Efficacy of supervised exercise prehabilitation programs to improve major abdominal surgery outcomes: A Systematic Review and Meta-analysis

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DISCLOSURES

Funding: This study is part of a project funded by DTA3/COFUND Marie Skłodowska-Curie PhD programme.

Protocol publication: The protocol of this systematic review and meta-analysis is registered with the title "The effect of supervised exercise programs prior to major abdominal surgery on surgical outcomes and functional recovery" with the ID number CRD42020180693 in PROSPERO.

Conflicts of interest/Competing interests: We declare that any of the authors listed in the authors list do not have a conflict of interest to declare. The author JM is the director of the prehabilitation program called prehab4cancer. This is a prehabilitation program including exercise intervention before major surgeries.

Availability of Data and Material: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable

Author's contribution statement: PD designed the study, conducted the search, screened the articles, extracted the data, analysed data and wrote the manuscript. FZ screened the articles and extracted the data. LB designed the study, screened the articles and actively contributed to the writing process of the manuscript and data analysis. AJ provided counselling about systematic review and meta-analysis methods. HD actively contributed to the writing process of the manuscript and data analysis. AB, JM, TQA and JM provided clinical insights to the study. All authors read and approved the manuscript.

Ethics approval: The study was approved by the Science and Engineering Research Ethics Committee at Manchester Metropolitan University.

ABSTRACT

The optimal package of components for a prehabilitation intervention remains unclear. The aim was to determine the efficacy of supervised exercise prehabilitation programs to enhance patient fitness and improve surgical outcomes. Protocol was preregistered (PROSPERO: CRD42020180693). PubMed, MEDLINE, CINAHL, AMED, CENTRAL, PeDro, ClinicalTrials.gov and the WHO International Clinical Trials Registry were searched. Randomized controlled trials (RCTs) of supervised prehabilitation programs before major abdominal surgery were included. Physical function, cardiorespiratory capacity and surgical outcomes were the primary outcomes measures. Risk of bias followed Cochrane guidelines for RCTs. Data is summarized narratively, and quantitatively as risk ratios (RR), mean difference of changes between baseline and follow-up time points and 95% confidence interval (CI). Twenty RCTs were included in the analysis with a total of 1258 patients. The 6-minute walking distance change was +33 m in the prehabilitation group compared to the usual care (UC) group after prehabilitation (95% CI: [13, 53], P<0.01). Only in studies with more than one supervised session per week changes in 6-minute-walk distance were significantly higher in the prehabilitation group (Mean difference: 47 m, 95% [CI]: [20-75]). The change in peak volume of oxygen uptake was +1.47 mL·kg^{-1}·min^{-1} in the prehabilitation compared to the UC group, after prehabilitation (95% CI: [0.68, 2.25], P<0.01). There was no significant difference in the change in oxygen uptake at anaerobic threshold between groups (Mean differences: 0.47, 95% CI: [-0.16, 1.10], P:0.14). Post-operative complications incidence was similar between groups (RR: 0.80, 95% CI: [0.61, 1.05], P:0.07) even when more than more than one supervised session per week was performed (RR: 0.67, 95% CI: [0.43, 1.03], P<0.01). Prehabilitation programmes with more than one supervised session per week improved physical function but did not significantly enhance surgical outcomes in the prehabilitation group prior to abdominal surgery~~.~~

Keywords: abdominal surgery, cardiorespiratory capacity, exercise, functional capacity, prehabilitation program, pre-operative care.

1. Introduction

Most patients facing major abdominal surgery are over 60 years old[1], an age when cardiorespiratory fitness and muscle function has already started to decline, even in highly active people[2, 3]. The negative impact of poor cardiorespiratory fitness[4-7] and muscle weakness[8-13] on surgical outcomes after abdominal surgeries is widely reported. Exercise programs that enhance cardiorespiratory fitness and muscle health may be effective "prehabilitation" strategies for abdominal surgeries. The big challenge of exercise prehabilitation programs, particularly in oncology surgery, is the short time interval available to improve patient fitness. The length of prehabilitation programs is commonly 4-6 weeks[14, 15], a period that may be insufficient to promote significant cardiopulmonary and muscular adaptations[16-18], and hence, limiting their potential clinical benefit. Thus, some studies report that exercise prehabilitation programs for major surgery resulted in a reduced length of stay in hospital (LOS)[19, 20] and incidence of post-operative complications[15, 21], while others report no significant effects on LOS[22] and incidence of post-operative complications[19]. These conflicting findings may be due to different factors related to prehabilitation program planning and training principles.

The optimal package of components for a prehabilitation intervention remains unclear. A previous systematic review did not see substantial differences in the effect size of exercise prehabilitation programs on post-operative complications between multimodal programs (including exercise alongside nutritional and psychological support) and unimodal exercise programs delivered prior to major abdominal surgery for cancer[23]. Nevertheless, this review and others have highlighted with sufficient clinical data that exercise training can be a safe and effective part of prehabilitation strategies [23-26]. However, if clinicians want to introduce exercise in their clinical practice, they must know specific details about the effects of exercise components. A published guideline of pre-operative exercise training for patients awaiting major non-cardiac surgery recommended exercise to be delivered under supervision[27], in line with previous meta-analysis including old population[28, 29]. However, the magnitude of effects of prehabilitation programs containing supervised exercise on outcomes following all types of major abdominal surgery remains unclear. This is important for optimising the outcomes of prehabilitation programs in clinical practice, and for providing estimates of effect that newer self-managed (unsupervised) or remote exercise programs (that are increasing in popularity) can be compared against. Previous reviews of prehabilitation for abdominal cancer surgery have either not attempted to perform a meta-analysis or have performed analyses irrespective of exercise supervision[23, 24, 26]. Therefore, the aim of this meta-analysis is to evaluate the efficacy of supervised exercise prehabilitation programs to enhance physical functionality before surgery and improve surgical outcomes. Furthermore, we aimed to understand whether efficacy of supervised exercise prehabilitation programs was influenced by type of surgery and exercise delivery (e.g. frequency of sessions).

2. Materials and methods

The methods for this review were pre-specified and registered in PROSPERO (Centre for Reviews and Dissemination international database of prospectively registered systematic reviews, CRD42020180693, 18-05-2020). Ethical approval was given by the Manchester Metropolitan University ethics committee (24-04-2020). This review is reported following PRISMA guidelines[30].

2.1. Search strategy

The search strategy was built in consultation with an academic librarian at Manchester Metropolitan University. Following the development of a search strategy according to the PICO framework, the following databases and trial registers were searched for relevant studies: PubMed, MEDLINE, CINAHL, AMED, CENTRAL (via Cochrane library), PeDro, ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp). The search was conducted in January 2022 and updated before publication in November 2022. See supplementary document 1 for further details of search strategies. In addition, citations in selected studies were checked for further references.

2.2. Eligibility criteria

Studies were included in the systematic review if they met the following inclusion criteria:

- Population: Adults (>18 years) that had abdominal surgery. Abdominal surgery was defined as surgery involving a cut in the abdominal cavity[1]. Selection of articles was not limited by choice of surgical technique. This included patients undergoing gastrointestinal, hepatobiliary, pancreatic, endocrine, urological, gynaecological, vascular and abdominal transplantation surgery for elective indications.
- Intervention: The exercise prehabilitation program included at least one supervised exercise session per week. Supervised exercise was controlled by a physician or health professional and had a duration of ≥ 3 weeks, as a previous meta-analysis reported only changes in 6-minute-walk distance (6MWD) in prehabilitation programs of ≥ 3 weeks [31]. The supervised exercise prehabilitation program should involve planned, structured and repetitive bodily movement to improve or maintain one or more components of physical fitness[32]. Programs involving only respiratory training were excluded.
- Comparator: Adults (>18 years) that underwent an abdominal surgery and followed usual care (UC) pathway. Patients in this group did not complete any supervised exercise program during the prehabilitation stage.
- Outcomes: At least one of the following outcomes was reported in the study: i) post-operative mortality, ii) total number of post-operative complications iii) severe post-operative complications defined as a) those requiring reoperation or b) ≥ 3 in the Clavien-Dindo scale[15, 19], iv) LOS, v) any functional test (with special attention to 6MWD and Timed-up-and-Go (TUG), peak volume of oxygen uptake during a maximum cardiopulmonary test (VO_2 peak), and oxygen uptake at anaerobic threshold (AT), or any strength measurement pre and post the exercise prehabilitation program.

2.3. Data extraction

Two researchers (PD and FZ) screened the titles and abstracts of all search results according to review eligibility criteria. The full text of records not excluded on title and abstract were obtained and screened independently by two researchers (PD and FZ). In case of a discrepancy in decision to include a study, a third researcher was consulted (LB).

For all eligible studies, data was extracted by one researcher (PD) and cross-checked by another (FZ). Extracted data included: authors and year of publication, participant characteristics (age, body mass index (BMI), type of surgery, involvement in neoadjuvant treatment), characteristics of the prehabilitation program (program length, frequency and duration of the supervised sessions, type and intensity of exercises, progression of the exercise program and any other type of support apart from the supervised exercise sessions) and outcome measures. The time points of interest were 'baseline (before surgery), pre-surgery (the end of UC or prehabilitation, just before surgery), and post-surgery. In one case[33], estimates of the effect of this study were extracted from previous meta-analysis[23] and a sensitivity analysis with this data was performed to evaluate if it significantly changed the outcome.

<<<Insert Fig. 1 here>>>

2.4. Data synthesis

Study, patients and prehabilitation program characteristics (Table 1), and risk of bias are summarized narratively.

Continuous outcomes (6MWD, VO_2 peak, AT, handgrip strength, TUG and LOS) and dichotomous outcomes (total number of post-operative complications, number of severe post-operative complications and mortality) are summarized narratively, as mean difference of changes between baseline and follow-up time points and 95% confidence interval (CI), and risk ratios (RR) and 95% CI.

2.5. Risk of bias assessment

Two researchers (PD and FZ) independently assessed the risk of bias of each included article for meta-analysis using the tool in the Cochrane handbook for RCTs[34]. In case of discrepancy between the researchers in any of the domains assessing a given article, a third researcher (LB) was consulted. The domains assessed are given in supplementary document 2. Blinding of the patients was not taken into consideration because it is impossible to blind an exercise session. Each domain was allocated either low, unclear or high risk of bias, following the recommendations of the Cochrane handbook[34].

2.6. Heterogeneity

Heterogeneity was assessed with the statistic I^2 and describes the percentage of variability due to other sources than sampling error[34]. More than 40% represents considerable heterogeneity[34]. In that case, a subgroup analysis was performed to reduce the heterogeneity between studies.

2.7. Statistical analysis

All data analysis was performed using RevMan 5.4 (Review Manager Version 5.4, The Cochrane Collaboration, 2020). To analyse differences between groups in mortality, total number of post-operative complications and number of severe post-operative complications, a meta-analysis for dichotomous data using the Mantel-Haenszel method with a random effects model was performed. A meta-analysis for continuous data using the inverse variance method with random effects model was performed for LOS. A meta-analysis for continuous data using the inverse variance method with random effects model was performed for 6MWD, handgrip strength of the right hand, TUG and VO_2 peak using the mean changes and SD of changes between baseline and after completing the prehabilitation (before surgery) and between baseline and 4-8 weeks after surgery (if reported). It was necessary to estimate the mean changes and SD of changes of 6MWD[14, 21, 35-37], handgrip strength of the right hand[35], TUG[38], five times sit to stand[36] and VO_2 peak[15, 35, 39-43] of some studies as they were not reported. The estimation was performed using Cochrane handbook guidelines[34]. To do so, a calculated correlation coefficient from other studies in this meta-analysis was used[19, 44, 45] to estimate SD of changes where this was not reported and authors could not be reached. Meta-analysis for continuous data using the inverse variance method with random effects model was performed for AT using the follow-up values (i.e., post-intervention, before surgery). In the case a study reported median and interquartile range or 95% CI instead of mean and SD, mean and SD were estimated[34, 46]. Data was presented as RR or mean difference of changes between baseline and follow-up time points (before surgery and 4-8 weeks after surgery) and 95% CI.

3. Results

3.1. Study characteristics

A total of 12025 records were identified in the initial search. After using the criteria indicated in the PRISMA flow diagram (Fig. 2), 20 studies were included in the meta-analysis.

3.2. Characteristics of the patients

A total of 1258 patients were included in these studies, of which 632 patients completed prehabilitation and 626 UC. The minimum mean age of the patients across studies is 49 years and the maximum 82 years. One study included only frail patients as defined by the Fried Frailty Index[14]. Another study included only patients considered at high risk of adverse events (age>70 years, and/or *'American society of anesthesiologists'* III/IV)[22].

<<<Insert Fig. 2>>>

3.3. Characteristics of the prehabilitation program

Nine studies had a prehabilitation program length of 3-4 weeks[14, 19, 33, 35, 40, 42, 44, 45, 47, 48], 4 studies a length of 3-6 weeks[15, 22, 37, 39, 49], 2 studies a length of 9[41] and 15[43] weeks, because the prehabilitation program lasted the duration of the neoadjuvant therapy, and 3 studies a length of 2-6 weeks[21, 36, 38]. These last three studies were included on the basis that interventions of ≥ 3 weeks were delivered. As not all participants in the studies received a prehabilitation program of ≥ 3 weeks, sensitivity analyses with the removal of these studies were undertaken on any meta-analyses that included data from these studies (Forest plot of these sensitivity analysis is reported in supplementary material). In one study, the prehabilitation until a liver transplantation was 4 weeks for some patients and up to 8 weeks for other patients due to longer preoperative period[35].

Ten studies[14, 15, 19, 35, 36, 38, 43, 45, 48, 49] included both resistance and endurance training as part of the prehabilitation program. The resistance training included exercises of upper and lower limbs, and functional exercises. Nine studies only included endurance training, seven in the form of high intensity interval training (HIIT)[22, 33, 39-42, 47] and two in the form of continuous endurance training[37, 44]. One study included continuous endurance training and global body mobilisation[21]. Seventeen studies reported a progressive and tailored exercise program according to the aerobic and/or muscle capacity of patients[14, 19, 21, 22, 33, 36-45, 47, 48]. One of these studies only reported tailored exercise and not progressive[47]. Another three studies included respiratory muscle training as part of the exercise prehabilitation program[21, 37, 38].

All prehabilitation programs involved supervised and unsupervised exercise sessions except seven that only included supervised exercise sessions[15, 33, 39-42, 49]. In twelve studies, patients were encouraged to complete an exercise program at home[14, 19, 35-37, 43, 44, 47, 48] or to increase daily physical activity with walking or cycling[21, 22, 38]. Five studies encouraged patients in the UC to do exercise at home during the pre-operative period[38, 42, 43, 47, 49]. In two studies, the UC and prehabilitation patients followed a post-surgery exercise program with a length of 7 days[21] and 8 weeks[19]. In another study, only UC patients followed a 4-weeek post-surgery exercise program[14].

<<<Insert table 1>>>

3.4. Risk of bias

All but seven studies[14, 33, 36, 38, 39, 42, 48] did not report whether the outcome assessors or statisticians were blinded, and two explicitly mentioned that data collectors were aware of group allocation[21, 49] (See supplementary document 2 for further information on risk of bias assessment).

Some studies experienced loss of follow-up data[14, 15, 19, 21, 33, 40, 42, 48]. In some cases, data of surgical outcomes were reported, but physical function, aerobic capacity and muscular strength data was missing. Hence, the Forest plots are accompanied by a risk of bias assessment for each outcome.

3.5. Physical function and strength changes

The most prevalent measure of physical function was the 6MWD. The change in 6MWD in the prehabilitation group was +33 m (CI: [13-53m]) compared to the change in the UC group before surgery (Fig. 3A)[14, 19, 21, 22, 35-37, 44, 45]. There was, however, substantial heterogeneity between the studies. The change in 6MWD in prehabilitation programmes with one supervised session per week in the prehabilitation group did not differ significantly from the change in the UC group[14, 19, 36, 37, 44], while programmes with more than one session per week resulted in a change in 6MWD in the prehabilitation group of +47m (CI: [20-75m]) compared to the change in the UC group (Fig. 3A)[21, 22, 35, 45] Substantial heterogeneity remained in both subgroups. Sensitivity analysis removing Steffens et al. (2021) and Soares et al. (2013) did not significantly change the results of the meta-analysis (Mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 29m, 95% CI: [8m, 51m], P: 0.006, I^2: 73%) (Fig. 6 supplementary document 3). At 4 weeks after surgery, the change in 6MWD in the prehabilitation group was +21m (CI: [3-38m]) compared to UC group, from baseline (Fig. 3B)[14, 19, 21, 37]. Sensitivity analysis removing Soares et al. (2013) showed no significant difference in the 6MWD change between groups 4 weeks after surgery (Mean differences of changes (pre-surgery-4 weeks after surgery) between prehabilitation group and UC group: 20m, 95% CI: [-7m, 46m], P: 0.46, I^2: 0%) (Fig. 7 supplementary material 3). At 8 weeks after surgery, the prehabilitation group and UC group had a similar change in 6MWD, from baseline (Fig. 3B)[19, 37].

<<<Insert Fig. 3>>>

While the change in TUG in the prehabilitation group was -0.6 s. compared to that seen in UC group before surgery[38, 45] (95% CI: [-1s, -0.2s], P<0.01, I^2: 3%) the changes in ‘five times sit to stand test’ did not differ significantly between groups (Mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 0.03s, 95% CI: [-0.9s, 0.9s], P: 0.71, I^2: 0%) (Fig. 8 and 9 of supplementary document 3). Chair rise test was not significantly improved by prehabilitation before surgery[38].

No significant differences were observed in the change of handgrip strength between groups before surgery (mean differences of changes (baseline-pre-surgery) between prehabilitation group and UC group: 2.8 kg, 95% CI: [-0.1, 5.7], P:0.05, I^2: 55%)[35, 43, 45] (Fig. 8 of supplementary document 3).

3.6. Cardiopulmonary changes

One study was excluded from the meta-analysis because the VO_2 peak was calculated indirectly using the physical work capacity at a heart rate of 170 beats test (PW_{170} test)[38]. In the remaining studies, the change in VO_2 peak in the prehabilitation group was +1.47 $mL \cdot kg^{-1} \cdot min^{-1}$ (95%CI: [0.68-2.25 $mL \cdot kg^{-1} \cdot min^{-1}$]) above the UC group (Fig. 4A)[15, 33, 35, 39-44, 47]. There was, however, substantial heterogeneity. As all studies, except one, delivered more than one supervised session per week in their prehabilitation programs, other pre-specified factors (apart from supervised training frequency) were considered to resolve the substantial heterogeneity. A subgroup analysis by the surgery type was performed. In subgroup analysis, VO_2 peak change of the prehabilitation group was not significantly different from that achieved by the UC group in patients preparing for an Abdominal aortic aneurysm (AAA) repair (Fig. 4A)[15, 40]. The two studies included in this subgroup were assessed as having high risk of bias due to the loss of follow-up data. Data from Blackwell et al. (2020) was retrieved from previous meta-analysis[23]. Excluding the data from this study (Fig. 11 of supplementary document 3) did not significantly change the outcomes reported above (Mean differences of changes (baseline-pre-surgery) between prehabilitation and UC: 1.45 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI: [0.644, 2.26], P<0.01, I^2:76%).

The change in AT between baseline and pre-surgery was not significantly different between groups (Fig. 4B)[15, 35, 39-43, 47]

<<<Insert Fig. 4>>>

3.8. Surgical outcomes

Meta-analyses were only performed with five studies for in-hospital and 30-day mortality[15, 21, 22, 37, 43]. Mortality risk was not significantly reduced after prehabilitation (Fig. 5A). Allen et al. (2022) also reported no mortal events in any of the groups 30 days after surgery. Another study, including liver transplantation patients, reported no mortality in any group 90 days after surgery[35].

The incidence of post-operative complications - incidents that prevented a participant from a normal recovery after surgery – was not significantly less in the prehabilitation group compared to UC group[14, 15, 19, 21, 22, 36-38, 42, 47-50]. Even after subgroup-analysis complications were not significantly reduced in the sub-group that included more than one supervised session per week and heterogeneity remained in that group (Fig. 5B). Sensitivity analysis excluding data from Steffens et al. (2021), Soares et al. (2013) and Dronkers et al. (2010) did not significantly change the results of the meta-analysis (RR: 0.77; 95% CI: [0.88, 1.06, P: 0.11, I^2: 79%) (Fig. 12 of supplementary document 3)

Severe post-operative complications were defined as those requiring further surgical interventions[15, 21, 22, 48] or complications assessed as ≥III by the Clavien-Dindo scale[14, 19, 37, 39, 42, 47, 49, 51]. The incidence of severe post-operative complications was not significantly different between groups (RR: 0.9~~8~~1; 95% CI: [0.63, 1.~~53~~32], P: 0.~~79~~63, I^2: 0%) (Fig. 1~~0~~3 of supplementary document 3).

The LOS is reported in table 2 of supplementary document 3. All studies, except five[33, 35, 40, 41, 44], reported LOS. One study reported the LOS in an unclear way, authors were contacted, and no answer was received, therefore the study was discarded from analysis[49]. LOS was not significantly reduced in the prehabilitation group compared to UC group (Fig. 5C).

<<<Insert Fig. 5>>>

4. Discussion

The key findings of this review are that supervised prehabilitation programs with more than one supervised training session per week favour improvements in functional capacity but did not have any significant effect on the surgical outcomes.

4.1. Physical function and strength changes

There was a greater improvement in the 6MWD in the prehabilitation group compared to the UC group before surgery. This is in support of findings from non-randomized controlled trials[20, 52-54] and previous meta-analysis[23] but disagrees with another two meta-analysis[25, 55]. It should be noted, however, that some studies included for these meta-analyses[25, 55] did not include any supervised session in the prehabilitation program. This meta-analysis reduced heterogeneity between studies, in this sense, including only studies with at least one supervised session per week. Hence, the findings of this meta-analysis highlight the importance of including supervised exercise sessions to provide an effective exercise stimulus that enhances the functional capacity of patients before surgery[27, 29]. Our pre-specified sub-group analysis showed that the effect of prehabilitation program is likely modulated by the frequency of supervised sessions. We showed that the effect of prehabilitation programs is stronger with more than 1 supervised session per week, even when patients reported high compliance with unsupervised exercise in the subgroup of studies with one supervised session per week[14, 44]. However, this should be interpreted with caution. Firstly, differences in the subgroup are observational in nature. Secondly, while our sub-group analysis depending on supervised session per week reduced the heterogeneity between studies, there was still substantial heterogeneity in both groups. The heterogeneity in both groups is caused by two studies[22, 37]. These two studies show opposite direction in the effect of prehabilitation programs on 6MWD and one included high risk[22] patients and the other any type of colorectal surgery patients[37]. Thus, no logical explanation can be given for this result. The lack of a significant clinical effect of the planned unsupervised exercise may be due to a lower exercise quality, resulting in lower intensity during the unsupervised sessions, leading to a lower training stimulus[28]. Supervised sessions could well provide the necessary stimulus to improve quality of exercise and thus, optimise the training effect.

To the best of our knowledge, this is the first meta-analysis assessing the changes in 6MWD after surgery to evaluate if patients involved in a prehabilitation program recover their physical function faster compared to those in the UC group. 6MWD is better preserved in the prehabilitation group compared to those who underwent UC, even if both groups participated in a post-surgery exercise rehabilitation[19, 21]. In fact, if only the UC group and not the prehabilitation group received post-surgical exercise rehabilitation, the recovery was still better in the prehabilitation group than the UC group[14]. However, these results should be interpreted with caution as the lower bound of the CI in the 6MWD analysis 4 weeks after surgery is 3 m. which is below the minimally clinical important difference (MCID)[14, 56]. Moreover, after sensitivity analysis removing Soares et al. (2013) data, the meta-analysis showed that there was not significant difference in the change of 6MWD between baseline and 4 weeks after surgery, indicating that the length of the prehabilitation program could not be a deterministic factor to improve the functional recovery after abdominal surgery. Three of the four studies in the analysis included only one supervised session per week in the prehabilitation program. More research is needed to ascertain if prehabilitation programs aid in accelerating physical function recovery after surgery as well as determining the optimum supervised training frequency. At 8 weeks after surgery both groups had similar 6MWD performance.

Handgrip strength and five times sit to stand did not show a significant improvement before surgery in prehabilitation group compared to the UC group, in contrast to what it was observed in TUG[38, 45]. The discrepancy between prehabilitation-induced improvements in handgrip and lower limb strength is most likely since exercise programmes are particularly focussed on improving lower leg, rather than handgrip strength. It should be noted that there were only few studies that measured handgrip strength, TUG and five-times-sit-to-stand with only a low number of participants, therefore any effects of prehabilitation programs on muscle function need to be interpreted with caution.

4.2. Cardiopulmonary changes

In contrast to a previous meta-analysis[23] where no change in VO_2 peak was found, here we observed that VO_2 peak was significantly improved in the prehabilitation group compared to UC group before surgery. Even though Waterland et al. 2021 did not see a significant improvement in VO_2 peak after prehabilitation, the observed a training effect (CI: [-0.03, 3.50 $mL \cdot kg^{-1} \cdot min^{-1}$, p=0.05] was similar to the one the one presented here. Additionally, seven more studies than in Waterland et al. (2021) were included in this meta-analysis improving the statistical power of our meta-analysis, further supporting the findings reported here.

When we analysed the benefits of prehabilitation programmes for the pre-surgery VO_2 peak in patients with AAA[15, 40], the analysis showed no difference between groups and opposing outcome between the two included studies. In addition, these studies have some risk of bias due to loss of follow-up data. Therefore, this finding should be interpreted carefully. The cause of the large heterogeneity cannot be ascribed to the diameter of the aneurysm as both studies included patients with similar aneurysm size (≈6 cm diameter). Nevertheless, this is worthwhile exploring further in future studies, as it has been reported that VO_2 peak and AT were significantly improved after prehabilitation in patients with an AAA ≤5 cm diameter[57-59]. The length of the program may be another factor to consider, as those studies that found significant positive adaptations in VO_2 peak and AT in AAA patients were those with exercise programs of more than 4 weeks[57-59].

As in previous meta-analysis[23], we did not observe a significant improvement in the AT after prehabilitation compared to UC. The AT is considered an important predictor of in-hospital morbidity[7, 60], and determining if prehabilitation programs can enhance this cardiopulmonary parameter is important. AT analysis was performed with follow-up values due to the lack of data to estimate SD of changes. The lower bound of the CI is -0.416 $mL \cdot kg^{-1} \cdot min^{-1}$, which may account for the small baseline differences between groups, to the disadvantage of prehabilitation group[15, 35, 42, 47], and the small variability that AT estimation may have[61]. Thus, even though data points to the inability of prehabilitation programs to improve AT, more research in this area is needed.

4.3. Surgical outcomes

Poor physical condition may be a risk factor for 30-day mortality after abdominal surgeries, but most likely other factors, unmodifiable by exercise (cirrhosis, diabetes, disseminated cancer, type of surgery, etc.) are probably more important contributors to the 30-day mortality. Our analysis on mortality is in line with others[23, 25] and showed no difference in 30-day and in-hospital mortality rate between groups. This lack of statistically significant effect on 30-day mortality may be caused by the low incidence of 30-day mortality in both groups. While increasing the number of patients in studies may allow for better detection of any effect of prehabilitation, the available evidence to data does not favour an effect of prehabilitation.

Here we found no significant reduction in the incidence of all kinds of post-operative complications. Previous meta-analyses, however, did report a significant reduction in the rate of complications in the prehabilitation group compared to UC group[6, 25, 55, 62], but another one, that included the larger number of studies (both supervised and unsupervised prehabilitation), found no such improvement after prehabilitation[23]. It was hypothesized that, the lack of impact of prehabilitation programs on the rate of post-operative complications, in this study and Waterland et al. (2021), may be due to the lack of effect of prehabilitation programs with less than two supervised sessions per week. However, after subgroup analysis no significant difference in the incidence of post-operative complications was found between groups. It is worth further research in this sense as the upper bound of the CI was 1.05 RR and 1.03 RR in the subgroup with more than one supervised session per week. Moreover, high risk of bias was found in 5 studies.

In the past, the use of LOS was reported as a conflicting surgical outcome due to the influence of non-clinical factors on LOS [63]. However, nowadays LOS is seen as an outcome measure of good care[64]. In fact, other reviews in the topic have included LOS as a surgical outcome to evaluate the effectiveness of prehabilitation programs[6, 55, 62]. Therefore, we decided to include LOS as an outcome to assess the efficacy of supervised prehabilitation programs. LOS was not significantly reduced in the prehabilitation group compared to the UC group as seen in other meta-analyses[6, 55, 62]. This is not unequivocal however, as another meta-analysis reported significantly shorter LOS in the prehabilitation group compared to UC group[23, 25]. It, therefore, remains to be seen how effective a large-scale supervised prehabilitation program is to reduce the LOS.

4.4. Implications for practice and research

It has been suggested that a change of 1 MET (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) in VO_2 peak is the MCID in different clinical settings[65]. Although the mean change in VO_2 peak as a result of prehabilitation programs was above that achieved by UC, it was not above the MCID nor was the upper bound of the CI. Nevertheless, it may have been enough to contribute to the mean of 33 m larger increase in 6MWD after prehabilitation compared to usual care, which is above the MCID for the 6MWD (>20 m)[14, 56]. The imprecision of this estimate of effect on 6MWD, however, means further trials of supervised prehabilitation programs are necessary to increase certainty in the evidence. Based on the current available evidence, the 95% CI around the best estimate of effect includes a change in 6MWD that would not be considered clinically meaningful.

Studies here included continuous or HIIT training, with both types of exercise promoting positive adaptations during prehabilitation. Recently, it was reported that HIIT resulted in a larger increase in AT 2 months after surgery[66]. This suggests that different types and intensities of exercise have different effects on the cardiopulmonary capacity of the patients. Such evidence, alongside that synthesised in the current review calls for head-to-head trials of prehabilitation programs that differ by supervision, intensity, type and duration of exercise to better understand the optimal exercise prescription within prehabilitation programs. Moreover, little is known about the effects of prehabilitation programs on muscle morphology and function and the best training stimulus to gain muscle mass and muscle strength. Future studies in this topic should grant muscle measurement due to the reported relation between muscle morphology and tissue composition with surgical outcomes [1, 67].

4.5. Applications and Limitations.

Similar to previous reviews in this area[23] we had to estimate the SD of changes for some studies. This approach and all calculations were performed in accordance with Cochrane guidance and best practice[34]. Nevertheless, it is important to acknowledge that our estimates of effect on 6MWD, handgrip strength of the right hand, TUG, five times sit to stand and VO2 peak included such imputations for missing data. AT meta-analysis was performed with follow-up values, due to a lack of reporting of the SD of changes in the literature.

Even though-we sought to reduce heterogeneity between studies by including only randomized controlled trials with at least one supervised training session per week for at least three weeks before surgery, there are still sources of heterogeneity that require acknowledgement. Four studies [14, 19, 37, 43] included a multimodal prehabilitation program (inclusion of nutritional and psychological support[68, 69]) with three of them having only one supervised session per week[14, 19, 37]. A previous meta-analysis[23], reported the lack of significancy of unimodal programs to improve 6MWD, in contrast to multimodal prehabilitation programs. However, the effect size of both types of prehabilitation programs were similar and the lack of significancy in unimodal programs may be due to the low statistical power of the subgroup, that included only two studies. Furthermore, both, unimodal and multimodal programs did not have any significant effect on the incidence of post-operative complications. The data presented here did not show significant difference in the incidence of post-operative complications between groups, but a bigger effect on the reduction of the incidence of post-operative was observed in those studies with more than one supervised session per week. Further research is needed to understand what factors of prehabilitation programs may be crucial to reduce the incidence of post-operative complications.

was not generally reported in the included studies. Future studies should ensure outcome assessment are blind to reduce bias during the analysis process. Loss of follow-up data was also seen in some studies. This was due to different reasons; appearance of adverse events that prevented patients to perform exercise programs [19, 40, 42, 47], rescheduling or not performing surgery[14, 21, 35, 40], mortality during the trial[14, 21] and withdrawal from the trial[15, 19, 21, 35, 47]. It may be reasonable to suggest that psychological support may motivate patients to remain in the exercise program which could prevent patients from withdrawing the trial. However, this is difficult to know as one of the studies included psychological support[19] and experienced loss of follow up data due to trial withdrawal and another one not[43].

4.6. Conclusions

Exercise prehabilitation programs need to include more than one supervised session per week to elicit improvements in functional capacity of patients preparing for abdominal surgery. However, improvements in 6MWD and VO_2 peak were not accompanied by an enhancement in surgical outcomes in the prehabilitation group.

ACKNOWLEDGEMENTS

We appreciate the help of Angela Boxer, professional librarian at Manchester Metropolitan University and James Steele, Assistant professor in Sport and Exercise Science at Southampton Solent University for their assistance in developing the search strategy and thoughts about the statistical analysis respectively.

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Table 1. Characteristics of included studies

First author	Prehabilitation group characteristics/Exercise apart of supervised prehabilitation program	Usual care group characteristics/additional non-supervised exercise apart of usual care	Surgery	Neoadjuvant therapy	Length of supervised prehabilitation program	Type of supervised prehabilitation program
Allen 2022	N=26; Age: 64±8 yrs; BMI: 28±5 kg·m^{-2}. Patients performed a home-based program and received nutritional and psychological support.	N=28; Age: 65±6 yrs; BMI: 28±5 kg·m^{-2}. Patients were encouraged to improve their fitness and received psychological and nutritional support.	esophagogastric cancer planned for neoadjuvant therapy plus esophagogastrectomy , or total gastrectomy	Y	15 weeks	*Frequency of supervised sessions:* 2/week *Session length:* 60 min *Type:* Aerobic cycling and resistance training with free weights and resistance bands. *Intensity:* 40-60% reserve heart rate or 1-14/20 RPE for aerobic training and 12-14/20 RPE for resistance training. *Progression:* Adjusting aerobic and resistance load to meet with the planned RPE. *Additional support:* Nutritional and psychological intervention.
Berkel 2022	N=28; Age: 74±7 yrs; BMI: 29.8±4.1 kg·m^{-2}. Moderate homebased exercise.	N=29; Age: 73±6 yrs; BMI: 30.5±4.9 kg·m^{-2}. No exercise suggested	Colorectal cancer.	Y	3 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* 60 min. *Type:* Moderate to high intensity interval training on cycle ergometer. Peripheral resistance training *Intensity:* 120% of the work rate achieved at the ventilatory anaerobic threshold was alternated with active recovery at 50% of the work rate achieved at the ventilatory anaerobic threshold. Resistance training was performed at 70%-82% of baseline 1 maximum repetition (RM).

						Progression: In the first week, exercise lasted 120 seconds and recovery lasted 180 seconds, which progressed to 140 and 160 seconds, respectively, in the second week, and 160 and 140 seconds in the third week. Resistance training progressed from 70% to 82% from the first to the third week *Additional support:* Not reported.
Gloor 2022	N=54; Age: 66 (24-90) yrs; BMI: 26 (20-35) kg·m^{-2}. Patients were encouraged to remain physically active.	N=53; Age: 65 (29-86) yrs; BMI: 27 (18-40) kg·m^{-2}. Patients were encouraged to remain physically active	Colorectal resection	N	3-6 weeks	*Frequency of supervised sessions:* 2/week. *Session length:* 90 min. *Type:* HIIT, resistance circuit training *Intensity:* HIIT was performed at 85-90% of maximum training capacity. *Progression:* Not reported *Additional support:* Not reported.
Woodfield 2022	N=28; Age: 66.5(13.5) yrs; BMI: Not reported. Encouraged to exercise more before surgery	N=35; Age: 66(15) yrs; BMI: 27.9±5.3 Not reported. Patients were encouraged to exercise more before surgery.	Major abdominal surgery		4 weeks	*Frequency of supervised sessions:* ~3/week *Session length:* 30 min. *Type:* HIIT *Intensity:* 60% maximum heart rate for active recovery and 90% of maximum heart rate during intense interval. *Progression:* Increased training load or duration of intense interval with the aim of achieving five 2 min. intense interval during the session. *Additional support*: Not reported

Fulop 2021	N=77; Age: 70(60-75) yrs; BMI: 27.9±5.6 $kg \cdot m^{-2}$. Repeating the in-hospital exercise at home.	N=72; Age: 70(64-75) yrs; BMI: 27.9±5.3 $kg \cdot m^{-2}$. No exercise suggested.	Colorectal surgery.	N	3-6 weeks	*Frequency of supervised sessions:* 1/week. *Session length:* 40-45 min. *Type:* Aerobic training and breathing exercises. *Intensity:* moderate aerobic exercise. *Progression:* training intensity was weekly increased according to patient's ability. *Additional support*: Nutritional supplementation if needed and psychological support.
Steffens 2021	N=11; Age: 62(48-72) yrs; BMI: 29.6 $kg \cdot m^{-2}$ (imputed from reported height and weight so variation was not possible to calculate). Home-based functional exercise and encourage to walk at least 30 min. daily	N=11; Age: 66(46-70) yrs; BMI: 26.97 $kg \cdot m^{-2}$ (imputed from reported height and weight so variation was not possible to calculate). No exercise suggested.	Pelvic exenteration.	N	2-6 weeks	*Frequency of supervised sessions:* 1/week. *Session length:* 60 min. *Type:* Aerobic, breathing and muscle strength exercise. *Intensity:* Aerobic exercise at 12-14 RPE and strength training at 40%-60% RM *Progression*: Increasing the number of intervals or adding further load to the flywheel. *Additional support:* Not reported
Loughney 2021	N=17; Age: 64±14 yrs; BMI: 26.0±4.0 $kg \cdot m^{-2}$. No more exercise suggested.	N=16; Age: 57±10 yrs; BMI: 27.0±3.0 $kg \cdot m^{-2}$. No exercise suggested.	Rectal cancer patients.	Y	9 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* 40 min. *Type:* HIIT on cycle ergometer. *Intensity:* 80 % of the oxygen uptake at ventilatory anaerobic threshold and power output half-way

						between ventilatory anaerobic threshold and VO_2 peak. *Progression*: Increasing the time of HIIT training from 30 min. to 40 min. *Additional support:* Not reported.
Blackwell 2020	N=19; Age: 71±2 yrs; BMI: not reported. No more exercise.	N=21; Age: 72±4 yrs; BMI not reported. No exercise suggested	Urological cancer.	N	4 weeks	*Frequency of supervised sessions:* 3-4/week. *Session length:* ~30 min. *Type:* HIIT on cycle ergometer. *Intensity:* 100-115% of maximal load reached during initial CPET *Progression:* Increased in wattage at mid-way point of training. *Additional support:* Not reported.
Carli 2020	N=55; Age: 78 (72-82) yrs; BMI 24.9 (23-30.1) $kg \cdot m^{-2}$ Frail patients/ Patients were encouraged to follow a homebased training program during the prehabilitation period.	N=55; Age: 82(75-84) yrs; BMI 26.4 (23.8-30.6) $kg \cdot m^{-2}$. Frail patients/ Patients were included in a 4-week rehabilitation program.	Non-metastatic colorectal cancer.	N	4 weeks.	*Frequency of supervised sessions:* 1/week. *Session length:* 60 min. *Type:* aerobic exercise and resistance exercises with elastic band. *Intensity:* Moderate aerobic exercise. Elastic band resistance training. *Progression:* Increased intensity in resistance exercise when patients reported 12 in Borg scale. *Additional support:* Nutritional and psychological support.

Wallen 2019	N=10; Age: 49 (40-60) yrs; BMI: not reported/Patients were encouraged to replicate the supervised program at home	N=11; Age: 49 (40-60) yrs; BMI: not reported/ No exercise suggested	Liver transplantation.	N	4 weeks (4 patients completed exercise for 8 weeks).	*Frequency of supervised sessions:* 2/week. *Session length:* Not reported. *Type:* Stationary walking or cycling and circuit-based resistance exercise. *Intensity:* Not reported. Progression: Not reported *Additional support:* Not reported.
Northgraves 2019	N=11; Age: 64.1±10.5 yrs; BMI: 30.3±4.3 $kg \cdot m^{-2}$. No more exercise suggested	N=11; Age: Age 63.5±12.5 yrs; BMI: 27.8±5.7 $kg \cdot m^{-2}$. No exercise suggested.	Elective cancer colorectal surgery.	Y 3 patients in UC. 4 in prehab.	22±7.5 days.	*Frequency of supervised sessions:* 3/week. *Session length:* 60 min. *Type:* Functional exercise training, including aerobic (cycle ergometer) and resistance exercises. *Intensity:* Aerobic exercise at 40-60% of heart rate reserve or 11-13 reported Borg-scale Progression: every 2-3 sessions increasing the repetitions/duration, adding resistance or increasing changing to an exercise that requires a more difficult technique. Aerobic exercise was increased 2-5 min. each session until a maximum of 25 min. *Additional support:* Not reported.
Banerjee 2018	N=30; Age: 71.6±6.8 yrs; BMI: 27.1±4.2 $kg \cdot m^{-2}$. No more exercise	N=30; Age: 72.5±8.4 yrs; BMI: 26.9±4.5 $kg \cdot m^{-2}$. No exercise suggested.	Bladder cancer surgery. Eligibility not limited by chose of surgical technique.	Y 5 patients in UC and 10 patients in prehab.	3-6 weeks	*Frequency of supervised sessions:* 2/week. *Session length:* 60 min. *Type:* HIIT on cycle ergometer. *Intensity:* 13-15 RPE equating to 70-85% of maximum heart rate.

						Progression: gradually added more load to maintain the target RPE. *Additional support:* Not reported.
Bousquet-Dion 2018	N=41; Age 74 (67.5-78) yrs; BMI: BMI 27.5±4.1 $kg \cdot m^{-2}$. Patients were encouraged to follow a homebased training program during the prehabilitation and post-surgery period.	N=39; Age 71 (54.5-74.5) yrs; BMI 28.6±4.5 $kg \cdot m^{-2}$. Patients were included in an 8-week home-based rehabilitation program.	Colon or rectal cancer resection.	N	4 weeks.	*Frequency of supervised sessions:* 1/week. *Session length:* 60 min. *Type:* aerobic exercise and resistance exercises with elastic band. *Intensity:* Moderate aerobic exercise and perceived mild exertion in resistance exercise: 12 in Borg scale. *Progression:* Increased intensity in resistance exercise to maintain 12 in Borg scale. *Additional support:* Nutritional and psychological support.
Barberan-Garcia 2017	N=62; Age: 71±11 yrs; BMI: 21±7 k $kg \cdot m^{-2}$ Patients were encouraged to increase the number of steps taken per day.	N=63; Age: 71±10 yrs; BMI: 22±7 $kg \cdot m^{-2}$. Physical activity recommendation.	Elective major abdominal surgery.	N	6 weeks.	*Frequency of supervised sessions:* 2/week. *Session length:* ~50 min. *Type:* HIIT exercise on cycle ergometer. *Intensity:* 70%-40% of peak work rate. *Progression:* After second week, every week, intensity increased 5% of peak work rate until a maximum of 85%-50% of peak work rate. *Additional support:* Psychological support.
Tew 2017	N=27; Age 74.6±5.5 yrs, BMI: 26.5±4.1 $kg \cdot m^{-2}$. No more exercise.	N=26; age 74.9±6.4 yrs, BMI:26.8±3.4 $kg \cdot m^{-2}$. No exercise suggested.	Open or endovascular repair of an infrarenal AAA.	N	4 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* ~50 min.

						Type: HIIT on cycle ergometer. *Intensity:* alternating intervals of 5-7 of 10 perceived exertion in Borg scale. *Progression:* Maintaining 5-7 of 10 perceived exertion in Borg scale. *Additional support:* Not reported.
Barakat 2016	N=62; Age: 73.8±6.5 yrs; BMI: 26.7±3.5 $kg \cdot m^{-2}$. No more exercise.	N=62; Age: 72.9±7.9 yrs; BMI: 27.4 ±4.2 $kg \cdot m^{-2}$. No exercise suggested.	Open or endovascular AAA repair.	N	6 weeks.	*Frequency of supervised sessions:* 3/week. *Session length:* 60 min. *Type:* bodyweight exercises and moderate aerobic training. *Intensity:* Not reported. *Progression:* Not reported *Additional support:* Not reported
Dunne 2016	N=20; Age: 61 (56-66) yrs; BMI: 29.7±4.2 $kg \cdot m^{-2}$. Patients were encouraged to follow clinical advice on home exercise before surgery.	N=18; Age: 62(53-72) yrs; BMI: 29.3±4.2 $kg \cdot m^{-2}$. Patients were encouraged to follow clinical advice on home exercise before surgery.	Colorectal liver metastasis resection.	11 in prehab and 7 in UC	4 weeks	*Frequency of supervised sessions:* 3/week. *Session length:* 30 min. plus warm-up and cool down. *Type:* HIIT on cycle ergometer. *Intensity:* Alternating moderate (less than 60 % of VO_2 peak) exercise and vigorous exercise (more than 90 per cent VO_2 peak). *Progression:* Not reported. *Additional support:* Not reported.

Soares 2013	N=18; Age: 58.5 (51.3–63.5) yrs; BMI: 23.6 (19.7–25.9) kg·m^{-2}. Patients were encouraged to perform inspiratory muscle training and follow a walking program at home 4 times a week that was part of the rehabilitation program. Patients were included in a 7-day rehabilitation program.	N=19; Age 55.0 (49.3–64.3) yrs; BMI: 24.2 (21.3–28.4) kg·m^{-2}. Patients were included in a 7-day rehabilitation program.	Elective open abdominal surgery (defined as opening of the peritoneal cavity).	N	2-3 weeks.	*Frequency of supervised sessions:* 2/week. *Session length:* 50 min. *Type:* stretching exercises, global body mobilization, deep breathing, respiratory muscle training and walking. *Intensity:* 20% of maximal inspiratory pressure. Walking never exceeded 15 on Borg scale. *Progression:* Every week the load in respiratory training was increased 2 cmH_2O. *Additional support:* Not reported.
Dronkers 2010	N=22; Age: 71.1±6.3 yrs; BMI 26.6±3.6 kg·m^{-2}. Patients were encouraged to follow an inspiratory training program and walk or cycle daily for 30 min at home.	N= 20; Age: 68.8±6.4 yrs; BMI 25.7±3.1 kg·m^{-2}. Patients were advised to follow a home-based training program.	elective colon surgery.	N	2-4 weeks. Depending on waiting time to surgery.	*Frequency of supervised sessions:* 2/week. *Session length:* 60 min. *Type:* Lower limb extensions, inspiratory muscle training, aerobic training and functional activities. *Intensity:* lower limb extensions performed with an intensity of 60-80% maximum repetition, inspiratory muscle training at 10-60% of maximal inspiratory pressure and aerobic exercise at 55-75% of maximum heart rate or 11-13 of Borg scale. *Progression:* Increased 10% of maximal inspiratory pressure if reported Borg scale was less than 13. *Additional support:* Not reported.
Kim 2009	N= 14; Age: 55±15 yrs; BMI: 26.6±5.9 kg·m^{-2}. The program was completed at home. Physiotherapist visited patients to make sure that patients were	N= 7; Age: 65±9 yrs; BMI: 25.3±2.7 kg·m^{-2}. No exercise suggested.	Colo-rectal surgery.	N	3.8±1.2 weeks.	*Frequency of supervised sessions:* ~1/week. *Session length:* 20-30 min. *Type:* Aerobic exercise on cycle-ergometer.

correctly completing and recording the exercise program.	*Intensity:* 40-65% of maximum heart rate or 11-16 of Borg scale. *Progression:* Increasing volume from 20 to 30 min, intensity from 40-65% of maximum heart rate or 11 to 16 of Borg scale along the prehabilitation program. *Additional support:* Not reported.

Data is presented as mean±SD or median (IQR).
Yrs: years; BMI: Body mass index; Y: Yes; N: No, AAA: Abdominal aortic aneurysm.