Prehabilitation for general surgery: a systematic review of randomized controlled trials

GENERAL SURGERY

Royal Australasian College of Surgeons

Prehabilitation for general surgery: a systematic review of randomized controlled trials

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This study was conducted in memory of Dr. Kollanur Ittimani, a Life Fellow of the Royal Australian College of General Practitioners and inspiration to many.

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Abstract

Background: Prehabilitation seeks to optimize patient health before surgery to improve outcomes. Randomized controlled trials (RCTs) have been conducted on prehabilitation, however an updated synthesis of this evidence is required across General Surgery to inform potential Supplementary discipline-level protocols. Accordingly, this systematic review of RCTs aimed to evaluate the use of prehabilitation interventions across the discipline of General Surgery.

Methods: This study was registered with PROSPERO (CRD42023403289), and adhered to PRISMA 2020 and SWiM guidelines. PubMed/MEDLINE and Ovid Embase were searched to 4 March 2023 for RCTs evaluating prehabilitation interventions within the discipline of General Surgery. After data extraction, risk of bias was assessed using the Cochrane RoB 2 tool. Quantitative and qualitative data were synthesized and analysed. However, meta-analysis was precluded due to heterogeneity across included studies.

Results: From 929 records, 36 RCTs of mostly low risk of bias were included. 17 (47.2%) were from Europe, and 14 (38.9%) North America. 30 (83.3%) investigated cancer populations. 31 (86.1%) investigated physical interventions, finding no significant difference in 16 (51.6%) and significant improvement in 14 (45.2%). Nine (25%) investigated psychological interventions: six (66.7%) found significant improvement, three (33.3%) found no significant difference. Five (13.9%) investigated nutritional interventions, finding no significant difference in three (60%), and significant improvement in two (40%).

Conclusions: Prehabilitation interventions showed mixed levels of effectiveness, and there is insufficient RCT evidence to suggest system-level delivery across General Surgery within standardized protocols. However, given potential benefits and non-inferiority to standard care, they should be considered on a case-by-case basis.

Introduction

Preoperative rehabilitation, or 'prehabilitation', is a modern approach to optimizing patient health before surgery to reduce the risks associated with surgery and improve postoperative outcomes.[1] Although they historically solely focused on improving cardiorespiratory fitness and reducing patient weight, prehabilitation interventions can now span any and all of the biopsychosocial domains of patient health,[2] and have been implemented in various ways by surgical units worldwide. Overall, prehabilitation interventions come with potential benefits of improved patient fitness, reduced anxiety, better outcomes (shorter hospital stays and lower complication rates), and increased

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perioperative patient engagement.[3] However they can also be associated with potential drawbacks such as time commitment, cost, physical limitations, delays for operations particularly for cancer patients, and lack of a conclusive evidence base supporting patient benefit.[3]

Given the large volume and range of operations that occur within the discipline of General Surgery globally, it is a global health priority to improve general surgery patient outcomes.[4,5] For patients undergoing cancer surgery, prehabilitation interventions may align or synergise with neoadjuvant or adjuvant therapy. While existing evidence suggests that most prehabilitation interventions are unlikely to worsen surgical outcomes,[6] effectiveness and benefit is likely to vary significantly depending on patient, surgery, system, and societal factors. To investigate this within the discipline of general surgery, a number of randomized controlled trials (RCTs) have been conducted evaluating prehabilitation interventions prior to many of the common operations. However, this incorporates a large degree of heterogeneity in procedures, pathology, therapies, and patient populations. While broad systematic reviews have been conducted synthesizing data across large portions of General Surgery,[7-17] many of these omit notable general surgery procedures (e.g., breast operations)[18] or patient populations. This is particularly relevant to Australia and New Zealand, where the discipline of General Surgery, as defined by the *Royal Australasian College of Surgeons*, encompasses many of these operations.[18] Accordingly, true translatability across Australian and New Zealand General Surgery and perioperative systems is unknown, as a systematic review synthesizing only RCT evidence has not been conducted across the entirety of General Surgery according to this definition.[7,13,18] Within Australia and New Zealand specifically, many surgeons within the discipline of General Surgery and anaesthetists do not routinely implement prehabilitation interventions in their practice despite the potential benefits, primarily as they perceive the RCT evidence base demonstrating these interventions' effectiveness as currently lacking.[19] Accordingly, an updated systematic review of the RCT evidence on prehabilitation interventions within General Surgery, adherent to the *Royal Australasian College of Surgeons*[18] definition, may be beneficial for General Surgery and perioperative systems in Australia and New Zealand. It is acknowledged that important differences exist across the variety of patient populations covered within this definition,[18] particularly between cancer and non-cancer surgical populations. However, a synthesis of this high quality literature may allow for the formation of clinical protocols that are evidence-based and applicable across the discipline, and may provide supplementary benefit alongside subspecialty or population-specific protocols. To address these gaps in the literature and particularly inform General Surgery and perioperative care systems in Australia and New Zealand, this systematic review of RCTs aimed to evaluate the use of prehabilitation interventions within the discipline of General Surgery, according to the definition from the *Royal Australasian College of Surgeons*.[18]

Methods

The methodology for this systematic review of randomized controlled trials (RCTs) was established within a protocol produced prior to the conduct of the review. This study was prospectively registered with PROSPERO (number CRD42023403289), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020),[20] and Synthesis Without Meta-Analysis (SWiM)[21] reporting guidelines (Supplementary material – appendix).

Search strategy and selection criteria

The population, intervention, comparator group, outcome (PICO) framework was used to develop the research question and inclusion criteria.[22] The population comprised patients undergoing operations within the discipline of General Surgery, as defined by the *Royal Australasian College of Surgeons*.[18] The intervention was any form of prehabilitation. Comparator group depended on the respective trials in question, and comprised either standard care (control) or another form of prehabilitation intervention. The outcome was dependent on the respective trials in question, and included any measure of the prehabilitation intervention's effectiveness. Only RCTs were included. RCTs with less than 10 patients in the intervention arm were excluded. Publications not reporting RCT data, such as cohort studies, editorials, perspectives, letters, or conference abstracts were excluded. For RCTs where multiple publications had arisen presenting results at different points of temporal follow-up, the publication with the longest follow-up period was included.[23,24] PubMed (incorporating MEDLINE) and Ovid Embase were searched from respective database inception to 4 March 2023 for studies of any design and in any setting. The full search strategies can be found in the Supplementary material – appendix. Searches were not limited by language, and no publication restrictions were implemented. During the process of searching, only one full-text could not be obtained.[25]

Data extraction and analysis

Titles and abstracts were independently screened by two reviewers, and data were extracted using a standard extraction form. A web application (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar)[26] was used to facilitate reviewer screening of titles and abstracts. Disagreements were resolved by consensus. Data that were extracted included study design and setting, population characteristics, intervention characteristics, comparator characteristics, outcomes, study follow-up, methodological quality information, and datapoints relevant to the study questions. Data were synthesized in narrative and tabular Meta-analysis was precluded due to heterogeneity in data across the included studies, particularly with regards to prehabilitation interventions, endpoints used to measure effect size, and comparator interventions. To ensure validity of the approach to data extraction, synthesis, and analysis without meta-analysis, the SWiM guidelines were adhered to.[21] Methodological quality of the included RCTs was independently assessed by two reviewers using the Cochrane RoB 2 tool.[27]

Results

Study characteristics

The searches identified a total of 929 records (554 unique reports), from which 104 full-text articles were retrieved, and

36 RCTs were included in the systematic review (Fig. 1). A list of the studies that were excluded at the stage of full-text review, with justification of exclusion for each potentially relevant study, can be found in the Supplementary material – appendix. The characteristics of all included RCTs are presented in Table 1. Publication dates ranged from 2009 to 2022. Regarding the region of the included RCTs, 17 (47.2%) were from Europe, 14 (38.9%) from North America, 5 (13.9%) from Asia-Pacific. A wide range of operations were investigated. Of the 36 included RCTs, 30 (83.3%) specifically investigated cancer patient populations. Regarding sample sizes, the prehabilitation intervention cohorts ranged from 10 to 317, and comparator cohorts ranged from 7 to 351. Primary and secondary outcomes used in the trials varied considerably. Length of follow-up ranged from the index hospital admission up to 2 years after surgery or randomisation. The included RCTs varied widely in the risk of bias upon critical appraisal using the Cochrane RoB 2.0 tool,[27] however most studies were considered to be at low risk of bias (Table 2).

Physical prehabilitation

Of the 36 included RCTs, 31 (86.1%) investigated prehabilitation interventions that aimed to promote physical activity and increased cardiorespiratory fitness before surgery (Table 1). Outcomes used varied widely and included measures of cardio-respiratory and general physical fitness, surgical outcomes, and postoperative complications. Within these 31 RCTs, and in relation to the primary outcome relative to the comparator cohort, these prehabilitation interventions resulted in no statistically significant difference in 16 (51.6%) RCTs,[23,28-41] and statistically significant improvement in 14 (45.2%) RCTs.[42-55] In one (3.2%) RCT,[56] the difference in effect between the intervention group and comparator group was unable to be discerned due to trial failure. In one (3.2%) RCT, the

Fig. 1. Study selection.

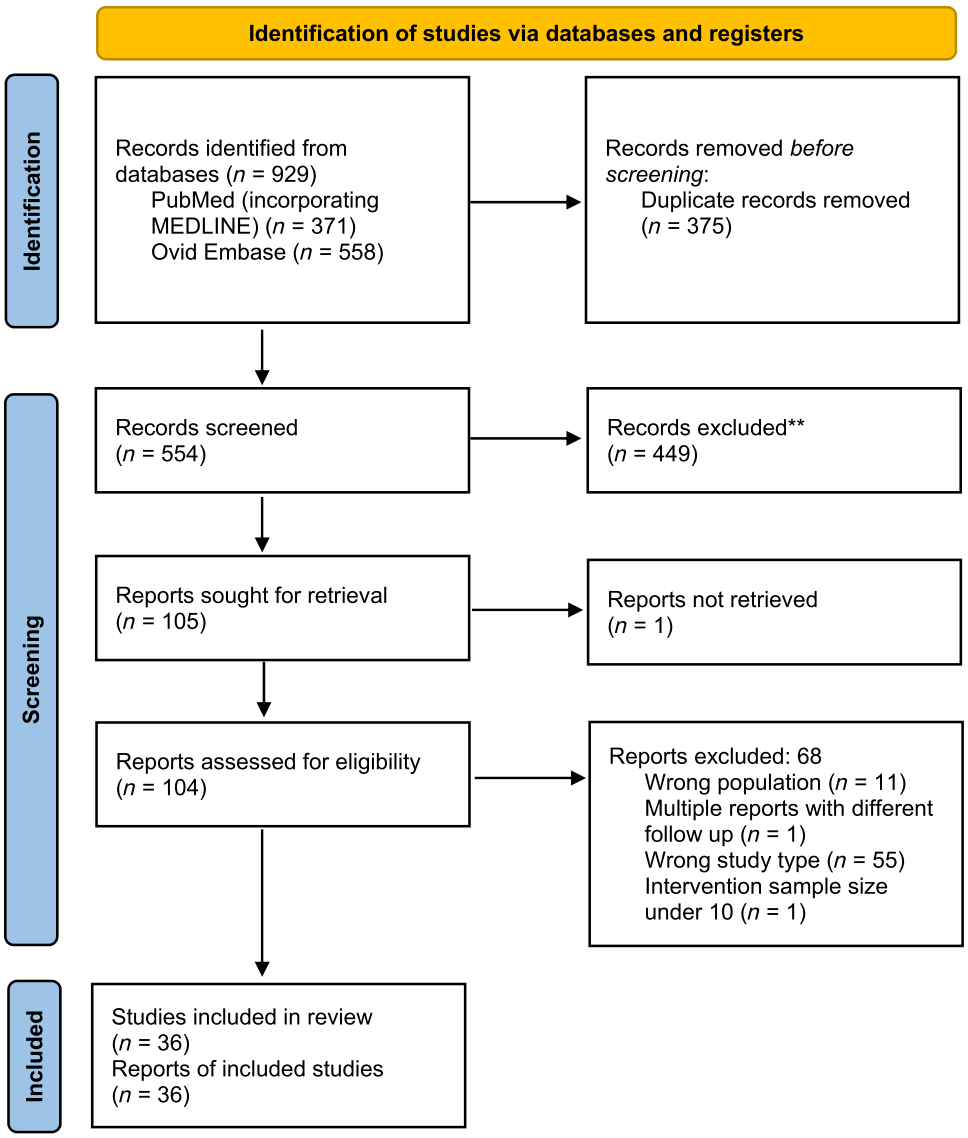

Table 1 Study characteristics

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
Allen[28]	2021	UK	Surgery (83%) Open oesophagectomy (84) Total gastrectomy (11) Resection abandoned (4)	Yes Oesophagogastric cancer	Cardiopulmonary exercise testing (CPET)	26	No prehabilitation	28	Anaerobic threshold	No difference. Better secondary outcomes in intervention group	Peak Oxygen uptake, skeletal mass, QOL, neoadjuvant therapy completion	CPET at baseline, 2 weeks after neoadjuvant therapy, 1 week preoperatively. QOL at restaging laparoscopy, and postoperatively at 2 weeks, 6 weeks and 6 months
Ausania[61]	2019	Spain	Pancreaticoduodenectomy	Yes – Pancreatic or periampullary cancer	Standard care + Nutritional support, control of diabetes and exocrine pancreatic insufficiency, physical and respiratory training	18	Standard care included nutritional counselling, physical activity counselling and smoking cessation advice	22	Postoperative complications	Prehab – 33.3% Control – 54.5	Pancreatic leak, delayed gastric emptying and hospital stay	Until hospital discharge, readmission follow up not specified
Barberan-Garcia[42]	2018	Spain	Oncological surgery (control 75%, intervention 76%) Oesophagectomy (control 8, intervention 13) Pancreaticoduodenectomy (control 2, intervention 5) Total gastrectomy (8; 0) Gastric bypass (5, 10) Total colectomy (2, 5) Rectal resection (11, 16) Major liver resection (2, 3) Pancreas resection (2, 3) Partial gastrectomy (2, 3) -Sleeve gastrectomy (6, 8) Segmental colon resection (41, 45) Minor liver resection (2,0) Right hemicolectomy (prehab 54%, control 41%) Transverse hemicolectomy (3, 4) Left hemicolectomy (7, 10) Sigmoid colectomy (4,0) Abdominal perineal resection (4,0) Low anterior resection (0,3) Subtotal colectomy (0,3) Other (0, 7)	Yes- Abdominal cancer	Endurance exercise training, promotion of physical activity	62	No prehabilitation	63	Postoperative complications	Prehab – 31% Control – 62%	Endurance time during cycle-ergometer exercise	Until hospital discharge
Berkel[43]	2022	Netherlands		Yes and no – Colorectal cancer and premalignancy colorectal lesion (grade I-III dysplasia)	Personalized exercise program	28	No participation in exercise program, nutritional counselling, smoking cessation advice	29	Postoperative complication	Prehab – 42.9% Control – 72.4%)	Changes in preoperative aerobic fitness, length of hospital stay, unplanned readmissions within 30 and 90 days after surgery	30 days post-surgery

Table 1 Continued

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
Bernardi[23]	2022	USA	Ventral hernia repair (control – 74.6%, prehab – 83.1%)	No	Nutritional counselling and exercise programs (aerobic and light aerobic) for up to 6 months	59	Nutritional and exercise counselling	59	Hernia free and complication free patients	At 2 years Prehab – 72.9% Control – 66.1%	–	2 years
Bousquet-Dion[29]	2018	Canada	Colon resection (prehab −68%, control 76%) Rectum resection (prehab-32%, control 24%)	Yes – non-metastatic colorectal cancer	Prehab – weekly supervised exercise session	41	Post-surgical rehab	39	Functional exercise capacity (6-minute walk test distance)	Improvement from baseline (>20 m) – Prehab (54%) Control (38%)	Community Healthy Activity Model Programme for Seniors questionnaire	Pre-operation, at 4 weeks and at 8 weeks
Carli, F[31]	2010	USA	Right hemicolectomy – prehab 29%, control 26% Left hemicolectomy (7, 10) Transverse colectomy (2, 0) Sigmoid colectomy (5, 7) Anterior resection (16, 19) Low anterior resection (9, 17) Abdominoperineal resection (7, 11) Proctocolectomy (9, 15) Small bowel resection (2) Ileorectal anastomosis (3, 4)	Yes – colorectal cancer, also other population (IBD and other)	Bike/strengthening	58	Walk/breathing	54	Mean functional walking capacity (6-minute walk test)	Improvement during Prehab period (Bike/ strengthening 22%, walk/ breathing 47%) Improvement in walking capacity after surgery (11%	Hospital anxiety and depression scale	Prehab period and 10 weeks after surgery
Carli[30]	2020	Canada	Ileocaecal resection (prehab 3.6%, control 1.8%) Right hemicolectomy (41.8, 41.8) Left hemicolectomy (9.1, 14.5) Subtotal colectomy (3.6, 1.8) Anterior/sigmoid resection (10.9, 16.4) Transverse colectomy (1.8, 1.8) Low anterior resection (18.2, 12.7) Abdominoperineal resection (7.3, 7.3) Other bowel surgery (3.6, 1.8)	Yes- colorectal cancer	Exercise, nutritional and psychological intervention before surgery	55	Exercise, nutritional and psychological intervention after surgery	55	Comprehensive complication index	Mean comprehensive index (prehab – 12.7, rehab 15.7)	30 day overall and severe complications, primary and total length of hospital stay, 30 day emergency department visits and hospital readmissions, recovery of walking capacity and patient reported outcome measures	30 days after surgery
Dunne[44]	2015	UK	Major liver resection (prehab 31%, control 26%) Minor liver resection (47, 52) No liver resection (13, 15)	Yes- colorectal liver metastasis	12 interval exercise sessions over 4 weeks	20	No exercise sessions	18	Oxygen uptake at anaerobic threshold (AT)	Mean change in Oxygen uptake in AT at baseline and post (prehab 1, control −0.5)	CPET, QoL	4 week programme

Table 1 Continued

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
Fulop, A[45]	2020	Hungary	Open (prehab 9%, control 10%) Laparoscopic (91, 90)	Yes – colorectal cancer	Trimodal prehab program (physical, emotional, nutritional)	77	No prehab program	72	6 minute walking distance (6MWD) and incentive spirometry and psychological elements (36 item questionnaires, hospital anxiety and depression score)	Percentage improvement 6MWD (prehab 131, control 107), incentive spirometry (113, 100). Mean anxiety scores (4, 5)	Morbidity and mortality	4 week prehab program
Gillis[62]	2015	Canada	Colon resection (prehab 50%, control 50%) Rectal resection (50, 55)	Yes – colorectal cancer	Nutrition counselling with whey protein supplemental	22	Nutrition counselling with non-nutritive placebo	21	Mean improvement in 6MWT	When protein +20.8 m, Placebo +1.2 m	Self-reported physical activity (CHAMPS), change in mental component, change in left and right hand grip strength	4 weeks post surgery
Gillis[46]	2014	Canada	Colon resection (prehab 53% comparator 59%) Rectal (37, 41)	Yes – colorectal cancer	Home based intervention of moderate aerobic and resistance exercises, nutritional counselling with protein supplementation and relaxation exercises at 4 weeks before surgery	38	Home based intervention of moderate aerobic and resistance exercises, nutritional counselling with protein supplementation and relaxation exercises immediately after surgery	39	Improvement in 6MWT (>20 m)	Prehab 53% Comparator 15%	Post surgical complications, hospital stay	8 weeks post surgery
Gloor[32]	2022	Germany	Sigmoid resection (prehab 67%, control 70%) Anterior rectum resection (6, 8) Ileocecal resection (15, 17) Left hemicolectomy 4,0) Abdominoerineal resection (2,0) Other bowel surgery 6.11)	Yes – colorectal cancer also other population (diverticular disease, polyps, IBS, other disease)	Physiotherapeutic prehab	54	Normal physical activity	53	Postoperative complication assessed by comprehensive complication index (CCI)	Mean CCI in Prehab group 18 Mean CCI in control group 15	Complications assessed according to Clavien-Dindo, length of hospital stay, reoperation rate, mortality	30 days post surgery
Heiman[33]	2022	Sweden	Breast conserving surgery (intervention 81%, control 77%) Mastectomy (19%, 23%)	Yes – breast cancer	30-min self-administered physical aerobic activity	139	Normal physical activity	148	QOL using FACT B and EQ VAS	No difference in FACT B scores at 4 weeks and 12 months after surgery odds ratio (intervention 0.975, control 0.817) No difference in EQ VAS (OR 1.163, 0.817)	RAND 36, single item QOL question	4 weeks and 12 months postoperatively
Humeidan[58]	2021	USA	General (intervention 38.4, control 36.5) Orthopaedic (41.6, 52.4) Gynaecologic (3.2, 4.8)	No	Electronic. Tablet based preoperative	125	Nil	126	Incidence of delirium	Control (23%) Intervention (14.4%)	Delirium characteristics – onset, duration,	Day 0 to 7 or discharge

Table 1 Continued

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
			Thoracic (1.6, 3.2) Urology (6.4, 0.8) Plastic (6.4, 2.4) Other – Vascular/ transplant/ otolaryngology (2.4, 0)		cognitive exercise						total delirium positive days	
Kim, D[47]	2009	USA	Major bowel resection	Yes – colorectal cancer also other (IBD, diverticulitis)	Aerobic exercise program	14	Nil	7	Maximal cardiopulmonary variables	% change in baseline and 1 day prior to surgery: VO2 max (prehab 3%, control −3%) Peak power (26, 0) HR peak (−2, −1) O2 pulse peak (2, −1) VE max (8, −4) RER max (1, −2)	Submaximal cardiopulmonary variables	Baseline and 1 day before surgery
Koc[59]	2022	Turkey	Abdominoperineal resection (group A 18%, group B 13.8%, group C 23.6%) Low anterior resection (40, 50.7, 57.9) Subtotal/total colectomy (14, 15.4, 7.9) Total colectomy + IPAA (10.4, 13.8, 7.9) Ileocaecal resection (3.8, 3, 1.3) Colostomy (13, 3, 1.3)	Yes – colorectal cancer also other (polyposis syndrome, IBD, diverticular disease, perianal benign disease)	Marking and preoperative education with introduction of the stoma appliance preoperatively and postoperative education (group C)	Group C (74)	Group A – Stoma marking and post operative education Group B – marking and pre-and postoperative education	Group A (77) Group B (64)	Self-care ability	Group A (31.2%), Group B (78.5), Group C (94.7%)	Anxiety and depression	12 weeks post discharge
Lemanu[34]	2018	New Zealand	Laparoscopic sleeve gastrectomy (100% population)	No	Preoperative daily text messages	44	Nil	44	Adherence to preoperative exercise and exercise activity	Adherence preoperatively (intervention 47.7%, control 54.5%), adherence post surgery (77.3, 56.8), adherence 6/52 post (30.6, 43.6) Mean 6MWD baseline (intervention 462 m, control 496 m), 6MWD post surgery (501.5, 513.6)	Post op complication, length of stay	30 days and 6 weeks post operatively
Ligibel[35]	2019	USA	–	Yes – breast cancer	Exercise program	26	Mind–body group	22	Expression of Ki67, insulin receptor, cleaved caspase-3 levels	Change from mean Ki67 (intervention −1.1, control −0.7), Insulin receptor (0.6, −1.7). Cleaved caspase 3 (−6.6, 6.2)	Tumour immune biomarkers	From enrolment to surgery (mean 29.3 days)

Table 1 Continued

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
Lopez-Rodriguez-Arias[36]	2021	Spain	Right hemicolectomy (intervention 66.7%, control 33.3%) Left hemicolectomy (100%, 0) Sigmoidectomy (80%, 20%) Low anterior resection (40%, 60%)	Yes – colorectal cancer	Home prehabilitation program	10	Enhanced recovery after surgery	10	Changes in lean mass and fat mass	Lean mass (intervention 1.7%, control 7.1%), fat mass (intervention −8.16%, control +8.72%)	Length of stay, post operative complication, anxiety and depression score	45 days and 90 days post surgery
Loughney[48]	2021	UK	Abdominoperineal excision (intervention 24%, control 19%) Anterior resection (47%, 19%) Central pelvic exenteration (0%, 13%) Hartmann's and liver resection (6%, 0%)	Yes – colorectal caner	Exercise program	17	Nil	16	Physical fitness (CEPT)	Mean VO2 at AT at week 0 (intervention 11.6, control 10.8) Mean V0O2 at AT at week 9 (intervention 15, control 11.5)	Effect of exercise prehabilitation on psychological health, effect of neoadjuvant chemoradiotherapy in physical fitness and psychological health	Weeks 0–9
McIsaac[37]	2022	Canada	Colorectal (control 25%, intervention 38.%), hepatobiliary (28.4, 22.3), thoracic (42.1, 35.1), urologic (4.6, 4.3)	Yes – not specified	Home based exercise program	94	Nil	88	6MWT	6MWD follow up (control 286 m, intervention 291 m)	Physical performance, QOL, disability, length of stay, non-home discharge, 30 day readmission	1st postop clinic or 30 days post op follow up
Minnella[50]	2020	Canada	Colorectal surgery Not specified	Yes – non metastatic colorectal cancer	High intensity interval training	21	Moderate intensity continuous training	21	VO2 at AT	At 2 months mean V02 at AT (intervention 2.5, comparator 0.13)	Peak VO2, VE/VCO2 at AT, PAT, peak, 6MWD	Baseline, before surgery, 1 and 2 months post surgery
Minnella[49]	2018	Canada	Oesophagectomy (prehab 75%, control 84%) Partial gastrectomy (17%, control 8%), total gastrectomy (8)	Yes – oesophagogastric cancer	Exercise and nutrition optimisation	26	Nil	25	6MWT	Postoperative 6MWD % change from baseline (intervention 15.4, control −81.8)	Post op complications, in-hospital mortality, length of stay, ED visits, readmission rate	4–8 weeks after surgery
Moug[57]	2019	UK	Anterior resection/ Hartmanns (intervention 59%, control 42%), APR (35, 47), Local excision/TAMIS (0,11), Palliative stoma formation (6,0)	Yes – Rectal cancer	Walking prehabilitiation	24	Nil	24	Median step count per day	Change from baseline Intervention −1105 Control −1853	Weight, BMI, waist circumference, sit-to-stand test, 6MWD, % of week spent active/ sedentary, BDI-II score, Positive/ negative affect score, FACT-C score	Baseline to 12 weeks
Northgraves[56]	2019	UK	Open (control 63.6%, intervention 60%) Laparoscopic (36.6, 40)	Yes- colorectal cancer and also diverticular disease	Exercise based	11	Nil	10	Postop length of stay	Median LOS (intervention 8, control 10)	Complication and physical functioning	3 months after surgery
Onerup[38]	2022	Sweden	Colon resection (control 40%, intervention 45%), Low anterior resection (24, 28). Rectum amputation (19), Missing 13, 13)	Yes – colorectal cancer	Home based exercise	317	Nil	351	Self-assessed physical recovery post op	Intervention 13% Control 15%	Comprehensive complication index, reoperation, readmission	4 weeks post operatively
Peng[51]	2021	China	Hemicolectomy (intervention 65.1%, control 67.3%) Total colectomy (22.9, 21.2)	Yes – colorectal cancer (also includes "non-malignant disease)	Exercise	109	Standardized enhanced recovery after surgery	104	Quality of GI recovery measured with I-FEED scoring	Intervention 78.9%, comparator 64.4%	QOL scores, strength of handgrips, post op complications	30 days post op

Table 1 Continued

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
Rengel[39]	2020	USA	Sigmoid resection (11.9, 11.5) Major noncardiac surgery – not specified further	Not specified	Cognitive and physical exercise program	17	Nil	8	Pattern comparison iADLs, grip strength, Dimensional change card sort, flanker-inhibitory control 2MWT	Graphical representation of data on paper	-	30 days post op
Swaminathan[52]	2020	India	Subtotal gastrectomy (control 65.5%, 62%) Distal gastrectomy (27.6, 27.6) Total gastrectomy (6.9, 10.3)	Yes – Gastric cancer	Incentive spirometry	29	No incentive spirometry	29	Length of hospitalization	Median length Intervention: 11 days Comparator 13 days)	Postop peak expiratory flow rate, incidence of surgical and pulmonary complications	Until hospital discharge
Taha, A[40]	2016	Germany	Rectosigmoidal resection (prehab 73.9%, control 64%) Right hemicolectomy (8, 13) Left hemicolectomy (0,0) Miscellaneous (17.4, 16)	Yes – colorectal cancer	Exercise based program	23	Nil	25	Hospital anxiety and depression scale	Change score: HADS anxiety (prehab −1.7 points, control −0.4 points), HADS depression (prehab 1, control −0.3)	–	30 days post operatively
Valkenet[41]	2018	The Netherlands	Oesophagectomy with gastric tube reconstruction	Yes – oesophageal cancer	Home-based inspiratory muscle training (IMT)	120	Usual care	121	Rate of postoperative pneumonia measured by the revised Uniform Pneumonia Score	Prehab: 39.2% Control: 35.5%	Postoperative complication, prescription of antibiotics for suspected pneumonia, in-hospital mortality, length of hospital stay, mechanical ventilation time, number of reintubations, respiratory muscle function, lung function, physical functioning.	4 weeks postoperatively
Vilsides[60]	2019	USA	Gastrointestinal (prehab 52%, control 28%) Urologic (20, 25) Spine (17, 40) Hepatobiliary (4.3, 10)	Not specified	Home based cognitive program	23	Nil	29	Postoperative delirium incidence	Prehab: 26% Comparator: 17%	Perioperative cognitive function score, length of hospital stay, physical therapy participation rate	Until hospital discharge
Waller[53]	2020	UK	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (Prehab 82%, control 64%) APR (0, 18) Total pelvic clearance (9) Right hemicolectomy + cystectomy (0, 9) Laparotomy + small bowel resection (9, 0)	Yes – colorectal cancer	Home base exercise, nutritional and dietary advice via smartwatch	11	Usual care with smart watch as placebo	11	Pre-operative 6MWT	Improvement in 6MWT Prehab: +85.6 m Comparator: +13.23 m	Change in body weight, hospital anxiety and depression score	Until hospital discharge

Table 1 Continued

First authors	Year	Country	Types of surgery (% of population)	Cancer population (yes / no)	Prehabilitation intervention	Prehabilitation intervention sample size	Comparator intervention	Comparator intervention sample size	Primary outcome	Primary outcome rate in each group	Secondary outcomes	Length of follow-up
Woodfield[54]	2022	New Zealand	Colonic resection (prehab 25%, control 26%) Rectal surgery (11%, 17%) Major oesophageal pancreatic surgery (6, 7) Large ventral hernia (3, 4) Urology (28, 49) Hysterectomy (4, 14) Cancelled *0, 6)	No	High intensity interval training	28	Nil	35	Increase VO2 peak	Mean VO2 increase Prehab: 2.87 Control: 0.15	Post op complications, SF 36 physical score, length of stay	6 weeks and 3 months post discharge
Yamana[55]	2015	Japan	Thoracoscopic thoracotomy (prehab 76.7%, control 70) Open thoracotomy (23.3, 30)	Yes – oesophageal cancer	Respiratory exercises	30	Nil	30	Incidence of Pulmonary complication using Clavien-Dindo classification and Utrecht Pneumonia Scoring system	Results subdivided by CDC classification and UPSS score (table 3 and 4)	–	Until hospital discharge

impact on surgical outcomes was not measured, however feasibility was confirmed.[57]

Psychological prehabilitation

Of the 36 included RCTs, nine (25%) investigated prehabilitation interventions that sought to improve psychological wellbeing preoperatively (Table 1). Of these, six (66.7%) RCTs found a statistically significant improvement in the primary outcome from psychological prehabilitation interventions relative to the comparator cohort. The other three (33.3%) RCTs found no statistically significant difference. Within these nine RCTs, six (66.7%)[30,39,45,46,49,53] were multimodal in that psychological prehabilitation was provided alongside other interventions, while three (33.3%)[58-60] delivered psychological prehabilitation only. Varying levels of effectiveness were seen in both the multimodal and unimodal delivery of psychological prehabilitation.

Nutritional prehabilitation

Of the 36 included RCTs, five (13.9%) investigated prehabilitation interventions that aimed to improve patient nutrition and diet prior to surgery (Table 1). With regards to intervention, all of these RCTs provided the nutritional prehabilitation intervention as part of a multi-modal prehabilitation approach,[23,45,46,61] apart from a study by Gillis *et al.*, who provided nutritional intervention (nutritional counselling and whey protein supplementation) only.[62] This latter study found no statistically significant difference compared to the comparator group.[62] Within the five RCTs, for the primary outcome relative to the comparator cohort, nutritional prehabilitation interventions resulted in no statistically significant difference in three (60%) RCTs,[23,61,62] and a statistically significant improvement in the other two (40%) RCTs.[45,46]

Discussion

This systematic review of RCTs provides a comprehensive and updated synthesis of prehabilitation interventions used across the discipline of General Surgery.[18] Within the included RCTs, prehabilitation interventions displayed mixed levels of effectiveness relative to their comparator cohorts, which is expected given heterogeneity in scope and method of delivery, patient population, and clinical circumstances. This was observed across interventions aiming to improve physical and cardiorespiratory fitness, interventions aiming to optimize psychological wellbeing, and interventions seeking to improve nutrition and diet preoperatively. Further, no significant difference was consistently observed when qualitatively comparing multimodal and unimodal delivery of prehabilitation interventions. For RCTs within the same subdiscipline or population (e.g., colorectal cancer surgery) that showed different levels of effectiveness, these discrepancies appeared to derive from differences in type or delivery of prehabilitation intervention, associated trial or institutional infrastructure and system components, specific endpoints used for measurement, numbers recruited, and length of trial follow-up. There was a paucity of trials conducted within Australia and New Zealand. Acknowledging this regional bias

Table 2 Risk of bias assessment for included studies

First author	Year	Reviewer 1 judgement	Reviewer 2 judgement
Allen[28]	2021	Low	Some concerns
Ausania[61]	2019	Some concerns	Some concerns
Barberan-Garcia[42]	2018	Low	Low
Berkel[43]	2022	Low	Low
Bernardi[23]	2022	Low	Some concerns
Bousquet-Dion[29]	2018	High	Low
Carli[31]	2010	High	Some concerns
Carli[30]	2020	Low	Low
Dunne[44]	2015	Low	Low
Fulop[45]	2020	Low	Low
Gillis[62]	2015	Some concerns	Low
Gillis[46]	2014	Some concerns	Low
Gloor[32]	2022	Low	Some concerns
Heiman[33]	2022	High	Some concerns
Humeidan[58]	2021	Low	Low
Kim,[47]	2009	High	High
Koc[59]	2022	Some concerns	Low
Lemanu[34]	2018	Low	Low
Ligibel[35]	2019	Low	Some concerns
Lopez-Rodriguez-Arias[36]	2021	Low	Low
Loughney[48]	2021	Low	Low
McIsaac[37]	2022	Low	Low
Minnella[50]	2020	Low	Low
Minnella[49]	2018	Low	Low
Moug[57]	2019	Some concerns	Some concerns
Northgraves[56]	2019	Some concerns	Low
Onerup[38]	2022	Some concerns	Low
Peng[51]	2021	Low	Low
Rengel[39]	2020	High	High
Swaminathan[52]	2020	Some concerns	Low
Taha[40]	2016	Low	Low
Valkenet[41]	2018	Low	Low
Vilsides[60]	2019	High	Low
Waller[53]	2020	Low	Low
Woodfield[54]	2022	Some concerns	Low
Yamana[55]	2015	Low	Low

within the literature, this synthesis of the current RCT evidence base suggests that internationally, but particularly in local Australian and New Zealand (as the definition from the *Royal Australasian College of Surgeons* was used for trial inclusion[18]) General Surgery and perioperative care systems, prehabilitation interventions should only be implemented in specific patient populations, as there is unlikely to be significant benefit (particularly when considering associated time and resource investment) from additional supplementary protocols implemented across the discipline of General Surgery.[18] Although within the surgical literature even the results of sub-population meta-analyses are mixed, examples of these specific General Surgery populations where particular benefit could be found include hepatobiliary and gastrointestinal cancer surgery, where prehabilitation likely reduces length of postoperative hospital stay,[63] in particular colorectal cancer surgery where functional capacity and complication rates may be improved,[8] and bariatric surgery where body composition, functional capacity, and quality of life may be improved.[64]

This systematic review adds to an evidence base that has historically found mixed results.[7-17] Past literature in colorectal cancer surgical populations has found that physical prehabilitation interventions are likely to improve functional capacity and reduce complication rates.[12] For major abdominal surgery the optimal protocol for delivery remains unclear, although if implemented effectively could reduce overall and pulmonary postoperative morbidity.[7] When considered across major elective operations, some interventions, particularly physical interventions, can decrease complication rates and length of postoperative hospital stay, however it has been reported that the overall quality of the relevant literature was low.[14] Within consideration of non-physical interventions, psychological prehabilitation is non-inferior and unlikely to harm patients, and may improve postoperative psychological outcomes, pain control, and length of stay.[15] The RCTs included within the present study represented a relatively recent literature, as the oldest RCT was published in 2009[47] and a large proportion of the included RCTs were published after 2019. Many of the interventions used within prehabilitation are intuitive. For example, as major General Surgery involves significant physiological stress it is logical that cardiorespiratory fitness should be optimized preoperatively, and as these procedures frequently involve or impact the gastrointestinal tract it is logical that nutrition should be optimized preoperatively. However, based on the present synthesis of RCT evidence, it cannot be concluded that prehabilitation interventions make sense from a healthcare system perspective when they involve considerable resource or patient investment. Accordingly, where possible, patient education and other low-cost measures should be encouraged and

pursued preoperatively, however lengthy and prescribed programs should only be recommended when clear benefit is expected following multidisciplinary discussion. During the process of perioperative assessment, and particularly preparation for major General Surgery, the endpoints used are crucial. Metrics for assessment should accurately reflect biopsychosocial health, and should be considered by general surgical staff both at baseline, at time of surgery, during postoperative hospital stays, and on post-discharge follow-up. Synthesized measures combining multiple datapoints, such as cardiopulmonary exercise testing, should be used where feasible. Social determinants of health and societal events such as COVID-19 can impact patient adherence to advised prehabilitation interventions, and these factors should be acknowledged.

The main challenges associated with prehabilitation interventions appear to be regarding the feasibility of implementing the associated preoperative programs in a manner that is scalable across the General Surgery population. Given that most included RCTs found differences that were not statistically significant, and many of the trials investigated interventions that required substantial time, resource, or staffing investment, the overall utility of prehabilitation at a system, or standardized-protocol level, is debatable. However, prehabilitation interventions on the whole are likely to be non-inferior to standard care, with potential benefits associated with certain interventions, patient populations, and clinical circumstances. Accordingly, prehabilitation interventions should be considered on a case-by-case basis for General Surgery patients, with patient-centred care and shared decision making the priority.[65] Interventions that are multimodal, and seek to improve patient health in multiple of the domains within a biopsychosocial model of care, may be more useful as they are more holistic in approach. This is intuitive, as the patient experience of undergoing surgery is known to be biopsychosocial in many respects.[2]

Recent technological advances may provide benefit for prehabilitation interventions, and their use should be investigated in future research. For example in a New Zealand population, Lemanu *et al* found that daily text messages improved physical prehabilitation adherence for bariatric surgery patients, but no significant benefit for postoperative outcomes.[34] More advanced technology is emerging, and is largely unexplored as an adjunct for prehabilitation interventions. The most notable example is artificial intelligence, which is already demonstrating potential benefits for surgical systems,[66] in particular those for general surgery.[67-69] For prehabilitation interventions specifically, artificial intelligence could assist with intervention personalisation according to patient characteristics and preferences, enhancement of information provision and experience for potentially improved adherence,[70] predictive metrics to allow for early modulation of interventions when required,[71] and decision aids[72] for both clinicians and patients. In studies that have drawn broad media attention, artificial intelligence chatbots have shown high levels of quality and empathy when providing clinical solutions for patient issues,[73] and these could potentially enhance patient communication approaches within prehabilitation interventions before general surgery.

This study has limitations. Given that the definition of General Surgery varies worldwide, some operations that may be considered to be within the discipline may have been missed given the definition used by the *Royal Australasian College of Surgeons*[18] was followed. Due to significant heterogeneity in study outcomes used, prehabilitation interventions delivered, study populations, and trial and clinical circumstances, meta-analysis was precluded and data synthesis and analysis was limited. Certainly no evidence of harm from prehabilitation interventions was identified and in some of the included studies there was evidence of benefit; however without undertaking statistical analysis of the overall dataset, it is not possible to determine the strength of the evidence for any potential benefits. This has led to a conclusion that routine application of prehabilitation across all General Surgery disciplines, including the associated resource expense, is not justified, when the reality may be different. However, only RCTs were included to ensure that only higher levels of evidence were considered, and upon methodological quality assessment the risk of bias was considered low in the majority of included RCTs. The majority of RCTs were conducted in Europe and North America, likely due to the resource requirements for conduct of such trials, and accordingly translatability to other parts of the world, particularly lower socioeconomic regions, may be limited. Of note, there were few RCTs conducted within Australia and New Zealand.

Conclusions

This systematic review of RCTs provides a comprehensive and updated synthesis of prehabilitation interventions used across the discipline of General Surgery. Prehabilitation interventions showed mixed levels of effectiveness, and there is insufficient evidence to suggest their system-level delivery across General Surgery within standardized protocols. However, given potential benefits and non-inferiority to standard care, they should be considered on a case-by-case basis, particularly when low levels of resource or patient investment are required. There is unlikely to be significant benefit from additional supplementary protocols implemented across the discipline of General Surgery. Future studies should seek to continue evaluate prehabilitation interventions in specific General Surgery patient cohorts, with measures of cost also included in the respective trials. Further, methods of technology integration, such as the use of artificial intelligence algorithms, should be explored when delivering prehabilitation interventions where potential benefit can be obtained.

Author contributions

Joshua G. Kovoor: Conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, final approval of the version to be published. Silas D. Nann: Conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published. Dwarkesh D. Barot: Conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published. Devanshu Garg: Conception and design, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content,

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Conflict of interest

None declared.

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