Appendix B). It should be noted that all of the studies in the traditional care group were nutrition-only prehabilitation studies and nearly all of the studies in the ERP group (except for Gillis 2016[244]) were multimodal prehabilitation studies. There were also comparably fewer ERP patients (4 ERP study groups, n=159 vs. 7 traditional care groups, n=279) contributing to this analysis.

Stratification of any prehabilitation intervention by underlying disease indicated that any prehabilitation significantly reduced LOS by approximately two days in studies of cancer only patients (WMD of LOS: -2.1, 95%CI: -4.0 to -0.2, I^2: 73.1%) and in studies that included cancer and non-cancer patients (WMD of LOS: -2.1, 95%CI: -3.5 to 0.6, I^2: 0.0%) (forest plot not shown).

Postoperative nutrition interventions in-hospital varied: three study groups did not receive a postoperative nutrition intervention[245-247], four study groups received ERP (which included standardized early oral feeding and ONS as per enhanced recovery protocols)[44, 168, 244, 249], three groups received ONS ranging from 7 – 30 days after surgery [247,246, 248], and one group received enteral nutrition[250]. Stratification of any prehabilitation intervention by whether or not a postoperative nutrition intervention was employed identified that in traditional surgical care settings (i.e., non-ERP), a postoperative nutrition intervention facilitates an earlier discharge compared with no in-hospital intervention (WMD of LOS, no postoperative intervention: -1.2, 95%CI: -3.5 to 1.1, I^2:0.0%; postoperative intervention: -3.4, 95%CI: -4.7 to -2.2; I^2: 40.0%) (Appendix C). This suggests that in a traditional surgical setting, nutrition prehabilitation alone does not significantly enhance hospital discharge, but it is the combination of nutrition prehabilitation with postoperative nutritional care that significantly reduces LOS. The ability to tolerate oral intake is part of hospital discharge criteria[251]. This finding, therefore, highlights the importance of establishing early postoperative oral intake on LOS.

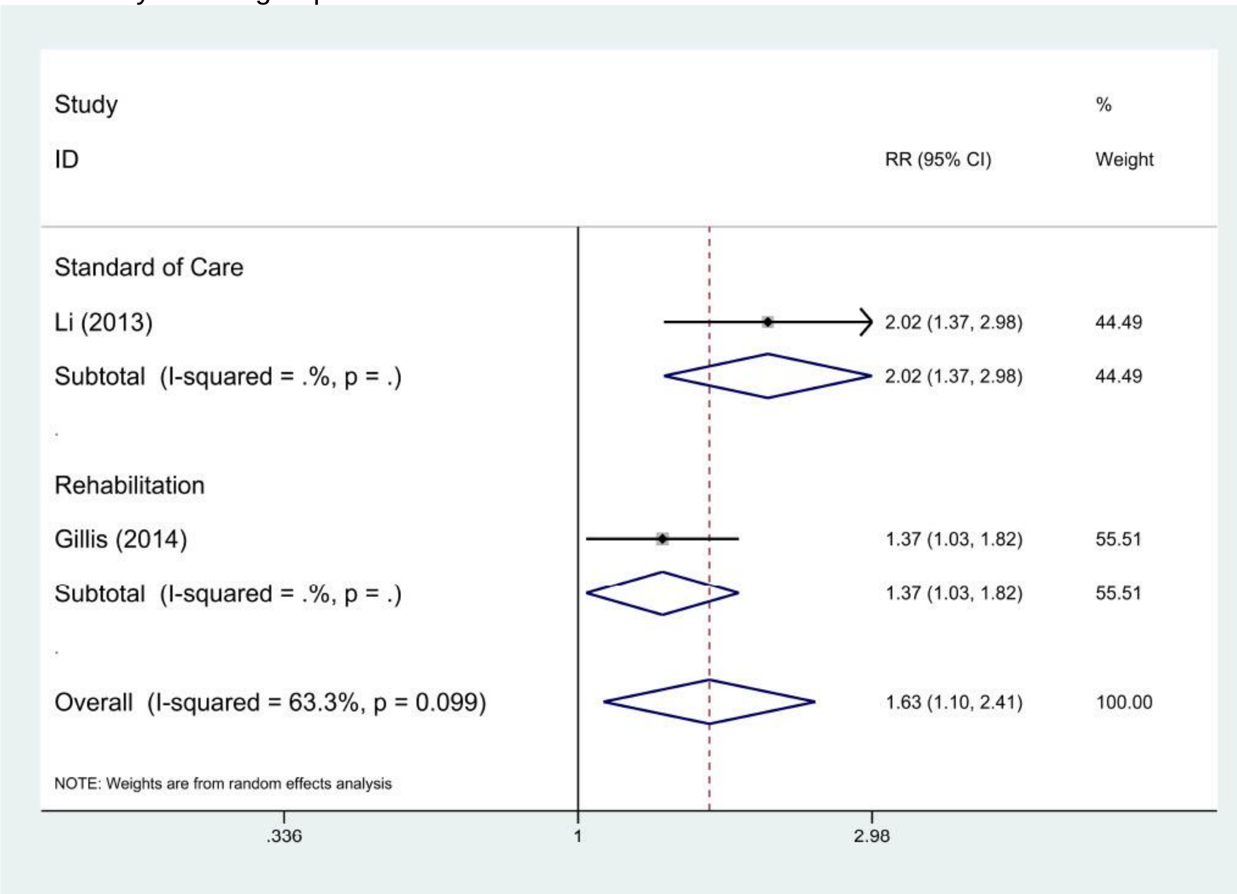
Stratification of any prehabilitation intervention by study design (WMD of LOS, RCT: - 1.8 days, 95%CI: -3.3 to -0.3 days, I^2: 2.5; observational: -2.4 days, 95%CI: -4.4 to -0.4 days, I^2: 0.0%) and concealment of randomization (WMD of LOS, concealed: -1.8 days, 95%CI: -3.3 to -0.3 days, I^2: 2.5%) produced consistent point estimates of an estimated significant savings of 2 hospital days (forest plots not shown).

Return to functional capacity

Two RCTs[168, 244] and one cohort study[44] reported return to functional capacity (mean 6MWT) at 4 weeks after colorectal surgery (Table 7, Appendix D). All three studies were conducted under ERP care. As a result of methodological heterogeneity (two studies were multimodal interventions[44, 168], the other a nutrition-only intervention[244]; the control groups were different among all three studies – one control group received no intervention[44], one control group received dietary advice[244], and the other received an equivalent rehabilitation intervention[168] post-surgery), a pooled analysis could not be performed. In the individual studies, at 4 weeks after surgery, a nutrition-only intervention with whey protein supplementation and individualized nutrition counselling did not significantly improve return to functional capacity compared to standard ERP care with preoperative dietary advice (RR: 0.95, 95%CI: 0.44 to 2.07)[244], whereas the multimodal prehabilitation intervention significantly enhanced functional recovery compared with ERP care alone (RR: 1.98, 95%CI: 1.17 to 3.35)[44]. Compared to postoperative rehabilitation under ERP care, multimodal prehabilitation did not significantly improve return to functional capacity at four weeks postoperatively (RR: 1.09, 95%CI: 0.67 to 1.77)[168].

One RCT[168] and one cohort[44] study provided data regarding the return to functional capacity (mean 6MWT) at 8 weeks after surgery; both studies were multimodal prehabilitation trials under ERP care. Again, a pooled analysis could not be performed due to methodological heterogeneity. However, individually, the studies suggested that multimodal prehabilitation significantly improved return to functional capacity compared to standard ERP care (RR: 2.02, 95%CI, 1.37 to 2.98)[44] and compared to rehabilitation under ERP care (RR: 1.37, 95%CI: 1.03 to 1.82)[168] (Table 7 & Figure 8) at 8 weeks after colorectal surgery. To put these effect estimates into perspective, GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) considers effect sizes >2 to provide evidence of a large magnitude of effect[252]; therefore, multimodal prehabilitation exerts a meaningful impact on functional recovery in an ERP setting.

Figure 8: Multimodal prehabilitation on functional capacity at 8 weeks after colorectal surgery, stratified by control group.



Standard of care refers to Enhanced Recovery Pathway (ERP) care. Rehabilitation was conducted under ERP care.

Postoperative complications

Complication data were reported as total number of complications[246, 247], any complication[250], dehiscence and infectious complications[248], and number of patients with at least one complication[44, 168, 244, 245, 249] (Table 7). The durations for the collected complication data varied, including primary hospital stay versus complications within 30 days of surgery, and were evaluated using various criteria, including, Copeland, Buzby, and Clavien-Dindo. Methodological heterogeneity prevented us from drawing sound conclusions regarding the impact of any prehabilitation on postoperative complications. The following analyses are explorations of the data only and further research is required.

First, to ensure the nutrition-only and multimodal interventions could be pooled, we examined separate meta-analyses of postoperative complications for the two interventions (forest plots not shown). We identified the effect estimates were similar and the 95% confidence intervals overlapped (RR, nutrition-only prehabilitation: 0.85, 95%CI: 0.61 to 1.18, I^2: 45.8%; RR of multimodal prehabilitation: 0.76, 95%CI: 0.52 to 1.10, I^2: 0.0%). The subsequent stratifications for postoperative complications follow the principle that the nutrition-only and multimodal prehabilitation interventions could be pooled.

As a result of this methodological heterogeneity, a meta-analysis of the complications data were stratified by the manner in which the data were reported (Appendix E). The pooled results of this meta-analysis suggest that there is statistically significant evidence in favour of any prehabilitation being protective against surgical postoperative complications (RR: 0.79, 95%CI: 0.64 to 0.98) with minimal statistical heterogeneity (I^2 value = 18.5%, p=0.273). The point estimate continued to suggest that any prehabilitation is protective against surgical postoperative complications when just the ERP studies were included (n=159) in the meta-analysis (Appendix F); although, the result was no longer statistically significant (RR: 0.77, 95%CI: 0.55 to 1.08).

A sub-analysis of a more homogeneous sample was conducted: the proportion of multimodal prehabilitated patients under ERP care with at least one serious complication, as defined by Clavien-Dindo >3, during primary hospital stay[44, 168, 249] (n=3 studies). This sub-analysis revealed a protective pooled RR against developing at least one serious complication (RR:0.65) for multimodal prehabilitation in an ERP setting, compared to control, which was not statistically significant (95%CI: 0.23 to 1.84) with 0% statistical heterogeneity (p=0.260) (Appendix G). The proportion of overall serious complications in these three multimodal studies was 4.4% (6/137) in the prehabilitation group and 6.9% (10/144) in the control group (p=0.362).

Risk of Bias

Of the RCTs, 80% reported randomization concealment, 40% reported blinding of the outcome assessment, and 100% described attrition (Appendix H & I). Of the cohort studies, 100% were completed with an adequate duration (i.e., duration of primary hospital stay), but none reported blinding of the outcome assessment or any assessment of potentially confounding variables, indicating high risk of bias among the cohort studies. Egger's test for small-study effects suggested that the findings were not subject to publication bias (P = 0.102).

Discussion

The present systematic review and meta-analyses identified that the receipt of any prehabilitation (nutrition-only or nutrition with exercise) significantly reduced LOS by two days post-colorectal surgery. However, nutrition-only prehabilitation significantly reduced LOS independent of exercise co-therapy in a largely traditional (non-ERP) surgical care setting. Preliminary evidence also suggested that any prehabilitation is protective against postoperative complications, however further study is required to verify this methodologically heterogeneous finding. Based on the limited evidence available, it is unclear whether these observed *clinical* benefits also apply in an ERP setting. However, our findings suggest that multimodal prehabilitation with nutrition does add unique value to an ERP by contributing additional, complementary, *functional* benefits to the colorectal surgery patient.

The present review suggests that nutrition is a key component of prehabilitation interventions and that "prehabilitation" should be at minimum defined by both its nutrition and exercise components. The pooled analysis of the nutrition-only and multimodal interventions demonstrated that any prehabilitation significantly reduced LOS by two days. Yet, when the two interventions were examined separately, only the nutrition-only prehabilitation interventions, not the multimodal interventions, revealed an overall significant effect on LOS. This finding might suggest that strong adherence to a nutrition-only prehabilitation intervention reduces LOS post-colorectal surgery. Indeed, the adherence to the nutrition-only interventions were consistently higher than the multimodal interventions; possibly because it may be easier to participate and fully comply with just one intervention. However, at four weeks after surgery, the nutrition-only interventions did not further enhance functional recovery, while the multimodal interventions significantly improved the return to pre-surgery functional capacity. Taken together, the limited available evidence (i.e., the multimodal studies contributed only a third of the sample size and only one small nutrition study examined functional outcomes at four weeks) appears to suggest that multimodal interventions comprised of nutrition as the main component and exercise as an adjunct component can promote a more holistic recovery that includes both clinical and functional benefits after colorectal surgery.

It is difficult to disentangle the contribution or impact of each intervention from the impact of the type of surgical care provided on the outcomes studied given the studies available for pooling. Two types of surgical care were pooled in our meta-analysis: traditional and ERP. ERPs, such as Enhanced Recovery After Surgery (ERAS), reduce LOS and complications post-colorectal surgery[35] such that there may be little space for further clinical improvements. Our findings clearly demonstrated that nutrition-only prehabilitation significantly reduced LOS by almost 3 days within a *traditional care system* (Appendix B). Only one small nutrition-only prehabilitation study (n=22) was conducted in an ERP setting; therefore, we cannot conclusively determine whether nutrition-only prehabilitation would have the same effect on LOS in an ERP setting. The multimodal interventions, however, were exclusively conducted under ERP care, and upon stratification, did not significantly reduce LOS. It is possible that because all three of the multimodal prehabilitation studies were conducted under ERP settings, which already significantly influences clinical outcomes, that LOS cannot be further reduced. In this case, multimodal prehabilitation would have little impact on LOS in an ERP setting. It is also possible, however, given that the point estimates were in favour of a reduction in LOS, that the smaller combined sample size of the multimodal studies were insufficiently powered for statistical significance. Indeed, a larger sample size is required to power a smaller change in outcome[241] (i.e., ERP already reduces LOS compared to traditional care). This means that prehabilitation studies would require a larger sample size to detect a statistically significant change in LOS in an ERP setting compared to a traditional care setting. Our analysis and interpretation are, therefore, limited by the availability of prehabilitation studies conducted under ERP care. Without additional data, we can only conclude that nutrition-only prehabilitation successfully reduced LOS in a traditional care setting, and that, overall, when the surgical care setting is unspecified, any prehabilitation significantly reduced LOS post colorectal surgery.

Several additional studies support the theory that nutrition is a key component of prehabilitation. Paddon-Jones et al[253], demonstrated that in healthy young subjects confined to 28 days of complete bedrest, supplementation with 16.5 g essential amino acids and 30g carbohydrates, in addition to nutritionally balanced meals, attenuated the loss of lean leg mass and strength compared to the control group who received only the balanced meals. These results suggest that adequate nutrition, even in the complete absence of activity, can support muscle health. Certainly, dietary intake of protein stimulates the transport of amino acids into muscle, even at rest[254]. It is generally accepted, however, that exercise provides the main anabolic stimulus and nutrition potentiates the muscle protein response[255]. After a healthy individual performs a single bout of resistance exercise, both muscle protein synthesis and muscle protein breakdown are simultaneously stimulated[226]. Yet, net protein balance (protein synthesis minus breakdown) in the muscle remains negative until exogenous amino acids are administered[226, 256]. Amino acids not only stimulate the synthesis of structural proteins, such as myofibrillar proteins, but also the synthesis of mitochondrial proteins required for aerobic metabolism and maintenance of functional exercise capacity[257]. Prehabilitation interventions should be designed to draw on this synergistic effect of nutrition and exercise.

The nutrition component of prehabilitation functions to complement the exercise regimen, but also stands alone to promote optimal patient outcomes. In particular, the dietary protein needs of the pre- and post-surgical patient must be addressed to compensate for the catabolic effects of illness and the additional amino acids required for postoperative healing[6]. Most older adults do not meet the minimal dietary protein requirements established for *healthy* individuals. The Quebec Longitudinal Study on Nutrition as a Determinant of Successful Aging[258], estimated that half of a cohort of 1793 community dwelling older adults consumed less than 1 g protein/(kg·day); recent evaluations of dietary protein requirements suggest that intakes in the range of at least 1.2 to 1.6 g/(kg·day) are required to support optimal health in aging[259]. Dietary supplementation with high-protein ONS has been found to be a useful strategy to successfully improve total protein intake by 22 g (95% CI 10–34 g, $p < 0.001$, $n = 1152$, 10 RCT) without interfering with dietary food intake in a variety of settings[260]. Furthermore, a series of meta-analyses carried out by Cawood et al[260] identified that high-protein ONS, providing greater than 20% energy from protein, compared to a control, reduced complications, readmissions to hospital, and improved grip strength in a wide variety of patient populations and settings. A recent RCT of abdominal and gastrointestinal cancer patients *without* clinical signs of malnutrition, under ERAS care, also found that 14 days of supplementation with high-protein ONS before surgery resulted in fewer serious postoperative complications[151]. Provision of adequate total protein intake should be the main focus of nutrition pre- and re-habilitation interventions.

The present review has several strengths. The findings are specific to colorectal surgery, which minimizes dilution from other types of surgery. This is the first systematic review to our knowledge to evaluate the impact of the type of prehabilitation intervention on clinical outcomes and to stratify the findings by ERP and traditional care. Given the evidence of a clinical impact of ERP on surgical outcomes[35], ERP may act as a modifier[241] of the prehabilitation-surgical outcome relationship and, as such, the impact of ERP should be evaluated separately. It is, therefore, important that any current review of surgical interventions be conducted with consideration of its impact in an ERP setting. Another strength of the present study is that the analyses for our primary finding, LOS, were stratified according to study design and study quality, which did not alter the point estimates and remained statistically significant, thus bestowing greater confidence in this finding. Finally, this review also focused on functional outcomes (i.e., 6MWT). Functional recovery is an important and often neglected patient-centered objective in the world of surgery. From a patient's perspective, recovery does not just refer to clinical outcomes such as length of hospital stay, but includes restoration of activities of daily living and function, resolution of clinical symptoms, and return to work[251]. A shift from evaluating interventions with clinical measures alone, to the inclusion of more patient-centered outcome measures of recovery, such as recovery of function, would enhance the patient-orientation of this area of research.

This review has limitations. First, this review contains a small number of studies (n=9) of small sample sizes, so had limited power to detect differences, especially upon stratification. Second, the statistical heterogeneity must be interpreted with caution because two of the included studies (MacFie et al [246] and Smedley et al [247]) each contributed two study groups, and this likely influenced our statistical heterogeneity. That said, multiple stratifications of our primary outcome by methodological and clinical characteristics did not alter our main finding. Third, quality assessment of studies revealed that the observational studies (4/9 studies) included were at high risk of bias. However, stratification of the LOS outcome by RCT and observational studies did not alter the magnitude nor statistical significance of this finding (WMD of LOS, RCT: - 1.8 days, 95%CI: -3.3 to -0.3 days; observational: -2.4 days, 95%CI: -4.4 to -0.4 days). Furthermore, given that LOS is an objective administrative outcome measure for both prehabilitation and control groups, the risk of bias from the assessment of this outcome is low. It is however worth noting, that LOS might follow a skewed distribution, yet the majority of studies included in our meta-analysis reported the mean and not the median for LOS. We therefore pooled the mean values and assumed that the mean difference between control and intervention groups followed a normal distribution.

The present findings might underestimate the true effect of prehabilitation on clinical and functional outcomes because an assessment of effect modification and confounding according to the preoperative condition of the patients, including nutritional status, was not possible. None of the included studies stratified their findings by preoperative characteristics, which would have permitted a pooled analysis. It has been established that the clinical response to nutrition interventions is partially conditional on nutritional status[261, 262]. Schricker et al [262], for instance, demonstrated, using stable isotope technology, that a significant correlation (r= 0.85) exists between the degree of catabolism before colorectal surgery and the anabolic effect achieved with the use of perioperative nutrition support. At minimum, risk stratification of outcomes by nutritional status might produce clearer findings. Stratifying outcomes by other preoperative patient characteristics, including functional capacity, smoking status and underlying disease, may also provide valuable information for risk stratification purposes.

Based on this systematic review, we have identified several practical suggestions for future investigators of prehabilitation to consider in order to gather the evidence to elucidate how well prehabilitation promotes clinical and functional well-being under different types of surgical care. We suggest: 1) functional recovery be measured in future prehabilitation trials. The 6MWT is a valid measure of colorectal surgery recovery and has already been used as a measure of functional change in a number of published prehabilitation trials[44, 168, 244]; 2) authors provide detailed data for postoperative complications, such as total number of patients with at least one complication, total number of complications, and severity of complications during both primary hospital stay and 30 days post-surgery to reduce between study heterogeneity and enable pooled analyses; 3) authors consider recording the impact of prehabilitation on preoperative administrative outcomes, such as surgery cancellations or delays; 4) stratify findings by nutritional status (at minimum); 5) authors include a standard measure of patient-reported outcomes[263]; 6) prehabilitation studies should assess outcome measures of "resiliency". To evaluate resiliency, we might collect the time to recover from a complication, the length of readmission, the time to return to activities of daily living, and return to intended oncological treatment for cancer patients[264]. Lastly, studies employing ERP should report their compliance to the standardized perioperative elements, so that outcomes could be pooled or stratified by degree of compliance[35].

Conclusion

In conclusion, our systematic review and meta-analysis revealed that nutrition is a key component of prehabilitation interventions. Nutrition prehabilitation alone and when combined with exercise significantly reduced LOS post-colorectal surgery. The available evidence also suggests that multimodal prehabilitation with nutrition would make a complementary addition to ERPs by promoting an earlier functional recovery at 4 and 8 weeks after colorectal surgery.

Chapter summary

The findings of this meta-analysis indirectly support the hypothesis that the patient's preoperative status modifies surgical outcomes. Although findings could not be stratified by preoperative status (e.g., malnutrition) due to limitations in available data, nutrition provision is a known modulator of physiologic reserve and function[83, 151, 153] (described in section 1.3.2); it is thus reasonable to assume that patients who received nutrition therapy were in better condition. The weight of the evidence suggested that nutrition prehabilitation (supplementation alone or in combination with counselling) for at least seven days before colorectal surgery reduced length of hospital stay, compared to a control, independent of exercise co-therapy. The heterogeneity in the data collected for complications and function prevented pooling; however, the individual studies provided some evidence that these outcomes were improved. The data largely originated from centers using traditional, not ERAS, surgical care. Therefore, while it was clear that nutrition prehabilitation shortened length of stay in a traditional care setting, it is not yet known whether this positive finding continues to hold true in an ERAS care setting. The results of this meta-analysis add to the body of literature on prehabilitation because, to the best of our knowledge, this is the first meta-analysis:

- to focus on nutrition optimization and to stratify findings by type of prehabilitation (nutrition vs. multimodal). The findings suggest that optimization of nutrition status might enable patients to withstand the surgical stress response, as evidenced by earlier hospital discharge.
- to focus specifically on colorectal surgery. Patient populations might respond differently to prehabilitation; it is, therefore, important to appraise stratified findings before pooling data across patient populations and surgical specialties.
- to consider the influence of surgical care (i.e., ERAS) on outcomes.

Chapter 5: Prehabilitation: A useful extension of Enhance Recovery After Surgery protocols for patients

Chelsia Gillis[1]*, Marlyn Gill[2]*, Leah Gramlich[3], S. Nicole Culos-Reed[4], Gregg Nelson[5], Olle Ljungqvist[6], Francesco Carli[7], Tanis R Fenton[1,8].

*first two authors contributed equally

[1]Cumming School of Medicine, Department of Community Health Sciences, University of Calgary; [2]Patient and Community Engagement Research, O'Brien Institute, University of Calgary; [3]Department of Medicine, University of Alberta; Edmonton; [4]Faculty of Kinesiology and Department of Oncology, Cumming School of Medicine, University of Calgary; Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services; [5]Departments of Oncology and Obstetrics & Gynecology, Cumming School of Medicine, University of Calgary, Calgary; [6]Faculty of Medicine and Health, School of Health and Medical Sciences, Department of Surgery Örebro University, Örebro, Sweden; [7]Department of Anesthesia, McGill University Health Center, Montreal, Quebec; [8]Nutrition Services, Alberta Health Services.

Status: Submitted to *Clinical Nutrition*

Abstract

Background: Enhanced Recovery After Surgery (ERAS) and prehabilitation programs are evidence-based and patient-focused, yet meaningful patient input could further enhance these interventions to produce superior patient outcomes and experiences.

Methods: Semi-structured interviews of colorectal surgery patients under ERAS care were conducted within three months post-surgery to describe: 1) how patients are currently preparing for surgery; 2) patient thoughts on prehabilitation, including whether patients felt a prehabilitation program would be an acceptable addition to future surgical care; and, how prehabilitation could be delivered to best meet patient needs. Patient interviews were independently analyzed using inductive thematic analysis by a researcher and a trained patient-researcher.

Results: Three main themes were identified from patient interviews (n=20). *Waiting for surgery*: patients described fear, anxiety, isolation and deterioration of their mental and physical states as they passively waited for surgery. *Preparing would have been better than just waiting*: patients perceived that a prehabilitation program could prepare them for their operation if it addressed their emotional and physical needs, provided personalized support, offered home strategies, involved family, and included surgery expectations. *Partnering with patients*: preoperative preparation should occur on a continuum that meets patients where they are at and in a partnership that respects patients' expertise and level of desired engagement.

Interpretation: We identified several patient priorities for the preoperative period that could be addressed with concerted action from ERAS and prehabilitation programs. Actively engaging patients in the recovery process might ameliorate some of the anxiety and fear associated with passively waiting for surgery.

Introduction

The Enhanced Recovery After Surgery (ERAS®) program for colorectal surgery involves the implementation and evaluation of >20 multimodal perioperative care elements[27]. Collectively, these elements standardize surgical practice, attenuate surgical stress, and support intermediary recovery, including earlier discharge from hospital[26, 265]. The clinical benefits observed with ERAS are largely attributed to modulation of the metabolic perturbations associated with the physiological response to surgical injury[266]. Complementary to ERAS, prehabilitation programs aim to work with patients to optimize their physical and mental well-being *before* surgery, enhancing metabolic capacity to withstand surgical stress and facilitating longer-term recovery, including return of pre-surgery strength and function[117]. Prehabilitation programs may be uni-modal[167] (e.g., exercise-only) or multimodal[168] (e.g., exercise, nutrition, anxiety-reduction) and are implemented during the natural waiting period for surgery. While both ERAS and prehabilitation programs are evidence-based and patient-oriented, there is a dearth of published evidence examining patient input to enhance either ERAS or prehabilitation programs. Meaningful patient input could enhance these interventions to produce superior patient outcomes and experiences. In fact, integrating patient engagement research within the healthcare system is a recognized strategy of the Canadian Institutes of Health Research (CIHR) to improve health outcomes by 2025[267].

The traditional role of patients and their families has long been as the recipients of care that is ‘done to’ them, and on occasion, as participants in clinical studies. Under the umbrella of patient engagement, however, patients are not passive recipients of healthcare, but assume shared responsibility for their health, healthcare decisions, and in the improvement of both health research and services[268]. Involving patients in healthcare decision-making has the potential to reduce costly mismatches between research and patient needs, improve the quality and uptake of interventions, and enhance patient satisfaction and outcomes[269, 270]. Additionally, commonly reported benefits of patient engagement by researchers include enhanced enrollment and retention of study participants[271]; thus, facilitating the achievement of important study objectives that enhance internal validity by avoiding selection and attrition bias.

A systematic review of 11 qualitative studies on patients' experiences of ERAS highlighted several patient-oriented issues that could be addressed to foster improvement[272]. Specifically, patients expressed a need to clearly understand the rationale for each ERAS element –*"it's all very well giving me the dos and don'ts, but I want to know why you do and why you don't do this?"*[272] – in order to feel convinced and motivated to make an effort to adhere to the elements. The authors of this review also concluded that patients were highly motivated to be active participants in their own recovery[272]. These findings resonate with our previous qualitative patient-led work with ERAS patients post-colorectal surgery, in which participatory analysis of patient interviews and focus groups produced the following overarching concept: *invite me into ERAS, from diagnosis to recovery, so that I can take responsibility for my own health* [273]. Building surgical care programs with patient input has great potential to enhance patient experience and improve outcomes.

The research objectives of the present qualitative study in colorectal surgery patients under ERAS care were to describe: 1) how patients are currently preparing for surgery; and 2) patient thoughts on prehabilitation, including whether patients felt a prehabilitation program would be an acceptable addition to future surgical care, and how prehabilitation could be delivered to best meet patient needs.

Methods

Enhanced Recovery After Surgery (ERAS)

The ERAS elements are executed throughout the perioperative period, with the majority of these elements focusing on the intra- and post-operative periods[27]. Preoperative education, however, is a central tenet of ERAS care. At our institution education is offered to all colorectal patients as an optional, single session group class before surgery. The class is co-taught by an ERAS-trained nurse and dietitian. The nurse explains the ERAS elements, what is expected of patients, and describes the surgical experience so that patients are better prepared for their operation. The dietitian explains the postoperative diet, encourages the use of oral nutrition supplements during admission, and lets patients know she is available to them upon request while they are in hospital.

Preoperative optimization with prehabilitation is not currently part of ERAS care. Prehabilitation programs for colorectal surgery are typically initiated four weeks before surgery and may include personalized counselling to optimize cardiorespiratory, nutrition, and mental wellbeing[168]. The elements of prehabilitation are not typically static, but dynamic and responsive to personalized patient risk factors, abilities, and willingness to participate[117]. The goal of most prehabilitation programs is to promote surgical resiliency, agency and self-efficacy[274].

Recruitment

Patients were enrolled between April 2018 and June 2019 through purposive sampling from one hospital in Alberta, Canada employing the ERAS Alberta Implementation Program for colorectal surgery[2]. Patients met inclusion criteria if they were >18 years of age, spoke English well enough to participate in an interview, had primary colorectal surgery under ERAS care within the preceding three months, and had not participated in a prehabilitation program previously. Patients who met inclusion criteria were approached by hospital staff during their admission for surgery and provided verbal permission for CG to explain study details. CG obtained informed consent and scheduled the interviews. The researchers had no prior relationship with any of the study participants. None of the participants withdrew from the study. Ethics approval for this study was obtained by the Conjoint Research Ethics Board (REB17-2138).

Data collection

Semi-structured interviews of colorectal surgery patients were conducted by CG within three months after each patient's operation, at a time and place that was convenient to the patient. Interview sites included at the patient's hospital bedside, in a private room at the library, and on the telephone. All interviews were audiotaped and transcribed by CG.

The interview questions were developed with input from our multi-disciplinary team along with input from our patient-researcher (MG). The questions included: 1) How did you spend your time while you waited for your surgery date? 2) How did you get ready for surgery? 3) What are your thoughts on offering future patients a prehabilitation program: a program that involves interventions (such as, but is not limited to, nutrition, exercise, and anxiety-reduction strategies) before surgery with the aim of getting patients in the best possible shape for their operation? 4) Would you have participated in a prehabilitation program if it had been offered? 5) What do you think a prehabilitation program should look like? Prompts and probing were used as appropriate to elicit more in-depth responses to the questions.

Data were analyzed iteratively, and data collection ceased when saturation was reached. Saturation was defined in our study as the point in which code saturation was reached or when no new information was raised by interviewed participants[275].

Data analysis

Patient transcripts were organized by CG and co-analyzed by CG and MG. For the purpose of being reflexive and transparent, CG is a Registered Dietitian and PhD Candidate who has been conducting ERAS and prehabilitation nutrition-related research for 10 years. MG is a patient with surgery experience and is a trained patient-researcher with the Patient and Community Engagement Research (PaCER) group at the University of Calgary. CG and MG independently analyzed the data for the purpose of achieving investigator triangulation, in which multiple perspectives are used to add breadth to the analysis and confirm findings[276]. Differences in observations between researchers were discussed before coming to a consensus.

The interviews were analyzed with a descriptive form of inductive thematic analysis, described by Braun and Clarke[277]. Using inductive thematic analysis, coding and theme development were formed from the “bottom-up”. That is, codes such as “anxiety”, were identified through prioritization of participants’ meanings and experiences. An inductive approach, rather than deductive (coding data based on pre-defined codes), was deemed appropriate for this work given the paucity of published research on the preoperative experiences of patients within an ERAS setting. The analysis involved six steps[277]: 1) familiarization with the data; 2) coding the data based on descriptive elements of the data; 3) identifying potential themes from the codes and sorting data according to identified themes; 4) reviewing and refining the themes (within and across the dataset); 5) defining the themes; and, 6) reviewing the analysis in the context of the current literature.

Results

Twenty colorectal surgery patients participated in interviews lasting 25-60 minutes at a mean 25 days (standard deviation, SD: 13 days) post-colorectal surgery. Ten interviews were conducted in hospital at the patient’s bedside, 6 interviews took place in-person after discharge from hospital, and 4 interviews were over the phone after discharge from hospital. Sixty percent of study participants attended the optional pre-surgery ERAS class. The mean age of participants was 62 years (SD:13 years). Indications for surgery included cancer (45%, n=9), benign polyp (10%, n=2), Crohn’s disease (20%, n=4), ulcerative colitis (15%, n=3), and diverticulitis (10%, n=2).

Three main themes were identified from semi-structured patient interviews: 1) Waiting for surgery; 2) Preparing would have been better than just waiting; and, 3) Partnering with patients. These themes are represented in Figures 9-11.

Figure 9: Waiting for surgery

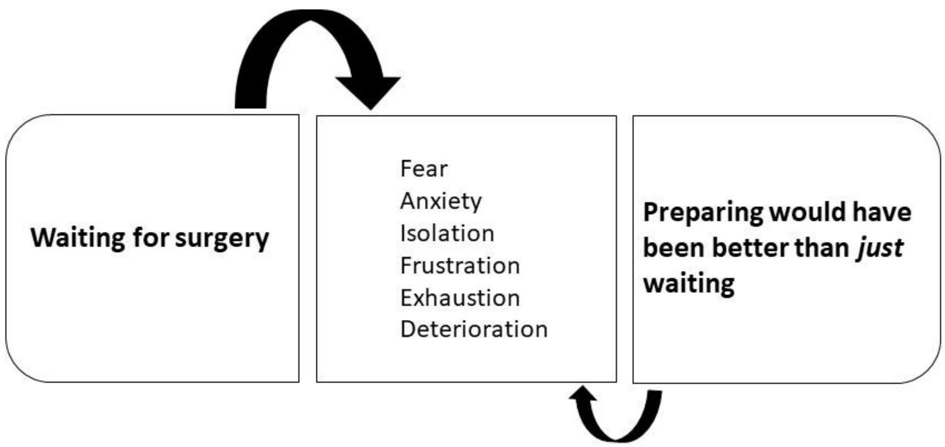
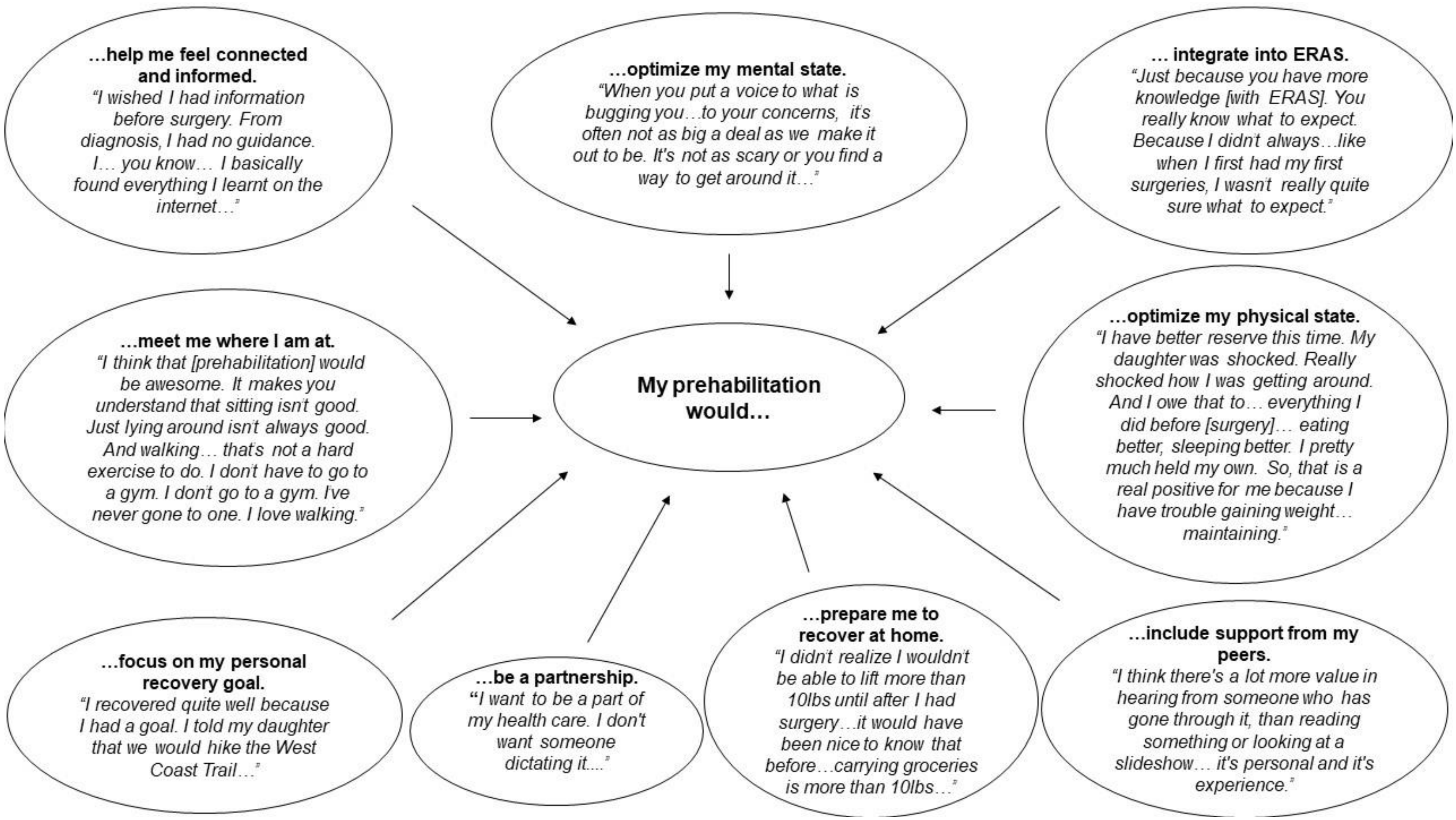


Figure legend: As patients *waited* for surgery, they experienced fear, anxiety, isolation and deterioration of their mental and physical states. The longer patients had to wait for surgery, the more their mental and physical states deteriorated. Actively engaging patients in the recovery process by *preparing* for surgery might attenuate some of the anxiety and fear associated with passively waiting for surgery.

Figure 10: Preparing would have been better than just waiting



My prehabilitation would…
…help me feel connected and informed.
"I wished I had information before surgery. From diagnosis, I had no guidance. I… you know… I basically found everything I learnt on the internet…"
…optimize my mental state.
"When you put a voice to what is bugging you…to your concerns, it's often not as big a deal as we make it out to be. It's not as scary or you find a way to get around it…"
… integrate into ERAS.
"Just because you have more knowledge [with ERAS]. You really know what to expect. Because I didn't always…like when I first had my first surgeries, I wasn't really quite sure what to expect."
…meet me where I am at.
"I think that [prehabilitation] would be awesome. It makes you understand that sitting isn't good. Just lying around isn't always good. And walking… that's not a hard exercise to do. I don't have to go to a gym. I don't go to a gym. I've never gone to one. I love walking."
…optimize my physical state.
"I have better reserve this time. My daughter was shocked. Really shocked how I was getting around. And I owe that to… everything I did before [surgery]… eating better, sleeping better. I pretty much held my own. So, that is a real positive for me because I have trouble gaining weight… maintaining."
…focus on my personal recovery goal.
"I recovered quite well because I had a goal. I told my daughter that we would hike the West Coast Trail…"
…be a partnership.
"I want to be a part of my health care. I don't want someone dictating it...."
…prepare me to recover at home.
"I didn't realize I wouldn't be able to lift more than 10lbs until after I had surgery…it would have been nice to know that before…carrying groceries is more than 10lbs…"
…include support from my peers.
"I think there's a lot more value in hearing from someone who has gone through it, than reading something or looking at a slideshow… it's personal and it's experience."

Figure legend: Patients perceived that a prehabilitation program could *prepare* them for their operation if it focused on optimizing their mental and physical states, offered personalized support from healthcare professionals and peers, provided strategies to help get their home and body ready for postoperative recovery, and included surgery expectations.

Figure 11: Partnering with patients

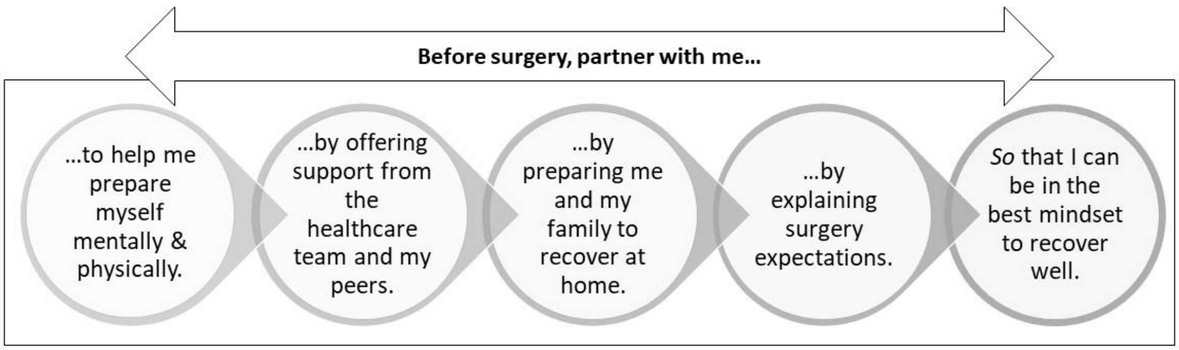


Figure legend: A patient-oriented preoperative program has the potential to ameliorate deterioration during the waiting period for surgery and promote a mindset to recover well. It is essential to recognize that preoperative preparation should occur on a continuum that meets patients where they are at and in a *partnership* that respects patients' expertise and level of desired engagement.

Waiting for surgery

Patients described the experience of waiting for surgery as one that is fearful and anxiety-inducing. For patients with cancer (many with limited healthcare encounters prior to their diagnosis), the fear centered around the unknown and an uncertainty of what is expected of them, as well as what to expect from their healthcare providers, their surgical treatment, and their cancer outcomes. The fears for the patients without cancer (many were “experienced patients” with several healthcare encounters and even prior bowel surgeries) tended to focus on whether they would require an ostomy, whether recovery would be slow, and whether the surgery would indeed improve their condition (this time).

> *"I was anxious. I was having a nervous breakdown, really, because my life had been turned upside down. I wasn't sure if I was going to die…What do I have to do to prepare myself if this is just the end of everything?" - Female; 70 years old; cancer*

> *"I'm so tired and fed up of thinking I'll have this surgery and everything will be fine afterwards and then you still deal with problems afterwards…I know it's a process…you have to heal and it takes awhile to do it. But you sorta wanna be done. Like you've been dealing with it for 20 years and you want it done and over with." - Female; 64 years old; non-cancer*

Patients often felt the period from diagnosis to surgery was isolating and observed little contact from healthcare professionals during this time. Many patients also described a deterioration of their mental (e.g., anxiety) and physical (e.g., weight loss) states; the longer they waited for surgery, the greater their mental and physical states deteriorated.

> *"What could I do to get ready? You know, as far as what to take with you [to the hospital] and that kind of thing that was in the [ERAS] booklet. But for earlier than that, it would have been nice to know things about diet… to try to get me better… if there's something I can do... I'm willing to give it a shot. But I don't know what, you know? What can make it better? That's the other thing I'm looking for." - Male; 78 years old; non-cancer*

> *"My body…since before the surgery date, my body started shutting down. I couldn't eat..." Female; 39 years old; non-cancer*

Most patients did not prepare for surgery. In fact, many patients were unaware of anything they could do to prepare for surgery. Patients expected that their healthcare providers would inform them how to prepare well for surgery, and since most patients were not provided with any preparatory advice, many perceived their role pre-surgery was to be passive.

> *"I would have to say no [preparation]…most medical professionals over my lifetime have said, you know, 'you're in pretty good shape'. So…" - Male; 84 years old; non-cancer*

> *"Basically, there was no preparation. I just…I had to come, I had to get it done… Not really any preparation at all." - Male; 46 years old; cancer*

> *"No [preparation], I just sat at home and stressed"* - Female; 44 years old; non-cancer

Interestingly, nearly all of the experienced surgery patients physically prepared for their operation either by building a reserve before surgery through diet and/or exercise, or by preparing with pre-made frozen meals for anticipated post-surgery immobility.

> *"Well just because I had a bad experience 13 years ago when I had this done… So, I said, If I'm having surgery, I have to be healthy and I have to have some weight on me. You can't go in there skin and bone… no reserve. Because it sure didn't work the last time. So, I ate lots and put on a few pounds just to be ready for this and it's worked. Because the last time I had surgery I was really low, I hadn't eaten, and the recovery was horrible like extremely slow… Nothing like this time. I'm much stronger. Much." - Female; 68 years old; non-cancer*

> *"…I know, like, if you're fit, as far as that goes, that you have an easier recovery afterwards." - Female; 64 years old; non-cancer*

> *"I got out every day with my dogs, so I was getting lots of exercise. Ate a little bit more food just to build up a little bit of fat and extra protein." - Male; 73 years old; non-cancer*

Preparing would have been better than just waiting

Patients perceived that a prehabilitation program could *prepare* them for their operation if it focused on optimizing their mental and physical states, offered connection and emotional support from healthcare professionals and peers, provided strategies to help patients and their families get their home ready for postoperative recovery, and included surgery expectations. This type of preoperative program, which addresses patient-identified priorities, has the potential to ameliorate the deterioration associated with passively waiting for surgery and "*promote a mindset to recover well*".

Patients recognized mental preparedness as vitally important to the success of their surgery and perceived that the greatest strength of a prehabilitation program could be the opportunity to receive additional support (emotional, social, opportunity to address any concerns that might arise). Some patients also saw a prehabilitation program as an opportunity for connection (a "link" to the system) during the perceived void that exists between diagnosis and surgery. This was particularly important for patients with long surgical wait-times (i.e., many patients without cancer).

"… at the Tom Baker [cancer center] they kept emphasizing positivity and positive attitude. So, I went through a lot of research…meditation and other things to improve my outlook…I think that has helped me a lot in that recognizing the mind-body connection and recognizing how our experiences, the way we perceive our experiences, is what makes us suffer, not the experience itself…alone. I can't do anything about it… I can't undo it. So, I will go forward and make it as easy an experience that I can possibly make it." - Female; 70 years old; cancer

"I know it [prehabilitation] costs money and stuff, but you know, I wish a program like this was made available to people, you know, so that you had somebody that you could talk to before surgery and somebody that you could go back to after surgery and say like, 'this is where I am now' and… and see the positive." - Female; 44 years old; non-cancer

Many patients felt that a prehabilitation team could primarily support them emotionally by listening to them. Several patients expressed a desire to share their fears and concerns with healthcare professionals and peers. From a patient perspective, "team" did not necessarily mean direct access to each "specialist" team member but having a single reliable contact with whom they could share their concerns and direct their questions.

"*I think when you're…going for surgery… you are worried about the surgery, worried about how you're going to feel after, worried about, like, are you going to have a pouch [ostomy]… what's that all going to look like? Cause you never know until you wake up. I think sharing some of that eases your mind. You go under the anesthetic in a better frame of mind, so you wake up in a better frame of mind." - Female; 68-year-old; non-cancer*

"If you've never gone through cancer, you've never gone through that fear… I can explain it to you, but you haven't gone through it yourself. So, the thing you can do to help me is to hear me. Let me explain my experience to you so that I can feel that you maybe get a little bit of it and I'm not alone. Because if you try to make me feel better or try to make it go away, then I don't feel heard and I don't feel that you understand." - Female; 70 years old; cancer

Additionally, patients identified that the prehabilitation team should include *peers with surgery experience*. Patient expertise was viewed as critical to alleviate stress and concerns, to help them prepare well (e.g., "*you don't know if you haven't been through it, what questions to ask")*, and to establish buy-in for participation in any program that aimed to get them ready for surgery. Although it was felt peer support should be regulated to avoid "*any horror stories*" being told. Additionally, patients viewed family as a source of support and felt their family or caregiver would benefit from participating in prehabilitation as well (e.g., learning what foods to prepare).

"I do believe that the deep breathing and whatever else can help. But rather than somebody that's read it in a book telling you, hearing it from someone else who has experienced it packs a lot more wallop than somebody that read it in a book.

You know that's not experience, strength and hope… that's just read out of a book. Just like my experiences the first time [surgery] were helpful and prepped me for this [second surgery]." -Female; 68-year-old; non-cancer

"But one thing in the post-recovery… there should have been a section in there for the spouse or a caregiver as to how to handle people: How to help lift patients out of bed, what signs to watch for trouble, and, you know, what foods would be better than others… that kind of thing… that is missing" - Male; 78 years old; non-cancer

Patients anticipated that a prehabilitation program comprised of exercise and nutrition strategies might indirectly help through preoccupation. Actively engaging patients in the recovery process might ameliorate some of the anxiety and fear associated with passively waiting for surgery.

"I think if I'd had some tips…here's some things that you can kind of do to not sit at home and stress all day long that something is going to go wrong. Like I think for me, that would have been beneficial… just, you know, to have a list of things that I could have done to preoccupy myself. "- Female; 44 years old; non-cancer

"…I think anything that helps them [patients] to get control is good and one of the things that we can do is eat properly…" - Female; 70 years old; cancer

The few patients that did not perceive exercise prehabilitation to be beneficial understood "exercise" as strenuous and/or involving gym attendance, which provoked worry related to safety and a possible delay in having their surgery. Another patient was convinced that her deteriorating condition could be improved *only* with surgery, making the idea of participating in any sort of prehabilitation intervention (i.e., exercise, nutrition, etc.) unhelpful. Interestingly, these patients also opted *not* to attend the optional preoperative ERAS education class.

"…wouldn't it be wonderful to find yourself getting ready for cancer operation, only to find out you've broken your leg trying to do this…or you've done something here that's screws something… or your biggest fear: you don't wanna come down with a cold, because if you come down with a sickness, your operation is cancelled. It's taken you 5 months to get in, what are you gunna do? I think that's nuts." - Male; 77 years old; cancer

***"**No [to prehabilitation]. I wasn't gaining any weight before that surgery, but I've gained about five pounds back now [postoperatively]" - Female; 59 years old, non-cancer*

Many patients proposed that the best delivery method for a prehabilitation program would be to offer a group class and then additional one-on-one sessions for those that need it or prefer it. A class setting was viewed by most as an environment that could be a relaxed, informal discussion and provide opportunity for sharing as well as for making peer connections.

> *"I think…I think…you know either a group or group meetings for pre-surgery stuff like that is always going to be helpful. Because there is so much for people to take in….if it is done in a group setting where maybe it's a little bit more relaxed and you're generally having a discussion about it... it may… might make it easier. People might take more in because you're not physically talking about that person who's having the surgery…you know …you're not directly dealing about me so I feel more comfortable because you're just talking about it in general you know. You know I think it would be a good thing."* - Male; 49 years old; cancer

All patients felt that being well-informed regarding their surgical procedure, expectations, and perioperative logistics was of utmost importance to their preoperative education. Nearly every patient praised the ERAS preoperative education class they attended for offering clear explanations of what they could expect postoperatively. However, many patients perceived that the ERAS class was missing discharge information that would have helped them better prepare their home and body for recovery. For example, patients wanted to be informed to buy heavy groceries before surgery (given the 10lbs weight limit post-surgery, which was a surprise for one ill-prepared patient), to prepare and freeze appropriate meals, and to learn how to get out of bed or cough properly with an incision. Patients identified the postoperative period as being too late to receive this information. Additionally, the postoperative period was identified by some as a time when they were inundated with information, which was also difficult to comprehend at that time given the pain medications.

> *"It was new to me and it was very frightening for awhile…when you get explained what is going to happen and how it's going to happen and all the steps to it, it makes you feel so much more comfortable." -Female; 71 years old; cancer*

> *"You don't realize what muscles you use to get out of bed" -Female; 75 years old; non-Cancer*

Partnering with patients

Some patients observed that setting realistic and personalized goals were important to their recovery. Prehabilitation programs could be beneficial if structured around partnering with patients to set pre- and post-surgery goals that *are relevant to them* (e.g., playing hockey again). It is important to meet patients where they are at.

> *"…it doesn't have to be exercises; It could just be a walk in nature, right? Do something that makes you feel better. Do something that gives you a little strength and for each person that will be something different, right? So that's what they can do. They can prepare themselves by making themselves as strong as possible today. What is important for you today to do to make you feel a little stronger? So I think that that can help. And then the other thing that can help is just to let them know, we… we're here for you…" - Female; 70 years old; cancer*

Lastly, patients expressed a desire to be treated as an expert on their body, and most patients want their expertise recognized in the form of a partnership with their providers. As an example, many experienced patients are aware of what foods aggravate their condition and were frustrated with healthcare professionals telling them what foods will or will not bother their digestive tract.

> *"I just couldn't seem to digest things properly and that…they told me a little bit of stuff ….but I also knew the facts with my body, what I was like, what I could eat and tolerate and what I couldn't." - Female; 64-year-old; non-cancer*

Discussion

Patients identified several preoperative items that they believed improved or could have improved their surgical experience and outcomes; these items included mental preparedness, emotional and social support, understanding surgical expectations, and having knowledge of post-surgical limitations to prepare themselves and their home for postoperative recovery. These identified patient-priorities suggest that patient needs can be met through the ERAS element of preoperative education together with prehabilitation. While prehabilitation largely focuses on patient optimization (mental/physical states and support), ERAS focuses on surgery expectations which could be modified to include home strategies (Figure 11). Together ERAS and prehabilitation might help patients achieve a mindset that permits optimal recovery and, perhaps, even a sense of agency.

Preoperative patient-related factors, such as anxiety, malnutrition, and poor functional capacity, contribute to an exaggerated, prolonged, or impaired response to surgical stress, and are associated with adverse outcomes[8, 278]. An aim of multimodal prehabilitation is to is to work with patients to prepare them metabolically by enhancing cardiorespiratory capacity and physiological reserves, as well as mentally through anti-anxiety and coping strategies, to withstand the impending surgical stress response[117]. Patients who additionally have surgery under ERAS care, benefit from the elements that reduce the metabolic response to surgery, making the surgical stress response more tolerable for vulnerable patients[8]. Collectively, these two surgical programs facilitate earlier recovery[43, 164, 166]. The present results add to this literature by highlighting that prehabilitation integrated within ERAS care is perceived to be of personal value to most patients as well.

Surgical recovery has traditionally been viewed as a passive process. In 1989 Baker[279] conceptualized recovery as a process that moves successively through three phases: passivity, activity and stabilization. Baker described passivity as a time of rest to support convalescence, and noted that patients progressed through these three phases by integrating physiological and healthcare provider cues with internal and external pressures[279]. Our qualitative findings reveal a similar patient experience today. Most of our patient-participants passively waited for surgery because they did not anticipate any sort of prehabilitation was necessary, and they relied on their healthcare providers to inform them of best surgical practices. Yet, nearly all patients instinctively agreed that preparing their body, through nutrition, and/or exercise, and/or stress reduction, for surgery would be beneficial once they were presented with the idea. It is clear that prehabilitation constitutes a paradigmatic shift in which recovery is *not a passive process* and it begins *before* surgery. This idea challenges long-standing beliefs and traditions, and thus it is unlikely that patients will take the initiative to prehabilitate themselves without direction from their healthcare providers.

Interestingly, many patients misunderstood “exercise” to be out of their reach given their illness, rather than as personalized movement plans that could be adapted to their unique condition, capabilities, and preferences. This misconception is an important finding that might impact prehabilitation recruitment rates and must be addressed in the educational component of prehabilitation, as well as during recruitment, to ensure understanding of how movement is beneficial.

Given that many patients reported feelings of isolation in the period from diagnosis to surgery, which they believed could possibly be attenuated with physical and emotional support from a prehabilitation program, establishing supports should be the foundation of prehabilitation programs. In particular, patients identified emotional and social support from peers, family, and healthcare providers to be of value. Social support is a significant predictor of health outcomes, with a recent meta-analysis of 148 studies (n=308,849) on the extent to which social relationships influence mortality risk, indicating a 50% higher likelihood of survival for participants with stronger social relationships [280]. Several qualitative studies have also identified that supportive care is important for psychological well-being during the recovery process[281, 282], and psychological well-being is a significant predictor of functional recovery at 4-6 weeks post-cancer surgery[283].

Group classes might be an important consideration for integration within existing ERAS and prehabilitation programs. Our participants identified group classes as a possible mechanism to share experiences, hope and strength with their peers and the prehabilitation team. Participants thought that the prehabilitation team should include a peer *with surgery experience* to answer their questions, provide insight based on experience (e.g., a list of questions you might want to ask your surgeon), validate their concerns (i.e., provide emotional reassurance and acceptance), and promote prehabilitative components (e.g., deep breathing for relaxation) deemed beneficial *based on firsthand experience*. Clinical and patient benefits reported by several peer support studies reinforce the value of this strategy[284-286]. For example, peer support provided by trained volunteers for adults with diabetes significantly reduced glycated hemoglobin relative to usual care[286]. Additionally, a randomized trial of self-management education with or without peer support identified that the peer-led group sessions with additional telephone support were successful in improving body mass index and cardiovascular risk factors compared to the same program offered without peer support[285]. Collectively, these findings suggest that with appropriate support and resources, patients can be empowered agents of change, actively developing their individual expertise to manage their health conditions[287].

While the current results highlight some potential points to consider within prehabilitation programs in colorectal surgery patients, we would like to acknowledge some limitations. Given that we did not interview patients pre-surgery, and relied on post-surgery accounts of pre-surgery needs, it is possible that we have not captured the full spectrum of patient experiences and priorities before surgery. In addition, as with all qualitative work, our findings are not necessarily generalizable to all colorectal surgery patients. For instance, at our site, we already have ERAS group classes in place, which might have encouraged a natural propensity to favour a class format. Also, our findings suggest that the preoperative needs of cancer patients and non-cancer patients somewhat differed (in terms of being “experienced” vs “inexperienced” patients and surgical wait-times), and this suggests that separate classes tailored to the unique needs of these groups might be appropriate. Our sample size, however, did not allow us to reach saturation to contextualize these group differences. Future studies might aim to explore the unique experiences of cancer and non-cancer patients.

Conclusion

Patients expressed positive feelings about prehabilitation as an addition to ERAS care. For most patients, passively waiting for surgery was associated with negative feelings and a recognized deterioration in their physical and mental states. Most patients appreciated the idea of a prehabilitation program directed at addressing their emotional and physical needs, but many had not thought to initiate a prehabilitation program on their own. Patients identified several preoperative items for potential inclusion in ERAS and/or prehabilitation programs, including emotional and social/peer support, mental preparedness, and having an available “link” to the healthcare team in case of any concerns or questions that arise. Patients noted the value in having knowledge of surgery expectations and post-surgical limitations so that they could, together with their family, practically prepare themselves and their home for postoperative recovery. Patients saw the postoperative period as being too late to receive this information. Integrating these identified patient-priorities within ERAS and prehabilitative services could improve patient satisfaction, experiences, and outcomes.

Chapter summary

While it is important to explore whether or not the preoperative condition of the patient modifies surgical outcomes, it is equally important to understand whether or not patients are receptive and interested in preoperative interventions, such as prehabilitation. That is, evidence that prehabilitation is a useful strategy to improve the preoperative condition (modify physiologic reserve and function) is of little value without the cooperation of the patient. By exploring patient perceptions of prehabilitation, we can begin to build programs that reflect patient needs and address their concerns, which will in turn, promote compliance to these programs and drive improvements in outcome.

This qualitative study adds to the body of literature on prehabilitation because:

- as far as we are aware this is the first study to investigate ERAS patient perceptions of prehabilitation. The findings suggest that patients perceive prehabilitation could complement the preoperative education offered by ERAS care through supporting patients to be mentally and physically well for their operation.
- exercise is the pillar of most prehabilitation programs. Yet, the findings of this study suggest that mental preparedness, emotional/social support, and connection are the highest priorities of patients waiting for surgery.
- the findings of this study suggest that preoperative classes meet the basic perceived needs of most patients. Group classes are a potential cost-effective and equitable strategy that offers all patients basic preoperative information, while conserving hospital resources for those who require additional support.

Chapter 6: An evaluation of third variable effects to understand who, when, why, and how patients benefit from surgical prehabilitation.

Chelsia Gillis[1], Leah Gramlich[2], S. Nicole Culos-Reed[3], Tolulope T Sajobi[1,4], Kirsten M Fiest[5], Francesco Carli[6], Tanis R Fenton[1,7]

[1]Cumming School of Medicine, Department of Community Health Sciences, University of Calgary; [2]Department of Medicine, University of Alberta, Edmonton; [3]Faculty of Kinesiology and Department of Oncology, Cumming School of Medicine, University of Calgary. Psychosocial Resources, Tom Baker Cancer Centre, Cancer Care, Alberta Health Services; [4] O'Brien Institute for Public Health, University of Calgary; [5]Department of Critical Care Medicine, Cumming School of Medicine, University of Calgary; [6]Department of Anesthesia, McGill University Health Center, Montreal, Quebec; [7]Nutrition Services, Alberta Health Services.

Status: Ready for submission

Abstract

Prehabilitation is a new field of research that aims to optimize modifiable surgical risk factors before surgery to improve patient-oriented outcomes pre- and post-operatively. As with any new intervention, the pressing questions that arise include what interventions work, for whom they work, and when do they work best? The objective of this paper is to describe the illuminating potential of including “third variable effects” into the integration of research design; by planning for and including measurements of mediators, moderators and confounders in the design and analysis of prehabilitation research, we can begin to answer practical, clinically-relevant questions.

Introduction

An understanding of epidemiological principles benefits the conduct of clinical trials and is an essential component of making appropriate inferences regarding the efficacy and effectiveness of surgical treatments as well as in establishing causal associations among preoperative factors and postoperative outcomes. The first objective of this paper is to define third variable effects of mediation, moderation, and confounding on outcomes. The second objective is to explain how careful consideration of third variables (also referred to as external or extraneous variables) enhances the design and analysis of investigative studies to accelerate knowledge generation and translation of evidence into practice. The final objective is to apply these epidemiological concepts to a new surgical innovation, prehabilitation, to illustrate how extraneous, third variables can enhance or hinder our understanding of prehabilitation to advance the evidence.

Prehabilitation

Prehabilitation interventions are designed to optimize modifiable surgical risk factors before surgery to improve functional, clinical, and patient-oriented outcomes pre- and ultimately post-operatively[117]. Prehabilitation interventions exist currently in several forms and include preoperative unimodal interventions focused on improving fitness and/or correcting deficiencies before surgery (e.g., exercise- or nutrition- only interventions[137, 166]), psychological preparation (e.g., stress management[164]), targeted functional interventions to attenuate treatment-related impairments (e.g., pelvic floor strengthening to prevent incontinence[288]), medical optimization to mitigate associated surgical risks (e.g., smoking cessation[289]), and multimodal interventions that involve a combination of the above interventions[290, 291].

Prehabilitation interventions are largely focused on improving patient-oriented measures of recovery. Frequently reported outcomes of prehabilitation research include improvement in health-related components of fitness such as functional walking capacity before and after gastrointestinal surgery[168, 292], improvements in health-related quality of life including a reduction in somatic and psychological symptoms in radical prostatectomy patients[164, 293], attenuation of functional impairments such as range of motion post-treatment for breast cancer [118] and reduced incontinence post-radical prostatectomy[288]. Additionally, the clinical outcomes that have been documented include fewer complications post-abdominal surgery[294] and prolonged disease-free survival in stage III colorectal cancer patients[295].

Third variable effects

The goal of prehabilitation research is typically to investigate whether or not a preoperative intervention (independent variable X) produces a desired outcome (dependent variable Y) [296]; and if a casual association between X and Y is identified, the goal is to quantify the strength of the association. Extraneous or third variables (variables Z_1, Z_2…), however, can produce misleading findings of the relationship between prehabilitation and a desired outcome, which cannot be discerned by simply investigating and measuring the X and Y variables alone[296-298].

Mediators, moderators, and confounders are all examples of third or extraneous variables (variable Z) that take place outside or alongside the prehabilitation-outcome relationship and might have an impact on findings, interpretations, and conclusions of prehabilitation research[298]. Thoughtful inclusion of third variables in prehabilitation research design can be useful to address several important interventional questions, including who benefits, why and how patients benefit[297].

What is a mediating variable?

If the third variable Z links X and Y through a causal chain of events, then Z is a mediating variable (ZMed)[296, 298]. The third variable imparts the causal effects of X to Y (X → ZMed → Y) (Figure 12A). Mediators, sometimes referred to as intermediates, can be useful in understanding the process by which X affects Y[299]. Mediating variables and mediation analysis are therefore useful to answer questions such as how does this intervention work and which interventions produce the desired outcome?[296] As such, mediation analysis can assist in identifying the key components of an intervention, so that the intervention can be refined to elicit optimal patient benefits and conserve resources.

Figures 12A & B: A schematic and an example of a mediating variable

A. Schematic	**B.** Example
X → ZMed → Y	Prehabilitation (X) → improves preoperative functional capacity (ZMed) → earlier return of postoperative functional capacity (Y)

Figure legend: X causes the mediator (third variable ZMed) and ZMed causes Y.

Prehabilitation interventions (variable X) are based on the theory that by improving the patients' preoperative fitness (third variable Z, the mediating variable ZMed), surgical outcomes can be improved (variable Y)[117]. By measuring and analyzing mediating variables in the design and conduct of prehabilitation studies, we can accomplish two important tasks: 1) Generate evidence that supports or refutes the theory that prehabilitation improves surgical outcomes by way of mediating (i.e., changing) preoperative variables; and, 2) Evaluate the impact of different interventions on mediating variables to test whether or not these interventions are integral components of prehabilitation.

To illustrate this point (Figure 12B), we have reanalyzed pooled data from the prehabilitation arm of Gillis et al.,[15] to build on evidence that either supports or refutes the theory behind the prehabilitation concept: *Do prehabilitation interventions (X) exert their effect on postoperative function (Y) through mediation of preoperative function (Zmed)?*

The prehabilitation group received home-based personalized exercises, individualized nutrition counselling and supplementation, as well as stress-reduction strategies for 4 weeks before colorectal cancer surgery and continued this same program for 8 weeks after surgery [15]. Functional capacity was measured using the six-minute walk test (6MWT) because it is a practical, well-tolerated, and patient-oriented measure of recovery in colorectal surgery (n=76; missing data=1)[72, 76]. The minimal important clinical difference for 6MWT based on longitudinal anchor-based methods is 19m[204].

Table 8: 2 x 2 contingency table of prehabilitated colorectal surgery patients

	RECOVERED 6MWT POSTOPERATIVELY [*Positive outcome*]	**DID NOT RECOVER 6MWT POSTOPERATIVELY [*Negative outcome*]**
IMPROVED 6MWT PREOPERATIVELY	39	2
NO IMPROVEMENT IN 6MWT PREOPERATIVELY	21	13

The Risk Ratio (RR): the ratio of two incidence proportions, can be calculated from the above 2x2 contingency table as the probability of a *positive outcome* in the group that improved 6MWT preoperatively / the probability of a *positive outcome* in the group that did not improve 6MWT preoperatively [298].

Risk Ratio (RR)= $\frac{39/(39+2)}{21/(21+13)}$ = 1.5 (95% Confidence Interval, CI: 1.2 to 2.2, P=0.003)

This finding shows a statistical difference in the likelihood of recovering functional walking capacity within 19m of the baseline measurement at 8 weeks post-colorectal surgery (the positive outcome) is 1.5x greater in those who improved functional walking capacity by at least 19 m in the preoperative period (the mediator), lending support to the theory that prehabilitation promotes an earlier functional recovery through optimization of preoperative function.

Given that we have evidence supporting the theory that a preoperative improvement in functional capacity is associated with earlier functional recovery, we might then ask, how can we effectively improve preoperative functional walking capacity? Again, we can measure and evaluate mediators of this relationship: *Does prehabilitation increase physical activity energy expenditure (mediator), which causes an improvement in preoperative functional capacity?*

We can test this new theory using the same pooled prehabilitation data[15]. The data collected on physical activity in these studies were a self-reported questionnaire known as Community Healthy Activities Model Program for Seniors (CHAMPS) (n=76; missing data =11). Patients were required to estimate the number of total hours spent performing 41 listed activities of various intensities during the previous week[209]. Weekly energy expenditure (kcal/kg/week) was then estimated by adding the energy cost of each of the activities performed over the week. The minimal important clinical difference for CHAMPS is reported to be 9 kcal/kg/week based on longitudinal anchor-based methods[204].

Table 9: 2 x 2 contingency table of prehabilitated colorectal surgery patients

	IMPROVED 6MWT PREOPERATIVELY ***[Positive outcome]***	**NO IMPROVEMENT IN 6MWT PREOPERATIVELY** ***[Negative outcome]***
INCREASED PHYSCIAL ACTIVTY PREOPERATIVELY	15	17
NO INCREASE IN PHYSCIAL ACTICITY PREOPERATIVELY	22	11
RR= $\frac{15/(15+17)}{22/(22+11)}$ = 0.7 (95% CI: 0.5 to 1.1, P=0.107)		

While the findings are not significant, the point estimate suggests that an increase in self-reported physical activity by at least 9kcal/kg/week in the preoperative period is an unhelpful strategy to improve preoperative functional walking capacity by at least 19m.

This example highlights the illuminating potential of mediation analysis. It is possible that this finding is a result of chance, type II error given the small sample size of 65, or the influence of unbalanced covariates from data pooling (see section on confounding). It is also possible that increasing physical activity alone is insufficient to improve preoperative functional walking capacity, especially in patients who are malnourished. Equally likely is that self-reported physical activity is not an effective way to measure energy expenditure from physical activity.

By including and appropriately analyzing mediators in the design of prehabilitation research and through mediation analysis, we can accomplish several things[296]:

1. Provide information on the processes by which prehabilitation achieves its effects on a desired outcome measure, including testing theories upon which prehabilitation programs are based. In this paper we have provided evidence that supports the theory that prehabilitation operates through mediation of preoperative variables.
2. Provide information on the effectiveness of the prehabilitation intervention and/or whether the measurements employed are appropriate. If the mediating variable did not change, it could be because the intervention was unsuccessful, the measurement of the mediating variable was inadequate, or by statistical chance. In this second example, our mediation analysis revealed that either physical activity alone is insufficient to improve preoperative function or that capturing physical activity through self-report is ineffective (possibly because of inaccurate reporting or because total time spent engaged in physical activity without consideration of intensity and type is incomplete), providing directions for future research.
3. Provide information on the components of the intervention that were successful. As an example, by incorporating appropriate mediators for all components of a multimodal prehabilitation intervention[168], such as nutrition, exercise, and psychology, we can identify successful and unsuccessful interventional components. If a component of the

intervention fails to change the mediating variable, it is unlikely to affect the desired outcome, and should be reconsidered.

4. Provide information on the length of prehabilitation required and/or on measurement timepoints. For instance, If the prehabilitation intervention does not have the desired effect on the targeted outcome variable, but does significantly alter the mediating variable, it is possible that the effects on outcome will be apparent over time (i.e., consider a later endpoint measurement) once the effects of the mediating variable have accrued.

Table 10 includes a preliminary list of suggested mediators to consider for inclusion in future prehabilitation research.

Table 10: A list of potentially mediating variables* to consider in the design, conduct and analysis of surgical prehabilitation research

Exercise-related	Nutrition-related	Psychology-related	Multi-interventions
Physical activity energy expenditure (e.g., metabolic equivalent of task) Step count Functional performance, such as handgrip strength (or other strength tests such as maximum bicep curl test), six-minute walk test, timed-up and go, flexibility, and balance. Procedure or disease-specific functional measures, such as pelvic floor strength Exercise performance, such as peak oxygen uptake as determined by cardiopulmonary exercise testing	Malnutrition status Weight changes, waist circumference Dietary intake, including caloric, macro- and/or micro-nutrient intakes, percent target achieved Nutrition behaviors or dietary patterns, such as that described by the healthy eating index[300] Biochemical indices and biomarkers of nutrient intake and nutritional status, such as urinary nitrogen for dietary protein, fructosamine for glycemic control, and serum 25-hydroxyvitamin D for vitamin D status [301] Gut microbiota	Self-perceived improvements in participant-reported outcomes. This may include measures of coping, indices of emotional distress (stress, anxiety, and depressive symptoms), self-efficacy, sense of control, attitude, social support, fatigue, pain, and quality of life.	Quality of life Body composition, including lean and fat mass Biomarkers of inflammation such as C-reactive protein, tumor necrosis factor alpha, and leukocyte count[164, 302, 303] Parameters of metabolic fitness, such as blood pressure, phase angle (through bioimpedance analysis as an indicator of cell membrane integrity[304]), and insulin response to an oral glucose tolerance test. Somatic symptoms, such as fatigue and pain.

*this list is not exhaustive and the appropriate variables to include in the study design, conduct and analysis will depend on the intervention-outcome relationship of interest

What is a moderating variable?

If the third variable Z is a moderating variable, the relationship between X and Y will vary across different levels of Z[296] (Figure 13A). In this case, there is an interaction that corresponds to a potentially different strength and form of association between X and Y at different values of the moderating variable Z. This is also referred to as modification, effect modification, or sometimes as interaction (although the meaning of interaction and modification are not synonymous; “interaction” should be reserved for when joint effects of two or more interventions are being examined)[299]. A mediating variable can also be a moderating variable.

Figures 13A & B: A schematic and an example of a moderating variable

A. Schematic

X →

Z → ZX → Y at Z_1, Z_2, Z_i...

B. Example

Prehabilitation (X) →

Baseline functional capacity measured with 6MWT (Z) →
Prehabilitation*Baseline function (ZX) → Change in preoperative function (Y) at baseline values of 6MWT at <400m & $\geq$400m (levels of Z)

Figure legend: Third variable Z interacts with the intervention (X), such that different values of the outcome (Y) are realized for different levels of Z. The moderating variable can be continuous or dichotomous. Moderators are considered a natural phenomenon that should be reported and described (i.e., report the estimates at each level of Z) and should not be pooled, controlled or adjusted for in statistical analysis.

The inclusion of potentially moderating variables in prehabilitation research and analysis could be useful to address questions such as who benefits most from the intervention (e.g., frail vs. non-frail)? What dosage of the intervention is required to elicit a change in the desired outcome? When should the intervention be initiated to have an impact on the desired outcome? These questions are critical for understanding the extent to which prehabilitation findings can be generalized to patient subgroups as well as to target subgroups that will benefit most, encouraging responsible use of healthcare resources.

As an example, Minnella et al.,[212] identified that colorectal cancer patients with lower baseline functional walking capacity (6MWT <400m), compared to those with higher baseline walking capacity (6MWT $\geq$400m), are more likely to experience meaningful improvement in physical function from prehabilitation before and after colorectal surgery. Are patients with lower baseline walking capacity a sub-group that can be targeted for future interventions? Using the full dataset from Gillis et al.,[15], which includes both prehabilitation (n=76) and control (n=63) arms, we can conduct an exploratory analysis to determine whether or not baseline functional walking capacity acts as a moderator of the prehabilitation-preoperative functional capacity relationship (Figure 13B). Our research question is as follows: *Does prehabilitation improve preoperative functional walking capacity, compared to control; Is baseline functional walking capacity a moderator of this relationship?* Our primary goal is to understand the relationship between prehabilitation (variable X) and preoperative functional walking capacity (variable Y), but based on previous literature, we know that baseline functional walking capacity (third variable, ZX) might influence (moderate) this relationship. In order to draw appropriate conclusions about the impact of prehabilitation vs. control on the change in functional walking capacity before surgery, we need to consider that prehabilitation might exert different effects at different levels of baseline functional walking capacity.

Table 11: 2 x 2 contingency table of prehabilitated colorectal surgery patients

Prehabilitation vs. control for colorectal surgery, unstratified 2x2 contingency table (n=139)		
	IMPROVED 6MWT PREOPERATIVELY [Positive outcome]	**NO IMPROVEMENT IN 6MWT PREOPERATIVELY [Negative outcome]**
PREHABILITATION	42	34
CONTROL	16	47
Crude RR= 2.2 (95% CI: 1.4 to 3.5, P=0.0004)		
Prehabilitation vs. control for colorectal surgery, stratified 2 x 2 table: A. Patients with poor functional walking capacity at baseline (n=42)		
	IMPROVED 6MWT PREOPERATIVELY [Positive outcome]	**NO IMPROVEMENT IN 6MWT PREOPERATIVELY [Negative outcome]**
PREHABILITATION	16	6
CONTROL	5	15

Stratum-specific RR= 2.9 (95% CI: 1.3 to 6.5, P=0.002)		
Prehabilitation vs. control for colorectal surgery, stratified 2 x 2 table: B. Patients with higher functional walking capacity at baseline (n=97)		
	IMPROVED 6MWT PREOPERATIVELY [Positive outcome]	**NO IMPROVEMENT IN 6MWT PREOPERATIVELY [Negative outcome]**
PREHABILITATION	26	28
CONTROL	11	32
Stratum-specific RR= 1.9 (95% CI: 1.1 to 3.4, P= 0.023)		

Our analyses do not suggest that baseline functional walking capacity is a moderator of the prehabilitation-preoperative functional capacity relationship (test of homogeneity: P=0.388). The likelihood of a prehabilitation intervention vs. control improving preoperative functional walking capacity is 2.9x greater in those with poor baseline functional walking capacity (<400m); the likelihood of a prehabilitation intervention vs. control improving preoperative functional walking capacity is 1.9x greater in those with higher baseline functional walking capacity (>400m). However, because the stratified estimates are similar, the findings suggest that the effect of prehabilitation on change in functional capacity before surgery is not different but rather is consistent for these two levels of baseline function; in this situation, poor baseline walking capacity was not a modifier of the prehabilitation-preoperative functional capacity relationship.

Whether subgroups of patients with different baseline functional capacities benefit equally, however, should still be investigated. Our simple stratified analysis had a small sample size, therefore low power to address this question and did not control for potentially unbalanced covariates resulting from data pooling (see the following section on confounding).

By including potential moderators in the design of prehabilitation research and through analysis of moderating variables, we can accomplish several things [296, 299]:

1) Provide information on whether prehabilitation has similar effects, no effects, improved effects, or negative effects across sub-groups. This information is critical to inform healthcare practitioners and administrators on the extent to which prehabilitation is

generalizable and which sub-groups to target. Likewise, if a prehabilitation intervention is found to be ineffective in a particular subgroup, the intervention can be redesigned and tested.

2) Provide information on the necessary components of the intervention. An interaction analysis can be used to determine whether the combined effect of two interventions produces an effect that is above and beyond the separate effect of each single intervention.

3) Provide information on dose-response. For instance, dosage, which might include the frequency of stress-reduction activities, the intensity and type of exercise, the quantity of a nutrition supplement, and the timing (i.e., length of intervention), could be evaluated as moderators. The size of the effect produced from a given prehabilitation intervention could differ across dosage levels.

4) Provide information on the “true” association between prehabilitation and the desired outcome. As an example, a prehabilitation intervention might be found ineffective, but moderation analysis could reveal that two subgroups within the population studied responded to the intervention in opposing ways, creating a null effect. Likewise, an association might be over- or underestimated based on the inclusion (or rather failure to isolate) certain sub-groups.

5) Provide information on the adequacy of the measurements employed. If a known subgroup fails to perform in an expected way, the failure might be related to the intervention itself, or because of the inadequate measurement of the moderator. As an example, many studies have examined the impact of prehabilitation on postoperative complications. Enhanced Recovery After Surgery (ERAS) modifies surgical outcomes: close adherence to the ERAS program reduces the proportion of adverse outcomes post-colorectal surgery[35]. If ERAS data in a prehabilitation study was captured as the dichotomy

of “patient received ERAS yes or no”, rather than the actual adherence (%) to the elements, the potential for this analysis to capture ERAS as a moderator might not be realized and the true impact of prehabilitation on postoperative complications in the ERAS context would remain unknown.

Table 12 includes a list of preliminary suggested moderators to consider for inclusion in future prehabilitation research.

Table 12: A list of potentially moderating variables* to consider in the design, conduct, and analysis of surgical prehabilitation research

Non-modifiable patient characteristics	Modifiable baseline characteristics	Psychological/ Behavioral characteristics	Intervention/ Implementation characteristics
Age Sex Genetics Social determinants of health Indication for surgery (e.g., cancer vs. irritable bowel disease) Comorbidities, such as diabetes or heart disease Preoperative medications, such as corticosteroids Anticancer treatments, such as neoadjuvant therapy	Level of fitness Nutritional status Cigarette and alcohol intake Frailty Body composition features, such as myopenia and myosteatosis[217] Anemia Biochemistry, such as blood glucose (e.g., glycated hemoglobin), inflammation (e.g., concentration of C-reactive protein)	Motivation, capability, and opportunity[305] (including barriers and facilitators) Psychological conditions, such as depression, anxiety, and stress Involvement of caregivers (i.e., support) Self-efficacy, sense of control, optimism/pessimism	Unimodal vs. multimodal interventions Compliance to the intervention, and adherence/maintenance measures Duration of the intervention (e.g., two weeks vs. four weeks pre-surgery) Exercise interventions: *Frequency* (e.g., 2 x per week vs. 5 x per week), *Intensity* (e.g., high intensity interval training vs. low intensity), *Time* (e.g., 30 min sessions vs. 60 min sessions), T*ype* (e.g., supervised vs. home-based) Nutrition interventions: *Frequency* (e.g., 1 vs. 2 sessions with the dietitian, supplementation on exercise days only vs. daily supplementation), *Intensity* (e.g., dosage of supplementation), *Timing* (e.g., supplementation post-exercise vs. before bed), *Type* (e.g., counselling-only vs. supplementation-only) Psychological interventions: *Frequency* (e.g., relaxation strategies practiced daily vs. as needed), *Intensity* (e.g., psychotherapy intervention vs. handout), *Timing* (e.g., 5 min deep breathing daily vs. 30 min deep breathing daily), *Type* (e.g., relaxation techniques vs. coping strategies)

*this list is not exhaustive and the appropriate variables to include in the study design, conduct and analysis will depend on the intervention-outcome relationship of interest

A mediation or moderation analysis requires that any potential confounders (defined in the following section) of the relationship under study be controlled, and, for this reason, these analyses are best undertaken with data from randomized controlled trials which should distribute known and unknown patient characteristics approximately equally between groups[299].

What is a confounding variable?

If the third variable Z is a confounding variable it will have an independent effect on the outcome of interest that becomes intermixed with the effect of the intervention, leading to an estimate that distorts the casual impact of prehabilitation on the outcome of interest[298] (Figure 14A). An evaluation of potential confounding variables is useful in prehabilitation research, especially when randomization procedures are not followed, because the effects of extraneous or third variables can become intermixed with the effects of the intervention. When confounding takes place, the estimates of the impact of prehabilitation on the outcome measured will be under- or overestimated.

Figures 14A & B: A schematic and an example of a confounding variable

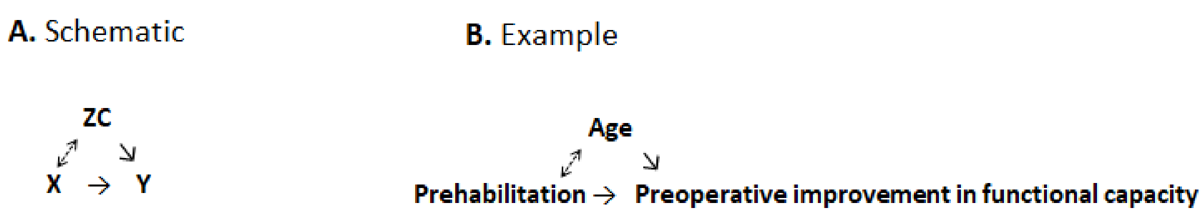


Figure legend: Third variable ZC becomes intermixed with the effect of X (intervention), making the interpretation of the causal impact of X on Y (outcome) difficult. ZC is a confounding variable because it is associated with X, and it exerts its independent casual effect on Y, but it is not a mediating variable.

The three characteristics of a confounding variable are depicted in Figure 14A and listed here [298]:

1) the potential confounder is associated with the outcome of interest (variable Y);
2) the potential confounder is associated with the intervention (variable X);

3) the potential confounder exerts its apparent etiological effects on the outcome of interest independent of the intervention; it is not an intermediate in the causal chain (X→Y).

A confounding variable is not a mediating or moderating variable. A confounding variable differs from a mediating variable because although it is related to both X and Y, a confounding variable is not part of the causal sequence (X → ZMed →Y) [298]. A confounding variable differs from a moderating variable because the X-Y association does not differ across levels of the confounding variable[296].

In epidemiology, age and sex are classically evaluated as potential confounders. Using the full dataset from Gillis et al.,[15] we can conduct an exploratory analysis to determine whether or not age confounds our estimates of the impact of prehabilitation on preoperative functional capacity (Figure 14B). For the sake of this example, age has been arbitrarily divided into 2 groups as above and below 70 years. Our research question is as follows: *Does prehabilitation improve preoperative functional walking capacity, compared to control; Does age confound this relationship?* Our primary goal is to understand the relationship between prehabilitation (variable X) and preoperative functional walking capacity (variable Y), but older age (third variable, ZC) might influence (confound) this relationship. In order to draw appropriate conclusions about the impact of prehabilitation vs. control on change in functional walking capacity before surgery, we need to evaluate whether age acts as a confounding variable. If age is a confounder, age would intermix with the effect of prehabilitation and distort our estimates of the impact of prehabilitation on preoperative functional capacity.

Before we evaluate age as a potential confounder, we must determine whether age meets the characteristics of a confounder in this analysis. First, the potential confounder should be associated with the outcome: age is casually related to functional capacity independent of prehabilitation. In fact, an individual's 6MWT value can be compared to a reference population by calculating their predicted score based on age and sex; older adults have a lower predicted

6MWT. Second, the potential confounder is associated with the intervention: age is associated with the implementation of prehabilitation interventions. Older adults tend to exercise less and are at higher risk of eating poorly, potentially making older adults exceptionally good candidates for prehabilitation. Third, age does not act as a mediator; that is, age is not part of the causal sequence whereby prehabilitation causes older age, which then leads to a preoperative change in functional capacity.

Table 13: 2 x 2 contingency table of prehabilitated colorectal surgery patients

Prehabilitation vs. control for colorectal surgery, unstratified 2x2 contingency table (n=139)			
	IMPROVED 6MWT PREOPERATIVELY [Positive outcome]	**DID NOT IMPROVE 6MWT PREOPERATIVELY [Negative outcome]**	**TOTAL**
PREHABILITATION	42	34	76
CONTROL	16	47	63
Crude RR= 2.2 (95% CI: 1.4 to 3.5, P=0.0004)			
Prehabilitation vs. control for colorectal surgery, stratified 2 x 2 table: A. Patients older than 70 years of age (n=62)			
	IMPROVED 6MWT PREOPERATIVELY [Positive outcome]	**DID NOT IMPROVE 6MWT PREOPERATIVELY [Negative outcome]**	**TOTAL**
PREHABILITATION	20	17	37
CONTROL	7	18	25
TOTAL	27	35	62
Stratum-specific RR = 1.9 (95% CI: 1.0 to 3.9, P= 0.042)			
Prehabilitation vs. control for colorectal surgery, stratified 2 x 2 table: B. Patients 70 years of age or younger (n=77)			
	IMPROVED 6MWT PREOPERATIVELY [Positive outcome]	**DID NOT IMPROVE 6MWT PREOPERATIVELY [Negative outcome]**	**TOTAL**
PREHABILITATION	22	17	39
CONTROL	9	29	38
TOTAL	31	46	77
Stratum-specific RR= 2.4 (95% CI: 1.3 to 4.5, P= 0.003)			
Mantel-Haenszel combined estimate for the RR = (8.06+10.86)/(4.17+4.55) = 2.2 Mantel-Haenszel weights for older patients = $\frac{20 * 25 / 62}{7 * 37 / 62} = \frac{8.06}{4.17}$ Mantel-Haenszel weights for younger patients = $\frac{22 * 38 / 77}{9 * 39 / 77} = \frac{10.86}{4.55}$ The Mantel-Haenszel formula[306] was used to calculate an effect estimate for prehabilitation on functional walking capacity that is unconfounded (i.e., adjusted) by older age. The Mantel-Haenszel combined estimate is a weighted average of the stratum-specific RRs based on the proportion of individuals in each stratum.			

If the unstratified (crude estimate) was confounded by older age, this estimate would be distorted by confounding. Instead, the crude estimate (RR: 2.2) is similar to the age-adjusted estimate (RR: 2.2), suggesting that older age does not act as a confounder in this situation. In this analysis, it appears as though adjustment or correction for age >70 years would not be necessary because older age does not distort the prehabilitation-preoperative functional capacity relationship.

Prevention and evaluation of potential confounders is critical in prehabilitation research because failure to adjust for the confounding variable will lead to incorrect conclusions about the impact of prehabilitation on the desired outcome. Confounding can be controlled by[298]:

1) Randomization. Random assignment of the intervention helps to ensure confounding variables are distributed approximately equally across the intervention and control arms.
2) Restriction. A known confounder can be excluded or controlled by restricting enrollment.
3) Matching. A known confounder could be matched in both the control and intervention arms so that the distribution of the confounding variable is matched approximately equally across groups.
4) Stratification. Unmix the effect of the confounding variable by separating outcome data according to the potential confounder and examine the effect of the intervention separately in each stratum (as the example above).
5) Regression modelling. Use regression modelling to produce adjusted estimates based on potential confounders.

Is the third variable a confounder or a moderator?

In the previous section on confounding variables we identified that age did not confound the prehabilitation-functional capacity relationship; however, an assessment of whether age acts as a modifier of this relationship should have been our first step. In epidemiology, third variables are examined in a hierarchical fashion with modification being evaluated *before* confounding[298].

Whether a third variable acts as a confounder or a modifier of a particular relationship will depend on the specific intervention-outcome relationship under investigation, the study design and conduct, and, to some extent, the analysis. The role played by a variable (mediator, moderator, or confounder) is not a property of the variable itself, but rather depends on how the variable is related to the intervention-outcome relationship under study[297]. For this reason, a variable that acts as a moderator in one study might be a confounder in another study[297].

Implications for future prehabilitation research

This paper was designed to delineate the benefits, consequences and uses of mediators, moderators, and confounders in the conduct of prehabilitation research. Mediating variables and their analysis (Table 10) are useful in understanding the process by which a prehabilitation intervention affects an outcome. Prehabilitation researchers might find mediation analysis useful in identifying the effective components of their intervention, so that the intervention can be distilled to its key elements. Without mediation analysis, prehabilitation interventions could consume unnecessary resources. Additionally, given that the implementation of behaviour change interventions is challenging, mediation analysis could focus the intervention to a few essential components only, which could improve the uptake of the intervention and drive outcome improvements. Moderating variables and their analysis (Table 12) are essential to understand how extraneous variables, such as patient-related factors, alter the effectiveness of a prehabilitation intervention. Prehabilitation researchers might find moderating variable analysis useful in developing risk stratification tools and dosage algorithms for their interventions. Without moderation analysis, prehabilitation interventions might be falsely recognized as ineffective, when perhaps the population, timing, or dose of the intervention simply needs to be adjusted to achieve efficacy. An evaluation of potentially confounding variables is essential when randomization procedures are not followed. Without a confounding analysis, inferences regarding the effectiveness of prehabilitation interventions might be inaccurate. Confounding distorts the estimate so that the effectiveness of a given prehabilitation intervention on a desired outcome could be under- or overestimated. Through consideration of mediation, moderation, and confounding, we can enhance our understanding of prehabilitation so that safe, acceptable, and effective prehabilitation interventions are implemented earlier into clinical practice.

Conclusion

Any study examining the potential causal association between prehabilitation and an outcome should consider third variable effects in the research planning, designing and analysis stages. Using data, particularly from randomized controlled trials, to examine the potential influence of extraneous, third variables on the outcomes achieved with a prehabilitation intervention is an efficient way to advance prehabilitation study by contributing to what interventions work, for whom they work, as well as when and how they work best.

Chapter summary

This tutorial-based paper was created to enhance research efforts and build the evidence base to support or refute the hypothesis that the patient's preoperative status modifies surgical outcomes through mediation of the surgical stress response. The idea for this paper was borne after I attended a prehabilitation conference and listened to a lecture on exercise-only prehabilitation; the presenter identified that a third of their participants did not respond to the intervention. When I asked for the nutritional status of these "non-responders", the presenter was unsure. Nutritional status had not been measured. The benefits from exercise and nutrition are intrinsically linked. While exercise supplies anabolic stimuli for maintaining energy reserves, nutrients provide the substrates for growth (i.e., hypertrophy) and support the maintenance of reserves. Exercise also alters nutritional requirements as nutrients are needed to fuel the energy processes that support physical activity[307]. In fact, *total energy expenditure increases as the amount of daily exercise increases*; the energy cost or debt associated with physical activity must be collected exogenously, endogenously, or through a combination of the two. A malnourished patient, already in an energy deficient state as evidenced by loss of body mass, must support total energy expenditure through food intake, body catabolism, or both. It is, therefore, likely that a potential explanation for "non-respondents" to exercise prehabilitation is nutrition status. Interventions designed with consideration of extraneous variables have the potential to improve knowledge generation and translation, so that the right patient receives the right care, at the right time.

Chapter 7: CONCLUSION

The collection of papers presented in this doctoral work broadly tested, and supports, the hypothesis that the patient's preoperative status modifies colorectal surgery outcomes. The first paper indicated that intermediately frail and frail patients with poor functional walking capacity (<400m 6MWD) suffer more complications than frail patients with better functional walking capacity (>=400m 6MWD). The second paper provided indirect evidence that the preoperative condition can be modified with prehabilitation to improve outcomes; the meta-analysis provided evidence that nutrition prehabilitation reduces length of hospital stay by two days. The third paper presented qualitative evidence that patients support the idea that prehabilitation would have enhanced their preparedness for surgery. The final paper specified methodological suggestions and strategies to progress our knowledge on preoperative interventions.

7.1 Future research directions and considerations

Carli and Mayo[308] proposed the following guidelines to measure and evaluate postoperative recovery: 1) It should be biologically plausible for the exposure/intervention to influence the outcome; 2) Both the outcome and exposure/intervention should be measured accurately; 3) Consider the statistical and clinical implications of performing the measurements/instruments; and, 4) External variables that influence the outcome-exposure/intervention relationship should be identified and accurately measured. These guidelines provide a good framework to continue researching the global hypothesis generated in Chapter 2: the patient's preoperative status modifies surgical outcomes through mediating the surgical stress response; and, that prehabilitation modifies surgical outcomes by enhancing the patient's preoperative condition (physiologic reserve and function). The following points are proposed as next steps to advance research in prehabilitation and test these hypotheses:

1. *It should be biologically plausible for the exposure/intervention to influence the outcome.* Mechanistic studies should be conducted to evaluate the influence of preoperative characteristics on the surgical stress response. Many of the empirical studies that elucidated the response to surgical stress were not conducted under modern ERAS practices. Knowledge of the stress response should be the foundation by which surgical interventions, such as prehabilitation, are based. By repeating these pivotal studies today, we could answer the following questions: Which preoperative characteristics *under ERAS care* impair the surgical stress response? Can we predict the direction of surgical stress response dysfunction (overexpressed or underexpressed) based on preoperative surgical characteristics?
2. *The outcome should be measured accurately*. The six-minute walk test is often used as the primary outcome in prehabilitation research. However, this is a measure of functional walking capacity and might not be sensitive to early changes in physiologic reserve[61]. A physiologic improvement, as a result of enhanced reserve, is likely to confer benefits even if it has not yet translated into an obvious functional improvement. In fact, improvements in physiologic function likely precede clinical presentation[110]; thus, measurement of reserve, along with function, should be considered in future trials to evaluate whether prehabilitation was successful.
3. *The intervention should be measured accurately*. Few studies have measured prehabilitation interventions well. How do we know if the prehabilitation intervention itself was successful? If malnourished patients fail to improve functional walking capacity, was prehabilitation unsuccessful? Currently, the available studies on prehabilitation provide little information regarding the implementation of the intervention. Proctor et al.,[309], proposed the following equation to conceptualize implementation success:

Implementation Success (I)= fE + IO's
fE = Effectiveness of the treatment being implemented
IO's = Implementation factors

When an intervention fails to deliver, it is critical that we are able to attribute failure to either the intervention itself (fE) or the factors associated with its implementation (IO's), or a combination of the two[309]. Therefore, if malnourished patients do not improve their functional walking capacity before surgery or remain in hospital for an extended period of time, inferring success or failure of the prehabilitation program using only these functional and clinical endpoints is problematic, as it is impossible to discern where the failure lies. Careful evaluation of the implementation of the intervention might reveal that the findings were confounded by failure to meet a therapeutic target due to poor compliance or an inability of the malnourished patient to consume enough food to meet the target. In this case, the failure of the intervention to impact functional walking capacity was a result of *implementation factors* rather than the effectiveness of the prehabilitation intervention itself. The prehabilitation intervention could then be re-designed to better meet patient needs and therapeutic targets.

4. *Consider the statistical and clinical implications of the measurements/instruments*. Bowyer and Royse[310] proposed that an ideal measure of recovery would, "determine whether the process of recovery has progressed to an acceptable threshold (dichotomous analysis) and then determine how much beyond the minimum threshold recovery has progressed (continuous analysis)". Therefore, an ideal outcome measure would be continuous, harnessing statistical power, but could also be dichotomized, for instance, by the *minimal important clinical difference* (MICD), permitting rich data analysis and conclusions. While we know the MICD for the six-minute walk test has been established to be 19m for colorectal surgery[76, 204], we do not know the MICD for other physical function measures, such as strength and balance, which, altogether,

might be more representative of an improvement in the patient's preoperative condition. For instance, poor balance might be the cause of a failure to achieve the MICD for six-minute walk test and does not reflect a true change in exercise capacity[61]. It is thus important that we determine the MICD for a battery of functional measures so that we do not have to rely on a single measure. Furthermore, is the established MICD for the six-minute walk test applicable in all colorectal patient populations? Is there a minimally important clinical difference for frail, malnourished, and sarcopenic patients that differs from the average colorectal surgery patient?

5. *External variables that influence the outcome-exposure/intervention relationship should be identified and accurately measured*. As described in chapter 6, measurement and evaluation of extraneous, "third" variables is an area of prehabilitation research in need of improvement. For instance, the results of published prehabilitation research are rarely stratified by preoperative characteristics. That is, the clinical or functional findings for malnourished patients, for instance, are not examined separately before pooling. Likewise, ERAS modifies clinical outcomes[35], thus when reporting the impact of prehabilitation on length of hospital stay, for example, stratum-specific estimates for patients with high compliance to ERAS elements and low compliance to elements should be examined separately before pooling. An examination of third variables could advance the literature by illuminating the true relationship between prehabilitation, preoperative characteristics, and outcomes.

7.2 Postoperative recovery beings before surgery

"Postoperative recovery" is a commonly used but poorly defined concept[311,312]. The anesthesiologist might characterize recovery as discharge from the Post-Anesthesia Care Unit, administrators might associate recovery with hospital discharge, and patients might define recovery as symptom resolution[251]. In fact, a single definition for postoperative recovery may not be appropriate: surgical recovery is a complex process involving multiple domains – physical, physiological, psychological, social, economic – all with different timeframes of restoration[313]. Recognizing that a single definition for postoperative recovery might not be attainable, several authors have proposed that postoperative recovery should be divided into three phases: early, intermediate, late[251, 310, 313]. *Early recovery* denotes the period immediately after surgery until discharge from the Post-Anesthesia Care Unit when patients have recovered their vital functions. *Intermediate recovery* is established with hospital discharge, and *late recovery* signifies the time from hospital discharge until baseline status in all domains has been achieved[251, 313].

Currently, the definitions for postoperative recovery do not include the preoperative phase. The findings of this PhD dissertation contribute to a growing body of literature suggesting that postoperative *recovery begins preoperatively*[117]. Literature on preoperative risk stratification tools[6, 216], preoperative interventions[168] and surgical resiliency[173, 314, 315] all suggest that key indicators of recovery (or delayed recovery) can be identified and optimized before surgery. This suggests that the definition of recovery should be broadened to include a "pre-surgery" phase of recovery. The following table (Table 14) describes phases of surgical recovery and has been adapted from Feldman et al.,[251] to include pre-surgery recovery. By adequately preparing patients for surgery, patients are better candidates for surgery, and, as a result, are likely to recover well from surgery. A definition of postoperative recovery that is truly comprehensive might thus recognize the contribution of the preoperative phase to the overall construct of recovery.

Table 14: Phases of surgical recovery

Phase of recovery	Definition	Timeframe	Example Measures
Pre-surgery (proposed)	Before surgery	Weeks to months	Adequate functional capacity to withstand surgical stress; Resolution of malnutrition; Sense of control and self-efficacy
Early	Until discharge from Post-Anesthesia Care Unit	Hours	Vital signs
Intermediate	Until discharge from hospital	Days	Flatus; Length of hospital stay
Late	Until illness no longer disrupts everyday life	Weeks to months	Patient-reported resolution of symptoms; Return to pre-surgery functional capacity

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Appendix A: Search string

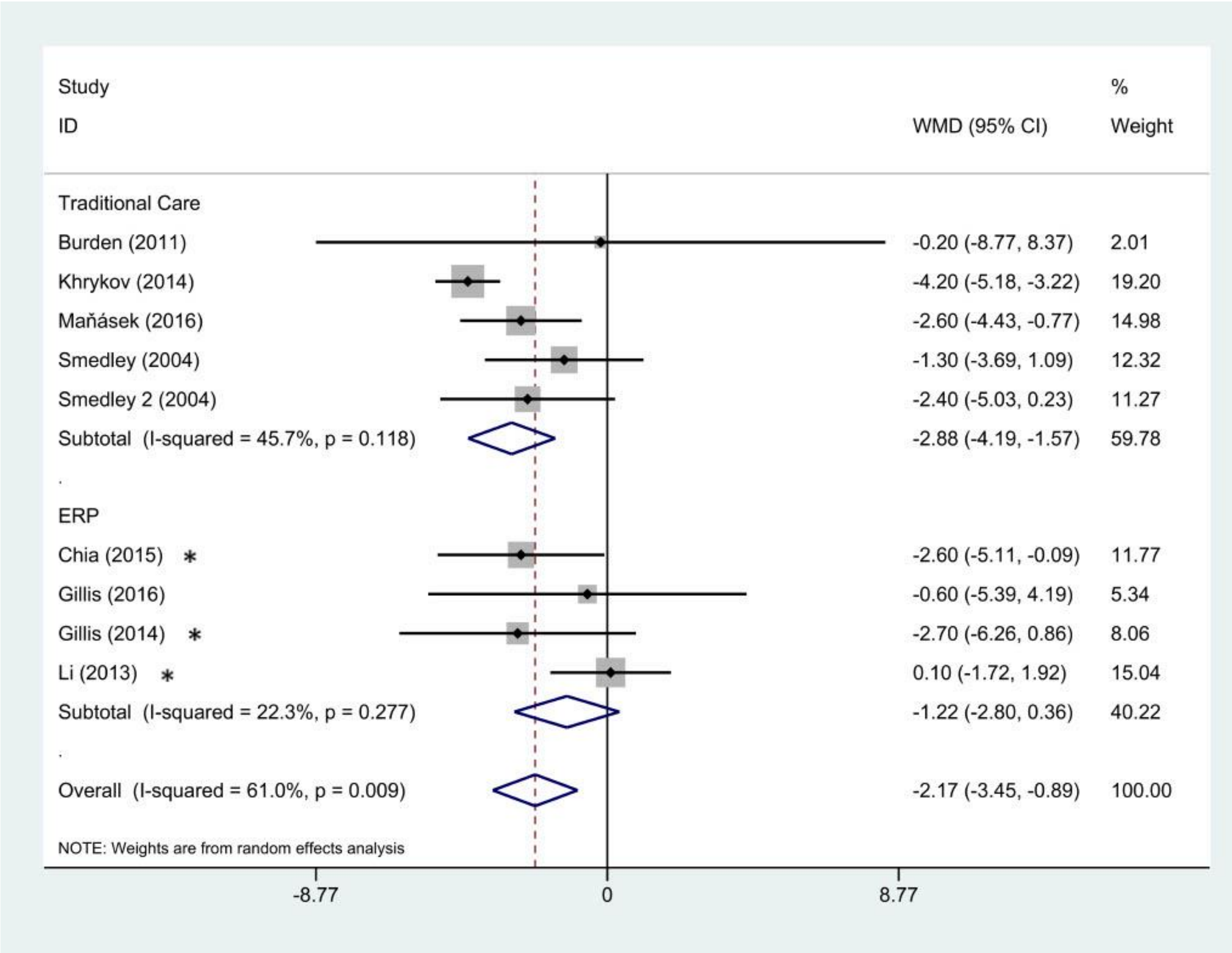
Search string in MEDLINE

((diet* OR food OR nutri*) adj3 counsel*) OR ((diet* OR food OR nutri*) adj3 modif*) OR ((diet* OR food OR nutri*) adj3 support*) OR ((pre-hab* OR prehab* OR pre hab*)) OR (((Energy OR protein OR nutri* OR oral nutri* OR diet*) adj3 supplement*) OR ONS)

Search string in ProQuest

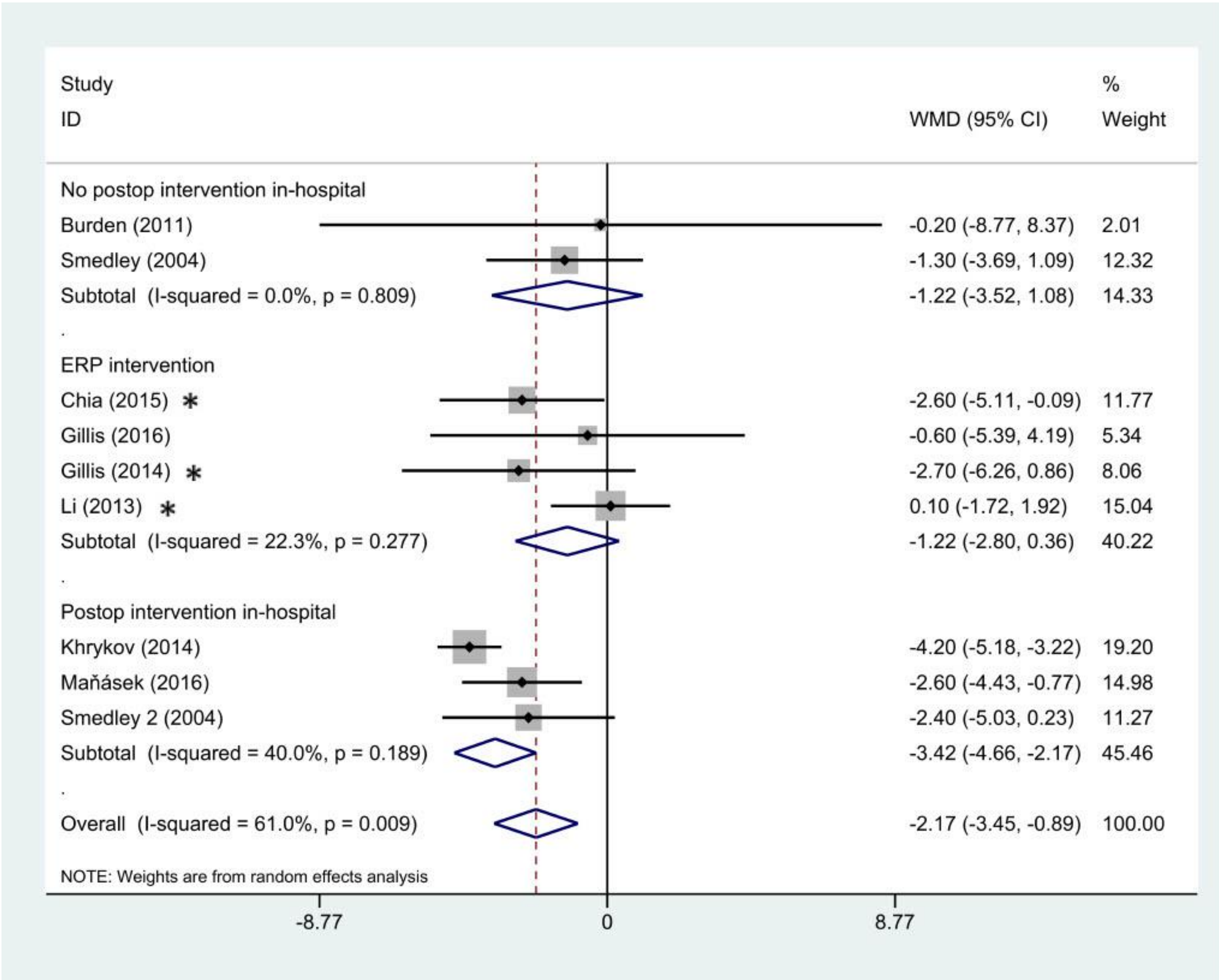
ab(Colorectal OR Colon OR rectum OR rectal OR bowel OR (intestin*) OR (gastrointestin*)) AND ab(((diet* OR food OR nutri* OR Energy OR protein) AND (counsel* OR supple* OR modif* OR support*)) OR prehab* OR pre-hab* OR ONS) AND (pre-surg* OR presurg* OR pre-operat* OR preoperat*)

Appendix B: Any prehabilitation (nutrition-only prehabilitation and multimodal prehabilitation) on length of hospital stay post-colorectal surgery, stratified by Enhanced Recovery Pathway (ERP) vs. traditional care.



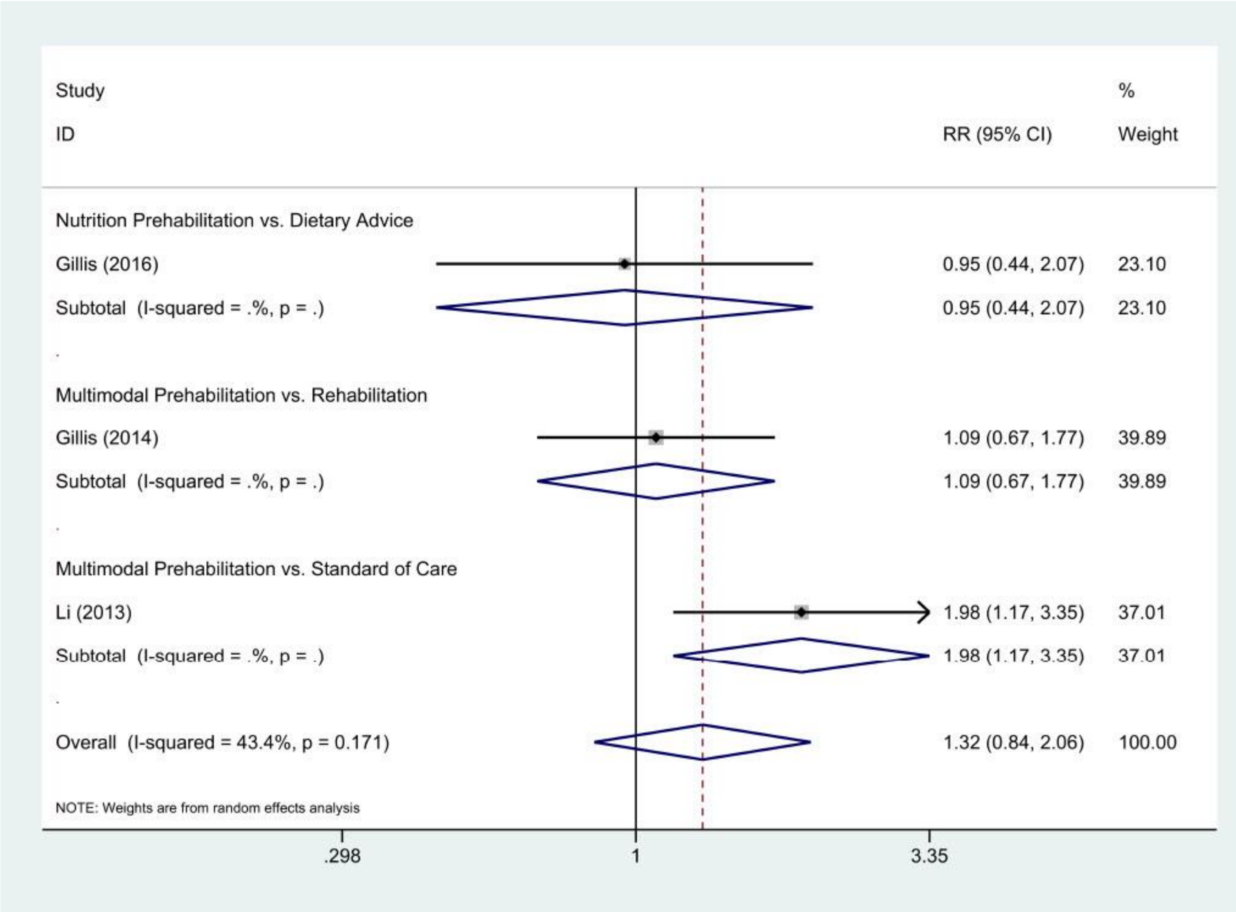
*Denotes multimodal prehabilitation

Appendix C: Length of hospital stay post-colorectal surgery for nutrition-only and multimodal prehabilitated patients, stratified by studies that included a postoperative nutrition intervention.

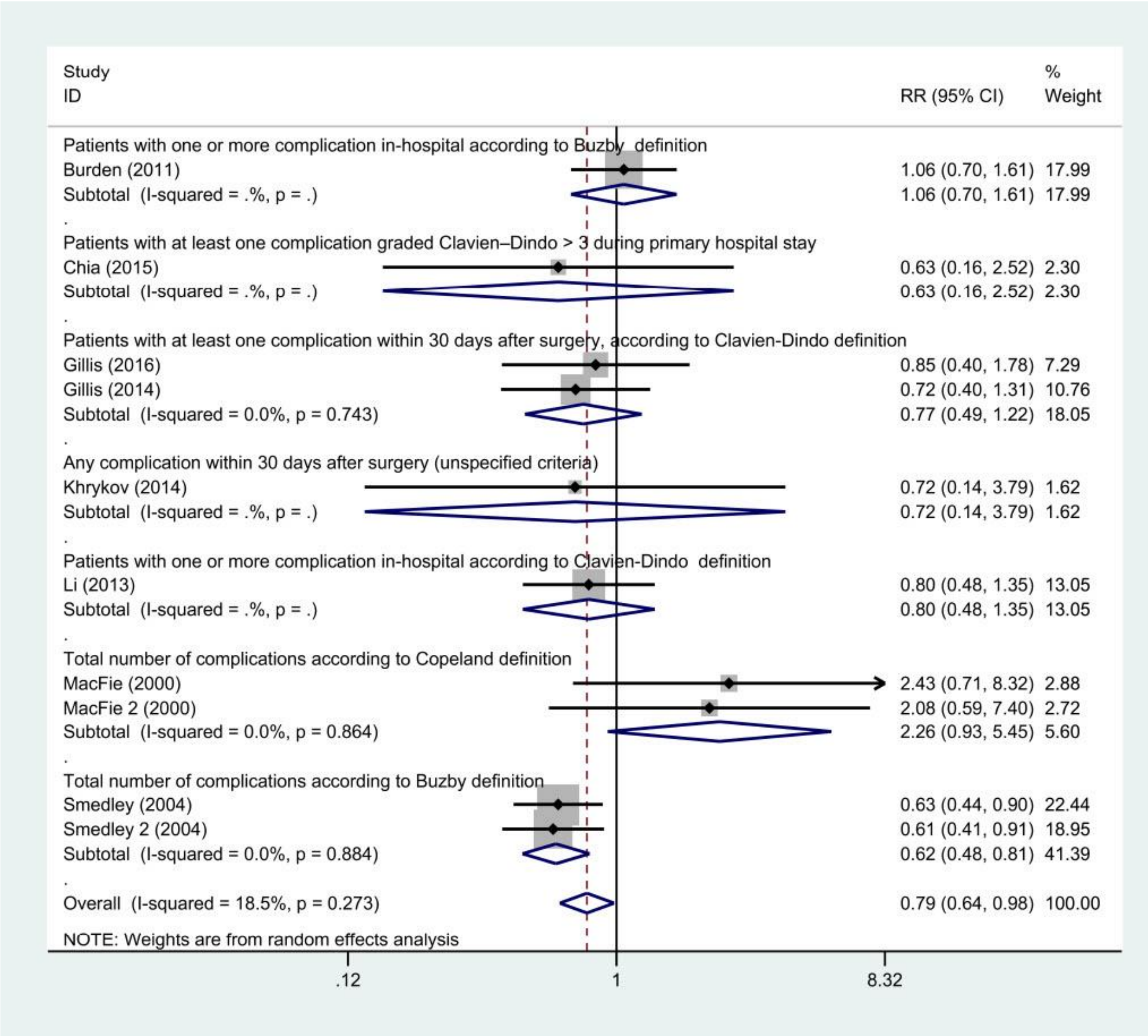


*Denotes multimodal prehabilitation

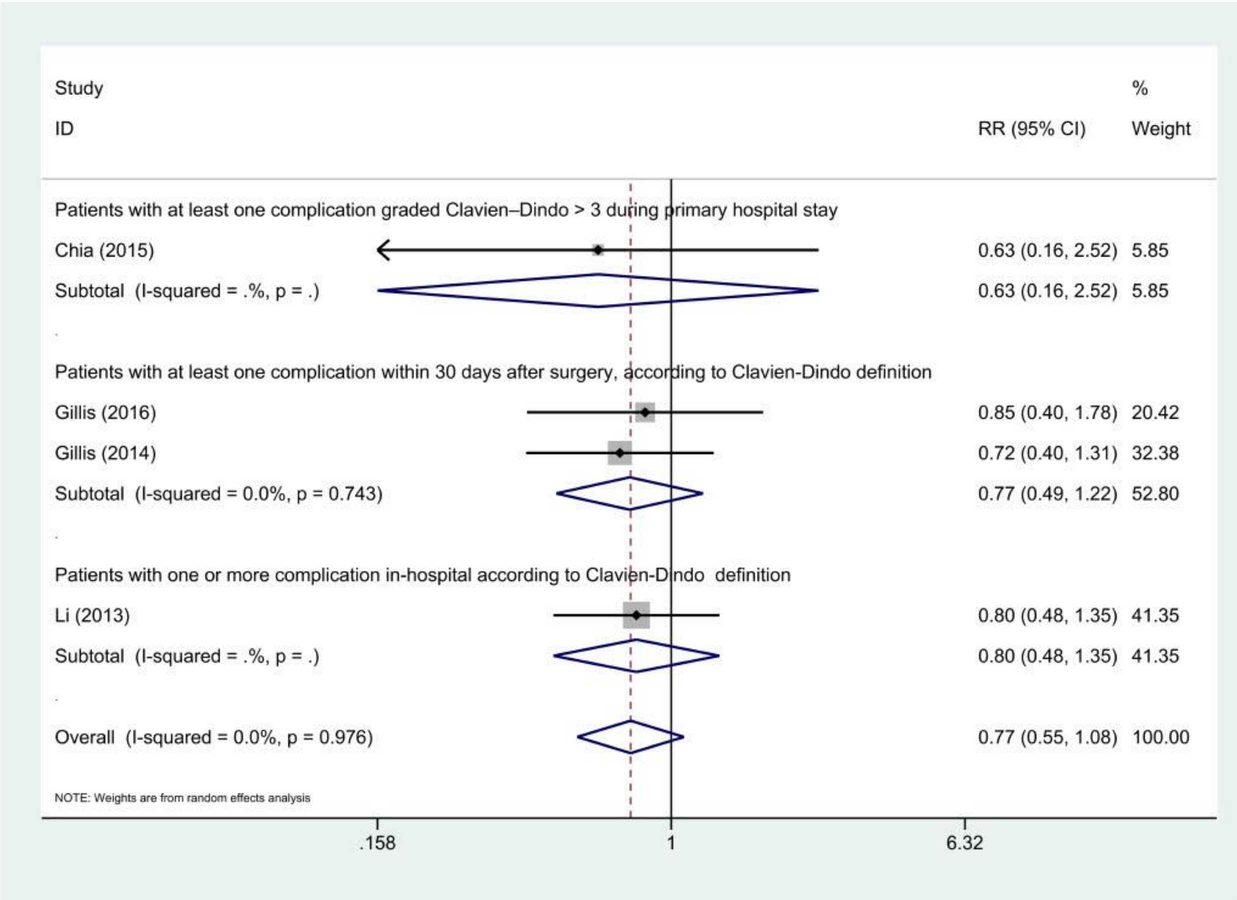
Appendix D: Nutrition-only prehabilitation and multimodal prehabilitation on return to functional capacity 4 weeks after colorectal surgery, stratified by each study.



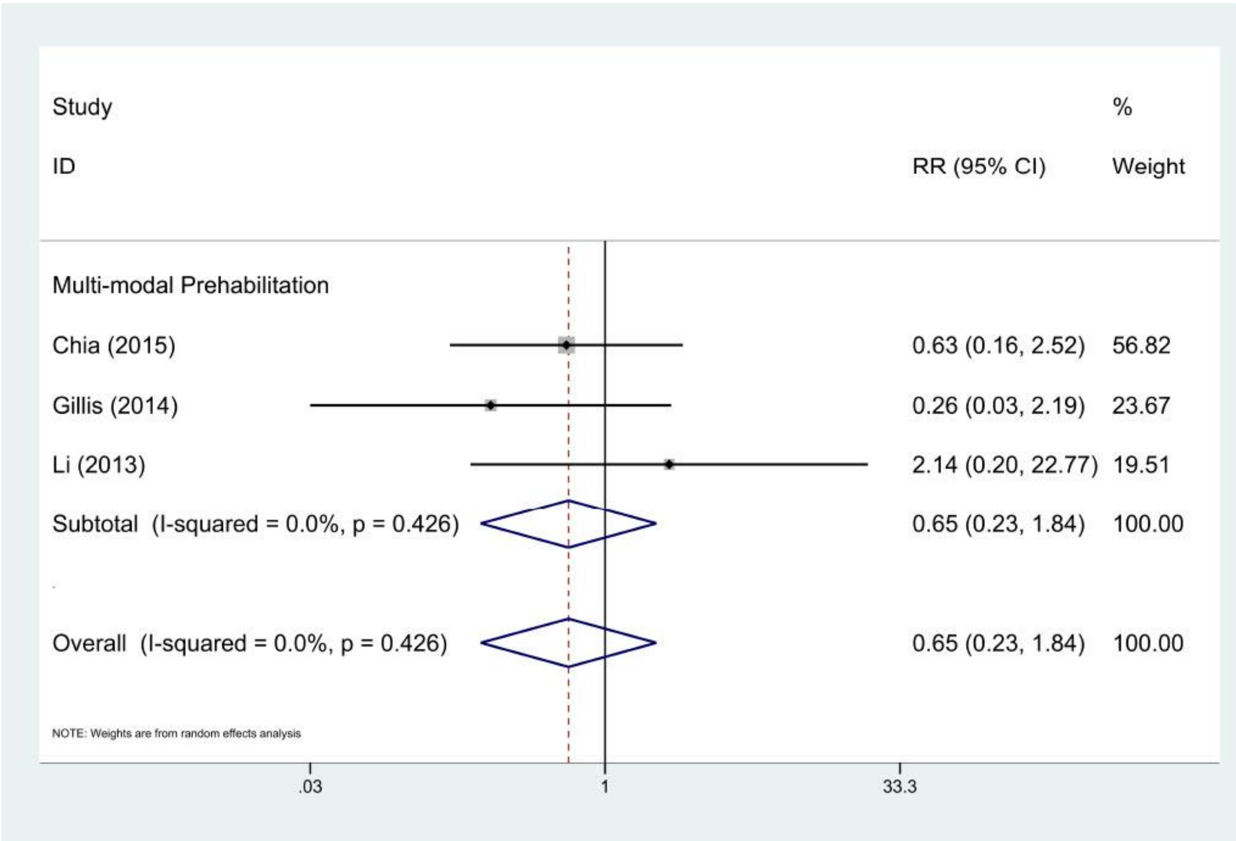
Appendix E: Any prehabilitation (nutrition-only prehabilitation and multimodal prehabilitation) on complications after colorectal surgery, stratified by the manner in which the complication data were collected



Appendix F: Any prehabilitation (nutrition-only prehabilitation and multimodal prehabilitation) on postoperative complications in patients under Enhanced Recovery Pathway care only for colorectal surgery, stratified by the manner in which the complication data were collected



Appendix G: Multimodal prehabilitation under Enhanced Recovery Pathway care on serious postoperative complications graded Clavien-Dindo >3 during primary hospital stay for colorectal surgery



Appendix H: Component-based evaluation of study quality for randomized controlled trials

Author	**Randomization concealment**	**Blinding of outcome**	**Attrition description**
Nutrition Prehabilitation			
MacFie, 2000	Not specified	X	✓
Smedley, 2004	✓	Not specified	✓
Burden, 2011	✓	X	✓
Gillis, 2016	✓	✓	✓
Multimodal Prehabilitation			
Gillis, 2014	✓	✓	✓
TOTAL	4/5	2/5	5/5

Appendix I: Component-based evaluation of study quality for observational trials

Author	Blinding of outcome	Adequate duration	Assessment of confounders
Nutrition Prehabilitation			
Maňásek, 2016	Not specified	✓	Not specified
Multimodal Prehabilitation			
Li, 2014	X	✓	X
Khrykov, 2014	Not specified	✓	Not specified
Chia, 2016	X	✓	Not specified
TOTAL	0/4	4/4	0/4