

Physical prehabilitation in colorectal cancer surgery patients

A systematic review of randomized controlled trials to assess whether the evidence (a) indicates that physical prehabilitation is effective in colorectal cancer surgery clinical outcomes, and (b) is sufficiently strong to support a recommendation for physical prehabilitation interventions to be included in ERAS® guidelines.

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1 INTRODUCTION

1.1 Colorectal Cancer

Colorectal cancer results in an average of 16,500 UK deaths annually, making it the second largest cause of cancer deaths per annum (Bowel Cancer UK, 2022a). With 44,706 new bowel cancer diagnoses in the UK in 2019, it was the second most common cancer in males and third in females (World Cancer Research Fund, 2022). Bowel cancer prevalence is strongly associated with age, 43% of all diagnoses between 2016 and 2018 occurred in people aged 75+ years (Cancer Research UK, 2022b). Disturbingly, a 2019 population-based study reported a significant (1.8%) increase in incidence in the under 50s in the UK (Araghi *et al.*, 2019).

The Covid-19 pandemic caused unprecedented delays in both detection and treatment of all types of cancer (McMillan Cancer Support, 2020). Detection rates dropped as screening programmes and diagnostic services were paused or scaled back. Endoscopic diagnoses of colorectal cancer reduced by 72% (Rutter *et al.*, 2021) and treatment was only provided for symptomatic cases meaning waiting times for treatment have increased. Research by Maringe *et al.* (2020) determined that delays in detection and treatment would lead to increases in colorectal cancer deaths of between 15.3% and 16.6% in England.

In Wales, 2513 colorectal cancer diagnoses were made in 2019, an 8.6% increase over the previous year and the highest annual increase since 2002 (Bowel Cancer UK, 2022b). When detected early, bowel cancer has a far greater 5-year survival rate (Cheng *et al.*, 2021). However, in 2018 Wales ranked 25th out of 29 European countries for five-year bowel cancer survival rates (Bowel Cancer UK, 2018)

1.1.1 What is Colorectal Cancer?

Colorectal cancer, commonly known as bowel cancer (Cancer Research UK, 2022a), describes the presence of malignant cells (Patel, 2020) in the colon and/or rectum located in the large intestinal section of the gastrointestinal tract. Both the colon and

rectum are lined with a mucosal membrane made up of glandular, mucus producing epithelial cells also containing lymphoid cells from the immune system (Allaire *et al.*, 2018). Ninety-five percent of colorectal cancers are “adenocarcinomas” (WCRF International, 2023), cancerous tumours formed the epithelial cells (Tape, 2017). Mucinous and signet ring tumours are specific and less common types of adenocarcinomas. Other, more rare, colorectal cancer types also exist: squamous cell and carcinoid tumours; sarcomas (specifically “leiomyosarcomas”); lymphomas; and melanomas, a skin cancer, which can begin in the rectum (Cancer Research UK, 2022a).

1.1.2 Who is at Risk of Developing Colorectal Cancer?

Other than age, genetic predisposition; conditions such as inflammatory bowel disease (Crohn’s Disease and Ulcerative Colitis) and diverticular disease; obesity and diabetes; environmental, and lifestyle factors such as: inadequate diet; smoking; alcohol abuse; and physical activity levels are all indicated in an increased risk of developing colorectal cancer (WCRF, 2018).

1.2 Colorectal Cancer Screening and Diagnosis

When detected early, 90% of colorectal cancer patients survive (Public Health Wales, 2022), a powerful statistic which strongly reinforces the importance of colorectal cancer screening programmes. Detecting colorectal cancers at an early stage is crucial to the avoidance of metastasis to other parts of the body (Hu *et al.*, 2019). The World Health Organization defines the purpose of health screening programmes as:

“...to identify people in an apparently healthy population who are at higher risk of a health problem or a condition, so that an early treatment or intervention can be offered and thereby reduce the incidence and/or mortality of the health problem or condition within the population.” (World Health Organization, 2020)

Additionally, for a specific disease or condition to be considered for screening, both guiding principles and established criteria set out by Wilson and Jungner (1968) need to be met (Wilson and Jungner, 1968). The criteria and principles ensure that screening is safe, accurate, effective and that the benefits to the at-risk population outweigh potential harm caused. Figure 1 provides an example of how the criteria in the column headed “Wilson and Jungner Criteria (paraphrased)” has relates to the evidence in the column headed “Evidence supporting screening for colorectal cancer” in the context of colorectal cancer screening programmes in the United Kingdom.

Further, the World Health Organization’s “Screening Programmes: a short guide” also sets out four aims for screening programme design:

- i) “to reduce mortality by early detection and early treatment of a condition;”
- ii) “to reduce the incidence of a condition by identifying and treating its precursors”
- iii) “to reduce the severity of a condition by identifying people with the condition and offering effective treatment”
- iv) “to increase choice by identifying conditions or risk factors at an early stage in a life-course when more options are available”

The guide also stipulates that the aims for screening programmes should be included in any screening policies published in statutes and official guidelines (World Health Organization, 2020). In Wales, the screening aims are summarised as: “to identify cancer early when treatment is more likely to be successful and also remove pre-cancerous growths.” (Public Health Wales, 2021a).

Wilson and Jungner Criteria (paraphrased)	Evidence supporting screening for colorectal cancer
The condition is an important health problem	3 rd most common cancer in the UK (Cancer Research UK 2009)
Its natural history is well understood	Adenoma-carcinoma sequence (Vogelstein 1988)
It is recognisable at an early stage	Premalignant lesion is the adenoma
An acceptable treatment exists	Polypectomy or surgery are acceptable treatments.
A suitable test exists	Faecal occult blood (FOB) testing has sensitivity for colorectal cancer of 50-70% (Steele 2005).
An acceptable test exists	FOB testing is accepted by approximately 50% of those invited.
Adequate facilities exist to cope with abnormalities detected	Colonoscopy and surgical services are adequately equipped to cope with demand (Dent et al 2009)
Screening is carried out at repeated intervals when the onset is insidious	Trials of FOB testing have used a biennial FOB test strategy.
The chance of harm is less than the chance of benefit	FOB testing is safe.
The cost is balanced against benefit	Similar cost effectiveness to breast cancer screening in the short term. Possibly superior in the long term (Whynes et al 1998)

Table 8- Criteria for a disease to be suitable for screening (after Wilson and Jungner 1968)

Figure 1: Illustration of the application of UK colorectal cancer justifications mapped to Wiltson and Jungner's screening criteria. Source: (Lee *et al.*, 2014)

1.2.1 Screening Sensitivity and Specificity

The gold standard for colorectal cancer screening is diagnostic colonoscopy (Nierengarten, 2023). This procedure, however, is invasive for the patient and requires specialist medical personnel and equipment making it neither feasible nor cost effective to offer as a mass screening tool in target populations. To overcome this, a simple, self-administered test to identify faecal blood is utilised for screening purposes. Sensitivity and specificity analyses allow for a comparison of the mass screening test accuracy compared to the gold standard colonoscopy procedure.

Between January and September 2019, Public Health Wales changed from the Guaiac Faecal Occult Blood test to the Faecal Immunochemical Test (FIT) (Public Health Wales, 2021). FIT has three benefits over the Guaiac Faecal Occult test: (i) it

is simpler for the individual to use, (ii) the test is more sensitive for detection and diagnostic purposes and (iii) it provides a quantitative result on a continuous scale rather than a “detected/not detected” result. (Tinmouth, Lansdorp-Vogelaar and Allison, 2015; Li *et al.*, 2020). Lee *et al* (2014) concluded that FIT are “moderately sensitive”, “highly specific”, and “have high overall diagnostic accuracy for detecting CRC”. However an important caveat was included which pointed to the dependency on the threshold set for a positive result with no recommended threshold suggested (Lee *et al.*, 2014). NHS England applied a threshold of 120 µg/g FIT for its screening programme in 2019 meaning only test results exceeding that threshold were referred for further investigation. A recent review has suggested a threshold of 120 µg/g may miss 51% of colorectal cancer cases. Further, a threshold of 20 µg/g was recommended which, it was estimated, would detect 82% of colorectal cancer cases (Li *et al.*, 2020). The NHS Wales threshold is currently set at 150 µg/g. The rationale provided for such a high threshold with low sensitivity was to avoid an increase in demand for diagnostic testing resources (Welsh Government, 2019). The implication for a threshold at this level being, that the number of false negative results will increase, and colorectal cancer cases will be missed.

1.2.2 Colorectal Cancer Screening Performance in Wales

In October 2021, Public Health Wales reported that, in the period April 2019 to March 2020, a total of 276,226 eligible participants aged between 60 and 74 years were recorded to have returned bowel cancer screening tests authorised in the 2.5 years up to March 2020. This represents an average of 61.5% uptake across all Health Boards, with 1.5% (2694 participants) of tests returning a definitive positive result requiring further testing to confirm a bowel cancer diagnosis. During the same period, 49.1% of participants with positive screening tests were offered diagnostic colonoscopy/sigmoidoscopy within 4 weeks, with a further 36.6% offered appointments between 4 and 8 weeks of notification of a positive screening test. Bowel cancer detection rates post-diagnostic testing across Wales were 12.6% (240 participants) (Public Health Wales, 2021b). Despite, or perhaps as a result of, the high levels of screening and diagnostic tests, as of October 2021 none of the Welsh

regional health boards had met their 75% target for commencement of bowel cancer treatment within 62 days of diagnosis (Bowel Cancer UK, 2021).

With effect from October 2022, Public Health Wales reduced its bowel cancer screening age from 58 to 55 years. This age will further reduce to 50 from October 2024 (Public Health Wales, 2022). In the 2021 census, the 55-59 age group accounted for 7.2% (n=222,700) of the general population; 50-54 age group accounted for 6.9% (n=215,700); and 45-49 age group accounted for 6.0% (n=186,100). It would be reasonable to make a conservative estimate of a doubling of the number of participants eligible for screening between 2022 and 2024. If the positive screening test result rate were to remain at 1.5%, and positive diagnosis at 12.6%, there would be a corresponding doubling in demand for diagnostic colonoscopy/sigmoidoscopy and cancer treatment. Should current post-diagnosis treatment times continue in parallel with increased incidence through volume despite low screening test sensitivity, the outlook for colorectal cancer patients in Wales appears bleak.

1.3 Colorectal Cancer Treatment

Treatment for colorectal cancers differ between colon cancer and rectal cancer and options are dependent on the tumour location, size, type and whether the cancer has metastasised (Cancer Research UK, 2022f). The severity of colon cancers are most commonly “staged” using the TNM scale (Keung and Gershenwald, 2018) which allows for a clinical staging of: “T” - how far the tumour has grown through the bowel wall (T1 – T4), “N” - whether the cancer has spread to the nodes (N0 – N2), and “M” - whether the tumour has spread to other parts of the body (M1-M2). From the TNM assessment, the cancer can be given a number stage between 1 and 4. Thus a staging code of T2N0M0 describes a tumour that has grown into the muscle wall but not spread to the lymph nodes or other areas of the body (Bowel Cancer UK, 2023).

Surgical resection is the main course of treatment for colorectal cancers and is performed in 65.7% of colonic cancers and 63.2% of rectal cancers respectively (Pallan *et al.*, 2021). Typically, treatment for stage 1 colon cancer is surgery alone; stage 2 is surgery, chemotherapy may also be recommended; most stage 3 colon

cancers require both surgery and post-operative chemotherapy; stage 4 cancers may need all or a combination of surgery, chemotherapy, radiotherapy, immunotherapy, or other targeted cancer drugs (Cancer Research UK, 2022f). Treatments are different for some rectal cancers where the cancer hasn't spread. Rather than opting immediately for surgery a patient may opt for neoadjuvant chemoradiotherapy (NACRT) which has been shown to be an effective alternative (Martin, Heneghan and Winter, 2012). When surgery is recommended in either colon or rectal cancer, surgeons will select the option most likely to be successful and least likely to result in complications, from either laparoscopic (keyhole) or laparotomy/celiotomy (open surgery) (Kirchhoff, Clavien and Hahnloser, 2010).

1.3.1 Laparoscopic Surgery

Laparoscopic surgery offers a less invasive surgical option which, in addition to being as effective as open surgery in colorectal cancers, presents a lower risk of blood loss (Kirchhoff, Clavien and Hahnloser, 2010) and post-operative infection (Caroff *et al.*, 2019). Laparoscopic surgery also results in a shorter length of hospital stay (Marsden, Parvaiz and Moran, 2015). In a condition where almost half (43%) of colorectal cancer patients are over 75, a factor which presents an increased surgical risk in itself, laparoscopic surgery is positively indicated and preferential for this higher risk population (Antoniou *et al.*, 2015).

1.3.2 Open Surgery

Open surgery, laparotomy (or celiotomy), is the method of surgery whereby a large incision is made the abdominal cavity to access the diseased section of bowel (Rajaretnam, Okoye and Burns, 2023) and is necessary in cases where a laparoscopic procedure is not appropriate. Conversion from laparoscopy to open surgery mid-procedure is sometimes required due to unexpected inter-surgical complications such as adhesions, internal bleeding, or the patient's individual anatomy (Stafford *et al.*, 2021). Despite advances in specialised laparoscopic techniques and equipment, open total mesorectal excision (TME) is the most common form of surgery for rectal cancer (Cancer Research UK, 2022f) due to its superior pathological outcomes (Conticchio *et al.*, 2020).

1.3.3 Neo-adjuvant and Adjuvant Therapies

Neo-adjuvant therapy refers to the use of chemotherapy and/or radiotherapy prior to surgery whereas adjuvant therapy takes place after surgery. The purpose of neo-adjuvant therapies is to reduce the tumour size to make surgical removal easier. Neo-adjuvant chemotherapy and radiotherapy (NACRT) is typically offered for localised rectal cancer (Cancer Research UK, 2022e). Chemotherapy may also be used as an adjuvant therapy for rectal and stage two and three colorectal cancer patients (Cancer Research UK, 2022d, 2022c)

1.3.4 Common Surgical Complications

As with any major surgical procedure, there is a risk of complications during and after surgery. Post-surgical complications are classified using either or both the Clavien-Dindo scale and Comprehensive Complication Index (CCI) (Smeyers *et al.*, 2021), and in colorectal cancer the complication rate has been reported to be as high as 35% (Pallan *et al.*, 2021). The most common complications are anastomatal leak, that is, a leak at the point of re-section (Van Helsdingen *et al.*, 2020). Estimates range from 3% to 15.3% for the incidence of anastomatal leaks, whilst 13% of patients experience surgical-site infections. Other common complications after colorectal surgery are “ileus, the slowing down of intestinal motility, and bowel obstructions though due to definitions for these morbidities it is difficult to accurately quantify the incidence, the highest being by 24%. (Kirchhoff, Clavien and Hahnloser, 2010; Tevis and Kennedy, 2016).

1.3.5 ERAS® Society Guidelines

The ERAS® Society published guidelines for the Enhanced Recovery after Surgery to provide an evidence-based framework for clinical best practices in colorectal cancer amongst other conditions. In both the 2013 and 2018 guidelines, prehabilitation was recommended but excluded physical prehabilitation due to the low graded evidence reviewed (Gustafsson *et al.*, 2013, 2019).

1.4 Physical Activity and Prehabilitation in Colorectal Cancer Surgery

Benefits of physical activity on cancer risk are universally accepted (World Health Organization, 2022). Physical activity has also been indicated as a factor in improved pre and post-surgery functional capacity (Minnella and Carli, 2018) and overall survival (Meyerhardt *et al.*, 2006; Choy, Lam and Kong, 2022). Whilst surgical resection is the main treatment for colorectal cancer (Brown *et al.*, 2019), research continues to investigate the use of adjuvant physical “prehabilitation” to improve patient physical and respiratory fitness in preparation for surgery and influence post-operative outcomes (Falz *et al.*, 2022). Many prehabilitation definitions exist. An appropriate definition in the context of colorectal cancer management would be “a systematic process of improving the physical, psychosocial, and nutritional status of cancer patients between diagnosis and post treatment recovery to increase the ability to cope with the upcoming physiological stress of the specific cancer-related therapy” (Palma *et al.*, 2021). Recent research points to multimodal interventions for the assessment and delivery of appropriate physiological, nutritional, and psychological support (Bolshinsky *et al.*, 2018; van Rooijen *et al.*, 2019).

1.4.1 Enhanced Recovery After Surgery (ERAS®)

The ERAS® Society publish guidelines for the Enhanced Recovery after Surgery, providing an evidence-based framework for clinical best practices in colorectal cancer amongst other conditions. The 2018 guidelines include nutritional prehabilitation with “moderate” certainty of evidence and a “strong” recommendation for inclusion, however, evidence reviewed for physical prehabilitation interventions was graded as “moderate” for functional capacity outcomes and “low” for postoperative clinical outcomes with a “weak” recommendation for guideline inclusion. The guidelines acknowledged that evidence existed to support structured physical prehabilitation and that for functional recovery, prehabilitation “shows promising results”. Despite this, based on the strength of evidence at the time, the ERAS Society was unable to recommend physical prehabilitation in its 2018 guidelines (Gustafsson *et al.*, 2019).

1.5 Review Aims and Objectives

Since the 2018 ERAS® guidelines review, research into physical prehabilitation for colorectal cancer has continued with, at the time of writing, 18 trials active randomized controlled trials registered on the Clinicaltrials.org and International Clinical Trials Registry Platform (ICTRP) databases (National Library of Medicine, 2023; World Health Organization, 2023). The aim of this review is to evaluate the strength of evidence published since 2018, specifically focussed on physical prehabilitation interventions in colorectal cancer. To do this, it will be necessary to systematically evaluate:

1. Relevant evidence published since 2018
2. The quality of evidence published using established critical appraisal tools
3. Whether any new evidence strengthens the use of physical prehabilitation in colorectal cancer
4. Whether any new evidence would be sufficient to support an upgrade of the ERAS® recommendation to mandate physical prehabilitation for colorectal cancer treatment in its guidelines

2 METHOD

Detailed instructions outlining the exact process steps undertaken whilst undertaking a systematic review provides transparency for reviewers and readers alike. A documented protocol means that the review conclusions can be replicated and validated if required. To this end, many tools, guidelines, and protocols exist to aid the researcher in their task. The Cochrane methodology is considered the gold standard for reviews of interventional studies, providing best practice checklists/guidelines for systematic review drafting (Sporstøl, 2019) and its Risk of Bias quality assessment tools (The Cochrane Collaboration, 2022).

Originally published as QUOROM guidelines for meta-analyses (Moher *et al.*, 1999), the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement superseded QUOROM in 2009 (Moher *et al.*, 2009), enhanced to include guidelines for both systematic reviews and meta-analyses.

Recently updated PRISMA guidelines, specifically, PRISMA 2020 (Page *et al.*, 2021), include a framework for systematic reviews including a checklist of sequential steps followed for this review. PICO processes were applied to identify key search parameters and relevant MeSH terms for the purpose of literature searches. The described protocol has not yet been registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (National Institute for Health Research, 2023).

2.1 Inclusion Criteria

2.1.1 Study Criteria

PICO process (Richardson *et al.*, 1995) was followed for the selection of studies for inclusion. The following criteria were used to identify randomised controlled trials with prehabilitation interventions in colorectal cancer surgery patients.

2.1.2 Participants

Human studies involving adults (aged 18+) with a diagnosis of colorectal cancer. Studies which include a diagnosis of grade IV colorectal cancer, metastasis or other forms of cancer will be excluded.

2.1.3 Interventions

To be able to compare the effectiveness of a range of different prehabilitation exercise protocols, studies including any type of physical prehabilitation intervention in any setting were retrieved for title and abstract screening.

2.1.4 Comparisons

Studies which include 'standard', 'usual' or no treatment. Superiority studies were also included. Studies which do not include physical prehabilitation were excluded.

2.1.5 Outcomes

Outcome(s): The primary outcomes were based on the umbrella review by Fuller et al(2018), namely cardiovascular fitness, muscle strength, health-related quality of life (HRQoL), depression, cancer-related fatigue and adverse events. However, other important outcomes included ineligible systematic reviews and/or meta-analyses were also considered for extraction.

Primary outcomes were chosen based on 2018 ERAS® guidelines which used post-operative functional capacity and complications from included studies as its measure of the effectiveness of physical prehabilitation. Therefore, primary outcomes included were: post-operative complications, functional and aerobic capacity, and also length of hospital stay which is an indicator of recovery. Other outcomes, such as quality of life and psychological outcome measures, were also captured.

2.2 Search Strategy

2.2.1 Systematic electronic database search

To identify suitable randomised controlled trials (RCT) and systematic reviews for inclusion in the review, a systematic search of PubMed and MedLine databases and Google Scholar was completed between 29th January 2023 and 4th February 2023.

2.2.2 Search Parameters

Key search terms used were “colorectal cancer” and “prehabilitation”. A MeSH search (National Institutes of Health, 2023) using these terms identified MeSH term subject headings “colorectal neoplasm” and “pre-operative exercise”. All terms were used where MeSH term searches were an option.

To limit the number of search results to those since the last ERAS® guidelines, publication dates between 2018 and 2023 were used.

A second search as described above was completed on 31st March 2023 to identify any new studies published or registered since the scheduled search date.

2.2.3 Hand Searches

A search of the Cochrane Library was completed to identify systematic reviews between 2018 and 2023 for hand searching references. The search results were also used for cross validation against RCTs identified during the systematic database search. Additionally, a manual search was undertaken using the UWTSD online library database BrowZine search tool to identify journals for related to colorectal cancer published between 2018 and 2022, and not captured as part of the electronic database search.

2.2.4 BrowZine Hand Searches

A search of the BrowZine journal search tool available through UWTSD library website was made on 25th February 2023 using the following search terms:

1. Colorectal cancer
2. Colorectal neoplasm

Relevant journals identified were:

- Colorectal Cancer
- Clinical Colorectal Cancer
- Colorectal Neoplasm

All available journal issues published since January 2018 were manually searched to identify any studies meeting the review inclusion criteria.

2.2.5 Systematic Review References Hand Searches

Systematic reviews returned in the database searches results datasets were title and abstract reviewed for the inclusion of both “colorectal cancer” and “prehabilitation” terms and publication dates between 2018 and 2023. Systematic reviews meeting the criteria from each database results dataset were cross referenced to remove duplicates. The reviews were then imported to Mendeley Reference Manager (Mendeley, 2022).

Systematic review references lists were hand searched to facilitate identification of randomised controlled trials meeting the inclusion criteria and not previously appearing in database search result datasets.

On completion of database and hand searches, a final list of studies was created. All studies were exported to Mendeley Reference Manager (Mendeley, 2022) for full text review and data synthesis.

2.2.6 Specific Registered Trial Database Search

For completeness, a cross reference to prehabilitation related registered trials was completed using Clinicaltrials.gov, CENTRAL and <https://trialsearch.who.int>.

2.3 Database Search Results File Processing

Database and Trial registry search results were saved in their original and separate .csv or .xlsx files. A robust process was followed to consolidate the database search result files, remove duplicate records and abstract and title screen. Detailed process steps and description can be found in Appendix 1.1. Logs of individual and consolidated search results files for each database are provided in Appendices 1.2 and 1.3.

The PRISMA flow diagram (figure1) refers to “records” and “reports”. “Records” are the results of systematic database searches and all other search types whereas “reports” are the studies selected from the “records” for assessment for screening. Henceforward, “records” will be referred to as studies.

2.4 Search Results – Study Selection

2.4.1 Title/Abstract Screening

Each database search result was manually reviewed for the terms “Colorectal Cancer”, “Prehabilitation” and “Randomised (/Randomized) Controlled (/Clinical) Trial”. Where the subject was not clear from the study title, the Abstract was briefly reviewed to ascertain the type and/or subject of the study. Studies not meeting these criteria were coded to categorise and marked for inclusion for full text screening or exclusion. Studies marked for full text screening were copied to an Excel file named “Full Text Screening Master File.xlsx”.

2.5 Studies Sought for Retrieval

Studies logged in the “Full Text Screening Master File” were retrieved using the Digital Object Identifier (DOI) (DOI Foundation, 2023), full text versions were downloaded to Mendeley Reference Manager (Mendeley, 2022). Studies where full

text was not available were not downloaded and the record coded to indicate the reason for exclusion.

2.6 Studies Assessed for Eligibility - Full Text Screening

Each study was reviewed in full to verify that they met the full selection criteria. At this stage studies were either kept for inclusion or rejected.

2.7 Data Extraction

Data were extracted from the included studies and consolidated in summary tables under the following headings:

2.7.1 Study Characteristics Summary Table

- 1 Author
- 2 Study Type
- 3 Setting
- 4 Cancer Type
- 5 Surgery Type
- 6 Sample Size
- 7 Age in Years
- 8 Intervention vs Control
- 9 Duration
- 10 Attrition
- 11 Main Outcome(s)
- 12 Quality Assessment

2.7.2 Intervention Characteristics Summary Table

- 1 Author
- 2 Prehabilitation Programme
- 3 Duration
- 4 Frequency
- 5 Intensity

- 6 Time
- 7 Type
- 8 Adherence
- 9 Adverse Events

Where available, supplementary data was retrieved to facilitate full key data extraction and quality assessment. Authors were contacted to request missing data and protocols. At the time of writing, no responses were received.

2.8 Data Synthesis

Meta-analysis was possible for the post-surgical complications, length of hospital stay, functional capacity and aerobic capacity outcomes. Due to the heterogeneity of reporting of other outcomes, meta-analysis was not feasible therefore data synthesis of was provided in a narrative format.

2.9 Statistical Analysis

Continuous data variables used for meta-analysis were extracted from individual study results. Where presentation of data format differed, a manual calculation was necessary to convert data to a standardised format for meta-analysis in RevMan (Cochrane Collaboration, 2020). These were calculated using the mean and standard deviation, or median and Interquartile ranges entered into the Cochrane RevMan calculator. Outcomes analysed were Post-Surgical Complications, Length of Hospital Stay, Functional and Aerobic Capacity and 6MWD. Confidence intervals were set to 95% for all meta-analysis. The application of random or fixed effect was decided according to the criteria described in the Cochrane Consumers and Communication Group Review (Ryan, 2016), namely where $I^2 > 40$ or $p < 0.10$ to indicate significant heterogeneity, a random effects model was selected.

Sensitivity analysis was undertaken for outcomes included in meta-analyses using a “leave one out” approach to analyse each study’s influence on both pooled estimates and heterogeneity.

3 RESULTS

3.1 Search Results

Following the systematic search and selection method described, 5259 “records” were identified of which 2018 were duplicates leaving 3241 records for abstract and title screening. Of these, 3103 were excluded leaving a total of 72 “reports” (12 studies, 62 trial registry records) for full text screening after which, 39 reports were identified as not meeting the criteria for inclusion leaving 37 reports for inclusion (8 studies, 29 trial registry records). Screening of hand search records returned 2 additional studies making a final total of 10 studies for inclusion in the review. The PRISMA 2020 flow diagram in figure 2 below provides an illustrates the number of studies identified, screened, excluded, and included.

PRISMA 2020 flow diagram for new systematic reviews which includes searches of databases, registers and other [sources](#)

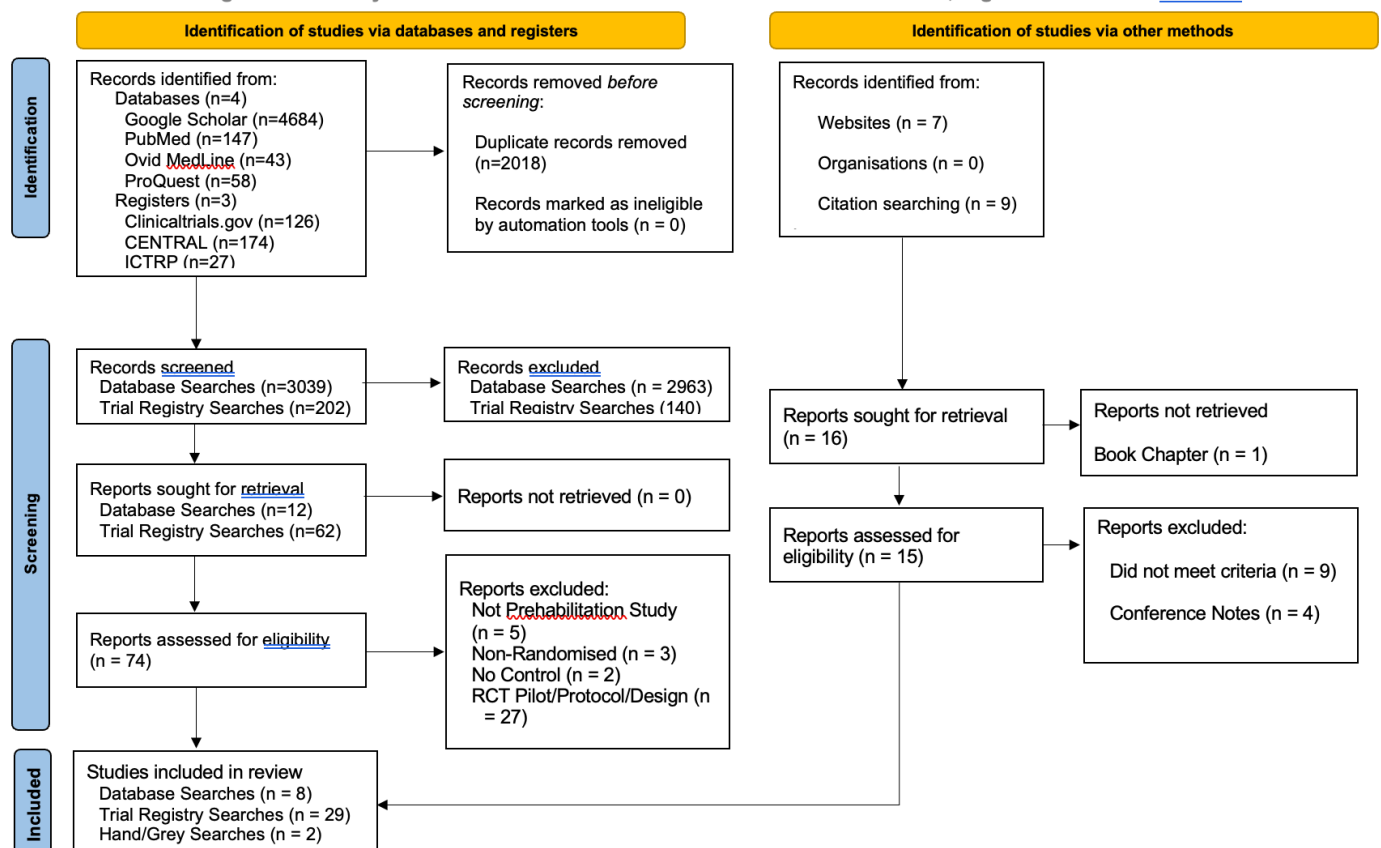


Figure 2: Adapted PRISMA 2020 Flow Diagram: Summary of database and hand search results inclusions and exclusions. Source: (Page *et al.*, 2021)

3.2 Excluded Studies

After full text screening, ten studies were excluded studies: two were protocols (Stefanus Van Rooijen *et al.*, 2019; Amaro-Gahete *et al.*, 2022), one reviewed the effects of prehabilitation on insulin sensitivity (Ferreira, 2018), one was solely on frail patients (Gillis *et al.*, 2021), two were feasibility studies (Karlsson *et al.*, 2019; Northgraves *et al.*, 2020); one was a process evaluation (Murdoch *et al.*, 2021); one was specific to the effects of prehabilitation on the insulin-like growth factor axis (Onerup *et al.*, 2020), one was specific to recovery of GI function (Peng *et al.*, 2021) and was investigating the effects of prehabilitation on chemotherapy in metastised colorectal cancers (Zimmer *et al.*, 2018).

3.3 Quality Assessment

Nine studies were randomized controlled trials (RCTs) and one used data from an included RCT. Due to the study design, it was not possible to blind participants in either group. To establish the quality of included studies, three distinct assessments were undertaken to assess risk of bias; quality of intervention reporting; and certainty of outcome evidence.

3.3.1 Risk of Bias

The Cochrane Risk of Bias tool, “RoB 2” (The Cochrane Collaboration, 2022) was used to assess five study domains resulting in a rating of “low”, “high” or “some concerns”. The algorithm assesses: the randomization process; blinding and deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported results and an overall rating. Six of the ten studies were rated low risk of bias due to the provision of clear, detailed, and unambiguous information (Carli *et al.*, 2020; Minnella *et al.*, 2020; Fulop *et al.*, 2021; Berkel *et al.*, 2022; Onerup *et al.*, 2022; Molenaar *et al.*, 2023). Four of the included studies were rated “some concerns”: one due to ambiguity over the randomization process (domain 1) (López-Rodríguez-Arias *et al.*, 2021); one due to the information provided relating to the blinding of participants and intervention providers/assessors (domain 2) (Bousquet-Dion *et al.*, 2018) and both of the studies by Moug *et al.* (2019, 2020) provided insufficient information to be able to be confident that blinding

(domain 2), outcome measurements (domain 3) and appropriate selection of the reported results (domain 5) were carried out according to the original trial design. As Moug et al (2020) was a sub-analysis of their 2019 study, scoring for domains 2 and 4 mirrored those of the assessment of the 2019 study (Moug et al., 2019b, 2020). Cochrane Risk of Bias assessments for included studies are presented in figure 3.

Study	D1	D2	D3	D4	D5	Overall	
Berkel et al (2022)	+	+	+	+	+	+	Low risk
Bousquet-Dion et al (2018)	+	?	+	+	+	!	Some concerns
Carli et al (2020)	+	+	+	+	+	+	
Fulop et al (2021)	+	+	+	+	+	+	
Lopez-Rodriguez-Arias (2021)	?	+	+	+	+	!	D1 Randomization process
Minnella et al (2020)	+	+	+	+	+	+	D2 Deviations from intended interventions
Molenaar et al (2023)	+	+	+	+	+	+	D3 Missing outcome data
Moug et al (2019)	+	?	+	?	+	!	D4 Measurement of the outcome
Moug et al (2020)	+	?	+	?	?	!	D5 Selection of the reported result
Onerup et al (2022)	+	+	+	+	+	+	

Figure 3: Cochrane Risk of Bias assessments for included studies

3.3.2 Quality of Intervention Documentation and Reporting

The Consensus on Exercise Reporting Template (CERT) checklist (Slade *et al.*, 2016) was used to evaluate the quality and completeness of intervention reporting within the included RCTs. The template consists of 18 questions with each question answered “Yes” or “No” and requires supporting evidence/explanation to justify the scoring. A “yes” answer scored 1 point whereas a “no” answer scored 0 points. Points are added together to produce a total score. One assessment template was completed per study, individual study scores were recorded on each assessment template and a matrix (Appendix 2.2) was created to consolidate all studies and facilitate comparison of reporting. The average CERT score was 11.45 (64% of all questions answered satisfactorily). The highest score achieved was 16/18 (89%) (Moug et al., 2019b, 2020), the lowest scored 7/18 (39%) (Bousquet-Dion *et al.*, 2018; López-Rodríguez-Arias *et al.*, 2021). Information to answer Question 4 (“Describe whether exercises are supervised or unsupervised; how they are delivered”) and question 10 (“Describe whether there are any non-exercise components”) was provided in all studies whereas only two studies (20%) provided

adequate information to answer question 8 (“Detailed description of each exercise to enable replication”).

3.3.3 Quality of Evidence for Reported Outcomes

Outcome summary tables from included studies were created and ‘graded’ using the GRADEpro tool. The grading system represents the level of confidence and strength of reported evidence per outcome and ranges from “High” to “Very Low”. A rating of “high” indicates that further research is not required to change the level of confidence in the reported estimate of effect. “Moderate” indicates that further research may have an “important impact” on estimate of effect. “Low” indicates that further research is likely to have an important effect and “very low” indicates that reported estimate of effect is considered “very uncertain” (McMaster University and Evidence Prime, 2022). Post-surgical complications, length of hospital stay, and functional capacity outcomes were assessed and due to the small sample sizes of some studies, the evaluations were downgraded to ‘Moderate’. GRADEpro summary finding tables for each outcome can be found in Appendix 2.3.

3.4 Study Characteristics

Ten studies met the inclusion criteria, nine of which were randomized controlled trials (Bousquet-Dion *et al.*, 2018; Moug *et al.*, 2019b; Carli *et al.*, 2020; Minnella *et al.*, 2020; Fulop *et al.*, 2021; López-Rodríguez-Arias *et al.*, 2021; Berkel *et al.*, 2022; Onerup *et al.*, 2022; Molenaar *et al.*, 2023), and one was a subanalysis of an included study (Moug *et al.*, 2020). All studies were published between 2018 and 2023, three were undertaken in Canada (Bousquet-Dion *et al.*, 2018; Carli *et al.*, 2020; Minnella *et al.*, 2020), two in the United Kingdom ((Moug *et al.*, 2019b, 2020), one in Hungary (Fulop *et al.*, 2021), one in the Netherlands (Berkel *et al.*, 2022), one in Spain (López-Rodríguez-Arias *et al.*, 2021) one in Sweden (Onerup *et al.*, 2022) and one was a multi-centre, international study (Molenaar *et al.*, 2023). Eight studies involved patients scheduled to undergo surgery for colon cancer resection, two specifically investigated the effects of prehabilitation on rectal cancer surgery with neoadjuvant chemoradiotherapy (NACRT). (Moug *et al.*, 2019b, 2020).

A total of 1452 participants were included across all studies comprising 840 (57.9%) men and 612 (42.1%) women. Allocation to intervention and control groups was 719 (49.5%) and 733 (50.5%) participants respectively. Pooled analysis indicated an even distribution of male and female participants intervention and control groups $I^2 = 0\%$, ($p = 0.89$). The largest study recruited 668 participants (Onerup *et al.*, 2022) whereas the smallest recruited 20 (López-Rodríguez-Arias *et al.*, 2021). Participant ages ranged from 33.7 years to 82.6 years. Table 1 provides a summary of included study characteristics, participants, outcomes, effect size and quality assessment results. GRADE evaluations were only conducted for outcomes where meta-analysis had been undertaken.

Table 1: Summary of Included Study Characteristics

Author	Study Type	Setting	Cancer Type	Surgery Type†	Sample Size	Age in Years	Intervention vs Control	Duration	Attrition	Main Outcome(s) (CI = 95%)	Quality Assessment		
											CERT	ROB2	GRADE
Berkel <i>et al.</i> , (2022)	Single Blind	Home with weekly community facility supervision	Colon Rectal	Laparoscopic:	Total <i>n</i> = 57	Intervention 74 ±7	Intervention (Prehabilitation)	3 weeks	n = 0 for either group	Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI) Intervention: 12 events in 28 patients Control: 21 events in 29 patients OR 0.76, [0.52, 1.10] <i>p</i> = 0.02	67%	Low Risk	⊕⊕⊕○ Moderate
	Randomised Controlled Trial		Non-Metastised	Intervention: 82%	Male = 30 Female = 27	Control 73 ±6	3-weeks of daily physical activity with one 60 minute supervised session of, personalised moderate-to-high intensity interval training per week						
				Control: 72%	Intervention <i>n</i> = 28 Male <i>n</i> =16 (57%) Female <i>n</i> = 12 (43%)		Control: Usual Care						
					Control <i>n</i> = 29 Male <i>n</i> = 14 (48%) Female <i>n</i> = 15 (52%)								
Bousquet-Dion <i>et al.</i> , (2018)	Single Blind	Home-based plus weekly hospital supervised session	Colon Rectal	Laparoscopic:	Total <i>n</i> = 63	Intervention: Median 74 [IQR 67.5–78]	Intervention (Prehabilitation)	4 weeks	Intervention Group: 4	Functional Capacity (6MWD) mean difference from baseline to pre-operative assessments Baseline: Intervention vs Control MD -13.00 [-69.58, 43.58] <i>p</i> = 0.66 Pre-operative: Intervention vs Control MD -1.00 [-57.29, 55.29] <i>p</i> = 0.97 Functional Capacity (6MWD) number of participants increasing walking distance by >20m Intervention: 20 (54%) vs control: 10 (38%) <i>p</i> = 0.26	39%	Some Concerns	⊕⊕⊕○ Moderate
	Parallel arm		Non-Metastised	Intervention: 84%	Male = 46 Female = 27	Age >=75 <i>n</i> = 16 (43%)	Addition of 1 supervised exercise session in addition to current Prehab protocols	Control Group: 6					
	Randomised Controlled Superiority Trial			Control: 81%	Intervention <i>n</i> = 37 Male <i>n</i> =30 (81%) Female <i>n</i> = 7 (19%)	Control: Median 71 [IQR 54.5–74.5]	Control: Standard ERAS® pathway (walking, ankle rotation, breathing exercises)						
					Control <i>n</i> = 26 Male <i>n</i> = 16 (62%) Female <i>n</i> = 10 (38%)	Age >=75 <i>n</i> = 6 (23%)							
Carli <i>et al.</i> , (2020)	Single Blind	Home-based plus weekly hospital supervised session	Colon Rectal	Laparoscopic:	Total <i>n</i> = 110	Intervention: Median: 78 [IQR 72-82]	Intervention: (Prehabilitation)	4 weeks	Intervention Group: 5	Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI) Intervention: 25 out of 55 patients Control: 25 out of 55 patients OR 1.00 [0.47, 2.12] <i>p</i> = 1.0 Functional Capacity (6MWT) - mean difference between baseline and pre-operative assessments Baseline: Intervention vs Control Mean Difference 21.30 [-20.31, 62.91] <i>p</i> = 0.32 Pre-operative: Intervention vs Control Mean Difference 30.30 [-17.86, 78.46] <i>p</i> = 0.23 Total length of hospital stay Intervention median (IQR) 4 (3 to 8) vs control 5 (3 to 9) MD–5.8 (–17.3 to 5.8) <i>p</i> = 0.32	50%	Low Risk	⊕⊕⊕○ Moderate
	Parallel arm		Non-Metastised	Intervention: 76%	Male = 52 (47%) Female = 58 (58%)	Age >=75 <i>n</i> = 32 (58.2%)	Multimodal program involving aerobic and resistance exercise, nutritional, and psychological interventions prior to surgery	Control Group: 5					
	Randomised Controlled Superiority Trial			Control: 81%	Intervention <i>n</i> = 55 Male <i>n</i> = 29 (53%) Female <i>n</i> = 26 (47%)	Control: Median: 82 [IQR 75-84]							
					Control <i>n</i> = 55 Male <i>n</i> = 23 (42%) Female <i>n</i> = 32 (58%)	Age >=75 <i>n</i> = 42 (76.4%)	Control: multimodal programme commenced after surgery Both intervention and control groups were treated within a standardized ERAS® pathway						

											Quality Assessment			
Author	Study Type	Setting	Cancer Type	Surgery Type	Sample Size	Age in Years	Intervention vs Control	Duration	Attrition	Main Outcome(s) CI = 95%	CERT	ROB2	GRADE	
Fulop <i>et al.</i> , (2021)	Single-centre	Home-based plus weekly hospital supervised session	Colon Rectal	Laparoscopic:	Total <i>n</i> = 149	Intervention: Mean: 70 (60–75) IQR [25–87]	Intervention (Prehabilitation):	3 - 6 weeks	Intervention Group: 16	Functional Capacity (6MWT) - mean difference between baseline and pre-operative assessments Baseline Assessment: Intervention vs Control Mean Difference -5.21 [-49.10, 38.68] <i>p</i> = 0.8 Pre-operative Assessment: Intervention: vs Control Mean Difference: 49.88 [5.64, 94.12] <i>p</i> = 0.029 Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI) Intervention: 17 out of 77 patients Control: 16 out of 72 patients OR 0.99 [0.46, 2.15] <i>p</i> = 0.98 Total length of hospital stay Intervention median (IQR) [range] 8 (7–10 [5–47]) vs control 8 (7–9 [5–21]) <i>p</i> = 0.712	58%	Low Risk	⊕⊕⊕○ Moderate	
	Randomised controlled trial		Non-Metastised	Intervention: 91%	Male <i>n</i> = 52 (47%) Female <i>n</i> = 58 (58%)	Control: 90%	Multimodal prehabilitation programme before surgery, in addition to standard ERAS® peri-operative care	Control Group: 18	Male <i>n</i> = 37 (48%) Female <i>n</i> = 40 (52%)		Control <i>n</i> = 72	Male <i>n</i> = 39 (54%) Female <i>n</i> = 33 (46%)	Control: Standard ERAS® protocol supplemented by nutritional assessment	⊕⊕⊕○ Moderate
Lopez-Rodriguez-Arias <i>et al.</i> , (2021)	Single-centre	Home-based	Colon Rectal	Not reported	Total <i>n</i> = 20	Intervention: Median: 66.5 (57.7–70) ±10.2	Intervention:	28.9 ±2.8 days	Intervention Group: 0	Total Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI) Intervention: 2 out of 10 patients Control: 5 out of 10 patients OR 0.25 [0.03, 1.82] <i>p</i> = 0.14 Total length of hospital stay Intervention mean: 4.8 days ±1 vs Control 7.2 days ±3.2 <i>p</i> =0.05	39%	Some Concerns	⊕⊕⊕○ Moderate	
	Randomised controlled trial		Non-Metastised	Male: <i>n</i> = 13 (65%) Female: <i>n</i> = 7 (35%)	Control: 8	Trimodal physical exercise, nutritional supplementation, and relaxation exercise prehabilitation programme performed at home before surgery and the first 30 days after hospital discharge	Control Group: 0	Intervention <i>n</i> = 10 Male: <i>n</i> = 6 (60%) Female: <i>n</i> = 4 (40%)	Control <i>n</i> = 10 Male: <i>n</i> = 7 (70%) Female: <i>n</i> = 3 (30%)		Enhanced recovery after surgery (ERAS®) protocol	⊕⊕⊕○ Moderate		

Author	Study Type	Setting	Cancer Type	Surgery Type	Sample Size	Age in Years	Intervention vs Control	Duration	Attrition	Main Outcome(s) CI = 95%	Quality Assessment		
											CERT	ROB2	GRADE
Minnella <i>et al</i> , (2020)	Single centre	Hospital supervised	Colon Rectal	Not reported	Total <i>n</i> = 42	Intervention: Mean: 67.0, CI 95% (60 to 72) Control: Mean: 67.0, CI 95% (50 to 76)	Supervised High Intensity Interval Training (HIIT) vs Moderate Intensity Continuous Training (MICT), Resistance training and relaxation exercises	4 weeks	Intervention Group: 2	Changes in Aerobic Capacity (VO2AT):	78%	Low Risk	
	Single-blinded		Non-Metastised	Male: <i>n</i> = 26 (62%) Female: <i>n</i> = 16 (38%)	Control Group: 0		Mean difference in oxygen consumption at the anaerobic threshold (VO2AT) between baseline and pre-operative assessments:						
	Randomised controlled study			Intervention <i>n</i> = 21			HIIT: VO2AT mean difference 1.97 (0.75 to 3.19) ml kg-1 min-1 vs MICT: 1.71 (0.56 to 2.85)						
				Male: <i>n</i> = 10 (48%) Female: <i>n</i> = 11 (52%)			3 x per week	Mean difference between groups: 0.26 (-1.41 to 1.94) ml kg-1 min-1 <i>p</i> = 0.753					
				Control <i>n</i> = 21			One month post-surgery: Mean difference between groups: 1.23 [-0.46, 2.92] ml kg-1 min-1 <i>p</i> = 0.15						
				Male: <i>n</i> = 16 (76%) Female: <i>n</i> = 5 (24%)			Total Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI)			⊕⊕⊕○ Moderate			
				Intervention: 5 out of 13 patients Control: 8 out of 14 patients OR 0.47 [0.10, 2.18] <i>p</i> = 0.33									
	Length of Hospital Stay: HIIT: mean 4.1 ±1.15 MICT: mean 4 ±0.68 MD 0.10 [-0.63, 0.83] <i>p</i> = 0.79												
Molenaar <i>et al</i> , (2023)	Two arm	Supervised hospital affiliated training departments or facilities	Colon Rectal	Laparoscopic:	Total <i>n</i> = 251	Median [IQR] age: 69 [60-76] years Intervention: 69 [60-77] years Control: 71 [60-76] years	Intervention: Physical Prehabilitation comprising 2 elements:	4 weeks	Intervention Group: 13	Total Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI)	61% (partial data)	Low Risk	⊕⊕⊕○ Moderate
	Seven Centre		Intervention: 36%	Male: <i>n</i> = 138 (55%) Female: <i>n</i> = 113 (45%)	Control Group: 5		Intervention: 21 out of 123 patients Control: 38 out of 128 patients OR 0.49 [0.27, 0.89] <i>p</i> = 0.02						
	International Randomized Controlled Trial		Control: 21%	Intervention <i>n</i> = 123			2 Resistance Training						
			Male: <i>n</i> = 62 (50.4%) Female: <i>n</i> = 61 (49.6%)	Plus nutritional and psychological support									
			Control <i>n</i> = 128	Smoking cessation if relevant									
			Male: <i>n</i> = 76 (59.4%) Female: <i>n</i> = 52 (40.6%)	Control:					15.6m –1.4 to 32.6; <i>p</i> = 0.07				
				All study sites followed established ERAS® pathway			Length of Hospital Stay, days [IQR] Intervention: 3 [3-5] Control: 3 [3-4] <i>p</i> = 0.2			⊕⊕⊕○ Moderate			

											Quality Assessment		
Author	Study Type	Setting	Cancer Type	Surgery Type	Sample Size	Age in Years	Intervention vs Control	Duration	Attrition	Main Outcome(s) CI = 95%	CERT	ROB2	GRADE
Moug <i>et al.</i> , (2019)	Two arm	Home-based	Rectal	Laparoscopic:	Total <i>n</i> = 48	Mean age of 65.9 years (range 33.7– 82.6)	Intervention:	13 - 17 weeks	Intervention Group: 6	Total Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI)	89%	Some Concerns	⊕⊕⊕○ Moderate
	Feasibility randomized controlled study (Rex)			Intervention: 36%	Male: <i>n</i> =31 (65%) Female: <i>n</i> =17 (35%)	Intervention: Mean age 65.2 (±11.4) Control: Mean age 66.5 (±9.6)	Exercise counselling session followed by a 13–17 week telephone-guided walking programme intended to increase average daily step count		Control Group: 2	Intervention: 12 out of 18 patients Control: 12 out of 22 patients OR1.67 [0.46, 6.06] <i>p</i> = 0.43			⊕⊕⊕○ Moderate
				Control: 21%	Intervention <i>n</i> = 24 Male: <i>n</i> = 18 (75%) Female: <i>n</i> = 6 (25%)					Functional Capacity (6MWT) - mean difference between baseline and pre-operative assessments			
					Control <i>n</i> = 24 Male: <i>n</i> = 13 (54%) Female: <i>n</i> = 11 (46%)					Baseline Assessment: Intervention vs Control Mean Difference 3.81 [-35.09, 42.71] <i>p</i> = 0.85			
										Pre-operative Assessment: Intervention: vs Control Mean Difference: 72.40 [-21.84, 166.64] <i>p</i> = 0.14			
Moug <i>et al.</i> , (2020)	Sub analysis of Moug <i>et al</i> (2019) Rex Study	Home-based	Rectal	Laparoscopic:	Total <i>n</i> = 44	Mean age of 66.8 years (SD ±9.6)	Intervention:	13 - 17 weeks		Changes in Body Composition	89%	Some Concerns	
				Intervention: 36%	Male <i>n</i> =28 (64%) Female <i>n</i> = 16 (34%)		Exercise counselling session followed by a 13–17 week telephone-guided walking programme intended to increase average daily step count in combination with NACRT			Difference in TPI (total psoas index) between baseline pre-operative assessments:			
				Control: 21%	Intervention <i>n</i> = 20 Control <i>n</i> = 24					Intervention: Median increase in TPI of 16.0 mm2/m2			
										Control: Median increase -8.4mm2/m2			
										Group difference in median change from baseline 24.4 mm2/m2, <i>p</i> = 0.07			
Moug <i>et al.</i> , (2020)	Sub analysis of Moug <i>et al</i> (2019) Rex Study	Home-based	Rectal				The control group received standard care in combination with NACRT						

Author	Study Type	Setting	Cancer Type	Surgery Type	Sample Size	Age in Years	Intervention vs Control	Duration	Attrition	Main Outcome(s) CI = 95%	Quality Assessment		
											CERT	ROB2	GRADE
Onerup <i>et al</i> , (2022)	A randomized, parallel, open-label trial in six university or regional hospitals in Sweden	Home-based	Colon Rectal	Laparoscopic:	Total $n = 668$	Age (Years) Mean 68 (± 11)	Intervention: 2 elements to be performed 14 (± 4) days pre-operatively	14 days	Intervention Group: 62	Total Complications measured at 30 days after surgery according to the Comprehensive Complications Index (CCI) Intervention: 21 out of 317 patients Control: 19 out of 351 patients OR 1.24 [0.65, 2.35] $p = 0.5$ Length of Hospital Stay, days Intervention: mean 9 ± 9 Control: mean 9 ± 8 MD 0.00 [-1.30, 1.30] $p = 1.0$	67%	Low Risk	⊕⊕⊕○ Moderate
				Intervention:	Male $n = 400$ (60%) Female $n = 268$ (40%)								
				Non-Metastised									
				Control: 52%									
					Intervention $n = 317$ Male $n = 190$ (60%) Female $n = 127$ (40%) Control $n = 351$ Male $n = 210$ (60%) Female $n = 141$ (40%)		1 Aerobic exercise: Individualized for type of aerobic activity and location, continued for 4 weeks after surgery 2 Inspiratory Muscle Training (IMT), pre-operative only Control: Usual care						

Notes: † The percentage of patients whose surgery was laparoscopic surgery rather than more invasive open surgery
Abbreviations: HIIT - High Intensity Interval Training | OR - Odds Ratio | ERAS® - Enhanced Recovery After Surgery | 6MWD/6MWT - Six Minute Walking Distance/Test | IQR - Interquartile Range | MICT - Moderate Intensity Continuous Training | VO2AT - VO2 At Threshold
MD - Mean Difference | NACRT - Neo-Adjuvant Chemoradiotherapy

3.5 Intervention Characteristics

3.5.1 Intervention Settings

Interventions were undertaken in three types of settings: two were fully hospital based supervised programmes (Minnella *et al.*, 2020; Molenaar *et al.*, 2023), four were home-based with a weekly hospital supervised session (Bousquet-Dion *et al.*, 2018; Carli *et al.*, 2020; Fulop *et al.*, 2021; Berkel *et al.*, 2022) and four were fully home-based (Moug *et al.*, 2019b, 2020; López-Rodríguez-Arias *et al.*, 2021; Onerup *et al.*, 2022). Lopez-Rodrigues-Arias *et al.* (2021) was a home-based intervention during Covid-19 lockdowns in Spain.

3.5.2 Intervention Durations

Interventions duration varied from 14 $\pm$ 4 days (Onerup *et al.*, 2022) to 13-17 weeks (Moug *et al.*, 2019b, 2020) with the remaining 70% of studies being either 3 (Berkel *et al.*, 2022) or 4 weeks (Bousquet-Dion *et al.*, 2018; Carli *et al.*, 2020; Minnella *et al.*, 2020; Fulop *et al.*, 2021; López-Rodríguez-Arias *et al.*, 2021; Molenaar *et al.*, 2023). In one study, the decision to early terminate was made following consideration of how Covid-19 restrictions would impact on the ability to deliver the intervention as planned if continued (Molenaar *et al.*, 2022).

3.5.3 Intervention Types

Eight (80%) studies compared prehabilitation to usual care (Moug *et al.*, 2019b, 2020; Carli *et al.*, 2020; Fulop *et al.*, 2021; López-Rodríguez-Arias *et al.*, 2021; Berkel *et al.*, 2022; Onerup *et al.*, 2022; Molenaar *et al.*, 2023), the remaining two (20%) were superiority trials comparing existing prehabilitation with an enhanced prehabilitation programme (Bousquet-Dion *et al.*, 2018).or high intensity interval training (HIIT) compared to moderate intensity continuous training (MICT) (Minnella *et al.*, 2020). The majority (90%) of interventions were multimodal, comprising of an exercise element combined with nutritional and psychological support. The remaining study, (Berkel *et al.*, 2022), described an exercise only intervention. Table 2 presents intervention characteristics including: exercise frequency, intensity, time and type. Programme adherence and reported adverse effected are also shown.

Table 2 Summary of Study Intervention Characteristics

Author	Prehabilitation Programme	Duration	Frequency	Intensity	Time	Type	Adherence	Adverse Events
Berkel <i>et al.</i> , (2022)	Usual care plus a personalised aerobic and resistance exercise programme prior to surgery supervised by trained physical therapists at a physical therapy practice in the catchment area of both hospitals Unsupervised exercises at home	3 weeks	Home-based Unsupervised: 3 x per week Hospital-based Supervised: 3 x per week	Supervised: Aerobic : HIIT = % VAT at baseline determined by CPET testing Warm up: 50% VAT Main Element: moderate-to-high-intensity exercise at 120% of the work rate achieved at the VAT alternating with active recovery at 50% of the work rate achieved at the VAT. Pedalling frequency throughout the interval training sessions of 60 to 80 revolutions/min. Resistance: Weeks 1 - 3 3 x 8 reps with 60-80 seconds rest 70%, 76%, 82% 1RM Unsupervised Home-based: moderate intensity	Aerobic: 40 minutes (cycle ergometer) Resistance Training: 20 minutes Unsupervised element >30 minutes	Moderate to high intensity interval training (cycle ergometer) Resistance Training: exercises targeting specific muscle groups using foundational movements: hinge, pull, push, brace Unsupervised walking, cycling, sit-to-stand exercises, or stair climbing decided by individual	90% to exercise programme	None
Bousquet-Dion <i>et al.</i> , (2018)	Usual prehabilitation enhanced with the addition "PREHAB+", the addition of 1 supervised exercise session in addition to current Prehab protocols Multimodal home-based exercise program: (1) exercise (2) nutritional (3) psychological interventions	4 weeks	Home Based Unsupervised: Aerobic: 3–4 days per week Resistance Training: 3–4 times per week Hospital Laboratory Supervised: 1 x per week in pre-operative period	Aerobic exercise intensity was prescribed based on the rate of perceived exertion (Borg scale) and from baseline 6MWD metrics. Resistance exercises prescribed were based on 8RM Unsupervised Home-based: Aerobic: Moderate intensity aerobic activity (60–70% of maximal heart rate calculated from the Karvonen formula consisting of either walking, cycling or jogging (according to patient abilities and preference) Resistance Training: 8–15 repetitions, dependent on volitional fatigue (<12 on Borg scale of 0-20) Hospital Laboratory Supervised: Aerobic: 60–70% of maximal heart rate calculated from the Karvonen formula Resistance Training: As for unsupervised	Unsupervised Home-based: 30 minutes per session Resistance Training: no time specified Hospital Laboratory Supervised: 5 minute warm up 30 minutes aerobic 25 minutes resistance training 5 minutes stretching	Unsupervised Home-based: Moderate intensity aerobic activity Resistance Training: eight exercises targeting major muscle groups of the core, upper and lower limbs Hospital Laboratory Supervised: Aerobic: recumbent stepper or a standard treadmill per participant preference and physical ability Resistance Training: eight exercises targeting major muscle groups of the core, upper and lower limbs	98% to multimodal exercise programme	Not reported
Carli <i>et al.</i> , (2020)	Usual care plus a multimodal program involving: (1) exercise (2) nutritional (3) psychological interventions	~4 weeks	Home Based Aerobic: daily Resistance Training: 3–4 times per week Hospital Laboratory Supervised: 1 x per week in pre-operative period	Home based Aerobic: Moderate intensity aerobic activity (60–70% of maximal heart rate calculated from the Karvonen formula) Resistance Training: Up to two sets of a range of 8–15 repetitions, dependent on volitional fatigue Hospital Laboratory Supervised: Aerobic: not reported Resistance Training: not reported	Home Based 30 minutes per day Resistance Training: no time limit Hospital Laboratory Supervised: Aerobic: 30 minutes Resistance Training 5 minute warmup 25 minutes of resistance 5 minutes of stretching	Aerobic: walking, cycling or jogging (according to patient abilities and preference) Resistance Training: eight exercises targeting major muscle groups of the core, upper and lower limbs Exact exercises not reported	68% to prehabilitation programme	None reported

Author	Physical Prehabilitation	Duration	Frequency	Intensity	Time	Type	Adherence	Adverse Events
Fulop <i>et al</i> , (2021)	Usual care plus a home-based trimodal prehabilitation programme consisting: (1) aerobic and breathing exercises (2) nutritional intervention (3) psychological intervention	4 weeks	Home-based: Aerobic - daily Breathing/spirometry exercises 4-5 x per day Hospital supervised: 1 x per week plus assessment, adherence check and intensity increased	Aerobic: Moderate intensity Breathing: to patient's maximal limit	Aerobic: 30 minutes Breathing: 10–15 minutes of incentive spirometer exercises	Aerobic: walking or jogging according to patient abilities Breathing: daily deep breathing/coughing and incentive spirometer exercises	Not reported	Not reported
Lopez-Rodriguez-Arias <i>et al</i> , (2021)	Usual care plus a home-based trimodal prehabilitation programme consisting: (1) aerobic and resistance training (by video) (2) nutritional supplementation (3) relaxation exercises	~4 weeks	Home-based: Daily	Not reported	30 - 45 minutes	Aerobic and resistance training not reported Relaxation exercises such as imagery, visualisation and deep breathing exercises Note: exact protocol requested but not received	Not reported	Not reported
Minnella <i>et al</i> , (2020)	Usual care plus a multimodal programme consisting: (1) Individually supervised, hospital based High intensity interval training (HIIT) (2) Resistance Training (3) Nutritional therapy (4) Anxiety reduction relaxation techniques	4 weeks	Hospital Supervised HIIT: 3 x per week	Endurance Training: four intervals of 2 min at 85 to 90% of peak power, alternating with four intervals of 3 min conducted at 80 to 85% power anaerobic threshold (PAT). Resistance Training: 3 sets x 8 to 12 repetitions.	Endurance Training: 30 minutes	Endurance Training: HIIT (cycle ergometer) Resistance Training: Eight exercises targeting major muscle groups (upper limb, trunk and lower limb)	88.5 ±19.9%	None reported
Molenaar <i>et al</i> , (2023)	Usual care plus a multimodal hospital supervised personalised exercise programme consisting: (1) aerobic and resistance training (2) nutritional support (3) psychological support, (4) smoking cessation advice	4 weeks	Hospital Supervised: 3 x per week	Aerobic High intensity 85-90% peak power as determined at baseline using CPET testing Moderate Intensity 30% peak power Resistance Training 65-70% 1RM for 2 x 10 reps	Total 1 hour per session: Aerobic: High intensity 4 x 2 mins alternating with Moderate intensity 4 x 4 mins plus resistance training	Aerobic: Cycle (preferably) Resistance: Targeting major muscle groups - Note: exact protocol requested but not received	77.20%	7 minor

Author	Physical Prehabilitation	Duration	Frequency	Intensity	Time	Type	Adherence	Adverse Events
Moug <i>et al</i> , (2019)	Usual care plus a walking and behavioural programme aimed at increasing step count week on week (1) Walking programme minimum 13 weeks alongside NACRT (2) Behavioural consultations using two behavioural theoretical frameworks: (a) self-regulatory theory (providing techniques to improve impulse control allowing walking targets to be reached) (b) the health action process approach (replacing behaviours that compromise health with those that enhance health)	13 - 17 weeks	Home-based: Daily	8 weeks consisted of graduated goals calculated from the baseline stepping count to achieve A graduated increase in steps over 5 days of the week corresponding to 150 min of moderate physical activity over the course of the week. For example: Weeks 1–2: extra 1500 steps on at least 3 days a week. Weeks 3–4: extra 1500 steps on at least 5 days a week. Weeks 5–6: extra 3000 steps on at least 3 days a week. Weeks 7–8: extra 3000 steps on at least 5 days a week. Weeks 9–17: maintenance of weeks 7–8 or individually increased		Walking	Not reported	Not reported
Moug <i>et al</i> , (2020)	Usual care plus a walking and behavioural programme aimed at increasing step count week on week (1) Walking programme minimum 13 weeks alongside NACRT (2) Behavioural consultations using two behavioural theoretical frameworks: (a) self-regulatory theory (providing techniques to improve impulse control allowing walking targets to be reached) (b) the health action process approach (replacing behaviours that compromise health with those that enhance health)	13 - 17 weeks	Home-based: Daily	8 weeks consisted of graduated goals calculated from the baseline stepping count to achieve A graduated increase in steps over 5 days of the week corresponding to 150 min of moderate physical activity over the course of the week. For example: Weeks 1–2: extra 1500 steps on at least 3 days a week. Weeks 3–4: extra 1500 steps on at least 5 days a week. Weeks 5–6: extra 3000 steps on at least 3 days a week. Weeks 7–8: extra 3000 steps on at least 5 days a week. Weeks 9–17: maintenance of weeks 7–8 or individually increased		Walking	Not reported	Not reported
Onerup <i>et al</i> , (2022)	Usual care plus a multimodal programme consisting of: (1) Aerobic exercise personalised to individual and location (2) Inspiratory muscle training (IMT) (3) Behavioural support	14 ±4 days	Home-based: Aerobic: Daily IMT: Thirty breaths 2 x daily	Aerobic: medium-intensity activity using the Borg scale of perceived exertion scale IMT: starting with a resistance of 30% of maximal inspiratory pressure with a threshold IMT device	Aerobic: 30 minutes in addition to usual physical activity routine	Aerobic: individualized in terms of type of aerobic activity and location Inspiratory Muscle Training breathing exercises	Not reported	None reported

Abbreviations: **HIIT** - High Intensity Interval Training | **CPET** - Cardiopulmonary Exercise Test | **VAT** - Ventilatory Anaerobic Threshold | **1RM** - One Repetition Maximum | **6MWD** - Six Minute Walk Distance | **8RM** - Eight Repetitions Maximum
IMT - Inspiratory Muscle Training

3.5.4 Intervention Outcomes

There were 25 different primary and intermediate outcomes across all ten studies which resulted in a total of 45 outcome measures. Outcome measures utilised were both quantitative (86% of outcomes) and qualitative (14% of outcomes). A summary of instruments used by each study per outcome can be found in Appendix 3.1.

Outcomes are grouped into post-surgical complications, length of hospital stay, functional capacity, aerobic capacity, psychological and health related quality of life, and “other”.

Post-surgical complications and length of hospital stay were both measured in 9 studies and account for 40% of all outcome measures. Functional capacity (9 studies and 20% of outcomes) was assessed by 6MWD (Moug *et al.*, 2019b; Carli *et al.*, 2020; Fulop *et al.*, 2021; Molenaar *et al.*, 2023), the number of participants increasing walking distance by >20m (Bousquet-Dion *et al.*, 2018), increased step count (Moug *et al.*, 2019b), median step count (Moug *et al.*, 2020) and grip strength (Bousquet-Dion *et al.*, 2018; Molenaar *et al.*, 2023). Aerobic capacity (5 studies and 11% of outcomes), was measured by VO₂ at ventilatory threshold (VO₂ at VAT) (Berkel *et al.*, 2022), peak VO₂ (Minnella *et al.*, 2020; Molenaar *et al.*, 2023), respiratory reserve (Fulop *et al.*, 2021) and ventilatory reserve (Minnella *et al.*, 2020). Psychological and health related quality of life outcomes (4 studies and 9% of outcomes), was measured by the Hospital Anxiety and Depression Scale (HADS) (Carli *et al.*, 2020; López-Rodríguez-Arias *et al.*, 2021), patient reported outcome measures (PROMS) (Carli *et al.*, 2020) and Health Related Quality of Life (Molenaar *et al.*, 2023). Other health and performance related outcomes reported were changes in body composition and self assessed physical recovery (Onerup *et al.*, 2022), hospital readmission (Berkel *et al.*, 2022), adverse events (Berkel *et al.*, 2022), and energy expenditure (Bousquet-Dion *et al.*, 2018). Procedural outcomes were also included: patient acceptance (Moug *et al.*, 2019b), patience adherence (Moug *et al.*, 2019) and fidelity with protocol (Moug *et al.*, 2019). Heterogeneity of outcomes prevented pooled meta-analysis for all outcomes to determine overall intervention effects however it was possible for post-surgical complications, length of

hospital stay and functional capacity. Individual intervention results are shown in Table 1.

3.5.5 Post-surgical Complications

Nine studies reported complications recorded 30 days post-surgery measured according to the Comprehensive Complication Index (Tamini *et al.*, 2021) and classified according to the Clavien-Dindo scale (Dindo, Demartines and Clavien, 2004). Meta-analysis (figure 4) showed that prehabilitation had a small but not statistically significant beneficial effect (OR 0.8 95%CI [0.60, 1.06], $p=0.14$). Sensitivity analysis showed that four studies indicated a significant benefit from prehabilitation (OR 0.42 95%CI [0.26, 0.68], $p= 0.0005$) (Minnella *et al.*, 2020; López-Rodríguez-Arias *et al.*, 2021; Berkel *et al.*, 2022; Molenaar *et al.*, 2023), two studies showed no benefit from prehabilitation (OR 1.00 95%CI [0.58, 1.71], $p = 0.99$) (Carli *et al.*, 2020; Fulop *et al.*, 2021) and the remaining three favoured usual care (OR 1.33 95%CI [0.80, 2.20], $p = 0.27$) (Bousquet-Dion *et al.*, 2018; Moug *et al.*, 2019; Onerup *et al.*, 2022).

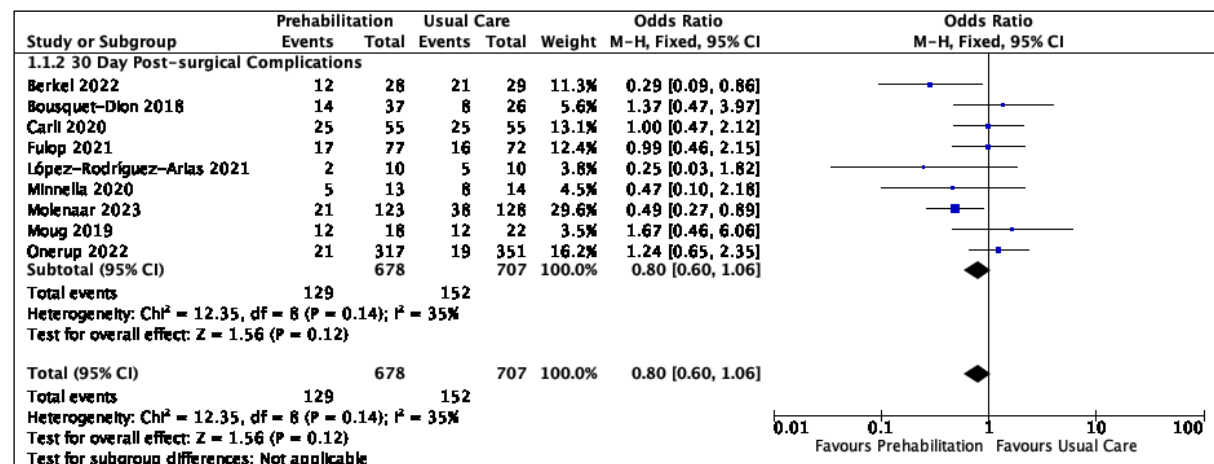


Figure 4 Meta-analysis of post-surgical complications

3.5.6 Length of Hospital Stay

The same nine studies also reported total length of hospital stay. Meta-analysis (figure 5) indicated a not statistically significant increase in hospital stay in the prehabilitation intervention group (MD 0.16 days 95%CI -0.18, 0.50; $p = 0.35$). Pooled sub-analysis of the studies reporting a reduction in the length of hospital stay

resulted in a statistically significant reduction of 0.99 days (MD -0.99 days 95%CI -1.89, -0.09; $p = 0.03$). One study, (Moug et al., 2019b), reported a mean stay of 16.3 days in the intervention group, a far higher mean length of stay than the other studies. Sensitivity analysis to remove this study effected the pooled mean difference of the remaining studies by -0.01 days from (MD 0.16 days 95%CI -0.18, 0.50; $p = 0.35$) to (MD 0.15 days 95%CI -0.20, 0.50; $p = 0.39$).

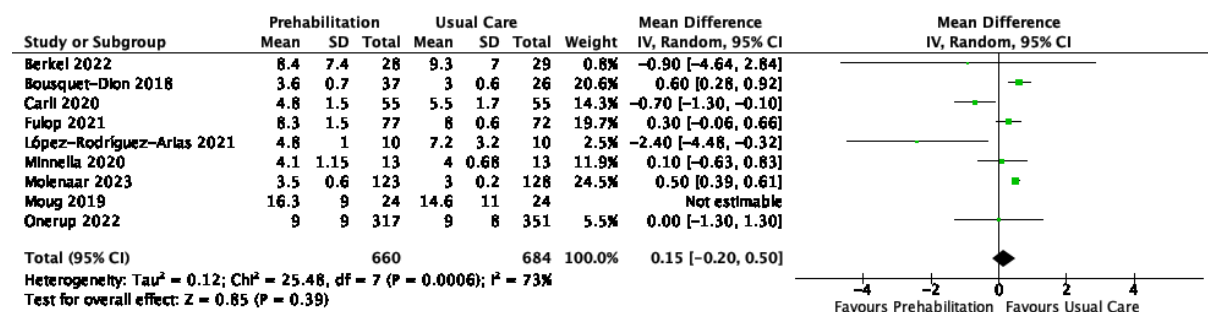


Figure 5 Meta-analysis of length of hospital stay

3.5.7 Functional Capacity

Functional capacity measured by 6MWT was reported in nine studies. Five studies provided total metres walked in the 6MWT at baseline assessment. Four of the five studies also provided mean differences in walking distances achieved between baseline and pre-operative assessments, three reported 4-week post-operatively, and two reported 8-weeks post-operatively. Meta-analysis (figure 6) identified that at baseline, the pooled mean 60minute walking distance 3.48 metres (95%CI: -23.97, 17.01; $p = 0.74$) less in the intervention group compared to the control group but not statistically significant. The prehabilitation group mean difference between baseline and pre-operative assessment was statistically significantly greater (33.85 metres 95%CI: 6.84, 60.87; $p = 0.01$) than the control group). At the 4-week post-operative assessment, the prehabilitation group mean difference was still greater than the control group though the difference was not statistically significant (9.24 metres 95%CI -20.16, 38.64; $p = 0.54$). At 8-weeks post-surgery, mean difference was in favour of the control group, though the difference was not statistically significant (7.92 metres 95%CI -41.31, 25.47; $p = 0.64$).

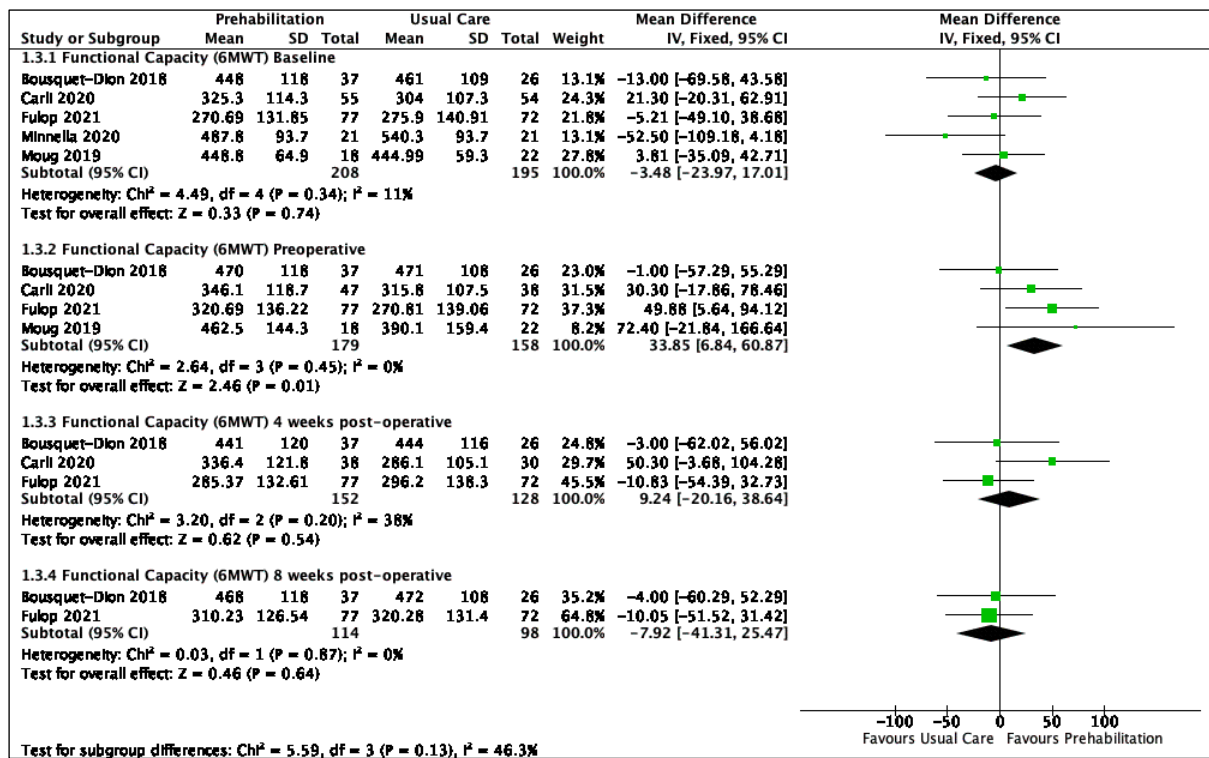


Figure 6 Meta-analysis of length of functional capacity (6MWD)

3.5.8 Adherence and Adverse Events

Adherence to the intervention was recorded in five studies. The highest reported adherence was 98% (Bousquet-Dion *et al.*, 2018), the lowest 68% (Carli *et al.*, 2020). Four studies analysed adverse events with one reporting 7 intervention related minor events (dizziness, nausea) deemed not sufficiently serious to prevent continuation with the programme (Molenaar *et al.*, 2023).

4 DISCUSSION

4.1 Review Results in the context of recent literature

Colorectal cancer represents the second highest cause of cancer related deaths in the UK, accounting for 16,500 deaths on average per annum (Bowel Cancer UK, 2022a). Ninety four percent of cancer diagnoses are over-50s with 59% over the age of seventy. Surgery is the main treatment, accompanied by chemo or radiotherapy dependent on tumour type and stage (Cancer Research UK, 2022d, 2022c). Resection of the large intestine carries a high risk of post-operative complication (Tevis and Kennedy, 2016) which ERAS® guidelines are intended to mitigate (Gustafsson *et al.*, 2019). The guidelines include nutritional and psychological support however to date, physical prehabilitation has been excluded due to a lack of high-quality evidence of its effectiveness on clinical outcomes (Gustafsson *et al.*, 2019). The aims of this review were twofold: (i) to critically evaluate research published since 2018 to assess the effectiveness of physical prehabilitation interventions for colorectal cancer surgery clinical outcomes, and (ii) to validate whether the literature evaluated is of sufficiently high quality to support a recommendation for the inclusion of physical prehabilitation in ERAS® guidelines.

In contrast to previous systematic reviews and meta-analyses of major abdominal cancer surgery (Hughes *et al.*, 2019; Thomas *et al.*, 2019; Heger *et al.*, 2020; Waterland *et al.*, 2021), this review and meta-analysis included randomized controlled trials of physical prehabilitation interventions specific to colon and rectal cancer patients preparing for surgery and additionally, in the case of rectal surgery, NACRT prior to surgery. The number of participants (1452) across all ten studies was higher than other systematic reviews and meta-analyses and at a pooled level, this review found that physical prehabilitation had a statistically significant improvement on functional capacity pre-operatively, and at 4-weeks post-surgery had a beneficial, albeit not statistically significant, effect on post-surgical complications. Conversely, length of hospital stay was marginally longer for the prehabilitation cohort. These findings are important because they strengthen the existing literature relating to the beneficial effect of physical prehabilitation on functional capacity and post-operative complications and were in line with the

findings of a 2022 systematic review of exercise-based prehabilitation in colorectal cancer patients (Falz *et al.*, 2022). Falz *et al* (2022) reported similar results for post-surgical complications and length of hospital stay. Notably, their reporting of a statistically significant pre-operative difference in functional capacity (6MWT distance) was in favour of the prehabilitation group. The difference between the statistically non-significant finding for functional capacity in this review compared to Falz *et al* may be explained by their inclusion of feasibility studies, protocols/process evaluations or specific sample characteristics which had been excluded from this review.

A systematic review of six studies by Looijaard *et al* (2018) found no evidence of benefit from either physical nor nutritional prehabilitation on complications or length of hospital stay outcomes in “older” colorectal cancer surgery patients aged between 64 and 73 (Looijaard *et al.*, 2018). Lund *et al* (2020) focussed on the effects of physical prehabilitation in 8 studies of middle-aged colorectal cancer patients undergoing chemotherapy, finding “low level of evidence for a small beneficial effect of exercise” using self-reported physical function assessments. Their systematic review included a reassuring conclusion that physical exercise is safe in the study population (Lund *et al.*, 2020). A Cochrane review of sixteen studies (992 participants) by McGettigan *et al* (2020) reported increased aerobic capacity in the immediate term but was unable to report on medium or longer-term effects (McGettigan *et al.*, 2020). Teo *et al* (2020) reviewed six studies (452 participants), of which three studies reported statistically significant differences in favour of prehabilitation in 6MWT distances. Their review also found statistically significant improvements in self-reported activity levels in two studies. Complications and length of hospital stay outcome results mirrored those of this review (Teo, Turner and Self, 2020). Finally, a meta-analysis of fifteen studies (1306 participants) by Zhang *et al* (2022) found no statistically significant effects from pre-operative exercise on physical capacity, reduction of complications or length of hospital stay (Zhang *et al.*, 2022)

A common theme across recent studies and reviews is the evaluation of physical and/or aerobic capacity at baseline assessment and prior to surgery. Major abdominal surgery is a form of controlled trauma on the body (Finnerty *et al.*, 2013),

carrying considerable risks in a population already compromised by age and physical condition due to cancer related cachexia (Ryan *et al.*, 2016). Improving physical and aerobic capacity increases the body's response to stress in advance of surgery and neo-adjuvant therapies, the resultant desired effect being earlier recovery of physical function and mobility leading to reduced post-surgical complications (Van Rooijen *et al.*, 2019). Prehabilitation is the means of producing the required physical adaptations yet, at the current time and despite a growing body of evidence supporting physical prehabilitation, the heterogeneity in exercise intervention durations, frequencies, intensities, and modalities means there is no consensus in the literature on the optimal exercise "dose" required to achieve the desired patient outcomes.

The majority of colorectal cancer patients are over fifty (Cancer Research UK, 2022b) and this is represented in physical prehabilitation research sample populations. Three of the studies in this review involving walking interventions (Moug *et al.*, 2019, 2020; Fulop *et al.*, 2021) reported improvements at the pre-operative assessment compared to only one of the HIIT interventions (Molenaar *et al.*, 2023) reporting improvements. The remaining HIIT and MICT interventions reported inferior outcomes (Bousquet-Dion *et al.*, 2018; Carli *et al.*, 2020; Minnella *et al.*, 2020; Berkel *et al.*, 2022). Walking interventions in the form of either a target time per day or incremental increases in step count appear to be as effective as HIIT and superior to MICT and may be better tolerated. Interventions such as home-based walking are accessible, and free (unless trackers are to be used), making this type of physical prehabilitation both cost effective and generalizable to a growing number of patients at a time when NHS services and resources are already facing unprecedented demand.

4.2 Review Limitations

4.2.1 Limitations in the evidence included

Due to the criteria selection, population and nature of the condition, recruitment to prehabilitation intervention trials in colorectal cancer can take a considerable period to achieve a suitably powered study sample. Half of the studies had small sample sizes with less than 50 participants in each group and half were underpowered

according to their stated sample size requirement, which has been reflected in the Grade evaluation. This review was as much about evaluating the exercise intervention design quality as it was about the resulting outcomes. CERT assessment revealed inadequate reporting of the intervention modality, highlighting a lack of precision in reporting exact exercise, exercise progression, and motivation strategies in up to eight of the studies included. This raises concerns around consistency, maximal participant effort and engagement with exercise. Adverse effects and participant acceptance of programmes were not generally reported meaning it was not possible to analyse adverse events according to exercise intensity. Heterogeneity in intervention type, protocols, outcomes and reporting formats limited the opportunity to complete meaningful analysis across all studies.

4.2.2 Limitations of the review process

This was the first systematic review undertaken by the author. As far as possible, PRISMA 2020 guidelines (Page *et al.*, 2021) were followed however database searching, MESH terms and quality evaluation tools were all new and had to be researched prior to use. Data, supplementary information, and protocols were missing or not available for all studies. Corresponding authors were contacted by email, however no responses were received and therefore the information extracted to summary tables was incomplete for the studies in question.

4.3 Future Research

The evidence from this and other recent reviews suggests that physical prehabilitation interventions have a beneficial effect on physical capacity prior to surgery. The evidence also leans towards physical prehabilitation reducing the number of post-operative complications. A number of factors need to be considered when designing physical prehabilitation programmes. Age, and poor physical and mental state at diagnosis may inhibit participant recruitment to an unknown intervention at a time when they may be feeling particularly vulnerable. There may be learnings from the successful recruitment of other studies to be applied to future study designs. Suitably powered multi-arm randomized controlled trials with homogenous outcomes and standardised protocols are needed to compare usual care with low, moderate and high intensity exercise interventions to establish the

most effective mode(s) for prehabilitation. This would move the evidence toward the grade of certainty required for the inclusion of physical prehabilitation in future ERAS® guidelines.

Colorectal resection surgery is also routinely required by patients with Inflammatory Bowel Disease and carries the same risks as surgery for colorectal cancer. In the lead up to surgery, physical condition can become extremely poor therefore future research may also be relevant for physical prehabilitation guidelines for IBD patients undergoing elective surgery.

Word Count: 8092

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APPENDICES

APPENDIX 1: METHOD SUPPORTING DOCUMENTS

- 1.1 DATABASE SEARCH RESULTS HANDLING PROCESS STEPS
- 1.2 SEARCH RESULTS FILES INDEX
- 1.3 CONSOLIDATED AND DE-DUPLICATED SEARCH RESULTS FILES INDEX

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- 2.3 GRADE_{pro} STUDY OUTCOME EVALUATION SUMMARY TABLES

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- 3.1 SUMMARY OF OUTCOMES AND MEASURES BY STUDY

APPENDIX 1

METHOD SUPPORTING DOCUMENTS

APPENDIX 1.1 – DATABASE SEARCH RESULTS HANDLING PROCESS STEPS

Results File Consolidation

Individual search result .csv files for each database search were imported to separate tabs within Excel spreadsheets and all records were consolidated into a single file per database to facilitate analysis and study selection purposes.

Consolidated files were saved as the new files detailed in the “Search Results Files Index” in Appendix 1.3.

Search Results Analysis – Duplicate Records Handling

Dependent on the database, results file formats varied. To combine all results and remove duplicate results would have been an extremely time-consuming process, therefore initial screening for duplicates found on each consolidated database results file was completed using search type unique identifiers.

Cochrane Results Files

All imported results were consolidated into a single worksheet. Duplicates were identified and removed using the “Cochrane Review ID” field.

PubMed Results Files

All imported results were consolidated into a single worksheet. Duplicates were identified and removed using the “PMID” field.

Google Scholar Results Files

All imported results were consolidated into a single worksheet. Duplicates were identified and removed using the “title” field.

ProQuest Results Files

The single results file was checked for duplicate records using the “storeid” field.

Ovid MedLine Results Files

The single results file was checked for duplicate records using the “DO” field.

Clinicaltrial.gov Results Files

All imported results were consolidated into a single worksheet. Duplicates were identified and removed using the “NCT number” field.

CENTRAL Trials Register Results Files

All imported results were consolidated into a single worksheet. Duplicates were identified and removed using the “CENTRAL ID” field.

Consolidated files with duplicates removed were saved as new files detailed in the “Consolidated and De-Duplicated Search Results Files Index” in Appendix 1.3.

Search Results – Exclusion of Records not meeting study type criteria

Remaining database search results were manually searched for the terms “Colorectal Cancer”, “Prehabilitation” and “Randomised (/Randomized) Controlled (/Clinical) Trial”. Where the subject was not clear from the study title, the Abstract was briefly reviewed to ascertain the type and/or subject of the study. Studies were coded to identify study characteristics and marked for inclusion or exclusion for title and abstract screening. Coded files were saved as detailed in the “Coded Results Files Index” in Appendix 1.4.

APPENDIX 1.2 - SEARCH RESULTS FILES INDEX

SEARCH RESULTS FILES INDEX

COCHRANE LIBRARY SEARCH RESULTS

Results File 1	2023 01 29 Cochrane Review Search.csv
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OVID MEDLINE DATABASE SEARCH RESULTS FILES

Results File 1	2023 01 29 Ovid MedLine MeSH Subject Heading Search.xls
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PROQUEST DATABASE SEARCH RESULT FILE

Results File 1	2023 01 29 ProQuest Results Download.xls
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PUBLISH OR PERISH GOOGLE SCHOLAR DATABASE SEARCH RESULTS FILES

Results File 1	2023 01 29 PoP Google Scholar 2018 - 2019 Search.csv
Results File 2	2023 01 29 PoP Google Scholar 2019 - 2020 Search.csv
Results File 3	2023 01 29 PoP Google Scholar 2020 - 2021 Search.csv
Results File 4	2023 01 30 PoP Google Scholar 2021 - 2022 Search.csv
Results File 5	2023 01 29 PoP Google Scholar 2022 - 2023 Search.csv

PUBMED DATABASE SEARCH RESULT FILES

Results File 1	2023 01 29 PubMed MeSH Term Search RCT only.csv
Results File 2	2023 01 29 PubMed MeSH Term Search.csv
Results File 3	2023 01 29 PubMed Title_Abtract Search RCT only.csv
Results File 4	2023 01 29 PubMed Title_Abtract Search.csv

CENTRAL CLINICAL TRIALS DATABASE SEARCH RESULT FILES

Results File 1	2023 01 29 CENTRAL Colorectal Cancer Preoperative Exercise.csv
Results File 2	2023 01 29 CENTRAL Colorectal neoplasm preoperative exercise.csv
Results File 3	2023 01 29 CENTRAL RCT Search.csv

Clinicaltrial.gov DATABASE SEARCH RESULT FILES

Results File 1	2023 01 29 Clinicaltrial Colorectal Cancer and Prehabilitation.csv
Results File 2	2023 01 29 Clinicaltrial Colorectal Cancer and Preoperative Exercise.csv
Results File 3	2023 01 29 Clinicaltrial Colorectal Neoplasms and Prehabilitation.csv
Results File 4	2023 01 29 Clinicaltrial Colorectal Neoplasms and Preoperative Exercise.csv

ICTRP DATABASE SEARCH RESULT FILES

Results File 1	2023 02 07 ICTRP Colorectal Cancer Exercise Search Results.xlsx
Results File 2	2023 02 07 ICTRP Colorectal Cancer Prehabilitation Search Results.xlsx

APPENDIX 1.3 – CONSOLIDATED AND DE-DUPLICATED SEARCH RESULTS FILES INDEX

CONSOLIDATED AND DE-DUPLICATED SEARCH RESULTS FILES INDEX

COCHRANE LIBRARY SEARCH RESULTS

Consolidated Results File	2023 01 30 Search Files - Consolidated Imported Data - Cochrane.xlsx
---------------------------	--

OVID MEDLINE DATABASE SEARCH RESULTS FILES

Consolidated Results File	2023 01 30 Search Files - Imported Data - Ovid MedLine.xls
---------------------------	--

PROQUEST DATABASE SEARCH RESULT FILE

Consolidated Results File	2023 01 30 Search Files - Imported Data - ProQuest.xls
---------------------------	--

PUBLISH OR PERISH GOOGLE SCHOLAR DATABASE SEARCH RESULTS FILES

Consolidated Results File	2023 01 30 Search Files - Consolidated Imported Data - Google Scholar.xlsx
---------------------------	--

PUBMED DATABASE SEARCH RESULT FILES

Consolidated Results File	2023 01 30 Search Files - Consolidated Imported Data - PubMed.xlsx
---------------------------	--

CENTRAL CLINICAL TRIALS DATABASE SEARCH RESULT FILES

Consolidated Results File	2023 01 30 Search Files - Consolidated Imported Data - CENTRAL.xlsx
---------------------------	---

Clinicaltrial.gov DATABASE SEARCH RESULT FILES

Consolidated Results File	2023 01 30 Search Files - Consolidated Imported Data - Clinicaltrial.xlsx
---------------------------	---

ICTRP DATABASE SEARCH RESULT FILES

Consolidated Results File	2023 02 07 Search Files - Consolidated Imported Data - ICTRP.xlsx
---------------------------	---

APPENDIX 1.4 – CODED SEARCH RESULTS FILES INDEX

CODED SEARCH RESULTS FILES INDEX

CENTRY SEARCH RESULTS

Coded Results File	2023 02 09 Search Files - Consolidated Imported Data - CENTRAL CODED.xlsx
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OVID MEDLINE DATABASE SEARCH RESULTS FILES

Coded Results File	2023 02 02 Search Files - Consolidated Imported Data - Ovid MedLine CODED.xls
--------------------	---

PROQUEST DATABASE SEARCH RESULT FILE

Coded Results File	2023 02 01 Search Files - Consolidated Imported Data - ProQuest CODED.xlsx
--------------------	--

PUBLISH OR PERISH GOOGLE SCHOLAR DATABASE SEARCH RESULTS FILES

Coded Results File	2023 01 30 Search Files - Consolidated Imported Data - Google Scholar CODED.xlsx
--------------------	--

PUBMED DATABASE SEARCH RESULT FILES

Coded Results File	2023 02 01 Search Files - Consolidated Imported Data - PubMed CODED.xlsx
--------------------	--

CENTRAL CLINICAL TRIALS DATABASE SEARCH RESULT FILES

Coded Results File	2023 01 30 Search Files - Consolidated Imported Data - CENTRAL.xlsx
--------------------	---

APPENDIX 2

QUALITY ASSESSMENT SUPPORTING DOCUMENTS

APPENDIX 2.1 RISK OF BIAS (ROB2) EVALUATIONS

Study	D1	D2	D3	D4	D5	Overall	
Berkel et al (2022)	+	+	+	+	+	+	+
Bousquet-Dion et al (2018)	+	?	+	+	+	!	?
Carli et al (2020)	+	+	+	+	+	+	+
Fulop et al (2021)	+	+	+	+	+	+	+
Lopez-Rodriguez-Arias (2021)	?	+	+	+	+	!	?
Minnella et al (2020)	+	+	+	+	+	+	+
Molenaar et al (2023)	+	+	+	+	+	+	+
Moug et al (2019)	+	?	+	?	+	!	?
Moug et al (2020)	+	?	+	?	?	!	?
Onerup et al (2022)	+	+	+	+	+	+	+

-  Low risk
 Some concerns
 High risk
- D1 Randomization process
 D2 Deviations from intended interventions
 D3 Missing outcome data
 D4 Measurement of the outcome
 D5 Selection of the reported result

APPENDIX 2.2 CONSENSUS OF EXERCISE REPORTING TEMPLATE (CERT) MATRIX OF INCLUDED STUDIES

MATRIX OF CONSENSUS OF EXERCISE REPORTING TEMPLATE (CERT) ITEMS REPORTED IN INCLUDED STUDIES

CERT Question Number	CERT Question	Berkel <i>et al.</i> , (2022)	Bousquet-Dion <i>et al.</i> , (2018)	Carli <i>et al.</i> , (2020)	Fulop <i>et al.</i> , (2021)	Lopez-Rodriguez- Arias <i>et al.</i> , (2021)	Minnella <i>et al.</i> , (2020)	Molenaar <i>et al.</i> , (2023)*	Moug <i>et al.</i> , (2019)	Moug <i>et al.</i> , (2020) *Subset of 2019 study	Onerup <i>et al.</i> , (2022)	Reporting Frequency %
1	Detailed description of the type of exercise equipment	Y	N	P	Y	Y	Y	N	Y	Y	N	70%
2	Detailed description of the qualifications, expertise and/or training	N	N	Y	Y	N	Y	Y	Y	Y	Y	70%
3	Describe whether exercises are performed individually or in a group	N	N	N	P	Y	Y	N	Y	Y	Y	60%
4	Describe whether exercises are supervised or unsupervised; how they are delivered	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
5	Detailed description of how adherence to exercise is measured and reported	N	N	Y	Y	N	Y	Y	Y	Y	Y	70%
6	Detailed description of the motivation strategies	N	N	N	N	N	Y	N	Y	Y	N	30%
7a	Detailed description of the decision rule(s) for determining exercise progression	Y	N	N	Y	N	N	N	Y	Y	N	40%
7b	Detailed description of how the exercise program was progressed	Y	N	N	N	N	N	N	Y	Y	N	30%
8	Detailed description of each exercise to enable replication	N	N	N	Y	Y	N	N	N	N	N	20%
10	Describe whether there are any non-exercise components	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
11	Describe the type and number of adverse events that occur during exercise	Y	N	Y	N	N	Y	Y	Y	Y	Y	70%
12	Describe the setting in which the exercises are performed	Y	Y	Y	Y	Y	Y	Y	N	N	Y	80%
13	Detailed description of the exercise intervention	Y	N	N	Y	N	Y	Y	Y	Y	Y	70%
14a	Describe whether the exercises are generic (one size fits all) or tailored	Y	N	Y	Y	Y	Y	Y	Y	Y	N	80%
14b	Detailed description of how the exercises are tailored to the individual	Y	N	N	N	N	Y	N	Y	Y	Y	50%
15	Describe the decision rule for determining the starting level	Y	Y	N	N	N	N	Y	Y	Y	Y	60%
16a	Describe how adherence or fidelity is assessed/measured	Y	Y	P	N	N	Y	Y	Y	Y	Y	80%
16b	Describe the extent to which the intervention was delivered as planned	N	Y	N	N	N	Y	Y	Y	Y	Y	60%
CERT Total Score		12	7	9	10.5	7	14	11	16	16	12	114.50
Percentage		67%	39%	50%	58%	39%	78%	61%	89%	89%	67%	64%

* supplemental protocol information unavailable, assessed using journal article information only | P = partly reported, scored as 0.5

APPENDIX 2.3 GRADEpro SUMMARY OF FINDINGS TABLES

SUMMARY OF FINDINGS TABLE – POST-OPERATIVE COMPLICATIONS AND LENGTH OF HOSPITAL STAY

Patient or population: Colorectal cancer surgery patients

Setting: Hospital/Home-based

Intervention: Prehabilitation

Comparison: Usual Care/HIIT vs MICT

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Prehabilitation
30-day post-operative surgical complications assessed with: CCI and Clavien-Dindo index	1385 (9 RCTs)	⊕⊕⊕○ Moderate ^a	OR 0.80 (0.71 to 1.04)	215 per 1,000	35 fewer per 1,000 (52 fewer to 7 more)
Length of Hospital Stay	1385 (9 RCTs)	⊕⊕⊕○ Moderate ^a	-		MD 0.16 days more (0.18 fewer to 0.5 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded due to the number of studies with a small sample size

SUMMARY OF FINDINGS TABLE – 6MWD

Patient or population: Colorectal cancer surgery patients
Setting: Hospital/Home-based
Intervention: Prehabilitation
Comparison: Usual Care/HIIT vs MICT

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Prehabilitation
Functional Capacity (6MWT) - at baseline assessed with: 6MWT	403 (5 RCTs)	⊕⊕⊕○ Moderate	-		MD 3.48 metres lower (23.97 lower to 17.01 higher)
Functional Capacity: mean difference in metres walked between baseline and preoperative tests assessed with: 6MWT	337 (4 RCTs)	⊕⊕⊕○ Moderate	-		MD 33.85 metres higher (6.84 higher to 60.87 higher)
Functional Capacity mean difference between groups in metres walked 4 weeks post-surgery assessed with: 6MWT	280 (3 RCTs)	⊕⊕⊕○ Moderate	-		MD 9.24 metres higher (20.16 lower to 38.64 higher)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

SUMMARY OF FINDINGS TABLE – 6MWD

Patient or population: Colorectal cancer surgery patients
Setting: Hospital/Home-based
Intervention: Prehabilitation
Comparison: Usual Care/HIIT vs MICT

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Prehabilitation

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

APPENDIX 3

RESULTS SUPPORTING DOCUMENTS

APPENDIX 3.1 SUMMARY OF OUTCOMES AND MEASURES BY STUDY

Author	Study Type	Setting	Participants	Outcome(s)	Measures
Berkel <i>et al.</i> , (2022)	Single Blind	Supervised using community based	n = 57 Male n = 30 (52.6%)	1 30 day post-operative complications	CCI & Clavien-Dindo
	Randomised Controlled Trial	hospital affiliated facilities	Female n = 27 (47.4%) Mean Age: 73.6 (±6.1) years	2 Changes in aerobic capacity 3 Length of hospital stay 4 Unplanned readmissions at 30 and 90 days 5 Adverse events	CPET VO2 at VAT Hospital Records Hospital Records Assessor Records
Bousquet-Dion <i>et al.</i> , (2018)	Single Blind	Home-based plus weekly hospital supervised session	n = 63 Male n = 46 (73%)	1 Functional walking capacity (>20m change)	6MWD
	Parallel arm Randomised Controlled Superiority Trial		Female n = 17 (27.0%)	2 Energy Expenditure 3 Grip Strength	METS Dynamometry
Carli <i>et al.</i> , (2020)	Single Blind	Home-based plus weekly hospital supervised session	n = 110 Male: n = 52 (47.3%)	1 30 day post-operative complications	CCI & Clavien-Dindo
	Parallel arm Randomised Controlled Superiority Trial		Female: n = 58 (52.7%) Mean Age: 78 (± 7) years	2 Length of hospital stay 3 Recovery of walking capacity 4 Patient-reported outcome measures	Hospital Records 6MWD HADS, SF-36
Fulop <i>et al.</i> , (2020)	Single-centre	Home-based plus weekly hospital supervised session	n = 149 Male: n = 76 (51%)	1 Physical Functional Capacity	6MWD
	Randomised controlled trial		Female: n = 73 (49%)	2 Respiratory Reserve 3 Length of hospital stay	Spirometry Hospital Records
Lopez-Rodriguez-Arias <i>et al.</i> , (2021)	Single-centre	Home-based	n = 20 Male: n = 13 (65%)	1 Body Composition Changes	Weight, Lean/Fat Mass %
	Randomised controlled trial		Female: n = 7 (35%) Median age: 66 (61.8 – 71.5) ±9.4 years	2 Depression/Anxiety 3 Length of hospital stay 4 Complications	HADS Hospital Records CCI & Clavien-Dindo
Minnella <i>et al.</i> , (2020)	Two arm Feasibility randomized controlled study (Rex)	Home-based	n = 42	1 Changes in aerobic capacity 2 Peak VO2 3 Ventilatory efficiency 4 Physical Functional Capacity	CPET VO2 at VAT CPET CPET (EV/VO2) 6MWT
Molenaar <i>et al.</i> , (2023)	Two arm Seven Centre International Randomized Controlled Trial	Supervised hospital affiliated training departments or facilities	n = 251 Male: n = 138 [55.0%] Female: n = 113 [45.0%] Median [IQR] age: 69 [60-76] years	1 30 day post-operative complications 2 Functional capacity: change in metres walked 3 Health Related Quality of Life (HRQoL) 4 Peak VO2 5 Ventilatory efficiency 5 Grip strength (1RM)	CCI & Clavien-Dindo 6MWT EORTC-QLQ-C30 Peak VO2 VO2AT Dynamometry
Moug <i>et al.</i> , (2019)	Two arm Feasibility randomized controlled study (REx)	Home-based	n = 48 Male: n=31 (65%) Female: n=17 (35%) Mean age of 65.9 years (range 33.7– 82.6)	1 Patient acceptance 2 Patient adherence 3 Fidelity with protocol 4 Median step count 5 Functional walking capacity	Consent, questionnaire Attendance Assessor Records Pedometry 6MWT
Moug <i>et al.</i> , (2020)	Subanalysis from the REx randomised controlled trial	Home-based	n = 44 Male n=28 (64%) Female n= 16 (34%) Mean age of 66.8 years (SD ±9.6)	1 Increased step count 2 Changes in body muscle mass	Pedometry Bioimpedence
Onerup <i>et al.</i> , (2022)	Randomized Parallel arm Non-blinded Randomized controlled trial	Home-based	n = 668 Gender Female n = 268 (40%) Male 4 n = 400 (60%) Mean Age: n = 68 (±11) years	1 Self assessed physical recovery 2 Complications 3 Length of hospital stay	Likert Questionnaire CCI & Clavien-Dindo Hospital Records