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REVIEW

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The effectiveness of prehabilitation interventions on biopsychosocial and service outcomes pre and post upper gastrointestinal surgery: a systematic review

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ABSTRACT

Purpose: This review synthesised the evidence for the effect of prehabilitation interventions on biopsychosocial and service outcomes.

Materials and Methods: A systematic review was conducted. 10 databases were searched to December 2023. Prospective experimental studies exploring prehabilitation interventions in adults undergoing upper gastrointestinal surgery were included. Prehabilitation was any preoperative intervention to improve physical or psychological outcomes. Included studies required a comparator group or alternative preoperative intervention as well as baseline, presurgical and postoperative assessment points. Study quality was assessed using the Cochrane risk of bias tool (v.2). Data synthesis was narrative (SWiM guidance).

Results: 6028 studies were screened, with 25 studies included. Prehabilitation interventions were: inspiratory muscle training (five studies $n=450$); exercise (nine studies $n=683$); psychological (one study $n=400$); and nutritional (ten studies $n=487$). High quality studies showed preoperative improvements in impairments directly targeted by the interventions. Generally, these did not translate into functional or postoperative improvements, but multimodal interventions were more promising.

Conclusion: Current evidence supports prehabilitation as safe to preserve or improve preoperative function. Heterogeneity in outcomes and variable study quality means definitive conclusions regarding interventions are not yet possible, limiting implementation. Agreement of clinical outcomes and cost effectiveness evaluation is required.

IMPLICATIONS FOR REHABILITATION

- Prehabilitation interventions are safe and when combined optimally may preserve or improve preoperative function in patients undergoing upper gastrointestinal surgery.
- Multimodal interventions (including exercise, nutritional, and psychological components) showed promise which supports the delivery of prehabilitation by multidisciplinary teams.
- Development of a core outcome set and agreed time points for both preoperative and postoperative outcomes is needed for effective evidence synthesis.
- Focus on long term outcomes is necessary to determine cost effectiveness and commissioning of resources.

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Introduction

Upper gastrointestinal (GI) surgery carries significant risk, with rates of postoperative complications as high as 60% [1]. It is performed on patients with conditions affecting the oesophagus, stomach, liver, spleen, pancreas, biliary tract, and duodenum. Although this includes patients with benign disease, like those awaiting a liver transplant, many patients undergo upper GI surgery in the hope of curative cancer treatment [2].

Surgery elicits a physiological stress response [3], increasing metabolic demands on organ function and placing patients at risk of developing postoperative complications [4]. In patients with upper GI conditions, pre-existing comorbidities coupled with new impairments from chemoradiotherapy before and/or following surgery, magnify the impact of the surgical stress response, elevating the risk of developing postoperative complications further [1, 5–7].

Postoperative complications increase morbidity and reduce short and long term quality of life [8–11]. Complications are resource intensive, increasing hospital readmission rates and overall healthcare costs [12,13]. Even in the absence of postoperative complications, many patients experience reduced physical function and significantly reduced quality of life following major upper GI surgery [14].

Prehabilitation, as part of the surgical rehabilitation continuum, is a broad and proactive concept with a focus on improving health and fitness to reduce surgery-related morbidity, and facilitate faster recovery [15]. It aspires to empower patients to take an active role in their care [16]. Prehabilitation has historically been administered in a brief window before surgery. It aims to optimise

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the patient's functional capacity, creating a buffer to help patients to cope with the surgical stress response and subsequently improving postoperative outcomes [17].

Prehabilitation in a cancer context can extend beyond the preoperative window. It has been described as a process at the start of the rehabilitative continuum of care that occurs between initial diagnosis and commencement of acute cancer treatment [18]. Integration of three core components are also recommended: physical activity and exercise; nutrition; and psychological and behavioural change, in order to provide personalised care and targeted interventions to reduce the incidence and impact of current and future impairments and improve health and wellbeing [19]. Whilst it's acknowledged that multicomponent interventions could optimise effect, previous research studies have often explored isolated components, due to the developing nature of the prehabilitation concept.

Although recommended, and with an expanding evidence base [20], prehabilitation is not currently standard practice, with no clinical guidelines for patients undergoing upper GI surgery. Rehabilitation specialists within clinical prehabilitation services generally cover the whole Upper GI speciality, despite the fact that it is sub-divided into two main subspecialties; hepato-pancreato-biliary (HPB) surgery and oesophagogastric (OG) surgery [2, 21]. The recent systematic review of rehabilitation and exercise recommendations in oncology by Stout et al. [22] included only two upper GI guideline documents [23,24]. These were limited to oesophageal cancer only. The existing evidence base for prehabilitation in this area, either covers a broad spectrum of elective surgery beyond upper GI surgery [15], or it is focused on a subspecialty area of upper GI surgery [25–27], limiting clinical implementation.

We therefore synthesised current evidence in order to describe prehabilitation interventions in upper GI surgery and their effect on biopsychosocial and service outcomes. Specifically, outcomes pre and post-surgery were considered.

Methods

This study is reported considering the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement and the Synthesis Without Meta-analysis (SWiM) in systematic reviews guideline [28,29]. The review protocol for this study was registered on the PROSPERO database on the 3rd of December 2019. CRD42019158668.

Information sources

Two reviewers (RS and OG) independently completed the initial database searches of: AMED (Allied and Complementary Medicine), BNI (British Nursing Index), CENTRAL (Cochrane Central Register of Controlled Trials), CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE (Excerpta Medical Database), EMCARE (Nursing, Allied Health Professions), HMIC (Health Management and Information Consortium), Medline (General Medical Database), PsycINFO (Psychology and Allied Fields) and PubMed (General Medical Database).

Final database search updates were undertaken on the 3rd of December 2023. Hand searches of reference lists of the included articles, conference proceedings and consultation with experts were used to ensure, wherever possible, no relevant studies that met the inclusion criteria for this systematic review were missed.

Eligibility criteria

The eligibility criteria for study inclusion are reported in Table 1.

Participants within the included studies were adults undergoing upper GI surgery for malignant or benign disease. Patients undergoing surgery for obesity management were excluded. Any standalone or multimodal preoperative interventions designed to improve physical or psychological well-being, and delivered in the preoperative period with the intention of improving pre and postsurgical outcomes were included. The included outcomes were deliberately broad. At least three essential time points were required for study inclusion. Outcomes measured at baseline and again before surgery were needed to investigate the effectiveness of the preoperative intervention. To assess the effects of the preoperative interventions on postoperative outcomes, postoperative measurements were also necessary. Any studies not including these three time points were excluded. No date restrictions were imposed. The included studies needed to be prospective experimental studies, published in English, investigating a preoperative intervention that was compared with standard care, or an alternative preoperative intervention.

Search strategy

The search strategy, formulated with support from the specialist librarians at Oxford Brookes University, can be seen in Supplementary file 1. This search strategy was used in all of the listed databases.

Selection process

The database search results were saved and exported into the web based application Rayyan™ to manage and record the study selection process made by the reviewing team [30].

Once duplicates were removed, the database search results were screened for study inclusion by title and abstract, and then by full-text against the protocol selection criteria. This was completed by two reviewers (RS and OG) independently. The reviewers then met to agree on final study inclusion. Disagreements were resolved through discussion between them, with oversight from the review team.

Data extraction

A structure for data extraction and narrative synthesis was piloted and agreed *a priori* by the research team. The data was grouped according to one of four prehabilitation intervention categories; inspiratory muscle training (IMT), exercise, psychological support, or nutrition, with a descriptive overview of the study type, study population, intervention details and reported outcome measures for each study [31]. The population was defined by the upper GI surgical type. The intervention aspect was expanded to incorporate synthesis of the duration of the intervention, followed by frequency, intensity, time, type (FITT) principles [32], to allow detailed comparison of the interventions and the levels of supervision, where appropriate. Details of the study comparator groups were recorded, followed by the reported study outcomes, divided into pre- and postoperative timeframes. Data extraction of the study results was performed and tabulated by the initial reviewer (RS). All extracted data was reviewed and cross-checked for accuracy by the second reviewer (OG), with oversight from the research team.

Table 1. Eligibility criteria table for the included prehabilitation studies in this systematic review, using the population, intervention, comparator, outcomes, studytype (PICOS) framework.

PICOS	Inclusion	Exclusion	Rationale
Population	Human adults, aged 18 and older, all genders	Animal studies Studies in children	Homogeneity of findings and conclusions.
	Participants undergoing all types of upper gastrointestinal (GI) surgery Oesophagogastric (OG) and Hepato-Pancreato-Biliary (HPB) surgical subgroups. Oesophagus, stomach, liver, spleen, pancreas, biliary tract and duodenum	Studies investigating Obesity and Metabolic Surgery Studies including mixed surgical populations, where upper GI surgery cohort data could not be separated out.	
Intervention	Prehabilitation – an intervention designed to improve physical or psychological well-being delivered or prescribed in the presurgery phase with the intention of improving pre and postsurgical outcomes. Studies investigating single interventions or multimodal interventions consisting of the following interventions • Exercise or physical activity • Respiratory muscle training • Nutritional interventions • Psychological interventions • Education interventions • Behaviour change interventions	Studies investigating postoperative interventions only or where the preoperative interventions can't be separated from postoperative care.	Answer the research question Adherence to aims of the literature review and research question
Comparison	English language text available No date restrictions		Time and financial constraints To ensure synthesis of all relevant studies
	Full text access	Conference abstracts without full dataset information.	To enable data extraction
	Usual or standard care (which is not prehabilitation) Comparison of different prehabilitation interventions.		Adherence to the research question and study aims
Outcomes	Outcome measures to evaluate the preoperative intervention i.e. measured at baseline and prior to surgical intervention • Measures of fitness e.g. pVO2max, VO2max, Chester step test, 6MWT, ISWT, CPET • Measures of peripheral and respiratory muscle strength e.g. MIP, grip strength • Patient reported quality of life scores e.g. EORTC, EQ5D, SF36 • Psychological outcomes e.g. Anxiety and Self-efficacy • Measures of adherence e.g. Self-reported adherence measures		Quantitatively determine the efficacy of prehabilitation interventions prior to surgery
	Postoperative outcome measures e.g. ICU length of stay, Quality of Life, Pain, Hospital length of stay, hospital readmission rate, postoperative complication rates, measures of muscle strength e.g. MIP, grip strength.		Quantitatively determine the efficacy and value of prehabilitation interventions after surgery
Study Type	Experimental studies included a comparator group.	Studies that don't include a control group e.g. cohort studies or service evaluation data	Reliability of data to determine the effects of specific prehabilitation interventions.

Study risk of bias assessment

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the risk of bias of the included studies [33]. RoB 2 was completed by the two reviewers (RS and OG) independently, and was then discussed to reach consensus. The proposed judgement about the risk of bias arising from each domain, generated by the algorithm software in the spreadsheet was used to calculate the overall risk of bias for each study, based on the inputted answers to the signalling questions.

Narrative synthesis of study results

As prehabilitation is considered to be an evolving complex intervention, with predicted high heterogeneity of data, narrative synthesis of prehabilitation outcomes was planned. The initial plan, as per the study protocol, was to use the method suggested by Popay et al. [34] however the Synthesis Without Meta-analysis (SWiM) guidance [29] was used instead, as the superseding recommended narrative synthesis method for systematic reviews.

Narrative synthesis of the study results was separated into synthesis of the preoperative outcomes and postoperative outcomes, in accordance with the research question and aims of the review. Synthesis of adherence and safety outcomes were also included. The primary reviewer (RS) completed the narrative synthesis process initially. The second reviewer checked the initial narrative synthesis methods (OG), to ensure accuracy and consistency with the agreed structure, and also to check for any additional or missed narrative themes.

Results

Study selection

Of 6028 de-duplicated records, 25 studies (from 26 reports) were eligible and included in the review (Figure 1). Most common reasons for exclusion were that the records were protocols for studies, conference abstracts or studies without a comparator group.

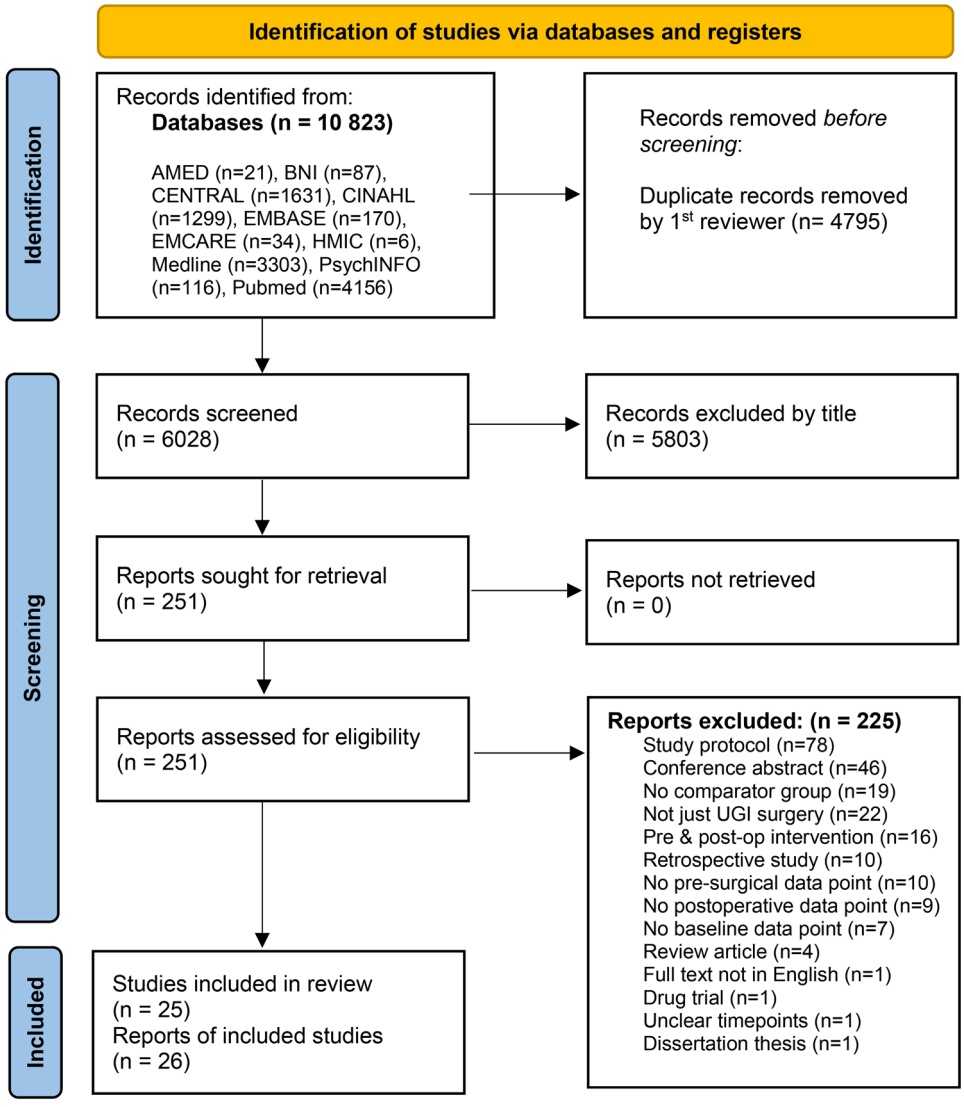

Figure 1. PRISMA flow diagram showing the results and decision making process of the database searches.

Study characteristics

Table 2 presents characteristics of the 25 included studies (described in 26 study reports). Of the 25 studies, 20 were Randomised Controlled Trials (RCTs) and five were comparative cohort studies.

Study populations included patients with cancer undergoing oesophageal surgery ($n=7$), gastric surgery ($n=1$), gastric, oesophageal or biliary tract surgery ($n=1$), gastric, oesophageal or pancreatic ($n=1$), oesophagogastric ($n=3$), liver surgery ($n=5$), pancreatic surgery ($n=4$), pancreatic or liver surgery ($n=1$) and hepatobiliary surgery ($n=2$).

The following results sections present further detail on study interventions, risk of bias, and estimates of effect for each of the four main intervention categories (in line with SWiM guidance [29]).

Studies of inspiratory muscle training interventions

Five studies ($n=450$) investigated the use of inspiratory muscle training (IMT) as a preoperative intervention [35–37,39,40]. One study explored the effects of IMT and exercise as a combined intervention [40].

Interventions

Duration. Four studies aimed for an IMT intervention of at least two weeks in length. Median duration was reported in three studies ranging between 17.5 and 25.9 days [37,39,40] and mean duration in one of 25.4 days [35]. One study had a fixed duration of 4 weeks [36].

Frequency. Intended frequency ranged from three to 7 days per week, either once or twice per day [35–37,39,40].

Intensity. Intended intensity was individualised and ranged from 20 to 80% of measured baseline maximal inspiratory pressure (MIP). All studies encouraged progression by either re-measuring MIP alongside rating of perceived exertion (RPE) [39] or just using RPE [35–37,39,40].

Time. Time was either based on absolute time of IMT session—ranging from 15 min [40] to 20 min [35,36,39], or number of breaths using the IMT device, ranging from 30 IMT breaths twice a day [37] to six cycles of six breaths with a progressive reduction in the rest time in the high intensity group [36,39].

Table 2. Characteristics Table of the 25 studies (26 reports) included in this systematic review, categorised by one of four main prehabilitation intervention types.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Inspiratory muscle training				
IMT	Dettling et al. [35] Comparative Cohort Study	Oesophageal cancer; Netherlands; *n* = 83 Patients living: <40 km from hospital = intervention >40 km from hospital = control	**Experimental** = IMT: 20 mins; 7 × weekly at 30% MIP; Mean (SD) duration = 25.4(12) days; partially supervised **Control** = standard care (not described beyond conventional care)	**Baseline and Preoperative:** MIP; RME **Postoperative on days 1, 3, 5, 7 and 10:** MIP; RME; Duration of MV; ICU LOS; No of reintubations Postoperative pneumonia; Hospital LOS **Feasibility:** IMT-related adverse events; patient reported training, compliance and satisfaction
IMT	Kumar et al. [36] Randomised Clinical Trial	Oesophageal cancer; India; *n* = 20	**Experimental** = High intensity IMT; 6 cycles of 6 breaths at 60% MIP; 3 × weekly for 4 weeks **Comparator** = Endurance IMT; 20 mins at 30% of MIP; 7 × weekly for 4 weeks; Both interventions unsupervised with a follow up phone call on alternate days	**Baseline and Preoperative:** MIP; RME; Lung function **Postoperative on day 7:** MIP; RME Lung function PPCs
IMT	Valkenet et al. [37] Randomised Control Trial Multicentre (*n* = 9)	Oesophageal cancer; Netherlands; Belgium; Ireland; Finland; *n* = 270	**Experimental =** IMT: 30 breaths × 2 daily × 7 weekly at 60% of MIP; Median (range) duration = 21(0–74) days; unsupervised **Control =** Standard care (Delivered according to local hospital policy – not standardised between centres).	**Baseline and Preoperative:** MIP; RME; lung function **Baseline and 4 weeks postoperative:** QoL: EQ-5D-3L; SF12 **Postoperative on days 3,6 and 9:** MIP; RME; lung function Duration of MV; ICU LOS; No of reintubations; Postoperative pneumonia; PCs, Hospital LOS **Feasibility:** IMT-related adverse events; patient reported training & compliance; hospital mortality
IMT	Guinan et al. [38] Randomised Control Trial (this was one of the centres that formed part of the Valkenet et al. [37] trial above)	Oesophageal cancer; Ireland; *n* = 72	**Experimental = as for Valkenet** et al. **Control =** Standard care (No preoperative intervention, but advised to be physically active in preparation for surgery)	**As for Valkenet** et al.. **plus:** **Baseline:** Habitual physical activity for 7 days **Baseline and Preoperative:** 6MWD **Postoperative on days 1 to 4:** SpO_2; FiO_2 **Postoperative on days 1 to 6:** Daily activity; step count **Postoperative on day 9:** 6MWD
IMT	van Adrichem et al. [39] Randomised Clinical Trial	Oesophageal cancer; Netherlands; *n* = 45	**Experimental =** High intensity IMT; 6 cycles of 6 breaths at 80% MIP; 3 × weekly; median (IQR) duration 25.9 (20.3-30.8) days; fully supervised. **Comparator =** Endurance IMT; 20 mins at 30% of MIP; 7 × weekly; median (IQR) duration 25.9 (21-30.8) days; partially supervised.	**Baseline and Preoperative:** MIP; Lung function **Postoperative:** Duration of MV; ICU LOS; No of reintubations PPCs; Hospital LOS **Feasibility:** IMT-related adverse events; patient reported training, compliance and satisfaction
IMT and Exercise	Soares et al. [40] Randomised Control Trial	Oesophageal, gastric or biliary tract surgery (81% cancer patients) Brazil; *n* = 32	**Experimental =** IMT: 15 mins × 6 weekly at 20% MIP Walking: 10 mins on flat groups × 6 weekly Exercise: 25 mins (inc: stretching, deep breathing, upper & lower limb exercises, relaxation) × 2 weekly; Median (IQR) 17.5(14.0-21.0) days; partially supervised **Control =** Standard care (No pre-op intervention)	**Baseline and Preoperative:** MIP; RME; lung function; 6MWD; FIM **Postoperative on days 1,7 and 30:** MIP; RME; lung function; FIM **Postoperative on days 7 and 30:** 6MWD PPCs (up to 7 days); Hospital LOS **Feasibility:** Patient reported adherence

(*Continued*)

Table 2. Continued.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Exercise without chemotherapy				
Exercise and nutrition	Ausania et al. [41] Randomised Control Trial	Pancreatic cancer; Spain; $n=40$	**Experimental =** High intensity endurance training on cycle-ergometer. 60 mins × daily; Median 12.6 days; partially supervised. **Control =** Standard care	**Baseline and Preoperative:** 10MWT; Lung function; SpO_2; HGS **Postoperative:** PCs; Hospital LOS; Hospital readmissions
Exercise	Dunne et al. [42] Randomised Control Trial	Liver cancer; UK; $n=38$	**Experimental =** Interval training on cycle-ergometer 30 mins alternating between moderate (<60% VO_2 at peak) and vigorous (>90% VO_2 at peak); 3 × weekly for 4 weeks; Fully supervised **Control =** Standard care	**Baseline and post intervention:** CPET testing: VO_2 at AT, VO_2 at peak, Oxygen pulse at AT; oxygen pulse at peak; Heart rate reserve QoL: SF-36® **Postoperative:** PCs; Hospital LOS; Hospital readmissions **Feasibility:** Exercise-related adverse events; compliance (% of completed exercise sessions)
Exercise	Morkane et al. [43] Comparative Cohort Study	Liver Cirrhosis; UK; $n=33$	**Experimental =** Interval training on cycle-ergometer (individualised according to CPET data) 40 mins (alternating between moderate and severe intensity) 3 × weekly for 6 weeks. Fully supervised. **Control =** Standard care (matched control) Both groups received structured nutritional advice.	**Baseline and post intervention:** CPET testing: VO2 at AT, VO_2 at peak, VE/VCO_2 at AT, max HR, Peak workload, Haemoglobin. BMI; HGS; MAC; MAMC **Postoperative:** Donor risk index; Hospital LOS; ICU LOS; **Week 12 post intervention:(if no surgery):** CPET testing: VO_2 at AT, VO_2 at peak, VE/VCO_2 at AT, max HR, Peak workload, Haemoglobin. **Feasibility:** Exercise programme completion rate; 6-month survival.
Exercise and nutrition	Nakajima et al. [44] Comparative Cohort Study	Pancreatic and liver cancer; Japan; $n=108$	**Experimental =** Aerobic and resistance training exercise programme. 60 min; at least 3 × per week Nutrition: A leucine-rich essential amino acid supplement within 30 mins after the start and end of exercise therapy; Median (IQR) =32(19–50) days; unsupervised. **Control =** Standard care. A backward consecutive series of patients who underwent surgery before the clinical trial, without preoperative exercise and nutritional therapy	**Baseline and Preoperative:** 6MWD; 10MWT; Knee extension strength; HGS; total skeletal muscle mass; total fat mass; muscle/fat ratio Body weight; BMI; Alb; PNI **Postoperative:** PCs; Hospital LOS
Exercise	Zarate Rodriguez et al. [45] Randomised Control Trial	Pancreatic surgery; USA; $n=152$	**Experimental =** Phone call intervention using a semi-structured script with information about importance of physical activity. Phone call took place on average 5.4 (±1.5) days before surgery. **Control =** No phone call intervention Both groups received written information about Fitbit device, encouraged to walk as much as possible and to incorporate exercise into daily routine.	**Baseline and Preoperative:** step count **Postoperative:** PCs

(*Continued*)

Table 2. Continued.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Exercise with chemotherapy				
Exercise and psychological coaching	Allen et al. [46] Randomised Control Trial	Oesophagogastric cancer; UK; $n = 54$	**Experimental** = 1 h supervised exercise programme (25 min aerobic (cycling), resistance training and flexibility × 2 weekly and 1 h home exercise programme (resistance and core stability) × 3 weekly; for 15 weeks; partially supervised. 6 sessions of psychological coaching (face to face or via teleconference). **Control** = Standard care	**Baseline, 2 weeks post NACT and Preoperative:** CPET testing: change in AT; change in peak VO_2; sarcopenia (CT cross sectional skeletal muscle surface at L3 level); HGS; weekly step count; EORTC QLQ-30; BAI; BDI II **Postoperative: 2 weeks, 6 weeks, 6 months:** HGS; EORTC QLQ-30; BAI; BDI II; PCs; 30-day hospital readmission; 3-year mortality
Exercise, nutrition and relaxation counselling	Bausys et al. [47] Randomised Control Trial	Oesophagogastric Cancer Lithuania; $n = 128$ 84% during NACT	**Experimental** = Personalised daily exercise programme for 60 mins (10–30 mins of daily endurance training, daily respiratory muscle training for 5–10 mins, resistance training 10–20 mins × 3 weekly, stretching for 5–10 mins × 3 weekly). Partially supervised. Nutritional support with energy requirements calculated at 25–30 kcal/kg and protein at 1.5 g/kg. 250 ml oral nutrition supplement administered for 10 days before surgery. Relaxation and anxiety management technique training for self-management at home. Mean (SD) 92(33) days. **Control** = no advice on prehabilitation related interventions apart from recommendation to use high-energy nutritional supplements 10-14 days before surgery.	**Baseline and Preoperative:** 6MWD; EORTC QLQ-30; Neoadjuvant treatment adherence. **Postoperative:** PCs (up to 90 days); Hospital LOS; Hospital readmission rate (up to 90 days).
Exercise	Christensen et al. [48] Comparative Cohort Study	Oesophageal cancer; Denmark; $n = 62$	**Experimental** = High-intensity aerobic (interval training on cycle ergometer) and resistance exercises for 75 mins ×2 weekly. Median (SD) 12(4.08) weeks; Supervised. **Control** = Standard care	**Baseline and Preoperative:** VO_2peak; 1RM muscle strength testing; DEXA scanning for fat mass, bone mass, fat-free mass and bone mineral density; Neoadjuvant treatment tolerability; Tumour response to treatment; QoL: FACT-E **Postoperative:** PCs; CCI score; Hospital LOS. **Feasibility:** Frequency of serious adverse events; adherence to prescribed exercise programme;
Exercise and nutrition	Minnella et al. [49] Randomised Control Trial	Oesophagogastric cancer; Canada; $n = 68$; 77% during NACT.	**Experimental** = Exercise programme 4 × weekly (30mins aerobic exercise × 3 weekly, 30mins strength and flexibility training × 1 weekly); Median 5.1 weeks; unsupervised. Food based dietary advice was given, with whey protein supplement prescribed if needed. **Control** = Standard care	**Baseline and Preoperative:** 6MWD; **Postoperative:** PCs; Hospital LOS; 30-day hospital readmission rate; Hospital mortality; **6-8 weeks after surgery:** 6MWD **Feasibility:** Adherence to planned NACT; compliance with exercise and nutritional interventions.

(*Continued*)

Table 2. Continued.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Psychological				
Psychological	Marinelli et al. [50] Randomised Control Trial	Pancreatic cancer; Italy; $n=400$	**Experimental =** A one-session psychological consultation lasting 1 h the day before surgery. **Control =** Standard care (no specific intervention to deal with pre-surgical anxiety)	**Baseline and Preoperative:** STAY-Y1; Visual analogue scale for self-efficacy **Postoperative between days 3 to 7:** STAY-Y1; Visual analogue scale for self-efficacy; BPI-I; VAS-P PCs (up to 30 days); Hospital LOS
Nutrition				
Perioperative nutrition care pathway	Deftereos et al. [51] Comparative Cohort Study	Gastric, Oesophageal or Pancreatic cancer; Australia; $n=70$	**Experimental =** Patients were included in a new multisite standardised nutrition care pathway from diagnosis to discharge **Control =** Standard care. Historical control group selected from consecutively from medical records.	**Baseline and Preoperative:** Weight; HGS; preoperative hospital admissions **Postoperative:** PCs; Hospital LOS
Preoperative parenteral nutrition	Fan et al. [52] Randomised Control Trial	Oesophageal cancer; Hong Kong; $n=40$	**Experimental =** Parenteral nutrition supplement (PPN) – synthetic amino acid (Vamin 250 mg N/kg/day), glucose and lipid emulsion (40 kcal/kg/day), electrolytes, trace elements and vitamins *via* a central venous catheter and oral feeding for 14 days before surgery. **Control =** usual care – oral feeding. Both groups received high protein, high calorie diet, with appropriate correction of dehydration, electrolyte disturbance, anaemia and concomitant pulmonary infection.	**Baseline and preoperative at baseline and day –1:** Body weight; Alb; total lymphocyte count; HGS; MAC; TSF; subscapular skinfold thickness. **Postoperative:** PCs; Hospital LOS
Preoperative oral nutrition	Le Cornu et al. [53] Randomised Control Trial	Liver transplant; UK; $n=82$	**Experimental =** oral supplement 500 ml (750 kcal, 20 g protein, 33.5 g fat, 9.75 mmol sodium, and 25 mmol potassium) plus personalised dietary advice; intervention median duration 77 days (range 1-395) **Control =** usual care – personalised dietary advice until transplantation; median duration 45 days (1–424).	**Baseline and preoperative:** MAC; TSF; MAMC; HGS **Postoperative:** Nutritional assessment on day 9 PCs; septic complications up to 6 months or death; non-infectious complications up to 6 months or death; 30-day mortality; 6-month mortality; frequency and severity of rejection; LOS in hospital, LOS in ICU; time on ventilatory support;
Dietary Counselling exercise and relaxation counselling	Kasvis et al. [54] Randomised Control Trial	Hepatobiliary cancer surgery; Canada; $n=61$	**Experimental =** personalised dietary advice at baseline appointment aiming for protein intake of 1.5 g/Kg/day and energy requirements of 25 kcal/kg or 30 kcal/day based on BMI. Exercise: personalised daily aerobic exercise programme with strength and flexibility training every second day. Unsupervised × 6 weekly and supervised × 1 weekly. Relaxation techniques following a meeting with a psychologist to complete at any time of day and at least 3 × per week. **Control =** Standard care which did not include preoperative nutrition, exercise or relaxation counselling.	**Baseline, preoperative and postoperative:** BMI; aPG-SGA; 3-day food diary to calculate overall energy and protein intake; HGS; FACT-G

(*Continued*)

Table 2. Continued.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Immunonutrition	Aida et al. [55] Randomised Control Trial	Pancreatic surgery; Japan; $n = 50$	**Experimental =** Oral supplementation (IMPACT – Ajinomoto Pharma Co., Ltd, Tokoyo, Japan) (1000 kcal/day) containing: arginine, ω-3 fatty acids and RNA for 5 days before surgery in addition to a 50% reduction in the amount of regular food (1,000 kcal/day). **Control =** Standard care – no artificial nutrition and allowed to consume regular food preoperatively (2,000 kcal/day)	**Baseline and Preoperative: days −6 & −1:** **Inflammatory response:** Plasma IL-6 Cell mediated immunity: Con A, PHA-stimulated lymphocyte proliferation Th1/Th2 differentiation: T-bet, GATA-3 and mRNA expression levels **Fatty acid composition:** EPA, EPA/AA ratio, plasma PGE2 **Postoperative: days 0,1,3,7,14:** **Inflammatory response:** Plasma IL-6 Cell mediated immunity: Con A, PHA-stimulated lymphocyte proliferation Th1/Th2 differentiation: T-bet, GATA-3 and mRNA expression levels **Fatty acid composition:** EPA, EPA/AA ratio, plasma PGE2 PCs (up to 30 days); infectious complications; SIRS duration; Clavien-Dindo score; Hospital LOS **Feasibility:** Compliance with intervention.
Immunonutrition	Ashida et al. [56] Randomised control Trial	Pancreatic surgery; Japan; $n = 24$	**Experimental =** Enteral supplementation (Prosure, Abbot Japan Co., Ltd., Tokyo, Japan) (600 kcal/day) enriched with EPA in addition to 1200 kcal/day of regular food for 7 days before surgery **Control =** isocaloric isonitrogenous standard nutrition (Procure A, Nisshin Oillio Group, Ltd., Tokyo, Japan) (600 kcal/day) without EPA in addition to 1200 kcal/day of regular food for 7 days preoperatively	**Baseline and Preoperative: days −7 & 0:** **Inflammatory response:** plasma IL-6; IL-1; TNF-alpha and CD4/8 T lymphocyte balance **Nutritional status:** Alb, prealbumin, transferrin and EPA/AA ratio **Postoperative: days 1, 4, 7, 14:** Inflammatory response: Plasma IL-6; IL-1beta; TNF-alpha and CD4/8 T lymphocyte balance **Nutritional status:** Alb, prealbumin, transferrin and EPA/AA ratio PCs; infectious complications; SIRS; Clavien-Dindo score
Immunonutrition	Mikagi et al. [57] Randomised control Trial	Liver cancer; Japan; $n = 26$	**Experimental =** 750 ml enteral supplementation (IMPACT – Ajinomoto Pharma, Tokyo, Japan) (750 kcal) and half meals (half sized hospital meals, 1000 kcal per day) for 5 days before surgery **Control =** Standard care – conventional hospital meals (1,800kcal/day).	**Baseline and preoperative: days −5 & −1:** **nutritional indices:** Alb, transthyretin **liver function:** AST; ALT **fatty acid metabolism:** EPA; TG; FFA **inflammatory reaction:** WBC **Postoperative on days 3 and 7:** **liver function:** AST; ALT; EPA; TG; FFA. **Postoperative on days 0 (immediately post-surgery), 3 and 7:** **inflammatory reaction:** WBC **Postoperative on days 0 (immediately post-surgery) and 3:** **inflammatory reaction:** IL-6 PCs; infectious complications; non-infectious complications; hospital LOS.

(*Continued*)

Table 2. Continued.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Immunonutrition	Okamoto et al. [58] Randomised control Trial	Gastric cancer; Japan; $n = 60$	**Experimental =** 750 ml oral supplement (IMPACT – Ajinomoto Pharma Co., Ltd, Tokyo, Japan) (759 kcal, 9.6 g arginine, 3.1 g, ω-3 PUFAs and 0.96 g RNA) plus meals as desired for 7 days before surgery **Control =** isoenergetic standard formulas (MEDIF – Ajinomoto Pharma Co., Ltd, Tokyo, Japan) plus meals as desired for 7 days preoperatively.	**Baseline and preoperative: days −7 & 0:** **Immunological function:** WBC; lymphocytes; CD4 + T-Cell; CD8 + T-cell; CD4/CD8 ratio; CD16+ **Protein synthesis:** Body weight; haemoglobin; serum concentrations of total protein; Alb; prealbumin; transferrin; RBP; total cholesterol, triglyceride; choline esterase; copper; zinc **Postoperative on day 7:** **Immunological function:** WBC; lymphocytes; CD4 + T-Cell; CD8 + T-cell; CD4/CD8 ratio; CD16 **Protein synthesis:** Body weight; haemoglobin; serum concentrations of total protein; Alb; prealbumin; transferrin; retinol binding protein (RBP) total cholesterol, triglyceride; choline esterase; copper; zinc PCs; infectious complications; non-infectious complications; SIRS duration; Hospital LOS
Immunonutrition	Russell et al. [59] Randomised control Trial	Liver Cancer; New Zealand; $n = 34$	**Experimental =** oral supplement (3 × 237 ml tetra packs of IMPACT, Advanced Recovery (Nestle) (providing 1020 kcal, 54 g protein, 12.6 g arginine, 1.3 g nucleotides, 3.3 g eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)) as well as other oral intake; for 5 days preoperatively **Control =** Standard care – usual oral intake. (pts in this group deemed as malnourished were provided with a standard nutritional supplement (Fortisip) twice daily (600 kCal, 24 g protein) in addition to their usual intake, in the period 5 days preoperatively.	**Baseline and preoperative day −1:** **Immune and inflammatory markers:** EPA + DHA:AA ratio; CRP; lymphocytes; WCC; TNF-alpha; IL-6; IL-8; IL-10 **Nutritional and functional status:** Christensen Fatigue Scale; Karnofsky performance scale; HGS **Postoperative on days 1, 3, 5, 7:** EPA + DHA:AA ratio; TNF-alpha; IL-6; IL-8; IL-10 **Postoperative on days 1, 3, 5, 7 & 30:** CRP **Postoperative on days 1, 3, 5, 10 and 30:** lymphocytes; WCC **Postoperative on days 7 and 30:** Christensen Fatigue Scale; Karnofsky performance scale; HGS PCs (up to 30 days); infectious complications; non-infectious complications; Clavien-Dindo score; Hospital LOS

(*Continued*)

Table 2. Continued.

Intervention Type	Study authors & type	Upper GI Population	Intervention Details	Outcome measures
Immunonutrition	Uno et al. [60] Randomised control Trial	Hepatobiliary surgery; Japan; $n = 40$	**Experimental =** oral supplementation (oral IMPACT; Nestle Health Science Co, Ltd, Kobe, Japan) (1000 kcal/day containing EPA, arginine, and nucleotides) in addition to 50% reduction in amount of regular food (1,000 kcal/day), for 5 days before surgery. **Control =** received no artificial nutrition and were allowed to consume regular food preoperatively (2000 kcal/day).	**Baseline and preoperative: days −6 & −1:** **fatty acid metabolism:** serum fatty acid, EPA and EPA/AA ratio **Inflammatory response:** plasma resolvin E1 levels; IL-6; CRP. **Postoperative: days 0 (immediately following surgery), 1,3,7 and 14:** **fatty acid metabolism:** serum fatty acid, EPA and EPA/AA ratio **Inflammatory response:** plasma resolvin E1 levels; IL-6; CRP. PCs (up to 30 days); infectious complications; non-infectious complications; SIRS duration; Clavien-Dindo score; Hospital LOS

Abbreviations Key: 6MWD = six-minute walk distance; 10MWT = 10 metre walk test; 1RM = one-repetition maximum; AA = arachidonic acid; Alb = serum albumin; ALT = alanine aminotransferase; aPG-SGA = abridged patient-generated subjective global assessment cancer therapy-general questionnaire; AT = anaerobic threshold; BAI = Beck anxiety inventory; BDI II = Beck depression inventory-II; BMI = body mass index; BPI-I = brief pain inventory; CCI = Charlson comorbidity index; CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; CPET = cardiopulmonary exercise testing; CRP = C-reactive protein; DEXA = dual energy X-ray absorptiometry; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; EORTC QLQ-30 = European Organisation for Research and Treatment of Cancer 30-item instrument core questionnaire; EQ-5D-3L = EuroQual measure of health-related quality of life; FACT-E = functional assessment of cancer therapy – Esophageal; FACT-G = functional assessment of cancer therapy - general; FFA = free fatty acids; FIM = functional independence measure; FiO_2 = fraction of inspired oxygen; HGS = hand grip strength; HR = heart rate; ICU = intensive care unit; IL-1 interleukin 1; IL-6 = interleukin 6; IL-8 = interleukin 8; IL-10 = interleukin 10; IMT = inspiratory muscle training; IQR = inter-quartile range; LOS = length of stay; MAMC = mid arm muscle circumference; MAC = mid arm circumference; MIP = maximal inspiratory pressure; MV = mechanical ventilation; NACT = neoadjuvant chemotherapy; PCs = post operative complications; PGE2 = prostaglandin E2; PHA = polyhydroxy acid; PNI = prognostic nutrition index; PPCs = post operative pulmonary complications; PPN = parenteral nutrition; QoL = quality of life; RME = respiratory muscle endurance; SD = standard deviation; SF12 = 12-Item short form survey; SF-36® = 36-Item short form survey; SIRS = systemic inflammatory response syndrome; SpO_2 = oxygen saturation; STAY-Y1 = state-trait anxiety inventory; TH1 = T-helper 1; Th2 = T-helper 2; TNF alpha = tumour necrosis factor alpha; TSF = triceps skinfold thickness; VAS-P = visual analogue scale for pain; VO_2 = maximal oxygen consumption; VE/VCO_2 = minute ventilation/carbon dioxide production; WBC = white blood cell count.

Type. Four studies used an inspiratory threshold-loading device [35,36,39,40] and one, a tapered flow resistive inspiratory loading device [37].

Supervision. Two studies used an unsupervised intervention [36,37], two used partial supervision [35,40], and one used a fully supervised (high intensity group) and partial supervision (endurance group) [39].

Comparators

The comparator groups consisted of standard care that was specific to the local centre in three studies [35, 37,40]. Two studies compared a high intensity IMT intervention with an endurance intervention (both interventions are included in the narrative synthesis) [36,39].

Outcomes

For *preoperative* outcomes, the studies reported four main outcome constructs – Respiratory Function (Maximal Inspiratory Pressure (MIP), Respiratory Muscle Endurance (RME), lung function), Physical Function (Six-Minute Walk Distance (6MWD), Functional independence measure (FIM)), Adherence and Adverse events.

For *postoperative* outcomes, the studies reported five main outcome constructs—Respiratory Function (maximal inspiratory pressure), Physical Function and Activity (6MWD, step count), Postoperative Pulmonary Complications (PPCs), Hospital Length of Stay (LOS) and Quality of Life (EQ5D and 12-item Short Form (SF-12)). Outcome measure time points varied with a median endpoint of nine days (range 1 to 30).

Risk of bias assessment

The RoB 2 assessment for the included IMT studies can been seen in Figure 2. One study was rated as "low" [37], two studies as "some concerns" [38,39] and three studies as "high" risk of bias overall [35,36,40]. The most common reason for concern around bias was deviation from the intended interventions.

Narrative synthesis of estimates of effect for IMT interventions

Table 3 presents summaries of the directions of effect of the interventions and the risk of bias of the included studies.

Preoperative outcomes

Respiratory. Three studies found significant preoperative improvement in MIP compared to the standard care control [35,37,40], with average between-group differences ranging from 9 to 34.5 cmH_2O. Two studies found no different in MIP between high intensity or endurance IMT [36,39].

Three studies found preoperative respiratory muscle endurance (RME) significantly improved compared to the usual care [35,37,40], with average between-group differences ranging from 5 to 16.5 cmH_2O. One study found no significant difference between groups [36].

No between-groups differences were found in the four studies that measured lung function via spirometry [36,37,39,40].

Physical Function. All three studies measuring physical function found no significant difference between groups (two using 6MWD [38,40] and one using FIM [40].

Adverse events. Three studies found no significant differences between groups for adverse effects [35,37,39].

Postoperative outcomes

Respiratory. Three studies found no significant difference between groups for postoperative MIP at 3 to 30 days [36,38,40], whereas one study found postoperative MIP was significantly higher (Median Difference (MD) 6.5 cmH_20) on postoperative day 10 [35].

Physical Function and Activity. Guinan et al. [38] found a significantly lower 6MWD in the IMT group compared to usual care at postoperative day nine (MD 74.9 m [95%CI 9.9–139.4], $p = 0.03$), indicating poorer physical function performance in the IMT group Also, the usual care group were significantly more physically active at moderate intensity than the intervention group between postoperative days one and five (MD 2.09%/day, $p = 0.04$).

Postoperative pulmonary complications (PPCs)/incidence of pneumonia. Van Adrichem et al. [39] reported a significant improvement in the rate of PPCs between the patients receiving high intensity compared to endurance IMT (4 patients (20%) vs. 11 patients (57.9%), $p = 0.015$). Soares et al. [40] reported a significant improvement in the rate of PPCs in favour of the intervention (5 patients vs. 11 patients, $p = 0.034$).

None of the five studies reported a significant difference in the rate of development of postoperative pneumonia between the different IMT interventions, or between the intervention and usual care groups [35–37,39,40]. In the multicentre trial that reported postoperative pneumonia as the primary outcome, postoperative pneumonia was diagnosed in 47 (39.2%) of the 120 patients in the IMT intervention group and in 43 (35.5%) of the 121 patients in the control group (not statistically significant, $p = 0.561$) [37].

Hospital length of stay (LOS). No studies found a significant difference in length of stay between IMT and usual care [35,37,40]. Van Adrichem et al. [39] found hospital LOS to be signifcantly shorter in the high intensity IMT group compared to the endurance IMT group ($p = 0.010$).

Quality of life. No significant difference in quality-of-life outcomes were reported [37].

Studies of exercise interventions

Nine included studies investigated the effect of exercise ($n = 683$) [41–49] (See Table 2).

Interventions

Five studies utilised additional components to exercise, three with nutritional interventions [41, 44, 49] and one with psychological coaching [46] and one with a nutritional intervention and relaxation counselling [47].

Duration. Three studies were conducted for fixed time periods of 4 weeks [42], 1 for 6 weeks [43] and one for 15 weeks [46]. Studies where the timed duration of exercise depended on the timing of surgery, ranged from a mean or median of 2.6 days to 13 weeks [41,44,45,47–49].

Frequency. Frequency of the exercise interventions across the seven studies ranged from twice per week to every day. The most common frequency was three times per week, utilised in three studies [42–44]. Additionally, one study comprised of a single telephone call to encourage increased physical activity [45].

Intensity. Four studies used high intensity exercise [41–43,48], and four moderate intensity exercise [44,46,47,49]. Four studies reported that exercise intensity was individually determined using a baseline exercise test [42,43,47,48], and two studies used RPE [46,49]. Five studies included a resistance component as part of their intervention [44,46–49].

Time. The length of the exercise interventions ranged from 30 to 75 min, with the most common length being 60 min in four of the included studies [41,44,46,47].

Type. Five studies utilised a cycling intervention [41–43,46,48], two a walking intervention [44,45], one a choice of walking, jogging or cycling [49] and one a choice of walking, stair climbing, dancing, water exercises or cycling [47].

In the studies that included a resistance component as part of their intervention, one study used resistance band [49], two studies used weights [44,48], one study used a combination of resistance band and weights [46] and one did not report the methods of resistance used [47].

Supervision. Exercise was unsupervised in three studies [44,45,49], partially supervised in three studies [41,46,47], and completely supervised in three studies [42,43,48].

Partial supervision varied. In Ausania et al. [41] and Bausys et al. [47], the exercise intervention was completely supervised for the first 5 and 3 days respectively, and then unsupervised until surgery. Whereas, in Allen et al. [46], the patients were

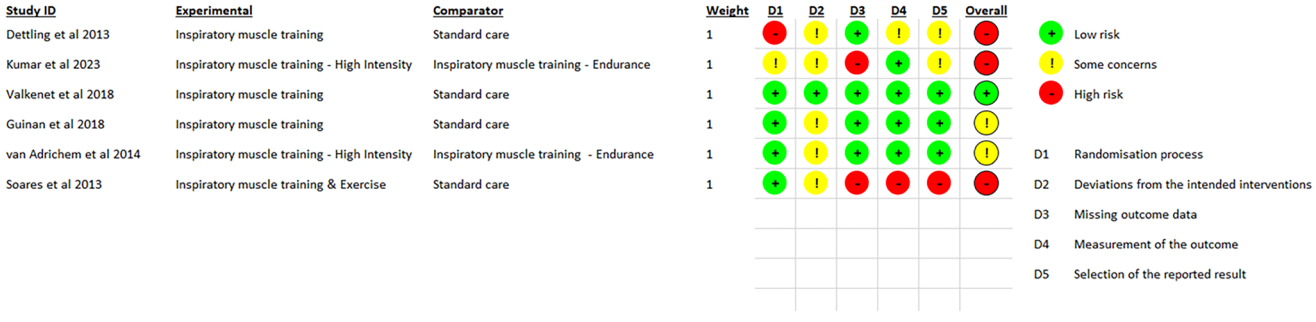

Figure 2. Risk of bias chart using the Cochrane risk of bias tool (version 2) for the six included studies investigating inspiratory muscle training interventions, where red depicts high risk of bias, yellow, some concerns, and green, low risk of bias. Risk of bias for each of the five domains is given as well as overall risk of bias.

Table 3. Summary table of the directions of effect of the intervention outcomes on the vertical axis according to the risk of bias of the included studies on the horizontal axis with "n" being the number of participants and the study reference number given in brackets.

	Favours Experimental			No Difference			Favours Control		
Risk of bias score	Low	Medium	High	Low	Medium	High	Low	Medium	High
Preoperative outcomes	**Inspiratory Muscle Training Interventions**								
Respiratory MIP	$n = 270$ [37]		$n = 135$* [35, 40]		$n = 45$ [39]	$n = 20$ [36]			
Respiratory RME	$n = 270$ [37]		$n = 115$* [35, 40]			$n = 20$ [36]			
Respiratory Spirometry				$n = 270$ [37]	$n = 45$ [39]	$n = 52$* [36, 40]			
Physical Function 6MWD					$n = 72$ [38]	$n = 32$* [40]			
Adverse Events				$n = 270$ [37]	$n = 45$ [39]	$n = 83$ [35]			
Postoperative outcomes	**Inspiratory Muscle Training Interventions**								
Respiratory MIP			$n = 83$ [35]		$n = 72$ [38]	$n = 52$* [36, 40]			
Physical Function 6MWD								$n = 72$ [38]	
Physical Activity Step counts								$n = 72$ [38]	
PPCs		$n = 45$ [39]	$n = 32$* [40]	$n = 270$ [37]	$n = 45$ [39]	$n = 135$* [35,36, 40]			
Hospital LOS				$n = 270$ [37]		$n = 115$* [35, 40]			
Quality of life				$n = 270$ [37]					
Preoperative outcomes	**Exercise interventions**								
Exercise Testing CPET VO_2 at AT	$n = 38$ [42]			$n = 54$ [46]		$n = 33$ [43]			
Exercise Testing CPET VO_2 max				$n = 92$ [42, 46]		$n = 33$ [43]			
Exercise Testing 10MWT						$n = 148$* [41, 44]			
Physical Function 6MWD	$n = 196$* [47, 49]								
Physical Function HGS				$n = 54$* [46]		$n = 181$* [33, 41, 44]			
Quality of Life	$n = 128$* [47]			$n = 92$* [42, 46]		$n = 62$ [48]			
Neoadjuvant therapy adherence	$n = 182$* [46,47]		$n = 62$ [48]	$n = 68$* [49]					
Postoperative outcomes	**Exercise interventions**								
Physical Function 6MWD	$n = 68$* [49]								
Physical Function HGS				$n = 54$ [46]					
PCs				$n = 288$* [42, 46,47, 49]		$n = 362$ [41, 44,45, 48]			
Hospital LOS			$n = 141$* [44, 46]	$n = 288$* [42, 46,47, 49]		$n = 102$ [41, 48]			
Hospital readmission rate				$n = 128$* [47]					
Quality of life	$n = 54$* [48]								
Preoperative outcomes	**Psychological Interventions**								
Anxiety			$n = 400$ [50]						
Self-efficacy			$n = 400$ [50]						
Postoperative outcomes	**Psychological Interventions**								
Pain BPI-emotional			$n = 400$ [50]						
Pain BPI physical						$n = 400$ [50]			
PCs						$n = 400$ [50]			
Hospital LOS						$n = 400$ [50]			
Preoperative outcomes	**Nutritional Interventions**								
Fatty acid composition	$n = 74$ [55,56]	$n = 100$ [57,59,60]							
Immune and inflammatory markers				$n = 74$ [55,56]	$n = 160$ [57–60]				
Physical Function: HGS					$n = 122$ [52,53]				
Body composition					$n = 212$ [51, 53, 58]				

(*Continued*)

Table 3. Continued.

	Favours Experimental			No Difference			Favours Control		
Risk of bias score	Low	Medium	High	Low	Medium	High	Low	Medium	High
Patient reported nutrition status					*n* = 61* [54]				
aPG-SGA									
Quality of Life					*n* = 61* [54]				
Preoperative hospital admissions					*n* = 61* [54]				
Postoperative outcomes	**Nutritional Interventions**								
Immune and inflammatory markers	*n* = 50 [55]	*n* = 66 [57, 60]		*n* = 74 [56]	*n* = 134 [58–60]			*n* = 24 [56]	
IL = 6; WBC; CRP; TNF-alpha; CD4/8 lymphocyte ratio									
Body composition					*n* = 60 [58]				
PCs Rates					*n* = 184 [51–53]				
General nutrition									
PCs—Infectious complications (immunonutrition)		*n* = 100 [58, 60]							
PCs—Non-infectious complications (immunonutrition)				*n* = 50 [55]	*n* = 160 [57–60]				
SIRS response		*n* = 60 [58]		*n* = 50 [55]	*n* = 40 [60]				
PCs Severity	*n* = 50 [55]		*n* = 74 [59,60]	*n* = 24 [56]		*n* = 70 [51]			
Hospital LOS		*n* = 40 [60]		*n* = 50 [55]	*n* = 242 [52,53, 57–59]	*n* = 70 [51]			
Patient reported nutrition status					*n* = 61* [54]				
aPG-SGA									
Quality of Life					*n* = 61* [54]				

Direction of effects of outcomes (vertical) according to intervention type and risk of bias of study (horizontal: n = number of participants, study reference in brackets, * Contains a study with a multi-component intervention.

Abbreviations Key: 6MWD = six-minute walk distance; 10MWT = 10 metre walk test; aPG-SGA = abridged patient-generated subjective global assessment cancer therapy-general questionnaire; AT = anaerobic threshold; BPI-I = brief pain inventory; CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; CPET = cardiopulmonary exercise testing; CRP = C-reactive protein; HGS = hand grip strength; IL-6 = interleukin 6; LOS = length of stay; MIP = maximal inspiratory pressure; PCs = post operative complications; PPCs = post operative pulmonary complications; RME = respiratory muscle endurance; SIRS = systemic inflammatory response syndrome; TNF alpha = tumour necrosis factor alpha; VO_2 = maximal oxygen consumption; WBC = white blood cell count.

supervised twice per week and unsupervised three times per week for 15 weeks.

In the six studies that utilised a supervised exercise element, three studies did not report the background of the supervising personnel [41–43]. In the other three studies, exercise was supervised by clinical exercise scientists with oncology expertise [46], a kinesiologist [49], and a physical medicine and rehabilitation physician and physiotherapist [47].

Comparators

The comparator groups in all nine included studies consisted of a usual care intervention [41–49].

Outcomes

For preoperative outcomes, studies reported four main outcome constructs—Exercise testing (Cardiopulmonary Exercise Testing (CPET) at Anaerobic Threshold (AT), Peak Oxygen Uptake (VO_2 peak), Ten metre walk test (10MWT), step count), Physical Function (6MWD, hand grip strength (HGS)), Quality of Life (36-Item Short Form Survey Instrument (SF-36®), Functional Assessment of Cancer Therapy-Esophagus (FACT-E), The EORTC Core Quality of Life questionnaire (EORTC-QLQ-30), Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI II)) and Neoadjuvant therapy adherence.

For postoperative outcomes, studies reported five main outcome constructs—Physical Function (6MWD, HGS), Postoperative complications (PCs), Hospital LOS, Hospital readmission rate and Quality of Life (EORTC-QLQ-30, BAI, BDI II). Outcome measure time points varied from 2 weeks to 6 months after surgery.

Risk of bias assessment

The RoB 2 assessment for the nine included exercise studies can been seen in Figure 3. Four studies scored "low" [42,46,47,49] and five studies scored "high" risk of bias [41,43–45,48]. The most common issues were the randomisation processes and deviations from intended interventions.

Narrative synthesis of estimates of effect for exercise interventions

Table 3 presents summaries of the directions of effect of the interventions and the risk of bias of the included studies.

Preoperative outcomes.

Exercise testing. One study found a significant improvement in mean VO_2 at AT in favour of the intervention group ($p = 0.029$) [42]. The other two studies found no between-group differences at the mid-neoadjuvant therapy [46] or at the preoperative assessment point [43, 46].

No significant between-group differences in Peak Oxygen Consumption (VO_2 peak) using CPET testing were found in three studies [42,43,46].

Two studies found no significant between-group differences for the preoperative 10MWT [41,44].

Physical Function. Two studies found a significant increase in preoperative 6MWD in the intervention group compared to usual care ($p = 0.02$ [49]) and ($p = 0.001$ [47]). One study also reported a significant increase in presurgical 6MWD in the intervention group ($p < 0.001$), however no between-groups comparison was possible due to the historical control group used in this study [44].

Four studies found no significant differences between groups for HGS [41,43,44,46].

Quality of life. No significant difference between the intervention and control groups was found for effect on quality of life at the presurgical point in three studies [42,46,48]. One study found a significant improvement in EORTC-QLQ-C30 ($p = 0.005$), with a 13 point increase in emotional functioning score ($p = 0.022$) [47].

Neoadjuvant therapy completion and adherence. Three studies found improved adherence to neoadjuvant therapy in the intervention group compared to control [46–48], with one study finding no difference [49].

Postoperative outcomes

Physical function. One study found significant improvement in 6MWD in the intervention group compared with the control group ($p < 0.001$) [49].

One study showed that HGS 6 months following surgery was 96.56% of baseline level in the intervention group compared to 91.40% in the control group, which was not signficant between groups ($p = 0.096$) [46].

Postoperative complications. None of the studies found a significant difference in the number of serious postoperative complications (classed as grade III and above) on the Clavien-Dindo classification scale [61] or Modified Accordion Grading System (MAGS) [62], between the intervention and control groups [41,42,44–49].

Hospital length of stay (LOS)

No significant improvement in the hospital LOS was found in six studies [41,42,46–49], whereas two studies did find a significant improvement in the median LOS [43,44].

Hospital readmissions rate (90 day)

One study reported hospital readmission rates, and found no significant improvement [47].

Quality of life. One study showed that global health was rated significantly higher at 2 weeks ($p = 0.001$), 6 weeks ($p = 0.001$) and 6 months ($p = 0.003$) following surgery, compared with the control group using the EORTC QLQ-30 questionnaire. BAI and BDI II anxiety and depression scores were significantly better 6 weeks (BAI, $p = 0.043$; BDI II, $p = 0.028$) and 6 months (BAI, $p = 0.014$; BDI II, $p = 0.029$) but not at 2 weeks post-surgery compared to the control group (BAI, $p = 0.102$; BDI II, $p = 0.564$) [46].

Studies of psychological interventions

One study ($n = 400$) investigated the effects of a preoperative psychological intervention for patients undergoing upper GI surgery [50] (See Table 2).

Intervention

The intervention consisted of a single, one hour consultation with a psychologist the day before surgery, where concerns and worries were disclosed to reduce anxiety and foster the patient's ability to cope with stress.

Comparator

The control group received usual care (no specific intervention to cope with presurgical anxiety, but access to a psychologist if requested).

Outcomes

For *preoperative* outcomes, the study measured two related psychosocial constructs—Anxiety (State-trait anxiety inventory (STAY-Y1)) and Self-efficacy of managing Anxiety on a Visual Analogue Scale.

For *postoperative* outcomes, the study measured Pain (Brief pain inventory (BPI-I)), as well as rates of postoperative complications (PCs) and hospital LOS.

Risk of bias assessment

The included study scored high risk of bias overall [50] (Figure 4). There were substantial concerns with deviations from the intended interventions, missing outcome data (a large number of participants were lost to follow-up and analysis) and possible reporting bias.

Narrative synthesis of estimates of effect of psychological interventions

Table 3 presents summaries of the directions of effect of the interventions and the risk of bias of the included studies.

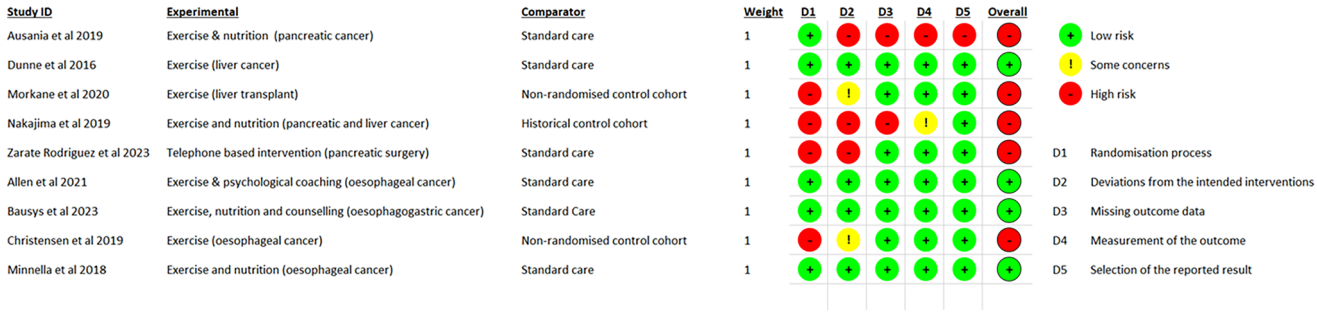

Figure 3. Risk of bias chart using the Cochrane risk of bias tool (version 2) for the nine included studies investigating exercise interventions, where red depicts high risk of bias, yellow, some concerns, and green, low risk of bias. Risk of bias for each of the five domains is given as well as overall risk of bias.

Preoperative outcomes

Anxiety. There was a significant decrease in anxiety between the groups (43.4 vs. 28.2; $t = 7.5$, $p < 0.01$) in favour of the intervention.

Self-efficacy. There was a significant increase in the self-efficacy in managing preoperative anxiety for the intervention group compared to the control group following the intervention (7.1 vs. 8.3; $t = 3.4$ $p < 0.01$).

Postoperative outcomes

Pain. The emotional component of pain on the Brief pain inventory (BPI-I) showed a significant decrease in the intervention group compared with the control group ($d = 1.4$ $p = 0.02$), however the physical component did not find a difference.

Postoperative complications. No difference was found in the frequency of postoperative complications at 30 days (intervention: 47.7%, control: 55.9% $p = 0.48$).

Hospital length of stay. No difference was found in Mean (SD) hospital LOS (Intervention: 12.5(12.0) days, control: 13.6(14.1) days $p = 0.62$).

Studies of nutrition interventions

Ten studies ($n = 487$) investigated nutritional preoperative interventions for upper GI surgery [51–60] (See Table 2).

Intervention

Six studies ($n = 234$) investigated the effects of short term preoperative immunonutrition interventions for the surgical stress response [55–60]. Four studies ($n = 253$) investigated nutritional interventions on surgical and postoperative outcomes [51–54], with one study including a multimodal intervention of exercise and relaxation techniques alongside a single dietary counselling appointment [54].

Duration

Duration of the six immunonutrition studies was either 5 days [55,57,59,60], or seven days [56,58] before surgery. Of the other four nutritional studies, two had fixed a duration of 14 days [52], or 4 weeks before surgery [54], one a median duration of 77 days (range 1 to 395 days) in the intervention group and 45 days (range 1 to 424 days) in the control group [53], and the fourth study did not report the overall duration of the intervention [51].

Frequency

Nutritional interventions were all delivered daily, as a proportion of, or in addition to daily nutritional intake.

Type

Six studies utilised oral supplementation [53,57–60] or advice on oral intake [54], two studies enteral supplementation [55,56], one study parenteral supplementation [52] and one was mixed according to individualised patient requirements [51].

One study used an oral supplement that consisted of a daily 500 ml drink (750 kcal, 20 g protein, 33.5 g fat, and 9.75 mmol sodium and 24 mmol potassium) in addition to personalised dietary advice [53]. One study used parenteral supplementation that consisted of a synthetic amino acid (Vamin 250mgN/kg/day), glucose and lipid emulsion (40 kcal/kg/day), trace elements and vitamins [52]. The other two studies used a calculation of energy and protein requirements according to individualised patient weight and dietary preferances to provide dietary advice [51,54].

The six studies investigating the effects of immunonutrition interventions all utilised supplements that contained combinations of arginine; ribnuclei acid (RNA), or it's sub-components (nucleic acid or nucleotides); and omega three fatty acids in the form of polyunsaturated acids fatty acids (PUFAs), eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) [55–60]. The participants in the intervention groups of two studies received 759 kcal or 1020 kcal of oral supplementation in addition to their normal oral intake [58,59], in two studies received 750 kcal or 1000 kcal of oral supplementation in addition to half of the their normal oral intake [57,60], in one study received 1000 kCal/day of enteral supplementation in addition to half of their normal oral intake (calculated as 1000 kCal per day) [55], and one study received 600 kcal of supplementation in addition to 1200 kCal/day of regular food [56].

Details of the immunonutrition interventions for comparison are presented in Supplementary File 2.

Comparators

In eight studies, the control group received a standard care intervention which involved no advice or artificial nutritional supplementation and consumption of normal meals [51–55,57,59,60]. In two studies, the control group received a control supplement intervention in addition to normal meals [56,58].

Outcomes

For *preoperative* outcomes, studies reported seven main outcome constructs—Fatty acid composition (EPA levels, EPA/AA ratio, EPA + DHA/AA ratio), Immune and inflammatory markers (Interleukin 6 (IL-6), White blood cell count (WBC), C reactive protein (CRP),

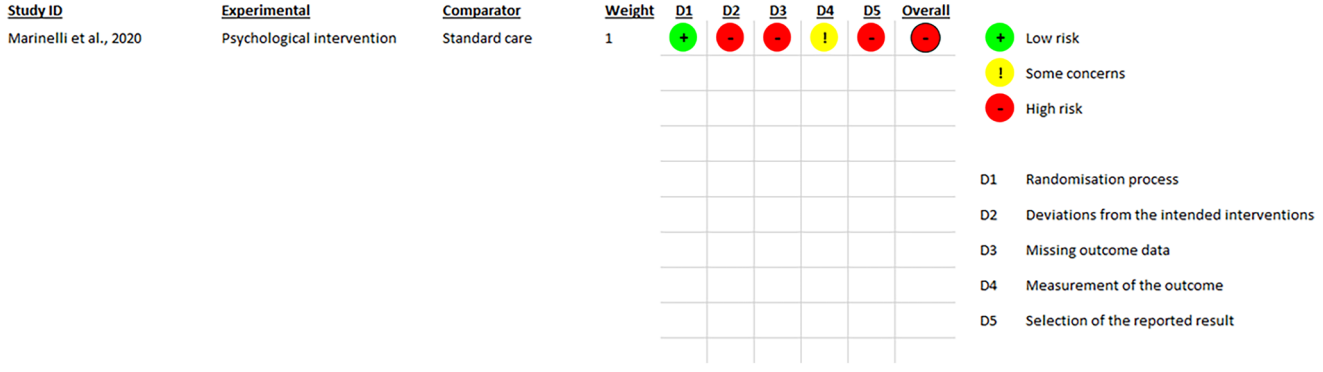

Figure 4. Risk of bias chart using the Cochrane risk of bias tool (version 2) for the included study investigating a psychological intervention, where red depicts high risk of bias, yellow, some concerns, and green, low risk of bias. Risk of bias for each of the five domains is given as well as overall risk of bias.

Tumour necrosis factor alpha (TNF-alpha), CD4/8 lymphocyte ratio), Physical Function (HGS), and Body Composition (Mid-Arm Circumference (MAC), Triceps Skinfold Thickness (TSF), Mid-arm Muscle Circumference (MAMC), body weight), Patient reported nutrition status (abridged Patient-generated Subjective Global Assessment of Cancer Therapy-General questionnaire aPG-SGA; 3-day food diary), Health related quality of life (The Functional Assessment of Cancer Therapy—General (FACT-G)), and preoperative hospital admissions.

For *postoperative* outcomes, studies reported six main outcome constructs—Immune and inflammatory markers (IL-6, WBC, CRP, CD4/8 ratio), body composition (body weight), postoperative complications (PCs—Clavien-Dindo classification scale, infection), Hospital Length of Stay, Patient reported nutrition status (aPG-SGA), Health related quality of life (FACT-G).

Risk of bias assessment

The RoB 2 assessment for the ten included studies can be seen in Figure 5. Two studies scored "low" risk of bias [55,56]. There were "some concerns" raised in seven studies [52–54,57–60], and one study scored high risk of bias [51]. The main reasons for concerns were either that the studies were not randomised or were underpowered. Issues with deviations from the intended interventions were again prevalent.

Narrative synthesis of estimates of effect of nutritional interventions

Table 3 presents summaries of the directions of effect of the interventions and the risk of bias of the included studies.

Preoperative outcomes

Fatty acid composition. Three studies showed significantly higher EPA levels at the presurgical assessment point in the intervention groups compared with the control groups ($p < 0.05$) [55,57,60].

Five studies showed significantly higher EPA/AA and EPA + DHA/AA ratios at the presurgical assessment point in the intervention groups compared with the control groups ($p < 0.05$) [55–57,59,60].

Immune and inflammatory markers. No significant differences ($p > 0.05$) between the intervention and control groups were found in IL-6 [55–57,59,60], WBC [57–59], CRP [59,60], TNF-alpha [56,59], or CD4/8 lymphocyte ratio outcomes [56,58].

Physical function. No significant differences between groups were found for HGS ($p > 0.05$) [52,53].

Body composition. No significant differences between groups were reported for MAC, TSF or MAMC [53] or changes in body weight [51, 58] in the intervention and control groups.

Patient reported nutrition status

Preoperative protein intake improved significantly in the intervention group compared with the control group following dietary counselling, but overall energy intake did not [54].

No significant changes in aPG-SGA between the intervention and control groups were found [54].

Health related quality of life

There was no significant change in quality of life score (FACT-G) preoperatively [54].

Preoperative hospital admissions. There was no significant different in preoperative hospital admissions [51].

Postoperative outcomes

Immune and inflammatory markers.

Interleukin-6 (IL-6) levels. Three studies found significantly lower IL-6 levels ($p < 0.05$) in the intervention groups compared to control immediately postoperative [55,57,60], and in one study these levels remained significantly lower ($p < 0.05$) on the first day following surgery [60]. No significant difference between the intervention and control groups were found for the other time points, apart from in one study where the intervention group had a significantly higher plasma IL-6 levels than the control group 7 days postoperatively ($p = 0.017$) [59].

White blood cell count (WBC). Two studies found no difference between the immunonutrition and control groups at any of the measurement points postoperatively [58,59]. One study demonstrated significant suppression indicated by a lower WBC on day 3 ($p = 0.02$) and day 7 ($p = 0.001$) postoperatively in the immunonutrition group compared to the control group [57].

C-reactive protein (CRP). Two studies found no significant differences in CRP postoperatively between the intervention and control groups [59,60].

Tumor necrosis factor alpha (TNF-alpha). Two studies found no significant differences in TNF-alpha at any postoperative timepoints between the intervention and control groups [56,59].

CD4/8 lymphocyte ratio. One study found that the rise curve of CD4/8 lymphocyte ratio was significantly larger ($p = 0.02$) immediately following surgery in the intervention compared to the control [56] whereas one study found no significant differences [58].

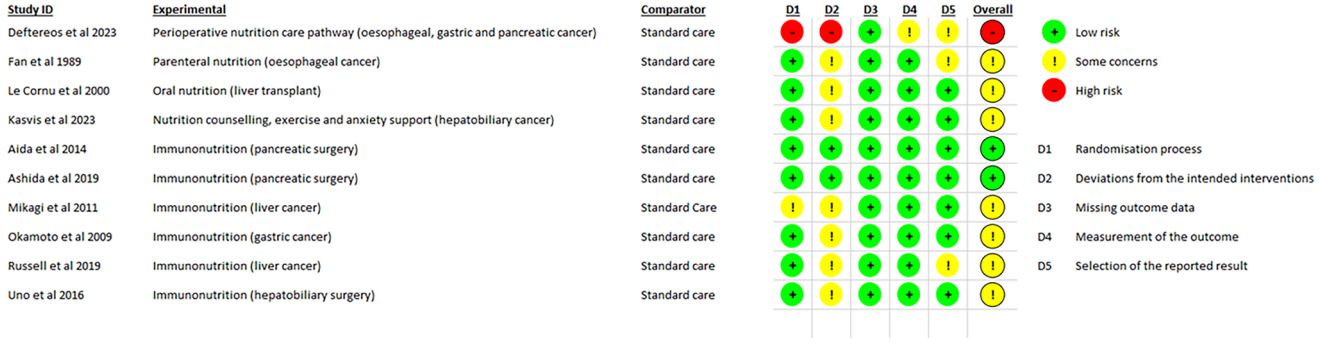

Figure 5. Risk of bias chart using the Cochrane risk of bias tool (version 2) for the ten included studies investigating nutrition and immunonutrition interventions, where red depicts high risk of bias, yellow, some concerns, and green, low risk of bias. Risk of bias for each of the five domains is given as well as overall risk of bias.

Body composition. There were no significant changes in body weight postoperatively [58].

Postoperative complications. Three of the four studies investigating general nutritional interventions reported no significant difference in postoperative complications [51–53].

In the six studies investigating the effects of immunonutrition interventions, the percentage of infectious complications ranged from 0% to 78% in the intervention groups and 8% to 75% in the control groups [55–60]. Significant between group differences were found in 2 studies [58,60]. No significant differences were found in non-infectious complication in five studies [55,57–60]. No significant difference in duration of SIRS was found between groups in two studies [55,60], but there was a significant difference in one study ($p = 0.04$) [58].

Significant improvement in the severity of postoperative complications (Clavien-Dindo classification scale grade III and above) between the intervention and control groups were found in three studies [55,59,60] with no difference reported in two [51,56].

Hospital length of stay (LOS). One study found a statistically significant difference ($p = 0.006$) in mean (SEM) hospital length of stay—36.9 ± 3.3 days in the intervention group compared with 53.9 ± 5.0 days in the control group [60], seven studies reported no difference [51–53,55,57–59].

Patient reported nutrition status

No significant changes in nutrition intake or PG-SGA between the intervention and control groups were found postoperatively [54].

Health related quality of life

There was no significant change in quality of life (FACT-G) score postoperatively [54].

Discussion

This systematic review has highlighted the paucity of high quality, adequately powered trials to inform the clinical delivery of prehabilitation interventions in the upper GI surgical patient populations. Nevertheless, it has revealed valuable insights to direct future research and the development of clinical oncology rehabilitation services [22]. The prehabilitation interventions produced some beneficial effects on preoperative physiological or psychological outcomes most directly associated with the target of the intervention type. However, these improvements often did not translate into improvements in functional outcomes, or result in reduced postoperative complications, length of stay or improved quality of life following surgery.

The small number of studies retrieved across the broad spectrum of patients undergoing upper GI surgery, as well as a high level of heterogeneity across the interventions and their outcomes means that definitive conclusions about prehabilitation for this surgical patient group are not yet possible. The results of high quality studies showed that inspiratory muscle training significantly improves pre-operative inspiratory muscle strength in patients undergoing surgery for oesophageal cancer [37]; exercise improved physical fitness in patients undergoing surgery for liver metastases [42]; and immunonutrition improved immune and inflammatory marker levels in patients undergoing hepatobiliary and gastric surgery [55–57, 59,60]. The most prevalent and highest quality of evidence was found for combined nutritional and exercise interventions [37,42,46,49,55,56].

When exercise and nutrition prehabilitation interventions were combined, significant improvements in functional capacity were seen both pre- and postoperatively in patients undergoing chemotherapy prior to oesophageal surgery [47,49]. Similarly, when exercise and psychological interventions were combined, there was an improvement in global health as well as anxiety and depression scores at six weeks and six months postoperatively in patients undergoing prehabilitation during chemotherapy prior to oesophageal surgery [46]. This supports multidisciplinary and multimodal interventions within prehabilitation as per recent recommended prehabilitation guidelines for cancer patients [19]. One study included in this review was described as multimodal, incorporating an intervention that consisted of nutrition, exercise and psychological support, and found a reduction in postoperative complications and improved quality of life [54]. Many of the included studies focused on feasibility and safety elements [35,37,39,42 46,48,49,51]. No adverse outcomes were reported in any of the studies, confirming that prehabilitation is safe for delivery in patients undergoing upper GI surgery.

Inspiratory muscle training interventions

IMT is currently recommended as a preoperative intervention to reduce PPC rates in patients undergoing cardiac, thoracic and upper or major abdominal surgery, supported by meta-analysis finding significant improvements in PPCs [63–67]. However, quality concerns regarding one of the reviews have also been raised [67], and the conclusions supporting the use of IMT in presurgical populations questioned [68]. There are currently no published systematic reviews exploring the effectiveness of Inspiratory Muscle Training (IMT) on surgical outcomes specifically in patients undergoing upper GI surgery. Despite this, IMT has been viewed as a potentially attractive intervention to reduce respiratory complications and length of hospital admission [69–71].

We found that even with considerable variation in their intervention protocols [72–74], all studies showed a signficant improvement in maximal inspiratory pressure (MIP) between baseline and surgery as a result of IMT training [35–37,39,40]. However, no improvements in postoperative PPCs or LOS were found in the high quality, multicentre trial [37]. These results have been confirmed by a recent cohort study that showed that a significant improvement in preoperative inspiratory muscle strength as a result of high intensity IMT training was not associated with a reduced risk of PPCs following oesophgeal surgery [75].

Soares et al. [40] investigated the effects of IMT and exercise which has previously been suggested to be superior to IMT alone [66]. Whilst a signficant improvement in PPCs was found, it should be noted that this study was deemed to be at high risk of bias.

Understanding the effects of IMT in patients with low baseline levels of physical activity, or those with multiple comorbidities, unable or unwilling to increase their physical activity levels may beneficial to guide personalised prehabilitation. The results of the UK NIHR-funded "INSPIRE" study [76] may improve understanding of the effects of IMT generally in surgical patients at high risk of post-operative pulmonary complications, but not specifically in patients undergoing upper GI surgery. The results of this review show that while IMT can improve respiratory muscle function, with a preference towards high-intensity interventions, current evidence does not support its use in improving postoperative outcomes in patients undergoing upper GI surgery.

Exercise interventions

The benefits of physical activity and exercise in cancer prevention and cancer survival are well established, with clear physical activity guidelines and recommendations for cancer populations [77–79]. Exercise is generally considered to be the main component of prehabilitation interventions with known benefits to physical fitness and improved muscle strength. There is increasing evidence to suggest physiological benefits to enhanced immunity and reduced inflammation, as well as a possible effect on delayed disease progression and improved survival in patients diagnosed with cancer [80,81]. We only found one study reporting a significant improvement in exercise outcomes prior to surgery [42]. This study also showed a deterioration of fitness in some patients in the control group highlighting the role of exercise in maintenance or prevention of deterioration of fitness prior to upper GI surgical intervention.

There is a growing body of evidence to support exercise interventions to improve neoadjuvant therapy tolerance and effectiveness [82,83]. We found improved adherence to neoadjuvant therapy in three studies [46–48], with one study finding no difference [49]. These results are similar to those reported in a systematic review by Gillis et al. [84], where combined exercise and nutrition interventions resulted in a quicker return to baseline functional capacity compared to nutrition only interventions, in patients undergoing colorectal surgery. These results combined demonstrate that exercise and nutrition help to maintain cardiopulmonary fitness during neoadjuvant therapy prior to surgery, with a quicker return to baseline following surgery.

Quality of life outcomes showed significant improvements in three studies, one exercise intervention [48] and two multimodal interventions, one combining exercise and psychological interventions [46], and the other exercise, nutrition and relaxation counselling [47]. These studies were all conducted on patients who were undergoing neoadjuvant therapy prior to elective surgery for oesophagogastric cancer. The results of these studies suggest the stress of impending surgery may limit benefits on short term outcomes. They suggest a need to explore outcomes during neoadjuvant treatment, particularly if several cycles are required, as well as long term outcomes. This may help to understand long-term effectiveness and cost implications on patient well-being, particularly in patients undergoing lengthy and complex treatment interventions.

Psychological interventions

Psychological support and behaviour change are listed as core components of prehabilitation, alongside exercise and nutrition [19]. The evidence base in this area is lacking generally in surgical and cancer populations, with some weak suggestions of benefits on postoperative outcomes [85], immunologic function and patient reported quality of life [86]. Only one study investigating the effects of a psychological intervention for patients undergoing pancreatic surgery was included in this systematic review [50]. The authors suggest that, as a result of a 1-h consultation session with a psychologist the day before surgery, the participants in this study had significantly less preoperative emotional distress and less emotional pain after pancreatic surgery. However, the study was deemed to be of high risk of bias across multiple domains, with no significant effects on post-operative complications or hospital length of stay demonstrated. While the use of preoperative education programmes to improve surgical outcomes has also been highlighted [87], the number of patients included in the final analysis of this study limits the reliability of any conclusions or recommendations.

Nutritional interventions

Cancer patients are at high risk of malnutrition as a result of cancer related disease and cancer treatments. There are published recommendations for prevention of cancer-related malnutrition [88]. Given the location of the upper GI structures and their role in digestion, managing nutrition in patients with conditions requiring surgical intervention is complex. There is a high prevalence of malnutrition in patients with benign or malignant disease, which is associated with worse outcomes and increased healthcare costs [89–92].

A recent scoping review exploring prehabilitation interventions in patients undergoing cancer treatment (for all types of cancer), with a specific focus on nutritional assessment and interventions, highlighted the paucity and inconsistency of evidence in this area [93]. Four of the ten studies included in this review explored the effects of nutritional interventions on nutritional status in patients undergoing upper GI surgery. There was no significant between-group difference in outcomes before or after surgery in patients undergoing oesophageal surgery [52] or liver transplant [53]. Both of these studies were in the "some concerns" category in their risk of bias assessment, due to small participant numbers, with insufficient study power to detect changes in postoperative outcomes. In the two more recent studies, a single consultation session with a dietician was shown to improve protein intake, demonstrating the importance of monitoring and personalised guidance regarding protein and energy intake [54]. Deftereos et al. [51], demonstrated that implementing a personalised, perioperative nutrition pathway is feasible and advantageous, across an upper GI service with patients undergoing three different types of UGI surgery. Larger studies of this complex nature are needed for better intervention development for patient with upper GI conditions.

Six of the ten included nutrition studies explored the effects of short term immunonutrition interventions on the surgical stress response in upper GI patients. Despite a significant serum response to the immunonutrition interventions between baseline and surgery, the effects on postoperative complications were mixed, with two studies reporting significant improvement in infectious complications [58,60] one in SIRS [58] and three an improvement in severity of complications [55,59,60]. Only one study reported a significant improvement in hospital length of stay [60]. Whilst these results are encouraging in terms of preliminary work, more research into immunonutrition in upper GI surgical populations is required for definitive conclusions to be made regarding their inclusion in preoperative interventions. Dobson [3] highlights the complexities of the immune response that occurs as a result of operative stress in surgical patients.

Although nutritional interventions form a core aspect of the cancer prehabilitation guidelines, there is scope for much further research in this area, particularly as part of multimodal interventions, in patients undergoing upper GI surgery. In patients undergoing colorectal surgery, a systematic review and meta-analysis exploring the effects of nutritional prehabilitation, with and without exercise found length of hospital admission by decreased by two days [84]. Optimal nutrition and prevention of weight loss is highly important to patients undergoing upper GI surgery, with links to improved outcomes [94] and may therefore be central for the optimisation of other aspects of the prehabilitation pathway, like exercise.

Given the lack of standardized guidance, the development and consensus of a core outcome set including both short- and long-term outcomes is also needed to evaluate nutritional interventions and their impact on functional capacity across the

different types of upper GI surgery. This would enhance the opportunities for evidence synthesis to inform the nutritional components of future multimodal prehabilitation interventions.

Strengths and limitations

This systematic review had broad and holistic criteria aiming to capture all current available research. The review included an extensive and detailed narrative synthesis utilising a transparent and systematic approach across the four main intervention types, in order to guide current clinical interventions in this complex and developing area, as well as to inform future research priorities. We excluded surgery for obesity management as these patient groups present with different comorbidities and treatment goals, and warrant separate synthesis. Limitations include the inclusion of small underpowered studies with fragmented evaluations, many showing limitations in terms of study quality and risk of bias, as well as being at the feasibility stage, in line with the developmental nature of the prehabilitation concept. The high heterogeneity in outcomes means that meta-analysis is not yet possible, impacting on robust effect-estimation and therefore well-informed commissioning of prehabilitation services in this area. Given the sequelae associated with conditions requiring upper GI surgery, it seems reasonable to propose that multimodal interventions would be optimal. However, direct evidence is lacking, with only one study evaluating a truly multimodal prehabilitation (nutritional, exercise and psychological components). Nevertheless, the result found in this study and inference from other combined approaches supports the promise of this holistic approach.

Conclusion and future recommendations

This systematic review found a large variation in prehabilitation interventions evaluated for effectiveness on pre- and postoperative biopsychosocial and service outcomes. There was low certainty of evidence (due to risk of bias, inconsistency and imprecision) for effectiveness of Inspiratory Muscle Training, Exercise, Psychological and Nutritional interventions. Multimodal interventions showed greater promise of increased efficacy, particularly when exercise is combined with nutritional or psychological interventions. In order to build the evidence base, more research is needed to inform competing or complementing multimodal interventions, within the complex and lengthy rehabilitation continuum in this patient group, to ensure effective personalised care. Additional high quality, adequately powered trials utilising a core outcome set and agreed time points for both preoperative and postoperative outcomes is required. This will allow for robust meta-analyses and more definitive conclusions to guide clinical decision making and commissioning. The multi-component interventions evaluated need to be constructed according to complex intervention development guidelines involving key stakeholders from patient, clinician and researcher perspectives.

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