# Perioperative exercise training for patients with gastrointestinal cancer undergoing surgery: A systematic review and meta-analysis

# Perioperative exercise training for patients with gastrointestinal cancer undergoing surgery: a systematic review and meta-analysis

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**Short title**
Perioperative exercise for patients with gastrointestinal cancer

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**Word counts**
Abstract: 249 words
Manuscript: 4984 words

**Number of figures**

3

**Number of tables**

**Key words**

Exercise oncology, surgical oncology, prehabilitation, rehabilitation, perioperative medicine

**Supplementary material**

Supplementary material 1 – Deviations from preregistered protocol

Supplementary material 2 – Search strings

Supplementary material 3 – Codes

Supplementary material 4 – Reasons for exclusion of studies

Supplementary material 5A-5E – Risk of bias

Supplementary material 6 – Meta-analyses of secondary outcomes

Supplementary material 7 – Narrative summary of outcomes not included in meta-analyses

## Abstract

Exercise training is emerging as a supportive treatment strategy in surgical oncology, but its effects remain uncertain in patients with gastrointestinal cancer. The primary objective of this systematic review and meta-analysis was to evaluate the effects of perioperative exercise training on gastrointestinal cancer-specific mortality, recurrence, and surgical outcomes (postoperative complications, hospitalization, surgical stress) in patients with gastrointestinal cancer. Randomized or quasi-randomized controlled trials evaluating the effects of perioperative exercise training versus control in patients with GI cancer were eligible. MEDLINE, EMBASE, CENTRAL, CINAHL, PEDro, and SPORTDiscus were systematically searched in June 20, 2020. Data were synthesized using random-effects meta-analyses. Risk of bias was assessed using the Cochrane risk of bias tool 2, and the certainty of evidence was assessed using GRADE. Study selection, data extraction, and risk of bias and GRADE assessments were performed independently by two authors. Ten randomized controlled trials comprising 448 participants with gastrointestinal cancer were eligible. Meta-analyses indicated no statistical effects of exercise on postoperative complications (risk ratio: 1.11, 95% CI: 0.84; 1.47), readmissions (risk ratio: 2.76; 95% CI: 0.00, 9394.76), or postoperative length of stay (difference in means: -0.47, 95% CI: -17.2; 16.2 days). None of the eligible studies assessed gastrointestinal cancer-specific mortality or recurrence. Overall risk of bias was high or of some concerns in all studies, and the certainty of evidence was very low. The effects of perioperative exercise on cancer-specific and surgical outcomes are unknown in patients with gastrointestinal cancer due to lack of studies and very low certainty of evidence.

# 1 Introduction

Gastrointestinal (GI) cancers, including esophageal, gastric, liver, pancreatic, and colorectal cancer, are associated with significant morbidity burden and poor prognoses. Surgery, in combination with pre- and postoperative systemic therapy, comprises the primary treatment modality in the intended curative management of these cancers [1,2]. Advances in operative techniques [3] and fast-track procedures [4] have improved surgical outcomes in patients with GI cancer; however, the perioperative period remains potentially detrimental due to risk of high surgical stress [5], postoperative complications [6], and toxicity of chemotherapy [7]. Such perioperative adverse effects can negatively impact both short- and long-term GI cancer outcomes [5,8], and the perioperative period represents a critical time frame along the cancer trajectory, where adjunct treatment strategies may hold significant prognostic potential.

Over the last decade, exercise training has gained considerable interest as an adjunct treatment strategy in GI surgical oncology [9], with several studies suggesting that exercise before or shortly after surgery is safe and feasible [10-15]. Furthermore, in patients with GI cancer, studies suggest that perioperative exercise shortens the length of postoperative hospitalization [16], reduces the incidence of postoperative complications [17], restores immune function following surgery [18], lowers the risk of treatment failure [15], and improves chemotherapy completion rates [19] and response [20]. These findings provide an intriguing rationale for applying exercise as a supportive perioperative care strategy in patients with GI cancer, with potential implications for treatment outcomes. However, there is currently no available systematic data synthesis to inform the application of perioperative exercise in the treatment of GI cancer. Although several previous systematic reviews and meta-analyses have been conducted, these are based on observational and non-randomized studies [21-27]; studies examining mixed populations, including non-cancer patients [27,28]; studies examining respiratory muscle exercises [29]; and studies examining exercise as part of multimodal strategies (e.g., in combination with nutritional and psychosocial interventions) [21,22,24-28].

We therefore performed the present systematic review and meta-analysis of randomized and quasi-randomized clinical trials with the primary objective to evaluate the effects of perioperative exercise on GI-cancer specific mortality, recurrence, and surgical outcomes (postoperative complications, hospitalization, and surgical stress) in patients with GI cancer. Secondary objectives were to evaluate the safety and feasibility of perioperative exercise and the effects on physiological, functional, treatment-related, and psychosocial outcomes.

# 2 Methods

## 2.1 Protocol and registration

This systematic review and meta-analysis was preregistered in the Open Science Framework (https://osf.io/6wezg) and is reported in accordance with the PRISMA statement [30]. Deviations from the preregistration are described and justified in Supplementary Material 1.

## 2.2 Eligibility criteria

### 2.2.1 Participants

Studies were eligible if they included adult (>18 years of age) participants diagnosed with GI cancer (ICD-10 C15-26) of any stage who either:

- were scheduled for surgery of any type for the treatment of GI tumors.
- were scheduled for treatment aiming to convert initially unresectable tumors to resectable tumors
- had undergone surgery of any type for the treatment of GI cancer within 6 weeks.

We excluded studies in which only a subset of the participants was diagnosed with GI cancer, unless separate data were available for the GI cancer subgroup.

### 2.2.2 Study design, interventions, and comparators

Studies were eligible if they were RCTs and quasi-RCTs comparing standard GI cancer treatment versus standard GI cancer treatment and peri-, pre-, or (early initiated) postoperative exercise. Studies were also eligible if they used a wait-list control or an attention control group. Exercise was limited to planned, structured, and repetitive physical activity [31]. No restrictions were made regarding intervention length, frequency, session duration, delivery, setting, or type of exercise. Thus, studies were eligible if they evaluated aerobic or resistance exercise, sport activities, or alternative exercise modalities (e.g., yoga, tai-chi). We excluded studies evaluating targeted physiotherapy (e.g., pelvic floor, breathing exercises) or acute responses to a single bout of exercise only. We also excluded studies combining exercise with other interventions (e.g., nutrition, education), unless isolation of the effects of the exercise intervention was possible.

### 2.2.3 Outcomes

The primary outcomes of this study were:

- GI cancer-specific mortality, defined as the time from date of randomization to death due to primary GI cancer.
- GI cancer recurrence, defined as time from date of randomization to emergence of local, regional, or distant recurrence.
- Postoperative complications (e.g., assessed using the Clavien-Dindo classification).
- Surgical stress (e.g., changes in immune or inflammatory factors during and after surgery).
- Postoperative hospitalization (e.g., length of postoperative stay, readmissions).

The secondary outcomes of this study were:

- All-cause mortality, defined as the time from randomization to death of any cause.
- Adverse events, defined as any untoward medical occurrence in a participant regardless of whether this has a causal relationship with any study procedures.
- Intraoperative factors (e.g., blood transfusion).
- Treatment response (e.g., imaging or tumor markers) and tolerability (e.g., assessed using the Common Terminology Criteria for Adverse Events)
- Aerobic (e.g., oxygen uptake) and neuromuscular capacity (e.g., muscle strength)
- Functional capacity (e.g., stair climbing).
- Body composition (e.g., fat mass) and anthropometrics (e.g., hip circumference)
- Bone health (e.g., bone mineral density)
- Psychosocial factors (e.g., anxiety, depression)
- Fatigue (e.g., assessed using questionnaires)
- Physical activity (e.g., assessed using questionnaires)
- Exercise adherence and fidelity (e.g., attendance rate)

## 2.3 Information sources

Systematic searches for relevant publications were performed on the following electronic databases: MEDLINE via PubMed (1946–present), EMBASE via Ovid (1974–present), CENTRAL, CINAHL

via EBSCO (1981–present), PEDro (1999–present), and SPORTDiscus via EBSCO (1975–present). Furthermore, we searched for relevant publications using manual forward and backward citation searches of eligible studies and relevant reviews. We only included fully published, peer-reviewed reports. The searches were performed on June 20, 2020, and updated searches were performed on September 7, 2020.

## 2.4 Search

The systematic searches were performed using three blocks of controlled vocabularies and free text words related to GI cancer, exercise, and surgery. The search string was developed for MEDLINE and modified to the other databases (Supplementary Material 2). No language or publication date restrictions were imposed.

## 2.5 Study selection

All records were merged in Covidence (Covidence Systematic Review Software, Veritas Health Innovation, Australia) and duplicates were removed automatically and checked manually by one author (SNT). Two authors (SNT and STM) independently screened titles and abstracts and excluded clearly ineligible records. Full reports of the remaining records were retrieved, and two authors (SNT and STM) independently assessed eligibility. Disagreements were resolved by discussion, involving two other authors (IL and JFC).

## 2.6 Data collection process

Two authors (SNT and STM) independently extracted data from the eligible publications (see Data items below). The earliest or most complete published report was used as the primary reference if multiple publications for the same trial were retrieved. Data provided in figures only were extracted using WebPlotDigitizer (www.automeris.io/WebPlotDigitizer/; v4.3). In the case of unclear data, two attempts separated by two weeks were made to contact the corresponding author by email to request further information.

## 2.7 Data items

The following data items were extracted:

- Basic study details (authors, publication year, title, journal, country of research, aims, funding).
- Methods (design, allocation sequence generation and concealment, blinding, study arms).
- Participants (eligibility criteria, number of randomized participants, age, sex, tumor site and stage).
- Treatment (type of surgery, chemotherapy (regimen, dose, timing)).
- Interventions (exercise modality, setting, delivery, frequency, intensity, session duration, intervention length, progression rules, timing (pre- and/or postoperative), time from surgery to initiation of exercise (if peri- or postoperative))
- Outcomes (outcome domains, outcomes, assessment methods, units, assessment time points).

## 2.8 Risk of bias

The Cochrane risk of bias tool 2 [32] was used to assess risk of bias for the primary outcome of the eligible studies, for our primary outcomes, and for adverse events. If studied did not specify primary outcomes or had multiple primary outcomes, risk of bias assessments were based on the most comprehensively reported outcome. Two authors (SNT and STM) independently performed the risk of bias assessments. Disagreements were resolved by discussion, involving two other authors (IL and JFC). To ensure consistency, two other authors (IL and JFC) assessed risk of bias in a random sample of 20% of the eligible studies. Additionally, we compared outcomes specified in prospective registrations with outcomes reported in the publications.

## 2.9 Data syntheses

We performed meta-analyses if an outcome was assessed in two or more studies. Analyses were performed separately for pre- and postoperative studies. Dichotomous outcomes were combined using the Mantel-Haenszel random-effects method with the Hartung-Knapp-Sidik-Jonkman adjustments [33]. Continuous outcomes were combined using the inverse variance random-effects Hartung-Knapp-Sidik-Jonkman [33] method for both change values (changes from baseline to

postintervention) and for immediate postintervention values. All analyses were performed via RStudio (v1.2.5033, release name: "Orange Blossom", R Foundation for Statistical Computing, Vienna, Austria) and primarily via the 'Meta' package [34] (Supplementary Material 3). If outcomes were assessed in one study only or if meta-analyses were considered inappropriate, results were summarized narratively by reporting postintervention values for each study arm along with results from test of between-groups significance.

Risk ratios (RR) with 95% CI were used as the summary measure for dichotomous outcomes. For continuous outcomes, difference in means was used as the summary measure when studies used the same assessment methods to evaluate a specific outcome, and standardized difference in means (SMD) was used when studies used different assessment methods to evaluate a specific outcome [35]. Confidence intervals were converted to SD using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), where necessary [35]. For calculation of SMD, differences in the direction of scales used to evaluate the same outcome domain were corrected by multiplying the mean values of one scale by -1 [36]. Statistical heterogeneity was evaluated using the $I^2$ statistics and interpreted as follows [35]:

- 0-40%: might not be important
- 30-60%: may represent moderate heterogeneity
- 50-90%: may represent substantial heterogeneity
- 75-100%: considerable heterogeneity

Two meta-analyses had moderate-to-substantial heterogeneity, but its causes were not investigated due to small number of studies (n=2).

We performed subgroups analyses by exercise modality, where possible. Prespecified subgroup analyses by tumor site and stage, chemotherapy, exercise delivery, intervention duration, intensity, and fast-track procedures were not possible due to poor reporting and lack of studies. Prespecified sensitivity analyses of small sample sizes and high risk of bias were also not possible due to lack of studies.

## 2.10 Certainty of evidence

Two authors (SNT and SMT) independently assessed the certainty of the evidence for our primary outcomes, using the Grades of Recommendations, Assessment, Development, and Evaluations

(GRADE) [37]. Summary of findings tables were produced via the GRADEpro Guideline Development Tool (McMaster University, 2015; www.gradepro.org). Disagreements were resolved by discussion, involving two other authors (IL and JFC).

# 3 Results

## 3.1 Search results

The systematic searches yielded a total of 4,785 records. After removing duplicates and screening of titles and abstracts, 133 records were selected for full-text screening. A total of 11 publications from ten trials met the inclusion criteria, whereas 122 records were excluded with reasons (Figure 1; Supplementary Material 4). Five non-English language records were selected for full-text screening. Of these, we were unable to translate three, and they were consequently excluded (Korean, n=1; Chinese, n=1; Polish, n=1).

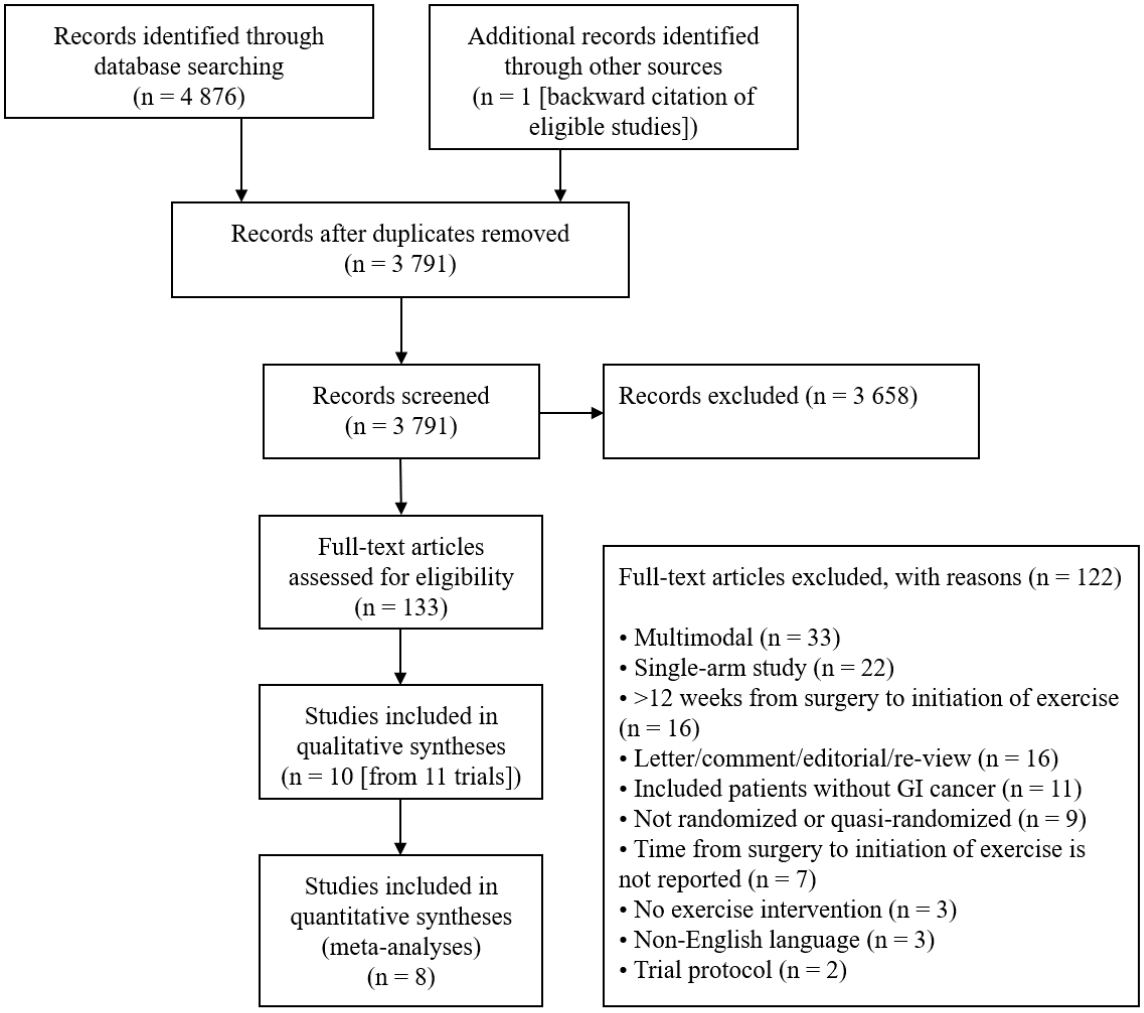



**Figure 1** PRISMA flow-chart

## 3.2 Description of included studies

The characteristics of the eligible studies are summarized in table 1.

### 3.2.1 Study design

All studies were described as RCTs. The median (range) sample size was 40 (8-110) participants. Four studies examined preoperative exercise [38-41], five studies examined postoperative exercise [16,18,42-44], and one study examined perioperative exercise [45]. Seven studies applied a two-arm design, comparing exercise and control [16,18,39-42,44]. One study compared exercise plus diet and diet only [45], whereas one study compared perioperative exercise and postoperative exercise [38]. Lastly, one study applied a three-arm design, comparing exercise, exercise plus behavioral reinforcement, and control [43]. Nine studies were single-center trials [16,18,38-42,44,45], and one study was a multi-center trial [43].

### 3.2.2 Participants

The studies included a total of 448 participants, with 224 participants in an exercise group and 216 participants in a control group. The average (SD) mean/median age was 64 (7) years, and 38% of the participants were females. Two studies excluded participants with high age (>70 [16] and > 80 years [45]). None of the eligible studies included old or high-risk participants only. The eligible studies evaluated participants with liver cancer [45], gastric cancer [18], pancreas or periampullary cancer [44], colon cancer [16,43], rectal cancer [40], colorectal cancer [38,41,42], and colorectal liver metastases [39]. Five studies evaluated participants with non-metastatic cancer [16,38,40,42,44], two studies evaluated both participants with non-metastatic and metastatic cancer [43,45], and one study

**Table 1** Characteristics of included studies.

| Study (design) | No. of randomized participants | Age in years | Sex (F/M) | Cancer site (stage) | Chemotherapy/ chemoradiotherapy | Intervention timing | Outcomes | Assessment timing |
|---|---|---|---|---|---|---|---|---|
| Bousquet-Dion 2018 [38] (RCT) | Total: 80<br>EX: 41<br>CON: 39 | All: NR<br>EX: 74<br>CON: 71 (median) | 17/46 | Colon/rectum (0-IV) | Neoadjuvant | Preoperative | **Primary**: 6MW<br>**Secondary**: PA, LOS, total hospitalization, emergency department visits, readmissions, postoperative complications, anxiety and depression, QoL. | Baseline, before surgery, 4 weeks after surgery, 8 weeks after surgery. |
| Dunne 2016 [39] (RCT) | Total: 38<br>EX: 20<br>CON: 18 | All: 62<br>EX: 61<br>CON: 62 (median) | 11/26 | Liver (CRLM) (IV) | Neoadjuvant | Preoperative | **Primary**: AT<br>**Secondary**: $\dot{V}O_{2peak}$, maximal workload during cycling, $O_2$ pulse at AT, $O_2$ pulse at $\dot{V}O_{2peak}$, HRR, elective critical care admissions, time in critical care, postoperative complications, LOS, readmissions, QoL, AE, extend of liver resection, additional operative procedures, no. of treated hepatic segments, no. of treated hepatic metastases. | Baseline, before surgery. |
| Moug 2019 [40,46] (RCT) | Total: 48<br>EX: 24<br>CON: 24 | All: 66<br>EX: 65<br>CON: 67 (mean) | 17/31 | Rectum (NR [non-metastatic]) | Neoadjuvant | Preoperative | **Primary**: Acceptability and feasibility of research procedures, PA<br>**Secondary**: Depression, QoL, positive and negative affects, fatigue, 6MWT, STS, psoas muscle mass, BW, BMI, waist circ., completion rate of chemoradiotherapy, failure to reach surgery, surgical procedure, circumferential resection margin, R0 resection, stoma formed, LOS, postoperative complications, serious AE. | Baseline, before surgery |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Northgraves 2020 [41] (RCT) | Total: 22<br>EX: 11<br>CON: 11 | All: 64<br>EX: 64<br>CON: 64<br>(mean) | 10/11 | Colon/rectum (NR) | Neoadjuvant | Preoperative | **Primary**: LOS<br>**Secondary**: TUG, STS, stair climbing performance, handgrip strength, 6MWT, QoL, depression, anxiety, postoperative complications, AE. | Baseline, before surgery. |
| Kaibori 2013 [45] (RCT) | Total: 51<br>EX: 25<br>CON: 26 | All: 70<br>EX: 68<br>CON: 71<br>(mean) | 15/36 | Liver (I-IV) | NR | Perioperative | **Primary**: NR<br>**Secondary**: BW, FM, LM, BMD, blood loss, blood transfusions, operating time, surgical procedure, surgical margins, serum insulin, serum glucose, HOMA-IR, LOS, postoperative morbidity, postoperative mortality. | Baseline (before surgery), POD3, POM1, POM3, POM6. |
| Ahn 2013 [16] (RCT) | Total: 41<br>EX: 21<br>CON: 20 | All: 57<br>EX: 56<br>CON: 57<br>(mean) | 14/17 | Colon (I-III) | No chemotherapy | Postoperative | **Primary**: LOS<br>**Secondary**: Time to flatus, time to first liquid diet, BW, BMI, LM, FM, STS, HR during stepping, $HR_{max}$, balance, postoperative complications, readmissions. | Baseline (before surgery), at discharge. |
| Mascherini 2020 [53] (RCT) | Total: 8<br>EX: 4<br>CON: 4 | All: 73<br>EX: NR<br>CON: NR<br>(mean) | 2/4 | Colon/rectum (I-II) | No chemotherapy | Postoperative | **Primary**: NR<br>**Secondary**: 6MWT, $HR_{peak}$, $HR_{rest}$, SBP, DBP, RMR, LM, FM, BW, BMI, waist circ., hip circ., biceps circ., STS, handgrip strength, flexibility. | Baseline (before surgery), day of discharge, 30 days after discharge, 90-100 days after discharge, 6 months after discharge |
| Na 2000 [18] (RCT) | Total: 35<br>EX: 17<br>CON: 18 | All: 55<br>EX: 58<br>CON: 52<br>(mean) | NR | Gastric (NR) | NR | Postoperative | **Primary**: NR<br>**Secondary**: Natural killer cell cytotoxicity, LOS. | POD2, POD7, POD14. |
| van Waart 2018 [43] (RCT) | Total: 15<br>EX: 7<br>CON: 8 | All: 57<br>EX: 58<br>CON: 57<br>(mean) | 11/4 | Colon (Stage II-IV) | Adjuvant | Postoperative | **Primary**: $Watt_{max}$, time at 70% of, elbow strength, knee strength, hand grip strength, fatigue, STS. | Baseline (before chemotherapy), 3 weeks after chemotherapy |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | **Secondary**: Psychological distress, QoL, PA, chemotherapy completion rate, AE, adverse effects of chemotherapy. | and 6 months after chemotherapy. |
| Yeo 2012 [44] (RCT) | Total: 110<br>EX: 54<br>CON: 48 | All: NR<br>EX: 66<br>CON: 67<br>(median) | 45/57 | Pancreas/periampullary (Stage I-III) | Adjuvant | Postoperative | **Primary**: Fatigue, self-reported physical function, QoL<br>**Secondary**: Overall survival, self-reported symptoms, PA, pain, AE | Baseline (after surgery), POM 3, POM 6. |

*6MWT* 6 minutes walking test, *AE* adverse events, *AT* anaerobic threshold, *BMD* bone mineral density, *BW* body weight, *Circ.* Circumference, *CRLM* Colorectal liver metastases, *CON* Control group, *DSP* diastolic blood pressure, *EX* Exercise group, *FM* fat mass, *HRR* heart rate reserve, *HOMA-IR* homeostatic model assessment for insulin resistance, *HR* heart rate, $HR_{rest}$ resting heart rate, *LM* lean mass, *LOS* length of postoperative stay, *NR* Not reported, *PA* physical activity, *POD* postoperative day, *POM* postoperative month, *QOL* quality of life, *RMR* resting metabolic rate, *SBP* systolic blood pressure, $\dot{V}O_{2peak}$ peak oxygen uptake.

evaluated participants with metastatic cancer only [39]. Two studies did not report disease stage [18,41]

### 3.2.3 Exercise intervention and comparison

The intervention characteristics of included studies are summarized in table 2.

*Delivery*

Three studies evaluated supervised exercise [39,41,43], three studies evaluated unsupervised exercise [40,44], and two of the studies used both supervised and unsupervised exercise [16,38,42].

*Modality*

Four studies evaluated aerobic exercise [39,40,44,45], one study evaluated resistance exercise [16], and five studies evaluated combined aerobic and resistance exercise [18,38,41,43]. None of the studies evaluated other types of exercise.

*Intensity*

The description of exercise intensity was unclear or not reported in all eligible studies. Dunne et al. [39] evaluated aerobic high-intensity exercise (intervals alternating between 90% and 60% of peak oxygen consumption) but did not report the length of the intervals; Bousquet-Dion et al. [38] evaluated low-to-moderate continuous aerobic home-based exercise (60-70% of estimated maximal heart rate) but did not report the intensity of the home-based resistance exercise and the supervised aerobic exercise; van Waart et al. [43] evaluated high intensity resistance exercise (8 repetitions at 80% of one repetition maximum) and moderate-to-high intensity continuous aerobic exercise (50-80% of $Watt_{max}$ for 30 min), but the prescription of exercise differed between publications [43,47]; Northgraves et al. [41] evaluated resistance exercise and low-to-moderate intensity continuous aerobic exercise with pre-planned increments in duration and intensity, but the intensity increments were not specified and the intensity of the resistance exercise was not reported. The remaining six studies did not report the intensity [16,18,40,42,44,45].

**Table 2** Intervention characteristics of included studies

| Study | Study arms | Modality | Session delivery (setting) | Intervention duration | Frequency | Session duration | Intensity | Time since surgery |
|---|---|---|---|---|---|---|---|---|
| Bousquet-Dion 2018 [38] | **EX**: Perioperative EX and standard care **CON**: Postoperative EX and standard care | Aerobic and resistance | Supervised and unsupervised (Exercise laboratory and home-based) | 4 weeks | 4-5/week | NR | Unclear | |
| Dunne 2016 [39] | **EX**: Preoperative exercise and standard care **CON**: Standard care | Aerobic | Supervised (Exercise laboratory) | 4 weeks | 3/week | 30 min | Unclear | |
| Moug 2019 [40,46] | **EX**: Preoperative EX and standard care **CON**: Standard care | Aerobic | Unsupervised (Home-based) | 14 weeks | 3-5/week | NA | NR | |
| Northgraves 2020 [41] | **EX**: Preoperative EX and standard care **CON**: Standard care | Aerobic and resistance | Supervised (Exercise laboratory) | 3 weeks | 3/week | 60 min | Unclear | |
| Kaibori 2013 [45] | **EX**: Perioperative EX, diet and standard care **CON**: Diet and standard care | Aerobic | NR (NR) | 1 month preoperative and 6 months postoperative | 3/week | 60 min | NR | 1 week |
| Ahn 2013 [16] | **EX**: Postoperative EX and standard care **CON**: Standard care | Resistance | Supervised and unsupervised (In-hospital) | POD1 to discharge | 1-2/day | 15 min | NR | 1 day |
| Mascherini 2020 [42] | **EX**: Postoperative EX and standard care **CON**: Standard care | Aerobic and resistance | Supervised and unsupervised (NR) | 6 months | 3-5/week | NR | NR | After discharge |
| Na 2000 [18] (RCT) | **EX**: Postoperative EX and standard care **CON**: Standard care | Aerobic and resistance | Supervised (In-hospital) | 2 weeks | 2-3/day | 30 min | NR | 2 days |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| van Waart 2018 [43] | **EX**: Postoperative EX and standard care<br>**CON**: Standard care | Aerobic and resistance | Supervised (Outpatient or general physical therapy practice) | Started with the first cycle of chemotherapy and until 3 weeks after the last cycle of chemotherapy | 2/week | 50 min | Unclear | 42 (13) days*,# |
| Yeo 2012 [44] (RCT) | **EX**: Postoperative EX and standard care<br>**CON**: Standard care | Aerobic | Unsupervised (At home, in the neighbourhood, in a gym, or in a shopping mall) | 12 weeks | 3-5/week | 20-40min | NR | 2-3 days* |

*CON* Control group, *EX* Exercise group, *NR* Not reported, *POD* Postoperative day. *Information provided by study authors. #Values are mean (standard deviation).

*Intervention duration*

The median (range) intervention duration was 4 (3-14) weeks in preoperative studies [38-41] and 7 (1-24) weeks in the postoperative studies [16,18,42-44]. The only perioperative study applied four weeks perioperative exercise and 24 weeks postoperative exercise.

*Session length*

The exercise session duration ranged from 10 min to 60 min, with a median session duration of 30 min. One study applied progressively increasing exercise session durations [44], two studies did not report the exercise session duration [38,42], and one study prescribed a weekly step count[51].

*Session frequency*

The median (range) frequency of prescribed exercise sessions was 3.5 (3-5) sessions/week in the preoperative studies and 5 (2-14) sessions/week in the postoperative studies. The most frequent exercise prescription was applied in postoperative studies conducted in the immediate postoperative phase (2-3 sessions/day) [16,18].

*Time from surgery to initiation of exercise in peri- and postoperative studies*

Two studies initiated exercise within two days after surgery [16,18], whereas another study prescribed exercise one week after surgery [45]. One study initiated exercise after discharge [42]. In two studies, the time from surgery to initiation of exercise was not reported but obtained following correspondence with study authors [43,44]; van Waart et al. [43] initiated the exercise on average (mean (SD)) 42 (13) days after surgery, and Yeo et al. [44] initiated exercise within 3-5 days of surgery.

### 3.2.4 Outcomes

All studies assessed participants at baseline and immediately post-intervention, three studies applied midway assessments [18,42,45], and two studies applied follow-up assessments [43,44]. A full list of outcomes assessed in each study is provided in table 1.

### 3.2.5 Exercise adherence and fidelity

Attendance rate was reported in only two studies. Dunne et al. [39] reported an attendance rate of 99% and Northgraves and colleagues [41] reported an attendance rate of 90%. No other metric of exercise adherence or fidelity were reported in the included studies.

## 3.3 Risk of bias

The risk of bias judgements are presented in figure 2. Justifications of the for the risk of bias judgements for the primary outcomes of the eligible studies are presented below. Justifications of the risk of bias judgements for the other outcomes are presented in Supplementary Material 5A-5E.

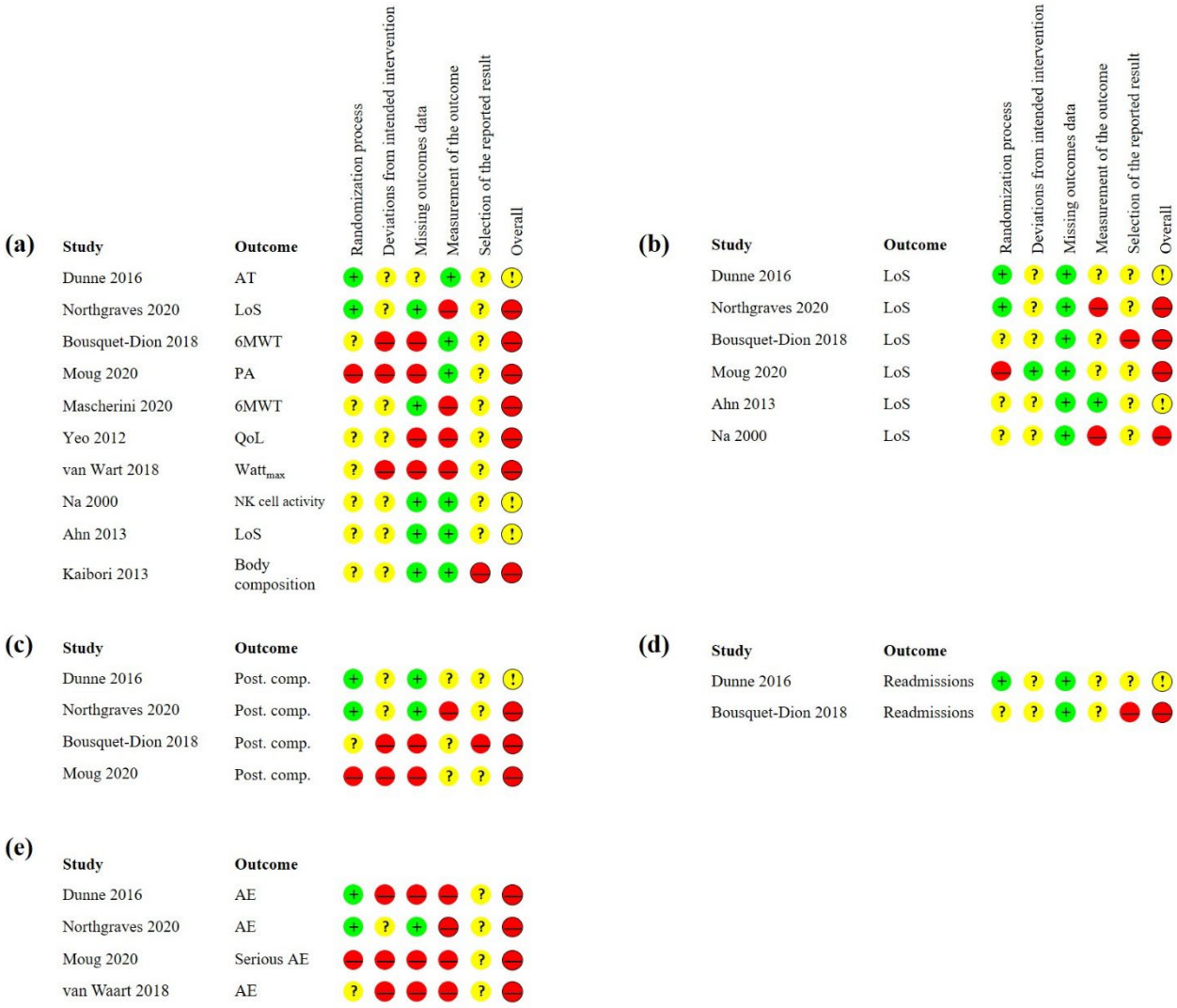


**Figure 2** Review authors' judgements of each risk of bias domain for the included studies for (A) the primary outcomes of the studies, (B) length of postoperative stay, (C) postoperative complications, (D) readmissions, and (E) adverse and serious adverse events. *AE* Adverse events, *SAE* Serious adverse events, *AT* Anaerobic threshold, *LoS* Postoperative length of stay, *6MWT* 6 minutes walking test, *QoL* Quality of life, *NK* Natural killer, *PA* Physical activity, $Watt_{max}$ Maximal workload during stationary cycling to exhaustion.

### 3.3.1 Overall risk of bias

Overall risk of bias was judged to raise some concerns in three studies [16,18,39]. In the seven remaining studies, overall risk of bias was judged to be of high risk [38,40-45].

### 3.3.2 Bias arising from the randomization process

Bias arising from the randomization process was judged to be of low risk of bias in two studies because the descriptions of the randomization sequence generation and the sequence generation concealment were adequate [39,41]. In seven studies, bias arising from the randomization process was judged to raise some concerns, as there was no information regarding randomization sequence generation and/or sequence generation concealment [16,18,38,42-45]. One study was judged to be of high risk of bias arising from the randomization process because prediction of group allocation was possible [40].

### 3.3.3 Bias due to deviations from the protocol

Bias due to deviations from the protocol was judged to be of high risk in three studies because a substantial number of randomized participants were excluded from the analysis [38,40,43]. In the remaining seven studies, bias due to deviations from the protocol was judged to raise some concerns as no prospective trial registrations were available [16,18,39,41,42,44,45].

### 3.3.4 Bias due to missing outcome data

Bias due to missing outcome data was judged to be low in five studies because data were available for all, or nearly all, participants [18,41,45] or because the missingness of data was unlikely to be related to its true value [16,42] . Bias due to missing outcome data was judged to raise some concerns

in one study [39], whereas four studies were judged to be of high risk of bias due to missing outcome data [38,40,43,44].

### 3.3.5 Bias in measurement of the outcome

We judged four studies to be at a high risk of bias in measurement of the outcomes because the assessment of the outcome could have been influenced by the outcome assessors´ knowledge of the intervention allocation [41-44]. The remaining six studies were judged to be of low risk of bias in measurement of the outcomes [16,18,38-40,45].

### 3.3.6 Bias in selection of the reported results

Bias in selection of the reported results was judged to raise some concern in nine studies because no prespecified analysis plan was available [16,18,38-44]. One study was judged to be of high risk of bias in selection of the reported results because only percentage changes were reported [45].

## 3.4 Differences between trial registrations and published reports

Only two studies [40,43,46] were prospectively registered in a trial database. Differences between the registrations and the published reports were found. In the trial registration of Moug et al. [40,46] (www.isrctn.com:ISRCTN62859294), reasons for dropout and cost of intervention delivery were listed as primary outcomes, whereas mortality, length of level 2 stay, and hip circumference were listed as secondary outcomes. None of these variables were reported in the published reports, and daily step count was added as a primary outcome and EORTC QOL CR29 score was added as a secondary outcome. No justifications were provided. In the trial registration of van Waart et al. [43] (www.trialregister.nl:NL2042), sleep quality, objectively measured physical activity, and satisfaction with the intervention were listed as secondary outcomes, but these variables were not included in the published report. In addition, adverse effects of chemotherapy and reasons for non-participation were added as secondary outcome in the published report. No justifications were provided.

## 3.5 Effects of preoperative interventions

### 3.5.1 Primary Outcomes

*Cancer-specific mortality and GI cancer recurrence*

None of the eligible studies assessed GI cancer-specific mortality or GI cancer recurrence.

*Postoperative complications*

Four preoperative studies [38-41] were included in meta-analyses of postoperative complications. We found no eligible evidence of an effect of preoperative exercise on postoperative complications (Figure 3A).

One postoperative study [16] assessed postoperative complications and reported no statistical effects of exercise (number of 30 days postoperative complications: EX: 1 [wound infection]; CON: 1 [ileus]; $P > 0.05$).

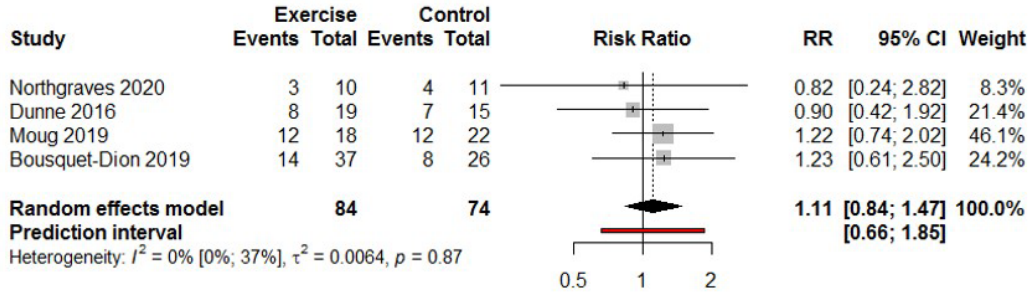
*Postoperative hospitalisation*

In meta-analysis of two preoperative studies [38,39], we found eligible no evidence of an effect of exercise on readmissions (Figure 3B). Length of postoperative stay was reported in four preoperative studies [38-41], but meta-analyses were not performed since only non-parametric data were reported. Bousquet-Dion et al. [38] (median [$Q_1$-$Q_3$]: EX: 3 [3-5] days; CON: 3 [2-4] days; $P = 0.111$) and Northgraves et al. [41] (median [IQR]: EX: 10 [7] days; CON: 8 [5] days; median difference [95% CI]: 1 [-3;6] day) reported no statistical differences in length of postoperative stay between the exercise group and the control group. Another preoperative study [40] reported descriptive data on length of postoperative stay (median [range]: EX:11.0 [6.0-37.0] days; CON:10.0 [0.0-38.2] days). In addition, Bousquet-Dion et al. [38] reported no statistical differences in total hospitalization (median [$Q_1$-$Q_3$]: EX: 3 [3-7] days, CON: 3 [2-4] days, $P = 0.057$) or number of 30-days emergency department visits (EX: 7, CON: 7, $P = 0.559$) between the exercise group and the control group [38]. Lastly, one preoperative study [39] reported length of postoperative stay, number of elective critical care admissions, and length of elective critical care admissions, but the data were unclearly reported (corresponding author did not respond to requests for further information).

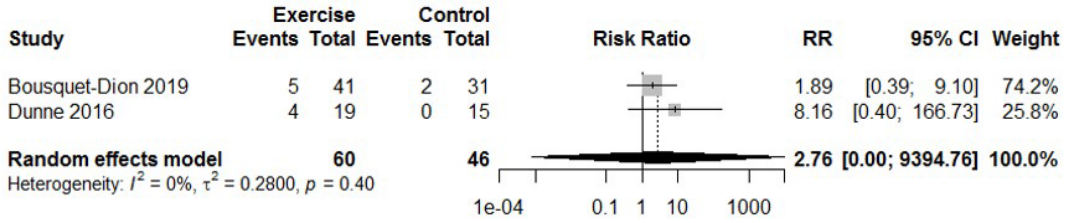
In meta-analysis of two postoperative studies, we found no eligible evidence of an effect of exercise on length of postoperative stay (Figure 3C). In addition, one postoperative study assessed readmissions, reporting no readmissions in the control and in the exercise group [16].

The only perioperative study [45] reported no statistical effect of perioperative exercise on length of postoperative stay (mean [SD]: EX: 13.7 [4.0] days; CON: 17.5 [11.3] days; $P = 0.120$).

**(a) Postoperative complications for preoperative exercise versus control**




**(b) Readmissions for preoperative exercise versus control**




**(c) Length of postoperative stay for postoperative exercise versus control**

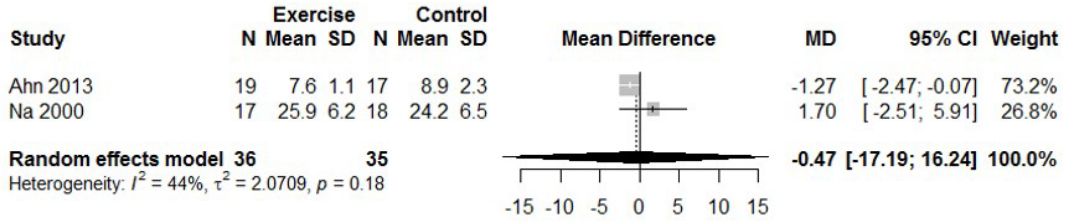



**Figure 3** (A) Risk ratio for postoperative complications for preoperative exercise versus control, (B) risk ratio for readmissions for preoperative exercise versus control, and (C) length of postoperative stay for postoperative exercise versus control. *CI* confidence interval, *RR* Risk ratio, *CON* control¸ *EX* exercise.

*Surgical stress*

Surgical stress was assessed in one postoperative study. Na et al. [18] reported statistically higher natural killer (NK) cell cytotoxic activity in the exercise group as compared to the control group 14 days after surgery (postintervention means: EX: 27.9%, CON: 13.3%; $P < 0.05$).

### 3.5.2 Secondary outcomes

Meta-analyses revealed no eligible evidence of an effect of exercise on cardiorespiratory fitness, grip strength, functional performance, or quality of life (Supplementary Material 6). Meta-analyses were considered inappropriate for adverse events (given poor ascertainment) and body composition (given very diverse timing and duration of the exercise interventions), and results for these outcomes are summarized narratively (Supplementary Material 7). In addition, given lack of studies, meta-analyses were not performed for all-cause mortality, treatment tolerability, treatment response, muscle strength, depression, anxiety, fatigue, intraoperative factors, physical activity, cardiovascular factors, and these outcomes are summarized narratively (Supplementary Material 7).

## 3.6 Certainty of evidence

The certainty of the evidence for our primary outcomes is presented in table 3. For all outcomes, we downgraded due to risk of bias, imprecision, and indirectness, resulting in very low certainty of evidence.

**Table 3** Certainty of the evidence (GRADE) for primary outcomes.

| Outcomes | Anticipated absolute effects* | | Relative effects | No. of randomized participants | Certainty of the evidence |
|---|---|---|---|---|---|
| | Risk with CON | Risk with EX (95% CI) | | | |
| **Preoperative exercise training** | | | | | |
| GI cancer-specific mortality | - | - | - | - | - |
| Recurrence | - | - | - | - | - |
| Postoperative length of stay | - | - | - | - | - |
| Postoperative complications | 42 per 100 | 47 per 100 (35 to 62) | RR 1.11 (0.84 to 1.47) | 158 (4 RCTs) | ⊕◯◯◯ Very low [a,b,c] |
| Readmissions | 4 per 100 | 12 per 100 (0 to 100) | RR 2.76 (0.00 to 9394.76) | 106 (2 RCTs) | ⊕◯◯◯ Very low [a,b,c] |
| Surgical stress | - | - | - | - | - |
| **Postoperative exercise training** | | | | | |
| GI cancer-specific mortality | - | - | - | - | - |
| Recurrence | - | - | - | - | - |
| Postoperative length of stay | Mean LoS ranged 8.9-24.2 days | MD was -0.5 days (-17.2 to 16.2) | - | 76 (2 RCTs) | ⊕◯◯◯ Very low [a,b,c] |
| Postoperative complications | - | - | - | - | - |
| Readmissions | - | - | - | - | - |
| Surgical stress | - | - | - | - | - |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI* Confidence interval, *CON* Control group, *EX* Exercise group, *MD* Mean difference, *RR* Risk ratio. [a] For all studies, overall risk of bias was judged to be high or of some concerns. Therefore, we downgraded by one for risk of bias [b] The studies evaluated participants with colorectal cancer or colorectal liver metastases, and the result may not be applicable to other types of gastrointestinal cancer; The studies evaluated aerobic exercise or combined aerobic and resistance exercise only, and the result may not be applicable to other types of exercise training. Therefore, we downgraded by one for indirectness. [c] The total number of participants is considered low. Therefore, we downgraded by one for imprecision.

## 4 Discussion

This systematic review and meta-analysis, comprised of 10 RCTs ($N$ = 448 participants), demonstrates that the effects of perioperative exercise on cancer-specific and surgical outcomes are unknown in patients with GI cancer due to a limited number of studies and very low certainty of evidence. Additionally, the safety of perioperative exercise as well as its effects on physiological, treatment-related, and psychosocial outcomes are largely unknown.

Postoperative complications and hospitalization remain a major burden in patients undergoing surgical treatment of GI cancer [6,8]. A prevailing hypothesis in the field of exercise oncology holds that exercise can reduce the incidence of postoperative complications and shorten hospitalization. We found no support for this assertion, as our meta-analyses indicate no eligible evidence of an effect of perioperative exercise on postoperative complications, readmissions, or postoperative length of stay. These findings are in accordance with a recent large-scale RCT, reporting no effect of home-based perioperative exercise on postoperative complications or length of postoperative stay in patients with colorectal cancer [48]. However, as discussed below, widespread methodological issues across all eligible studies lower the certainty of the evidence and limit the interpretation of our findings. It should also be noted that most eligible studies applied short, generic, low-to-moderate intensity exercise interventions. Higher volumes and intensities of individually tailored exercise may be required to induce clinically meaningful adaptations within the perioperative period, which typically is short and entails a high risk of adverse effects [6,7,49]. Finally, none of the eligible studies were targeted high risk patients. In one of the largest preoperative exercise trials to date, Barberan-Garcia et al. [17] found that individualized aerobic exercise reduced postoperative complications in high-risk patients undergoing major abdominal surgery, including a heterogenous group of patients with GI cancer. Future studies, however, are needed to confirm these promising findings in samples including specific patient populations with GI cancer undergoing diverse perioperative trajectories and different surgical procedures.

Surgical treatment of GI cancer suppresses immune function [50]. This may have negative implications for subsequent disease progression and survival, and strategies to ameliorate immunosuppression following surgery hold promising antimetastatic effects [50]. Only one eligible study [18] assessed immune function in the early postoperative period and found a statistical beneficial effect of postoperative exercise on NK cell cytotoxicity, warranting future studies to evaluate the ability of exercise to counteract perioperative immunosuppression.

Exercise is generally considered an effective therapeutic treatment for improvements of physical and psychosocial health in patients with cancer [9]. However, our meta-analyses yielded no eligible evidence of an effect of perioperative exercise on cardiorespiratory fitness, functional performance, or health-related quality of life. These findings, however, are based on a limited number of studies and should be interpreted with caution. For the remaining of our secondary outcomes, including muscle function, treatment response and toxicity, body composition, and immunological factors, we were unable to synthesize data due to lack of eligible trials. Exercise has potential to improve these clinically important factors in patients with cancer [9,51,52], but it remains unknown whether this translates to the perioperative setting in GI cancer.

Safety is arguably the single most important consideration for the application perioperative exercise. The ascertainment and reporting of adverse event was poor and, in some studies, completely absent. Nevertheless, several eligible studies stated that perioperative exercise is safe [16,40,43,45]. Given the poor ascertainment of adverse events, this may be misleading, and we contend that the eligible evidence is insufficient to draw conclusions regarding safety of perioperative exercise. A more rigour approach adhering to current guidelines on adverse events reporting in RCTs [53] should be adopted to establish the safety of perioperative exercise.

Fidelity of perioperative exercise remains unknown due to inadequate description of the exercise interventions. Notably, none the eligible studies provide sufficient specification of the interventions to enable replication. This is consistent with previous reviews of exercise oncology studies [54] and limits the utility, interpretation, replicability, and clinical translation of the eligible studies. A second concern is that the reporting of completed exercise was exclusively confined to attendance rate. Attendance rate provides limited insights into the completed exercise dose and may be of little value in the evaluation of exercise feasibility [55,56]. More comprehensive reporting metrics have recently been applied in patients with gastroesophageal cancer undergoing perioperative exercise [14,15] and should be considered in future studies.

The certainty of evidence was very low for all our primary outcomes. The overall risk of bias was judged to be high or to raise some concerns in all eligible studies due to no description of allocation sequence generation and concealment; lack of prospective and sufficiently detailed trial registrations; missing outcome data; lack of outcome assessor blinding; and selection of reported outcomes. Furthermore, our meta-analysis effect estimates are based on small studies. Although we pooled data from several trials, each of our meta-analyses had relatively low sample sizes and are, therefore, potentially statistically underpowered and likely imprecise.

The evaluated exercise interventions were confined to aerobic and resistance exercise of low-to-moderate or unclear intensity, and the effects of other exercise modalities and intensities are unknown. Most eligible studies were conducted in participants with colorectal cancer, and other types of GI cancers are underrepresented in the literature. In addition, only one study was designed to evaluate participants with advanced cancer [39]. The average age of the included participants is slightly lower than the general population of patients with GI cancer. Of note, however, studies evaluating exercise in the immediate postoperative phase included younger participants [16,18]. Lastly, only one perioperative study [45] was identified, and we propose that future trials evaluate combined pre- and postoperative interventions to target adverse effects across the entire perioperative trajectory.

Bias in the review process should be considered in the interpretation of our findings. We were unable to assess eligibility of three non-English studies, and we excluded four studies because it was unclear whether the exercise intervention was initiated within six weeks of surgery. Given the low number of included studies, the exclusion of these potentially eligible studies may have impacted our findings. In addition, four eligible studies [16,18,42,45] claimed to be randomized but did not describe the allocation sequence generation and concealment. We considered these studies as RCTs, although they may not have been truly randomized.

The present study has strengths. In contrast to recent systematic reviews in the field [21-26,29], we applied a more comprehensive search strategy, using six databases as well as forward and backward citation searches of eligible studies and relevant reviews; preregistered a detailed protocol; synthesized a wider range of outcomes, providing more comprehensive evidence on the effects of perioperative exercise; and used the GRADE approach to evaluate the certainty of evidence. Furthermore, we excluded studies that evaluated multimodal interventions. We acknowledge that other types of interventions (e.g., nutrition, targeted physiotherapy, psychosocial support) may hold potential as viable adjunct treatments and that effective perioperative therapy conceivably is multimodal. However, perioperative exercise is in the early stage of development and may differ markedly in intended purpose, efficacy, safety, and fidelity compared to other interventions. Thus, we contend that a systematic evaluation of the isolated effects of perioperative exercise is critical to inform its application as a stand-alone treatment as well as in combination with other interventions. In addition, we only included studies that evaluated patients with cancer. Although this led to the exclusion of several studies (see Supplementary Materials 4), it increases the utility and clinical translation of our findings. In contrast, previous meta-analyses synthesised data from studies

evaluating mixed populations, including non-cancer patients [27], leading to potentially misleading recommendations of exercise for patients undergoing surgery of GI cancer. Lastly, we included both pre-, post-, and perioperative exercise trials. The perioperative period is critical for long-term outcome of cancer [5], and we contend that exercise hold potential to mitigate adverse effects and to induce clinically relevant adaptations along the entire perioperative treatment trajectory.

# 5 Conclusions

The effects of perioperative exercise on cancer-specific and surgical outcomes are unknown in patients with GI cancer due to lack of studies and very low certainty of evidence. Additionally, the safety and feasibility of exercise in the perioperative period is unknown. Adequately powered and robustly designed RCTs are needed to evaluate the effect of perioperative exercise in patients with GI cancer undergoing surgery.

**Competing interests**

The authors declare no competing interests.

**Acknowledgement**

Jesper Frank Christensen is supported by research grants from Rigshospitalet, The Danish Cancer Society, The Capital Region of Denmark, and TrygFonden. The Centre for Physical Activity Research (CFAS) is supported by TrygFonden (grants numbers 101390; 20045). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

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