

Peer Review File

Article Information: <https://dx.doi.org/10.21037/dmr-21-84>

Reviewer A

Comment 1

Prehabilitation may include other components than exercise (e.g., nutrition, psychosocial support). The authors seem to use the terms “prehabilitation” and “exercise prehabilitation” interchangeably. I suggest to use the same term consistently throughout the manuscript.

Reply 1: Changed to exercise prehabilitation throughout the text where appropriate.

Comment 2

There seem to be a mismatch between the primary aim and the primary outcome. The aim is to evaluate the effects of exercise on postoperative complications. Yet, the primary aim is changes in functional capacity, and the secondary outcome is postoperative complications.

Reply 2: Primary aim is the same as primary outcome – to assess the feasibility of exercise prehabilitation by seeing an objective change in functional capacity preoperatively. Secondary outcome is effect on post-operative complications.

Changes in the text:

- Added Primary Outcome and Secondary Outcome headings in Aims section – lines 123 and 127.
- Amendments in abstract – lines 28/29.

Comment 3

Please write out abbreviations in the abstract.

Reply 3: Abbreviations written out throughout abstract.

Comment 4

The authors seem to have overly focus on positive results. Please do also mention non-findings and negative findings. E.g., in line 284, the authors state: “Of the studies looking at VO₂ max, only one did not show any significant improvement”. This is in stark contrast to the conclusion of the abstract.

Reply 4: The abstract concludes that exercise prehabilitation is feasible as significant improvements in functional capacity were found which would support the line that only one study looking at VO₂ max did not see an improvement.

Changes to text: Page 13 line 333 – added “out of four”

Comment 5

There is a mismatch between the aim/outcome and the conclusion. In the conclusion, the authors state that exercise is feasible, but feasibility is not an outcome of the study.

Reply 5: Feasibility is the primary outcome of the study – please see aims section.

Comment 6

The authors should mention the result of the risk of bias assessment in the abstract.

Reply 6: Added in abstract results section.

Changes to text: Page 2, Line 44.

Comment 6b

Line 38: the authors state that: “high-quality non-randomized were included”. Did you exclude low-quality non-randomized studies? In that case, this should be clarified in the method section.

Reply 6b: Changes have been made to the method section.

Changes in text: lines 195-203

Comment 7

Many recent SR/MA exist on this topic. The authors should acknowledge recent SR (e.g., Lambert et al 2021, Annals of surgery and Thomsen et al. 2021, European Journal of Surgical Oncology) and justify the need for a new SR. What does this SR add compared to Lambert (2021) and Thomsen (2021)?

Reply 7:

- Thomsen et al 2021
 - o Includes patients with colorectal cancers. Due to successful surveillance programs these cancers are generally picked up earlier and have less of an impact on nutritional intake/deconditioning prior to surgery. We wanted to assess the feasibility of prehabilitation programs on patients that were in the upper GI cancer cohort who are generally starting from a position of malnourishment, sarcopenia, and frailty.
 - o The Thomsen et al review focused on perioperative exercise – only 4 studies included looked at preoperative exercise, the other 6 were postoperative.
- Lambert et al 2021
 - o Includes colorectal cancer patients. 9 out of 15 studies included were colorectal. This cohort has a reasonable evidence base now to show improvement in length of stay following prehabilitation – therefore we were keen to focus solely on the UGI cohort.

Changes to text: Paragraph added in introduction – Lines 87-94

Comment 8

Aims differ between abstract and introduction. Please correct this.

Reply 8: Corrected – see above changes to similar comments

Comment 9

In line 137, the authors state that they conducted the review in accordance with PRISMA. Conducted should be replaced with reported.

Please refer to the PRISMA checklist in the text.

Also, this is already stated in line 133.

Changes to text:

- Line 133 deleted
- Changed wording to reported line 137

Comment 10

Please also provide a PRISMA-S checklist.

Comment 11

Please provide a reference to HDAS. The reader may not be familiar with this tool.

Changes in text: Reference 22 added in line 144

Comment 12a

In line 154, the authors state that “All studies had to include an objective measure of functional capacity assessment.” Why was this a requirement? It gives the impression that functional capacity was the primary outcome of the study, since no restrictions were made regarding the other outcomes of the study.

Reply 12a: The main objective as stated in abstract and the Aims section was feasibility – an exercise prehabilitation program would be considered feasible if the patients were able to adhere to it and if it succeeded in producing the desired results of improving preoperative functional capacity. A significant change in an objective functional capacity measurement is a good way of measuring both these aspects.

Changes in text: Additional line to above sentence to provide more clarity – line 161

Comment 12b

The eligibility criteria are insufficiently described. Please specify what type of studies that were eligible (e.g., RCTs, quasi-RCTs, single-arm trials, non-randomized controlled trials, etc).

Reply 12b: Answered in new paragraph in methods

Changes to text: 181-189

Comment 13

In line 157-158, the authors state that “All articles requiring full text review during the eligibility screening process were available online and therefore no request for additional details from authors was required”. This is an invalid argument. Details could easily be missing although the full text was available online.

Reply 13: No required details were missing from the full texts available. Text changed to reflect this more clearly

Changes to text: Line 169-170

Comment 14

Line 160 and onwards: Please be more specific. What is meant by e.g. “study characteristics” and “composition of prehabilitation program”?

Changes to text: Lines 173-4

Comment 15

Why were QoL scores extracted? Was this an outcome? In that case, it should be listed with the other outcomes throughout.

Reply 15: QoL was an outcome as stated in the Aims section – line 128.

Comment 16

The risk of bias assessment is insufficiently described. Who performed the assessment? Was it performed independently by more than one author?

Changes to text: Lines 193-4

Comment 17

Was the study pre-registered? If not, this should be clearly stated to allow the reader to judge the quality of the study.

Reply 17: The study went through the Brighton Medical School dissertation committee and was approved in June 2020.

Changes to text: Additional sentence in method – lines 138-140.

Comment 18

In the PRISMA flow chart, boxes seem to be missing.

Also, was Google Scholar used? In that case, it should be listed with other databases. It also appears from the flow chart that the authors performed citation searches. This should be specified in the methods. Also specify whether you performed forward citations, backward citations, or both.

Reply 18: Not sure what boxes are missing on the PRISMA flow chart – the latest revised version from 2020 is used so it may look different to what the reviewer has seen previously? Google scholar and citations were used – this has been updated in methods section

Changes to text: 158-161

Comment 19

Line 186 (and abstract): what is meant by feasibility study? A study that assessed feasibility? Single-arm study or quasi-controlled studies? Elsewhere in the manuscript (e.g., line 215) the authors refer to the studies as observational.

Reply 19: Feasibility was used as that was the term described to the study by the authors – however they are all observational cohort studies. Changes in the text have been made to reflect this.

Changes to text:

- Table 1 – studies changed from feasibility to cohort
- Abstract line 43
- Results – Line 217-8

Comment 20

It is unclear whether grey literature was searched or not. Grey literature is mentioned in the abstract and in the results, but not in the method section. Please clarify in methods.

Reply 20: Grey literature research was carried out – this has been added to the method section

Changes to text: Lines 157-161.

Comment 21

Line 190: The authors state that “The risk of bias in the RCTs was assessed using the ROB-2 tool as described 190 in section 2.7.” This is already written in the methods section.

Changes to text: This sentence has been deleted

Comment 22

The authors should provide justifications for the ROB2 assessment where judgments were made (i.e., where authors used “probably yes” or “probably no” to answer signaling question).

Reply: The explanation for the bias assessment can be found in lines 229 to 240

Comment 23

It seems like the authors are simply counting the number of studies that found a statistically significant change in their outcomes of interest. This may be very misleading, as small studies and studies with high risk of bias are more likely to result in significant results. Instead, the authors should provide a table presenting the results

of all eligible studies for all your outcomes (i.e., pre- and post-intervention values, change values, results of significance test, if available).

Reply 23: Significant test results and change values can be seen in Table 4 in the appendix.

Comment 24

The result section does not provide any results regarding feasibility.

Reply 24: Results has a section on changes in functional capacity – using this as a surrogate marker for feasibility is discussed in the method section.

Changes to text: Line 330 + Line 181

Comment 25

The authors should acknowledge the limitations of their review, including the use of only one reviewer in the study selection process, exclusion on non-English language trials, the lack of a pre-registered protocol, and lack of safety outcomes.

Changes to text: Lines 583-87

Comment 26

The authors seem to have missed several studies in the field (Christensen 2019, British Journal of Surgery Open; Xu, 2015, The Oncologist). This may be due to a somewhat limited search strategy (very few search terms, no use of e.g., MESH terms). The authors should discuss this.

Reply 26:

- **Christensen 2019: QoL surveys on patients with rectal cancer – this would not have met the criteria for inclusion in the study**
- **Xu 2015: This was a study looking at patients undergoing exercise during their chemotherapy treatment with no surgical focus. The information from this although useful in terms of whether patients will adhere to an exercise program during this kind of treatment, would not have met the inclusion criteria as we were looking specifically at patients prior to surgical procedures with definitive time constraints.**

Comment 27

The conclusions of the review are in stark contrast to a recent SR/MA (Thomsen, 2021, European Journal of Surgical Oncology). The authors should discuss this discrepancy in the discussion.

Reply 27: See reply 7 re: the differences between our study and the Thomsen review – given the different review questions and different studies eligible for inclusion it is possible that different conclusions could be drawn.

Comment 28

The authors state the prehabilitation exercise is feasible in the eligible population. There seem to be no data to support this claim (see comment 24).

Reply 28: Feasibility and the data to support this is discussed in the discussion.

Reviewer B

Overall, the review is well written. My biggest concern is that it doesn't seem to draw any novel conclusions, because several similar reviews (or at least reviews focusing on exercise in a subset of the clinical population included here) have been published. I have only a few comments for improvement.

1. There are several places with grammar or punctuation errors, or with sentence structure that doesn't make sense. This manuscript could use some careful editing for run-on sentences, pedestrian phrasing, etc. I have highlighted some of the odd word or sentence structures that were most obvious to me.

Reply 1: The authors have re-read and edited parts throughout

2. Page 17, line 410, the authors state that these results appear to suggest that the type of aerobic exercise is less important than the frequency of the sessions and the duration of the program. What about intensity of exercise?

Reply 2: The intensity also appears to be less important as HIIT and walking both caused significant changes in functional capacity.

Changes to text: Line 451

3. I'm not totally convinced that combining exercise studies performed in patients with different types of UGI cancer is reasonable, given the different clinical characteristics of patients with oesophageal compared to pancreatic cancer, for example. Some mention of these potential differences should be included.

Changes in text – added in limitations of review. Lines 567-72