Depression and Functional Status in Colorectal Cancer Patients Awaiting Surgery; Impact of a Multimodal Prehabilitation Program

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Abstract: English

Objective: Depression and functional impairment frequently co-occur. Though both predict complications and mortality following surgery, there is a paucity of research examining functional status (FS) in depressed cancer patients awaiting surgery. Prehabilitation, a preoperative intervention including exercise, nutrition and stress-reducing strategies, may help to improve FS; however, the extent to which depressed individuals can benefit from this intervention has not yet been explored. The primary objectives were to assess whether preoperative depression is associated with poor FS, and whether prehabilitation can improve FS in depressed individuals. ***Method:*** A secondary analysis was conducted on 172 colorectal cancer (CRC) patients enrolled in three studies comparing prehabilitation with a control group (rehabilitation). FS was assessed with the Six-Minute Walk Test (6MWT), measuring distance walked during 6-minutes (6MWD), and the Hospital Anxiety and Depression Scale (HADS) was used to assess psychological symptoms. Measures were collected twice preoperatively, at 4-weeks and 48 hours before surgery, and at 4- and 8-weeks postoperatively. Subjects were divided into 3 groups: depression (HADS-D), anxiety (HADS-A), or no psychological symptoms (HADS-N). Main hypotheses were tested using analysis of variance, Chi-Square tests, and multivariate logistic regression. ***Results:*** At baseline, depressed individuals had lower 6MWD (p=0.003), and a greater proportion walked <400m (45%; p<0.001). Prehabilitation was associated with significant improvements in 6MWD in HADS-D group (OR=2.36, 95% CI:1.53-3.66), but not in HADS-N (OR=0.97 95% CI:0.44-2.16) or –A groups (OR=1.47 95% CI:0.69-3.16). ***Conclusion:*** CRC patients with depressive symptoms had poorer FS, and these individuals benefited most from prehabilitation intervention.

Abstract: French

Objectifs : La dépression et la déficience fonctionnelle sont souvent observées ensemble. Alors qu'elles permettent de prédire les complications et la mortalité après une intervention chirurgicale, il y a peu de recherche sur la capacité fonctionnelle (CF) des cancéreux souffrant de dépression avant chirurgie. Des exercices préopératoires (préadaptation) pourraient améliorer la CF, mais l'étendue des bénéfices sur les personnes déprimées n'ont pas encore été explores. Les objectifs principaux étaient d'évaluer le lien entre la dépression préopératoire et une piètre CF, et l'amélioration de la CF par la préadaptation des personnes déprimées. ***Méthodes*** : Une analyse secondaire a été faite sur 172 patients atteints de cancer colorectal et participant à trois études comparant la préadaptation à un groupe témoin (réadaptation). La CF a été évaluée grâce au test mesurant la distance marchée en six minutes (6MWT). Les symptômes psychologiques ont été déterminés par l'échelle clinique de mesure d'anxiété et de dépression (HADS). Les relations entre les symptômes psychologiques préopératoires et la CF, chez les sujets répartis en trois groupes : déprimés (HADS-D), anxieux (HADS-A) et sans symptôme (HADS-N), ont été évalués par analyse de variance et tests Chi carré. Au moyen de régression logistique, l'effet de la préadaptation sur la CF des patients déprimés a été analysé par équation d'estimation généralisée. ***Résultats*** : Les individus déprimés ont marché significativement moins (6MWT, p=0.003) et une plus grande proportion a marché <400m au niveau de référence (45%, p<0.001). La préadaptation a amélioré significativement le 6MWT du groupe HADS-D (RO=2.36, IC95% : 1.53-3.66), mais pas des groupes HADS-N (RO=0.97, IC95% : 0.44-2.16) ou HADS–A (RO=1.47, IC95% : 0.69-3.16). ***Conclusion*** : Cette étude démontre pour la première fois que les patients cancéreux déprimés ont une CF plus faible et bénéficient le plus physiquement d'un programme de préadaptation.

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Preface and Contribution of Authors

Meagan Barrett-Bernstein: Conceptualization of project, review of the relevant literature, analysis of data, and preparation of thesis

Colorectal cancer (CRC) is the second most common cancer in Canada, accounting for approximately 13% of the cancer burden and for 12% of all cancer deaths (Canadian Cancer Society, 2017). Fortunately, in recent decades, medical research has furthered our understanding of the pathogenesis of the disease and its associated risk factors, and has led to improvements in and the adoption of both preventive and screening initiatives (Canadian Cancer Society, 2017). Additionally, innovations in surgical technology, anaesthesia, and quality of perioperative care have led to significant advances in the overall quality of cancer care, thus allowing individuals access to safe and effective treatment (Carli, Charlebois, Baldini, Cachero, & Stein, 2009). Taken together, these improvements have led to earlier detection, improved prognosis, and higher rates of survival following treatment for CRC (Austin, Jane Henley, King, Richardson, & Eheman, 2014; Edwards et al., 2010).

Though treatment has improved over the years, there still exist many challenges in the management of this disease. As our population continues to grow and age, and increasingly engage in behaviours associated with risk of developing cancer, rates of the disease continue to rise (Canadian Cancer Society, 2017). Moreover, colorectal resection, the primary and only curative treatment for CRC, is associated with a multitude of adverse events, including prolonged hospital stay, and postoperative complications (Schilling, Dimick, & Birkmeyer, 2008; Shaw et al., 2012). Following surgery, individuals can expect to experience significant reductions in postoperative physiologic reserve and functional capacity (FC; Carli et al., 2002; Christensen, Bendix, & Kehlet, 1982; Lawrence et al., 2004), and deteriorations in psychological well-being and health-related quality of life (HR-QOL; Arndt, Merx, Stegmaier, Ziegler, & Brenner, 2004; Jansen et al., 2011; Ramsey, Berry, Moinpour, Giedzinska, & Andersen, 2002). These impairments can persist for up to 12-months post-surgery (Dunn et al., 2013; Lawrence et

al., 2004), and can delay the return to independent living, to work, and to social and community activities. Thus, many individuals entering survivorship are at risk for enduring physical and psychological effects, which can delay or prevent the return to preoperative level of function.

Prehabilitation, a relatively new innovative approach to facilitating postoperative recovery, is an intervention delivered in the preoperative period with the goal of optimizing patient health status (Silver & Baima, 2013). This concept emerged from observations that poor preoperative physical health is strongly associated with poor surgical outcome and delayed recovery (Cohen, Bilimoria, Ko, & Hall, 2009; Wilson, Davies, Yates, Redman, & Stone, 2010). Improvements in preoperative health can enable individuals to better withstand the stress of surgery, and return to function more quickly postoperatively. Prehabilitation programs, implementing structured exercise, nutritional counselling and/or stress reduction strategies in the preoperative period, have demonstrated an ability to improve physical fitness levels prior to surgery, and to facilitate the return to pre-intervention (baseline) level of function postoperatively (Gillis et al., 2014). Though prehabilitation interventions have been shown to improve physical fitness before surgery, recent research in the field has demonstrated that individuals who are less physically fit show the greatest improvements before surgery (Minnella et al., 2016). These findings suggest that certain patients, like those with low baseline physical function, may benefit most from preoperative interventions.

Patients with depression (or Major Depressive Disorder; MDD), a mood disorder characterized the presence of depressed mood and/or loss of interest or pleasure (American Psychiatric Association, 2013), may represent one subset of individuals at higher risk for poor physical function before surgery. Depression is highly prevalent in the cancer population, with rates far exceeding those observed in the general population (Krebber et al., 2014; Massie, 2004).

Its presence has been associated with a wide range of adverse outcomes (DiMatteo & Haskard-Zolnierek, 2010; Satin, Linden, & Phillips, 2009), including poor psychological and physical recovery following cancer surgery. More specifically, preoperative depression has been associated with greater postoperative functional impairment and poorer physical recovery following a variety of surgeries (Chunta, 2009; Kohlmann, Rimington, & Weinman, 2012; Poole et al., 2017). In the general population, physical disability and depression commonly co-occur (Lenze et al., 2001); however, despite this well-documented association (Lenze et al., 2001), the relationship between physical and psychological health is understudied in the surgical oncology literature. Moreover, there is a paucity of studies examining this relationship before cancer surgery, and using objective measures of functional status (FS). As such, it remains unclear whether, and to what extent, objective and self-reported measures of physical function are affected by the presence of preoperative depressive symptoms in individuals with CRC awaiting surgery. Moreover, it remains to be examined whether a prehabilitation program implemented before surgery can improve the physical function of individuals who are depressed. Given the high prevalence of distress in the cancer population (Massie, 2004), and its association with physical function (Lenze et al., 2001) and surgical outcome (Britteon, Cullum, & Sutton, 2017; Satin et al., 2009), this area merits further study.

Thus, the objectives of the current research are to explore the gaps in research regarding the physical status of depressed patients with colorectal cancer, and to determine to whether these individuals can benefit physically from a prehabilitation program. More specifically, the aims of this research are to: 1) examine the psychological status of colorectal cancer patients awaiting surgery, and to examine objective and self-reported functional status of individuals with

depressive symptoms, and 2) determine whether prehabilitation can significantly increase functional status pre- or postoperatively in depressed individuals.

Review of the Literature

Colorectal Cancer: Risk factors and Patient Population

Colorectal cancer (CRC) is a disease of the digestive system, characterized by the development of a malignant tumour from cells in the large intestine, and more specifically in the inner lining of the colon or rectum. CRC has been linked to several non-modifiable risk factors such as older age (over 50-years of age), a personal or family history of adenomatous polyps and/or CRC, inflammatory bowel disease, type II diabetes, and to the presence of inherited gene mutations (which account for approximately 5 to 10% of CRC cases; Canadian Cancer Society, 2011). Modifiable lifestyle factors have also been implicated in the development of CRC, including physical inactivity, being overweight or obese, consuming a diet high in red and/or processed meat, smoking, and heavy alcohol consumption (Canadian Cancer Society, 2011).

Overall, the CRC population is quite heterogeneous; however, there do exist age- and sex-related differences within this group and several lifestyle behaviours and health problems are characteristic of individuals with this disease. CRC is more prevalent in men than in women (1 in 13 vs 1 in 16 respectively) and is commonly diagnosed later in life, with more than half of new cases identified in adults over the age of 70 (Canadian Cancer Society, 2017). Although diagnosis of this disease typically occurs in older adults, rates of CRC in this population have been steadily declining in recent years. Conversely, rates have been steadily rising in individuals under the age of 60 (Brenner et al., 2017). Given the risk factors associated with the development of CRC, many individuals diagnosed with this disease are diabetic, sedentary, undernourished, and/or overweight or obese (Bardou, Barkun, & Martel, 2013; Coups, Manne, Meropol, &

Weinberg, 2007; Larsson, Orsini, & Wolk, 2005). Moreover, in addition to the physical health problems characteristic of this population, many individuals are distressed, worried, and fearful, as they confront a cancer diagnosis, its treatment, and the uncertainty surrounding this major life event (Andersen, Kiecolt-Glaser, & Glaser, 1994; Massie, 2004).

Surgery and Postoperative Status of CRC Patients

For individuals with CRC, surgery is the primary and only curative treatment for their disease. In Canada, all patients staged with I-III CRC undergo surgical resection (Canadian Cancer Statistics, 2011). Advances in surgical technology, anaesthesia, and quality of perioperative care, alongside superior prevention strategies and screening initiatives, have led to significant reductions in overall mortality rates in the CRC population and a rise in 5-year relative survival rates, which are as high as 90% in those with localized disease (defined as stages I-II; National Cancer Institute, 2014). As life expectancy increases, and the number of individuals surviving after diagnosis and treatment continues to grow, patients' expectations are shifting from merely surviving the disease and its aggressive treatment to maintaining their functionality and quality of life (Holzer, Gyasu, Schiessel, & Rosen, 2006; Kleinbeck & Hoffart, 1994; Meropol, et al., 2008).

Although it is hypothesized that improvements in cancer treatment have ameliorated postoperative outcome (Lang et al., 2009; Law, Lee, Choi, Seto, & Ho, 2007), to return fully and completely to pre-treatment level of function following surgery remains a significant challenge. Major abdominal surgery (MAS), when compared to other general surgical procedures, is associated with prolonged hospital stay and higher rates of postoperative complications (Neudecker et al., 2009; Schilling et al., 2008). These complications occur in approximately 30% of those undergoing MAS (Neudecker et al., 2009; Schwegler et al., 2010), and these individuals

are at higher risk for protracted recovery, impaired quality of life, and reduced survival time (Khuri et al., 2005). Furthermore, it is estimated that following discharge after colorectal resection, approximately 11.6% of patients return to the emergency room due to surgical site infections, wound complications, and urinary tract infections, and 8.2% require hospital readmission (Wood et al., 2017).

Even in the absence of intra- and postoperative complications, the average patient undergoing colorectal resection can expect to experience a significant reduction in both physiologic reserve and FC postoperatively (Lawrence et al., 2004). These reductions include greater fatigue (Christensen et al., 1982; which for approximately 50% of individuals persists beyond 30 days, Rubin, Hardy, & Hotopf, 2004), cognitive dysfunction, muscular weakness and physical limitations (Carli et al., 2002). Reductions in postoperative FC can be attributed in part to the stress of surgery (surgical insult), in addition to even short periods of physical inactivity (for instance during hospitalization), which together precipitate a rapid and marked loss of muscle mass, strength and function (Coker, Hays, Williams, Wolfe, & Evans, 2015; Drummond et al., 2012; Drummond et al., 2013; Kortebein, Ferrando, Lombeida, Wolfe, & Evans, 2007). While these reductions in function are most prominent in the days following surgery (King, Blazeby, Ewings, & Kennedy, 2008), they often remain present at hospital discharge and persist for many weeks or months after (Andersson et al., 2013; Janson, Lindholm, Anderberg, & Haglind, 2007; Lawrence et al., 2004; van Zutphen et al., 2017).

Several studies examining long-term outcome after MAS have found that for many individuals, deteriorations in functional ability persist for months following their procedure (Mayo et al., 2011). For example, it has been demonstrated that after abdominal surgery, over 50% of individuals remain well below preoperative levels of physical function after 6 months

(Andersson et al., 2013; Lawrence et al., 2004; van Zutphen et al., 2017), and that the recovery of physical function and the resumption of household, social/community, and work responsibilities after surgery is delayed for up to 1-year, and in some cases more (Lawrence, 2004). One study evaluating functional recovery after laparoscopic or open surgery for colorectal cancer found that although individuals undergoing laparoscopic surgery recovered more quickly, both surgical approaches were associated with prolonged recovery extending beyond the 12-month follow-up (King et al., 2008). King and colleagues (2008) found that only 74% of those undergoing surgery (58% of those open and 90% in laparoscopic) reported feeling "fully" recovered one year after surgery and that deteriorations in standardized physical performance indicators after surgery persisted, and remained below preoperative values, for more than 12 months. Moreover, many individuals with CRC are treated with either neoadjuvant or adjuvant chemotherapy (Canadian Cancer Society, 2011), and in some cases, both, which can lead to additional deteriorations in mental and physical health. Fatigue, muscular weakness, neuropathy, and bone and muscle loss, are some of the most common physical consequences of chemotherapy (Gilliam & St. Clair, 2011; Quach et al., 2015; Sorensen et al., 2016; Windebank & Grisold, 2008), which when combined with the effects of surgery, can greatly reduce functioning.

In cancer survivors, physical disability is one of the leading causes of distress following treatment (Banks et al., 2010; Cheville, Beck, Petersen, Marks, & Gamble, 2009; Omran, Saeed, & Simpson, 2012). Physical limitations lead to delays in returning to work and social activities, and to difficulties in ability to independently perform activities of daily living (ADL), such as eating, bathing, and dressing oneself, and instrumental activities of daily living (IADL), such as the management of medication, going grocery shopping, cooking, and cleaning. The inability to

perform ADLs and IADLs, or even severe limitations in ability to perform these activities, are strongly associated with impaired quality of life (QOL; Andersen, Wittrup-Jensen, Lolk, Andersen, & Kragh-Sørensen, 2004), higher caregiver burden, greater use of resources (Millán-Calenti et al., 2010), institutionalization (Covinsky, Justice, Rosenthal, Palmer, & Landefeld, 1997), increased morbidity, and mortality (Millán-Calenti, et al., 2010). As the number of individuals entering survivorship continues to rise, and as patients' expectations shift from survival to the return to normality, it is essential that risk factors for poor outcome be identified, and for effective strategies to help mitigate postoperative impairment be developed.

Preoperative Health Status and Impact on Postoperative Outcome

One of the strongest predictors of adverse outcome following surgery is poor preoperative health status. Individuals at the highest risk for complications and prolonged recovery after surgery, are those with poor health before surgery (Cohen et al., 2009; Wilson et al., 2010), such as the elderly (Boyd et al., 2008; Kennedy et al., 2011; Leung, Gibbons, & Vu, 2009), the overweight and obese (Manilich et al., 2013), the malnourished (Kuzu et al., 2006), the chronically ill (Boyd et al., 2008; Gustafsson et al., 2013; Kennedy et al., 2011; Leung et al., 2009), and those who smoke (Bluman, Mosca, Newman, & Simon, 1998) or consume alcohol in excess (Tønnesen & Kehlet, 1999). In a seminal article examining factors which contribute to the varying rates of complications across different hospitals (Ghaferi, Birkmeyer, & Dimick, 2009), the authors concluded that postoperative complications were "related more to patient factors than to quality of care (p. 1372)."

Poor physical health, such as low or poor FS in the preoperative period has also been linked to poor operative outcome, such as all-cause mortality (Wilson et al., 2010), complications, length of hospital stay, readmission rates and discharge destination (Dronkers,

Chorus, Van Meeteren, & Hopman-Rock, 2013; Robinson et al., 2013), and high hospital and health care costs (Robinson, Wu, Stiegmann, & Moss, 2011). A great deal of the research demonstrating the association between preoperative physical health and operative outcome comes from studies examining the effects of sarcopenia and cancer cachexia on various outcomes. Sarcopenia is defined as an age-associated progressive decline and generalized loss of muscle mass and strength (Marty, Liu, Samuel, Or, & Lane, 2017). Cancer cachexia is defined as a "multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (p. 490; Fearon et al., 2011). Both these metabolic disorders lead to significant reductions in muscle mass and strength, cause progressive physical deconditioning, and are associated with a high risk of functional impairment, physical disability and subsequent inability to perform ADLs, loss of independence, and institutionalization (Deans & Wigmore, 2005; Fearon, Voss, & Hustead, 2006; Malafarina, Úriz-Otano, Iniesta, & Gil-Guerrero, 2012; Marty et al., 2017). In the context of surgery, sarcopenia and cachexia are independently associated with poor clinical and surgical outcome such as prolonged hospitalization, postoperative complications, morbidity and mortality, and functional impairment after surgery (Lieffers, Bathe, Fassbender, Winget, & Baracos, 2012; Mason et al., 2016; Miyamoto et al., 2015; Nakanishi et al., 2017; Prado, Cushen, Orsso, & Ryan, 2016). These adverse outcomes have been observed in other non-sarcopenic and non-cancer cachexic populations. Impairments in FC and poor cardiorespiratory fitness in the preoperative period have been associated with increased all-cause mortality after major abdominal surgery (Wilson et al., 2010) and have been shown to predict greater morbidity following major CRC surgery (West et al., 2016).

The Six-Minute Walk Test (6MWT; Crapo et al., 2002), a frequently used assessment of physical performance, measures the distanced walked, at a brisk pace, in 6 minutes. This test is used as a measure of an individual's FS, and has been shown to be associated with postoperative outcomes. For example, studies examining postoperative outcome in surgical populations have found that poor preoperative physical performance on the 6MWT and deteriorations in walk distance prior to surgery are associated with increased risk of complications after major non-cardiac surgery (Snowden et al., 2010), and for prolonged recovery after abdominal surgery (Mayo et al., 2011). Moreover, the inability to walk at least 400m during the 6MWT has been associated with a greater risk of mortality, cardiovascular disease, and limitations in mobility after surgery (Newman et al., 2006; Pahor et al., 2014; Rolland et al., 2004).

These findings, when applied to the CRC population, are especially important to consider as older age, underlying illness (i.e., cancer and/or chronic disease), neoadjuvant therapy, excess weight, and poor lifestyle habits (smoking, excessive drinking, and physical inactivity) increased the risk of reduced muscle mass and function before surgery, and for adverse outcome following surgery (Fearon et al., 2006; Jones, Gordon-Weeks, Coleman, & Silva, 2017; Mason et al., 2016; Miyamoto et al., 2015).

Depression in the Cancer Population

Onset and prevalence.

In addition to the myriad of physical impairments accompanying cancer and its treatment, a diagnosis of cancer often leads to significant psychological stress (Andersen, Kiecolt-Glaser, & Glaser, 1994). Following diagnosis, feelings of fear, pessimism, and inevitability of death are not uncommon (Powe & Finnie, 2003), and according to these authors, "individuals may feel powerless in the face of cancer and may view a diagnosis of cancer as a struggle against

insurmountable odds" (p. 456). Stressful life events, such as the diagnosis of a serious disease, are strongly linked to the development and clinical course of depressive symptoms and MDD (Hammen, 2005; Holsboer, 2000; Mazure, 1998; Monroe & Simons, 1991; Slavich & Irwin, 2014; Van Manen et al., 2002). Given the life-threatening nature of the disease, and the lengthy and aggressive treatment accompanying its diagnosis, it is not surprising that MDD is among the most frequently observed mental disorder among patients with malignant disease (Pasquini & Biondi, 2007).

Research has demonstrated that across the trajectory of illness, 30-40% of individuals receiving cancer care, experience significant psychological distress (Carlson et al., 2004; Carlson & Bultz, 2003; Mitchell et al., 2011; Zabora, Brintzenhofeszoc, Curbow, Hooker, & Piantadosi, 2001). Distress, as defined by the National Comprehensive Cancer Network (2018; p. 2), is a "multi-determined unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social and/or spiritual nature that may interfere with ability to cope effectively with cancer, its physical symptoms and its treatment". Distress extends along a continuum, ranging from normal feelings of sadness and fear, to problems that can become disabling such as MDD, generalized anxiety disorder (GAD), or panic disorder. For some, this distress is manageable, does not require intervention, and will naturally decrease over time (Zabora et al., 2001). However, for many this distress can lead to clinically significant depression and may require psychological intervention (Zabora et al., 2001). Approximately 58% of individuals diagnosed with cancer are affected by depressive symptoms and up to 38% meet the diagnostic criteria for MDD (For diagnostic criteria, see (American Psychiatric Association, 2013; Massie, 2004; Mitchell et al., 2011; Ng, Boks, Zainal, & De Wit, 2011).

Though rates of depression tend to be highest during active treatment (Krebber et al., 2014), the periods immediately following diagnosis and while awaiting treatment are associated with significant distress (Fitch, 2008; Holland, et al., 2014). When compared to both breast and prostate cancers, a diagnosis of CRC is associated with the highest risk for newly diagnosed depression (Alwhaibi et al., 2017). There is substantial evidence which shows that the psychological impact of cancer and its treatment can persist for years following diagnosis (Holland et al., 2014; Veach, Nicholas, & Barton, 2002). Compared to age-matched controls and in the general population, CRC survivors report greater limitations in their psychological and social functioning, more fatigue, and report significantly higher rates of depression one-year following diagnosis (Arndt et al., 2004; Ramsey et al., 2002). Dunn and colleagues observed that 5 months following diagnosis and cancer treatment, 44% of CRC survivors continued to report clinically significant distress, and at 5 years post-diagnosis this figure remained just as high (42%; Dunn et al., 2013).

Comorbid health burden.

Depression is also associated with high rates of other psychiatric problems and with a greater burden of somatic symptoms. It is estimated that approximately two thirds of cancer patients who are depressed also report clinically significant symptoms of anxiety, and between 30 to 50% of the psychological burden experienced by cancer patients is a combination of both anxiety and depression (Brown, Kroenke, Theobald, Wu, & Tu, 2010; Lamers et al., 2011; Massie, 2004). These disorders, when comorbid, have been linked to increased symptom severity, longer time to recovery, increased use of healthcare resources, and poorer outcome when compared to those with just one disorder (Grady-Weliky, 2002). Moreover, depression reliably predicts greater pain (Bair, Robinson, Katon, & Kroenke, 2003), poorer sleep quality and

fatigue (Prue, Rankin, Allen, Gracey, & Cramp, 2006; Roscoe et al., 2007; Sharma et al., 2012), as well as lower QOL in individuals with cancer (Zabora et al., 2001).

Impact on health behaviours.

Depression can undermine the ability to manage cancer and its accompanying challenges through its influence on engagement in key health behaviours. For example, depressed individuals have been shown to miss more medical appointments, ask fewer questions during these appointments, retain less information, have more difficulty following instruction, and to be less likely to adhere to medical recommendations (DiMatteo & Haskard-Zolnierek, 2010; Grenard et al., 2011). Depressed individuals are also more likely to engage in and maintain detrimental health-related behaviours including smoking, excessive drinking, unhealthy diet (Bonnet et al., 2005), and be physically inactive (Roshanaei-Moghaddam, Katon, & Russo, 2009). These are not only known risk factors for the development of CRC (Canadian Cancer Society, 2011), but are also associated with poor immunity, cancer progression and shortened survival following diagnosis and treatment (Boyle, Fritschi, Platell, & Heyworth, 2013; Meyerhardt et al., 2007). Depression is also associated with higher health care utilization and concomitant costs (Simon, Vonkorff, & Barlow, 1995).

Impact on immunologic function.

Chronic stress, a risk factor for the development of depression, has been linked to immune dysregulation and to inflammation (Blume, Douglas, & Evans, 2011; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002), a seminal biological process recognized as promoting tumor growth and metastasis (Green McDonald, O'Connell, & Lutgendorf, 2013; Hanahan & Weinberg, 2011; Kiecolt-Glaser et al., 2002). In the cancer population, the presence of depression is associated with impaired immune function, tumor progression, cancer metastases

(Reiche, Nunes, & Morimoto, 2004), and an elevated risk of mortality (Pinquart & Duberstein, 2010; Satin et al., 2009).

Impact on surgical outcomes.

In the context of surgery, preoperative psychological health is strongly linked to a variety of postoperative outcomes. Patients with preoperative depression are at an increased risk for wound complications post-surgery, are more likely to be readmitted for these complications, and tend to stay in hospital for significantly longer than those without depression (Britteon et al., 2017). Depression in the preoperative period has also been linked to postoperative cognitive decline and delirium, chronic post-surgical pain, lower HR-QOL, and increased risk of mortality (For review see Ghoneim & O'Hara, 2016). See **Figure 1** for flowchart depicting development of depression and its impact on cancer outcomes.

Psychological health has also been implicated in functional recovery after both cancer and non-cancer surgeries. This relationship has been studied most extensively in the cardiac population. Major findings from this field have demonstrated a strong association between preoperative depression and postoperative morbidity (Burg, Benedetto, Rosenberg, & Soufer, 2003), and have identified preoperative depression as an independent risk factor for mortality following cardiac surgery (Ho et al., 2005). Furthermore, individuals with preoperative depression, and/or negative beliefs regarding their illness tend to stay in hospital longer after surgery, are more likely to be readmitted, experience higher rates of cardiac events, and report worse functional recovery and lower physical quality of life for up to one year after surgery (Chunta, 2009; Kohlmann et al., 2012; Poole et al., 2017). Postoperative depression is also associated with poor emotional and physical recovery after cardiac surgery. Doering, Moser, Lemankiewicz, Luper, and Khan (2005) found that individuals who reported higher depressive

scores at hospital discharge were significantly more likely to achieve shorter walking distances and to report poorer emotional and physical recovery 6 weeks after surgery compared to those with no or low levels of depression at discharge.

The observation that depression is associated with poor physical recovery following surgery has been further substantiated by findings in non-cancer surgery. The role of emotional health has been studied extensively across various orthopedic procedures, including spine surgery, trauma care, fracture repair, sports related surgery, total hip and knee replacements (For review, see: Ayers, Franklin, & Ring, 2013). Findings in this field have consistently demonstrated a strong relationship between emotional health and physical outcome following surgery. While positive emotional health before surgery is associated with better physical outcomes following orthopedic surgery, such as greater pain relief and better functional outcomes (Ayers et al., 2013), preoperative depression is associated with greater patient dissatisfaction, poorer functional outcomes, greater perceived disability, and minimal functional gain (Ayers et al., 2013).

One study examining factors associated with recovery of functional ability in adults following surgical treatment for cancer found that after controlling for age, comorbidities, site of disease, and symptom severity, preoperative psychological well-being was a significant prognostic factor for functional recovery (Hodgson & Given, 2004). More specifically, these authors found that individuals reporting lower psychological well-being at baseline were less likely to report full functional recovery after surgery (Hodgson & Given, 2004). Preoperative depression has been shown to predict failure to return to work and failure to report improved functional ability in older lung cancer patients 1 year after surgery (Decoster et al., 2017), and

lower self-reported physical function in men 3 months after radical prostatectomy (Ene, Nordberg, Johansson, & Sjöström, 2006).

Impact on physical function.

Depression may also lead to difficulties in managing cancer and its accompanying challenges through its impact on physical health. In the general population, depression and physical disability commonly co-occur. Rates of physical disability in depressed individuals far exceed those observed in the general population, and the severity of this disability is comparable to or greater than the disability observed in those with a primary physical disease, like cancer or diabetes (Ormel et al., 1998; Wells et al., 1989).

Evidence shows that individuals with poor physical function are more likely to report depressive symptoms, and those with depressive symptoms are more likely to report impairments in physical function (Bruce, 2001; Lenze et al., 2001). The existence of this bidirectional relationship is further supported by observations that physical disability, functional impairment and deteriorations in physical status are associated with and predict the onset and course of major depressive disorder (Roberts, Kaplan, Shema, & Strawbridge, 1997; Weinberger et al., 2008). Conversely, depressive symptomatology is associated with impairments and deteriorations in physical function (Brenes et al., 2008; Cronin-Stubbs et al., 2000; Rhebergen et al., 2010).

Depression has been identified as a significant predictor of functional decline and disability in older adults (Hybels, Pieper, & Blazer, 2009; Iwasa et al., 2009; Wang, Van Belle, Kukull, & Larson, 2002), and its onset has been shown to precipitate a significant increase in functional impairment in the elderly (Hajek et al., 2017). Studies examining the nature of this relationship have demonstrated a strong association between the level of functional disability and severity of depression (Kruijshaar, Hoeymans, Bijl, Spijker, & Essink-Bot, 2003), with

improvements in physical function coinciding with improvements in psychological health (Spijker et al., 2004). In a population-based longitudinal study (Cronin-Stubbs et al., 2000) of over 3000 community-dwelling individuals, burden of depressive symptoms was found to be associated with the development and recovery from physical disability. Cronin-Stubbs and colleagues (2000) found that with each additional symptom of depression, the likelihood of developing disability increased and likelihood of recovering from disability decreased. Interestingly, poor physical function has been associated with depressive symptoms or subthreshold depression (not meeting diagnostic criteria for MDD), suggesting that patients need not be clinically depressed to experience significant impairments in their function (Hybels et al., 2009).

Preoperative depression and physical function in surgical oncology.

Despite the well-documented association between depression and poor physical health, there is a paucity of research demonstrating this association using objective measures of functional performance. Incorporating objective measures, especially in the context of depression and cancer surgery, is critical for several reasons: 1) self-perceptions of physical health in depressed individuals may inaccurately reflect their objective level of physical function. For example, in individuals with depression, perceptions of physical health status and objective severity of functional impairment have been shown to be discrepant (Kohen, Burgess, Catalán, & Lant, 1998). Thus, self-report methods may provide a biased, and incomplete picture of functional status in depressed individual. 2) functional performance measures are important tools in preoperative risk assessment (Mayo et al., 2011; Snowden et al., 2010), and can be used to guide interventions aimed at enhancing preoperative functional status. If functional impairment

is a risk factor for poor operative outcome, understanding whether depression is associated with poor physical function before surgery is critical.

Studies examining the relation between depression and objective FS are limited in number, have been conducted in cancer survivors rather than those awaiting treatment, and findings from these studies have been inconsistent. For example, Tomruk, Karadibak, Yavuzşen, and Akman (2015) examined predictors of FS in CRC patients. While they found a significant correlation between depression and self-reported performance status, they found no correlation between depression and measures of objective physical performance. Similarly, Vardar-Yagli et al. (2015) examined associations between physical activity (PA), FS, peripheral muscle strength and depression in breast cancer survivors. Depression scores were found to be inversely associated with PA level; however, the authors failed to find any association between depression and any of the physical performance measures (FS and muscle strength). Conversely, an association between depression and objective FS was demonstrated in colorectal cancer survivors following completion of surgery and chemotherapy (Lee et al., 2015). After controlling for confounding variables, Lee and colleagues (2015) found that performance on the 6MWT and on the chair stand test, which assesses ability to stand up and sit down as many times as possible in 30 seconds, were negatively associated with depressive symptoms. These authors further explored the relationship between 6MWT and depression. Dividing participants into three groups based on their 6MWT results, these authors found that individuals in the lowest tertile reported higher depression scores than those in the highest tertile (Lee at al., 2015).

These findings, while discrepant, suggest that depression may be associated with objective measures of FS. Further support for the relationship between objective FS and depression comes from research conducted in non-cancer populations. Symptoms of depression

have previously been demonstrated to correlate with shorter 6MWD in the elderly (Enright et al., 2003), and with diminished physical work capacity in patients with a clinical diagnosis of depression (Martinsen, Strand, Paulsson, & Kaggestad, 1989). A study conducted in individuals with pulmonary arterial hypertension found depressive symptomatology (though not statistically significant), to be related to lower 6MWD (McCollister et al., 2010). These authors found a negative linear relationship between change in depression and improvement in 6MWD, and found that in patients with baseline depressive symptoms, improvements in these symptoms were associated with improvements in 6MWD.

Lastly, despite evidence suggesting that anxiety and depressive disorders may independently affect physical function (Lenze, et al., 2001), few studies have examined differences using objective measures of physical function in individuals with symptoms of one disorder or the other. This is noteworthy, as increasingly there is evidence to suggest that impairments in physical function differ according to the presence of depression, anxiety, or comorbid depression and anxiety (Lenze et al., 2001; Stegenga et al., 2012).

Prehabilitation: Targeting preoperative physical health to improve post-surgical outcome

Traditionally, interventions aimed at improving recovery have focused on the intra- and post-operative periods; however, the preoperative period may provide a better opportunity to target patients at increased risk for poor outcome, like those who are elderly, overweight, or burdened by chronic illness. Waiting until after surgery, when patients are in the process of recovering, comes with several disadvantages and important implementation challenges, such as a general concern, shared by both patients and doctors, about disrupting the healing process, as well as more fatigue, pain, and muscular weakness (Christensen et al., 1982; Christensen & Kehlet, 1993; Silver & Baima, 2013). Patients may also be apprehensive about initiating a

recovery program after surgery (rehabilitation), as many are adjusting to changes in bowel function, functional ability, and independence, and are distressed as they await results from the procedure (Cheema et al., 2011; Silver & Baima, 2013). Thus, to overcome these challenges, and to help prepare patients for surgery, interventions aimed at addressing modifiable risk factors could be more effective if implemented in the preoperative period (prehabilitation).

In oncology, prehabilitation is defined as "a process on the cancer continuum of care that occurs between time of cancer diagnosis and the beginning of acute treatment, and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments" (Silver & Baima, 2013; p. 716). The goal of prehabilitation is to help mitigate the loss of and/or facilitate gains in muscle mass and strength, improve physical fitness, and increase physiologic reserve prior to surgery through structured exercise, nutritional support, and stress-reducing strategies. Improvements in preoperative health status can help individuals better withstand the stress of surgery, attenuate drastic postoperative declines in physical function and accelerate the return to preoperative levels of function. See **Figure 2**.

In the CRC population, prehabilitation programs implementing structured exercise, and nutritional counselling during the preoperative period have been shown to be feasible, and well tolerated, with low dropout rates and relatively high adherence to unsupervised and supervised exercise protocols (Chen et al., 2017). Additionally, patients participating in these programs preoperatively are more likely to increase their engagement in moderate- and vigorous- intensity physical activity and to meet current physical activity guidelines before surgery (Chen et al., 2017). Recently, a study was conducted in the CRC cancer population comparing the effects of a

tri-modal prehabilitation (exercise, nutrition, and diaphragmatic breathing) versus a tri-modal rehabilitation program on changes in physical function both before and after surgery. The major findings from this study were that individuals receiving prehabilitation were more likely to see significant improvements in their physical function preoperatively, less decline in physical function 4 weeks after surgery and were more likely to return to baseline function 8 weeks after surgery, when compared to those receiving rehabilitation (Gillis et al., 2014). In individuals undergoing major abdominal surgery, prehabilitation has also been shown to reduce the rate and the number of patients with postoperative complications (Barberan-Garcia et al., 2018).

While preoperative interventions have been shown to improve level of physical fitness prior to surgery and to accelerate functional recovery after abdominal surgery, to our knowledge, no study to date has examined whether prehabilitation can improve FS in depressed cancer patients (Carli et al., 2009; Santa Mina, Clarke, et al., 2014). There is evidence to suggest that prehabilitation interventions may be more effective in specific subgroups, like those with poor physical health at baseline. For example, an analysis was performed on previously collected data from two randomized control trials (RCT) and a pilot study on prehabilitation in the CRC cancer population (Minnella et al., 2016); the purpose of this analysis was to identify those with low FS at the onset of the program and to assess whether their baseline fitness level predicted improvements in FS in the pre- and postoperative periods. Authors found that when compared to those in good physical condition before surgery, patients who were unable to walk 400m at baseline improved significantly more with a prehabilitation intervention. More specifically, these patients saw significantly greater improvements in FS in the preoperative period, and were more likely to return to their baseline function 4-weeks after surgery when compared to those with higher baseline walking capacity (>400m). So, while individuals who walk <400m at baseline

may be at higher risk for poor surgical outcome, they may also be more likely to improve during the preoperative period and more likely to return to or surpass their baseline function than those in better physical condition at baseline, with a prehabilitation program. Therefore, these individuals could be ideal candidates for preoperative interventions and could thus be identified and targeted when selecting at-risk patients to receive a prehabilitation program.

Since depression appears to be associated with lower functional status, prehabilitation may be especially effective for depressed individuals. Physical activity interventions have been shown to be effective in improving physical function in depressed individuals and have shown promise in reducing depressive symptoms (Craft, VanIterson, Helenowski, Rademaker, & Courneya, 2012; A. L. Dunn, Trivedi, & O'Neal, 2001; Oeland, Laessoe, Olesen, & Munk-Jørgensen, 2010; Penninx et al., 2002). Given the high prevalence of depression in patients prior to oncological surgery, and the increasing use of prehabilitation interventions before a variety of surgeries (Baima et al., 2017; Gillis et al., 2014; Jack, West, & Grocott, 2011; Nielsen, Jørgensen, Dahl, Pedersen, & Tønnesen, 2010; Santa Mina, Matthew, et al., 2014; Topp, Swank, Quesada, Nyland, & Malkani, 2009), there is a need to examine whether depression is associated with FS in these patients and whether FS can be improved.

Aim and Research Questions

The primary objective of this study was to examine self-reported and objective preoperative FS in colorectal cancer patients with depressive symptoms. It was hypothesized that CRC patients with depressive symptoms would report lower FS, and would perform more poorly on objective tests of FS when compared to patients with no depressive symptoms. The second objective of the current study was to examine the impact of a multimodal prehabilitation program, compared to a multimodal rehabilitation program, on improving the FS of depressed

individuals. It was hypothesized that a prehabilitation intervention, when compared to a rehabilitation program, would significantly improve FS in depressed individuals.

Methods

Design

In the present study, a reanalysis was performed on the data of two published randomized controlled trials (RCT; Bousquet-Dion et al., 2018; Gillis et al., 2014), and an additional cohort study (NCT02586701). Similar protocols guided both RCTs and the cohort trial, which investigated the effects of a multimodal prehabilitation program on perioperative FS in patients awaiting resection for colorectal cancer.

Participant Characteristics

One hundred and eighty-three adults scheduled for curative resection of non-metastatic colorectal cancer, were recruited at the Montreal General Hospital, a University Centre Hospital in Montreal, Quebec, Canada, between November 2011 and October 2016. Before being contacted by telephone, all potential subjects were informed of the study during their initial surgical consultation. Individuals were then called by the clinical research coordinator who assessed eligibility, explained the program, and invited those meeting the inclusion criteria to participate. Eligibility for participation included: a) diagnosis of non-metastatic colorectal cancer; and b) scheduled elective surgery for colorectal resection. Individuals meeting the following criteria were not considered eligible: a) inability to understand or read English or French; b) inability to provide informed consent; or c) presence of premorbid conditions contraindicating exercise (e.g., severe cardiovascular and neuromuscular disease). Individuals were not offered financial, or any other form of compensation for their participation. However, individuals for whom the price of parking was the main refusal reason for program participation

were offered an amount of $20 per visit for indoor parking fees. All subjects provided informed consent before the baseline assessment, all three studies were approved by the McGill Research Ethics Board (McGill University Health Centre, Quebec, Canada), and data were collected at the MGH in accordance with ethical standards.

Original Study Protocols

Following a baseline assessment, subjects in both RCTs were randomized to receive either a prehabilitation or rehabilitation program consisting of a moderate-intensity exercise program, nutritional counselling, and stress-reducing strategies. Subjects in the cohort study received prehabilitation-only. Those in the prehabilitation arm received the intervention at baseline, scheduled approximately four-weeks prior to surgery, and continued the program at home for eight-weeks postoperatively. Those in the rehabilitation arm completed a baseline assessment (4 weeks before surgery), were sent home and received the intervention at 24-48 hours before surgery. These individuals were instructed to initiate the program on return home from the hospital, and to continue for eight-weeks postoperatively. All subjects were seen at 4 time points, including twice before surgery, at baseline, scheduled 4 weeks before surgery, and 24-48 hours before surgery, and twice following surgery, at 4 and 8 weeks postoperatively. See **Figure 3** for assessment timeline.

Exercise intervention: Individuals met with a trained kinesiologist who, following the American College of Sports Medicine guidelines, assessed level of physical fitness and prescribed a three-times per week home-based training program (with a once per week in-hospital training session for Bousquet-Dion, 2018 and cohort: NCT02586701) consisting of aerobic, resistance, and flexibility exercises (**Table 1**). Resistance exercises were designed to target major muscle groups and were performed using elastic bands, selected and adjusted to

each subject's level of physical strength. The rate of perceived exertion, measured using the Borg scale (Appendix 1; Borg, 1982) during the 6MWT at baseline, was used to help guide the intensity of aerobic exercise (biking, walking, or swimming). This was adjusted throughout the program to ensure progress.

In-hospital exercise sessions: Patients in the prehabilitation program were asked to come in for weekly supervised exercise sessions with the kinesiologist (Note. Subjects in Gillis, et al., 2014 followed a home-only based program with no in-hospital supervision), who ensured proper form and technique, and modified the program according to the needs of each patient (i.e. to adjust resistance, modify the exercises, etc.). The duration of each session was approximately one hour, and included both aerobic and resistance exercises, performed at a moderate level of intensity (Of 13/20 on the Borg; measure described below). The aerobic exercise was performed on a recumbent cross trainer machine (NuStep; Gatineau, QC, Canada), which lasted between 10 and 20 minutes, with a 5-minute warm up and 5-minute cool down (not included in actual exercise time). Following the aerobic portion, patients performed a resistance exercise routine, consisting of ten exercises targeting major muscle groups. Patients performed 1-3 sets of 8-15 repetitions of each exercise at moderate intensity. To maintain the desired moderate level of exertion and to ensure progress over the course of the program, the intensity of each workout was adjusted according to patient volition and to exertion ratings using the Borg scale (13/20).

Nutritional intervention: A registered dietician met with patients to assess nutritional status and to ensure the provision of tailored care. A three-day estimated food record (including 2 week days and 1 weekend day) was used to help calculate macronutrient and energy intake (grams of carbohydrates, fat, and protein), and to determine the amount of whey protein supplementation (Immunocal®; Immunotec Inc., Vaudreuil, Quebec, Canada) required to meet

current European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations (1.2g/kg/day of body weight). Given that enhancing functional walking capacity was the primary objective of the multimodal program, the protein supplement was used to ensure patients met daily protein requirements, to optimize protein synthesis, and to help facilitate increases in muscle mass. Patients were instructed to take the supplement in the hour following the performance of their exercises, and were encouraged to continue taking it for the entire duration of the program, excluding the post-surgical in-hospital stay. If needed, patients received additional support to help manage cancer-related symptoms, facilitate changes in body composition (weight loss or gain), regulate blood glucose levels, and/or to provide general instruction on how to make healthier food choices (using the "balanced plate method"; See **Appendix B** for example).

Stress-reducing intervention: A relaxation specialist, trained by a clinical psychologist, met with patients to teach and prescribe diaphragmatic breathing exercises to help encourage the use of stress-reducing strategies before and after surgery. Additionally, a compact disc was given, in English or French, to help instruct and guide patients through the breathing exercises once at home.

Post-operative period: After surgery, patients in the prehabilitation group were instructed to continue the exercise and nutritional program once home from the hospital. Patients were encouraged to begin taking the protein powder and instructed to gradually increase the intensity of the exercise over the weeks following surgery. Those in the rehabilitation group received a home-based equivalent of the same program given to those in the prehabilitation group preoperatively. During the first postoperative month, all patients were discouraged from

engaging in abdominal exercises (to avoid discomfort and so as not to perturb the healing process).

Subjects were called weekly, pre- and postoperatively, to answer questions or state concerns regarding the exercises, nutrition, and stress-reduction, to record adherence to the exercise program, and to assess the amount of whey protein supplement taken. Additionally, patients were given a booklet with an explanation of the program, nutritional guidelines, written instructions and visual depictions of each exercise, as well as a diary to record exercise activity throughout the program (See **Appendix B**).

ERAS protocol: All patients were managed within an Enhanced Recovery After Surgery (ERAS) program for elective colonic surgery (Gustafsson et al., 2013). Briefly, ERAS programs aim to minimize the surgical stress response and accelerate postoperative functional recovery through preoperative risk assessment and optimization of health, through various intraoperative and surgical techniques, and early mobilization and pain management after surgery.

Measures

The baseline assessment included the collection of demographic and clinical information, medical and surgical history, and a medication inventory. At baseline, and at subsequent visits (scheduled 24-48 hours before surgery, and at 4- and 8-weeks postoperatively), body composition (height, body mass index (BMI), lean body mass (LBM) and percent body fat) was determined using a stadiometer and a bioelectrical impedance analysis machine. Preoperative physical status, graded using the American Society of Anesthesiologists Classification of Physical Health (ASA; Dripps, 1963). The following postoperative outcome measures were collected and were obtained from hospital records postoperatively: length of hospital stay, intra- and postoperative complications (graded using the Clavien-Dindo Classification; Dindo,

Demartines, & Clavien, 2004), hospital readmission in 30-days post-surgery, tumour pathology, and cancer stage. A series of functional tests, listed in **Table 2,** and questionnaires (described below), assessing physical and psychological health, HR-QOL, and physical activity were also collected at each time point (baseline, 24-48 hours before surgery, and 4- and 8-weeks postoperatively).

Six-Minute Walk Test (6MWT; Enright et al., 2003) is a brief performance-based measure of functional exercise capacity which evaluates an individual's ability to sustain a moderate level of physical activity for 6 minutes. The 6MWT integrates balance, endurance, muscle strength and speed, and reflects subjects' ability to engage in activities of daily living. It is easy to administer, well tolerated, does not require exercise equipment or specialized personnel, and can be performed in nearly any clinical location (Crapo et al., 2002). Standardized instructions, provided by the American Thoracic Society (2002), were used to guide patients. Using the following formula:

$$\text{6-minute (m)} = 868 - (\text{age} \times 2.9) - (\text{female} \times 74.7)$$

age- and sex-predicted norms can be calculated for expected six-minute walk distance (6MWD), where age is in years, and a value of 1 is assigned for females, and 0 assigned for males.

The 6MWT has been shown to predict complications after major abdominal surgery (Lee et al., 2013) and has been validated as a measure of postoperative recovery after abdominal surgery (Moriello, Mayo, Feldman, & Carli, 2008; Pecorelli et al., 2016). This test correlates well with formal exercise testing (Lee et al., 2013), specifically, with cardiopulmonary exercise testing (CPET), which is widely considered the gold standard for evaluating physical fitness (American Thoracic Society, 2003). Poor performance on the CPET has been shown to predict

postoperative morbidity and mortality in patients undergoing intra-abdominal surgery (Moran et al., 2016)

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a brief, 14-item self-administered rating scale designed to assess anxiety and depression in patients with physical illness. HADS is the most extensively used measure in oncological settings (Mitchell, Meader, & Symonds, 2010), due to its exclusion of many physical symptoms common in those with physical illness (e.g., fatigue and change in sleep and appetite). Items are rated on a 4-point Likert response scale, scored from 0 to 3, and are summated to form two 7-item subscales assessing anxiety (HADS-A) and depression (HADS-D). Each subscale is scored out of 21, with higher scores denoting greater severity of anxiety and depression. Optimal cutoff scores of ≥8 for possible cases and ≥11 for safe cases on each scale have been proposed for evaluating primary-care patients (Bjelland, Dahl, Haug, & Neckelmann, 2002; Zigmond & Snaith, 1983). In the current analyses, adjusted cutoff scores of HADS-A ≥7 (detect 75% of cases with a specificity of 0.56) and HADS-D ≥5 (detect 82% of cases with a specificity 0.49) were used as they have been shown to better fit oncological settings (Singer et al., 2009).

Medical Outcome Study 36-Item Short Form Health Survey (SF-36; Ware & Sherbourne, 1992) is the most widely used generic health questionnaire evaluating HR-QOL. This 36-item self-report questionnaire covers eight health dimensions, assessing physical and mental health, social functioning, and general health perceptions. Items are scored on a scale from 0 to 100, with higher scores reflecting better health (100 represents best health state, and 0 represents worst health state). The 8 subscales can be used to derive two summary component scores: Physical Component (includes physical functioning, role physical, bodily pain and general health perception subscales), and Mental Component (includes vitality, social

functioning, mental health and role emotional subscales; Ware, Kosinksy & Keller, 1994). Four subscales measure dimensions related to physical health: physical functioning, physical role functioning, bodily pain, and general health perceptions. Published norms exist for the Canadian population (Hopman et al., 2000) with scores on all 8 subscales surpassing values of 65. A difference of 5 points is accepted as a clinically and socially meaningful difference (Ware, 1993). Overall, SF-36 demonstrates good construct validity and has been shown to be a valid measure of postoperative recovery after colorectal surgery (Antonescu, Scott, Tran, Mayo, & Feldman, 2014).

Community Health Activities Model Program for Seniors (CHAMPS; Stewart et al., 2001), is self-report questionnaire used to measure physical activity (PA), and more specifically, the efficacy of exercise interventions in increasing PA in older adults. From a list of 41 activities (of varying intensities), individuals estimate the total number of hours spent during the previous week engaging in various forms of PA. An estimate of weekly energy expenditure (kcal/kg per week), in light, moderate and vigorous, and total activity are calculated by multiplying the number of hours spent engaging in each activity by the metabolic equivalent of its task (MET). CHAMPS is sensitive to changes in PA over time and varying levels of intensity of PA (2001). Its validity as a measure of recovery following laparoscopic cholecystectomy has previously been demonstrated (Feldman et al., 2009).

The Borg Rating of Perceived Exertion Scale (BORG; Borg, 1982) is a figure designed to rate perceived exertion during or immediately after physical activity. Participants are asked to rate their exertion, taking into consideration heart rate, respiration, muscle fatigue, and sweating, from a value of 6 (no exertion at all) to 20 (maximal exertion). The Borg scale is widely used in sports medicine, primarily as a tool to help plan and adjust intensity of various training regimes.

The Borg scale was used to judge, and subsequently modify, the intensity of exercise in the aerobic and strength training component of all three protocols.

Clavien-Dindo Classification (Dindo et al., 2004) is a ranking system used to classify and grade postoperative complications. Complications are graded from I-V, ranging from minor complications requiring little intervention to those requiring invasive intervention (surgical, endoscopic, radiological, etc.; For detailed description of grading classification, see Dindo et al., 2004). In the current analyses, patients were categorized as either 0, 1, or 2 and above.

American Society of Anesthesiologists Classification of Physical Health (ASA; Dripps, 1963) is a grading system used to categorize preoperative physical health status of surgical patients, and to assess and predict anaesthetic risk. ASA grades range from I-VI (For detailed description see Daabiss, 2011). In the current analyses, patients were categorized as either ASA Grade I, Grade II, or Grade III or above (IV, V, or VI).

Sample Size Justification and Power Analyses for Original Studies

Sample size estimation was performed for both RCTs using G*Power 3.1 (Erdfelder, Faul, Buchner, & Lang, 2009). Analyses were conducted using standard conditions ($\alpha = 5\%$, power = 80%) and were based on a two-sample (repeated measures) comparison of FS. Calculations for Gillis et al. (2014) were based on mean changes in FWC at 8 weeks postoperative compared to baseline, assuming the 6MWT at 8 weeks in the rehab group would be 25±66m lower than at baseline and would be 35±68 above baseline in the prehabilitation group. Calculations for Bousquet-Dion (2018) were based on the proportion of patients improving 6MWT (>19m) over the preoperative period, and considering an attrition rate of 20%. These analyses yielded a sample size of 40 per arm ($n = 80$) and 44 per arm ($n = 88$),

respectively. A sample size of $n = 40$ for the cohort study was established, anticipating a rate of 20% due to withdrawal or loss to follow-up.

Primary Outcome

The primary outcome in the current analysis was FS. Self-reported FS was assessed using SF-36, and using the specific subscales pertaining to physical health (physical function, physical role functioning, bodily pain, and general health perceptions), while objective FS was assessed during the 6MWT.

For the first objective FS was assessed at baseline (scheduled 4-weeks before scheduled surgery) and prior to receiving the intervention. Low FS was defined as achieving a 6MWD under 400m at baseline, as it has been demonstrated that individuals who are unable to walk this distance (or unable to achieve gait speed necessary to achieve this distance) are at higher risk for mortality, cardiovascular disease, mobility limitations and disability (Newman et al., 2006; Pahor et al., 2014; Rolland et al., 2004). A 6MWD of less than 409 m has been shown to correlate with poor performance during CPET, and is predictive of low peak oxygen intake (peak VO_2: <15mL O_2 kg^{-1} min^{-1}; Sinclair, Batterham, Davies, Cawthorn, & Danjoux, 2012), a threshold which independently predicts postoperative morbidity, complications, and early postoperative death (Bayram, Candan, & Gebitekin, 2007; Grant et al., 2015; Loewen et al., 2007; Smith, Stonell, Purkayastha, & Paraskevas, 2009; West, Jack, & Grocott, 2011).

For the second objective, the likelihood of improving perioperative (including the pre- and postoperative periods) 6MWD by at least 20 m was selected, as this distance has been identified as the minimal clinically important difference (MCID), defined as "smallest change in an outcome measure perceived as beneficial by patients or physicians" (p. 320; Antonescu et al., 2014), in individuals going for colorectal resection (2014; Moriello et al., 2008).

Statistical analyses

Subjects with missing data on the HADS questionnaire or 6MWT at baseline were excluded from the following analysis. Descriptive analyses were conducted on baseline demographics, physical health characteristics, illness- and surgery-related variables, postoperative outcome (See **Tables 3 and 4** for summary of measures included in descriptive analyses), and results of physical and psychological measures (CHAMPS, 6MWT, SF-36 and HADS) of the total sample. Ordinal data are presented in the form of frequencies, and percentages and continuous data are presented in the form of means (M) and standard deviations (SD).

Subjects were categorized into one of three distinct groups based on their distress status at study baseline. Cutoff scores of HADS-A: ≥7 and HADS-D: ≥5 were used to identify cases (Singer et al., 2009). Subjects were grouped based on: no symptoms (HADS-N), symptoms of anxiety-only (HADS-A), or symptoms of depression with or without comorbid anxiety (HADS-D). Individuals with HADS-A: ≥7 and HADS-D: ≥5 were assigned to the HADS-D group, to ensure that the anxiety group did not include any individuals with depressive symptoms. Thus, the HADS-D group represented not only a depressed group but a comorbid anxiety and depression group. Groups were compared on baseline demographics, physical health status, surgery- and illness-related factors, and postoperative outcomes. A series of ANOVAs were conducted for continuous variables, and Chi-Square tests were conducted for categorical variables.

To examine differences in self-reported and objective FS prior to intervention, these groups were compared on SF-36 and 6MWD at baseline (scheduled 4-weeks before surgery). ANOVA was performed to examine SF-36 (subscales analysis) and 6MWD, and a Chi-Square

test was performed to compare difference in proportion of subjects in each group walking below 400m at baseline. To examine differences in PA between groups, a subscales analysis of CHAMPS (mild, moderate and vigorous, and total) was performed using ANOVA.

To examine the effect of prehabilitation on the primary outcome (i.e., likelihood of improvement of at least 20m in perioperative 6MWD compared to baseline), Generalized Estimating Equation (GEE) analyses were conducted using logistic regression. Using this method, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated after adjusting for *a priori* and empirical confounders (baseline age, sex, BMI, smoking, alcohol consumption, and ASA classification, and postoperative length of stay and Clavien-Dindo Classification). GEE was selected due to its ability to account for the correlated nature of data resulting from repeated measures of the same individuals over time. We treated intervention (prehabilitation vs rehabilitation) as an exposure variable in the current model. We also stratified these results by baseline distress status. The statistical analysis was conducted using STATA 14.2 (Stata-Corp, College Station, TX, USA).

Results

Descriptive Statistics of Overall Sample

Eleven subjects were excluded in the analyses due to missing data on the HADS at baseline ($N = 172$). Descriptive statistics, calculated for baseline demographics, clinical factors, physical health status, and illness- and surgery-related variables are reported in **Table 3**. At study baseline, the mean age of subjects ($N = 172$) was 67 years ($SD = 11.2$) ranging from 34 to 94 years of age. The sample was majority male ($n = 107$, 62%), had completed post-secondary education ($n = 90$, 52%), not currently working ($n = 95$, 56%) and were diagnosed with cancer of the colon ($n = 110$; 65%). The sample ($N = 172$) scored below standard clinical cutoffs (HADS-

A<8 and HADS–D<8) for both HADS-A (M = 6.6, SD = 4.2) and HADS-D (M = 3.9, SD = 3.6). Self-reported PA (CHAMPS), and objective and self-reported FS (SF-36 and 6MWD) of the overall sample at baseline are summarized in **Table 3.**

Distress Group Comparison: Patient Characteristics at Baseline

Using baseline HADS-A and HADS-D subscale scores, 47% (n = 81) of the sample were allocated to HADS-N group, consisting of those with neither anxiety nor depressive symptoms, 16% (n = 27) were allocated to HADS-A, consisting of those with anxiety-only, and 37% (n = 64) were allocated to HADS-D (See **Figure 4** for flowchart of group allocation based on distress status). Of the 64 individuals assigned to the HADS-D group, 49 (77%) had comorbid symptoms of anxiety (HADS-A: ≥7). **Tables 3 and 4** describes baseline characteristics of HADS-N, HADS-A, and HADS-D. Demographics, clinical factors, physical health status, and surgery- and illness-related factors were compared between distress groups (**Tables 3 and 4)**. Of the 21 variables examined, only hospital readmission 30-days postoperatively was significantly different between distress groups. Higher rates of readmission were observed in the HADS-D (n = 6, % = 9.5) and HADS-N (n = 6, % = 7.9) groups, compared to HADS-A (n = 1, % = 3.7;), $\chi^2(6, N = 165) = 12.767$, $p = 0.047$**.**

Distress Group Comparisons: Baseline Functional Status and Physical Activity Level

Baseline PA level, and self-reported and objective FS were compared between distress groups at baseline (See **Table 5).** All three groups reported engaging in similar levels of light, moderate and vigorous PA.

A subscales analysis of the SF-36 showed significant group differences across all ten subscales, suggesting that HR-QOL (mental and physical) varied significantly according to baseline distress status (see **Table 5** for all comparisons). Overall, the HADS-D group reported

poorer functioning on all subscales compared to both the HADS-A and HADS-N groups. The four SF-36 subscales related to self-reported FS were substantially lower in HADS-D group compared to HADS-A and HADS-N groups. HADS-D reported lower overall physical functioning (M = 59.6, SD = 30.5; HADS-A: M = 81.9, SD = 26.4; HADS-N: M = 73.8, SD = 32.6), $F(2, 166) = 6.1$, $p = 0.003$; poorer physical role functioning (M = 49.6, SD = 41.6; HADS-A: M = 73.8, SD = 32.9; HADS-N: M = 78.6, SD = 35.5), $F(2, 166) = 10.97$, $p < 0.001$; more bodily pain (M = 61.5, SD = 26.4; HADS-A: M = 71.9, SD = 20.3; HADS-N: M = 77.1, SD = 22.5), $F(2, 166) = 7.59$, $p < 0.001$; and lower general health perceptions (M = 50.3, SD = 32.6; HADS-A: M = 64.4, SD = 17.3; HADS-N: M = 72.8, SD = 24.3), $F(2, 166) = 12.55$, $p < 0.001$. On average, HADS-A and HADS-N scores on SF-36 subscales were within 6.9 points from each other, with the greatest difference observed in emotional role functioning (15 points lower in HADS-A compared to HADS-N). HADS-D, when compared to HADS-N and HADS-A, reported lower functioning on SF-36 subscales of on average 22.4 and 15.5 points, respectively. See **Figure 5** for SF-36 mental health subscales and **Figure 6** for physical health subscales according to baseline distress status.

An ANOVA revealed statistically significant differences in average 6MWD between groups at baseline $F(2, 169) = 4.86$, $p = 0.003$. 6MWD was lower in the HADS-D group (M = 413, SD = 109.7), which was on average 50m less than those in HADS-N (M = 463, SD = 94.6), and 55m less than those in HADS-A (M = 468, SD =111.6). See **Figure 7** for 6MWD at baseline according to distress status**.** Furthermore, there was a significant difference in proportion of patients with low FS at baseline between distress groups. Forty-five percent of the HADS-D sample (n = 29) walked <400m compared to 15% of HADS-A (n = 4) and 19% of HADS-N

group, $\chi^2(2, N = 172) = 17.646$, $p < 0.001$. See **Figure 8** for proportion of individuals in each distress group with 6MWD below 400m at baseline**.**

Distress Group Comparisons: Likelihood of Improving Perioperative FS by Intervention Status

Table 6 presents adjusted odds estimates (ORs) for improvement in perioperative FS according to intervention (prehabilitation vs rehabilitation) and distress status at baseline. Overall, individuals receiving prehabilitation were significantly more likely to improve perioperative FS by ≥20m compared to those receiving rehabilitation (OR = 1.72, 95% CI: 1.27–2.32). For individuals with no distress at baseline (HADS-N), and those with anxiety at baseline (HADS-A), prehabilitation was not associated with appreciable or significantly increased likelihood of improving perioperative FS (HADS-N: OR = 0.97, 95% CI: 0.44–2.16; HADS-A: OR = 1.47, 95% CI: 0.69–3.16). In contrast, for individuals with depressive symptoms at baseline (HADS-D), prehabilitation was associated with appreciable and significantly increased likelihood of improving perioperative FS by ≥20m (OR = 2.36, 95% CI: 1.53–3.66).

Post-Hoc Analyses: Characteristics of Low Versus Normal Functional Status in HADS-D

Post-hoc analyses were conducted on the HADS-D group to examine differences between those with low FS and those with normal FS at baseline. To do this, the HADS-D group ($N = 64$) was divided into two sub-groups 1. 6MWD >400m at baseline, and 2. 6MWD <401 m at baseline (low FS). A series of two-sample t-tests (assuming unequal variance with alpha 0.05) were conducted to compare these groups on: age, BMI, LBM, percent body fat, CHAMPS (mild, moderate and vigorous, and total), and SF-36 subscales. Chi square tests were used to compare groups on categorical variables (percent elderly, comorbidities, smoking and alcohol consumption, type of tumour and stage, and neoadjuvant therapy); See **Table 7 and 8** for results.

Forty-five percent (n = 29) of the HADS-D sample walked <401 m at baseline. Compared to those who walked above 400m at baseline (n = 35), a greater proportion of individuals with low FS were elderly (n = 13, 45%, vs >400: n = 4, 11.4%), $\chi^2(3, N = 64)$, = 9.07, p = .003. These individuals were also significantly older (M = 74, SD = 9.1; vs those >400: M = 61.1, SD = 9.9), $t(61) = 5.37$, $p < .001$, had lower lean body mass (M = 48.4, SD = 8.4, vs those >400: M = 54.6, SD = 11.9), $t(60) = 2.42$, p = .018, and reported engaging in less overall PA (M = 21.1, SD = 18.8; vs those >400: M = 51.6, SD = 49.8), $t(45) = 3.33$, p = .002. When examining differences in light and in moderate and vigorous PA at baseline, individuals with low FS reported significantly less time spent engaging in moderate and vigorous activity (M = 3.2, SD = 6.1), when compared to those walking >400m (M = 28.3, SD = 43.4), $t(35) = 3.34$, p = .002, whereas they reported comparable engagement in light PA (M = 16.5, SD = 16.8, vs >400 M = 22.2, SD = 17.5), $t(59) = 1.31$, p = 0.193.

T-tests revealed significant differences in four SF-36 subscales pertaining to physical health. Those with low FS at baseline reported significantly poorer physical function (M = 48, SD = 28; vs >400: M = 69, SD = 30), $t(57) = 2.51$, p = .01, more bodily pain (M = 54, SD = 24; vs >400: M = 67, SD = 27), $t(59) = 1.96$, p = .054, poor physical role functioning (M = 35, SD = 39; vs >400: M = 61, SD = 41), $t(58) = 2.81$, p = .007, and lower total-physical component scores (M = 40, SD = 12; vs >400: M = 55, SD = 18), $t(59) = 4.23$, $p < .001$.

Discussion

This study's aims were twofold. First, it aimed to address the gaps in knowledge regarding the association between the presence of depressive symptoms and objective and self-reported FS in CRC patients awaiting surgery. Second, it aimed to examine whether a prehabilitation intervention, compared to a rehabilitation intervention, could significantly

improve the FS, pre- and/or postoperatively, of CRC patients with baseline depressive symptoms. Our analyses of distress and FS at baseline demonstrated significant differences between distress groups in both self-reported and objective FS. As hypothesized, subjects with depressive symptoms reported lower FS and performed more poorly on the 6MWT at baseline compared to those with anxiety-only and those with no psychological symptoms. In line with our second hypothesis was the observation that prehabilitation, compared to rehabilitation, was associated with significant improvements in FS in individuals with baseline depressive symptoms.

A descriptive analysis of the total sample illustrated that the characteristics of our sample resembled those of the Canadian CRC population (i.e., older, and majority male, overweight, and cancer of the colon; Canadian Cancer Statistics, 2011). However, comparison of baseline demographics, physical health, illness- and surgery-related variables, and surgical outcome between distress groups yielded several unexpected results. Firstly, we did not find any significant group differences in variables which have reliably been shown to be associated with depression, such as younger age, female sex, higher BMI, comorbid health conditions, smoking, alcohol consumption, advanced cancer, and neoadjuvant therapy (Howell et al., 2015). Secondly, though depression has been shown to increase the risk for adverse postoperative outcomes (Britteon et al., 2017), such as complications and prolonged hospitalization, we did not observe significant group differences in the incidence of these outcomes. We did observe a significant group difference in hospital re-admission 30 days after surgery; however, we found that compared to HADS-A, both HADS-N and HADS-D had higher rates of readmission suggesting that something other than psychological symptoms had an impact on hospital readmission. The inconsistency of these findings with previous research may reflect our small sample size, and/or

our use of lower cutoff scores, which may have been too low to significantly impact these variables.

The finding that self-reported FS was lower in individuals with depressive-symptoms is largely consistent with previous work on physical disability and depression in the general population (Bruce, 2001; Lenze et al., 2001). In the current sample, individuals with depressive symptoms consistently scored lower on all SF-36 physical health subscales compared to both other distress groups. Compared to those with no psychological symptoms (HADS-N), individuals with depressive symptoms scored an average of 20.3 points lower on the SF-36 subscales related to physical health. In contrast, those with anxiety-only scored an average of 2.5 points lower than those with no psychological symptoms. Using Wares (1993) recommendation of 5 points on SF-36 subscales as the clinically meaningful difference, our findings suggest that FS was no different between individuals with anxiety-only and those with no psychological symptoms. These findings substantiate observations in the literature that depression, but not anxiety, is associated with poorer self-reported FS (Lenze et al., 2001; Stegenga et al., 2012). Though these links have been observed in the general population, this is the first study to our knowledge which 1) demonstrates an association between depressive symptoms and poor self-reported FS in cancer patients awaiting surgery, and 2) uses an anxiety-only and no-symptom comparison groups.

To expand on the current literature and address the gaps in research on objective FS in depressed cancer patients awaiting surgery, we examined this relationship using a validated performance based measure of FS (6MWT), one which is frequently used in surgical oncology research. Interestingly, our objective measure of FS yielded similar results to that of the self-reported measure. Subjects with depressive symptoms performed more poorly on the 6MWT

compared to both the anxiety-only group and to those with no psychological symptoms, whereas the anxiety-only group performed equally well compared to those with no psychological symptoms. The observation that differences in FS persisted when examining both self-reported and objective measures suggests that perceptions of FS in HADS-D group were congruent with actual functional performance measures. Subjects with depressive symptoms walked, on average, 60m less than those with no psychological symptoms and 65m less than those with anxiety-only. Furthermore, a greater proportion of depressed individuals showed a 6MWD of below 400m at baseline, a cutoff score previously shown to predict poor performance during CPET (Sinclair et al., 2012) and adverse outcome following surgery (Newman et al., 2006; Rolland et al., 2004). Interestingly, differences in variables which are known to directly impact FS, such as percentage body fat, BMI, LBM, age, presence and burden of comorbidities, neoadjuvant therapy, and cancer stage were not significantly different between distress groups. Though symptoms of depression have previously been demonstrated to correlate with shorter 6MWD in the elderly (Enright et al., 2003), and with diminished physical work capacity in patients with a clinical diagnosis of depression (Martinsen et al., 1989), this is the first study, to our knowledge, to demonstrate this association in CRC patients awaiting surgery. These results, in the context of surgery, are especially important to consider, as poor physical health is an established risk factor for poor operative outcome. If depressed individuals are more likely to be in poor physical health before surgery, PA interventions could be used to help improve FS in this population.

To advance our knowledge of factors contributing to low FS in some depressed individuals but not in others, we examined differences in physical health characteristics and health behaviours in depressed individuals who walked below 400m versus those who walked above 400m at baseline. We found that depressed individuals with low FS were older, had lower

LBM, and engaged in significantly less moderate and vigorous PA compared to depressed individuals with normal FS. These findings are consistent with previous research demonstrating a strong association between older age, lower levels of PA, low LBM, and poorer physical function (Enright et al., 2003; Hairi et al., 2010; Pecorelli et al., 2016). In contrast, we found no differences in BMI or body fat in depressed individuals with low FS versus those with normal FS. This is surprising, as excess weight has been shown to negatively impact functional performance measures, and to correlate with shorter 6MWD (Enright et al., 2003; Hulens, Vansant, Claessens, Lysens, & Muls, 2003). The relationship between LBM, engagement in moderate and vigorous physical activity, and FS should be further explored. More specifically, the question of whether lower levels of PA, and/or lower LBM moderates the relationship between depression and poorer objective FS in depressed individuals need elucidation.

Lastly, our results illustrated the potential benefit of implementing a multimodal prehabilitation intervention in improving the FS of cancer patients with depressive symptoms. This area has received little to no attention in research thus far. We found prehabilitation to be associated with significantly increased odds of improving perioperative FS in individuals with depressive symptoms. In contrast, prehabilitation was not associated with increased odds of improving FS in subjects with symptoms of anxiety-only or those with no psychological symptoms at baseline. Previous research examining the impact of PA interventions on depressed individuals (Oeland et al., 2010; Penninx et al., 2002) support our observation that FS in depressed individuals can significantly improve with PA. These findings suggest that preoperative interventions (prehabilitation) yield superior results compared to postoperative interventions (rehabilitation) in individuals with depressive-symptoms at baseline, but yield similar results in individuals with no depression at baseline.

The findings of this work have important clinical and practical implications. The treatment of depression in the context of surgical oncology remains a major challenge. Limited time and resources, which can be compounded by patient apprehension about receiving psychological support, may lead to under recognition by treating physicians and oncologists, and inadequate treatment of depression. If psychological counselling or pharmacologic therapy is not feasible, an innovative and lower cost approach to its treatment would be to promote physical activity. Physical activity is relatively easy to prescribe, safe in individuals with cancer (Schmitz et al., 2010), and is associated with wide range of improvements in physical and psychological health (Penedo & Dahn, 2005). Moreover, exercise has shown great promise in alleviating symptoms of depression (Lawlor & Hopker, 2001). Thus, identifying patients with low FS at baseline and implementing a physical activity intervention could be an effective strategy to not only improve FS but also reduce depressive symptoms and mitigate postoperative impairments following surgery.

Limitations of the Study

Findings in the current study are limited by the data collected in the primary studies, by slight variations in study protocols, and by inherent limitations associated with retrospective analysis. Several potentially important confounding or moderating variables were not examined. For example, no data was collected on the subjects' history of clinical diagnosis of depression, level of social support, living situation, marital status, nutritional status, amount or frequency of alcohol consumption, use of narcotics (marijuana, stimulants, etc.), or important demographic information such as ethnicity and/or socioeconomic status. Furthermore, we were unable to examine differences in FS according to severity of depression due to inadequate sample size in individuals reporting depressive symptoms at baseline. Severity of depression has been shown to

be related to severity of functional impairment (Kruijshaar et al., 2003). Thus, examining differences in FS among subjects with depressive symptoms, a clinical diagnosis of depression, and those with no symptoms, would be informative. A further limitation was the inclusion of comorbid anxiety within our HADS-D group. We were unable to analyze differences in FS according to anxiety-only, depression-only and comorbid anxiety and depression due to a very small number of subjects with symptoms of depression only. These disorders, when comorbid, have been shown to be associated with poorer outcomes than those with a single disorder. Thus, our HADS-D group may be more representative of the FS of individuals with comorbid anxiety and depressive symptoms rather than the FS of depressive symptoms alone. This body of literature could greatly benefit from a better understanding of how anxiety, depression, and comorbid depression and anxiety influence FS.

It is possible that our results partially reflect the exercise principle of diminishing returns, which refers to the relationship between initial training status and expected degree of improvement; individuals with no depressive symptoms had higher initial FS and, thus, were less likely to benefit from the intervention to the same degree than those with depressive symptoms and lower initial FS. We conducted GEE analyses using uni- and multivariate logistic regression, estimating ORs and 95% CI, to examine change in FS according to distress status (HADS-A and HADS-D) and 6MWD at baseline (6MWD <400m or ≥400). Low baseline FS was not associated with appreciable or significantly increased likelihood of improving perioperative FS, which suggests that low baseline FS does not adequately explain the improvement observed in depressed individuals (See **Table 9**). Future studies should explore the factors which could contribute to increased likelihood of improving FS in depressed cancer patients.

Our analysis was merely a "snapshot" of depressive symptoms and FS at baseline, and therefore, does not provide information regarding the temporal nature of the relationship. Moreover, we used only one objective measure of FS. Future research should examine this relationship using more sophisticated and direct measures of FS, such as CPET. Though we found prehabilitation to be associated with improvement in FS in depressed individuals, we cannot ascertain at which point in time changes in FS in HADS-D occurred (i.e. whether they occurred pre- or postoperatively), what specifically accounted for these changes (i.e. PA intervention, improved nutritional status, enhanced social support, or alleviation of depressive symptoms), or whether these changes co-occurred with changes in depressive symptoms. Future research should examine why individuals with depressive symptoms are more likely to improve FS with a PA intervention, and how many visits are linked to improved outcome. Slight variation in study protocols regarding delivery of the exercise intervention (entirely home-based versus home-based with a once per week in-hospital training session) may have influenced likelihood of improving FS during the perioperative period. Studies examining the difference between home- versus centre-based exercise programs on various outcomes have been inconsistent in their findings. However, while a few trials have reported better outcomes in favour of centre-based approach (Bäck, Jivegard, Johansson, Nordanstig, Svanberg, Adania, & Sjögren, 2015), several reviews of the literature have concluded both methods appear to be similarly effective in improving clinical and HR-QOL outcomes (Anderson, et al., 2017; Taylor, Dalal, Jolly, Zawada, Dean, Cowie, & Norton, 2015; Jolly, Taylor, Lip, & Stevens, 2006). Future research should examine whether supervised versus home-based PA interventions yield similar improvements in FS specifically in the depressed cancer patient, as greater social interaction and support resulting

from in-hospital exercise sessions may have been especially beneficial for patients with depressive symptoms.

Conclusion and Summary

In conclusion, our data demonstrates 1) an association with preoperative depressive symptoms and low FS in colorectal cancer patients awaiting surgery, and 2) the superiority of a prehabilitation versus rehabilitation intervention in improving FS in those with baseline depressive symptoms. These findings bring about important questions regarding causality. Firstly, do depressive symptoms lead to poorer FS, or does poor FS lead to the development of depressive symptoms, or both? In terms of surgical outcome, and choosing the optimal preoperative treatment approach, does it matter whether depressive symptoms precede functional impairment or vice versa? This relationship calls for more speculation, and future research should examine the temporal nature of FS and depressive symptoms. Secondly, what lead to improvement in FS in patients with depressive symptoms, and why was prehabilitation more effective for these individuals than for those with anxiety or no psychological symptoms at baseline needs further elucidation.

These findings raise important questions and concerns with regards to how these patients should be managed within a prehabilitation framework. There is evidence to suggest that PA interventions can lead to significantly improvements in depression; however, in the context of cancer care, it is recommended that patients with more severe depression be referred out for psychiatric evaluation and intervention. Because PA is not recommended as the primary treatment for those with more severe forms (i.e. MDD; Howell, et al., 2015), research is needed to explore whether there is a role for prehabilitation in the management of depressive symptoms in patients with cancer. Specifically, to assess whether prehabilitation is an appropriate

intervention for those with greater distress, future research must examine whether these interventions can reduce depressive symptoms, and if so, what is the best approach (concurrent prehabilitation and psychiatric intervention; exercise alone vs exercise combined with nutrition; home-based vs supervised; aerobic vs strength training, etc.).

Though more research is needed to understand the temporal relationship of depression and FS, these findings highlight the importance of screening for depression before surgery, and assessing and treating any accompanying impairments, specifically those related to physical health. While it remains unclear what the impact of prehabilitation is on depressive symptoms, this intervention appears to be especially advantageous in improving the FS of CRC patients with depressive symptoms before surgery. Given the association between depression and FS, and the efficacy of prehabilitation interventions in patients with depressive symptoms, these individuals should be targeted and selected in preoperative interventions.

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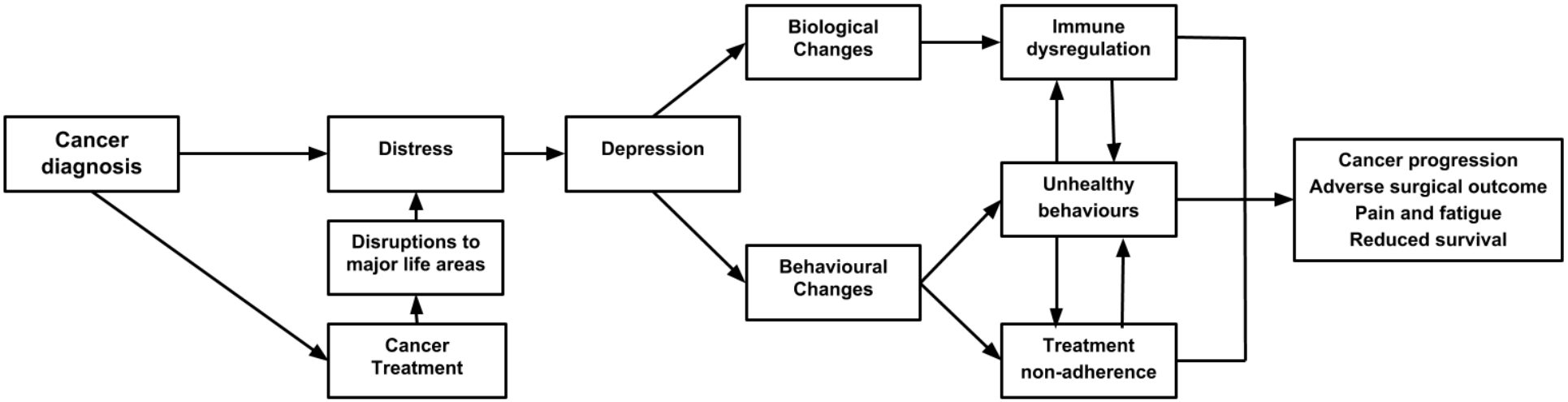


Figure 1. Flowchart of the development of depression following cancer diagnosis and its impact on biological and behavioural factors, and cancer outcomes.

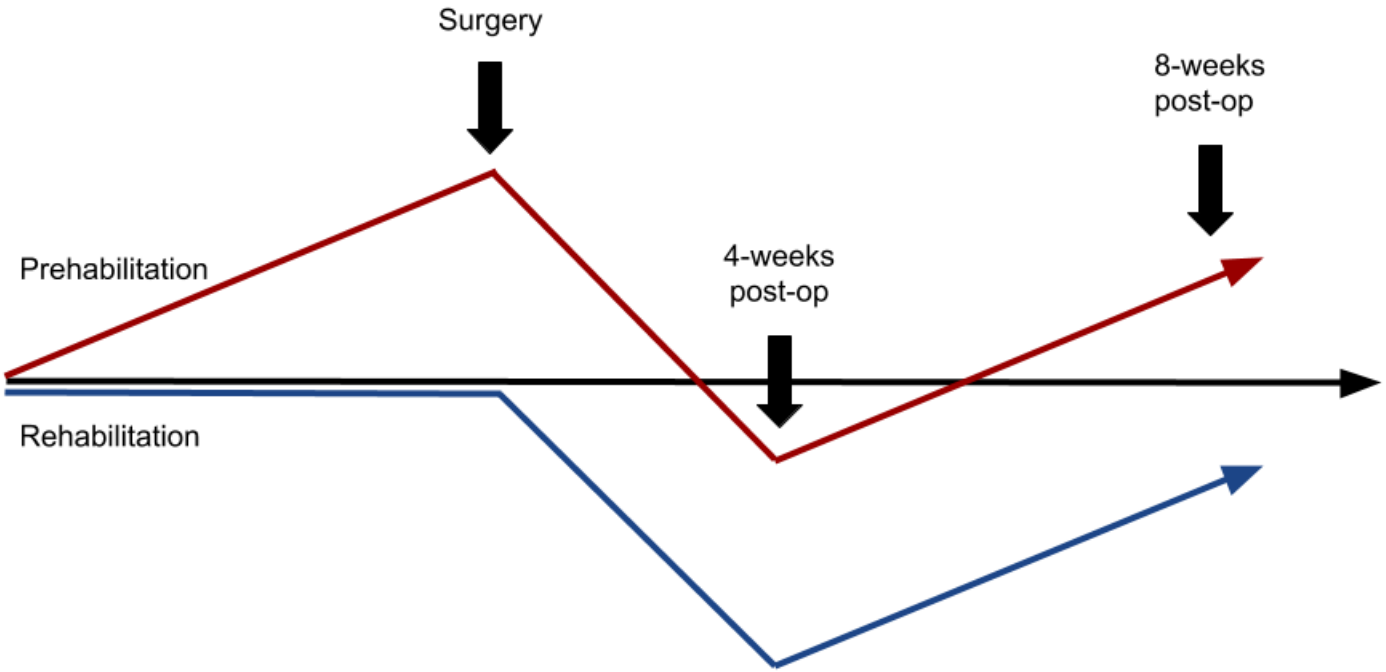


Figure 2. Expected trajectory of functional capacity pre- and postoperatively with a prehabilitation versus a rehabilitation intervention. Red line represents expected six-minute walk distance (6MWD) in individuals receiving a prehabilitation program 4-weeks prior to colorectal cancer surgery; Blue line represents expected 6MWD in individuals receiving a rehabilitation program, beginning after hospital discharge following colorectal cancer surgery; Black line represents baseline 6MWD.

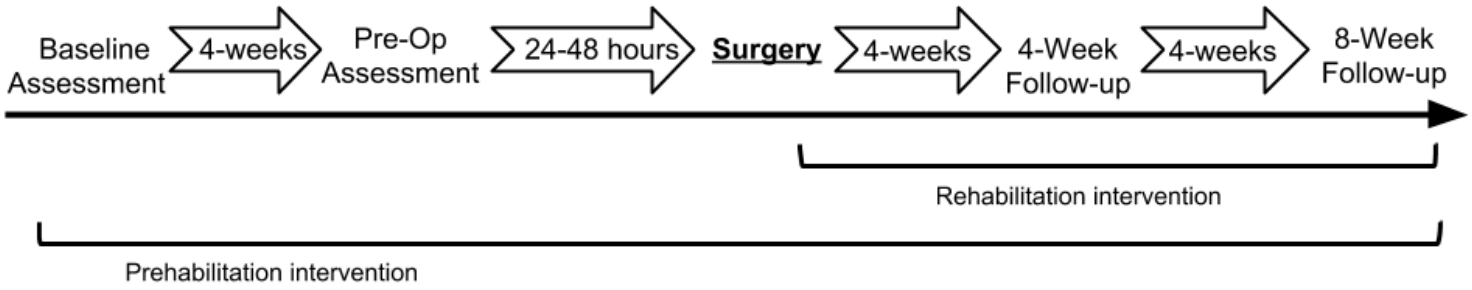


Figure 3. Program timeline and assessment timepoints for subjects enrolled in a multimodal prehabilitation or multimodal rehabilitation program. Four assessments included:: baseline (4-weeks prior to surgery), pre-op (24-48 hours prior to surgery), 4-week (4-weeks after date of operation), and 8-week (8-weeks after date of operation). Prehabilitation intervention was delivered immediately following baseline assessment and. rehabilitation intervention was delivered following the pre-op assessment.

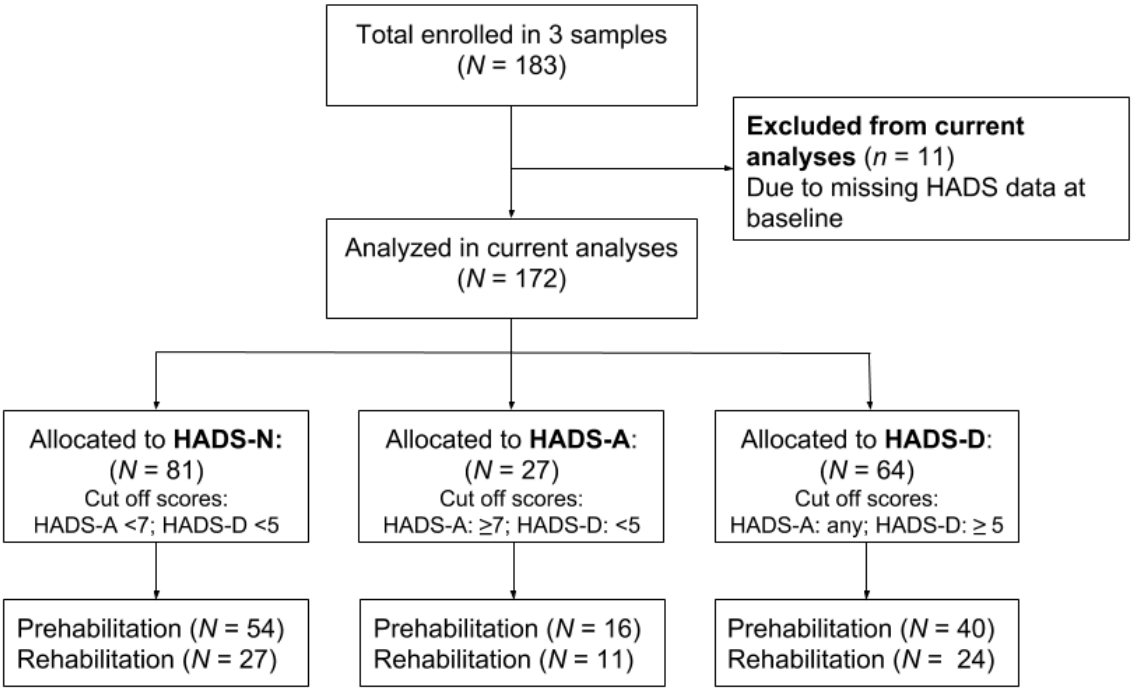


Figure 4. Flowchart of subjects included in final analyses and group allocation based on distress status at baseline.

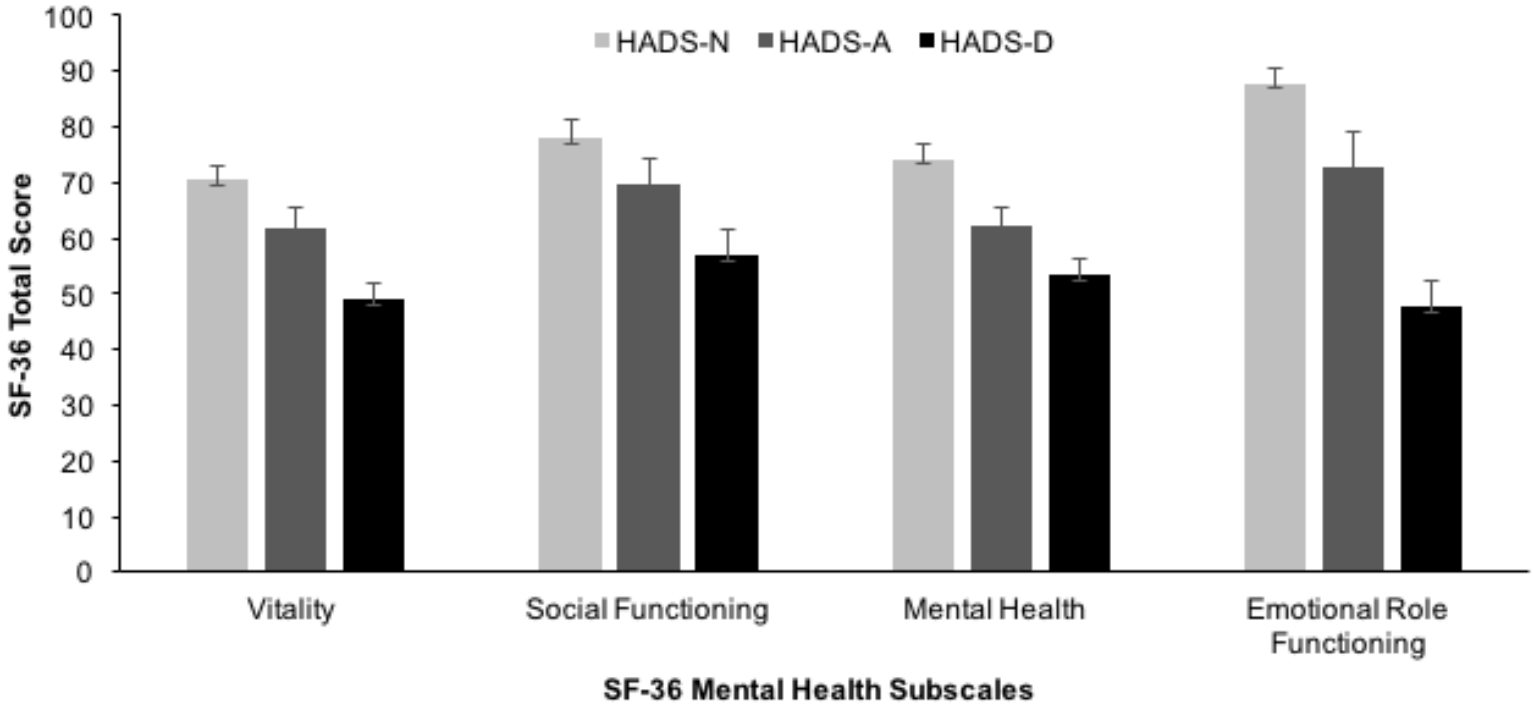


Figure 5. SF-36 Mental health subscales according to baseline distress status. Error bars represent standard error.

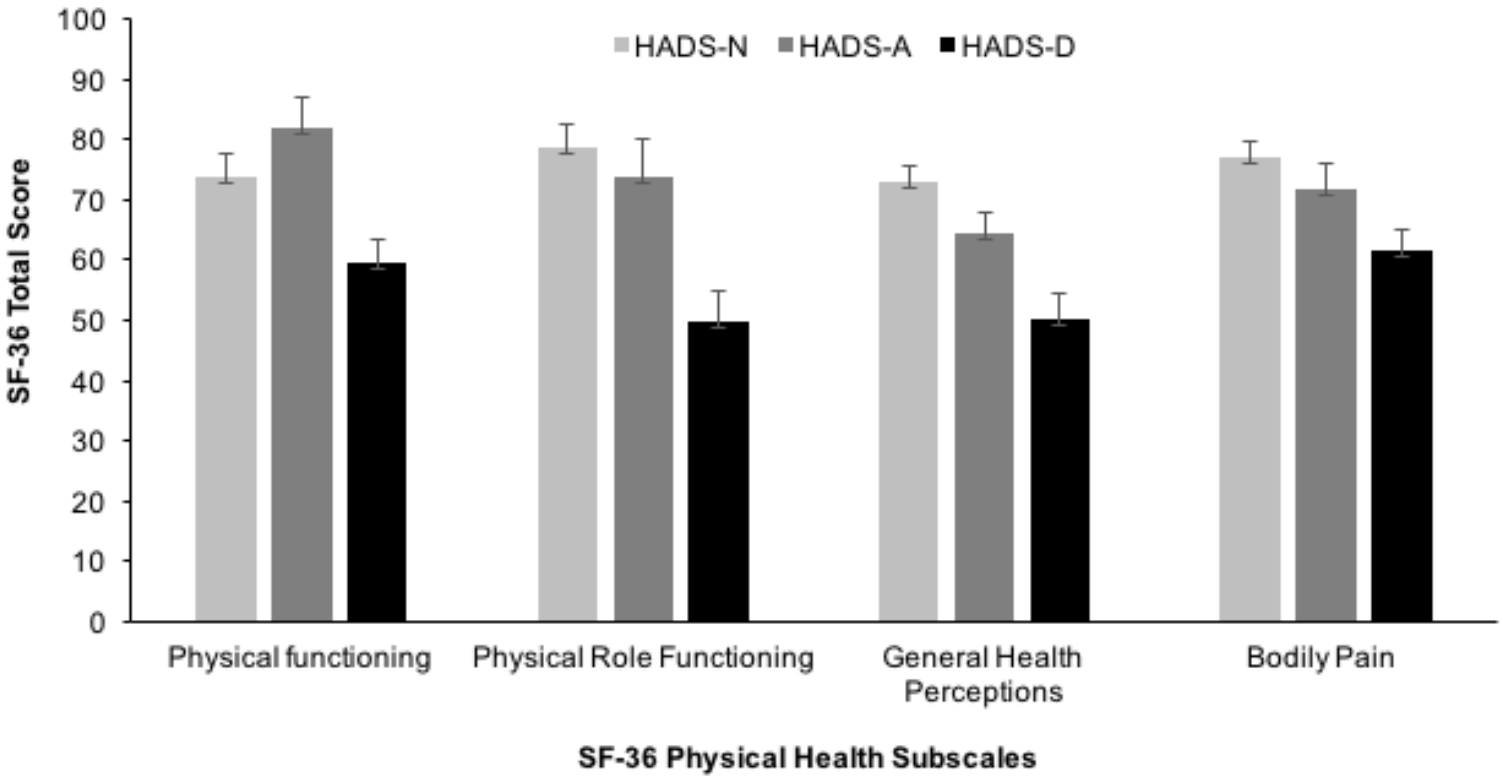


Figure 6. SF-36 physical health subscales according to baseline distress status. Error bars represent standard error.

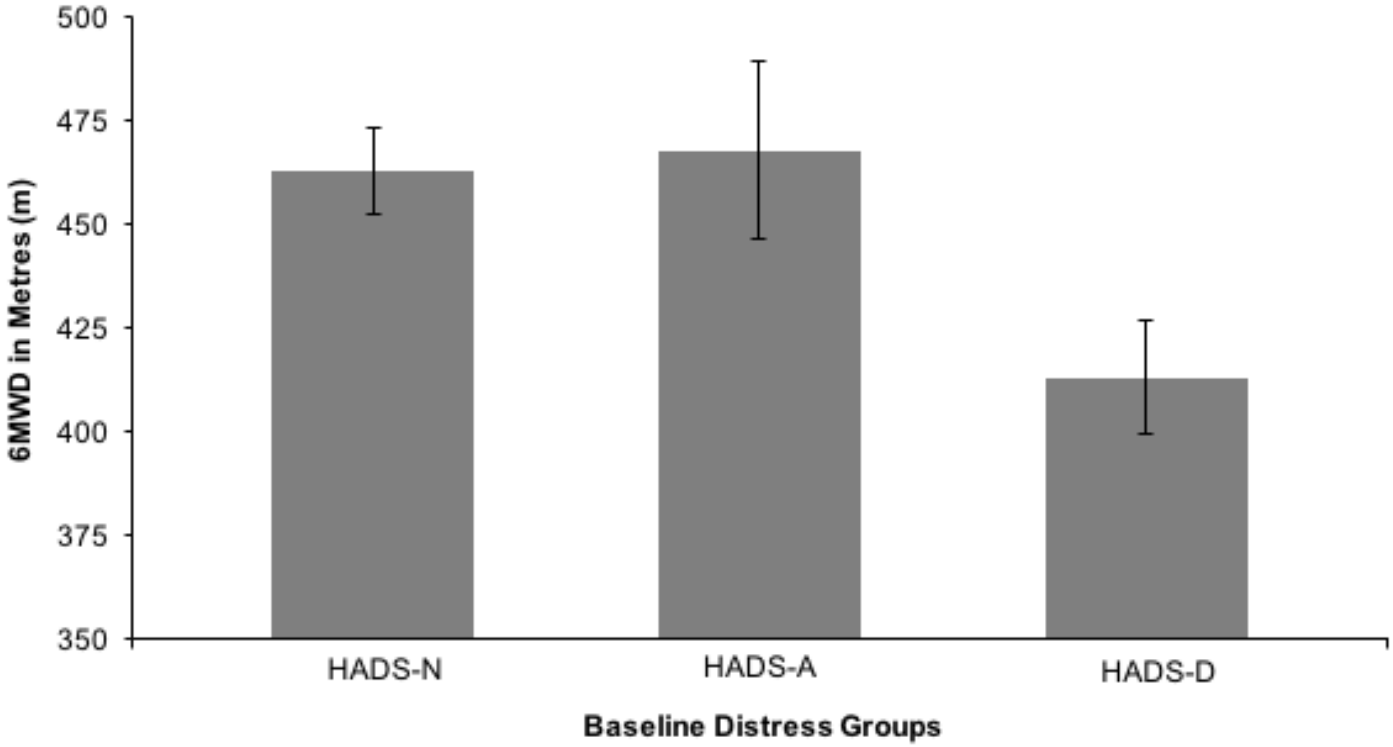


Figure 7. Average Six-Minute Walk Distance (6MWD) by distress group at baseline. Error bars represent standard errors.

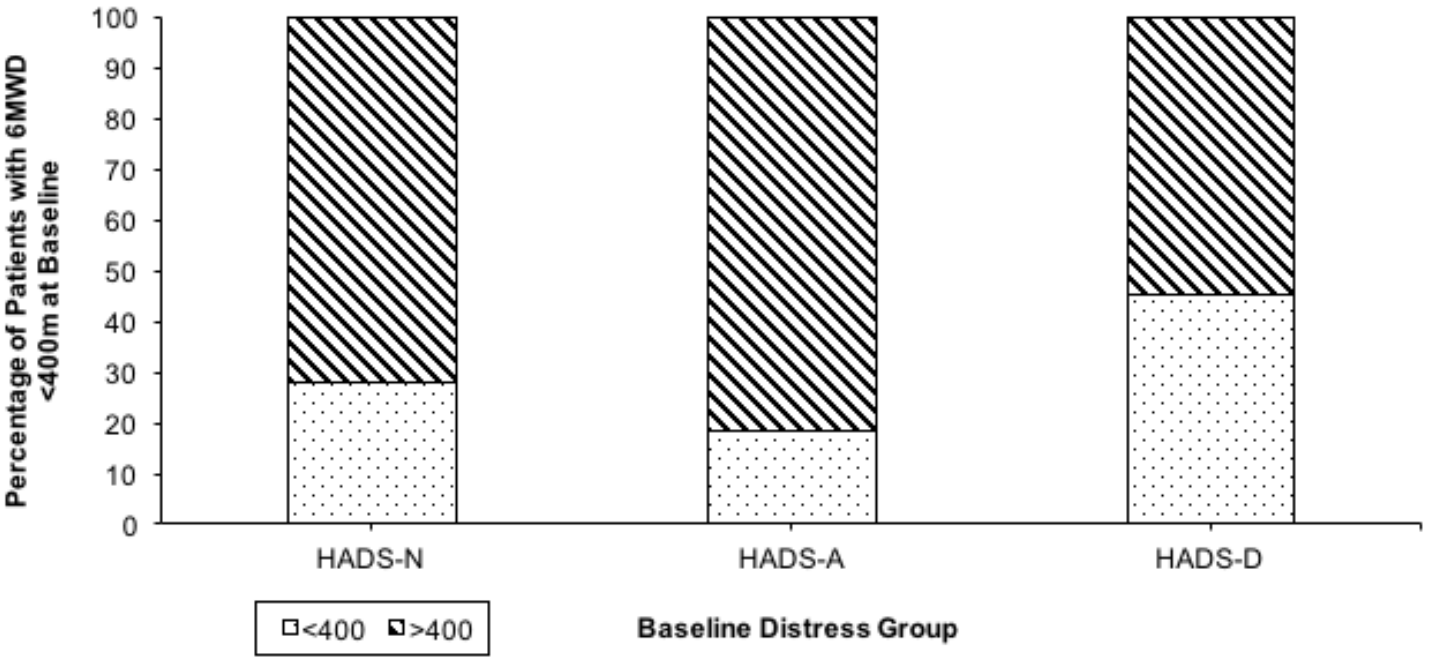


Figure 8. Proportion of Indviduals with low functional capacity in each distress group at baseline.

Table 1
Aerobic, resistance and flexibility exercise program for patients receiving prehabilitation and rehabilitation Interventions

Type of Exercise	Duration and Intensity	Repetitions	Sets	Times per week	Target Muscle Groups	Exercises
Aerobic	30 minutes; Moderate intensity	N/A	N/A	Every day	Cardiovascular	In hospital: NuStep, treadmill or bike; Home: Walking, treadmill, etc.
Resistance	N/A	12-15	3	3 days/week	Arms and shoulders	Push-ups, seated row, chest fly, deltoid lift, bicep and tricep curls
					Legs and glutes	Chair and touch squats, hamstring curls, standing calf raises
					Abdominal	Abdominal crunches
Flexibility	>20 seconds/each	N/A	2	3 days/week	Arms and shoulders Legs and glutes Abdominal	

Table 2.

Functional tests collected at each assessment time point

Functional Tests	Equipment and Conditions	Purpose of Test	Assessment Timepoints
1. Timed-up and Go	Chair, 6-metre loop	Evaluation of gait speed	All functional tests performed at each of the following timepoints: Baseline, Pre-Op, 4-week and 8-week post-op
2. Arm Curl Test	5-lb and 7-lb weight	Evaluation of arm strength	
3. Sit-to-Stand	Timer: 30 seconds; chair	Evaluation of leg strength	
4. Six Minute Walk Test	Timer: 6 minutes; 15-metre corridor	Evaluation of functional walking capacity	
5. Grip Strength	Dynamometer	Evaluation of grip and arm strength	

Table 3

Baseline demographic and physical health characteristics: Combined sample and by baseline distress status

		Baseline Distress Status			
	Combined sample (*N* = 172)	HADS-N (*n* = 81)	HADS-A (*n* = 27)	HADS-D (*n* = 64)	
Variable	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*p*
Demographic variables					
Age	67 (11.2)	67 (12)	68 (9)	67 (11)	0.946
Elderly (No, %)	42 (24.4)	20 (24.7)	5 (18.5)	17 (26.6)	0.715
Sex (male; No, %)	107 (62.2)	56 (69.1)	14 (51.9)	36 (56.3)	0.149
Physical Health Status					
BMI	27 (10.7)	26.8 (5.4)	25.5 (9.3)	29.5 (6.2)	0.994
LBM	49.6 (25.4)	55.1 (16.2)	52.9 (15.8)	50.7 (17.7)	0.586
% BF	29 (19.7)	29.1 (8.3)	30.6 (10.9)	34.3 (10.3)	0.668
Comorbidities (No, %)					
Diabetes	35 (20.5)	17 (21.3)	5 (18.5)	13 (20.3)	0.954
Hypertension	76 (44.4)	33 (41.3)	12 (44.4)	31 (48.4)	0.689
COPD	10 (5.8)	5 (6.3)	1 (3.7)	4 (6.3)	0.875
Dyslipidemia	35 (20.7)	14 (17.5)	3 (11.1)	19 (30.2)	0.173
ASA Status (No, %)					
1	15(8.9)	7 (8.9)	3 (11.1)	5 (7.9)	0.827
2	102 (60.4)	48 (60.8)	18 (66.7)	36 (57.1)	
3+	52 (30.8)	24 (30.4)	6 (22.2)	22 (34.9)	
Current Smoker (No, %)	18 (10.4)	9 (11.1)	1 (3.7)	7 (10.9)	0.503
Current Alcohol Consumption (No, %)	98 (56.6)	48 (59.3)	18 (66.7)	32 (50.0)	0.290

Note. All values represented as *M(SD)* unless otherwise indicated. Age = years; Elderly = 75+ years old; BMI = body mass index; LBM = lean body mass (kg); % BF = percentage body fat; COPD = Chronic obstructive pulmonary disease; The American Society of Anesthesiologists Classification of Physical Health (ASA) is from the American Society of Anesthesiologists (2014); One-way ANOVA tests were used for continuous variables; Chi-Square analyses were used for categorical variables. P values are statistically significant at the alpha = 0.05 level, two-tailed, and are in boldface.

Table 4

Illness- and surgery-related variables and postoperative outcomes: Combined sample and by baseline distress status

		Baseline Distress Status			
	Combined sample (*N* = 172)	HADS-N (*n* = 81)	HADS-A (*n* = 27)	HADS-D (*n* = 64)	
Variable	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*p*
Illness and Surgery-Related Variables (No, %)					
Type of tumor (colon; No, %)	110 (65.1)	28 (35.4)	9 (33.3)	21 (33.9)	0.971
Tumor stage (No, %)					0.578
0	23 (13.7)	12 (15.4)	4 (14.8)	7 (11.1)	
1-2	89 (53)	37 (47.4)	17 (63.0)	35 (55.6)	
3-4	56 (33.3)	29 (37.2)	6 (22.2)	21 (33.3)	
Neoadjuvant therapy (No, %)	35 (20.6)	21 (26.6)	5 (18.5)	9 (14.1)	0.176
Site of resection (No, %)					
Right hemicolectomy	59 (35.1)	25 (31.7)	10 (37.0)	24 (38.7)	
Transverse colectomy	2 (1.2)	1 (1.3)	0 (0.0)	1 (1.6)	
Left hemicolectomy	17 (10.1)	8 (10.1)	3 (11.1)	6 (9.7)	
Sigmoid anterior resection	28 (16.7)	13 (16.5)	6 (22.2)	9 (14.5)	
Low anterior resection(rectum)	45 (26.8)	21 (26.6)	8 (29.6)	16 (25.8)	
Abdominoperineal resection	13 (7.7)	9 (11.4)	0 (0.0)	4 (6.5)	
Subtotal or total colectomy	4 (2.4)	2 (2.5)	0 (0.0)	2 (3.2)	0.907
Site of resection (No, %)					
Right hemicolectomy	59 (35.1)	25 (31.7)	10 (37.0)	24 (38.7)	
Transverse colectomy	2 (1.2)	1 (1.3)	0 (0.0)	1 (1.6)	
Left hemicolectomy	17 (10.1)	8 (10.1)	3 (11.1)	6 (9.7)	
Sigmoid anterior resection	28 (16.7)	13 (16.5)	6 (22.2)	9 (14.5)	
Low anterior resection(rectum)	45 (26.8)	21 (26.6)	8 (29.6)	16 (25.8)	
Abdominoperineal resection	13 (7.7)	9 (11.4)	0 (0.0)	4 (6.5)	
Subtotal or total colectomy	4 (2.4)	2 (2.5)	0 (0.0)	2 (3.2)	0.907
Postoperative Outcome					
Length of hospital stay (days)	5 (6.4)	3 (2)	3 (3)	3 (2)	0.668
New Stoma (No, %)	35 (20.7)	20 (25.3)	5 (18.5)	10 (15.9)	0.368
Readmission in 30 days (No, %)	14 (8.5)	6 (7.9)	1 (3.7)	6 (9.5)	**0.047**
Clavien Classification (No, %)					0.739
0	118 (71.1)	51 (66.2)	19 (73.1)	48 (76.2)	
1	25 (15.1)	14 (18.2)	4 (15.4)	7 (11.1)	
2+	23 (13.9)	12 (15.6)	3 (11.5)	8 (12.7)	

Note. All values represented as *M(SD)* unless otherwise indicated; Tumour stage was graded using Canadian Cancer Society TNM staging system for Colorectal Cancer; Clavien Classification is from the Clavien-Dindo Classification (Dindo, Demartines, & Clavien, 2004); One-way ANOVA tests were used for continuous variables; Chi-Square analyses were used for categorical variables. P values are statistically significant at the alpha = 0.05 level, two-tailed, and are in boldface.

Table 5

Baseline functional outcomes: Combined sample and baseline distress status

		Distress status			
	Combined sample (*N* = 172)	HADS-N (*n* = 81)	HADS-A (*n* = 27)	HADS-D (*n* = 64)	
Variable	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*p*
CHAMPS (kcal/kg/week)					
Total	39.8 (39.7)	40.3 (40.9)	43.7 (30.3)	38.0 (41.8)	0.8219
Light	20.0 (21.1)	19.2 (22.4)	23.3 (25.4)	19.6 (17.3)	0.6832
Moderate+Vigorous	19.0 (32.2)	20.2 (33.4)	19.9 (21.6)	17.0 (34.6)	0.8267
SF36					
Total Physical	58.9 (19.4)	65.9 (18.9)	62.1 (15.3)	48.6 (17.2)	**<0.001**
Total Mental	59.3 (19.2)	68.9 (17.2)	58.8 (16.9)	47.2 (15.4)	**<0.001**
Physical functioning	69.9 (31.9)	**73.8 (32.6)**	81.9 (26.4)	59.6 (30.5)	**0.003**
Physical role functioning	67.2 (39.7)	**78.6 (35.5)**	73.8 (32.9)	49.6 (41.6)	**<0.001**
Emotional role functioning	70.7 (35.1)	87.9 (22.7)	72.6 (35.1)	47.7 (35.9)	**<0.001**
General health perceptions	66 (18.9)	72.8 (24.3)	64.4 (17.3)	50.3 (32.6)	**<0.001**
Vitality	61.3 (27.8)	70.7 (21.6)	61.6 (20.2)	49.2 (22.7)	**<0.001**
Bodily pain	70.6 (24.6)	77.1 (22.5)	71.9 (20.3)	61.5 (26.4)	**<0.001**
Social Functioning	71.8 (25.7)	77.9 (30.1)	69.7 (24.3)	56.9 (38.4)	**<0.001**
Mental health	64.7 (25.3)	74.3 (23.7)	62.3 (17.4)	53.3 (25.5)	**<0.001**
Six Minute Walk Distance (m)					
Baseline 6MWD	445.3 (105.5)	462.7 (94.6)	468 (111.6)	413 (109.7)	**0.003**
Percent predicted 6MWD	68.9 (15.3)	71.0 (13.5)	74.1 (18.2)	64.0 (14.8)	**0.009**
Patients with 6MWD <400; (No, %)	48 (27.9)	15 (18.5)	4 (14.8)	29 (45.3)	**<0.001**

Note. All values represented as M(SD) unless otherwise indicated; Community Health Activities Model Program for Seniors (CHAMPS) and corresponding three subscales are from Stewart, Mills, King, Haskell, Gillis & Ritter, 2001; The Medical Outcome Study 36-Item Health Survey (SF-36) and corresponding 10 subscales are from Ware & Sherbourne (1992); One-way ANOVA tests were used for continuous variables (CHAMPS, SF-36, and mean distance (m) in 6MWT); chi-squared analyses were used for categorical variables. P values are statistically significant at the alpha = 0.05 level, two-sided, and are in boldface.

Table 6

Estimated odds ratio using Generalized Estimating Equation of improving perioperative functional status by ≥20m according to baseline distress status and intervention status

	Adjusted *OR*							
	HADS-N		HADS-A		HADS-D		All Cases	
Variable	*OR*	95% CI	*OR*	95% CI	*OR*	95% CI	*OR*	95% CI
Rehabilitation	1.00		1.00		1.00		1.00	
Prehabilitation	0.97	[0.44, 2.16]	1.47	[0.69, 3.16]	**2.36**	**[1.53, 3.66]**	1.72	[1.27, 2.32]
Age	1.01	[0.99, 2.05]	1.07	[1.03, 1.10]	1.01	[0.93, 3.66]	1.01	[1.00, 1.02]
Sex (Male)	1.03	[0.62, 1.70]	1.39	[0.89, 2.18]	1.23	(1.00-1.64)	1.07	[0.84, 1.36]
BMI	1.06	[0.98, 1.15]	0.94	[0.89, 1.00]	1.02	[0.97, 1.08]	1.03	[0.99, 1.07]
ASA Status	1.03	[0.66, 1.63]	3.08	[2.00, 4.74]	0.83	[0.60, 1.16]	1.06	[0.83, 1.65]
Lengh of stay	0.94	[0.88, 1.01]	0.79	[0.63, 0.99]	1.00	[0.99, 1.01]	1.00	[0.98, 1.02]
Smokers	1.39	[0.58, 3.37]	0.56	[0.27, 1.16]	1.28	[0.87, 1.89]	1.29	[0.96, 1.74]
Alcohol drinkers	0.60	[0.34, 1.04]	0.78	[0.43, 1.42]	0.61	[0.41, 0.91]	0.68	[0.51, 0.91]
Clavien Classificatior	0.97	[0.69, 1.36]	1.29	[0.77, 2.17]	1.05	[0.84, 1.32]	0.94	[0.80, 1.10]

Note. *OR* = odds ratio; CI = confidence interval; BMI = body mass index; ASA = American Society of Anaesthesiologists; Age, sex, BMI, and length of stay were modelled as continuous variables.

Table 7

Demographic and clinical characteristics, and illness- and surgery-related variables of HADS-D group at baseline: Comparison of low vs normal functional capacity at baseline

	HADS-D (*N* = 64)		
	<401 (*n* = 29)	>400 (*n* = 35)	
Variable	*M (SD)*	*M (SD)*	*p*
Demographic variables			
Age	73.9 (9.1)	61.1 (9.9)	**<0.001**
Elderly (No, %)	13 (45)	4 (11.4)	**0.003**
Sex (male) (No, %)	15 (52)	21 (60)	0.506
Physical Health Status			
BMI	29 (4.6)	28.8 (4.9)	0.906
LBM	48.4 (8.4)	54.6 (11.9)	**0.018**
% BF	35.9 (12)	33 (8.8)	0.297
Comorbidities (No, %)			
Obese	14 (48)	16 (46)	0.838
Diabetes	8 (28)	5 (14)	0.188
Hypertension	17 (58.6)	14 (40)	0.138
COPD	2 (7)	2 (6)	0.846
Dyslipidemia	10 (35)	9 (26)	0.445
Current Smoker (No, %)	4 (14)	3 (9)	0.505
Current Alcohol Consumption (No, %)	11 (38)	21 (60)	0.079
Illness and Surgery-Related Variables (No, %)			
Type of tumor (colon; No, %)	21 (72)	20 (61)	0.327
Tumor stage (No, %)			
0	4 (14)	3 (9)	0.805
1-2	16 (55)	19 (56)	
3-4	9 (31)	12 (35)	
Neoadjuvant therapy (No, %)	4 (14)	5 (14)	0.955

Note. All values represented in Mean (SD) unless otherwise indicated; <401 represents individuals in HADS-D group who achieved 6MWD of 400m or below at baseline, and >400 represents individuals who walked above 400m at baseline; elderly = 75 years and older; BMI = body mass index; LBM = lean body mass; % body fat = percentage of body fat; HADS-A ≥7 = score of seven or above on HADS-A subscale of HADS. P values are statistically significant at the alpha = 0.05 level, two-tailed, and are in boldface.

Table 8

Comorbid anxiety, PA, and subjective FS of HADS-D group at baseline: Comparison of low vs normal functional capacity at baseline

	HADS-D (*N* = 64)		
	<401 (n = 29)	>400 (n = 35)	
Variable	Mean (*SD*)	Mean (*SD*)	*p*
HADS-A ≥7 (No, %)	22 (76)	27 (77)	0.904
CHAMPS			
Total	21.1 (18.8)	51.6 (49.8)	**0.002**
Light	16.5 (16.8)	22.2 (17.5)	0.193
Moderate+Vigorous	3.2 (6.1)	28.3 (43.4)	**0.002**
SF-36			
Total Physical	40 (12)	55 (18)	**<0.001**
Total Mental	44 (14)	50 (16)	0.147
Physical functioning	48 (28)	69 (30)	**0.007**
Physical role functioning	35 (39)	61 (41)	**0.01**
Emotional role functioning	47 (36)	49 (36)	0.831
General health perceptions	52 (17)	57 (20)	0.287
Vitality	46 (21)	52 (24)	0.283
Bodily pain	54 (24)	67 (27)	**0.054**
Social Functioning	57 (27)	66 (26)	0.173
Mental health	55 (25)	52 (26)	0.676

Note. All values represented in Mean (SD) unless otherwise indicated; <401 represents individuals in HADS-D group who achieved 6MWD of 400m or below at baseline, and >400 represents individuals who walked above 400m at baseline; HADS-A ≥7 = score of seven or above on HADS-A subscale of HADS. P values are statistically significant at the alpha = 0.05 level, two-tailed, and are in boldface.

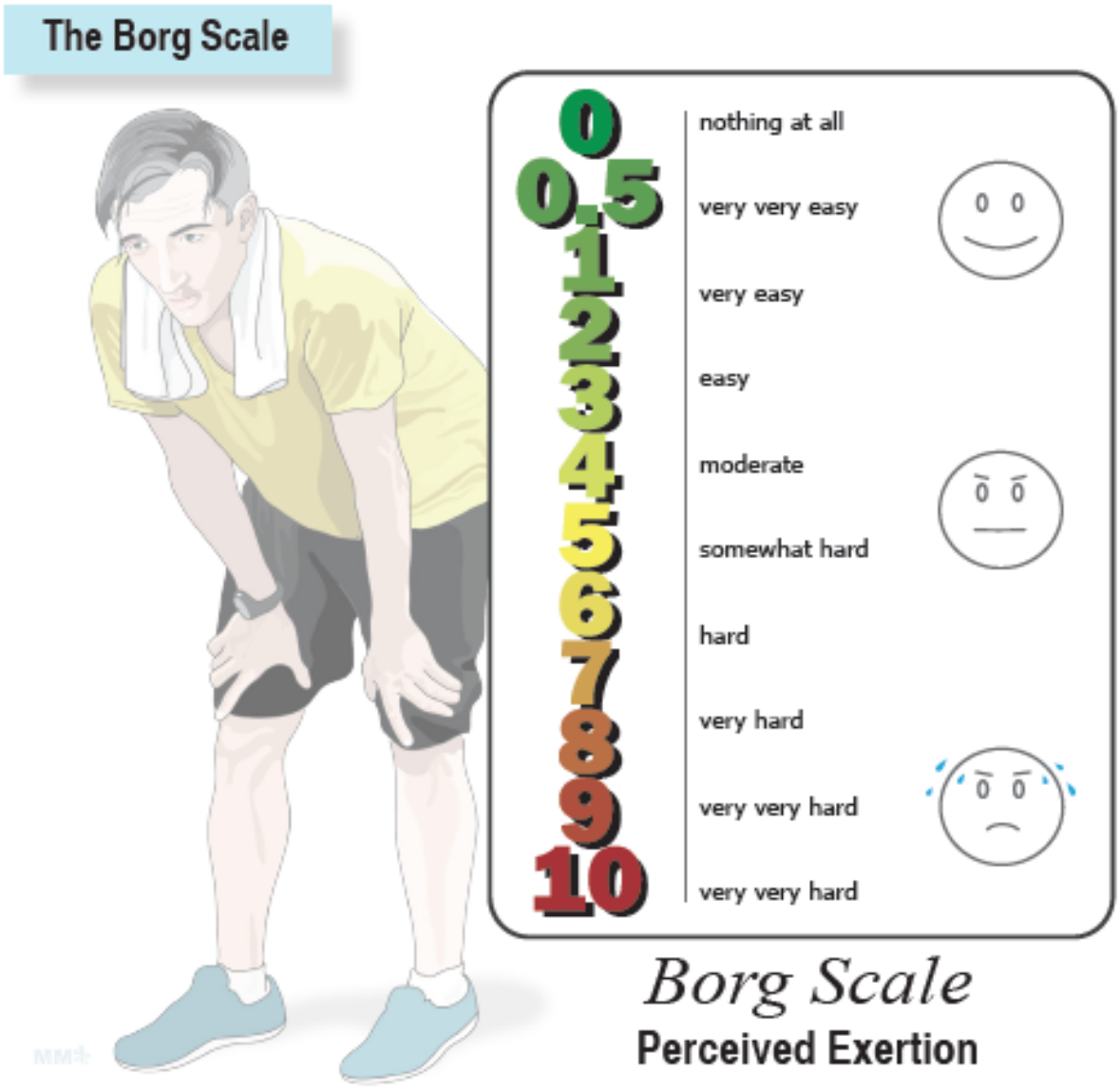
Table 9

Generalized Estimation Equation using interval change of 6MWD by baseline distress and walking status

	Univariate		Multivariate	
Variable	*OR*	95% CI	*OR*	95% CI
Baseline <400 meters, Any distress	1.00		1.00	
Baseline <400, No distress	1.10	[0.46-2.62]	1.00	[0.37-2.67]
Baseline 400+, Any distress	1.00	[0.54-1.84]	0.98	[0.49-1.99]
Baseline 400+, No distress	0.99	[0.54-1.79]	1.11	[0.56-2.22]
Age			1.02	[1.00-1.03]
Gender			1.06	[0.83-1.36]
BMI			1.02	[0.98-1.06]
ASA1			1.11	[0.87-1.43]
Length of stay			1.00	[0.97-1.02]
Smoking			1.45	[1.05-2.00]
Alcohol conusmption			0.91	[0.77-1.08]
Clavien Classification			1.47	[0.98-2.19]

Note. OR = odds ratio; CI = confidence interval; Any distress = HADS-A and HADS-D groups combined; Age, gender, BMI, length of stay were modelled as continuous variables.

APPENDIX A
Borg Scale



The Borg Scale measures how hard you feel that you are exercising.

After your exercise, identify which number corresponds to how hard you worked throughout your training. A number 6 represents **very, very easy** exertion while number 10 signifies a **very very hard** effort.

Use these cues to help determine how hard you worked.

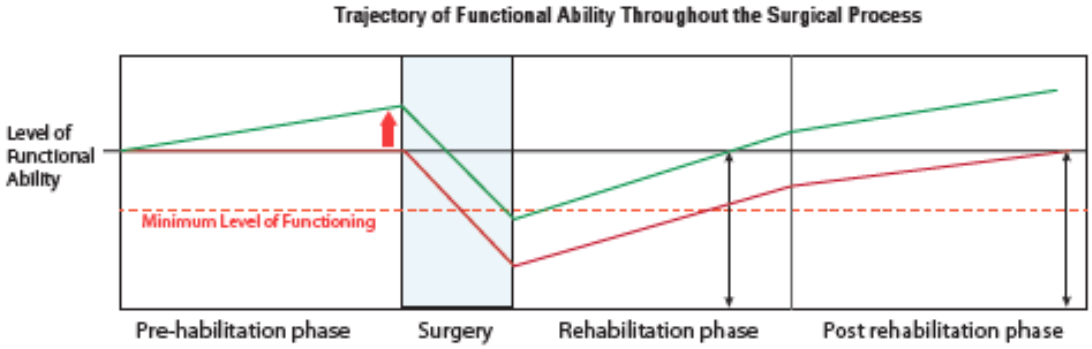
APPENDIX B

Examples from exercise and nutritional booklet

Your Guide to Prehabilitation

What is Prehabilitation?

Prehabilitation is a home-based program. The purpose of the program is to accelerate recovery time.



What does Prehabilitation Involve?

After a medical visit, you will meet with a kinesiologist who will propose a program you can do at home. During this appointment your body strength, nutritional state, and mood will be assessed by the project coordinator. You will also be asked to answer a few questionnaires.

The following is a brief overview of the programs:

A Physical Activity Program

- The kinesiologist will prescribe a moderate intensity aerobic and resistance exercise program that will be performed 3 times per week.

A Nutrition Program

- The nutritionist will provide advice on optimal nutrition and prescribe nutritional supplements as needed.

Measurements

- With the help of our project coordinator we will assess your strength, mood, and nutritional state at each visit

Prehabilitation Schedule

Prior to Surgery

You will be contacted by the project coordinator who will arrange your appointment with the kinesiologist and a nutritionist. At this appointment, you will fill-out a number of questionnaires, and have your physical strength, mood, and nutrition assessed. At this time, we ask that you start your first week of training. Please keep track of your progress by writing in the "log" section of this booklet daily. Remember, if you have any questions, please do not hesitate to contact the project coordinator. You will be contacted from time to time to discuss your program.

1 Week Prior to Surgery

During the week prior to your surgery, you will meet the project coordinator for a short reassessment. Please bring your booklet at each visit so we can track your progress! **Remember to only stop your exercise the day before your surgery.**

In Hospital Stay

During the days you are in hospital we will visit you regularly, and before you go home, the kinesiologist will visit you to remind you what you need to do when you are discharged from hospital and return home.

4-8 Weeks Post Surgery

You will be asked to return to the hospital for your final assessments. The same tests and assessments will be performed as in the first two meetings. **Remember to bring your booklet** so that we can track your progress, and **please return your heart rate monitor and pedometer to us at the 8 week appointment.**

Nutritional Program

A nutritionist is a health professional who teaches you about food and nutrition.

He or she will assess your nutritional state, what you eat regularly, your appetite, weight loss, and your likes and dislikes.

You will be asked to keep a diary of everything you eat and drink for 3 days. This will include **ALL** foods, supplements, and liquids that you eat or drink over a *3 day* period. Be as specific as you can. Write down brand names and the amounts you eat or drink. You can use our serving size guide to help you figure out how much you eat or drink. To fill out your food diary precisely, you may also measure all your food and beverages with measuring cups and spoons at home. The nutritionist will ask you to bring in your diary on your first visit.

Learning Serving Sizes

Your hands can help you with portion sizes.

The best way to find out how much food you are eating, or your portion size, is to use measuring cups, spoons or a scale. Sometimes, such as when you eat out, you can't do this. Here are a number of ways you can use your hands to help you find out about how much you are eating.

*** The portion sizes in each food group use an adult *woman's* hand as a guide**

1 fist = 8 fluid oz
cold and hot beverages

palm of hand = 3 oz
cooked meats
canned fish

1 hand = 1/2 cup
pasta, rice
hot cereal (oatmeal)
fruit salad
tomato sauce
beans
mashed potatos
cottage cheese

2 thumbs = 1 tbsp
peanut butter
salad dressing
sour cream
dips
margarine
mayonnaise

2 hands = 1 cup
breakfast cereal
soup
green salads
mixed dishes (chili, stew etc.)
Chinese food

Eating Healthy

What is healthy eating?

Healthy eating means choosing among different foods, and not over-eating any one type of food (i.e., controlling your portions), so that you get all the nutrition required for your body to work at its best. The three major nutrients found in food are carbohydrates, protein, and fat. Ideally, half of the food you eat should contain carbohydrates and the other half should be split between food that are rich in protein and fats. The concept is simple, but it can be hard to put into practice. This guide will help make it easier for you to eat healthy.

Why is this important for surgery?

Surgery puts a stress on your body. The goal is to prepare your body for this stress, similar to the way athletes prepare for a marathon. By eating healthy you can make sure your body has all the nutrients it needs to work well before and after surgery. By following the healthy eating guidelines listed below and our exercise program, you will build up your muscular strength to prepare your body for the stress of surgery.

We may ask you to take a whey protein supplement. This protein supplement comes from milk, is easily digested, and helps build muscles when you exercise. You will be asked to take this supplement before and after your exercise program. The nutritionist will explain how much you should take and will ask you to keep a diary.

The Plate Method:

This is a guide to help you naturally meet your daily nutrient requirements and maintain portion control

Your lunch and dinner plate should look like this! Follow the same example at breakfast, although the vegetables are optional at breakfast time.

Milk & Alternatives:

Milk (including milk-based soups and sauces), fortified soy beverages, yogurt, kefir, cheese, cottage cheese, homemade pudding/custard (made with milk). These foods also contain protein.

Tip aim for 1%

Fruit:

Try fresh or frozen fruit that are that are bright in colour and limit fruit juices

Starch:

Pasta, rice, quinoa, barley, couscous, bread, tortilla, pita bread, cereal, oats, crackers corn, potato, sweet potato, peas, parsnips, pumpkin

Tip: Make at least half of your choices whole grain. Choose barley, brown or wild rice, oats, and quinoa more often.

Fats:

Limit butter, margarine, mayonnaise & salad dressing to two tablespoons per day

Protein:

Eggs, fish, seafood, meat, poultry, nuts, nut butters, seeds, soy products, beans lentils, chickpeas.

Tip: Choose lean meats, trim fat and remove skins from animal products before cooking. Try natural peanut butter without added sugar or salt. Choose beans, lentils and fish more often.

Non-Starchy Vegetables

Yellow or green beans, broccoli, brussels sprouts, cabbage, cauliflower, celery, kale, cucumber, eggplant, palm hearts, endive, leeks, lettuce, spinach, mushrooms, okra, onion, peppers, radish, tomatoes, zucchini

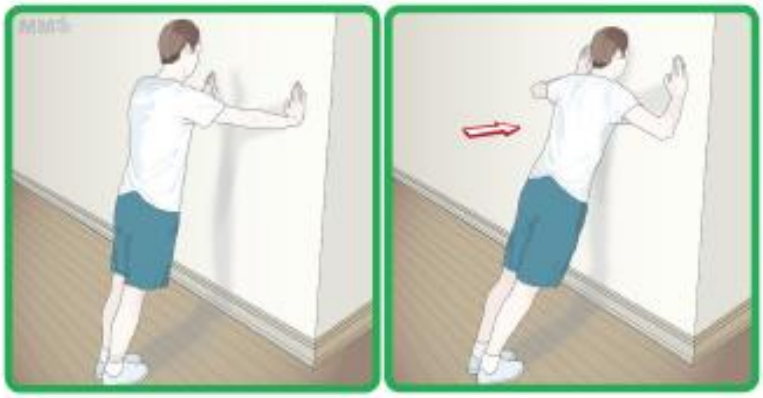
Tip: Try salad, vegetable soup, stir fry, boiled or steamed vegetables.

Cooking Tips:

- Instead of frying foods with oil or butter, use a vegetable oil cooking spray, a little water, non-fat soup broths, or herbal teas.
- Try baking, broiling, and steaming instead of frying.
- When you cook with oil, grease your pan with a small amount of oil on a paper towel.
- Line baking pans with parchment paper or cooking spray instead of oil.
- Instead of cooking with cream use evaporated skim milk.
- Thicken soups with puréed carrots, lentils, or silken tofu instead of cream.
- Yogurt can often be used to replace sour cream or mayonnaise. For example, replace 1/2 the mayonnaise in an egg salad recipe with low fat plain yogurt.
- Reduce 1/2 the oil in marinades or salad dressing recipes and increase ingredients like wine vinegar, balsamic vinegar, fruit juice, or fat-free broth.
- Use a smaller amount of a sharp or strong tasting cheese instead of a larger amount of a mild tasting one.
- Buy tuna packed in water instead of oil and fruit packed in juices instead of syrup.

Resistance Exercises

☐ **Push-up Against the Wall**



Instruction: Place hands at shoulder height on a wall. Stand slightly angled towards the wall. Keeping your back straight, bend your elbows to allow your upper body to come close to the wall.

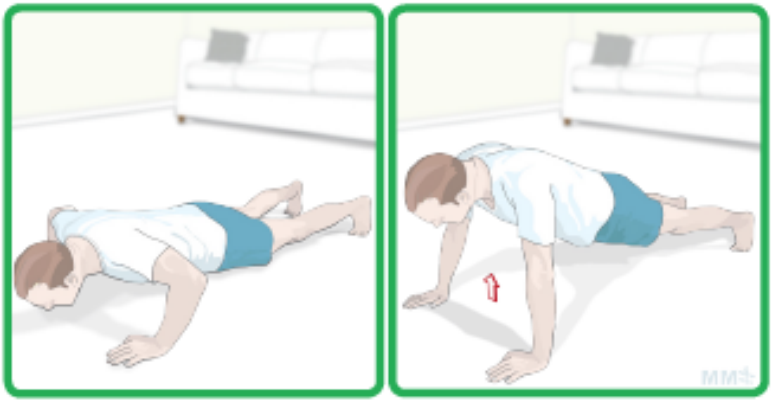
Reminder: Keep your neck inline with your spine. Make sure to fully extend your arms.

☐ **Modified Push-up**

Instruction: Put both hands on the floor and push yourself up from your knees.

Reminder: Try to keep the body in a straight line.

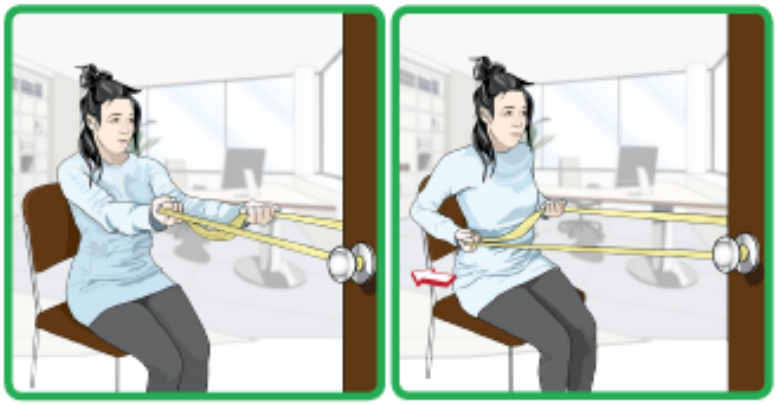
☐ **Full Push-up**



Instruction: Put both hands on the floor shoulder width apart Extend your legs and place your toes on the floor with your back straight.

Reminder: Make sure to fully extend your arms.

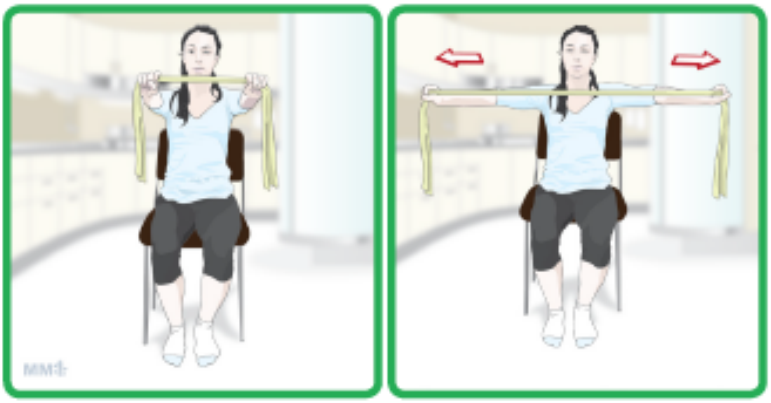
☐ **Seated Row (with theraband)**



Instruction: Holding the band, bend your elbows to 90 degrees. Without changing the angle in your arms, swing your arms backward so that your elbows are now behind you. Squeeze your shoulder blades together.

Reminder: Try to keep your back straight.

☐ **Chest (with theraband)**



Instruction: Hold elastic up at shoulder height with both hands. Pull the elastic out to the sides.

Reminder: Keep your back straight against the seat of the chair

☐ **Deltoid Lift (with theraband)**

Instruction: Place your feet on the band and raise your arm to the side so that your arm is now parallel to the floor.

Reminder: Keep a small bend in your elbow throughout the movement. Perform the exercise one arm at a time.

☐ **Biceps Curls (with theraband)**

Instruction: Place both feet on the band. Keeping your elbows attached to your sides, bend your elbows.

Reminder: Try to keep your back straight. Keep your wrists inline with your forearm.

☐ **Triceps Extensions**

Instruction: Hold the elastic in one hand at your chest. Pull the elastic back down to your side with the other hand.

Reminder: Keep the elbow of the moving arm glued to your body during the entire movement.

☐ **Chair Squats**

Instruction: Sit at the edge of the chair with your legs at an angle of 90 degrees. Stand up without using your hands.

Reminder: Always keep your legs at an angle of 90 degrees. The feet should not move at the beginning of the movement.

☐ **Touch Squats**

Instruction: Stand relatively close to the edge of your chair (facing away from it). Slowly lower your body to a sitting position.

Reminder: Do not fully sit on your chair.

☐ **Hamstring Curls**

Instruction: Hold the back of a chair. Kick your heels back one at a time.

Reminder: Do not put all of your body weight on the chair but on the standing leg instead. Keep your knees close together.

☐ **Standing Calf Raises**

Instruction: Stand facing the wall and hold for support. Lift your heels at the same time so that you are standing on your toes.

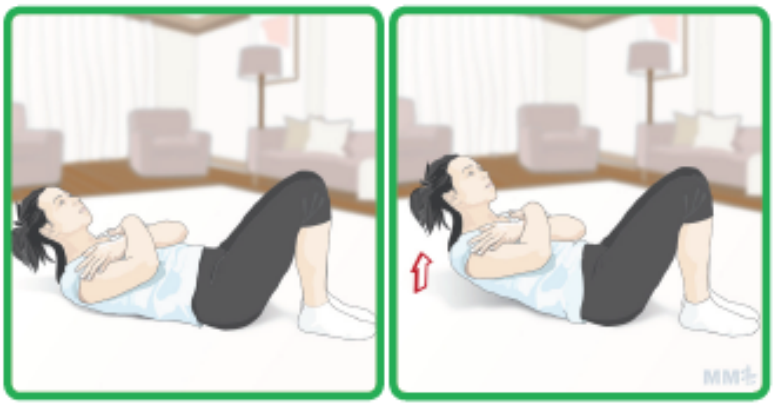
Reminder: Keep your body straight (perpendicular to the floor)

☐ **Abdominal Crunches (chair) :** ***to be done only before surgery***

Instruction: Sit at the edge of your chair with your hands crossed over your chest. Lower your back to the back of the chair. Hold for two seconds and then come back to a seated position.

Reminder: Keep your back straight during the entire movement. Do not let your feet come off of the floor.

☐ **Abdominal Crunches (floor) :** ***to be done only before surgery***



Instruction: Lie down on the floor/bed with both hands on the chest and slightly lift your shoulder off the floor/bed

Reminder: Try not to curve your neck and keep your head straight.

Flexibility Exercises

Repeat 2 times per exercise.
Hold the position for at least 20 seconds

☐

Chest

Instruction: Keep hands at shoulder height.

Reminder: Try to keep your back straight.

☐

Biceps

Instruction: Extend one arm with the palm of your hand facing upwards. With the other hand, push the fingers backwards

Reminder: Keep your arm at shoulder height.

☐

Triceps

Instruction: Raise your arm up, and bend your elbow so that your hand is now touching between your shoulder blades. With the opposite hand, slightly pull your elbow to the opposite side.

Reminder: Do one arm at a time.

☐

Quadriceps

Instruction: Place one leg onto a chair behind you while holding on to an object in front of you for support.

Reminder: Make sure to place your leg as far back as you can on the chair.

☐

Hamstrings

Instruction: Sit at the end of a chair with one leg fully extended. Place the heel of your foot on the floor and lean forward.

Reminder: Go as far as you can without feeling pain.

☐

Calf Stretches

Instruction: Stand with your hands against a wall. Place the toes of one of your feet on the wall in front of you and slightly push.

Reminder: Only do one foot at a time.

week 1 before surgery

Aerobic Training

	SUN	MON	TUES	WED	THUR	FRI	SAT
Resting Heart Rate							
Type of Exercise							
Duration							
Exercise Heart Rate							
Perceived Effort (BORG scale)							
Post Exercise Heart Rate							
Pedometer : number of steps							

Dates _____ to _____
Target Heart Rate: _____
% of Heart Rate Reserve: _____

Duration: _____
Frequencey: _____
Number of Steps: _____

Notes:

week 1 before surgery

Resistance Training

	SUN	MON	TUES	WED	THURS	FRI	SAT
Nutrition - Protein Powder							

Exercises	p.	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps
Wall Push-Ups	17														
Modified Push-Ups	17														
Full Push-Ups	18														
Seated Row	18														
Chest	19														
Deltoids	19														
Biceps Curls	20														
Triceps Curls	20														
Chair Squats	21														
Touch Squats	21														
Hamstring Curls	22														
Standing Calf Raises	22														
Abdominal Crunches (chair)	23														
Abdominal Crunches (floor)	23														

Flexibility		SUN	MON	TUES	WED	THURS	FRI	SAT
Chest	24							
Biceps	24							
Triceps	25							
Quads	25							
Hamstrings	26							
Calfs	26							

Nutrition - Protein Powder							

Notes: