**Prehabilitation before surgery: Is it for all patients?**

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**Abstract (129/150 words)**

**Purpose:** To evaluate the role of prehabilitation interventions in adult patients before elective major surgery.

**Recent findings:** Exercise training before elective adult major surgery is feasible and safe. Efficacy has been determined but the clinical effectiveness remains uncertain. Early data suggests a reduction in morbidity, length of stay and an improvement in quality of life.  Nutritional and psychological interventions are less well evaluated and when they are, it is often in combination with exercise interventions as part of multimodal prehabilitation.

**Summary:** Studies evaluating multimodal prehabilitation interventions before elective major surgery in adults are producing encouraging early results, but definitive clinical effectiveness is currently very limited.  Future research should focus on refining interventions, exploring mechanisms, establishing minimum dosage, interrogating interactions between therapies and urgent implementation of large-scale clinical effectiveness studies.

**Introduction**

Prehabilitation describes personalised, multimodal, needs-based interventions, designed to improve the physiological, metabolic, psychological resilience of an individual prior to an expected major stressor, in this case major surgery (1). Surgical trauma, the physiological consequences of anaesthesia, perioperative therapies (including neoadjuvant cancer treatment, fluids and oxygen etc.) along with poor nutritional reserves and psychological distress are major perioperative stressors. Resilience to these stressors is dependent on a number of fixed patient factors like age, sex, cancer biology as well as other modifiable factors including co-morbidity, toxicity (smoking and alcohol misuse), malnutrition, poor physical activity, poor fitness, poor psychological preparedness and acute physiological derangements consequent upon the presenting illness. A number of these factors are directly related to long-term behaviours key to perioperative physiological resilience. In turn, these factors interact with disease-related-factors including cancer cachexia, malabsorption/ malnutrition, and myopathy. There is little doubt that improving physical activity, malnutrition, fitness and psychological factors for people in general (even when not awaiting major surgery) is beneficial to their long-term survival. This becomes even more urgent when awaiting surgery with potentially life-altering consequences.

Surgery remains a cornerstone of modern medicine. Minimally invasive and robotic techniques recently revolutionised surgical access and mitigate the surgical insult. Together with improved perioperative medicine strategies (improved preoperative risk stratification, intra-operative fluid monitoring, optimised perioperative analgesia and improved post-operative high dependency care) and enhanced recovery pathways are significant innovations that have become standards of care in the majority of centres for all surgical patients. Combined, these novel approaches have made surgery safer, with a significantly lower stress response and improved clinical and oncological outcomes. Despite these innovations, major surgery, in particular cancer surgery, still carries a substantial mortality (2–4) and high morbidity (5,6). Postoperative complications prolong length of hospital stay, increase costs, increase readmissions and worsen cancer outcomes. Moreover, outcomes from surgery have far reaching effects that may not be appreciated by perioperative health professionals, including an impaired ability to return to a pre-illness level of activity, fitness, and quality of life. This persistent post-operative impairment is especially apparent in the frail and elderly, and may be one of the main mechanisms underpinning the recognised relationship between short-term complications and long-term survival following surgery (7,8).

Patients arriving at the doorstep of major elective surgery rarely benefit form a tailored perioperative optimisation package, mainly due to surgical pathways designed with different aims in mind and rigid time constraints between the time surgery is first contemplated and the actual surgical date, especially for cancer patients. Opportunities to optimise modifiable risk factors such as pre-existing co-morbidity, toxicity, fitness, nutrition, psychology and deleterious effects from cancer therapies are being missed (9). Patients are likely to be particularly amenable to interventions that positively change behaviour when faced with an impending major life event, such as major surgery, and this may offer a particular “teachable moment”. Health professionals are uniquely placed to deliver tailor-made interventions, in order to instigate a positive influence on perioperative outcomes.

Multimodal surgical prehabilitation including exercise to improve physical fitness, nutrition optimisation, smoking/alcohol cessation and psychological stress reduction interventions are gaining traction worldwide. Routine preoperative optimisation using a multimodal prehabilitation approachs has the potential to benefit a large number of patients through benefits on short-term clinical outcome as well as offering the possibility of long-term behavioural change and health benefits. This radical shift in ethos will in many cases require radical re-design of the “surgical pathway” so that perioperative physicians interact with patients earlier in the perioperative journey, opening up numerous opportunities to improve patient care. Such a change will also offer enhanced collaborative decision-making ensuring that patients make the most-informed decision about which treatment option they wish to pursue, including whether to have an operation or not, well before the day of surgery. Pathway re-design and prehabilitation offer a route to improving modifiable behavioural characteristics prior to surgery through active programmes of alcohol and smoking cessation, activity/exercise and dietary intervention. The advent of ‘Surgery Schools’ gives us the opportunity to share such knowledge with our patients and thereby guide them towards healthier behaviours. Surgery schools also offer the opportunity to manage expectations in relation to the in-hospital surgical journey, improve buy-in to enhanced recovery pathways and improve psychological preparation for surgery. Together, this multimodal package offers an opportunity for a multitude of gains to be made prior to surgical interventions with the aim of maximizing our patients’ resilience to the physiological and psychological stresses of surgery through targeted management of modifiable risk factors.

Here we seek to investigate the utility of prehabilitation interventions prior to major surgery in particular cancer surgery, with the aim of understanding if their applicability and benefits are generalisable to all patients.

***Unimodal Exercise Prehabilitation***

Lack of physical activity is one of the major modifiable risk factor of ill-health (10) and premature death, along with poor nutrition, smoking and alcohol (11). A large body of evidence supports the notion that physical fitness has benefits in almost every context of health and disease, advocating better outcomes for fitter people (12,13). Furthermore, physical *inactivity* is one of the leading public health issues we face (14,15). A decline in physical activity as a result of ageing or critical illness results in a significant increase in perioperative risk that may be attenuated by physical exercise interventions.

The link between physical activity and cancer risk is quite clear. The largest review (16) was a pooled analysis of 12 prospective European and US cohorts concluding that high levels of physical activity during leisure time (the 90th percentile compared with the 10th percentile) were associated with reduced risks of 13 types of cancer. A review (17) of 126 studies found a 10% reduction in risk across cancer types associated with physical activity, with a threshold effect, meaning that physical activity exceeding two times the current recommendations did not provide any additional benefit. Increasing patient physical activity is therefore believed to reduce the risk of developing cancers because of its role in helping to maintain a healthy weight, although activity has numerous other beneficial effects on health and disease risk. The biological bases underlying the associations between physical activity and cancer risk are incompletely defined (13).

Interventions to improve post-surgical recovery are usually targeted at the intra-operative and immediately postoperative periods. For high-risk patients about to undergo major surgery however, this is likely to be too late. Poor objectively measured physical fitness is linked to poor postoperative outcomes (18–20), therefore identifying interventions to optimise preoperative fitness prior to major surgery is a priority.

Aerobic and muscular strength training in major surgical patients has been shown to increase endurance, improve objective markers of physical fitness, reduce weight gain, and improve muscle strength. Although constraints to proceeding with surgery limit the time for the initiation of prehabilitation, a 3-week period may still be sufficient to obtain a moderate gain in aerobic and muscle strength reserve. Importantly, neoadjuvant cancer therapies have opened up a time window to train patients prior to major cancer surgery. A critical aspect of improving physiological reserve lies in the ability to cope with surgical trauma/stress. Although a decrease in functional capacity in the period after surgery is recognized, primarily caused by surgical trauma, inflammation, or the cancer itself (1), this is further amplified by a reduced innate patient reserve. The need to ‘take it easy’ when diagnosed with cancer coupled with inactivity due to cancer treatments all compound the poor outcomes we observe postoperatively.

Early studies on prehabilitation before major thoracic and abdominal surgery have shown an increase in preoperative physical fitness, physical activity, and shorter hospital stay (21–24). Feasibility and safety, even after neoadjuvant cancer treatments, as well as improvements in physical activity and quality of life, have also been demonstrated (24–27). Reviews on pre-surgical exercise training in patients undergoing cancer treatments in both adjuvant and neoadjuvant periods also show a reassuring improvement in fitness, however again fall short on clearly identifying a postoperative outcome benefit (26,28). In the surgical oncology setting (adjuvant), only 1 study in breast cancer patients showed significant improvements in physical fitness after a 16-week exercise-training program. Yet other exercise training studies showed improvements in other important outcomes such as quality of life and fatigue. In people with newly diagnosed cancer (neoadjuvant setting), 3 pilot studies showed clinical and significant improvements in objectively measured fitness variables after a supervised in-hospital interval training in people with rectal cancer (23) and breast cancer (29). More recently, interest has shifted toward designing high-intensity training (HIT) programs in the preoperative setting, which may allow for effective and time-efficient exercise training before surgery (30). Supervised HIT programs, carefully designed and individually tailored, targeting the upper and the lower body, may be a valuable addition to the perioperative pathway.

More recently several systematic reviews have reviewed exercise prehabilitation in abdominal cancer surgery especially in colorectal surgery (26,27). They all agree that exercise prehabilitation is a possible means of enhancing physical fitness and quality of life, however no clear impact on postoperative outcomes is currently acknowledged. When comparing inspiratory muscle training, aerobic and resistance exercise training, these appear to decrease the incidence of postoperative complications (especially respiratory) in patients undergoing intra-abdominal surgery. The potential for interventions that achieve maximum results over short periods need to be urgently explored. A recent meta-analysis concluded that interval training was more effective than continuous training at increasing fitness and demonstrated a similar safety profile for moderate-intensity training (31). A preoperative, supervised, high-intensity program of interval training may increase a patient’s aerobic capacity prior to an operation within a short time frame (30), however an easier alternative is a walking-based intervention, which can be performed feasibly by patients at home (32) . However, this type of moderate-intensity exercise may not create the improvements necessary within a short time frame. The minimum clinically important dose for prehabilitation programs to improve aerobic fitness should be established in future research.

Encouragingly this area of research is gaining traction with new studies attempting to answer specific questions relating to longer term outcomes e.g. CHALLENGE study (Colon Health and Life-Long Exercise Change)(33), the INTERVAL-MCRPC study (Intense Exercise for Survival among men with Metastatic Castrate-Resistant Prostate Cancer) and the PANTERA study (Exercise as Treatment for Men with Prostate Cancer) starting enrolment in 2016. PREPARE ABC (SupPoRtive Exercise Programmes for Accelerating REcovery after major ABdominal Cancer surgery), PREHAB (Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications), WesFit (a pragmatic parallel group design randomised controlled study to assess the efficacy of the implementation of a prehabilitation programme in patients undergoing elective major cancer surgery in Wessex, UK) along with SafeFit (prehabilitation interventions delivered virtually to maintain and improve mental and physical health in cancer patients in response to the COVID-19 pandemic) trials have all started recruiting.

Improving our understanding of the optimal training duration, dose, pattern, intensity, and composition of such interventions is needed to maximize efficacy. Furthermore, in order to maximize the effectiveness of training, a better understanding of the complex interplay between adherence, efficacy, ‘responders vs. non-responders’ to exercise and cost for in-hospital supervised training interventions vs. self-directed outpatient approaches is also urgently needed. The impact of exercise prehabilitation and its impact on traditional surgical outcomes like major morbidity, overall survival and oncological outcomes, as well as the mechanisms driving these changes in physiology and cancer biology also need exploring.

***Unimodal Nutritional Prehabilitation***

Approximately 55% of all surgical patients are malnourished on admission to hospital(34). Malnutrition is recognised as an independent risk factor for patients undergoing surgery. There is no doubt that adequately nourished patients have better outcomes. Prospective cohort studies suggest that malnourished hospitalised surgical patients have significantly worse clinical outcomes, including a fourfold greater risk of mortality (35), greater odds of complications (36,37) and increased health care costs (36,38). Malnutrition does not usually exist in isolation in surgical patients, this is usually coupled with frailty and sarcopenia (reduction of quality and quantity of skeletal muscle). A large meta-analysis showed that 84% of patients were frail, with 37% of them also being sarcopenic and 66% being malnourished (39).

Malnutrition is a modifiable risk factor (40). Malnutrition arises from inadequate intake and/or metabolic and inflammatory alterations that alter nutrient utilization (hypermetabolism/catabolism), requirement or absorption, which, ultimately leads to wasting, cachexia, decreased physical fitness and reduced metabolic reserve. The primary goal of nutritional prehabilitation is to optimise nutrient stores and metabolic reserve preoperatively and provide an adequate buffer to compensate for the catabolic response of critical illness or surgery. Nutritional prehabilitation is different from acutely replacing nutritional deficits. Nutritional intervention are required to start at contemplation of surgery to ensure early patient engagement (41) and must extend into the perioperative and postoperative periods. The shift to pre-emptive, rather than reactive nutrition assessments and intervention must be emphasized. The recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines clearly show the prognostic influence of nutritional status on complications and mortality (34). This risk of malnutrition is often most significant prior to and following major gastrointestinal (GI) and cancer surgery (11,42,43) who also often demonstrate the greatest risk of iatrogenic and baseline malnutrition (~65%) (44). It is essential that the chronically malnourished cachectic cancer patient as well as the sarcopenic obese patient is reliably identified using early preoperative screening and assessment techniques and that adequate nutritional intervention is prescribed prior to major surgery (41,43,45), even if it means delaying surgery to optimize nutrition status first. Appropriate perioperative nutritional interventions have been shown to specifically improve perioperative outcomes in GI and cancer surgical patients (44), specifically reducing surgical site infections (11,34,46,47). There is a long history of randomized controlled trials (RCTs) and meta-analyses demonstrating that preoperative nutrition (regardless of route of administration) in malnourished patients prior to GI surgery reduces postoperative morbidity by 20% (48).

A recent Cochrane review interrogating evidence of preoperative nutritional interventions on post-operative outcomes with standard preoperative oral nutritional supplements (ONS) in patients undergoing GI surgery was undertaken (49). A significant reduction in total post-operative complications with immune and parenteral nutrition was found, predominantly in malnourished patients. In high risk patients, the incidence of surgical-site-infections was significantly lower in the group receiving adequate energy support via oral, enteral (EN) and/ or parenteral (PN) nutrition for at least 10 days. In multivariate analysis, nutritional therapy was an independent factor associated with fewer surgical site infections (50). When ONS is unable to meet the protein and calorie requirements in malnourished patients; enteral supplementation should be preferred over PN whenever possible. A period of 7-14 days of PN is recommended.  If PN is required to meet energy needs, it should be combined whenever possible with EN or ONS. For surgical patients, the benefits of nutritional interventions have been confirmed by two recent meta-analyses (51,52), especially in cases of severe preoperative malnutrition (53–55).

A large body of data demonstrates benefits of high-protein ONS with specific benefits to all patients undergoing surgery of all types requiring hospitalization. Meta-analysis of data including a range of hospitalized medical, surgical and orthopedic patients, demonstrates a clinically significant reduction in mortality, in-hospital complications, readmissions, length of stay, and hospital costs with ONS (56–58). ONS use in 724,000 patients matched with controls (i.e not receiving ONS) showed a 21% reduction in hospital LOS and for every $1 (US Dollar) spent on ONS, $52.63 was saved in hospital costs (59). Further research focused on the assessment, screening and intervention of perioperative patients is urgently needed to optimize perioperative nutrition delivery.

Unfortunately, the success of surgery does not exclusively depend on technical surgical skills, but on a multitude of factors mainly on how patients respond to surgical and physiological stressors. Delivering personalised nutrition, ideally pre-emptively (beginning pre-operatively) and not reactively in the postoperative period is of utmost importance. The major protein catabolism effect of surgery and critical illness needs to be understood and its impact emphasised. Provision of protein, independent of whether energy or total calorie requirements are met, can maintain lean muscle mass, induce anabolism and reduce the risk of subsequent frailty in the elderly (60,61). These are simple interventions that can be built into any prehabilitation programme for any patient cohort to improve outcome and value-based healthcare.

***Multimodal Prehabilitation***

Early prehabilitation studies were focused on unimodal interventions (either exercise alone or nutrition alone). A contemporary model has adopted a multimodal approach, attempting to address complex needs in patients having complex treatment pathways. Multimodal prehabilitation may be defined as the ‘incorporation of two or more intervention components specifically selected for their potential cumulative or synergistic effects on health outcomes’. Multimodal prehabilitation interventions have often comprised of two or more of the following: i) aerobic and resistance training to attenuate cardiorespiratory and musculoskeletal deconditioning, respectively; ii) dietary interventions to counteract disease and/or treatment-related malnutrition and to support anabolism and the metabolic cost of exercise; iii) psychological interventions to reduce stress and associated morbidity; iv) cessation of adverse health behaviours (e.g., alcohol abuse, smoking); v) medical optimization (e.g., assessing/treating anemia; medication corrections); and vi) behavioural counseling to support intervention initiation and adherence in the perioperative setting and establish self-management skills for long-term health behaviour maintenance. Multimodality prehabilitation is a complex intervention that is able to enhance fitness, nutrition, psychological resilience (62–66).

Denison and colleagues (67) conducted a systematic review including 17 randomized controlled trials (RCTs) to explore the effect of combined exercise and nutrition intervention to improve muscle mass, muscle composition (measures of sarcopenia), and physical performance in older people (all over 60 years old). They concluded that further studies were needed to provide evidence upon which public health and clinical recommendations could be based. A recently updated systematic review from the same group (68) was published identifying 21 additional RCTs (total of 37 RCTs). In 79% of the studies (27/34 RCTs), muscle mass increased with exercise, but an additional effect of nutrition was only found in 8 RCTs (23.5%). Muscle strength increased in 82.8% of the studies (29/35 RCTs) following exercise intervention, and dietary supplementation showing additional benefits in only a small number of studies (8/35 RCTS, 22.8%). The majority of studies increase physical performance following exercise intervention (26/28 RCTs, 92.8%) but interaction with nutrition supplementation was only found in 14.3% of these studies (4/28 RCTs). The review concludes that physical exercise has a positive impact on muscle mass and muscle function in healthy subjects aged 60 years and older with a large effect seen with exercise interventions of any type. However, using the predefined inclusion criteria, studies that were captured in this review mostly included well-nourished elderly subjects. Albeit an important addition to the literature, the translatability to an often-malnourished surgical population is limited.

Very few well-designed multimodal exercise and nutrition prehabilitation studies have been undertaken. Gillis and colleagues (64) showed that prehabilitation increased functional walking capacity compared with rehabilitation alone. Complication rates and duration of hospital stay were similar between the groups. The same group (63) undertook a study to interrogate the impact of nutrition counseling and whey protein supplementation on preoperative functional walking capacity and recovery in patients undergoing colorectal cancer resection. A double-blinded randomized controlled trial in 48 patients scheduled for elective colon cancer surgery were randomized to receive either individualized nutrition counseling with whey protein supplementation to meet protein needs or individualized nutrition counseling with a nonnutritive placebo. Clinically meaningful improvements in functional walking capacity were achieved before surgery with whey protein supplementation. Burden (65) evaluated the effect of preoperative standardized ONS in a cohort of colorectal cancer patients. In a randomised controlled trial, patients were assigned to receive 400 mL of oral supplement and dietary advice or dietary advice alone. The intention-to-treat analysis identified no statistically significant difference between the intervention and control groups for the primary outcome (i.e. total postoperative complications). Minnella and colleagues (69) recently published on the utility of multimodal prehabilitation in improving functional capacity when delivered during neoadjuvant chemotherapy for esophageal cancer patients. This is the first time that prehabilitation was delivered during neoadjuvant esophageal cancer treatment in this high risk (of poor fitness and malnurtiriton) cohort.

Meta-analyses of RCTs comparing nutrition prehabilitation alone or in combination with exercise showed that multimodal prehabilitation significantly decreased length of hospital stay in patients undergoing colorectal surgery (70). Pooled analyses of RCTs from the Carli group (71) using trimodal prehabilitation (exercise, nutrition and anxiety-reduction interventions) show that patients undergoing prehabilitation had significantly more absolute and relative lean body mass at 4 and 8-weeks post-operatively, attenuating the post-surgical los of lean mass compared to controls. Interestingly, Carli an colleagues assessed the extent to which a prehabilitation program affected 30-day operative complications in frail patients undergoing colorectal cancer surgery compared with postoperative rehabilitation alone (72). No difference in the comprehensive complication index measured at 30-days after surgery was found between the groups. Using the same pooled RCT data the same group reported that prehabilitation independently predicted improved 5-year disease-free survival in stage III colorectal cancer (73). Together with these data, encouraging data from our group reveled that exercise prehabilitation improves pathological and radiological determined tumor regression in locally advanced rectal cancer patients undergoing neoadjuvant chemoradiotherapy (74). This together with pre-clinical animal data from our group (75) and others (76) are very exciting and warrant further validation.

There is also a growing concern about the importance of psychological morbidity in patients undergoing surgery. Surgery, as discussed, is a potentially life-altering stage in a patient’s life especially when undergoing complex cancer surgery, especially if perioperative morbidity is encountered. ﻿This has led to the emergence of psychological prehabilitation and the trimodal approach to prehabilitation incorporating psychological intervention, predominantly addressing anxiety and depression and enhancing coping skills, as well as exercise and nutritional optimization. A recent review (77) found that ﻿patients need to be mentally fit prior to surgery; it is increasingly acknowledged that prehabilitation should include psychological components mitigating anxiety, depression and low self-efficacy. ﻿There is currently insufficient evidence to be sure that pre-operative psychological interventions are of benefit, or which interventions are most effective.

***Future Direction***

Despite substantial gains to improve surgical outcomes using improved perioperative and surgical techniques, optimisation utilising multimodal prehabilitation demonstrate efficacy but not yet effectiveness. We know that patients exhibiting poor preoperative fitness, nutrition and mental state do badly. Attempting to rescue these modifiable risks with prehabilitation can improve fitness, nutrition and quality of life. A number of promising opportunities are being developed in perioperative medicine, including increasingly sophisticated risk prediction, collaborative decision-making, personalized co-morbidity mitigation, and anemia management need to be bundled together with targeted multimodal prehabilitation interventions. Enhancing screening and assessment methods in order to fine tune perioperative risk prediction and direct prehabilitation interventions is urgent. The idea of ‘‘fitness for surgery’’ is essential for discussions about the specific risks and benefits of a particular procedure for a particular patient. Personalised interventions that are prescribed and tailored to the individual, aiming to guide operative interventions, post-operative care, cancer therapies (including the selection of chemotherapy and timing of cancer treatments in relation to surgery), and long-term outcomes are clinically urgent. Exploring intervention generalizability both as research interventions delivered in multi-center settings and more importantly as ‘business as usual’ incorporation into routine clinical care is now vital.

**CONCLUSIONS**

Improving resilience to the physiological stresses of surgery, anaesthesia and the perioperative journey is an attractive approach to improving long-term outcomes following surgery. Multimodal prehabilitation interventions are important candidates that fulfil this role.  Efficacy around feasibility, safety and improvement in fitness has been achieved, but the clinical effectiveness remains uncertain.  Early data suggests a reduction in morbidity, length of stay and quality of life, but the results of larger definitive studies are awaited.  Nutritional and psychological interventions are less well evaluated and when they are, it is often in combination with exercise interventions as part of a prehabilitation package.  These encouraging early results merit further evaluation that should focus on refining interventions, defining a minimum clinically important dose, exploring mechanisms, evaluating interactions between therapies and most importantly undertaking large-scale clinical effectiveness studies.

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