Centre universitaire de santé McGill

McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre (MUHC)

Evaluating the value of a prehabilitation clinic for surgical patients at the MUHC

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Report prepared for the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC)

by

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TAU Committee

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REPORT REQUESTOR

This report was requested by Ewa Sidorowicz, Director of Professional Services at the MUHC in January 2020. The new report will be presented to her on completion.

TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

Type of recommendation	Explanation
Approved	• Evidence for relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, is sufficiently strong to justify a recommendation that the technology be accepted, used and funded through the institutional operating budget
Approved for evaluation	• There is a *probability* that relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, are favorable but the evidence is not yet sufficiently strong to support a recommendation for permanent approval. • The evidence is sufficiently strong to recommend a *temporary* approval for the purposes of evaluation, funded through the institutional operating budget.
Not approved	• There is insufficient evidence for the relevant decision criteria, including efficacy, safety, and cost; • The costs of any use of the technology (e.g. for research purposes) should not normally be covered by the institutional budget.

DISCLAIMER

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ABSTRACT

- Post-surgery complications have been linked to poor functional capacity. Prehabilitation aims to enhance patient preoperative functional capacity through physical exercise to better withstand the stress from surgery.
- The objective of this report was to assess the evidence on the effectiveness of prehabilitation, consisting of physical training with or without other components (psychological support, nutritional supplementation, education), on postoperative outcomes compared to control group (no prehabilitation or sham intervention).
- We performed a literature review to evaluate the evidence from systematic reviews and meta-analyses as well as from large observational studies recently published. Studies conducted at the MUHC on the association between prehabilitation and postoperative outcomes were also assessed.
- Most systematic reviews or meta-analyses reported that prehabilitation was associated with a decreased postoperative complication rate (overall or pulmonary) and a shorter length of stay (LOS) in patients undergoing lung, cardiac or cardiothoracic/upper abdominal surgery, and a lower postoperative pulmonary complication rate in patients scheduled for abdominal surgery.
- The majority of systematic reviews or meta-analyses found that trimodal prehabilitation consisting of physical exercise, nutritional supplement and psychological support was associated with an improved functional capacity in patients undergoing gastrointestinal, colorectal or abdominal surgery.
- A systematic review found that LOS and pain were reduced in the prehabilitation group compared to the control group in patients scheduled for spinal surgery.
- However, the quality of evidence from the systematic reviews or meta-analyses was mainly low due to the high risk of bias, small sample size and clinical heterogeneity in the primary studies.
- Low-quality evidence from 2 large observational studies did not support an association between prehabilitation and postoperative outcomes in patients undergoing abdominal or non-small-cell lung cancer surgery.

- Overall, low-quality evidence from the 5 RCTs and observational studies conducted at the MUHC suggests that postoperative outcomes did not differ between the prehabilitation and control groups.
- Our review of the large volume of available data, while lacking high quality evidence, indicates that prehabilitation is beneficial in patients undergoing lung, cardiac or cardiothoracic/upper abdominal surgery to reduce complications (overall and pulmonary) and length of stay, and that trimodal prehabilitation is beneficial for patients undergoing abdominal, colorectal or gastrointestinal surgery to improve functional capacity. Higher quality evidence is needed to confirm these results and in further surgical populations.

RÉSUMÉ

- Les complications postopératoires sont associées à une capacité fonctionnelle réduite. La préadaptation (réhabilitation préopératoire) vise à améliorer la capacité fonctionnelle du patient via l'exercice physique afin de mieux résister au stress lié à la chirurgie.

- L'objectif de ce rapport était d'évaluer les preuves sur l'efficacité de la préadaptation, consistant d'un entrainement physique avec ou sans autres composants (soutien psychologique, supplémentation nutritionnelle, éducation), sur les événements postopératoires par rapport au groupe témoin (sans préadaptation ou intervention fictif).

- Nous avons effectué une revue de la littérature pour évaluer les preuves provenant des revues systématiques et méta-analyses ainsi que de récentes larges études observationnelles.

- La plupart des revues systématiques ou méta-analyses ont rapporté que la préadaptation était associée à une diminution de complications postopératoires (globales ou pulmonaires) et à une durée de séjour plus courte chez les patients ayant eu une chirurgie cardiaque, cardiothoracique ou au poumon, et une diminution postopératoire de complications pulmonaires chez les patients ayant eu une chirurgie abdominale.

- Une revue systématique a montré que la durée de vie et la douleur étaient réduites dans le groupe de préadaptation par rapport au groupe témoin chez les patients ayant eu une chirurgie de la colonne vertébrale.

- Cependant, la qualité des preuves provenant des revues systématiques ou méta-analyses était principalement faible en raison du risque de biais élevé, de la petite taille de l'échantillon et de l'hétérogénéité clinique dans les études primaires.

- Deux larges études observationnelles avec une faible qualité de preuves n'ont pas montré l'existence d'une association entre la préadaptation et les événements postopératoires chez les patients ayant eu une chirurgie abdominale ou un cancer du poumon non à petites cellules.

- En général, les preuves de faible qualité provenant des 5 études cliniques randomisées (ECR) et des études observationnelles menées au CUSM suggèrent

que les événements postopératoires ne différaient pas entre les groupes de préadaptation et de contrôle.

- Notre revue de l'abondante littérature disponible, bien que contenant peu de preuve de grande qualité, indique que la préadaptation est bénéfique chez les patients devant subir une chirurgie pulmonaire, cardiothoracique/abdominale supérieure ou cardiaque pour réduire les complications (globales et pulmonaires) et la durée du séjour, et que la préadaptation trimodale est bénéfique pour les patients devant subir une chirurgie abdominale, colorectale ou gastro-intestinale pour améliorer la capacité fonctionnelle. Des preuves de meilleure qualité sont nécessaires pour confirmer ces résultats et également dans d'autres populations chirurgicales.

LIST OF ABBREVIATIONS

CI	Confidence interval
HTA	Health technology assessment
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
RCT	Randomized controlled trial
TAU	MUHC Technology Assessment Unit
NRS	Non-randomized study
LOS	Hospital length of stay
QoL	Quality of life
6MWT	6-minute walking test
CCI	Comprehensive Complications Index
SF-36	Short form 36 questionnaire
ASA	American Society of Anesthesiologists
PPC	Pulmonary postoperative complications
WHO	World Health Organization
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis
FACT-P	Functional Assessment of Cancer Therapy-Prostate
PORPUS	Patient-Oriented Prostate Utility Scale
HADS	Hospital Anxiety and Depression Scale
EORTC	European Organisation for Research and Treatment of Cancer
OS	Overall Survival
DFS	Disease-Free Survival

EXECUTIVE SUMMARY

Background

Surgery is a major stress on the body and patients with poor physical capacity are more likely to develop postoperative complications, which in turn could translate into longer hospital length of stay. Prehabilitation is a process to increase a patient's functional capacity in order to endure the surgical trauma. Several studies had examined the association between prehabilitation and postoperative outcomes. Yet, no clear consensus was reached on this matter.

Objectives

The objective of this report was to assess the evidence on the effectiveness of prehabilitation, consisting of physical training with or without other components (psychological support, nutritional supplementation, education), on postoperative outcomes compared to control group (no prehabilitation or sham intervention) in patients scheduled for surgery.

Methods

We reviewed evidence from relevant systematic reviews and meta-analyses on the association between prehabilitation and postoperative outcomes. Recent studies on the effectiveness of prehabilitation on outcomes following surgery conducted at the MUHC as well as observational studies with large sample size were also evaluated. In addition, we searched for clinical guidelines and health technology assessment (HTA) reports pertaining to this subject.

Results: Literature review

We identified 48 systematic reviews and meta-analyses examining the association between prehabilitation and postoperative outcomes in twelve surgical populations.

- For patients scheduled for **lung surgery**, 8 of the 9 systematic reviews or meta-analyses reported that prehabilitation was associated with 48% to 75% reduction of postoperative complications (overall or pulmonary) as well as a shorter LOS compared to the control group. Among the meta-analyses that included only RCTs, the largest meta-analysis (5 RCTS, n=332) reported a relative risk (RR) of 0.52 (95% CI: 0.36, 0.74) for overall complications; for pulmonary complications, the largest meta-analysis (4 RCTs, n=185) reported a RR of 0.32 (95% CI: 0.16,

0.66); and for LOS, the largest meta-analysis (6 RCTs, n=467) reported a decrease (standardized mean difference: -0.58, 95% CI: -0.97, -0.20) in the prehabilitation group compared to the control group.

- For patients undergoing **cardiac surgery**, 5 of the 6 meta-analyses found that prehabilitation decreased postoperative overall complications (the only meta-analysis [6 studies, n=833]: RR=0.41, 95% CI: 0.28, 0.62) and decreased pulmonary complications (largest meta-analysis [4 RCTs, n=416]: RR=0.57, 95% CI: 0.40, 0.81). Four meta-analyses also reported reduced LOS for the prehabilitation group. However, no significant difference was observed for quality of life (QoL) or risk of mortality between the prehabilitation and control groups.

- For patients undergoing **cardiothoracic/upper abdominal surgery**, all 3 meta-analyses found that prehabilitation was associated with a decrease in pulmonary complications rate by at least 46% (largest meta-analysis [4 RCTs, n=406]: RR=0.40, 95% CI: 0.23, 0.72). Two of 3 systematic review or meta-analyses reported a shorter LOS in the prehabilitation group. On the other hand, one meta-analysis reported that the risk of mortality was not different between prehabilitation and control groups, while 2 meta-analyses reported contradicting results for functional capacity recovery.

- For patients undergoing **vascular surgery**, one systematic review (1 RCT, n=124) reported that unimodal prehabilitation was associated with a shorter LOS (median=7 [interquartile range: 5-9] vs. median=8 [interquartile range: 6-12.3] days, P=0.025). The same systematic review (3 RCTs, n=197) reported no association between prehabilitation and postoperative complication rate compared to standard care.

- For patients scheduled for **gastrointestinal or colorectal surgery**, all 7 systematic reviews or meta-analyses found that trimodal but not unimodal prehabilitation improved postoperative functional capacity (largest meta-analysis [3 RCTs, n=191]: MD=48.22m, 95% CI: 1.53, 94.9). No difference was reported for the other postoperative outcomes (complications, LOS, readmission or QoL).

- For patients scheduled for **abdominal surgery**, a systematic review and a meta-analysis (2 RCTs, n=164) found that trimodal prehabilitation was associated with improved postoperative functional capacity (RR=1.63, 95% CI: 1.10, 2.41). Additionally, 5 of the 8 systematic reviews or meta-analyses reported 37% to 65% reduction in overall complication rate (largest meta-analysis [9 RCTs, n=708]:

RR=0.63, 95% CI: 0.46, 0.87) and in pulmonary complications (largest meta-analysis [8 RCTs, n=490]: RR=0.40, 95% CI: 0.23, 0.68) in the prehabilitation group compared to the control group. However, LOS and QoL did not differ between the 2 groups.

- For patients scheduled for **esophageal surgery**, a systematic review (3 studies, n=396) and a meta-analysis (2 studies, n=99) reported that postoperative complication and LOS did not differ between unimodal prehabilitation and control groups.

- For patients undergoing **surgery for liver transplant**, a meta-analysis (1 RCT, n=23) found that preoperative aerobic exercise did not reduce postoperative complication rate compared to non-prehabilitation.

- For patients undergoing **knee surgery**, the majority of the 11 systematic reviews or meta-analyses found that functional capacity, LOS, readmission rate, pain or QoL did not differ between the prehabilitation and control groups.

- For patients scheduled for **hip surgery**, 3 meta-analyses found that prehabilitation was not associated with functional capacity recovery, pain reduction or QoL improvement compared to standard care.

- For patients undergoing **spinal surgery**, preoperative aerobic exercise and strength training reduced LOS and pain compared to standard care according to a systematic review (1 RCT, n=92).

- However, the results reported by the systematic reviews or meta-analyses had several limitations, including moderate to high risk of bias and small sample size in the primary studies, clinical heterogeneity in the interventions for the prehabilitation and control groups and usage of inappropriate or not robust methodology. Furthermore, the overlapping of primary studies across several systematic reviews or meta-analyses artificially amplified the strength of evidence of the positive association between prehabilitation and some postoperative outcomes.

Two large and recently published observational studies were evaluated.

- A study by Janssen et al. assessed the effect of prehabilitation on LOS, postoperative complication rate, 30-day readmission and 30-day mortality in patients ≥70 years (n=627) undergoing abdominal surgery. No association was found for any postoperative outcome.

- A study by Uda et al. examined the association between short-term prehabilitation and overall mortality or in-hospital postoperative pulmonary complications following surgery for non-small-cell lung cancer by using a nationwide administrative claims and discharge database. After matching patients (n=7518 pairs) for confounding factors by a one-to-one propensity score, the authors reported that both outcomes did not differ between the prehabilitation and control groups.

- No official clinical guideline or recommendations from HTAs for prehabilitation have been published.

Experience at the MUHC

- Five recent studies, 3 RCTs and 2 observational studies, conducted at the MUHC were identified. Overall, multimodal prehabilitation was not associated with a decrease in the risk of complication or mortality, readmission rate or LOS, nor an improved QoL in patients scheduled for abdominal (colorectal or prostate) surgery. The largest RCT (n=120) reported no difference in 30-day complications (OR=0.9, 95% CI: 0.4, 2.2), 30-day LOS (MD= -5.8 days, 95%CI: -17.3, 5.8), walking capacity as measured by the 6MWT (MD=11.2m, 95%CI: -13.7, 36.1 before surgery and MD=18.5m, 95%CI: -20.2, 57.3 at 4-week post-surgery), and QoL as measured by the SF-36 questionnaire (MD= -0.43, 95% CI: -7.2, 6.3 at 4-week post-surgery for physical component and MD= -2.3, 95% CI: -9.7, 5.1 at 4-week post-surgery for mental component). It is possible this study was underpowered to detect an association with the studied outcomes.

CONCLUSIONS

- Our review of the large volume of available data, while lacking high quality evidence, indicates that prehabilitation consisting of physical training with or without other components, is beneficial in the following surgical populations:

    - Patients undergoing lung, cardiac or cardiothoracic/upper abdominal surgery to reduce complications (overall and pulmonary) and hospital length of stay;

    - Patients undergoing abdominal, colorectal or gastrointestinal surgery benefit from trimodal prehabilitation to improve functional capacity.

- Current systematic reviews and meta-analyses are limited by several methodological issues in the primary studies (small sample sizes, issues with random allocation and blinding) as well as in the systematic reviews and meta-analyses (e.g., high heterogeneity). In addition, many primary studies were included in multiple systematic reviews or meta-analyses.
- An accrual of studies with larger sample sizes and better methodology is needed to confirm the above findings and improve evidence for further surgical populations.

RECOMMENDATIONS

- The TAU Policy Committee, made up of stakeholders from across the McGill University Health Centre, reviewed the evidence and issued the following recommendation: Not Approved
- This recommendation was reached based on the following:
    - Benefits of prehabilitation are not supported by strong, high-quality evidence. Local evidence, gathered within the context of care at the MUHC, does not support a beneficial effect of prehabilitation on patient outcomes.
    - Given these findings, prehabilitation does not fit the criteria to be funded by the MUHC institutional budget. Further research is necessary to understand the comparative-effectiveness of prehabilitation (vs. standard care), as well as the relative contribution of different interventions used within prehabilitation. Several of these interventions (e.g. counseling, education, nutritional management) can be embedded with existing MUHC clinics (e.g. the preoperative clinic).
- This recommendation may be reviewed in 3 years, if new data from the literature and/or the local context become available.

SOMMAIRE

Contexte

La chirurgie est un stress important pour le corps et les patients ayant une faible capacité physique sont plus susceptibles de développer des complications postopératoires, qui à leur tour pourraient se traduire par une durée d'hospitalisation plus longue. La préadaptation est un processus visant à augmenter la capacité fonctionnelle d'un patient afin de supporter le traumatisme d'une chirurgie. Plusieurs études ont examiné l'association entre la préadaptation et les issues postopératoires. Pourtant, aucun consensus clair n'a été atteint sur cette question.

Objectifs

L'objectif de ce rapport était d'évaluer les preuves sur l'efficacité de la préadaptation, consistant d'un entrainement physique avec ou sans autres composants (soutien psychologique, supplémentation nutritionnelle, éducation), sur les issues postopératoires par rapport au groupe témoin (sans préadaptation ou intervention fictif) chez les patients ayant subi une intervention chirurgicale

Méthodologie

Nous avons examiné les données probantes provenant de revues systématiques et méta-analyses pertinentes sur l'association entre la préadaptation et les issues postopératoires. Des études récentes sur l'efficacité de la préadaptation sur les résultats après une chirurgie menées au CUSM, ainsi que des études observationnelles avec un large échantillon de patients ont également été évaluées. De plus, nous avons recherché des lignes directrices cliniques et des rapports d'évaluation des technologies de la santé relatifs à ce sujet.

Résultats

Nous avons identifié 48 revues systématiques et méta-analyses examinant l'association entre la préadaptation et les issues postopératoires chez douze populations chirurgicales.

- Pour les patients devant subir une **chirurgie du poumon**, 8 des 9 revues systématiques et méta-analyses ont rapporté que la préadaptation était associée à une réduction de 48 % à 75 % des complications postopératoires (globales ou pulmonaires), ainsi qu'à une durée de vie plus courte par rapport au groupe

témoin. Parmi les méta-analyses qui n'incluaient que des ECR, la plus grande méta-analyse (5 ECR, n=332) a rapporté un risque relatif (RR) de 0,52 (95% IC: 0,36, 0,74) pour les complications globales; pour les complications pulmonaires, la plus grande méta-analyse (4 ECR, n=185) a rapporté un RR de 0,32 (95% IC: 0,16, 0,66); et pour la durée de vie, la plus grande méta-analyse (6 ECR, n=467) a reporté une diminution (différence moyenne standardisée: -0,58, 95% CI: -0,97, -0,20) dans le groupe de préadaptation par rapport au groupe contrôle.

- Pour les patients devant subir une **chirurgie cardiaque**, 5 des 6 méta-analyses ont trouvé que la préadaptation réduisait les complications globales postopératoires (l'unique méta-analyse [6 études, n=833]: RR= 0,41, 95% IC: 0,28, 0,62) et réduisait les complications pulmonaires (la plus grande méta-analyse [4 ECR, n=416]: RR=0,57, 95% IC: 0,40, 0,81). Quatre méta-analyses ont également rapporté une réduction de la durée de séjour pour le groupe de préadaptation. Cependant, aucune différence significative n'a été observée pour la qualité de vie ou le risque de mortalité entre les groupes de préadaptation et de contrôle**.**

- Pour les patients devant subir une **chirurgie cardiothoracique/abdominale supérieure**, toutes les 3 méta-analyses ont trouvé que la préadaptation était associée à une diminution du taux de complications pulmonaires d'au moins 46% (la plus grande méta-analyse [4 ECR, n=406]: RR=0,40, 95% IC: 0,23, 0,72). Deux des trois revues systématiques ou méta-analyses ont rapporté une durée de séjour plus courte pour le groupe de préadaptation. D'autre part, une méta-analyse a rapporté que le risque de mortalité n'était pas différent entre les groupes de préadaptation et de contrôle, tandis que 2 méta-analyses ont rapporté des résultats contradictoires pour la récupération des capacités fonctionnelles.

- Pour les patients devant subir une **chirurgie vasculaire**, une revue systématique (1 ECR, n=124) a rapporté que la préadaptation unimodale était associée à une durée de vie plus courte (médiane=7 [intervalle interquartile: 5-9] vs médiane=8 [intervalle interquartile: 6-12,3] jours, p=0,025). La même revue systématique (3 ECR, n=197) a rapporté aucune association entre la préadaptation et le taux de complications postopératoires par rapport aux soins standard.

- Pour les patients devant subir une **chirurgie gastro-intestinale ou colorectale**, toutes les 7 revues systématiques ou méta-analyses ont trouvé que la préadaptation trimodale mais pas unimodale améliorait la capacité fonctionnelle postopératoire (la plus grande méta-analyse [3 ECR, n=191]: DM=48,22 m, 95%

IC: 1,53, 94,9). Aucune différence n'a été rapportée pour les autres issues postopératoires (complications, durée de séjour, réadmission ou qualité de vie).

- Pour les patients devant subir une **chirurgie abdominale**, une revue systématique et une méta-analyse (2 ECR, n=164) ont trouvé que la préadaptation trimodale était associée à une amélioration de la capacité fonctionnelle postopératoire (RR=1,63, 95% IC: 1,10, 2,41). De plus, 5 des 8 revues systématiques ou méta-analyses ont rapporté une réduction de 37% à 65% de complications globales (la plus grande méta-analyse [9 ECR, n=708]: RR=0,63, 95% IC: 0,46, 0,87) et complications pulmonaires (la plus grande méta-analyse [8 ECR, n=490]: RR=0,40, 95% IC: 0,23, 0,68) dans le groupe de préadaptation par rapport au groupe contrôle. Cependant, la durée de séjour et la qualité de vie ne différaient pas entre les 2 groupes.

- Pour les patients devant subir une **chirurgie de l'œsophage**, une revue systématique (3 études, n=396) et une méta-analyse (2 études, n=99) ont rapporté que les complications postopératoires et la durée de séjour ne différaient pas entre les groupes de préadaptation unimodale et de contrôle.

- Pour les patients devant subir une **chirurgie pour une transplantation du foie**, une méta-analyse (1 ECR, n=23) a montré que l'exercice aérobie préopératoire ne réduisait pas les complications postopératoires par rapport à une intervention non-préadaptation.

- Pour les patients devant subir une **chirurgie du genou**, la majorité des 11 revues systématiques ou méta-analyses ont trouvé que la capacité fonctionnelle, la durée de séjour, le taux de réadmission, la douleur ou la qualité de vie ne différaient pas entre les groupes de préadaptation et de contrôle.

- Pour les patients devant subir une **chirurgie de la hanche**, 3 méta-analyses ont trouvé que la préadaptation n'était pas associée à la récupération des capacités fonctionnelles, à la réduction de la douleur ou à l'amélioration de la qualité de vie comparer aux soins standard.

- Pour les patients devant subir une **chirurgie de la colonne vertébrale**, l'exercice aérobie préopératoire et l'entraînement musculaire ont réduit la durée de séjour et la douleur par rapport aux soins standard selon une revue systématique (1 ECR, n=92).

- Cependant, les résultats rapportés par les revues systématiques ou les méta-analyses présentaient plusieurs limites, notamment un risque de biais modéré à

élevé et une petite taille d'échantillon dans les études primaires, l'hétérogénéité clinique dans les interventions pour les groupes de préadaptation et de contrôle, ainsi que l'utilisation de méthodes inappropriées ou méthodologie non robuste. De plus, l'inclusion des mêmes études primaires dans plusieurs revues systématiques ou méta-analyses a artificiellement amplifié la force des preuves de l'association positive entre la préadaptation et certaines issues postopératoires.

Deux récentes et larges études observationnelles ont été évalué.

- Une étude de Janssen et al. a évalué l'effet de la préadaptation sur la durée de séjour, les complications postopératoires, la réadmission à 30 jours et la mortalité à 30 jours chez les patients de ≥70 ans (n=627) devant subir une chirurgie abdominale. Aucune association n'a été trouvée pour aucun des issues postopératoires.

- Une étude d'Uda et al. a examiné l'association entre la préadaptation à court terme et la mortalité globale ou les complications pulmonaires postopératoires à l'hôpital après une chirurgie pour un cancer du poumon non à petites cellules en utilisant une base de données nationale sur les réclamations et les congés de l'hôpital. Après avoir apparié les patients (n=7518 paires) pour les facteurs de confusion par un score de propension un-à-un, les auteurs ont trouvé que les deux issues postopératoires ne différaient pas entre les groupes de préadaptation et de contrôle.

Aucune directive clinique officielle ou recommandation des unités d'évaluation des technologies de la santé pour la préadaptation n'a été publiée.

Préadaptation au CUSM

- Cinq études récentes, 3 ECR et 2 études observationnelles, menées au CUSM ont été identifiées. En général, la préadaptation multimodale n'était pas associée à une diminution du risque de complication ou de mortalité, du taux de réadmission ou de la durée de séjour, ni à une amélioration de la qualité de vie chez les patients devant subir une chirurgie abdominale (colorectale ou prostate). La plus grande ECR (n=120) a rapporté aucune différence dans les complications à 30 jours (OR=0,9, 95% IC: 0,4, 2,2), durée de vie à 30 jours (DM = -5,8 jours, 95% IC: -17,3, 5,8), capacité de marcher mesurée par le 6MWT (DM = 11,2 m, 95% IC: -13,7, 36,1 avant la chirurgie et DM=18,5 m, 95% IC: -20,2, 57,3 à 4 semaines

après la chirurgie) et la qualité de vie mesurée par le questionnaire SF-36 (DM= -0,43, 95% IC: -7,2, 6,3 à 4 semaines après la chirurgie pour la composante physique et DM = -2,3, 95% IC: -9,7, 5,1 à 4 semaines après la chirurgie pour la composante mentale). Il est possible que cette étude n'ait pas la puissance statistique nécessaire pour détecter une association avec les résultats étudiés.

CONCLUSIONS

- Notre revue de l'abondante littérature disponible, bien que contenant peu de preuve de grande qualité, indique que la préadaptation consistant en un entraînement physique avec ou sans autres composants, est bénéfique dans les populations chirurgicales suivantes :
    - Les patients devant subir une chirurgie pulmonaire, cardiaque ou cardiothoracique/abdominale supérieure pour réduire les complications (globales et pulmonaires) et la durée du séjour à l'hôpital;
    - Les patients devant subir une chirurgie abdominale, colorectale ou gastro-intestinale bénéficient d'une préadaptation trimodale pour améliorer leurs capacités fonctionnelles.
- Les revues systématiques et les méta-analyses actuelles sont limitées par plusieurs problèmes méthodologiques dans les études primaires (petites tailles d'échantillons, problèmes d'allocation aléatoire et de mise en aveugle) ainsi que dans les revues systématiques et les méta-analyses (par exemple, hétérogénéité élevée). De plus, de nombreuses études primaires ont été incluses dans plusieurs revues systématiques ou méta-analyses.
- Une accumulation d'études avec des échantillons de plus grande taille et une meilleure méthodologie est nécessaire pour confirmer les résultats ci-dessus et améliorer les preuves pour d'autres populations chirurgicales.

RECOMMANDATIONS

- Le comité des politiques de TAU, composé d'intervenants de tout le Centre Universitaire de Santé de McGill, a examiné les preuves et a émis la recommandation suivante : Non approuvé
- Cette recommandation a été formulée sur la base des éléments suivants :

  - Les bénéfices de la préadaptation ne sont pas appuyés par des preuves solides et de haute qualité. Les preuves locales, recueillies dans le contexte des soins au CUSM, ne soutiennent pas un effet bénéfique de la préadaptation sur les évènements des patients.

  - Compte tenu de ces constatations, la préadaptation ne correspond pas aux critères pour être financée par le budget institutionnel du CUSM. Des recherches supplémentaires sont nécessaires pour comprendre l'efficacité comparative de la préadaptation (par rapport aux soins standard), ainsi que la contribution relative des différentes interventions utilisées dans le cadre de la préadaptation. Plusieurs de ces interventions (ex. consultation, éducation, gestion nutritionnelle) peuvent être intégrées aux cliniques existantes du CUSM (ex. la clinique préopératoire).

- Cette recommandation pourrait être revue dans 3 ans, si de nouvelles données issues de la littérature et/ou du contexte local deviennent disponibles.

EVALUATING THE VALUE OF A PREHABILITATION CLINIC FOR SURGERY PATIENTS AT THE MUHC

1. BACKGROUND

In 2008, it was estimated that over 230 million major surgery procedures were performed annually in 56 member countries of the World Health Organization (WHO).[1] Despite technological progress and advanced knowledge in medical care, surgery remains a burden on the patients. Postoperative complications are still frequently observed in patients after surgical procedure. Approximately 46% of patients who underwent colorectal surgery developed complications.[2] Almost a third of patients had complications after radical cystectomy[3], while 16.2% to 23.5% of patients experienced complications following surgery for pancreas.[4] Moreover, postoperative complications increase the likelihood of readmission (OR= 2.2, 95%CI: 1.55, 3.18) and prolonged hospital length of stay (OR= 1.44, 95%CI: 1.26, 1.65) after pancreatic resection.[5]

Multiple factors affect the risk of postoperative complications. One of them is the patient's functional capacity, which reflects the body's ability to cope with the physiological stress of surgery on the premise that a patient with higher exercise capacity will have higher physiologic reserve. It can be objectively evaluated with cardiopulmonary exercise testing (CPET) by measuring the highest oxygen uptake ($VO_{2\ max}$ or $VO_{2\ peak}$) and anaerobic threshold (AT). Low exercise capacity has been associated with worst postoperative outcomes. A meta-analysis found that patients without postoperative pulmonary complications (PPC) had higher exercise capacity at baseline, as measured by VO_{2max}, than those with PPC following lung resection (MD= 3.00 ml/kg/min, 95%CI: 1.98, 4.01).[6] A recent systematic review reported similar findings for patients undergoing esophageal or gastric surgery.[7] These results suggest that an intervention that can improve exercise capacity, a modifiable risk factor, could potentially reduce postoperative pulmonary complications.

Prehabilitation intervention aims to prepare the patient to withstand surgical stress by taking advantage of the preoperative period to enhance functional capacity through physical exercise.[8] It ideally involves the expertise of a multidisciplinary team (e.g., surgeon, anaesthetist, physiotherapist, nutritionist) to support the patient in the preoperative pathway. Prehabilitation has gained a lot of attention over the years, resulting in an abundance of published studies (RCTs, observational studies, systematic

reviews and meta-analyses) involving several surgical populations with unclear or conflicting results on the effectiveness of prehabilitation on postoperative outcomes.

Therefore, TAU was requested by Ewa Sidorowicz, director of professional services at the MUHC, to conduct an evaluation of the effectiveness of prehabilitation in reducing postoperative adverse events, such as postoperative complications and length of stay.

2. POLICY AND EVALUATION QUESTIONS

2.1 Policy Question

- What is the added clinical value of implementing a prehabilitation clinic for surgical patients at the MUHC?

2.2 Evaluation questions (Objective of this report)

- What is the evidence on the effectiveness of prehabilitation, consisting of physical training with or without other components (psychological support, nutritional supplementation, education), on postoperative outcomes, including postoperative complications and length of stay, compared to the control group (no prehabilitation or sham intervention) in patients scheduled for surgery?

3. METHODS

3.1 Literature search and quality assessment

We conducted a literature search on the effect of prehabilitation on postoperative outcomes following surgery by searching PubMed, the Cochrane library and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination. A librarian at the MUHC also performed a systematic search on Medline. Details on the search strategy and selection process are shown in Appendices and Figure 1, respectively. The most recent search was done on June 29, 2020.

Since a preliminary search resulted in substantial number of articles, our literature search was limited to reviews such as systematic reviews and meta-analyses published in the last 10 years. The most recent and high quality randomized controlled trials (RCTs)

or non-randomized studies (NRS) with large sample size published in the last 2 years were also considered. Clinical guidelines assessing the use of prehabilitation were also found.

Reviews assessing any form of physical activity as a prehabilitation intervention for adult patients scheduled for surgery were considered for the report. The intervention program could also include other components, such as nutritional support, psychological support and/or education. Prehabilitation could have been compared to a non-prehabilitation program (e.g., standard care) or sham intervention. Postoperative outcomes were limited to postoperative functional capacity pertaining to the surgical population, quality of life (QoL), overall complications, pulmonary complications, hospital length of stay (LOS), mortality, readmission and pain. All surgical populations were included.

The quality of evidence was graded as low, moderate or high. It was based primarily on the risk of bias assessment performed by the authors of the systematic reviews and meta-analyses. The quality was graded as low if the risk of bias was reported as high. For low (moderate) risk of bias, the quality was graded as high (moderate), but it could be downgraded by inappropriate methodology or biases introduced by the authors. If the risk of bias assessment was not done or unclear, the quality was graded as low.

The risk of bias assessment for RCTs was performed according to a modified Cochrane tool for assessing risk of bias.[9] The classification system was modified to low, moderate, high or unclear instead of low, high and unclear. The risk of bias assessment for observational studies was inspired by the ROBIN-I tool.[10] The following domains were evaluated: confounding bias, selection bias, intervention classification bias, outcome measurement bias and missing data bias. The risk of bias was classified as low, moderate, high or unclear. Subsequently, the same grading procedure, described in the previous paragraph, was used to evaluate the quality of evidence.

3.2 MUHC experience

The current policy for prehabilitation intervention for patients undergoing surgery at the MUHC is described. Furthermore, relevant articles on studies conducted recently at the MUHC were evaluated. The same classification and grading procedures, described previously, were used to assess the risk of bias and quality of evidence.

4. LITERATURE REVIEW

A total of 48 relevant systematic reviews or meta-analyses were included in the report. The physical training was performed as a stand-alone intervention (unimodal prehabilitation) or combined with other components such as psychological support (multimodal prehabilitation). The population was comprised of patients undergoing lung, cardiovascular, cardiothoracic/upper abdominal, abdominal, gastrointestinal, colorectal, esophageal, vascular, liver transplantation, knee, hip or spinal surgery. Multiple outcomes were examined in each review, either as the main or secondary outcomes. An overview of the outcomes by surgical population summarizes the results from the systematic reviews and meta-analyses in Table 1. The number of included systematic reviews and meta-analyses are summarized by surgical population and postoperative outcomes in Table 2. Two recent observational studies with large sample size were also included in the report.

4.1 Lung surgery

We identified 9 systematic reviews or meta-analyses assessing the effect of prehabilitation on postoperative outcomes following surgery for lung cancer or chronic obstructive pulmonary disease.[11–19] The interventions in the primary studies were mainly a combination of breathing technique, aerobic exercise, strength and/or resistance training without other components. In general, the training frequency varied from 2 to 10 times per week and lasted 1 to 10 weeks. The main findings and quality of evidence evaluations are summarized in Table 3.

Postoperative complications

The effectiveness of prehabilitation on postoperative complications were evaluated by 4 meta-analyses.[11–14] Low-quality evidence from the 4 reviews suggests that prehabilitation reduced the risk or odds of complications by 48% to 75% compared to control group, regardless of the study design included in the meta-analysis. Evidence was based on 3 to 8 primary studies, 2 of which were included in all of the 4 meta-analyses.

Postoperative pulmonary complications

Of the 5 reviews assessing postoperative pulmonary complications, 4 performed a meta-analysis.[14–18] They reported that the odds or risk of pulmonary complications was reduced by 55% to 68% in the prehabilitation group compared to the control group. Two

of the meta-analyses also did a subgroup analysis by pneumonia or atelectasis. One of them included 5 primary studies (n=319) and found a similar reduction in the odds of pneumonia (OR=0.47, 95%CI: 0.24, 0.95). The second meta-analysis was based on 2 RCTs (n=77) and 3 RCTs (n=137) for pneumonia and atelectasis, respectively, and did not report a significant reduction in either outcome [(OR=0.59, 95%CI: 0.19, 1.85) or atelectasis (OR=0.50, 95%CI: 0.10, 2.50)]. The only systematic review reported that 1 out of 2 RCTs (n=43) found a lower rate of pulmonary complications among patients receiving prehabilitation. However, the quality of evidence was low for all of the studies and 4 of the 10 primary studies were included in multiple reviews.

Length of stay (LOS)

Eight of the 9 reviews assessing the outcome LOS performed a meta-analysis.[11–17,19] The results indicate that LOS was shorter in the prehabilitation group compared to the control group in all of the 8 meta-analyses. The mean difference from 7 of the meta-analyses ranged from -4.98 days to -2.86 days, while the last meta-analysis found a standardized mean difference of -0.58 (95%CI: -0.97, -0.20). The systematic review reported that 1 out of 2 studies found a shorter LOS among the patients receiving prehabilitation.[18] However, the evidence was of poor quality for all of the studies and 8 out of 13 primary studies were included in at least 2 reviews.

4.2 Cardiac surgery

We identified 6 systematic reviews and meta-analyses assessing the effect of prehabilitation on postoperative outcomes following cardiac surgery.[20–25] The interventions in the primary studies were unimodal prehabilitation consisting mostly of inspiratory muscle training and could include aerobic exercises, strength training and/or resistance training. In general, the training frequency varied from 1 to 7 times per week and lasted mostly 1 to 10 weeks. The main findings and quality of evidence assessment are summarized in Table 4.

Postoperative complications

Low-quality evidence from 1 meta-analysis (6 studies, n=833) suggests a 59% reduction of the odds of complications in the unimodal prehabilitation group compared to the control group (OR=0.41, 95%CI: 0.28, 0.62).[21]

Postoperative pulmonary complications

Five meta-analyses evaluated the association between prehabilitation and postoperative pulmonary complications.[20,22–25] Results from 3 of the meta-analyses, including one with moderate-quality of evidence, show that the risk or odds of complications was decreased by at least 39% in the prehabilitation group compared to the control group. However, 2 of these 3 meta-analyses included the same 3 primary studies but reported 2 different measures of effect (odds ratio or risk ratio). The last 2 meta-analyses specifically assessed both atelectasis and pneumonia complications and found that prehabilitation reduced the risk by at least 40% compared to the control group for either pulmonary complication. However, for both reviews, the results for pneumonia complication were based on the same 5 primary studies and the quality of evidence was low.

Length of stay

Four meta-analyses, including one with moderate-quality of evidence, found that LOS was shorter in the prehabilitation group compared to the control group.[21,23–25] The mean difference from 3 of the meta-analyses ranged from -3.21 days to -1.82 days, while the last meta-analysis found a standardized mean difference of -0.56 (95%CI: -1.13, -0.01). However, the results from 2 of the meta-analyses were based on the same 2 primary studies and the quality of evidence was poor for the 4 other meta-analyses.

Mortality

Low-quality evidence from 1 meta-analysis (2 studies, n=306) suggests that the risk of overall mortality did not differ between the prehabilitation and control groups (RR=0.66, 95%CI: 0.02, 18.48).[25]

4.3 Cardiothoracic/Upper abdominal surgery

We identified 3 systematic reviews and meta-analyses assessing the effect of prehabilitation on postoperative outcomes following cardiothoracic/upper abdominal surgery.[20,26,27] The interventions in the primary studies were mostly unimodal prehabilitation consisting of inspiratory muscle training. In general, the training frequency varied from 6 to 7 times per week and lasted 2 to 4 weeks. The main findings and quality of evidence assessment are summarized in Table 5.

Postoperative functional capacity

Two meta-analyses assessed the maximal inspiratory pressure and maximal inspiratory muscle strength, 2 measures of functional capacity.[20,26] One meta-analysis found that the maximal inspiratory pressure was better in the prehabilitation group compared to the control group when measured within 5 days of surgery (MD=10.04, 95%CI: 2.92, 17.15), based on 4 studies (n=122). On the other hand, a pooled estimate from 3 studies (n=125) suggests no significant effect after 5-10 days of surgery (MD=7.02, 95%CI: -7.55, 21.58). The other meta-analysis (3 RCTs, n=80) found that prehabilitation did not significantly improve maximal inspiratory muscle strength compared to standard care (MD= -7.87, 95%CI: -21.36, 5.61). However, the uncertainty around the 3 estimates was substantial and the quality of evidence was low for both reviews.

Postoperative pulmonary complications

Three meta-analyses assessed the effectiveness of prehabilitation on postoperative pulmonary complications.[20,26,27] Low-quality evidence from 2 of the meta-analyses (4 or 6 primary studies) shows that prehabilitation decreased the risk of pulmonary complications by at least 50% compared to standard care or sham training. Two of the primary studies were included in both meta-analyses. Similar observation was reported by the third meta-analysis (4 RCTs) with high-quality evidence since the risk of pneumonia (RR=0.40, 95%CI: 0.21, 0.76) or atelectasis (RR=0.54, 95%CI: 0.33, 0.88) was decreased by at least 46% in the prehabilitation group compared to the control group.

Length of stay

Three meta-analyses assessed the association between prehabilitation and LOS.[20,26,27] Two meta-analyses with low-quality evidence found contradicting results. One meta-analysis (5 RCTs, n=392) reported a shorter LOS (MD= -1.33 days, 95%CI: -2.53, -0.13) in the prehabilitation group. The other meta-analysis found no significant association, though the effect size was similar (MD= -1.66 days, 95%CI: -3.64, 0.31) and based on smaller sample size (3 studies, n=83). The third meta-analysis with moderate-quality evidence reported that prehabilitation reduced LOS compared to standard care, based on 2 out of 2 primary studies (n=522). The same primary study was included in the 3 reviews.

Mortality

One meta-analysis (3 RCTs, n=343) with low-quality evidence found that the risk of overall mortality did not differ significantly between the prehabilitation and control groups (RR=0.40, 95%CI: 0.04, 4.23).[20]

4.4 Vascular surgery

We identified 1 systematic review assessing the effect of prehabilitation on postoperative outcomes following vascular surgery.[28] The interventions in the primary studies were unimodal prehabilitation consisting of aerobic exercises or inspiratory muscle training. The training frequency varied from 3 to 6 times per week and lasted mostly 2 to 6 weeks. The main findings and quality of evidence assessment are summarized in Table 6.

Postoperative complications

One systematic review with low-quality evidence found that postoperative complication rate did not differ between the prehabilitation and control groups, based on 2 out of 3 RCTs (n=197).[28]

Length of stay

One systematic review found that LOS was shorter in the prehabilitation group compared to the control group (median=7 days, interquartile range: 5-9 days vs. median=8 days, interquartile range: 6-12.3 days, p=0.025).[28] However, the quality of evidence was low and based on 1 RCT (n=124).

4.5 Gastrointestinal cancer surgery

We identified 4 systematic reviews and meta-analyses assessing the effect of prehabilitation on postoperative outcomes following surgery for gastrointestinal cancer, which included colorectal cancer.[29–32] Gastrointestinal surgery encompasses organs such as the small and large intestines, esophagus, rectum and stomach. The interventions in the primary studies were mostly unimodal or trimodal prehabilitation consisting of aerobic exercises and resistance training with or without nutritional and psychological supports. The training frequency varied from 1 to 7 times per week and lasted 2 to 8 weeks. The main findings and quality of evidence assessment are summarized in Table 7.

Postoperative functional capacity

Three systematic reviews and 1 meta-analysis evaluated walking capacity as a measure of functional capacity.[29–32] Two systematic reviews, based on the same 2 primary studies (2 studies, n=164), reported that trimodal prehabilitation improved walking capacity 4 or 8 weeks after surgery compared to standard care. The third systematic review also found similar improvement 8 weeks after surgery but only in 1 out of 2 RCTs (n=157). On the other hand, unimodal prehabilitation was not found to be more effective than walking/breathing exercise by the 3 systematic reviews, though the only evidence was from the same primary study (1 RCT, n=112). The positive effect of multimodal prehabilitation on walking capacity recovery after 4 or 8 weeks of surgery was also supported by the pooled estimate (MD=48.22m, 95%CI: 1.53m, 94.9m) from the meta-analysis (3 RCTs, n=191). However, the quality of evidence was low in all the reviews.

Postoperative complications

Three systematic reviews and 1 meta-analysis assessed the effectiveness of prehabilitation on postoperative complications.[29–32] The 3 systematic reviews, including one with moderate-quality evidence (4 RCTs, n=352), reported no association between binomial or trimodal prehabilitation and complication in most of the primary studies. However, the evidence from 2 of the systematic reviews was based on the same 2 studies (n=164). Similarly, all 3 systematic reviews as well as the meta-analysis (2 RCTs, n=75, RR=0.99, 95%CI: 0.58, 1.67) found no association between unimodal prehabilitation and complications, though the quality of evidence was poor.

Length of stay

Three systematic reviews and 1 meta-analysis (2 RCTs, n=75, MD= -0.05 days, 95%CI: -1.17, 1.06) with low-quality evidence found that LOS did not differ between the prehabilitation and control groups, regardless of the prehabilitation modality.[29–32] However, the evidence from 2 of the 3 systematic reviews was based on the same 2 primary studies (n=164) for trimodal prehabilitation.

Quality of life

Two systematic reviews (2 or 3 primary studies) reported that QoL, as assessed by SF-36, HADS or EORTC questionnaire, did not differ between the prehabilitation and control groups.[31,32] However, the quality of evidence was low and the same 2 primary studies were included in both reviews.

Readmission

One systematic review (3 RCTs, n=191) with low-quality evidence reported no association between readmission rate and prehabilitation.[30]

4.6 Colorectal surgery

We identified 4 systematic reviews assessing the effect of prehabilitation on postoperative outcomes following colorectal surgery.[33–36] The interventions in the primary studies were either unimodal or trimodal prehabilitation consisting of aerobic exercises, resistance training and/or inspiratory muscle training with or without nutritional and psychological supports. The training frequency varied from 2 to 7 times per week and lasted mostly 2 to 4 weeks. The main findings and quality of evidence assessment are summarized in Table 8.

Postoperative functional capacity

Three systematic reviews assessed the effectiveness of prehabilitation on walking capacity.[33–35] All 3 reviews, including one with moderate-quality evidence, reported that trimodal prehabilitation improved walking capacity 8 weeks after surgery. However, the evidence was based on the same 2 primary studies (n=164) for the 3 reviews. On the other hand, low-quality evidence from 2 of the 3 reviews suggests that unimodal prehabilitation did not have an effect. However, the evidence was based on the same primary study (n=112) for both reviews.

Postoperative complications

Low-quality evidence from 4 systematic reviews show that complication rate was not different in the prehabilitation group (unimodal or trimodal) compared to the control group.[33–36] However, 2 of the systematic reviews included the same 4 primary studies (n=315).

Length of stay

Low-quality evidence from 4 systematic reviews show that LOS was not different in the prehabilitation group (unimodal or trimodal) compared to the control group.[33–36] However, 2 of the systematic reviews included the same 4 primary studies (n=315).

Quality of life

One systematic review with low-quality evidence reported that QoL, as measured by the SF-36 questionnaire, did not differ between trimodal prehabilitation and control groups in 2 out of 2 primary studies (n=164).[33]

Readmission

Two systematic reviews reported that readmission rate did not differ between the trimodal prehabilitation group and control group.[33,36] However, the evidence was based on the same primary study (n=77) and the quality was poor.

4.7 Abdominal surgery

We identified 8 systematic reviews and meta-analyses assessing the effect of prehabilitation on postoperative outcomes following abdominal surgery.[20,37–43] This surgical procedure involves organs in the abdomen, including the prostate, liver and gastrointestinal organs (e.g. colon, small and large intestines). The interventions in the primary studies varied from unimodal to trimodal prehabilitation and consisted of combinations of aerobic exercises, strength training, resistance training and/or inspiratory muscle training with or without nutritional and/or psychological supports. The training frequency varied from 1 to 7 times per week and lasted mostly 2 to 6 weeks. The main findings and quality of evidence assessment are summarized in Table 9.

Postoperative functional capacity

One systematic review (2 studies, n=164) and 1 meta-analysis (4 studies, n=277) assessed functional capacity as measured by walking capacity.[37,38] Result from the meta-analysis shows that trimodal prehabilitation improved walking capacity compared to standard care (RR=1.63, 95%CI: 1.10, 2.41). This result was corroborated by similar findings in 4 out of 4 primary studies included in the systematic review. However, the quality of evidence was low for both reviews.

Postoperative complications

Three systematic reviews and 4 meta-analyses assessed the association between prehabilitation and postoperative complications.[37–43] Results from 3 of the meta-analyses suggest that prehabilitation decreased the odds of complications by 37% to 65% compared to no prehabilitation. However, many primary studies overlapped in the 3 meta-analyses. The latter results were corroborated by similar findings in 4 out of 5

primary studies included in 1 of the systematic reviews. The pooled estimate from the fourth meta-analysis (RR=0.65, 95%CI: 0.23, 1.84) indicates that prehabilitation did not decrease the risk of complication significantly. The other 2 systematic reviews reported no difference between the 2 groups. The quality of evidence was poor for all the 7 reviews.

Postoperative pulmonary complications

Of the 4 reviews assessing the association between prehabilitation and postoperative pulmonary complications, 3 were meta-analyses.[20,39–41] Two of the meta-analyses found that the odds of pulmonary complications was reduced by approximately 60% in the prehabilitation group compared to the control group. In the third meta-analysis, pulmonary complications were analyzed as atelectasis and pneumonia complications. The authors found similar effect size reduction for atelectasis (RR=0.41, 95%CI: 0.19, 0.90) and pneumonia (RR=0.46, 95%CI: 0.16, 1.33), though result for pneumonia complication was not significant. The systematic review reported no difference between the 2 groups in 2 out of 3 primary studies (n=203). The quality of evidence was low in all the reviews and some primary studies were included in all 4 reviews.

Length of stay

Of the 5 reviews assessing the association between prehabilitation and LOS, 4 were meta-analyses.[37–40,43] The 4 meta-analyses found that LOS did not differ between the prehabilitation and the control groups. This finding was corroborated by similar observations in 4 out of 5 primary studies included in the systematic review (n=291). However, the quality of evidence was low in all the reviews and some primary studies were included in the 5 reviews.

Quality of life

Low-quality evidence from 1 systematic review (n=276) suggests that QoL did not differ between the prehabilitation and control groups since 2 out of 3 primary studies found no association.[42]

4.8 Esophageal or gastric surgery

We identified 1 systematic review and 1 meta-analysis assessing the effect of prehabilitation on postoperative outcomes following surgery for esophageal or gastric cancer.[11,44] The interventions in the primary studies were unimodal prehabilitation

consisting of inspiratory muscle training or aerobic exercises with resistance training. The training frequency varied from 2 to 7 times per week and lasted 2 to 4 weeks. The main findings and quality of evidence assessment are summarized in Table 10.

Postoperative complications

One systematic review (n=396) with low-quality evidence found that complication rate did not differ between the prehabilitation and standard care in 3 out of 3 primary studies.[44]

Length of stay

One meta-analysis (2 studies, n=99) with low-quality evidence reported that prehabilitation did not significantly reduce LOS compared to control group (MD=2.00 days, 95%CI: -2.35, 6.35).[11]

4.9 Liver cancer surgery

We identified 1 meta-analysis assessing the effect of prehabilitation on postoperative outcome following surgery for liver transplant.[45] The intervention in the only primary study was a bimodal prehabilitation consisting of aerobic exercise with nutritional supplement. No details on the intervention frequency or duration were provided. The main findings and quality of evidence assessment are summarized in Table 11.

Postoperative complications

The meta-analysis from Brustia et al. (1 RCT, n=23) reported that the odds of complications (OR=2.11, 95%CI: 0.08, 57.61) was not significantly higher in the prehabilitation group than the control group.[45] However, the pooled estimate was based on 1 primary study with zero events in the control group, resulting in very large confidence intervals. In addition, the quality of evidence was low.

4.10 Knee surgery

We identified 11 systematic reviews and meta-analyses assessing the effect of prehabilitation on postoperative outcomes following knee surgery.[46–56] The interventions in the primary studies were either unimodal or bimodal prehabilitation consisting mostly of aerobic exercises, resistance training and/or strength with or without education. In general, the training frequency varied from 1 to 5 times per week

and lasted 3 to 12 weeks. The main findings and quality of evidence assessment are summarized in Table 12.

Postoperative functional capacity

Two systematic reviews and 6 meta-analyses used different indicators to assess prehabilitation effect on postoperative functional capacity.[46–53] Low-quality evidence from both systematic reviews suggests that functional capacity, as measured by WOMAC function or knee extension strength, did not differ between the prehabilitation and control groups. This finding was corroborated by most of the meta-analyses. Only 2 meta-analyses found a positive association between prehabilitation and knee range of motion 3 months after surgery (3 RCTs, n=219, MD=3.62, 95%CI: 0.09, 7.15) or quadriceps strength after surgery (7 RCTs, n=421, SMD=0.42, 95%CI: 0.16, 0.68). However, evidence from all 6 meta-analyses was of poor quality and some of the primary studies were included in multiple systematic reviews.

Length of stay

Three systematic reviews and 2 meta-analyses investigated the association between prehabilitation and LOS.[46,50,51,53,54] The 2 meta-analyses found contradicting results. Chen et al. included 5 RCTs with 664 patients and reported a positive association (MD= -0.80 day, 95%CI: -1.11, -0.48), while Wallis et al. reported no association (MD= -0.04 day, 95%CI: -0.64, 0.56) with a smaller sample size (2 RCTs, n=141). On the other hand, all 3 systematic reviews found that LOS did not differ between the prehabilitation and control groups. However, some primary studies were included in 2 or 3 systematic reviews. In addition, the quality of evidence was low for all 5 reviews.

Readmission

A meta-analysis from Cabilan et al. found that readmission rate did not differ significantly between the prehabilitation and control groups (OR=0.57, 95%CI: 0.25, 1.27).[49] However, sample size was small (2 RCTs, n=138) and the quality of evidence was poor.

Pain

Two systematic reviews and 2 meta-analyses with low-quality evidence found that pain relief after surgery, as measured by VAS or WOMAC score, was not better in the prehabilitation group than in the control group.[49,50,53,55] However, some primary studies were included in several systematic reviews.

Quality of life

Low to moderate quality of evidence from 1 systematic review and 1 meta-analysis found that QoL, as measured by SF-36 score, did not differ between the prehabilitation and control groups.[49,56]

4.11 Hip surgery

We identified 3 systematic reviews and meta-analyses assessing the effect of prehabilitation on postoperative outcomes following hip surgery.[49,52,53] The interventions in the primary studies were either unimodal or bimodal prehabilitation consisting mostly of aerobic exercises, resistance training and/or strength with or without education. In general, the training frequency varied from 1 to 5 times per week and lasted 4 to 8 weeks. The main findings and quality of evidence assessment are summarized in Table 13.

Postoperative functional capacity

Low-quality evidence from 3 meta-analyses suggests that self-reported postoperative functional capacity did not differ between prehabilitation and standard care.[49,52,53]

Pain

A meta-analysis (2 RCTs, n=72) with low-quality evidence found that self-reported pain did not differ between prehabilitation and standard care.[49]

Quality of life

One systematic review (2 RCTs, n=72) with low-quality evidence found that QoL did not differ between prehabilitation and standard care based on 2 out of 2 RCTs.[49]

4.12 Spinal surgery

We identified 1 systematic review assessing the effect of prehabilitation on postoperative outcomes following spine surgery.[57] The intervention in the only primary study was unimodal prehabilitation consisting of aerobic exercises and strength training. The training frequency was once a day and lasted 6 to 8 weeks. The main findings and quality of evidence assessment are summarized in Table 14.

Length of stay

One systematic review (1 RCT, n=92) reported that LOS was shorter in the prehabilitation group than in the control group (median=5 days vs. median=7 days, p=0.007).[57] However, the quality of evidence was low and based on 1 primary study.

Pain

One systematic review (1 RCT, n=92) found that pain relief was better in the prehabilitation group compared to control group (p=0.02).[57] However, the quality of evidence was low and based on 1 primary study.

4.13 Recent observational studies

We identified 2 recent observational studies with large sample size investigating the effect of prehabilitation on postoperative outcomes following surgery. Details on the risk of bias assessment are presented in Table 15, while the main findings and quality of evidence assessment are summarized in Table 16.

An observational study by Janssen et al. compared a prehabilitation group (bimodal program) to a historical control group to assess postoperative outcomes after abdominal surgery among 70 years or older patients (n=627).[58] The authors found no significant difference between the 2 groups for LOS (MD= -0.89 day, 95%CI: -2.7, 0.99), complications (OR= 1.12, 95%CI: 0.80, 1.57), 30-day readmission (OR= 1.42, 95%CI: 0.75, 2.68) or 30-day mortality (OR= 1.50, 95%CI: 0.61, 3.72). Although the regression models were adjusted for age, the American Society of Anesthesiologists (ASA) score >3 and surgical type, potential confounding factors such as tumour stage and BMI were not considered, resulting in high risk of bias.

A retrospective study by Uda et al. used a nationwide administrative claims and discharge database to examine the association between short-term prehabilitation and postoperative outcomes following surgery for non-small-cell lung cancer (n=21,259).[59] The authors used one-to-one propensity score matching to select patients among those eligible in the prehabilitation group (n=13,741) and control group (n=7518). A total of 6374 matched pairs were included in the analysis. No difference in overall mortality (OR= 0.79, 95%CI: 0.32, 1.86) and in-hospital postoperative pulmonary complications (OR=0.84, 95%CI: 0.66, 1.07) was found between patients receiving prehabilitation with rehabilitation and patients receiving only rehabilitation. As it is an observational study, the risk of residual bias remains despite the adjustment for important confounding

factors. Moreover, problems inherent to administrative database, such as insufficient information on the prehabilitation program and variability in the prehabilitation assessment, increased the risk of bias. Although the authors have addressed the missing data problem by using the missing indicator method, it is a biased approach when data are not missing completely at random, which is a strong assumption that is rarely met.[60]

4.14 Guidelines or HTAs

- Presently, no official guideline or recommendations from HTAs have been issued for prehabilitation.
- The Macmillan cancer support, a British charity organization, published in partnership with the Royal College of Anaesthetists and the National Institute for Health Research Cancer and Nutrition Collaboration a guidance on prehabilitation for people with cancer.[61] They recommend that prehabilitation should be included in the cancer care pathway for all people diagnosed with cancer. It should include exercise, nutritional and psychological support.
- Saur et al. published a summary from the 2019 American Society of Colon and Rectal Surgeons Annual meeting on the care of older patients undergoing colorectal surgery.[62] Prehabilitation is proposed as a strategy to help patients withstand the surgical stress and should be part of an Enhanced Recovery After Surgery (ERAS) protocol. Prehabilitation program should be patient-centered, but include aerobic exercise and resistance training for optimal results.
- A recent guideline in the UK by Tew et al. recommended that supervised preoperative exercises should be offered to patients scheduled for major non-cardiac surgery as a combination of inspiratory muscle training, resistance and aerobic training, and be included in a multimodal prehabilitation program.[63] Functional capacity and QoL should be measured at different time points to assess patient progress and response to the intervention.

4.15 Main limitations of studies/Risk of bias

Several limitations hindered the quality of the findings reported in the systematic reviews and meta-analyses. Some of them were inherent limitations in the primary studies included in the reviews.

- Although most of the included studies were RCTs, the risk of bias was often classified as moderate to high due to the non-blinding of participants and/or

assessors, as well as inappropriate randomization and/or allocation concealment methods.

- Sample size was small, often less than 50 patients per intervention group, in most of the primary studies included in the reviews.
- Standard care was one of the interventions used in the control group. However, it is not a uniform process across hospitals. Its definition could differ according to the practices or policies of the hospitals where patients had surgery.

Other common limitations were due to inappropriate methodology used by the authors of the reviews or lack of detail on the characteristics of the primary studies.

- Usage of inappropriate appraisal tool for the risk of bias such as the Cochrane Tool for RCT used for non-randomized studies, but it does not evaluate confounding bias.
- Meta-analyses were performed despite high clinical heterogeneity between the primary studies. The robustness of the results was not often assessed in sensitivity analyses.
- Several primary studies overlapped in multiple reviews. Sometime, 2 reviews included the same primary studies to assess the same outcome, leading to an artificial increase of the evidence.
- Evidence was based on limited number of primary studies, sometime only 1 study, leading to a large uncertainty observed in the pooled estimate in meta-analyses.
- Study selection, data extraction and/or risk of bias assessment were not performed independently by 2 persons or no information was provided.

Insufficient information collected from the primary studies for the interpretation of the results such as the time point the outcomes were measured.

5. PREHABILITATION AT THE MUHC

5.1 Current treatment policy

Prehabilitation at McGill is implemented at the Peri Operative Program (POP) clinic located at the Montreal General Hospital.[64] Patients potentially at risk are referred to the clinic through the recommendation of their surgeon. Prehabilitation at the POP is a multimodal program consisting of physical activity, nutrition and mental support and is given by a multidisciplinary team.

5.2 MUHC experience with prehabilitation

We identified 5 recent studies done at the MUHC assessing the effect of prehabilitation intervention on postoperative outcomes following abdominal surgery. Details on the risk of bias assessment for RCTs and non-randomized studies are presented in Table 17 and Table 18, respectively. The main findings and quality of evidence assessment are summarized in Table 19.

Recent studies

A RCT by Carli et al. compared a multimodal program consisting of exercise, nutritional supplement and psychological support done during the preoperative period (prehab group) versus during the postoperative period (rehab group) in frail patients undergoing surgery for colorectal cancer (n=120).[65] There was no difference in 30-day complications (MD= -3.2, 95 %CI: -11.8, 5.3), LOS (MD= -5.8 days, 95%CI: -17.3, 5.8), walking capacity as measured by the 6MWT (MD=11.2m, 95%CI: -13.7, 36.1 **before surgery** and MD=18.5m, 95%CI: -20.2, 57.3 at 4-week post-surgery), QoL as measured by SF-36 physical component (MD=0.16, 95%CI: -6.7, 7.0 **before surgery** and MD= -0.43, 95%CI: -7.2, 6.3 at 4-week post-surgery) or mental component (MD= -2.8, 95%CI: -10.7, 5.0 before surgery and MD= -2.3, 95%CI: -9.7, 5.1 at 4-week post-surgery) and readmission (OR=0.3, 95%CI: 0.03, 1.9) between the 2 groups. The major biases of the study were from the non-blinding of participants and intervention staff, and the missing data. Although multiple imputation is an appropriate approach to handle missing data, serious problem could compromise the validity of the imputed data. The imputation models for the outcomes LOS, QoL and readmission were not properly specified since they did not include all the variables from the corresponding regression model. For LOS and readmission, the imputation models were used for <2% of missing data and bias should be minimal. However, over a third of data was missing for QoL and bias could be substantial. Also, the statistical method used did not take into consideration the

correlation between repeated measurements for the walking capacity and QoL outcomes. The authors mentioned that intention-to-treat analysis was performed for the main analysis. However, some of the randomized patients were excluded from the analysis.

A RCT conducted by Minnella et al. investigated the effect of multimodal prehabilitation (exercise, nutritional and psychological components) on walking capacity, as measured by 6MWT, following elective radical cystectomy (n=70).[66] A linear mixed model was used to estimate the change in walking distance from baseline between the prehabilitation and standard care groups. During the perioperative period, the change in walking distance was not different between both groups. Whereas during the postoperative period, the change in walking distance was different at 4-week (-15.4m, SD=142.5 vs. -97.9m, SD=123.8, p=0.014) but not 8-week (5.6m, SD=173.5 vs. -35.5, SD=131.8, p=0.42) post-surgery. The authors also reported that changes in QoL (before surgery, at 4-week and 8-week post-surgery), complications, LOS and 30-day readmission were similar in both groups. One of the main sources of biases is from the non-handling of missing data, which were >50% at certain time points for the walking capacity and QoL outcomes. The non-blinding of participants and intervention staff are also an important source of biases.

One of the objectives of a RCT by Santa Mina et al. was to evaluate the effect of prehabilitation (total-body exercises with pelvic floor exercises) on postoperative outcomes compared to a control group (pelvic floor exercises) after radical prostatectomy (n=86).[67] Linear mixed models adjusted for age, stage of cancer, surgical waiting time, surgical approach and treatment center were used to estimate the mean difference in functional capacity as measured by 6MWT and grip strength, and in QoL as measured by Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Patient-Oriented Prostate Utility Scale (PORPUS) before surgery, at 4-week, 12-week and 26-week post-surgery. Except for 6MWT at 4-week post-surgery (MD=38.7m, 95%CI: 11.3, 66.1), no difference was detected between the two groups for 6MWT (e.g. MD=22.7m, 95%CI: -5.2, 50.5 at 12-week post-surgery), grip strength (e.g. MD=1.67, 95%CI: -2.01, 5.35 at 4-week post-surgery), QoL FACT-P (e.g. MD=-2.11, 95%CI: -8.34, 4.12 at 4-week post-surgery), QoL PORPUS (e.g. MD= -0.41 95%CI: -5.06, 4.24 at 4-week post-surgery), complications (18/42 vs. 14/40, p=0.61) and LOS (1.7 days, SD=0.9 vs. 1.8 days, SD=1.0, p=0.77). The risk of bias is high in this trial since the methods used for the randomization and allocation concealment were not specified. Moreover, information on the blinding of participants, intervention staff and outcome assessors were not provided. Also, 53% of eligible patients did not consent to participate and a comparison between baseline

characteristics of the participants and non-participants was not done. Although adjusted regression models were used for walking capacity and QoL outcomes, no adjustment was done for LOS and postoperative complications.

Trépanier et al. combined the data from 2 RCTs and 1 observational study to evaluate the association between prehabilitation and disease-free survival (DFS) or overall survival (OS) after surgery for colorectal cancer (n=202).[68] The prehabilitation program for the 3 studies consisted of exercises, nutritional and mental support. As for the comparator group, patients from the RCTs had the same trimodal program but after surgery, while patients from the observational study had standard care. The authors reported that both 5-year DFS (85.3% vs. 79.3%, p=0.25) and 5-year OS (96.4% vs. 91.7%, p=0.23) were similar in the prehabilitation and comparator groups. Although the adjusted risk of recurrence (HR=0.45, 95%CI: 0.21, 0.93) differs between the two groups, the adjusted overall mortality was similar (HR=1.99, 95%CI: 0.5, 8.02). The risk of bias is considered to be high since the regression models were not adjusted for some confounding factors and description of the patient selection process in the comparator group for the observational study was not provided.

Minnella et al. pooled the same 3 studies as Trépanier et al to increase sample size and assess the association between prehabilitation and postoperative outcomes following colorectal cancer surgery (n=179).[69] Although LOS (median=4 days, IQR: 3-5 vs. median=3 days, IQR: 3-6, p=0.81) and complications (42/110 vs. 23/68, p=0.75) did not differ between the 2 groups, change in walking capacity from baseline was better for the prehabilitation group than the control group at all time points (before surgery, 4-week and 8-week post-surgery) (e.g. MD= -11.2m, SD=72 vs. MD= -72.5m, SD=129, p<0.01 at 4-week post-surgery). However, the risk of bias is high since the statistical methods used did not account for confounding factors. Furthermore, the correlation between the repeated measurements was not considered in the analysis.

6. DISCUSSION

6.1 Summary of the efficacy/safety results and concerns with the evidence

Regardless of the intervention modality, several meta-analyses consistently reported a substantial reduction (30 to 75%) in the risk or odds of overall and pulmonary complications, as well as a shorter length of stay, in the prehabilitation group compared to the control group following surgery for lung cancer or chronic obstructive pulmonary

disease. Caution is needed in the interpretation of these results as the quality of evidence was poor to moderate due to considerable risk of bias in the primary studies, small sample size in the primary studies and methodological limitations in the reviews.

According to several meta-analyses, including one with moderate-quality evidence, patients undergoing cardiac surgery appear to benefit from prehabilitation in reducing pulmonary complication risk and length of stay. Although prehabilitation seems to improve physical function and reduce overall complications, the quality of the evidence was generally low. Similar reduction in pulmonary complication risk and length of stay among patients undergoing cardiothoracic surgery were reported by multiple reviews, including two with moderate to high quality evidence. The reviews assessing cardiothoracic surgery and cardiac surgery shared the same limitations of small sample size and risk of bias. Currently, there is no evidence that prehabilitation has a positive effect on QoL and mortality rate after cardiac surgery or functional capacity recovery and mortality rate after cardiothoracic surgery.

Limited evidence suggests that trimodal but not unimodal prehabilitation could have a positive effect on the functional capacity recovery of patients undergoing abdominal, gastrointestinal or colorectal surgery. There is also some evidence that prehabilitation is associated with reduced postoperative complications (overall or pulmonary) following abdominal but not colorectal or gastrointestinal surgery. No other association was found between prehabilitation and other postoperative outcomes (LOS, QoL and readmission). Since these 3 surgical types shared common patients, the available evidence was mainly based on the same primary studies for these surgical populations. Another concern is that the included primary studies overlapped across multiple reviews within a surgical population. Given the generally low quality of the evidence, the effectiveness of prehabilitation to improve postoperative functional capacity or reduce complications is uncertain for patients scheduled for abdominal, gastrointestinal or colorectal surgery.

Three RCTS conducted at the MUHC on the effect of prehabilitation among patients undergoing colorectal surgery reported no association between multimodal prehabilitation and LOS, readmission rate, the risk of complications or mortality compared to standard care or rehabilitation. However, these studies appeared to be underpowered to detect a difference in their stated outcomes.

As for the other surgical populations, current evidence either does not support an association between prehabilitation and postoperative outcomes (esophageal, liver transplantation, knee or hip surgery) or there is some evidence of an effect (vascular or spinal surgery). Given the available evidence was of poor quality, mainly due to the high

risk of bias and small sample size in the primary studies as well as the limited number of primary studies included in the reviews, a definitive conclusion cannot be made.

6.2 Applicability of a prehabilitation clinic at the MUHC

The cares for patients undergoing surgery at MUHC are provided within the enhance recovery program (ERP) since 2008. It is a standardized program based on the Enhanced Recovery After Surgery (ERAS) protocol, a multidisciplinary patient-centered approach aiming for an early recovery and improved outcomes. Guidelines were created for several surgical types. The ERAS protocol for colorectal surgery integrates 24 core elements that are applied throughout the patient journey, before admission until discharge from hospital.[70] ERAS incorporates elements such as smoking cessation (preadmission), carbohydrate treatment (preoperative), usage of minimally invasive surgical procedures (intraoperative) and early mobilization (postoperative) but not preoperative physical exercise.[70]

ERAS efficacy has been extensively studied since its inception in 1990 and several studies had found a positive association between ERAS protocol and postoperative outcomes. A meta-analysis by Varadhan et al. assessed ERAS in patients undergoing major elective open colorectal surgery (6 RCTs, n=452).[71] The authors reported a shorter LOS (MD= -2.55 days, 95%CI: -3.24, -1.85) and reduced risk of complications (RR= 0.53, 95%CI: 0.44, 0.64) in the ERAS group compared to the conventional care group. Similar results for LOS (MD= -2.44 days, 95%CI: -3.06, -1.83) and overall complications (RR= 0.71, 95%CI: 0.58, 0.86) were obtained by a meta-analysis with larger sample size (13 RCTs, n=1910) comparing ERAS versus traditional care in patients undergoing elective colorectal surgery.[72] A more recent meta-analysis from Greer et al. included RCTs and non-randomized trials to evaluate ERAS versus usual care in patients scheduled for colorectal surgery (n=3787).[73] The authors also found a shorter LOS (MD= -2.6 days, 95%CI: -3.2, -2.0) and reduced risk of complications (RR= 0.66, 95%CI: 0.54, 0.80) in the ERAS group.

Like prehabilitation intervention, ERAS is a protocol ultimately designed to reduce postoperative complications and hospital length of stay. As such, a prehabilitation program within the context of ERAS might not bring additional benefit to patients waiting for surgery in regard to clinical outcomes. This could explain, in part, the lack of association between prehabilitation intervention and LOS or postoperative complications in the studies conducted at MUHC.

7. CONCLUSIONS

- Our review of the large volume of available data, while lacking high quality evidence, indicates that prehabilitation consisting of physical training with or without other components, is beneficial in the following surgical populations:
    - Patients undergoing lung, cardiac or cardiothoracic/upper abdominal surgery to reduce complications (overall and pulmonary) and hospital length of stay;
    - Patients undergoing abdominal, colorectal or gastrointestinal surgery benefit from trimodal prehabilitation to improve functional capacity.
- Current systematic reviews and meta-analyses are limited by several methodological issues in the primary studies (small sample sizes, issues with random allocation and blinding) as well as in the systematic reviews and meta-analyses (e.g., high heterogeneity). In addition, many primary studies were included in multiple systematic reviews or meta-analyses.
- An accrual of studies with larger sample sizes and better methodology is needed to confirm the above findings and improve evidence for further surgical populations.

8. RECOMMENDATIONS

- The TAU Policy Committee, made up of stakeholders from across the McGill University Health Centre, reviewed the evidence and issued the following recommendation: Not Approved
- This recommendation was reached based on the following:
    - Benefits of prehabilitation are not supported by strong, high-quality evidence. Local evidence, gathered within the context of care at the MUHC, does not support a beneficial effect of prehabilitation on patient outcomes.
    - Given these findings, prehabilitation does not fit the criteria to be funded by the MUHC institutional budget. Further research is necessary to understand the comparative-effectiveness of prehabilitation (vs. standard

care), as well as the relative contribution of different interventions used within prehabilitation. Several of these interventions (e.g. counseling, education, nutritional management) can be embedded with existing MUHC clinics (e.g. the preoperative clinic).

- This recommendation may be reviewed in 3 years, if new data from the literature and/or the local context become available.

FIGURES

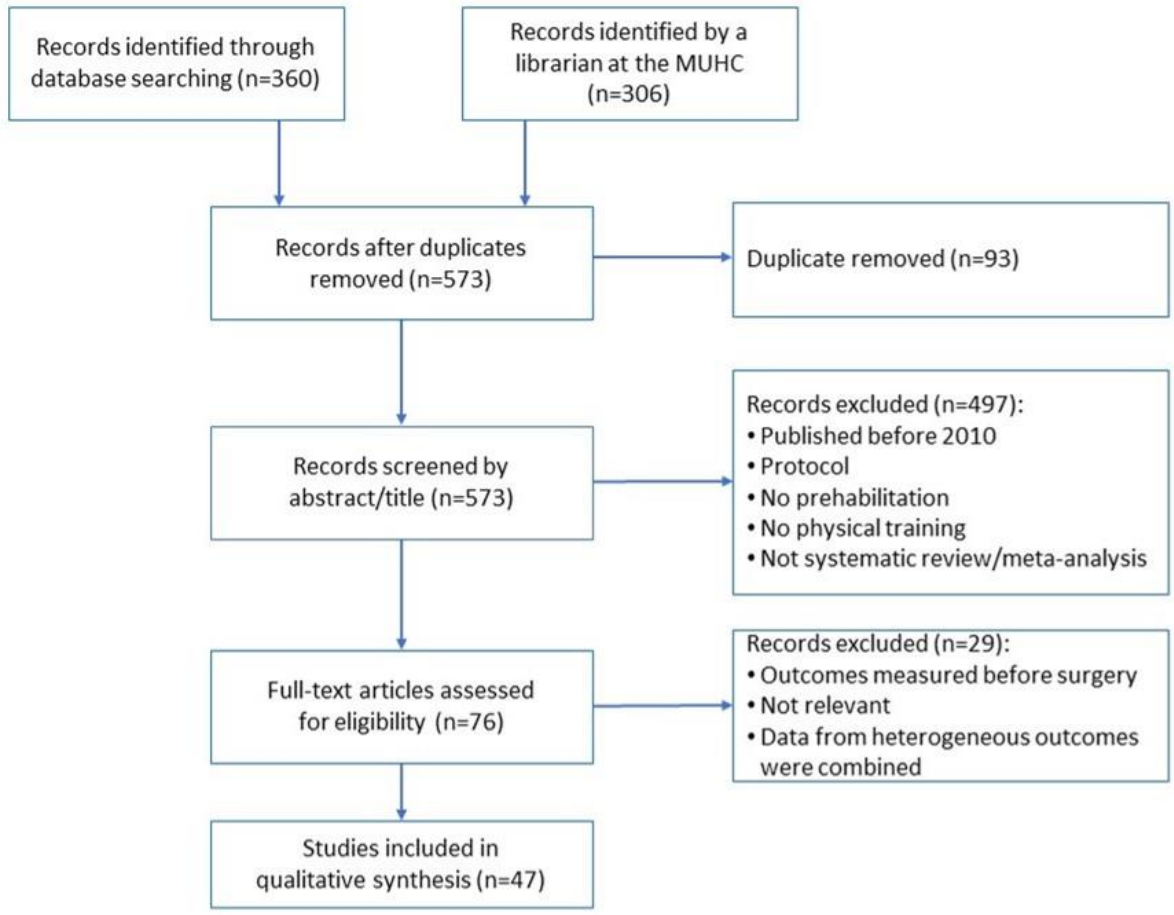

Figure 1. Flowchart of the included systematic reviews and meta-analyses

TABLES

Table 1. Overview summarizing the results from systematic reviews and meta-analyses

Postoperative Outcomes	Summary of Evidence			Quality of the Evidence
	No. of SR *	No. of MA *	Summary of Results	
Lung				
Complications	-	4	Reduces complications	Low
Pulmonary complications	1	4	Reduces complications	Low
LOS	1	8	Reduces LOS	Low
Cardiac				
Complications	-	1	Reduces complications	Low
Pulmonary complications	-	5	Reduces complications	Low to Moderate
LOS	-	4	Reduce LOS	Low to Moderate
Mortality	-	1	No difference	Low
Cardiothoracic				
Functional capacity	-	2	Inconclusive	Low
Pulmonary complications	-	3	Reduces complications	Low to High
LOS	1	2	Reduce LOS	Low to Moderate
Mortality	-	1	No difference	Low
Vascular				
Complications	1	-	No difference	Low
LOS	1	-	Reduce LOS	Low
Gastrointestinal				
Functional capacity	3	1	Improves walking capacity (trimodal)	Low
Complications	3	1	No difference	Low to Moderate
LOS	3	1	No difference	Low
QoL	2	-	No difference	Low
Readmission	1	-	No difference	Low
Colorectal				
Functional capacity	3	-	Improves walking capacity (trimodal)	Low to Moderate
Complications	4	-	No difference	Low
LOS	4	-	No difference	Low
QoL	1	-	No difference	Low
Readmission	2	-	No difference	Low

Postoperative Outcomes	Summary of Evidence			Quality of the Evidence
	No. of SR *	No. of MA *	Summary of Results	
Abdominal				
Functional capacity	1	1	Improves walking capacity (trimodal)	Low
Complications	3	4	Inconclusive	Low
Pulmonary complications	1	3	Reduces complications	Low
LOS	1	4	No difference	Low
QoL	1	-	No difference	Low
Esophageal				
Complications	1	-	No difference	Low
LOS	-	1	No difference	Low
Liver cancer				
Complications	-	1	No difference	Low
Knee				
Functional capacity	2	6	No difference	Low
LOS	3	2	No difference	Low
QoL	1	1	No difference	Low to Moderate
Readmission	-	1	No difference	Low
Pain	1	3	No difference	Low
Hip				
Functional capacity	-	3	No difference	Low
QoL	1	-	No difference	Low
Pain	-	1	No difference	Low
Spine				
LOS	1	-	Reduces LOS	Low
Pain	1	-	Reduces pain	Low

* For a given surgical population and outcome, the same primary studies can be included in multiple systematic reviews and meta-analyses

SR, systematic review; MA, meta-analysis; LOS, length of stay; QoL, quality of life

Table 2. Number of systematic reviews and meta-analyses by surgical type and postoperative outcomes

Surgical types	Postoperative outcomes							
	Functional capacity	Pulmonary complications	Complications	LOS	Readmission	Pain	QoL	Mortality
Lung	-	5	4	9	-	-	-	-
Gastrointestinal	4	-	4	4	1	-	2	-
Colorectal	3	-	4	4	2	-	1	-
Esophageal	-	-	1	1	-	-	-	-
Abdominal	2	4	7	5	-	-	1	-
Liver transplant	-	-	1	-	-	-	-	-
Vascular	-	-	1	1	-	-	-	-
Cardiac	-	5	1	4	-	-	-	1
Spine	-	-	-	1	-	1	-	-
Cardiothoracic	2	3	-	3	-	-	-	1
Knee	8	-	-	5	1	4	2	-
Hip	3	-	-	1	-	1	-	-
Total	**22**	**17**	**23**	**38**	**4**	**6**	**6**	**2**

Table 3. Summary of findings for the effects of prehabilitation on postoperative outcomes after lung surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Complications						
Steffens 2018[11]	332 (5 RCTs, quasi-RCTs)	Standard care or unknown[1]	Unimodal Aerobic exercises, respiratory muscle training and/or resistance training, 2-10 times/week for 1-2 weeks	• RR=0.52 95%CI: 0.36, 0.74 • Number of events: Prehab: 31/165 Control: 63/167	Low	• Moderate risk of bias • Small sample size in most primary studies • Insufficient Information on some study characteristics • Clinical heterogeneity
Ni 2017[12]	180 (4 RCTs, NRS)	Standard care or breathing exercise[1]	Unimodal Aerobic exercise, resistance training, strength training and/or breathing exercise, 2-10 times/week for 1-4 weeks	• OR=0.33 95%CI: 0.15, 0.74 • Number of events: Prehab: 19/73 Control: 59/107	Low	• Low risk of bias • Risk of bias score exceeds the maximum allowed score for 1 study • Some bias domains were not assessed for NRS, i.e. confounding factors • Small sample size in primary studies • Study selection and risk of bias assessment were not done by 2 persons • Insufficient Information on some study characteristics
Treanor 2017[13]	137 (3 RCTs)	Standard care	Unimodal Strength training, inspiratory muscle training, aerobic exercise and/or breathing exercise, daily for 1 week[1]	• OR=0.25 95%CI: 0.10, 0.66 • Number of events: Prehab: 8/69 Control: 21/68	Low	• High risk of bias (no detail provided) • Small sample size in primary studies • Insufficient Information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Sebio Garcia 2016[14]	779 (8 RCTs, NRS)	Standard care, breathing exercise or unknown[1]	<u>Unimodal or Bimodal</u> • Aerobic exercise, strength training, inspiratory muscle training and/or other breathing techniques, 2-10 times/week for 1-10 weeks[1] • Education	• RR=0.45[1] 95%CI: 0.28, 0.73 • Number of events: Prehab: 47/245 Control: 190/534	Low	• High risk of bias • Small sample size in most primary studies • Insufficient Information on some study characteristics • High statistical heterogeneity (I^2=65%) • Clinical heterogeneity
Pulmonary complications						
Li 2019[15]	382 (6 RCTs, NRS)	Standard care or chest physical therapy[1]	<u>Unimodal</u> Aerobic exercise, breathing exercises, strength training, inspiratory muscle training, education, 3-5 times/week for 1-4 weeks	<u>Overall</u> • OR=0.44 95%CI: 0.27, 0.71 • Number of events: Prehab: 39/171 Control: 78/211	Low	• Risk of bias reported as “not serious” (no detail) • Risk appraisal tool used for NRS is not appropriate (Cochrane**)** • Small sample size in most primary studies • Unclear if selection of studies and risk of bias assessment were done by 2 persons • Insufficient Information on some study characteristics • Clinical heterogeneity
	319 (5 RCTs, NRS)	Standard care or chest physical therapy[1]	<u>Unimodal</u> Aerobic exercise, breathing exercises, strength training, inspiratory muscle training, education, 3-5 times/week for 1-4 weeks	<u>Pneumonia</u> • OR=0.47 95%CI: 0.24, 0.95 • Number of events: Prehab: 13/141 Control: 32/178	Low	• Risk of bias reported as “not serious” (no detail) • Risk appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in most primary studies • Unclear if selection of studies and risk of bias assessment were done by 2 persons • Insufficient Information on some study characteristics • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Wang 2019[16]	185 (4 RCTs)	Standard care[1]	Unimodal Breathing exercises, aerobic exercise, resistance training, chest physiotherapy, inspiratory muscle training and/or strength training, 3-7 times/week for 54.5 days or 1-2 weeks	Overall • OR= 0.32 95%CI: 0.16, 0.66 • Number of events: Prehab: 18/92 Control: 37/93	Low	• High risk of bias • Small sample size in most primary studies • Data extraction was not done by 2 persons • Limited selection of studies • Insufficient Information on some study characteristics • Clinical heterogeneity
	77 (2 RCTs)	Standard care[1]	Unimodal Inspiratory muscle training with or without aerobic exercise and strength training, daily for 1 week	Pneumonia • OR= 0.59 95%CI: 0.19, 1.85 • Number of events: Prehab: 6/39 Control: 9/38	Low	• High risk of bias • Small sample size in most primary studies • Data extraction was not done by 2 persons • Limited selection of studies • Insufficient Information on some study characteristics • Clinical heterogeneity
	137 (3 RCTs)	Standard care[1]	Unimodal Aerobic exercise, chest physiotherapy, inspiratory muscle training, strength training and/or inspiratory muscle training, daily for 1 week	Atelectasis • OR= 0.50 95%CI: 0.10, 2.50 • Number of events: Prehab: 2/69 Control: 4/68	Low	• High risk of bias • Small sample size in most primary studies • Data extraction was not done by 2 persons • Limited selection of studies • Insufficient Information on some study characteristics Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Cavalheri 2017[17]	158 (4 RCTs)	Standard care	Unimodal Aerobic exercise with resistance training, inspiratory muscle training or other breathing exercises, 3-10 times/week for 1-4 weeks	• RR= 0.33 95%CI: 0.17, 0.61 • Number of events: Prehab: 10/81 Control: 28/77	Low	• High risk of bias • Small sample size in most primary studies • Clinical heterogeneity
Sebio Garcia 2016[14]	543 (5 RCTs, NRS)	Standard care or breathing exercise[1]	Unimodal or Bimodal • Aerobic exercise, strength training, inspiratory muscle training and/or other breathing techniques 2-10 times/week for 1-10 weeks[1] • Education	• RR= 0.55 95%CI: 0.34, 0.89 • Number of events: Prehab: 23/131 Control: 108/412	Low	• Moderate risk of bias • Small sample size in most primary studies • Insufficient Information on some study characteristics • Clinical heterogeneity
Pouwels 2015[18]	43 (2 RCTs)	Standard care or breathing exercise	Unimodal Aerobic exercise, strength training, resistance training and/or inspiratory muscle training, 5-10 times/week for 1-4 weeks[1]	1/2 studies found no difference in pulmonary complication rate between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Insufficient Information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hospital length of stay						
Rosero 2019[19]	467 (6 RCTs)	Standard care	Unimodal Aerobic exercises that can include breathing, strength training, inspiratory muscle training, 3-10 times/ week for 1-4 weeks	SMD= -0.58 95%CI: -0.97, -0.20	Low	• Moderate risk of bias • Small sample size in most primary studies • High statistical heterogeneity (I^2=70.7%) • Clinical heterogeneity
Li 2019[15]	231 (5 RCTs, NRS)	Standard care or chest physical therapy	Unimodal Aerobic exercise, breathing exercises, strength training, inspiratory muscle training, education, 3-5 times/week for 1-4 weeks	MD= -4.23[1] days 95%CI: -6.14, -2.32	Low	• Risk of bias reported as “serious” • Risk appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in most primary studies • Unclear if selection of studies and risk of bias assessment were done by 2 persons • Insufficient Information on some study characteristics • High statistically heterogeneity (I^2= 66%) • Clinical heterogeneity
Wang 2019[16]	99 (3 RCTs)	Standard care[1]	Unimodal Breathing exercises with resistance training, strength training and/or aerobic exercise	MD= -4.25 days 95%CI: -5.64, -2.86	Low	• High risk of bias • Small sample size in most primary studies • Data collection not done by 2 persons • Limited selection of studies • Insufficient Information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Steffens 2018[11]	332 (5 RCTs, quasi-RCTs)	Standard care or unknown[1]	Unimodal Combination of aerobic exercises, respiratory muscle training or resistance training, 2-10 times/week for 1-2 weeks	MD= -2.86 days 95%CI: -5.40, -0.33	Low	• Moderate risk of bias • Small sample size in most primary studies • Insufficient Information on some study characteristics • Clinical heterogeneity
Cavalheri 2017[17]	158 (4 RCTs)	Standard care	Unimodal Aerobic exercise with resistance training, inspiratory muscle training or other breathing exercises, 3-10 times/week for 1-4 weeks	MD= -4.24 days 95%CI: -5.43, -3.06	Low	• High risk of bias • Small sample size in most primary studies • Clinical heterogeneity
Ni 2017[12]	180 (4 RCTs, NRS)	Standard care or breathing exercise[1]	Unimodal Aerobic exercise, resistance training, strength training and/or breathing exercise, 2-10 times/week for 1-4 weeks	MD= -4.98 days 95%CI: -6.22, -3.74	Low	• Low risk of bias • Risk of bias score exceeds the maximum allowed score for 1 study • Small sample size in primary studies • Study selection and risk of bias assessment were not done by 2 persons • Insufficient Information on some study characteristics • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Treanor 2017[13]	137 (3 RCTs)	Standard care	Unimodal Strength training, inspiratory muscle training, aerobic exercise and/or breathing exercise, daily for 1 week[1]	MD= -4.20 days 95%CI: -5.45, -2.95	Low	• High risk of bias (no detail provided) • Small sample size in primary studies • Insufficient Information on some study characteristics
Sebio Garcia 2016[14]	729 (7 RCTs, NRS)	Standard care, breathing exercise or unknown[1]	Unimodal or Bimodal • Aerobic exercise, strength training, inspiratory muscle training and/or other breathing techniques, 2-10 times/week for 1-10 weeks[1] • Education	MD= -4.83 days 95%CI: -5.90, -3.76	Low	• High risk of bias • Small sample size in most primary studies • Insufficient Information on some study characteristics • Clinical heterogeneity
Pouwels 2015[18]	43 (2 RCTs)	Standard care or breathing exercise	Unimodal Aerobic exercise, strength training, resistance training and/or inspiratory muscle training, 5-10 times/week for 1-4 weeks[1]	1/2 studies found no difference in LOS between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Insufficient Information on some study characteristics

[1] Insufficient information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; NRS, non-randomized study; LOS, length of stay; OR, odds ratio; RR, risk ratio; MD, mean difference; SMD, standardized mean ratio; CI, confidence interval

Table 4. Summary of findings for the effects of prehabilitation on postoperative outcomes after cardiac surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Complications						
Marmelo 2018[21]	833 (6 RCTs, NRS)	Standard care and/or respiratory training for 1 day	Unimodal Inspiratory muscle training, aerobic exercise, resistance training and/or strength training 1-7 times/week for 2-10 weeks	• OR=0.41 95%CI: 0.28, 0.62 • Number of events: Prehab: 59/418 Control: 105/415	Low	• Unclear risk of bias as appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in 3 of the primary studies • Study selection and data extraction were done by one person • Unclear if risk assessment was done by 2 persons
Pulmonary complications						
Ge 2018[22]	416 (4 RCTs)	Standard care or sham training	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	• RR=0.57 95%CI: 0.40, 0.81 • Number of events: NR	Low	• Moderate risk of bias • Small sample size in most primary studies • Unclear if study selection was done by 2 persons
Gomes Neto 2017[23]	386 (3 RCTs)	Standard care or sham training[1]	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks	• RR= 0.61 95%CI: 0.46, 0.80 • Number of events: Prehab: 42/195 Control: 69/191	Low	• Unclear risk of bias as the appraisal results were not reported • Small sample size in most primary studies • Unclear if risk assessment was done independently by the reviewers • Insufficient information on most study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Katsura 2015[20]	334 (3 RCTs)	Standard care or unknown	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks	Atelectasis complication • RR= 0.59 95%CI: 0.35, 1.00 • Number of events: Prehab: 19/169 Control: 31/165	Low	• Unclear risk of bias • Small sample size in most primary studies
	448 (5 RCTs)	Standard care, sham training or unknown	Unimodal: Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	Pneumonia complication • RR= 0.44 95%CI: 0.23, 0.83 • Number of events: Prehab: 13/226 Control: 29/222	Low	• Unclear risk of bias • Small sample size in most primary studies
Snowdon 2014[24]	386 (3 RCTs)	Standard care or sham training	Unimodal Inspiratory muscle training 6-7 days/week for 2-4 weeks or ≥2 weeks	• OR= 0.42 95%CI: 0.21, 0.82 • Number of events: NR	Moderate	• Low risk of bias • Small sample size in most primary studies • Limited study selection

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hulzebos 2012[25]	379 (4 RCTs)	Standard care or unknown	Unimodal Inspiratory muscle training 6-7 days/week for 2-4 weeks or ≥2 weeks or respiratory training with breathing exercises 7 times/week for 1 week	Atelectasis complication • RR= 0.52 95%CI: 0.32, 0.87 • Number of events: Prehab: 19/194 Control: 35/185	Low	• Unclear risk of bias • Small sample size in most primary studies • Unclear if risk assessment was done by 2 persons
	448 (5 RCTs)	Standard care, sham training or unknown	Unimodal Inspiratory muscle training 6-7 days/week for 2-4 weeks or ≥2 weeks	Pneumonia complication • RR= 0.45 95%CI: 0.24, 0.83 • Number of events: Prehab: 13/226 Control: 29/222	Low	• Unclear risk of bias • Small sample size in most primary studies • Unclear if risk assessment was done by 2 persons
Hospital length of stay						
Marmelo 2018[21]	946 (8 RCTs, NRS)	Standard care, mobilization with no respiratory training or respiratory training for 1 day	Unimodal Inspiratory muscle training, aerobic exercise, resistance training and/or strength training 1-7 times/week for 2-10 weeks	SMD= -0.56 95%CI: -1.13, -0.01	Low	• Moderate risk of bias • Risk appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in most primary studies • Study selection and data extraction were done by one person • Unclear if risk assessment was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Gomes Neto 2017[23]	302 (2 RCTs)	Standard care[1]	Unimodal Inspiratory muscle training for 7 days/week for 2-4 weeks	MD= -2.04 days 95%CI: -3.37, -0.72	Low	• Unclear risk of bias as the appraisal results were not reported • Small sample size in 1 primary study • Unclear if risk assessment was done independently by the reviewers • Insufficient information on most study characteristics
Snowdon 2014[24]	302 (2 RCTs)	Standard care	Unimodal Inspiratory muscle training 7 days/week for 2-4 weeks or ≥2 weeks	MD= -2.08 days 95%CI: -3.41, -0.76	Moderate	• Low risk of bias • Small sample size in 1 primary study • Limited study selection
Hulzebos 2012[25]	347 (3 RCTs)	Standard care	Unimodal Inspiratory muscle training 6-7 days/week for 2-4 weeks or ≥2 weeks or respiratory training with breathing exercises 7 times/week for 1 week	MD= -3.21 days 95%CI: -5.73, -0.69	Low	• Unclear risk of bias • Small sample size in most primary studies • Unclear if risk assessment was done by 2 persons
Mortality						
Hulzebos 2012[25]	306 (2 RCTs)	Standard care	Unimodal Inspiratory muscle training 7 days/week for ≥2 weeks	All cause mortality • RR= 0.66 95%CI: 0.02, 18.48 • Number of events: Prehab: 3/154 Control: 5/152	Low	• Unclear risk of bias • Small sample size in 1 primary study • Unclear if risk assessment was done by 2 persons • Very large uncertainty

[1] Insufficient information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses
RCT, randomized controlled trial; NRS, non-randomized study; RR, risk ratio; OR, odds ratio; MD, mean difference; SMD, standardized mean difference; CI, confidence interval; NR, not reported

Table 5. Summary of findings for the effects of prehabilitation on postoperative outcomes after cardiothoracic or upper abdominal surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Functional capacity						
Mans 2015[26]	122 (4 RCTs)	Standard care	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	Maximal inspiratory pressure <5 days after surgery MD= 10.04 95%CI: 2.92, 17.15	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection, data extraction and risk of bias assessment were done independently by the reviewers • Very large uncertainty
	125 (3 RCTs)	Standard care or sham training	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	Maximal inspiratory pressure 5-10 days after surgery MD= 7.02 95%CI: -7.55, 21.58	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection, data extraction and risk of bias assessment were done independently by the reviewers • Substantial statistical heterogeneity (I^2=64%) • Very large uncertainty
Katsura 2015[20]	80 (3 RCTs)	Standard care	Unimodal Inspiratory muscle training for 5-6 days/week for 2-4 weeks or ≥2 weeks	Maximal inspiratory muscle strength postoperative change from baseline MD= -7.87 95%CI: -21.36, 5.61	Low	• Unclear risk of bias • Small sample size in primary studies • Very large uncertainty

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Pulmonary complications						
Katsura 2015[20]	359 (4 RCTs)	Standard care	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	Atelectasis complication • RR= 0.54 95%CI: 0.33, 0.88 • Number of events: Prehab: 21/181 Control: 37/178	High	• Low risk of bias • Small sample size in most primary studies
	418 (4 RCTs)	Standard care	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	Pneumonia complication • RR= 0.40 95%CI: 0.21, 0.76 • Number of events: Prehab: 11/190 Control: 31/228	High	• Low risk of bias • Small sample size in most primary studies
Mans 2015[26]	217 (6 RCTs)	Standard care or sham training	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	• RR= 0.48 95%CI: 0.26, 0.89 • Number of events: Prehab: 10/109 Control: 21/108	Low	• Moderate risk of bias • Small sample size in most primary studies • Unclear if study selection, data extraction and risk of bias assessment were done independently by the reviewers
Valkenet 2011[27]	406 (4 RCTs)	Standard care or sham training	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	• RR= 0.40 95%CI: 0.23, 0.72 • Number of events: Prehab: 14/205 Control: 34/201	Low	• Low risk of bias • Small sample size in most primary studies • Study selection was done by one person • Unclear if data extraction was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hospital length of stay						
Katsura 2015[20]	392 (5 RCTs)	Standard care or exercise advice	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	MD= -1.33 days 95%CI: -2.53, -0.13	Low	• Unclear risk of bias • Small sample size in most primary studies
Mans 2015[26]	83 (3 RCTs)	Standard care or sham training	Unimodal Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks	MD= -1.66 days 95%CI: -3.64, 0.31	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection, data extraction and risk of bias assessment were done independently by the reviewers
Valkenet 2011[27]	522 (2 RCTs)	Standard care	Unimodal or Bimodal • Inspiratory muscle training for 7 days/week for ≥2 weeks or unspecified exercise training 2 times/week for 8 weeks • Education	2/2 studies found that LOS was reduced in the prehabilitation vs. control groups	Moderate	• Low risk of bias • Study selection was done by one person • Unclear if data extraction was done by 2 persons
Mortality						
Katsura 2015[20]	343 (3 RCTs)	Standard care	Unimodal Inspiratory muscle training for 7 days/week for ≥2 weeks	All-cause mortality • RR= 0.40 95%CI: 0.04, 4.23 • Number of events: Prehab: 3/172 Control: 10/171	Low	• Unclear risk of bias • Small sample size in most primary studies • Large uncertainty

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses
RCT, randomized controlled trial; LOS, length of stay; RR, risk ratio; MD, mean difference; CI, confidence interval

Table 6. Summary of findings for the effects of prehabilitation on postoperative outcomes after vascular surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Complications						
Wee 2019[28]	197 (3 RCTs)	Standard care	Unimodal Inspiratory muscle training for 6 times/week for 2 weeks or moderate to intense training 3 times/week for 4-6 weeks	2/3 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Unclear risk of bias as the assessment results were not reported • Small sample size in primary studies
Hospital length of stay						
Wee 2019[28]	124 (1 RCT)	Standard care	Unimodal Moderate to intense training 3 times/week for 4-6 weeks	1/1 study found that LOS was reduced in the prehabilitation vs. control groups (median=7 days, IQR: 5-9 days vs. median=8 days, IQR: 6-12.3 days, p=0.025)	Low	• Unclear risk of bias as the assessment results were not reported • Small sample size in primary studies • Only 1 primary study

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; LOS, length of stay; IQR, interquartile range

Table 7. Summary of findings for the effects of prehabilitation on postoperative outcomes after gastrointestinal surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Functional capacity						
Lau 2019[29]	191 (3 RCTs)	Standard care[1]	Bimodal or Trimodal • Aerobic exercise, resistance training and strength training 3-4 times/week for 4 weeks or median 36 days[1] • Nutritional support • Psychological support	Walking capacity 4-8 weeks after surgery MD= 48.22m 95%CI: 1.53, 94.9m	Low	• Moderate risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment • Small sample size in primary studies • Unclear if study selection, data extraction and risk of bias assessment were done by 2 persons • Statistical heterogeneity assessed, but results were not reported • Insufficient Information on primary studies • Clinical heterogeneity • Very large uncertainty
Thomas 2019[30]	157 (2 RCTs)	Standard care	Trimodal • Aerobic exercise and resistance training 3-4 times/week for 4 weeks • Nutritional support • Psychological support	1/2 studies found no difference in walking capacity between the prehabilitation and control group 8 weeks after surgery	Low	• High risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons
	112 (1 RCT)	Walking and breathing exercise	Unimodal Aerobic exercise and resistance training everyday for 3-9 weeks	1/1 study found no difference in walking capacity between the prehabilitation and control groups after surgery	Low	• High risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Only 1 primary study

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Vermillion 2018[31]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training 3 times/week for 4 weeks or 21-46 days • Nutritional support • Psychological support	2/2 studies found that walking capacity was improved in the prehabilitation vs. control group 4 or 8 weeks after surgery	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies
	112 (1 RCT)	Walking and breathing exercise	Unimodal Aerobic exercise and resistance training everyday for an average 59 days	1/1 study found no difference in walking capacity between the prehabilitation and control groups after surgery	Low	• High risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies • Inaccurate interpretation of the result • Only 1 primary study
Bolshinsky 2018[32]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training for a median 25 or 33 days • Nutritional support • Psychological support	2/2 studies found that walking capacity was improved in the prehabilitation vs. control group 4 or 8 weeks after surgery	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Limited selection of studies
	112 (1 RCT)	Walking and breathing exercise	Unimodal Daily aerobic exercise and resistance training for an average of 59 days[1]	1/1 study found no difference in walking capacity between the prehabilitation and control groups after surgery	Low	• High risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Selective reporting of results • Limited selection of studies • Only 1 primary study

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Complications						
Lau 2019[29]	75[1 2] (2 RCTs)	Exercise advice or Standard care[1]	Unimodal Aerobic exercise, resistance training and inspiratory muscle training 2 times/week for 2-4 weeks, or moderate to intense exercise 12 times in 4 weeks	• RR= 0.99 95%CI: 0.58, 1.67 • Number of events: NR	Low	• Low risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment • Small sample size in primary studies • Unclear if study selection, data extraction and risk of bias assessment were done by 2 persons • Statistical heterogeneity assessed, but results were not reported • Insufficient Information on some study characteristics
Thomas 2019[30]	352 (4 RCTs)	Standard care or nutritional support	Bimodal or Trimodal • Aerobic exercise and resistance training 2-7 times/week for 4-6 weeks • Nutritional support • Psychological support	3/4 studies found no difference in complication rate between the prehabilitation and control groups	Moderate	• Low risk of bias • Small sample size in primary studies • Unclear if data extraction were done by 2 persons
	185[1] (3 RCTs)	Walking and breathing exercise or Standard care	Unimodal Aerobic exercise and resistance training 1-3 times/week for 2-8 weeks	3/3 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Vermillion 2018[31]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training 3 times/week for 4 weeks or 21-46 day • Nutritional support • Psychological support	2/2 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies
	223[1] (3 RCTs, NRS)	Standard care, walking and breathing, exercise advice	Unimodal Inspiratory muscle training, aerobic exercise, strength training and/or resistance training 3-7 times/week for 2-4 weeks or an average 59 days	2/3 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Unclear risk of bias as appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Bolshinsky 2018[32]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training for a median 25 or 33 days • Nutritional support • Psychological support	2/2 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Limited selection of studies
	98 (2 NRS)	Standard care or same as prehabilitation (non-responder group)[2]	Unimodal aerobic exercise and strength training 3-5 times/week for 28 or 74 days	1/2 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Inaccurate Information on some study characteristics • Limited selection of studies • Results from two studies were not reported
Hospital length of stay						
Lau 2019[29]	75[1] (2 RCTs)	Exercise advice or Standard care[1]	Unimodal Aerobic exercise, resistance training and inspiratory muscle training 2 times/week for 2-4 weeks, or moderate to intense exercise 12 times in 4 weeks	MD= -0.05 day 95%CI: -1.17, 1.06	Low	• Low risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment • Small sample size in primary studies • Unclear if study selection, data extraction and risk of bias assessment were done by 2 persons • Statistical heterogeneity assessed, but results were not reported • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Thomas 2019[30]	536[1] (7 RCTs)	Walking and breathing exercise, Standard care or nutrition support	Unimodal, Bimodal or Trimodal • aerobic exercise, resistance training 1-7 times/week for 2-8 weeks • nutritional support • psychological support	7/7 studies found no difference in LOS between the prehabilitation and control groups	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons
Vermillion 2018[31]	164 (2 RCT, NRS)	Standard care	Trimodal • aerobic exercise and resistance training for 3 times/week for 4 weeks or 21-46 days • nutritional support • psychological support	2/2 studies found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies
	223[1] (3 RCTs, NRS)	Standard care, walking and breathing or exercise advice	Unimodal inspiratory muscle training, aerobic exercise, strength training and/or resistance training 3-7 times/week for 2-4 weeks or an average 59 days	2/3 studies found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Bolshinsky 2018[32]	164 (2 RCT, NRS)	Standard care	Trimodal • aerobic exercise and resistance training for a median 25 or 33 days • nutritional support • psychological support	2/2 studies found no difference in LOS between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Limited selection of studies
Quality of life						
Vermillion 2018[31]	276 (3 RCT, NRS)	Walking and breathing exercise or Standard care	Unimodal or Trimodal • aerobic exercise and resistance training for 3-7 times/week for 4 weeks, 21-46 days or an average 59 days • nutritional support • psychological support	3/3 studies found no difference in QoL between the prehabilitation and control groups after surgery (SF-36, HADS or EORTC)[1]	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Limited selection of studies • Inaccurate Information on the results
Bolshinsky 2018[32]	164 (2 RCT, NRS)	Standard care	Trimodal • aerobic exercise and resistance training for a median 25 or 33 days • nutritional support • psychological support	2/2 studies found no difference in QoL between the prehabilitation and control groups after surgery (SF-36)	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Limited selection of studies

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Readmission						
Thomas 2019[30]	191[2] (3 RCTs)	Standard care	Unimodal or Trimodal • aerobic exercise and resistance training 3-4 times/week for 4 weeks • nutritional support • psychological support	3/3 studies found no difference in readmission between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Insufficient Information on some study characteristics

[1] Insufficient information reported by authors

[2] Inaccurate information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; NRS, non-randomized study; LOS, length of stay; QoL, quality of life; RR, risk ratio; MD, mean difference; CI, confidence interval; NR, not reported

Table 8. Summary of findings for the effects of prehabilitation on postoperative outcomes after colorectal surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Functional capacity						
Looijaard 2018[33]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training 3 times/week for a median 24.5 or 33 days • Nutritional support • Psychological support	2/2 studies found that walking capacity was improved in the prehabilitation vs. control group 8 weeks after surgery	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Risk appraisal done by one person • Small sample size in primary studies • Limited selection of studies
Bruns 2016[34]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise, resistance training 3 times/week for a median 24 or 33 days • Nutritional support • Psychological support	2/2 studies found that walking capacity was improved in the prehabilitation vs. control group 8 weeks after surgery	Moderate	• Low risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons
	112 (1 RCT)	Walking and breathing exercise	Unimodal Aerobic exercise and resistance training everyday for a median 38 days	1/1 study found no difference in walking capacity between prehabilitation and control groups after surgery	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Selective reporting of results • Only 1 primary study

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Boereboom 2016[35]	164 (2 RCT, NRS)	Standard care[1]	Trimodal • Aerobic exercise, resistance training 3 times/week for a median 25 or 33 days • Nutritional support • Psychological support	2/2 studies found that walking capacity was improved in the prehabilitation vs. control group 8 weeks after surgery	Low	• Unclear risk of bias as results for NRS were not reported • Small sample size in primary studies • Unclear if data extraction was done by 2 persons
	112[2] (1 RCT)	Walking and breathing exercise	Unimodal Aerobic exercise and resistance training everyday for a median 38 days[1]	1/1 study found no difference in walking capacity between prehabilitation and control groups after surgery	Low	• Unclear risk of bias as results for NRS were not reported • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Inaccurate Information on some study characteristics • Only 1 primary study
Complications						
Nunns 2019[36]	228[1] (3 RCTs)	Walking and breathing exercise or exercise advice	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-7 times/week for 2-4 weeks or a median 24.5 or 38 days[1] • Nutritional support • Psychological support	3/3 studies found no difference in complication rate between the prehabilitation and control groups	Low	• High risk of bias • Small sample size in primary studies

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Looijaard 2018[33]	205[1] (3 RCTs, NRS)	Standard care or exercise advice	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-3 times/week for 2-4 weeks or a median 24.5 or 33 days • Nutritional support • Psychological support	3/3 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Risk appraisal done by one person • Small sample size in primary studies • Limited selection of studies
Bruns 2016[34]	315[1] (4 RCTs, NRS)	Standard care, walking and breathing exercise or exercise advice[2]	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-7 times/week for a median 24, 33 or 38 days or average 21 days • Nutritional support • Psychological support	4/4 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Inaccurate Information on some study characteristics
Boereboom 2016[35]	315[1] (4 RCTs, NRS)	Standard care, walking and breathing exercise or exercise advice[1]	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-7 times/week for a median 25, 33 or 38 days or 2.5 weeks[1] • Nutritional support • Psychological support	4/4 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Unclear risk of bias as results for NRS were not reported • Small sample size in primary studies • Unclear if data extraction was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hospital length of stay						
Nunns 2019[36]	227[1] (3 RCTs)	Walking and breathing exercise or exercise advice	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-7 times/week for 2-4 weeks or a median 24.5 or 38 days • Nutritional support • Psychological support	3/3 studies found no difference in LOS between the prehabilitation and control groups	Low	• High risk of bias • Small sample size in primary studies
Looijaard 2018[33]	205[2] (3 RCTs, NRS)	Standard care or exercise advice	Unimodal or trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-3 times/week for 2-4 weeks or a median 24.5 or 33 days • Nutritional support • Psychological support	3/3 studies found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Risk appraisal done by one person • Small sample size in primary studies • Limited selection of studies
Bruns 2016[34]	315[2] (4 RCTs, NRS)	Standard care, walking and breathing exercise or exercise advice[2]	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-7 times/week for a median 24, 33 or 38 days or average 21 days • Nutritional support • Psychological support	4/4 studies found no difference in LOS between the prehabilitation and control groups	Low	• Low risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Inaccurate Information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Boereboom 2016[35]	315[1] (4 RCTs, NRS)	Standard care or exercise advice[1]	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 2-7 times/week for a median 25, 33 or 38 days or 2.5 weeks[1] • Nutritional support • Psychological support	4/4 studies found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as results for NRS were not reported • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Inaccurate information on some results
Quality of life						
Looijaard 2018[33]	164 (2 RCT, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training 3 times/week for a median 25 or 33 days • Nutritional support • Psychological support	2/2 studies found no difference in QoL between the prehabilitation and control groups (SF-36)	Low	• Unclear risk of bias as the appraisal tool used for NRS is not appropriate (Cochrane) • Risk appraisal done by one person • Small sample size in primary studies • Limited selection of studies
Readmission						
Nunns 2019[36]	77[1] (1 RCT)	Standard care	Trimodal • Aerobic exercise and resistance training 3 times/week for a median 24.5 days[1] • Nutritional support • Psychological support	1/1 study found no difference in readmission between the prehabilitation and control groups	Low	• High risk of bias • Small sample size in primary studies • Only 1 primary study

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Looijaard 2018[33]	77 (1 RCT)	Standard care	Trimodal • Aerobic exercise and resistance training for 3 times/week • Nutritional support • Psychological support	1/1 study found no difference in readmission between the prehabilitation and control groups	Low	• Moderate risk of bias • Risk appraisal tool used for NRS is not appropriate (Cochrane) • Risk appraisal done by one person • Small sample size in primary studies • Limited selection of studies • Only 1 primary study

[1] Insufficient information reported by authors

[2] Inaccurate information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; NRS, non-randomized study; LOS, length of stay; QoL, quality of life; CI, confidence interval

Table 9. Summary of findings for the effects of prehabilitation on postoperative outcomes after abdominal surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Functional capacity						
Teo 2020[37]	277 (4 RCTs, NRS)	Standard care	Trimodal • Aerobic exercise and resistance training 3-4 times/week for 28-33 days • Nutritional support • Psychological support	4/4 studies found that walking capacity was improved in the prehabilitation vs. control groups after surgery	Low	• Unclear risk of bias as appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if risk of bias assessment was done by 2 persons • Unclear if data extraction was done independently by the reviewers
Gillis 2018[38]	164 (2 RCTs, NRS)	Standard care or rehabilitation	Trimodal • Aerobic exercise and resistance training for 4 weeks • Nutritional support • Psychological support	Walking capacity 8 weeks after surgery RR=1.63 95%CI: 1.10, 2.41	Low	• Moderate risk of bias • Some bias domains were not assessed, i.e. blinding of patients and randomisation method for RCT, or selection of patient for NRS • Small sample size in primary studies • Substantial statistical heterogeneity (I^2=63.3%)
Complications						
Teo 2020[37]	291 (5 RCTs, NRS)	Standard care	Trimodal • Aerobic exercise, resistance training and strength training 3-4 times/week for 28-33 days • Nutritional support • Psychological support	5/5 studies found no difference in complication rate between prehabilitation and control groups	Low	• Unclear risk of bias as appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if risk of bias assessment was done by 2 persons • Unclear if data extraction was done independently by the reviewers

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Gillis 2018[38]	281 (3 RCTs, NRS)	Standard care or rehabilitation	<u>Bimodal or Trimodal</u> • Aerobic exercise, strength training and/or resistance training for 2-4 weeks • Nutritional support • Psychological support	• RR=0.65 95%CI: 0.23, 1.84 • Number of events: NR	Low	• High risk of bias • Some bias domains were not assessed, i.e. blinding of patients and randomisation method for RCT, or selection of patient for NRS • Small sample size in primary studies • Clinical heterogeneity
Hughes 2019[39]	708 (9 RCTs)	Standard care, walking and breathing, exercise advice or diet supplement	<u>Unimodal or Trimodal</u> • Aerobic exercise, resistance training and/or inspiratory muscle training 1-7 times/week for 2-6 weeks or 30 days • Nutritional support • Psychological support[1]	• OR=0.63 95%CI: 0.46, 0.87 • Number of events: Prehab: 116/354 Control: 153/354	Low	• Moderate risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Clinical heterogeneity • Insufficient information on some study characteristics • Clinical heterogeneity
Heger 2019[40]	329 (5 RCTs)	Standard care, exercise advice or nutrition support	<u>Unimodal, Bimodal or Trimodal</u> • Aerobic exercise, resistance training and/or inspiratory muscle training 1-3 times/week for 2-6 weeks • Nutritional support • Psychological support	• OR=0.52 95%CI: 0.30, 0.88 • Number of events: Prehab: 50/166 Control: 74/163	Low	• Unclear risk of bias • Small sample size in primary studies • Unclear if risk of bias assessment was done by 2 persons • Limited study selection • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Luther 2018[41]	395 (5 RCTs, NRS)	Standard care or exercise advice[1]	Unimodal Aerobic exercise, resistance training and/or inspiratory muscle training for 2-7 times/week for 2-6 weeks	4/5 studies found that complication rate was decreased in the prehabilitation vs. control groups	Low	• Unclear risk of bias as the appraisal results for NRS were not reported • Small sample size in primary studies • Unclear if study selection study was done independently by the reviewers • Unclear if data extraction and risk of bias assessment were done by 2 persons • Insufficient information on some study characteristics
Hijazi 2017[42]	422 (5 RCTs, NRS)	Standard care, exercise advice or walking and breathing exercise[1]	Unimodal or Trimodal • Aerobic exercise, resistance training and/or strength training 2-7 times/week for 2-6 weeks • Nutritional support • Psychological support	5/5 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Low risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment (Delphi) • Some bias domains were not assessed for NRS, i.e. confounding factors • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Selective reporting of results • Insufficient information on some study characteristics
Moran 2016[43]	166 (4 RCTs)	Standard care	Unimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 3-7 times/week for 2-4 weeks[1] • Nutritional support • Psychological support	• OR=0.35 95%CI: 0.17, 0.71 • Number of events: Prehab: 20/82 Control: 38/84	Low	• Unclear risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Pulmonary complications						
Hughes 2019[39]	490 (8 RCTs)	Standard care, exercise advice or trimodal rehabilitation	<u>Unimodal or Trimodal</u> • Aerobic exercise, resistance training and/or inspiratory muscle training 1-7 times/week for 2-6 weeks[1] • Nutritional support • Psychological support	• OR=0.40 95%CI: 0.23, 0.68 • Number of events: Prehab: 27/246 Control: 53/244	Low	• Low risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Clinical heterogeneity • Insufficient information on some study characteristics • Clinical heterogeneity
Heger 2019[40]	370 (6 RCTs)	Standard care or exercise advice	<u>Unimodal or Trimodal</u> • Aerobic exercise, resistance training and/or inspiratory muscle training with stretching and strength training 1-5 times/week for 1-6 weeks • Nutritional support • Psychological support	• OR=0.37 95%CI: 0.20, 0.67 • Number of events: Prehab: 25/187 Control: 48/183	Low	• Unclear risk of bias • Small sample size in primary studies • Unclear if risk of bias assessment was done by 2 persons • Limited study selection • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Luther 2018[41]	203 (3 RCTs, NRS)	Standard care[1]	Unimodal Inspiratory muscle training with or without aerobic exercise for 6 days/week for 2-4 weeks or ≥1-2 weeks.	2/3 studies found no difference in pulmonary complication rate between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal results for NRS were not reported • Small sample size in primary studies • Unclear if study selection study was done independently by the reviewers • Unclear if data extraction and risk of bias assessment were done by 2 persons • Insufficient information on some study characteristics
Katsura 2015[20]	77 (3 RCTs)	Standard care	Unimodal or Trimodal • Inspiratory muscle training for 6-7 days/week for 2-4 weeks or ≥2 weeks • Nutritional support • Psychological support	Atelectasis complication • RR=0.41 95%CI: 0.19, 0.90 • Number of events: Prehab: 6/37 Control: 15/40	Low	• Unclear risk of bias • Small sample size in primary studies • Clinical heterogeneity
	195 (5 RCTs)	Standard care	Unimodal or Trimodal • Inspiratory muscle training and can included resistance training for 5-7 days/week for ≥2 weeks • Nutritional support • Psychological support	Pneumonia complication • RR=0.46 95%CI: 0.16, 1.33 • Number of events: Prehab: 4/76 Control: 13/119	Low	• High risk of bias • Small sample size in primary studies • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hospital length of stay						
Teo 2020[37]	291 (5 RCTs, NRS)	Standard care	Trimodal • Aerobic exercise, resistance training and strength training 3-4 times/week for 28-33 days • Nutritional support • Psychological support	4/5 studies found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as appraisal tool used for NRS is not appropriate (Cochrane) • Small sample size in primary studies • Unclear if risk of bias assessment was done by 2 persons • Unclear if data extraction was done independently by the reviewers
Gillis 2018[38]	281 (3 RCTs, NRS)	Standard care or rehabilitation	Bimodal or Trimodal • Aerobic exercise, strength training and/or resistance training for 2-4 weeks • Nutritional support • Psychological support	MD= -1.42 days 95%CI: -3.44, 0.60	Low	• High risk of bias • Some bias domains were not assessed, i.e. blinding of patient and method of randomisation for RCT, or selection of patient for NRS • Small sample size in primary studies • Clinical heterogeneity
Hughes 2019[39]	462 (6 RCTs)	Standard care, walking and breathing, exercise advice or diet supplement	Bimodal or Trimodal • Aerobic exercise, resistance training and/or inspiratory muscle training 1-7 times/week for 2-4 weeks • Nutritional support	MD= -2.39 days 95%CI: -4.86, 0.08	Low	• Moderate risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment • Small sample size in primary studies • Unclear if data extraction was done by 2 persons • Clinical heterogeneity

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Heger 2019[40]	361 (6 RCTs)	Standard care, exercise advice or nutrition support	<u>Unimodal, Bimodal or Trimodal</u> • Aerobic exercise, resistance training and/or inspiratory muscle training with stretching 1-3 times/week for 2-6 weeks • Nutritional support • Psychological support	MD= -0.58 day 95%CI: -1.28, 0.13	Low	• Unclear risk of bias • Small sample size in primary studies • Unclear if risk of bias assessment was done by 2 persons • Limited study selection • Clinical heterogeneity
Moran 2016[43]	200 (3 RCTs)	Nutrition support, exercise advice or walking and breathing exercise	<u>Unimodal or Bimodal</u> • Aerobic exercise, resistance training and/or inspiratory muscle training 3-7 times/week for 2-4 weeks[1] • Nutritional support • Psychological support	MD= -1.62 days 95%CI: -7,57, 4.33	Low	• Unclear risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Quality of life						
Hijazi 2017[42]	276 (3 RCTs, NRS)	Standard care or walking and breathing exercise[1]	Unimodal or Trimodal • Aerobic exercise, resistance training and/or strength training 3-7 times/week for 3-6 weeks • Nutritional support • Psychological support	2/3 studies found no difference in QoL between the prehabilitation and control groups (SF-36)[1]	Low	• Low risk of bias • Risk appraisal tool used for RCT does not assess for allocation concealment (Delphi) • Some bias domains were not assessed for NRS, i.e. confounding factors • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Insufficient information on some study characteristics

[1] Insufficient information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; NRS, non-randomized study; LOS, length of stay; QoL, quality of life; RR, risk ratio; OR, odds ratio; MD, mean difference; CI, confidence interval; NR, not reported

Table 10. Summary of findings for the effects of prehabilitation on postoperative outcomes after esophageal surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Complications						
Bolger 2019[44]	396 (3 RCTs, NRS)	Standard care[1]	Unimodal Inspiratory muscle training for ≥2 weeks or aerobic exercise and resistance training for 3-4 weeks	3/3 studies found no difference in complication rate between the prehabilitation and control groups	Low	• Risk of bias reported as "significative" (no detail) • Risk appraisal tool used for RCT does not assess for allocation concealment (Jadad) • Small sample size in most primary studies • Unclear if risk of bias assessment were done by 2 persons • Unclear if data extraction was done independently by the reviewers • Insufficient Information on some study characteristics
Hospital length of stay						
Steffens 2018[11]	99 (2 RCT, quasi-RCT)	Standard care or unknown[1]	Unimodal Inspiratory muscle training. 5-7 times/week for 2-3 weeks	MD=2.00 days 95%CI: -2.35, 6.35	Low	• High risk of bias • Small sample size in primary studies • Insufficient Information on some study characteristics • Very large uncertainty

[1] Insufficient information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; NRS, non-randomized study; MD, mean difference; CI, confidence interval

Table 11. Summary of findings for the effects of prehabilitation on postoperative outcomes after liver transplantation from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Complications						
Brustia 2018[45]	23 (1 RCT)	Leucyne supplement	Bimodal • Aerobic exercise • Leucyne supplement	• OR=2.11 95%CI: 0.08, 57.61 • Number of events: Prehab: 1/14 Control: 0/9	Low	• Risk of bias reported as "medium" (no detail) • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Very large uncertainty • Only 1 primary study

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses
RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval

Table 12. Summary of findings for the effects of prehabilitation on postoperative outcomes after knee surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Functional capacity						
Chen 2018[46]	168 (3 RCTs)	Upper body strengthening or Standard care[1]	Unimodal or Bimodal • Lower body strengthening or resistance training with strength training 3 times/week for 3-6 weeks[1] • Education	Change from baseline in quadriceps strength 3 months after surgery[1] MD= 0.20 95%CI: -0.25, 0.64	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • High statistical heterogeneity (I^2=69%) • Insufficient information on some study characteristics
	187 (4 RCTs)	Standard care	Unimodal Strength training and/or resistance training of upper body for 3-4 weeks	Change from baseline in knee extension 8-12 weeks after surgery[1] MD= -0.87 95%CI: -2.13, 0.40	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Insufficient information on some study characteristics
	187 (4 RCTs)	Standard care	Unimodal Strength training and/or resistance training of upper body for 3-4 weeks	Change from baseline in knee flexion 8-12 weeks after surgery[1] MD= 2.72 95%CI: -0.50, 5.94	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • High statistical heterogeneity (I^2=76%) • Insufficient information on some study characteristics • Very large uncertainty

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
	219 (3 RCTs)	Standard care[1]	Unimodal or Bimodal • Resistance training and/or strength training 2-3 times/week for 3-6 weeks[1] • Education	Change from baseline in knee range of motion 3 months after surgery[1] MD= 3.62 95%CI: 0.09, 7.15	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Insufficient information on some study characteristics • Very large uncertainty
Peer 2017[47]	44 (2 RCTs)	Standard training or upper body strengthening	Unimodal Highly intensive resistance training with standard training or lower body strengthening 2-3 times/week for 6 weeks	Quadriceps strength 6 weeks after surgery SMD= -0.02 95%CI: -0.26, 0.23 Quadriceps strength after 12 weeks SMD= -0.12 95%CI: -0.45, 0.21	Low	• Moderate risk of bias • Small sample size in primary studies • Study selection and data extraction were done by one person • Unclear if risk of bias assessment was done by 2 persons • Limited study selection • Unclear statistical method used
Moyer 2017[48]	421 (7 RCTs)	Standard care or upper body strengthening[1]	Unimodal Strength training, resistance training, aerobic exercise, flexibility training and/or lower body strengthening 3 times/week for 3-8 weeks	Quadriceps strength after surgery[1] SMD= 0.42 95%CI: 0.16, 0.68	Low	• Moderate risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Cabilan 2016[49]	143 (2 RCTs)	Standard care[1]	Unimodal Strength training, flexibility training, extension techniques and/or functional training 3 times/week for ≥6 weeks	WOMAC function 3 months after surgery SMD= -0.06 95%CI: -0.39, 0.26	Low	• Risk of bias reported as "acceptable", but "unclear or inadequate" for investigator blinding and allocation concealment for 1 study (no detail) • Authors decided not to assess for patient blinding • Small sample size in primary studies • Unclear if data extraction was done by 2 persons
Chesham 2016[50]	153 (2 RCTs)	Standard care or upper body strengthening	Unimodal or Bimodal • Strength training and resistance or lower body strengthening 3 times/week for 4-6 weeks • Education	2/2 studies found no difference in knee extension strength between the prehabilitation and control groups 12 weeks after surgery	Low	• Moderate risk of bias • Small sample size in primary studies • Limited study selection
	236 (4 RCTs)	Standard care, upper body strengthening or unknown	Unimodal or Bimodal • Strength training, resistance training, flexibility training, aerobic exercise, proprioception exercises and/or lower body strengthening, 1-3 times/week for 4-6 weeks • Education	4/4 studies found no difference in WOMAC function between the prehabilitation and control groups 6-12 weeks after surgery	Low	• Moderate risk of bias • Small sample size in primary studies • Limited study selection

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Jordan 2014[51]	160[1] (3 RCTs)	Standard care or upper body strengthening	Unimodal or Bimodal • Strength training, resistance training, flexibility training, aerobic exercise and/or lower body strengthening 3 times/week for 4-6 weeks • Education	3/3 studies found no difference in WOMAC function between the prehabilitation and control groups after surgery	Low	• Unclear risk of bias as the appraisal tool used is not appropriate (CONSORT) • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Limited study selection • Insufficient information on some study characteristics
Hoogeboom 2012[52]	230 (6 RCTs, quasi-RCT)	Standard care or advice leaflet	Unimodal Strength training, resistance training, aerobic exercise and/or flexibility training 1-3 times/week for 4-6 weeks	Observed function ≤3 months after surgery[1] SMD= -0.15 95%CI: -0.41, 0.11	Low	• High risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics
	220 (4 RCTs)	Standard care or advice leaflet	Unimodal Strength training, resistance training and/or aerobic exercise 1-3 times/week for 4-6 weeks	Self-reported function ≤3 months after surgery[1] SMD= 0.14 95%CI: -0.13, 0.41	Low	• High risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics
Wallis 2011[53]	150 (2 RCTs)	Standard care or advice leaflet[1]	Unimodal Strength training, resistance training, flexibility training and/or aerobic exercise 1-3 times/week for 6 weeks	WOMAC function 8-12 weeks after surgery SMD= -0.08 95%CI: -0.40, 0.24	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Insufficient information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hospital length of stay						
Vasta 2020[54]	347 (3 RCTs)	Standard care or advice leaflet	Unimodal Strength training, flexibility training and/or resistance training 1-5 times/week for 6-12 weeks[1]	2/3 studies found no difference in LOS between the prehabilitation and control groups[1]	Low	• High risk of bias • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Insufficient information on some study characteristics
Chen 2018[46]	664 (5 RCTs)	Standard care or advice leaflet[1]	Unimodal or Bimodal • Resistance training, strength training, flexibility and extension training and/or functional training 1-5 times/week for 4-6 weeks or ≥3 visits [1] • Education	MD= -0.80 day 95%CI: -1.11, -0.48	Low	• Unclear risk of bias • Small sample size in most primary studies • Unclear if study selection was done by 2 persons • Insufficient information on some study characteristics • Clinical heterogeneity
Chesham 2016[50]	295[1] (3 RCTs)	Standard care or exercise and advice leaflet[1]	Unimodal Strength training, resistance, flexibility and/or balance training 1-5 times/week for 4-6 weeks[1]	2/3 studies found no difference in LOS between the prehabilitation and control groups	Low	• Moderate risk of bias • Small sample size in primary studies • Limited study selection • Insufficient information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Jordan 2014[51]	115 (1 RCT)	Advice leaflet	Unimodal Strength training, flexibility training or aerobic exercise 3 times/week for 6 weeks	1/1 study found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal tool used is not appropriate (CONSORT) • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Limited study selection • Only 1 primary study
	358 (2 RCTs)	Standard care	Unimodal or Bimodal • Strength training and/or resistance training 3 times/week for 4 weeks • Education	1/2 studies found no difference in LOS between the prehabilitation and control groups	Low	• Unclear risk of bias as the appraisal tool used is not appropriate (CONSORT) • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Limited study selection • Insufficient information on some study characteristics
Wallis 2011[53]	141 (2 RCTs)	Advice leaflet[1]	Unimodal Strength training, flexibility training, resistance training and/or aerobic exercise 1-3 times/week for 6 weeks	MD= -0.04 day 95%CI: -0.64, 0.56	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Insufficient information on some study characteristics

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Readmission						
Cabilan 2016[49]	138 (2 RCTs)	Standard care	<u>Unimodal or Bimodal</u> • Strength training, flexibility training, and/or resistance training 3 times/week for 4-6 weeks • Education	<u>Admission to acute rehabilitation</u> • OR=0.57 95%CI: 0.25, 1.27 • Number of events: Prehab: 29/65 Control: 42/73	Low	• Risk of bias reported as "acceptable", but "unclear or inadequate" for investigator blinding and allocation concealment for both study (no detail) • Authors decided not to assess for patient blinding • Small sample size in primary studies • Unclear if data extraction was done by 2 persons
Pain						
Tedesco 2017[55]	60 (2 RCTs)	Standard care or upper body strengthening[1]	<u>Unimodal</u> Proprioception training, resistance training and/or lower body strengthening, 3-7 times/week for 6 weeks[1]	<u>WOMAC Pain 6 weeks after surgery</u> MD= 0.34 95%CI: -0.32, 0.99	Low	• High risk of bias • Small sample size in primary studies • Unclear if study selection was done by 2 persons • Insufficient information on some study characteristics • Clinical heterogeneity
Cabilan 2016[49]	297 (2 RCTs)	Standard care[1]	<u>Unimodal or Bimodal</u> • Strength training, and/or resistance training 3-7 times/week for 4 weeks • Education	<u>Pain 1 month after surgery</u> SMD= -0.14 95%CI: -0.37, 0.09	Low	• Risk of bias reported as "acceptable", but "unclear or inadequate" for investigator blinding and allocation concealment for 1 study (no detail) • Authors decided not to assess for patient blinding • Small sample size in 1 primary study • Unclear if data extraction was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Chesham 2016[50]	236 (4 RCTs)	Standard care, upper body strengthening or unknown[1]	Unimodal or Bimodal • Strength training, resistance training, flexibility training, aerobic exercise, proprioception exercises and/or lower body strengthening, 1-3 times/week for 4-6 weeks • Education	4/4 studies found no difference in WOMAC pain between the prehabilitation vs. control groups 6-12 weeks after surgery	Low	• Moderate risk of bias • Small sample size in primary studies • Limited study selection • Insufficient information on some study characteristics • Clinical heterogeneity
Wallis 2011[53]	204 (3 RCTs)	Standard care or advice leaflet[1]	Unimodal Strength training, resistance training, flexibility training and/or aerobic exercise 1-3 times/week for 6 weeks or ≥3 sessions/week	VAS or WOMAC Pain 8-12 weeks after surgery SMD= 0.01 95%CI: -0.26, 0.29	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Insufficient information on some study characteristics
Quality of life						
Cabilan 2016[49]	252 (3 RCTs)	Standard care	Unimodal or Bimodal • Strength training, flexibility training, resistance training, extension techniques and/or functional training 3 times/week for 4 to ≥6 weeks • Education	3/3 studies found no difference in QoL between the prehabilitation and control groups 3 months after surgery (SF-36)	Low	• Risk of bias reported as “acceptable”, but “unclear or inadequate” for investigator blinding and allocation concealment for 2 studies (no detail) • Authors decided not to assess for patient blinding • Small sample size in primary studies • Unclear if data extraction was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Simmons 2013[56]	115 (2 RCTs)	Standard care	<u>Unimodal or Bimodal</u> • Strength training and resistance training 3 times/week for 4 weeks, or flexibility and extension techniques and functional training for ≥3 sessions • Education	<u>SF-36 physical function 12 weeks after surgery</u> MD= -4.18 95%CI: -10.16, 1.81	Moderate	• Moderate risk of bias • Small sample size in primary studies

[1] Insufficient information reported by authors

[2] Inaccurate information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; NRS, non-randomized study; LOS, length of stay; QoL, quality of life; OR, odds ratio; MD, mean difference; SMD, standardized mean difference; CI, confidence interval

Table 13. Summary of findings for the effects of prehabilitation on postoperative outcomes after hip surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Functional capacity						
Cabilan 2016[49]	72 (2 RCTs)	Standard care	Unimodal Strength training, flexibility training, 3-5 times/week for 4-6 weeks	Self-reported function after 3 months SMD= -0.38 95%CI: -1.22, 0.46	Low	• Risk of bias reported as "acceptable", but "unclear or inadequate" for investigator blinding and allocation concealment for 2 studies (no detail) • Authors decided not to assess for patient blinding • Small sample size in primary studies • Unclear if data extraction was done by 2 persons
Hoogeboom 2012[52]	72 (2 RCTs)	Standard care	Unimodal Strength training, resistance training, aerobic exercise and/or flexibility training 3-5 times/week for 4-6 weeks	Observed function ≤3 months after surgery[1] SMD= -0.30 95%CI: -1.46, 0.85	Low	• High risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics • High statistical heterogeneity (I^2=80%)
	188 (4 RCTs)	Standard care	Unimodal Strength training, resistance training, aerobic exercise and/or flexibility training 0.5-5 times/week for 4-8 weeks	Self-reported function ≤3 months after surgery[1] SMD= -0.37 95%CI: -0.80, 0.06	Low	• High risk of bias • Small sample size in primary studies • Insufficient information on some study characteristics • Substantial statistical heterogeneity (I^2=51%)

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Wallis 2011[53]	106 (2 RCTs)	Standard care[1]	Unimodal Strength training, aerobic exercise and/or flexibility training 3-4 times/week for 6-8 weeks	WOMAC function 3-8 weeks after surgery SMD= 0.28 95%CI: -0.23, 0.78	Low	• High risk of bias • Small sample size in primary studies • Unclear if study selection and data extraction were done by 2 persons • Insufficient information on some study characteristics
Pain						
Cabilan 2016[49]	72 (2 RCTs)	Standard care[1]	Unimodal Strength training, flexibility training, 3-5 times/week for 4-6 weeks	3 months after surgery SMD= -0.10 95%: -0.56, 0.36	Low	• Risk of bias reported as “acceptable”, but “unclear or inadequate” for investigator blinding and allocation concealment for both studies (no detail) • Authors decided not to assess for patient blinding • Small sample size in primary studies • Unclear if data extraction was done by 2 persons

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Quality of life						
Cabilan 2016[49]	72 (2 RCTs)	Standard care	Unimodal Strength training, flexibility training, 3-5 times/week for 4-6 weeks	2/2 studies found no difference in QoL between the prehabilitation and control groups 3 months after surgery (SF-36)	Low	• Risk of bias reported as "acceptable", but "unclear or inadequate" for investigator blinding and allocation concealment for both studies (no detail) • Authors decided not to assess for patient blinding • Small sample size in primary studies • Unclear if data extraction was done by 2 persons

[1] Insufficient information reported by authors

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses

RCT, randomized controlled trial; QoL, quality of life; SMD, standardized mean difference; CI, confidence interval

Table 14. Summary of findings for the effects of prehabilitation on postoperative outcomes after spinal surgery from systematic reviews and meta-analyses

First author/ Year	No of patients (studies)	Intervention		Results (Prehabilitation vs. Control)	Quality of evidence	
		Control	Prehabilitation		Score	Comment *
Hospital length of stay						
Gometz 2018[57]	92 (1 RCT)	Standard care	Unimodal Aerobic exercise and strength training for 30min/day for 6-8 weeks	1/1 study found that LOS was reduced in the prehabilitation vs. control groups (median=5 days vs. median=7 days, p=0.007)	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Only 1 primary study
Pain						
Gometz 2018[57]	92 (1 RCT)	Standard care	Unimodal Aerobic exercise and strength training for 30min/day for 6-8 weeks	1/1 study found that pain was reduced in the prehabilitation vs. control groups (p=0.02)	Low	• Moderate risk of bias • Small sample size in primary studies • Unclear if data extraction and risk of bias assessment were done by 2 persons • Only 1 primary study

* Risk of bias score was based on the assessment of the risk of bias done by the authors of the systematic reviews and meta-analyses
RCT, randomized controlled trial; LOS, length of stay

Table 15. Risk of bias assessment of recent and large non-randomized studies

Outcomes	Confounding bias	Selection bias	Intervention classification bias	Outcome measurement bias	Missing data bias	Comments	Overall Risk of bias
Janssen 2019[58]							
Complications	H	H	H	H	U	– Regression models were not adjusted for factors like BMI, tumour stage, smoking status – Self-reported methods used to assess adherence to training program – Unknown amount of missing data – Assessor was not blinded	H
Length of stay	H	H	H	L	U	– Regression models were not adjusted for factors like BMI, tumour stage, smoking status – Self-reported methods used to assess adherence to training program – Unknown amount of missing data – Assessor was not blinded	H
Mortality	H	H	H	L	U	– Regression models were not adjusted for factors like BMI, tumour stage, smoking status – Self-reported methods used to assess adherence to training program – Unknown amount of missing data	H
Readmission	H	H	H	L	U	– Regression models were not adjusted for factors like BMI, tumour stage, smoking status – Self-reported methods used to assess adherence to training program – Unknown amount of missing data – Assessor was not blinded	H

Outcomes	Confounding bias	Selection bias	Intervention classification bias	Outcome measurement bias	Missing data bias	Comments	Overall Risk of bias
Uda 2018[59]							
Pulmonary complications	M	M	L	L	M	– Potential residual bias – 7367 patients who received prehabilitation were excluded due to the one-to-one propensity score matching and no comparison between excluded and included patients – Unknown amount of missing data – Missing indicator used to handle missing data – Insufficient description on the prehabilitation program – Variability in the assessment of prehabilitation inherent to administrative database	H
Mortality	M	M	L	L	M	– Potential residual bias – 7367 patients who received prehabilitation were excluded due to the one-to-one propensity score matching and no comparison between excluded and included patients – Unknown amount of missing data – Missing indicator used to handle missing data – Insufficient description on the prehabilitation program – Variability in the assessment of prehabilitation inherent to administrative database	H

L, low; M, moderate; H, high; U, unclear

Table 16. Summary of findings for the effect of prehabilitation on postoperative outcomes after surgery from recent and large non-randomized studies

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Complications							
Janssen 2019[58]	NRS	N=627/714 of eligible ≥70 years Dutch patients scheduled for colorectal cancer or abdominal aortic aneurysm surgery between 2013 and 2015 for control and 2015 and 2018 for prehab	Bimodal prehabilitation • Aerobic exercise, resistance training and respiratory muscle training at home for mean=39 days • Nutritional supplement Control Standard care	267/360	Overall complications • OR=1.12, 95%CI: 0.80, 1.57 • Number of events: Prehab: 109/267 Control: 133/360	Low	• High risk of bias • Low compliance (73.9%)
Uda 2018[59]	NRS	N=12748/21259 of eligible ≥18 years Japanese patients scheduled for non-small-cell lung cancer surgery between July-2010 and March-2015 prehab: n=13741 control: n=7518	Prehabilitation At least 20min of physical therapy within 3 days of surgery + postoperative physical therapy for 1-2 days Control Postoperative physical therapy for 1-2 days	6374 one-to-one matched pairs	Pulmonary complications • OR=0.84, 95%CI: 0.66, 1.07 • Number of events: Prehab: 128/6374 Control: 152/6374	Low	• High risk of bias • Insufficient information on prehabilitation program • No information on the assessment method for the prehabilitation program

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Length of hospital stay							
Janssen 2019[58]	NRS	N=627/714 of eligible ≥70 years Dutch patients scheduled for colorectal cancer or abdominal aortic aneurysm surgery between 2013 and 2015 for control and 2015 and 2018 for prehab	Bimodal prehabilitation • Aerobic exercise, resistance training and respiratory muscle training at home for mean=39 days • Nutritional supplement Control Standard care	267/360	MD= -0.89 day, 95%CI: -2.7, 0.99	Low	• High risk of bias • Low compliance (73.9%)
Mortality							
Janssen 2019[58]	NRS	N=627/714 of eligible ≥70 years Dutch patients scheduled for colorectal cancer or abdominal aortic aneurysm surgery between 2013 and 2015 for control and 2015 and 2018 for prehab	Bimodal prehabilitation • Aerobic exercise, resistance training and respiratory muscle training at home for mean=39 days • Nutritional supplement Control Standard care	267/360	30-day or during admission mortality • OR=1.50, 95%CI: 0.61, 3.72 • Number of events: Prehab: 21/267 Control: 16/360	Low	• High risk of bias • Low compliance (73.9%)

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Uda 2018[59]	NRS	N=12748/21259 of eligible ≥18 years Japanese patients scheduled for non-small-cell lung cancer surgery between July-2010 and March-2015 prehab: n=13741 control: n=7518	Prehabilitation At least 20min of physical therapy within 3 days of surgery + postoperative physical therapy for 1-2 days Control Postoperative physical therapy for 1-2 days	one-to-one 6374 matched pairs	30-day mortality • OR=0.79, 95%CI: 0.32, 1.86 • Number of events: Prehab: 11/6374 Control: 14/6374	Low	• Moderate risk of bias • Insufficient information on prehabilitation program • No information on the assessment method for the prehabilitation program
Readmission							
Janssen 2019[58]	NRS	N=627/714 of eligible ≥70 years Dutch patients scheduled for colorectal cancer or abdominal aortic aneurysm surgery between 2013 and 2015 for control and 2015 and 2018 for prehab	Bimodal prehabilitation • Aerobic exercise, resistance training and respiratory muscle training at home for mean=39 days • Nutritional supplement Control Standard care	267/360	30-day readmission • OR=1.42, 95%CI: 0.75, 2.68 • Number of events: Prehab: 22/267 Control: 22/360	Low	• High risk of bias • Low compliance (73.9%)

NRS, non-randomized study; OR, odds ratio; MD, mean difference; CI, confidence intervals

Table 17. Risk of bias assessment of RCTs conducted recently at the MUHC

Outcomes	Sequence generation	Allocation concealment	Blinding of participant	Blinding of personnel	Blinding of assessors	Incomplete outcome data	Selective outcome reporting	Comments	Overall Risk of bias
Carli 2020[65]									
Functional capacity	L	L	H	H	L	H	L	– Patients and intervention staff were not blinded – Proportion of missing data (41%) is high	H
Complications	L	L	L	L	L	L	L	–	L
Length of stay	L	L	H	L	L	L	L	– Patients were not blinded – Imputation model did not include the outcome LOS (2/110 missing data)	L
Quality of life	L	L	H	H	L	H	L	– Patients and intervention staff were not blinded – Proportion of missing data (38%) is higher than the number of imputed datasets (20) – Imputation model did not include all the covariates in the regression model	H
Readmission	L	L	H	L	L	L	L	– Patients were not blinded – Imputation model did not include the outcome readmission (2/110 missing data)	L

Outcomes	Sequence generation	Allocation concealment	Blinding of participant	Blinding of personnel	Blinding of assessors	Incomplete outcome data	Selective outcome reporting	Comments	Overall Risk of bias
Minnella 2019[66]									
Functional capacity	L	L	H	H	L	H	L	– Patients and intervention staff were not blinded – No appropriate method used to handle substantial missing data (up to 43/70 missing data)	H
Complications	L	L	L	L	L	M	L	– No appropriate method used to handle missing data (12/70 missing data)	L
Length of stay	L	L	H	L	L	M	L	– Patients were not blinded – No appropriate method used to handle missing data (12/70 missing data)	M
Quality of life	L	L	H	L	L	H	L	– Patients and intervention staff were not blinded – No appropriate method used to handle substantial missing data (up to 43/70 missing data)	H
Readmission	L	L	H	L	L	M	L	– Patients were not blinded – No appropriate method used to handle missing data (12/70 missing data)	M

Outcomes	Sequence generation	Allocation concealment	Blinding of participant	Blinding of personnel	Blinding of assessors	Incomplete outcome data	Selective outcome reporting	Comments	Overall Risk of bias
Santa Mina[67]									
Functional capacity	U	U	U	U	U	L	L	– Unclear what methods was used for the random sequence generation and allocation concealment – Unclear if patients, intervention staff and assessors were blinded	H
Complications	U	U	L	L	U	L	L	– Unclear what methods was used for the random sequence generation and allocation concealment – Unclear if assessors were blinded	H
Length of stay	U	U	U	L	U	L	L	– Unclear what methods was used for the random sequence generation and allocation concealment – Unclear if patients and assessors were blinded	H
Quality of life	U	U	U	U	U	L	L	– Unclear what methods was used for the random sequence generation and allocation concealment – Unclear if patients, intervention staff and assessors were blinded	H

L, low; M, moderate; H, high; U, unclear

Table 18. Risk of bias assessment of non-randomized studies conducted recently at the MUHC

Outcomes	Confounding bias	Selection bias	Intervention classification bias	Outcome measurement bias	Missing data bias	Comments	Overall Risk of bias
Trepanier 2019[68]							
5-year Survival	H	H	U	L	L	– No adjustment for confounding factors – Insufficient information on patient selection process for the control group in the non-randomized study – Justifications to exclude 17% of patients (n=42/244) from analysis were not reasonable for OS outcome – Insufficient information on the method used to assess compliance	H
Risk of overall death	H	H	U	L	L	– Regression model was not adjusted for potential confounding factors like tumour stage, BMI and smoking status – Insufficient information on the patient selection process for the control group in the non-randomized study – Justifications to exclude 17% of patients (n=42/244) from analysis were not reasonable for OS outcome – Insufficient information on the method used to assess compliance	H
Risk of recurrence	H	U	U	L	L	– Regression model was not adjusted for potential confounding factors like BMI and smoking status – Insufficient information on the patient selection process for the control group in the non-randomised study – Insufficient information on the method used to assess compliance	H

Outcomes	Confounding bias	Selection bias	Intervention classification bias	Outcome measurement bias	Missing data bias	Comments	Overall Risk of bias
Minnella 2017[69]							
Functional capacity	H	U	M	L	U	– No adjustment for confounders – Insufficient information on the patient selection process for the control group in the non-randomized study – Self-reported methods used to assess compliance – Unknown amount of missing data for outcome before surgery and 8-week post-surgery – No appropriate method used to handle missing data	H
Complications	H	U	M	L	L	– No adjustment for confounders – Insufficient information on the patient selection process for the control group in the non-randomized study – Self-reported methods used to assess compliance – No appropriate method used to handle missing data (7/178 missing data)	H
Length of stay	H	U	M	L	U	– No adjustment for confounders – Insufficient information on the patient selection process for the control group in the non-randomized study – Self-reported methods used to assess compliance – Unknown amount of missing data – No appropriate method used to handle missing data	H

L, low; M, moderate; H, high; U, unclear

Table 19. Summary of findings for the effect of prehabilitation on postoperative outcomes after abdominal surgery from RCTs and observational studies conducted recently at the MUHC

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Functional fitness							
Carli 2020[65]	RCT	N=120/120 of eligible >65 years frail patients scheduled for nonmetastatic colorectal cancer surgery between Sept-2015 and June-2019	Trimodal prehabilitation • Moderately intense aerobic exercise everyday + resistance training at home 3 times/week and under supervision 1 time/week for 4 weeks before surgery • Nutritional supplement • Psychological support Control Same as prehabilitation but done after surgery for 4 weeks	Baseline: 55/54 Before surgery: 47/38 4-week post-surgery: 38/30	Change in walking capacity relative to baseline • Before surgery: MD=11.2m, 95%CI: -13.7, 36.1 • 4 weeks after surgery: MD=18.5m, 95%CI: -20.2, 57.3 Clinically significant increased walking capacity (≥20m relative to baseline) 4 weeks after surgery (6MWD) • OR=1.9, 95%CI: 0.6, 5.9 • Number of events: Prehab: 26/38 Control: 16/30	Low	• High risk of bias • Training adherence assessment was done, in part, with self-reported methods • Low in-hospital adherence to training in prehab group (68%) • Correlation between repeated measurement was not considered in analyses • Small sample size • Intention-to-treat analysis was not done as mentioned (excluded 10 randomized patients)

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Minnella 2019[66]	RCT	N=70/90 of eligible ≥18 years patients scheduled for nonmetastatic bladder cancer between Aug-2013 and Oct-2017	<u>Trimodal prehabilitation</u> • Moderately intense aerobic exercise + resistance training 3 times/week at home for 4 weeks before surgery • Nutritional supplement • Psychological support <u>Control</u> Standard care	Baseline: 35/35 Before surgery: 17/21 4-week post-surgery: 21/21 8-week post-surgery: 11/16	<u>Change in walking capacity relative to baseline (6MWD)</u> • Before surgery: MD=40.8m (SD=114.0) vs. MD= 9.7m (SD=108.4), p=0.25 • 4 weeks after surgery: MD= -15.4m (SD=142.5) vs. MD= -97.9m (SD=123.8), p=0.014 • 8 weeks after surgery: MD= -5.6m (SD=173.5) vs. MD= -35.5 (SD=131.8), p=0.42	Low	• High risk of bias • Self-reported methods used to assess adherence to training program • 16% of eligible patients did not consent to participate • Small sample size

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Santa Mina 2018[67]	RCT	N=86/185 of eligible 40 to 80 years men scheduled for radical prostate surgery for localized prostate cancer between Feb-2014 and Sept-2015	<u>Prehabilitation</u> • Moderately intense total-body exercise 3-4 days/week at home • Daily pelvic floor muscle exercises <u>Control:</u> Daily pelvic floor muscle exercises	Baseline: 44/42 Before surgery: 38/35 4-week post-surgery: 37/34 12-week post-surgery: 34/32 26-week post-surgery: 33/28	<u>Walking capacity (6MWD)</u> • Baseline: MD=3.2m, 95%CI: -21.5, 27.8 • Before surgery: MD=14.6m, 95%CI: -13.9, 43.1 • 4 weeks after surgery: MD=38.7m, 95%CI: 11.3, 66.1 • 12 weeks after surgery: MD=22.7m, 95%CI: -5.2, 50.5 • 26 weeks after surgery: MD=24.2m, 95%CI: -3.6, 52.0 <u>Grip strength</u> • Baseline: MD=0.88, 95%CI: -2.46, 4.23 • Before surgery: MD= -0.68, 95%CI: -4.45, 3.08 • 4 weeks after surgery: MD=1.67, 95%CI: -2.01, 5.35 • 12 weeks after surgery: MD=3.68, 95%CI: -0.09, 7.44 • 26 weeks after surgery: MD=4.44, 95%CI: 0.65, 8.23	Low	• High risk of bias • Low adherence to training program in prehab group (69%) • 53% of eligible patients did not consent to participate • Small sample size

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Minnella 2017[69]	Pooled of 2 RCTs + 1 NRS	N=185/186 of eligible ≥18 years patients scheduled for colorectal cancer surgery (any stage) between Oct-2010 and Aug-2015	<u>Trimodal prehabilitation</u> • Moderately intense aerobic exercise 3 days/week + resistance training 2 times/week, at home or supervised for 4 weeks before surgery and 2 months after surgery • Nutritional supplement • Psychological support <u>Control</u> Same as prehabilitation but done after surgery	Baseline: 113/72 Before surgery: NR 4-week post-surgery: 104/65 8-week post-surgery: NR	<u>Change in walking capacity relative to baseline (6MWD)</u> • Before surgery: MD=30m (SD=46.7) vs. MD= -5.8m (SD=40.1), p<0.001 • 4 weeks after surgery: MD=-11.2m (SD=72) vs. MD= -72.5m (SD=129), p<0.01 • 8 weeks after surgery: MD=17m (SD=84) vs. MD= -8.8m (SD=74), p=0.047	Low	• High risk of bias • Correlation between repeated measurement was not considered in the analysis • Low compliance (70-98% for preoperative period)

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Complications							
Carli 2020[65]	RCT	N=120/120 eligible >65 years frail patients scheduled for nonmetastatic colorectal cancer surgery between Sept-2015 and June-2019	Trimodal prehabilitation • Moderately intense aerobic exercise everyday + resistance training at home 3 times/week and under supervision 1 time/week for 4 weeks before surgery • Nutritional supplement • Psychological support Control Same as prehabilitation but done after surgery for 4 weeks	55/55	30-day CCI score MD= -3.2, 95 %CI: -11.8, 5.3 30-day Overall complications • OR=0.9, 95%CI: 0.4, 2.2 • Number of events: Prehab: 25/55 Control: 25/55	Low	• Low risk of bias • Training adherence assessment was done, in part, with self-reported methods • Low in-hospital adherence to training in prehab group (68%) • Small sample size • Intention-to-treat analysis was not done as mentioned (excluded 10 randomized patients)
Minnella 2019[66]	RCT	N=70/90 of eligible ≥18 years patients scheduled for nonmetastatic bladder cancer between Aug-2013 and Oct-2017	Trimodal prehabilitation • Moderately intense aerobic exercise + resistance training 3 times/week at home for 4 weeks before surgery • Nutritional supplement • Psychological support Control Standard care	30/28	Proportion of patients with severe complications 16/30 vs. 16/28, p=0.53	Moderate	• Low risk of bias • Self-reported methods used to assess adherence to training program • 16% of eligible patients did not consent to participate • Small sample size

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Santa Mina 2018[67]	RCT	N=86/185 of eligible 40 to 80 years men scheduled for radical prostate surgery for localized prostate cancer between Feb-2014 and Sept-2015	Prehabilitation • Moderately intense total-body exercise 3-4 days/week at home • Daily pelvic floor muscle exercises Control: Daily pelvic floor muscle exercises	42/40	Proportion of patients with complications 18/42 vs. 14/40, p=0.61	Low	• High risk of bias • Low adherence to training program in prehab group (69%) • 53% of eligible patients did not consent to participate • Small sample size
Minnella 2017[69]	Pooled of 2 RCTs + 1 NRS	N=185/186 of eligible ≥18 years patients scheduled for colorectal cancer surgery (any stage) between Oct-2010 and Aug-2015	Trimodal prehabilitation • Moderately intense aerobic exercise 3 days/week + resistance training 2 times/week, at home or supervised for 4 weeks before surgery and 2 months after surgery • Nutritional supplement • Psychological support Control Same as prehabilitation but done after surgery	110/68	Proportion of patients with complications 42/110 vs. 23/68, p=0.75	Low	• High risk of bias

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Length of hospital stay							
Carli 2020[65]	RCT	N=120/120 eligible >65 years frail patients scheduled for nonmetastatic colorectal cancer surgery between Sept-2015 and June-2019 N=120 randomised	Trimodal prehabilitation • Moderately intense aerobic exercise everyday + resistance training at home 3 times/week and under supervision 1 time/week for 4 weeks before surgery • Nutritional supplement • Psychological support Control Same as prehabilitation but done after surgery for 4 weeks	55/55	30-day total LOS MD= -5.8 days, 95%CI: -17.3, 5.8	Low	• Low risk of bias • Training adherence assessment was done, in part, with self-reported methods • Low in-hospital adherence to training in prehab group (68%) • Small sample size • Intention-to-treat analysis was not done as mentioned (excluded 10 randomized patients)
Minnella 2019[66]	RCT	N=70/90 of eligible ≥18 years patients scheduled for nonmetastatic bladder cancer between Aug-2013 and Oct-2017	Trimodal prehabilitation • Moderately intense aerobic exercise + resistance training 3 times/week at home for 4 weeks before surgery • Nutritional supplement • Psychological support Control Standard care	30/28	median=9 days, IQR: 7, 15 vs. median=10 days, IQR: 7.5, 14.5, p=0.36	Low	• Moderate risk of bias • Self-reported methods used to assess adherence to training program • 16% of eligible patients did not consent to participate • Small sample size

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Santa Mina 2018[67]	RCT	N=86/185 of eligible 40 to 80 years men scheduled for radical prostatectomy for localized prostate cancer between Feb-2014 and Sept-2015	Prehabilitation • Moderately intense total-body exercise 3-4 days/week at home • Daily pelvic floor muscle exercises Control: Daily pelvic floor muscle exercises	NR	mean=1.7 days (SD=0.9) vs. mean=1.8 days (SD=1.0), p=0.77	Low	• High risk of bias • Low adherence to training program in prehab group (69%) • 53% of eligible patients did not consent to participate • Small sample size
Minnella 2017[69]	Pooled of 2 RCTs + 1 NRS	N=185/186 of eligible ≥18 years patients scheduled for colorectal cancer surgery (any stage) between Oct-2010 and Aug-2015	Trimodal prehabilitation • Moderately intense aerobic exercise 3 days/week + resistance training 2 times/week, at home or supervised for 4 weeks before surgery and 2 months after surgery • Nutritional supplement • Psychological support Control Same as prehabilitation but done after surgery	NR	Total LOS median=4 days, IQR: 3-5 vs. median=3 days, IQR: 3-6, p=0.806	Low	• High risk of bias

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Quality of life							
Carli 2020[65]	RCT	N=120/120 eligible >65 years frail patients scheduled for nonmetastatic colorectal cancer surgery between Sept-2015 and June-2019	<u>Trimodal prehabilitation</u> • Moderately intense aerobic exercise everyday + resistance training at home 3 times/week and under supervision 1 time/week for 4 weeks before surgery • Nutritional supplement • Psychological support <u>Control</u> Same as prehabilitation but done after surgery for 4 weeks	Baseline: 53/52 Before surgery: 42/33 4-week post-surgery: 38/30	<u>SF-36 physical component</u> • Before surgery: MD=0.16, 95%CI: -6.7, 7.0 • 4 weeks after surgery: MD= -0.43, 95%CI: -7.2, 6.3 <u>SF-36 mental component</u> • Before surgery: MD= -2.8, 95%CI: -10.7, 5.0 • 4 weeks after surgery: MD= -2.3, 95%CI: -9.7, 5.1	Low	• High risk of bias • Training adherence assessment was done, in part, with self-reported methods • Low in-hospital adherence to training in prehab group (68%) • Correlation between repeated measurement was not considered in the analysis • Small sample size • Intention-to-treat analysis was not done as mentioned (excluded 10 randomized patients)

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Minnella 2019[66]	RCT	N=70/90 of eligible ≥18 years patients scheduled for nonmetastatic bladder cancer between Aug-2013 and Oct-2017	<u>Trimodal prehabilitation</u> • Moderately intense aerobic exercise + resistance training 3 times/week at home for 4 weeks before surgery • Nutritional supplement • Psychological support <u>Control</u> Standard care	Baseline: 35/35 Before surgery: 17/21 4-week post-surgery: 21/21 8-week post-surgery: 11/16	<u>Change in QoL physical score relative to baseline (SF-36)</u> • Before surgery: MD=6.4 (SD=27.7) vs. MD=3.1 (SD=24.2), p= 0.60 • 4 weeks after surgery: MD= -13.5 (SD=29.5) vs. MD= -14.9 (SD=27.5), p=0.84 • 8 weeks after surgery: MD= -3.2 (SD=31.8) vs. MD=8.4 (SD=28.4), p= 0.12 <u>Change in QoL mental score relative to baseline (SF-36)</u> • Before surgery: MD=6.3 (SD=28.5) vs. MD=2.1 (SD=24.9), p= 0.51 • 4 weeks after surgery: MD=-7.4 (SD=58.8) vs. MD= -5.8 (SD=28.2), p=0.81 • 8 weeks after surgery: MD= -0.8 (SD=32.5) vs. MD=7.0 (SD=28.9), p=0.29	Low	• High risk of bias • Self-reported methods used to assess adherence to training program • 16% of eligible patients did not consent to participate • Small sample size

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Santa Mina 2018[67]	RCT	N=86/185 of eligible 40 to 80 years men scheduled for radical prostatectomy for localized prostate cancer between Feb-2014 and Sept-2015	<u>Prehabilitation</u> • Moderately intense total-body exercise 3-4 days/week at home • Daily pelvic floor muscle exercises <u>Control:</u> Daily pelvic floor muscle exercises	Baseline: 44/42 Before surgery: 38/35 4-week post-surgery: 37/34 12-week post-surgery: 34/32 26-week post-surgery: 33/28	<u>Prostate cancer-specific QoL (FACT-P)</u> • Baseline: MD=1.21, 95%CI: -4.54, 6.96 • Before surgery: MD=2.11, 95%CI: -4.25, 8.47 • 4 weeks after surgery: MD=-2.11, 95%CI: -8.34, 4.12 • 12 weeks after surgery: MD=-4.30, 95%CI: -10.81, 2.21 • 26 weeks after surgery: MD= -1.37, 95%CI: -7.91, 5.18 <u>Prostate cancer-specific QoL (PORPUS)</u> • Baseline: MD= 1.92, 95%CI: -2.25, 6.10 • Before surgery: MD= 2.48 95%CI: -2.3, 7.26 • 4 weeks after surgery: MD= -0.41 95%CI: -5.06, 4.24 • 12 weeks after surgery: MD= 3.11 95%CI: -1.64, 7.86 • 26 weeks after surgery: MD= 3.90 95%CI: -0.89, 8.69	Low	• High risk of bias • Low adherence to training program in prehab group (69%) • 53% of eligible patients did not consent to participate • Small sample size

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Mortality							
Trepanier 2019[68]	Pooled of 2 RCTs + 1 NRS	N=202/244 of eligible adult patients scheduled for nonmetastatic colorectal cancer surgery between July-2009 and Aug-2015	Trimodal prehabilitation: • Moderately intense aerobic exercise and resistance training, 3-4 times/week at home or supervised for 4 weeks before surgery and 8 weeks after surgery • Nutritional supplement • Psychological support Control: Standard care or same as prehabilitation but done after surgery for 8 weeks	104/98	5-year OS 96.4% vs. 91.7% (p=0.226) 5-year DFS 85.3% vs. 79.3% (p=0.245) Risk of overall death • HR=1.99, 95%CI: 0.5, 8.02 • Number of events: NR Risk of recurrence • HR=0.45, 95%CI: 0.21, 0.93 • Number of events: NR	Low	• High risk of bias • Low compliance (median=80%, IQR: 50-100)

Author/ Year	Study design	Population	Interventions	N (prehab/ control)	Results (prehabilitation vs. control)	Quality of evidence	
						Score	Comments
Readmission							
Carli 2020[65]	RCT	N=120/120 eligible >65 years frail patients scheduled for nonmetastatic colorectal cancer surgery between Sept-2015 and June-2019	Trimodal prehabilitation • Moderately intense aerobic exercise everyday + resistance training at home 3 times/week and under supervision 1 time/week for 4 weeks before surgery • Nutritional supplement • Psychological support Control Same as prehabilitation but done after surgery for 4 weeks	55/55	• OR=0.3, 95%CI: 0.03, 1.9 • Number of events: Prehab: 2/55 Control: 5/55	Low	• Low risk of bias • Training adherence assessment was done, in part, with self-reported methods • Low in-hospital adherence to training in prehab group (68%) • Small sample size • Intention-to-treat analysis was not done as mentioned (excluded 10 randomized patients)
Minnella 2019[66]	RCT	N=70/90 of eligible ≥18 years patients scheduled for nonmetastatic bladder cancer between Aug-2013 and Oct-2017	Trimodal prehabilitation • Moderately intense aerobic exercise + resistance training 3 times/week at home for 4 weeks before surgery • Nutritional supplement • Psychological support Control Standard care	30/28	Proportion of patients readmitted within 30 days after surgery 3/30 (10%) vs. 3/28 (10.7%), p=0.93	Low	• Moderate risk of bias • Self-reported methods used to assess adherence to training program (diary and phone calls) • 16% of eligible patients did not consent to participate • Small sample size

RCT, randomized controlled trial; NRS, nonrandomized study; OS, overall survival, DFS, disease-free survival; MD, mean difference; CI, confidence intervals; NR, not reported; p, p-value

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APPENDICES

APPENDIX A: SEARCH STRATEGY

Table A: Keywords used for literature search by the librarian at MUHC

#	Searches	Results
1	(prehabilitat* or pre-habilitat*).tw,kf.	656
2	*Preoperative period/ or *Perioperative period/ or *Preoperative Care/ or *Perioperative care/	28347
3	((preoperativ* or pre-operativ* or preop* or pre-op* or presurg*) adj5 (care or cares or caring or procedur* or physic* or physiotherap* or physio-therap*)).tw,kf.	11561
4	2 or 3	37247
5	exp Exercise/ or exp Sports/ or exp Exercise Therapy/ or exp Exercise Movement Techniques/ or Physical Therapy Modalities/ or Physical Therapy Specialty/ or Rehabilitation/	369000
6	exp Nutrition Therapy/	100870
7	exp Health Education/	242800
8	exp Psychotherapy/ or exp Mind-Body Therapies/ or exp Spiritual Therapies/	216868
9	exp Social Support/	70763
10	Self Care/	32950
11	5 or 6 or 7 or 8 or 9 or 10	956424
12	4 and 11	2769
13	1 or 12	3289
14	*postoperative complications/	158728
15	((post-op* or postop* or surg* or postsurg*) adj3 complicat*).ti,kf. or ((post-op* or postop* or surg* or postsurg*) adj3 complicat*).ab. /freq=2	49333
16	(quality-of-life or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI).ti,kf. or (quality-of-life or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI).ab. /freq=2	142877

17	(disabilit* or disabl* or productiv*).ti,kf. or (disabilit* or disabl* or productiv*).ab. /freq=2	130342
18	*Chronic pain/	11482
19	*Pain/ or *Pain management/	96843
20	((chronic or lifelong or life-long or manage*) adj2 (disease* or ill or illness* or pain*)).ti,kf. or ((chronic or lifelong or life-long or manage*) adj2 (disease* or ill or illness* or pain*)).ab. /freq=2	140175
21	*treatment outcome/	7472
22	*disease free survival/	275
23	prognosis/	505797
24	limit 23 to yr="1980 - 1994"	83539
25	*survival rate/	1183
26	follow-up studies/	642549
27	limit 26 to yr="1966 - 1989"	97894
28	*length of stay/	12166
29	hospitalization/	106787
30	limit 29 to yr="1966 - 1968"	1348
31	((length or hospital*) adj2 stay*).ti,kf. or ((length or hospital*) adj2 stay*).ab. /freq=2	46534
32	*morbidity/	7723
33	morbidit*.ti,kf. or morbidit*.ab. /freq=2	89481
34	*Digestive System Surgical Procedures/	13469
35	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 24 or 25 or 27 or 28 or 30 or 31 or 32 or 33 or 34	978351
36	13 and 35	857
37	limit 36 to yr="2000 -Current"	767
38	limit 37 to (controlled clinical trial or meta-analysis or randomized controlled trial or "systematic review")	243
39	Clinical trials as topic/ or Randomized Controlled Trials as Topic/ or Meta-Analysis/	405042
40	(placebo or randomized or randomly).tw.	898200
41	trial.ti.	220638
42	39 or 40 or 41	1259309

43	37 and 42	259
44	38 or 43	306
45	37 not 44	463

APPENDIX B: GLOSSARY OF TERMS

Atelectasis

A medical condition in which the lung is partially or completely collapsed. It is one of the most common respiratory complications after surgery.[74]

Comprehensive Complication Index (CCI)

A continuous scale ranking surgical morbidity based on the sum of all postoperative complications that are weighted for their severity. The score ranges from 0 (uneventful course) to 100 (death).[75]

European Organisation for Research and Treatment of Cancer-C30 (EORTC-C30)

A self-administered questionnaire developed by a non-profit clinical cancer research organisation. It measures health-related quality of life specific to cancer patients based on functional scales, symptom scales and global quality of life. The score range is 0-100 after a linear transformation. Higher score in functional scales and global quality of life reflects a better level of functioning, while higher score in symptom scales reflects more problems.[76]

Functional Assessment of Cancer Therapy-Prostate (FACT-P)

A 12-item self-administered questionnaire measuring health-related quality of life of ≥18 year-old patients with prostate cancer. It assesses 5 domains: physical well-being, social/family well-being, functional well-being and additional concerns. The score range is 0-156, with higher score reflecting better quality of life.[77]

Hospital Anxiety and Depression Scale (HADS)

A 14-item self-administered questionnaire assessing the severity of depression and anxiety in multiple settings. The score range is 0-21 for depression and 0-21 for anxiety, with higher score indicating more severe anxiety and/or depression.[78]

Patient-Oriented Prostate Utility Scale (PORPUS)

A 10-item self-administered questionnaire evaluating preference-based (PORPUS-U) and health-related (PORPUS-P) quality of life in patients with prostate cancer. It assesses 5 broad quality of life domains and 5 prostate cancer-specific domains. The score range is 0-1 for PORPUS-U and 0-100 for PORPUS-P, with higher score indicating worst quality of life.[79]

Short-Form 36 (SF-36)

A 36-item self-administered questionnaire evaluating health status in medical outcome study. It assesses 8 domains and gives 2 summary scales (physical and mental components). The score range is 0-100, with higher score indicating better health status.[80]

Six-minute walking test (6MWT)

It tests exercise tolerance in patients with chronic respiratory disease and heart failure by measuring the distance a person can walk in 6 minutes on a flat and hard surface. Normal range is 400-700m in healthy adults.[81]

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

A 24-item self-administered questionnaire evaluating the condition of patients with osteoarthritis of the knee or hip. It assesses 3 domains: pain, stiffness and physical function. The score range is 0-96, with higher score indicating worse quality of life.[82]