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Meta-analyses

The impact of prehabilitation on outcomes in frail and high-risk patients undergoing major abdominal surgery: A systematic review and meta-analysis

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SUMMARY

Background & aims: Prehabilitation comprises multidisciplinary preoperative interventions including exercise, nutritional optimisation and psychological preparation aimed at improving surgical outcomes. The aim of this systematic review and meta-analysis was to determine the impact of prehabilitation on postoperative outcomes in frail and high-risk patients undergoing major abdominal surgery.

Methods: Embase, Medline, CINAHAL and Cochrane databases were searched from January 2010 to January 2023 for randomised clinical trials (RCTs) and observational studies evaluating unimodal (exercise) or multimodal prehabilitation programmes. Meta-analysis was limited to length of stay (primary end point), severe postoperative complications (Clavien-Dindo Classification $\geq$ Grade 3) and the 6-minute walk test (6MWT). The analysis was performed using RevMan v5.4 software.

Results: Sixteen studies (6 RCTs, 10 observational) reporting on 3339 patients (1468 prehabilitation group, 1871 control group) were included. The median (interquartile range) age was 74.0 (71.0–78.4) years. Multimodal prehabilitation was applied in fifteen studies and unimodal in one. Meta-analysis of nine studies showed a reduction in hospital length of stay (weighted mean difference −1.07 days, 95 % CI −1.60 to −0.53 days, $P < 0.0001$, $I^2 = 19$ %). Ten studies addressed severe complications and a meta-analysis suggested a decline in occurrence by up to 44 % (odds ratio 0.56, 95 % CI 0.37 to 0.82, $P < 0.004$, $I^2 = 51$ %). Four studies provided data on preoperative 6MWT. The pooled weighted mean difference was 40.1 m (95 % CI 32.7 to 47.6 m, $P < 0.00001$, $I^2 = 24$ %), favouring prehabilitation.

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence intervals; CCI, Comprehensive Complication Index; CINAHL, The Cumulative Index to Nursing and Allied Health Literature; ESPEN, European Society for Clinical Nutrition and Metabolism; ERAS, Enhanced Recovery after Surgery; HADS, Hospital Anxiety and Depression Scale; LOS, length of hospital stay; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-S, Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension; QoL, quality of life; RCT, randomised clinical trial; RevMan, ReviewManager; RR, relative risk; WHO, World Health Organization; WMD, weighted mean difference; 6MWT, 6-min walk test.

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Conclusion: Given the significant impact on shortening length of stay and reducing severe complications, prehabilitation should be encouraged in frail, older and high-risk adult patients undergoing major abdominal surgery.

1. Introduction

Complications occurring after major surgery are associated with long-term declines in survival [1,2], reduced quality of life [3,4], and increased healthcare-related costs [4–6]. Increasing age and the associated decrease in physical fitness are among important risk factors for the development of surgical complications [7]. As medical technology advances, surgical techniques develop, and the population ages, an increasing number of older persons are opting for major elective surgery [8]. Thus, interventions that facilitate safe surgery and improve patient outcomes are highly relevant.

Prehabilitation is one example of an intervention with potential to improve postoperative outcomes by enhancing functional capacity, metabolic flexibility and psychological resilience to improve the patient's tolerance to surgical stress [9,10]. Core components of prehabilitation include supervised or unsupervised exercise, nutritional optimisation, and psychological preparation. Although there is a growing interest in implementing prehabilitation programmes, high-quality evidence of benefit is still lacking [10–13]. For example, the type of exercise, adherence, and possible adverse effects related to the complexity of the exercise programmes vary greatly between studies [10]. In addition, the pre-existing fitness of patients recruited to studies on prehabilitation is variable and the inclusion of physically fit patients can potentially reduce the significance of findings [10].

Preoperative sarcopenia [14,15], malnutrition [7,15,16], reduced physical fitness [3,9,17,18], impaired psychological reserves [3,6,19] and anxiety [3,4] in the preoperative period have been identified as markers of poorer outcomes in surgical patients and are thus of concern for surgeons, anaesthetists and perioperative care physicians. These negative characteristics are typically present in older adults and comprise the *frailty syndrome* (i.e., frailty) [20]. Frailty is characterised by a deterioration of physiological systems that accumulates over time [20]. In 2020 in England, the prevalence of frailty was estimated to be 8.1 % [95 % CI: 7.3 to 8.8 %] among those aged 50 years and older, with the prevalence increasing with age [8]. In addition, the prevalence of pre-frailty and frailty in older patients with cancer increases to more than 50 % [21]. Frailty is also observed in patients under the age of 65 years [22] and negatively impacts the host immune response [23] and tissue healing [24], and is an independent risk factor for postoperative complications [8,21,25,26]. If frailty is present in addition to natural ageing, it is unlikely to result in a return to baseline quality of life after surgery [27].

We hypothesised that prehabilitation would be beneficial for older, frail patients who have reduced physiological reserves. This systematic review and meta-analysis aimed to determine the impact of prehabilitation on postoperative outcomes, including length of hospital stay (LOS), severe complications and quality of life (QoL) in frail and high-risk patients undergoing elective major abdominal surgery.

2. Methods

2.1. Search strategy

MEDLINE, Embase, ClinicalTrials.gov (www.clinicaltrials.gov), CINAHL, Google Scholar, and Cochrane Library databases were searched comprehensively to identify relevant studies published between January 1, 2010 and January 30, 2023 that evaluated the effect of prehabilitation in patients who were frail, older, and undergoing elective abdominal surgery. Due to the relatively recent use of the term prehabilitation in clinical trials, a date restriction was imposed to facilitate comparability of terms among studies. The following search terms were used: (prehabilitation OR perioperative OR presurgery) AND (abdominal surgery OR gastrointestinal surgery). Further information on the search strategy is provided in Supplementary Table 1. Bibliographies of included studies and previous systematic reviews and meta-analyses were reviewed to ensure that relevant papers were included. Study selection, evaluation of eligibility criteria, data extraction, and statistical analyses followed the Cochrane methodology standards [28] and findings are reported in accordance with PRISMA-S (Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension) guidelines [29] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements [30]. All co-authors participated in discussions to refine the search strategies. In accordance with the Cochrane search strategy recommendations and to further reduce the likelihood of missing relevant studies within the population of interest, the terms frailty and old adults were not applied to the search strategy [28]. The initial search was performed in October 31 2022, and a search for additional studies was done in January 2023 (Supplementary Table 1).

2.2. Criteria for considering studies for review

Consideration was given to all studies on patients undergoing major abdominal surgery which consisted of elective gastrointestinal, hepatobiliary, pancreatic and vascular procedures. The intervention of interest was prehabilitation which was defined as a physical (exercise) component of the prehabilitation programme (unimodal prehabilitation), or an exercise component combined with a nutritional and/or psychological support (multimodal prehabilitation). Restrictions on exercise duration, frequency, type, or supervision (supervised or unsupervised programs) were not applied.

2.3. Outcome measures

The primary outcome measure was LOS. Secondary outcomes of interest included severe postoperative complications (Clavien-Dindo Classification $\geq$ Grade 3 [31]), comprehensive complication index (CCI), QoL, quality of recovery, 6-minute walk test (6MWT). CCI combines all complications with their respective severities on a continuous scale from 0 (no burden due to complications) to 100 (death as a result of complications) [32]. Meta-analysis was limited to LOS, postoperative complications and 6MWT.

2.4. Inclusion criteria

Randomised clinical trials (RCTs) and observational studies reporting at least one relevant clinical outcome were included. To be included in this review, the methodological section of a study had to describe its study population as individuals over 60 years of age (frail or not) or persons under 60 who were experiencing frailty. These criteria enabled the inclusion of high-risk patients, This age limit was chosen with respect to the definition of an old person defined by the United Nations [33]. As the definition of frailty varies considerably in the literature, a single score was not selected. Definitions used for frailty are listed in Table 1. The frail patient could have been younger than 60 years of age, as this syndrome has no age restrictions. Thus, our goal was to determine whether prehabilitation is important for high-risk patients, rather than those under the age of 60 years and in good health. The control arm comprised those receiving standard care or rehabilitation. There were no restrictions regarding language of publication.

2.5. Exclusion criteria

Studies which failed to fulfil the inclusion criteria with regards to type of prehabilitation (e.g., providing only nutrition support without exercise regimes) were excluded. Studies that exclusively reported on postoperative rehabilitation programs were excluded. Additionally, studies that failed to report patient data, duplicated studies, those with restricted access to study report or data, review articles, letters to the editor, editorials, case reports, and conference abstracts with no access to the entire study or report were excluded.

2.6. Data extraction, collection and synthesis

The search results from all databases were imported in EndNote 20.5 software (https://endnote.com) and deduplicated using the method described by Bramer et al. [34]. Rayyan software (www.rayyan.ai) was used to ensure a blind and efficient data extraction procedure [35]. The identified studies were screened for relevance independently by 2 reviewers (P.S. and K.F.) according to review eligibility criteria. All discordant studies were adjudicated by a third reviewer (D.N.L.). Data were collected on publication details, study design, number of participants, type of surgery, implementation of Enhanced Recovery After Surgery (ERAS) protocols, participant age, frailty score, nutritional score, details of prehabilitation interventions (modality, duration, frequency, supervision), adverse events, postoperative complications, LOS, 30-day mortality, readmissions, 6MWT, patient reported outcomes and QoL. Risk of bias was assessed for the RCTs included using the Cochrane Collaboration RoB2 tool [28] within the RevMan v5.4 software [36]. Risk of bias for cohort studies was assessed using the Newcastle–Ottawa scale [37].

2.7. Statistical analysis

For the meta-analysis, dichotomous outcome measures were summarised as odds ratios (ORs) or weighted mean differences (WMDs) with 95 % confidence intervals (CI) for continuous variables. The presence of statistical heterogeneity was to some degree expected, given the between-study variability [38] in type of surgery evaluated, number of patients per study, percentage of study population that were malnourished, type of prehabilitation intervention used, duration of intervention and choice of control group. Therefore, quantitative synthesis of the pooled data was performed using RevMan v5.4 software assuming a random-effects meta-analysis [36]. Differences were considered statistically significant at $P < 0.05$. Inconsistency and heterogeneity between studies were estimated using the I^2 statistic with the following interpretation of values as outlined in the Cochrane Handbook [39].

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

Assessment of publication bias was undertaken by judging symmetry of the funnel plot for the primary outcome. Data from RCTs and cohort studies were included separately within each forest plot, with a summative analysis of all the evidence performed in addition.

2.8. Registration of the protocol

The protocol for this systematic review and meta-analysis was registered with the PROSPERO database (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=340986), and the registration number assigned was CRD42022340986.

3. Results

3.1. Inclusion of studies

A total of 13,236 records were identified in the initial search. After screening using the inclusion criteria specified in the PRISMA flow diagram (Fig. 1), 142 full-text articles were evaluated of which 16 studies met the inclusion criteria [4,6,17,18,40–51]. Of these, 6 were RCTs [4,17,18,41,43,45] and 10 were cohort (case control) studies [6,40,42,44,46–51]. Reasons for exclusion of potentially eligible articles are detailed in Supplementary Table 2.

3.2. Study and patient characteristics

The 16 studies included evaluated a total of 3339 patients (prehabilitation group: 1468; control group: 1871) [4,6,17,18,40–51]. Table 1 provides an overview of study and patient characteristics. The included clinical trials were published between 2015 and 2022. Ten studies included patients undergoing surgery for colorectal cancer [6,18,40–46,49]. Of the remaining studies, two investigated prehabilitation in patients undergoing major gastrointestinal surgery [4,17], one combined patients undergoing surgery for oesophageal, gastric and pancreatic cancer [47], one included patients undergoing surgery for colorectal, hepatobiliary and pancreatic cancer [50], one consisted of hepatobiliary and pancreatic surgery [48] and one was performed in patients requiring surgery for gastric cancer [51]. In 11 studies, patients underwent either laparoscopic or open surgery [4,6,17,18,40–42,44–46,49]; two studies were limited to open surgery [48] while three studies did not specify the operative technique [43,47,50]. In eight studies [18,41,42,45–47,49,50], a proportion of the patients received neoadjuvant therapy; in one study [48], only patients without neoadjuvant therapy were included; in seven studies [4,6,17,40,43,44,51] it was not stated whether patients received neoadjuvant or adjuvant therapy. An age limit of 65 years and older was applied in six studies [41,43,44,46,50,51], in another five studies patients were 70 years and older [4,6,17,42,45], in one study the limit was 60 years and older [18] and in one study patients were 75 years and older [49]. Five frailty scores were used among studies: the Fried Frailty Index was used in two [41,44], the Duke Activity Status Index in two [4,17], the Clinical Frailty Score in two [6,51], a modified Frailty Index in one [47] and the Edmonton frail scale in one [50]. In six studies [18,40,42,45,46,48], a mix of different factors [American Society of Anesthesiologists (ASA) score III/IV, body mass index, serum albumin concentration, Veterans Specific Activity Questionnaire, World Health Organization (WHO) performance status, Charlson Comorbidity Index] that were thought to be important to the patient's physical condition and indicative of frailty was used. Two studies were included in the

Table 1
Patient demographics in the studies included.

Study, year	Country	Study methodology	Sample size	Type of surgery	Laparoscopic (%)	Neoadjuvant therapy (%)	Age in years (median (IQR) or mean ± SD	Male sex (%)	Nutritional status (median (IQR) or mean ± SD	Definition of frailty
Barberan-Garcia et al., 2018 [17]	Spain	RCT, single centre	Total: 125 I: 62 C: 63	Major gastrointestinal surgery	I: 79 C: 89	Not stated	Age >70 y I: 71 (10) C: 71 (11)	I: 68 C: 80	BMI I: 21 (7) C: 22 (8)	Duke activity status index score ≤46
Barberan-Garcia et al., 2019 [4]	Spain	RCT, single centre, reanalysis of new data	Total: 125 I: 62 C: 63	Major gastrointestinal surgery	I: 79 C: 89	Not stated	Age >70 y I: 71 (10) C: 71 (11)	I: 68 C: 80	BMI I: 21 (7) C: 22 (8)	Duke activity status index score ≤46
Berkel et al., 2021 [18]	Netherlands	RCT, two centres	Total: 57 I: 28 C: 29	Colorectal cancer surgery	I: 82 C: 72	I: 2.8 C: 2.9	age >60 y I: 74 (7) C: 73 (6)	I: 57 C: 48	BMI I: 29.8 (4.1) C: 30.5 (4.9)	A metabolic equivalent of task (MET) score ≤7 on the Veterans–Specific Activity Questionnaire (VSAQ), for definite inclusion, patients also had to have a low preoperative aerobic fitness (high risk for postoperative complications) at the baseline CPET, defined as a VO2 at the VAT <11 mL/kg/min
Bojesen et al., 2022 [40]	Denmark	Observational	Total: 839 I: 364 C: 475	Colorectal cancer surgery	I: 96 C: 91	Not stated	I: 70 (9.4) C: 69 (10)	I: 56 C: 53	Not stated	The screening tool: timed up and go, weight loss, BMI, albumin, ASA classification, and WHO performance status
Carli et al., 2020 [41]	Canada	RCT, 2 centres	Total: 110 I: 55 C: 55	Colorectal cancer surgery	I: 76.4 C: 81.2	I: 12.7 C: 11.1	Age >65 y I: 78 (72–82) C: 82 (75–84)	I: 52.7 C: 41.8	BMI I: 24.9 (23.0–30.1) C: 26.4 (23.8–30.6)	Fried frailty index (1 indicates no frailty; 2–3, intermediate frailty; and 4–5, frailty)
Chen et al., 2017 [43]	Canada	RCT, reanalysis of new data, single centre	Total: 116 I: 57 C: 59	Colorectal cancer surgery	Not stated	Not stated	Age >65 y I: 67.9 (1.5) C: 67.3 (1.2)	I: 63 C: 63	Albumin (g/L) I: 40.0 (0.8) C: 38.8 (0.5)	Not stated
Chia et al., 2016 [44]	Singapore	Observational	Total: 117 I: 57 C: 60	Colorectal surgery	I: 24.6 C: 16.7	Not stated	Age >65 y I: 79 (65–93) C: 80.5 (75–97)	Not stated	Not stated	Fried frailty index (1 indicates no frailty; 2–3, intermediate frailty; and 4–5, frailty), the weighted Charlson comorbidity index score (WCIS) and the patient's ambulatory status
de Klerk et al., 2021 [46]	Netherlands	Observational	Total: 351 I: 76 C: 275	Colorectal cancer surgery	I: 1 C: 2	I: 9 C: 13	Age ≥65 y I: 75.01 (9.2) C: 73.97 (8)	I: 51 C: 52	BMI I: 26.2 (5.4) C: 26.5 (6.2)	High-risk patients defined as ASA 3 or ≥65 years
Karlsson et al., 2019 [45]	Sweden	RCT, single centre	Total: 21 I: 10 C: 11	Colorectal cancer surgery	I: 70 C: 73	I: 10 C: 20	Age ≥70 y I: 83.5 (76–85) C: 74 (73–76)	I: 40 C: 36	Albumin (g/L) I: 36 (34–38) C: 35 (32–36)	Without a frailty score, the physical activity scale for elderly was used to report level of preoperative physical activity
Koh et al., 2022 [6]	Singapore	Observational	Total: 81 I: 58 C: 23	Colorectal cancer surgery	I: 62.1 C: 30.4	Not stated	Age ≥70 y I: 78.5 (70–93) C: 77 (70–90)	I: 56.9 C: 52.2	Albumin (g/L) I: 40 (25–51) C: 39 (18–46)	Clinical frailty scale
Mazzola et al., 2017 [47]	Italy	Observational	Total: 76 I: 41 C: 35	Oesophageal, gastric and pancreatic cancer surgery	Not stated	I: 27 C: 14	Age ≥18 y I: 75 (44–90) C: 75 (59–91)	I: 66 C: 66	Not stated	A modified frailty index (mFI), patients with a score 2 were considered frail
Nakajima et al., 2019 [48]	Japan	Observational	Total: 152 I: 76 C: 76	Hepato-pancreato-biliary surgery	I: 0 C: 0	I: 0 C: 0	I: 69 (65–76) C: 75 (60–75)	I: 67 C: 70	BMI I: 22.2 (20.4–23.7) C: 21.4 (19.6–23.7)	Charlson comorbidity index + age
Souwer et al., 2018 [49]	Netherlands	Observational	Total: 224 I: 86 C: 138	Colorectal cancer surgery	I: 83 C: 77.5	I: 18.8 C: 17	Age ≥75 y I: 80.6 (6.1) C: 80.5 (6.2)	I: 51.5 C: 49	BMI I: 26.0 (3.8) C: 26.1 (4.9)	Not stated

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Pang et al., 2021 [50]	Singapore	Observational	Total: 591 I: 335 C: 256	Colorectal, hepatobiliary and pancreatic surgery	Not stated	I: 21.7 C: 12.6	Age ≥65 y I: 72.9 (5.6) C: 73.5 (6.1)	I: 59.4 C: 57.0	BMI I: 23.9 (4.7) C: 23.6 (4.1)	Edmonton frail scale
van der Hulst et al., 2021 [42]	Netherlands	Observational	Total: 296 I: 86 C: 210	Colorectal cancer surgery	I: 96.3 C: 89.4	I: 19.3 C: 14.3	Age >70 y I: 80 (76–83) C: 74 (72–78)	I: 53.2 C: 58.6	BMI I: 26.6(23.6–29.4) C: 26.0 (23.6–28.7)	Walking-aid, 2 comorbidities and ASA score III, 2 comorbidities and walking-aid, ASA score III and walking-aid 2 comorbidities, walking-aid and ASA score III, clinical impression
Wada et al., 2022 [51]	Japan	Observational	Total: 58 I: 15 C: 43	Gastric cancer surgery	I: 0 C: 0	Not stated	age ≥65 y I: 74.9 (2.5) C: 70.7 (1.7)	I: 66.7 C: 33.3	BMI I: 18.7 (0.5) C: 19.8 (0.3)	Clinical frailty score, frailty was defined as CFS >4 (apparently vulnerable)

ASA – American Society of Anesthesiologists; BMI – body mass index (kg/m^2); C – control group; I – intervention group (prehabilitation); RCT – randomised clinical trial; WHO – World Health Organization.

analysis solely on the basis of meeting the criteria for old age, without providing a delineation of frailty [43,49] (Table 1).

3.3. Characteristics of the prehabilitation programmes

In 15 studies, prehabilitation was multimodal, with five studies investigating all three modalities (exercise intervention, nutritional and psychological support) [4,17,41,43,50] and 10 studies using two modalities (exercise intervention and nutritional support) [6,40,42,44–49,51]. One study used a unimodal (exercise) intervention [18]. Eight studies used a prehabilitation programme that lasted a minimum of 4 weeks [4,17,40–43,46,49], two studies evaluated a minimum prehabilitation length of 3 weeks [6,18], two studies had a minimum length of 2 weeks [44,45] and the length of intervention was not specified in three studies [47,48,50]. In the majority of studies, the exercise setting consisted of a combination of supervised and home-based exercises [4,17,41,42,44–46,49], in three studies it was supervised only [6,18,40], in two studies home-based only [47,51] and in one study the first exercise session was supervised and then continued as home-based [48]. The duration and frequency of supervised and home based exercise sessions varied and included 40–60 minutes three times a week [18,43,46], 60 minute sessions 2–3 times a week [45], 50 minute sessions 1–3 times a week [4,17], 30–45 minutes twice a week [44,49] and 60 minutes once a week [41]. Two studies did not specify the duration and frequency of exercise sessions [6,40]. Home-based exercise occurred for 60 minutes daily [51] or for 30 minutes 3 thrice a week [47]. Table 2 summarises characteristics of the interventions. In the majority of studies, a combination of aerobic exercise (i.e., a cycle ergometer) and strength exercise were used [18,41,43,45,46,48]. Strengthening techniques, followed by stretching were also utilised [41]. For at-home exercises, walking [47,51] or a series of physiotherapist-prescribed exercises were most recommended [43]. Table 3 summarises details of prehabilitation interventions.

3.4. Summary of the review and meta-analysis results

Table 4 summarises the results of the primary and secondary outcomes of the studies included in the systematic review and meta-analysis.

3.4.1. Primary outcome: length of stay

Nine studies provided complete data on LOS [6,17,18,41,44–47,50]. The pooled WMD was −1.07 (95 % CI −1.60 to −0.53, $P < 0.0001$, $I^2 = 19$ %; Fig. 2a). Two studies reported data on postoperative LOS [48,51]. Nakajima et al. provided data on the median (IQR) postoperative LOS, which were considerably shorter in the prehabilitation group compared with the control group (median, 23 *vs.* 30 days; $P = 0.045$) [48]. In the cohort study by Wada et al., the mean postoperative LOS for the prehabilitation group was 13.0 ± 1 days compared with 15.9 ± 0.7 days for the control group ($P = 0.03$) [51]. Souwer et al. reported a reduction in extended LOS longer than 14 days from 27 % in 2010–2011 to 13 % in 2012–2013 and 6 % in 2014–2015 (OR 0.1, 95 % CI 0.01 to 0.97, $P = 0.047$ and OR 0.2, 95 % CI 0.1 to 0.5, $P = 0.001$), respectively in their cohort study [49]. In another cohort study Bojesen et al., showed that the odds ratio (95 % CI) for a 10-day or longer hospital stay was 0.61 (0.38 to 1.00) in the prehabilitation group ($n = 839$) and 1.53 (0.99 to 2.37) in the control group [40].

3.4.2. Secondary outcomes

The secondary outcomes of clinical significance consistently reported in the included studies were severe complications, CCI, and 6MWT. However, the timing when the impact of

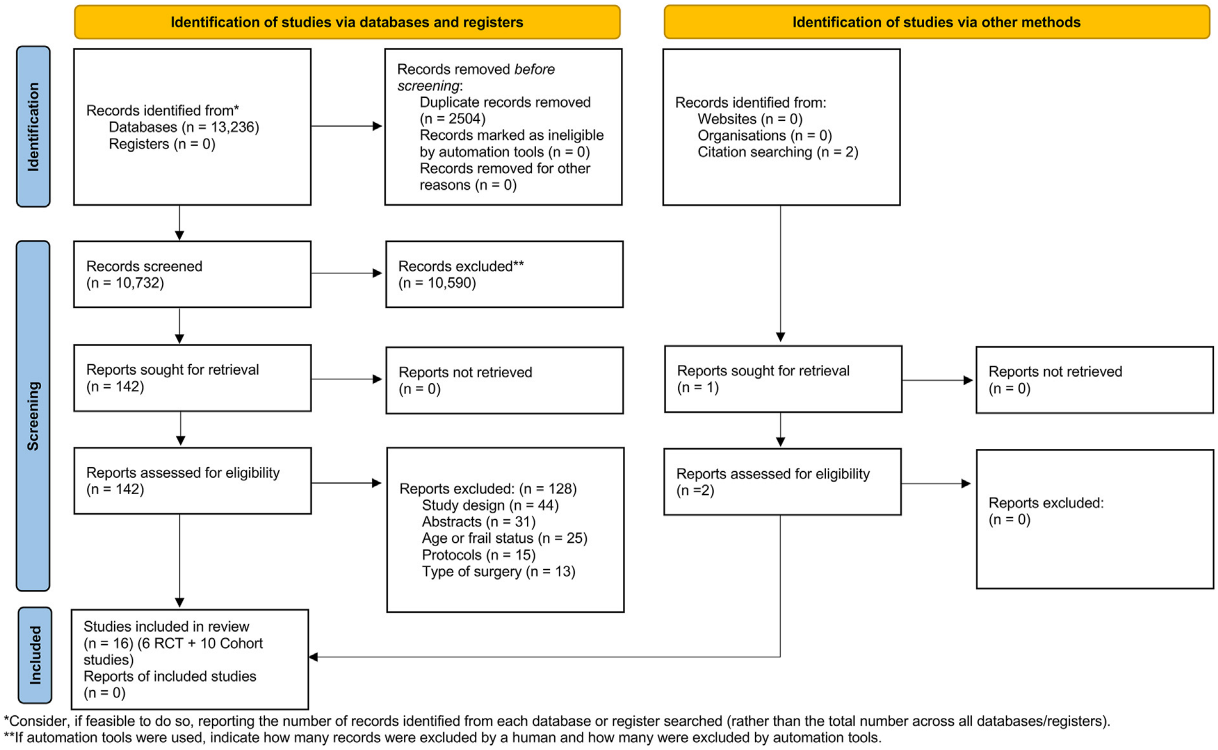

Fig. 1. PRISMA diagram.

prehabilitation on 6MWT was measured varied highly, either preoperatively or at different times after surgery. The functional, cost-effectiveness, psychological and nutritional variables reported by some studies were not investigated consistently, nor were they reported in a manner that allowed for accurate pooling of their results.

3.4.3. Secondary outcomes: severe complications

Eleven studies provided relevant data for a meta-analysis of serious complications classified as Clavien-Dindo ≥ Grade 3. Figure 2b shows the incidence rates of severe complications in the treated (prehabilitation) versus untreated (control) groups. The event rate of this outcome was 11.8 % (129/1093) patients in the prehabilitation group compared with 18.1 % (242/1338) patients in the control group in the cohort subgroup. In the RCT subgroup 11.8 % (11/93) patients in the prehabilitation group compared with 15.8 % (15/95) patients in the control group had severe complications. Overall (cohort and RCT) 11.8 % (140/1186) patients in the prehabilitation group and 17.9 % (257/1433) patients the control group had severe complications. The pooled OR for severe complications after prehabilitation was 0.56 (95 % CI 0.37 to 0.82, $P < 0.004$, $I^2 = 51$ %).

3.4.4. Secondary outcomes: comprehensive complication index

Four studies provided data on CCI. Carli and co-investigators, demonstrated that there was no between group difference in the CCI (adjusted mean difference, 3.2; 95 % CI, 11.8 to 5.3; $P = 0.45$) [41] and similar results were reported in the clinical trials by Pang et al. [50] and Berkel et al. [18] (12.2 vs. 10.1, $P = 0.156$ and 17.3 vs. 18.4, $P = 0.24$ respectively). Other authors have shown that the implementation of a prehabilitation programme resulted in a significant decrease in CCI in the prehabilitation group ($P = 0.01$) compared with the control group ($P = 0.59$) [40].

3.4.5. Secondary outcomes: 6-minute walk test

Four studies provided data on preoperative 6MWT [6,17,41,43]. The pooled WMD was 40.18 m (95 % CI 32.75–47.60 m, $P < 0.00001$, $I^2 = 24$ %; Fig. 2c). In addition, in the study by de Klerk et al., 53 patients showed a median improvement in 6MWT of 36 m (IQR 19–59), (17 %; IQR 4–13) before surgery [46].

3.4.6. Secondary outcomes: quality of life

Three RTCs [4,17,41] and 1 observational study [6] addressed quality of life domains. Preoperative and postoperative patient-reported outcome measures revealed no differences between the prehabilitation and control groups (rehabilitation) in self-reported generic health status (36-Item Short Form Survey), anxiety and depression (Hospital Anxiety and Depression Scale), or energy expenditure (Community Healthy Activities Model Program for Seniors questionnaire) [41]. At prehabilitation programme discharge (presurgery), neither quality of life nor psychological status improved in the prehabilitation group [17]. In comparison, 30 days after surgery, the prehabilitation group in the study by Barberan-Garcia et al. showed lower anxiety and depression levels (HADS score) compared with the control group (9 vs. 6, $P = 0.008$) [6]. In addition, follow-up assessments using the EuroQol-5 Dimension Health Questionnaire (EQ5D) at each evaluation interval (1, 3, 6 months) revealed an increasing trend from 0.70 (range: 0.30–1.00) to 0.80 (range: 0.50–1.00, $P = 0.001$) six months after surgery.

3.5. Heterogeneity and publication bias

Statistical heterogeneity in this meta-analysis was relatively low to moderate, ranging from 19 % to 51 % (Fig. 2a–c). The possibility of publication bias was assessed in the funnel plot for the primary outcome of LOS, and this was found to show a minor degree of asymmetry, suggesting low risk of publication bias. Due to the

Table 2
Characteristics of prehabilitation programmes and control group.

Study, year	Prehabilitation modality	E	N	P	Exercise setting	Prehabilitation duration	Exercise frequency	Prehabilitation adherence or compliance with sessions (mean)	Reasons for non-adherence	Adverse events	ERAS
Barberan-Garcia et al., 2018 [17]	Multimodal	+	+	+	Supervised and home-based	≥4 weeks	1 to 3 sessions (47 min each)	Not stated	19 discontinued the study • 4 Incapacity to perform the exercise testing • 4 Decided to abandon the study • 11 Change of surgical plan	No adverse events	Yes
Barberan-Garcia et al., 2019 [4]	Multimodal	+	+	+	Supervised and home-based	≥4 weeks	1 to 3 sessions (47 min each)	Not stated	19 discontinued the study • 4 Incapacity to perform the exercise testing • 4 Decided to abandon the study • 11 Change of surgical plan	No adverse events	Yes
Berkel et al., 2021 [18]	Monomodal	+	−	−	Supervised only	3 weeks	3 sessions (60 min each)	90 % (8.1 (SD 2.4) of the 9 supervised exercise training sessions	1 patient felt overwhelmed by all appointments	No adverse events	Yes
Bojesen et al., 2022 [40]	Multimodal	+	+	−	Supervised only	≥4 weeks	Not stated	Not recorded	Not stated	Not stated	Yes
Carli et al., 2020 [41]	Multimodal	+	+	+	Supervised and home-based	4 weeks	1 session (60 min)	68 % (38 %) in the Prehab group and 14 % (27 %) in the Rehab group	Not stated	No adverse events	Yes
Chen et al., 2017 [43]	Multimodal	+	+	+	Supervised first session than home-based	4 weeks	3 sessions (40 min each)	Not stated	Not stated	Not stated	Not stated
Chia et al., 2016 [44]	Multimodal	+	+	−	Supervised or home-based (according to the patient's preferences)	2 weeks	2 sessions	Compliance goals for prehabilitation in 80 % of patients	Not stated	Not stated	Yes
de Klerk et al., 2021 [46]	Multimodal	+	+	−	Supervised and home-based	≥4 weeks	3 sessions	90 % (76 of 84 patients)	Six patients discontinued the prehabilitation program: two for logistical reasons, two for imminent tumour obstructions, one for physical discomfort after a fall (not related to the program), and one patient for being physically too frail and there was decided not to perform surgery.	3 serious adverse events: one hospital admission due to anaemia requiring suppletion, a collapse during training after which the cardiologist was consulted, and renal insufficiency for which the protein intake had to be stopped.	Yes
Karlsson et al., 2019 [45]	Multimodal	+	+	−	Supervised and home-based	≥2 weeks	2 to 3 sessions (60 min each)	97 %	1 session missed due to the physiotherapist being unable to conduct the last session, and one due to medical reasons resulting in rescheduling surgery	One patient reported knee joint pain	Yes
Koh et al., 2022 [6]	Multimodal	+	+	−	Supervised only	3 weeks	Not stated	Not stated	Not stated	Not stated	Yes
Mazzola et al., 2017 [47]	Multimodal	+	+	−	Home-based only	Weeks (not specified)	3 sessions (30 min each)	Not stated	Not stated	Not stated	Not stated

(*continued on next page*)

Table 2 (*continued*)

Study, year	Prehabilitation modality	E	N	P	Exercise setting	Prehabilitation duration	Exercise frequency	Prehabilitation adherence or compliance with sessions (mean)	Reasons for non-adherence	Adverse events	ERAS
Nakajima et al., 2019 [48]	Multimodal	+	+	−	Supervised first session than home-based	Weeks (not specified)	3 sessions (60 min each)	Not stated	Not stated	Not stated	Not stated
Souwer et al., 2018 [49]	Multimodal	+	+	−	Supervised and home-based	4–6 weeks	2 sessions (30–45 min each)	85 %	Not stated	Not stated	Yes
Pang et al., 2021 [50]	Multimodal	+	+	+	Supervised and home-based	Weeks (not fixed)	Not stated	Not stated	Not stated	Not stated	Yes
van der Hulst et al., 2021 [42]	Multimodal	+	+	−	Supervised and home-based	≥4 weeks	2 sessions (30–45 min each)	Compliance with programme 69,4 %, non-compliance patients were excluded from the final analysis	Mainly due to a shortened surgical waiting time, no further details.	Not stated	Not stated
Wada et al., 2022 [51]	Multimodal	+	+	−	Home-based only	1–3 weeks	Daily (60 min)	Not stated	Not stated	No adverse events	Yes

E – exercise intervention; N – nutritional support; P – psychology support; ERAS – enhanced recovery after surgery.

nature of prehabilitation and the type of interventions, no study was able to blind participants or care providers. The risks of bias for the RCTs and cohort studies included are summarised in Fig. 3 and Table 5 respectively.

4. Discussion

4.1. What our study found

This meta-analysis demonstrated that prehabilitation was associated with a 44 % lower risk of developing severe complications (Clavien-Dindo classification ≥ Grade 3) following major abdominal surgery. Additionally, the prehabilitation group also experienced a 1-day reduction in LOS, which may be related to the decrease in severe complications. Individual studies did not demonstrate a significant positive effect of prehabilitation on complications determined by the CCI. Compared with the control group, the prehabilitation group demonstrated a 40 m improvement in 6MWT before surgery. Studies included patients undergoing various abdominal surgical procedures, each with unique risks of complications and morbidity. Patients were also at higher risk of developing complications based on their age or a well-defined frailty score. Incorporating a variety of abdominal surgical procedures, the majority of which were performed on patients with cancer, increases the likelihood that the results can be generalisable in this population.

4.2. Prehabilitation programme details

Fifteen out of the sixteen prehabilitation programmes were multimodal, included supervised or unsupervised exercise sessions, and had an average duration of two to four weeks. The optimal prehabilitation regimen for this population is difficult to determine due to variation in the type of interventions, frequency, intensity and duration of individual exercises used in published studies. A lower intensity prehabilitation programme may not be sufficient to optimally prepare patients for surgery [10]. It is also possible that after a certain level of intensity, the exercises may no longer be effective or, on the contrary, detrimental to the entire body. The high degree of heterogeneity in both exercise intensity and study results supports the need for further prospective, well-designed studies. The most frequently used exercise in the studies in included our review consisted of a combination of moderate-to-high-intensity aerobic and anaerobic exercise for up to 60 minutes 2–3 times per week for at least 3 weeks (Table 3), with regard to the minimum adverse event thus, this may be the optimal exercise strategy for a high-risk population.

The nutritional component of prehabilitation was guided by a registered dietitian in most studies. The primary focus of nutritional support was adequate protein intake (1.2–1.9 g/kg body weight), which was in some cases supplemented by a dose of protein (e.g., 0.4 g/kg) after exercise. Oral nutritional support, occasionally fortified with immunonutrition [47] or leucine-rich essential amino acid supplements [48], were also advised in some programmes. A trained psychologist or trained nurse was responsible for the psychological preparation, during which states of anxiety and depression were typically discussed, as well as counselling regarding the cessation of smoking and consuming alcohol.

4.3. What is available in the literature

In older patients, preoperative physical condition is a significant determinant of postoperative recovery [15,52]. Low muscle mass and low functional capacity reduce the capacity to overcome stress during and after open surgery, are both associated with

Table 3
Details of prehabilitation interventions.

Study, year	Exercise intervention	Nutritional support	Psychological support and/or smoking cessation	Control group
Barberan-Garcia et al., 2018 [17]	The unsupervised program focused on increasing patient's steps per day, measured by a pedometer and/or optimization of walking intensity, home-based functional exercises (sit-to-stand exercise, stairs climbing, elastic bands, indoor walking, among others) to decrease sedentary behaviour at home, the supervised program consisted of a high-intensity endurance training performed on the cycle-ergometer stationary bicycle for 47 min	In those at high-risk of malnutrition (Malnutrition Universal Screening Tool) nutritional intervention was done by a registered dietician.	Interview to reinforce patients' motivation and to raise the compromise with the behaviour change regarding the program objectives. Provided smoking cessation advice.	Physical activity recommendation, nutritional counselling, and advice on smoking cessation and reduction of alcohol intake.
Barberan-Garcia et al., 2019 [4]	The unsupervised program focused on increasing patient's steps per day, measured by a pedometer and/or optimization of walking intensity, home-based functional exercises (sit-to-stand exercise, stairs climbing, elastic bands, indoor walking, among others) to decrease sedentary behaviour at home, the supervised program consisted of a high-intensity endurance training performed on the cycle-ergometer stationary bicycle for 47 min.	In those at high-risk of malnutrition (Malnutrition Universal Screening Tool) nutritional intervention was done by a registered dietician.	Interview to reinforce patients' motivation and to raise the compromise with the behaviour change regarding the program objectives. Provided smoking cessation advice.	Physical activity recommendation, nutritional counselling, and advice on smoking cessation and reduction of alcohol intake.
Berkel et al., 2021 [18]	Moderate-to-high intensity interval training on a cycle ergometer (TechnoGym, Bike Med, Gambettola, Italy) to improve aerobic fitness (40 min), and resistance training to improve peripheral muscle strength (20 min)	No intervention	No intervention.	Nutritional counselling and advice on smoking cessation.
Bojesen et al., 2022 [40]	Training was performed by referral to a physiotherapist in the patient's respective municipality. No further information's.	Performed by a dietician with a specialty in colorectal cancer in one session approximately 1 h in length. The current intake was estimated by a general diet history and a 24-h recall. Total energy requirements were estimated by the Harris–Benedict equation with an added factor of 1.3–1.5, depending on daily activities. Total protein consumption was aimed at greater than or equal to 1.5 g protein/kg bodyweight. Further, three to four protein drinks (Fresubin, Fresenius Kabi®) daily.	No intervention.	No intervention.
Carli et al., 2020 [41]	Moderate aerobic exercise for 30 min, resistance exercises using an elastic band for 25 min, stretching for 5 min, home-based program of aerobic activities (walk daily for a total of 30 min as moderate-intensity aerobic activity) and resistance training (elastic band routine 3 times per week).	Target protein intake 1.5 g/kg of body weight (or adjusted body weight in obese patients), if needed whey protein supplementation (Immunocal; Immunotec, Inc)	Assessment by a psychology trained nurse, potential causes of perioperative fatigue, anxiety, and depression were discussed, counselling regarding smoking and alcohol cessation, the use of nicotine replacement therapy.	The identical multimodal program was prescribed for patients in the rehabilitation group; the interventions started only after postoperative discharge from the hospital (4 weeks).
Chen et al., 2017 [43]	50 min of home-based, unsupervised exercise for at least 3 days per week (walking, jogging, swimming, or cycling at patient discretion), 20 min of aerobic exercise followed by 20 min of resistance exercise 3 times per week.	Whey protein isolate supplementation (Immunotec Inc., Vaudreuil, QC) to reach a daily intake of up to 1.2 g of protein per kilogram of body weight, as per the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines for surgical patients.	A trained psychologist provided patients with relaxation and breathing exercises to reduce anxiety. Patients practiced with the psychologist during the initial visit, after which they were provided with an instructional compact disk for performing these exercises at home.	An intervention program similar, but only to commenced after surgery as rehabilitation.
Chia et al., 2016 [44]	Prehabilitation in the outpatient setting either at home or in the day rehabilitation centre, education and ensuring compliance, cardiovascular strengthening, mobilizing, muscle strengthening, no further details.	Dietitian, attention to nutrition, no further details.	No intervention.	No intervention.

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Table 3 (*continued*)

Study, year	Exercise intervention	Nutritional support	Psychological support and/or smoking cessation	Control group
de Klerk et al., 2021 [46]	Two components: high-intensity training (three times per week supervised by a physiotherapist at the hospital) and low-intensity training (four times per week as independent home endurance training).	Tailored nutritional advice from a dietician to meet individual energy and protein needs, where the goal was to achieve a total protein intake of 1.9 g per kilogram of lean body mass per day. In addition, patients were advised to use 0.4 g protein per kg within 1 h of the high-intensity training and daily at bedtime to support muscle synthesis.	Help with smoking cessation at the outpatient clinic was offered.	No intervention.
Karlsson et al., 2019 [45]	Home supervised sessions included three blocks. Block I consisted of inspiratory muscle training, block II consisted of high-intensity functional strength exercises, block III consisted of endurance training	Dietician was initiated if a risk for malnutrition appeared, the dietician conducted a registration of dietary intake, gave individual diet advice, and prescribed supplements if needed.	No intervention	The advice to follow the recommendation of 150 min/week of moderate physical activity.
Koh et al., 2022 [6]	Resistance exercise using a resistance band with weekly review by the physiotherapies (no further details).	Oral nutrition supplementation as recommended by the dietetics team (no further details).	No intervention	No intervention.
Mazzola et al., 2017 [47]	Deep breathing exercise (3 sessions per day of 10 inspiration/expiration cycles), moderate intensity walking for 30 min three times a week.	A mixture containing immuno-nutritional products, oral nutritional support (Impact Oral, 2 bricks during 12 h) for 5–7 days prior to surgery independently from risk assessment. High nutritional risk patients received oral nutritional support	Provided smoking cessation advice.	No intervention.
Nakajima et al., 2019 [48]	60 min of home-based, unsupervised exercise once a day at least 3 times per week. Moderate aerobic exercise and resistance training were combined. In the aerobic exercise, the patients were asked to walk for at least 30 min with an exercise intensity of 3–4 according to the modified Borg Scale score	A leucine-rich essential amino acid supplement within 30 min after the start and end of exercise session.	No intervention	No intervention.
Souwer et al., 2018 [49]	Resistance training as well as endurance training. All training sessions were supervised by a local physiotherapist and each session was at 30–45 min, also instructions for home-exercises and breathing exercises were given.	Nutrition support with a targeted intake of protein of 1.2–1.5 g/kg/day.	No intervention	No intervention.
Pang et al., 2021 [50]	Aerobic, strengthening, and balancing exercises were taught and practised over a 45-min session	Caloric requirement was determined by Schofield equation with a stress factor of at least 1.2. Protein requirement was calculated as 1.3 g/kg body weight.	Detailed counselling on what to expect during the perioperative period was carried out by a specialist nurse, with the aim of allaying fear and anxiety in older patients scheduled to undergo a major operation	No intervention.
van der Hulst et al., 2021 [42]	Exercise program with a local physiotherapist for 30–45 min, twice a week, also instructed to perform home-exercises. No further details.	Referred to the dietician for nutritional support if needed	No intervention.	No intervention.
Wada et al., 2022 [51]	The preoperative exercise program consisted of walking and resistance training. Walking was recommended about 1 h per day and patients were asked to perform leg press, leg lunge, and squats according to normal activities of daily life of each patient by rehabilitation specialists for resistance training	Advised to aim for a total daily caloric intake of 25–30 kcal/kg ideal body weight and a daily protein intake of 0.8–1.2 g/kg ideal body weight.	No intervention	No intervention

adverse outcomes, and are modifiable risk factors through prehabilitation [14,53,54]. During the preoperative period under supervision of specialists, prehabilitation interventions such as exercise, inspiratory muscle training, oral nutrition supplements or immunonutrition, and psychological support have the potential to improve postoperative outcomes [11,55].

The role of frailty in the surgical recovery process has been reported inconsistently in the literature. A study of older patients

Table 4
Summary of main outcomes and results.

Study, year	Primary endpoint	Secondary endpoint	Postoperative outcomes	Functional outcomes	Psychological outcomes
Barberan-Garcia et al., 2018 [17]	Postoperative complications	LOS in the ICU, LOS, endurance time (aerobic capacity), Yale physical activity survey, short form health survey (SF-36), hospital anxiety and depression scale	↓ All postoperative complications in prehabilitation group (31 % versus 62 %, $P = 0.001$) → Postoperative complications using Clavien-Dindo classification between the groups ↓ LOS in the ICU in the prehabilitation group (1 versus 4 days, $P = 0.078$) ↓ LOS in the prehabilitation group (8 versus 13 days, $P = 0.078$)	↑ Endurance time (aerobic capacity) in prehabilitation group presurgery (325 s baseline to 765 s, $P = 0.001$) → 6MWT between the groups	→ SF-36 quality of life between the groups presurgery → HAD score of anxiety and depression between the groups presurgery
Barberan-Garcia et al., 2019 [4]	–	Endurance time at 3 months, Yale physical activity survey at 3 and 6 months, short form health survey (SF-36) at 3 and 6 months, HAD, emergency room visits, hospital readmissions, surgical reinterventions at 30 days, 3 and 6 months, all-cause mortality at 30 days, 3 and 6 months, cost analysis	↓ Hospital readmissions at 30 days in the prehabilitation group (3 % versus 18 %; $P = 0.009$) → Emergency room visits between the groups → All-cause mortality at 30 days and at 3 and 6 months between the groups	↑ Endurance time (aerobic capacity) at 3-month in prehabilitation group ($P = 0.01$) ↑ Yale physical activity survey at 6-month in prehabilitation group ($P < 0.001$)	↓ Anxiety and depression levels (HAD score) at 30 days after surgery in prehabilitation group ($P = 0.008$) ↑ SF-36 physical component at 6 months in prehabilitation group → SF-36 mental component at 6 months between the groups
Berkel et al., 2021 [18]	The number of patients with one or more complications within 30 days of surgery	Changes in preoperative aerobic fitness (the VO2 at the VAT) in the prehabilitation group, LOS, unplanned readmissions within 30 and 90 days after surgery	↓ Complication rate in prehabilitation group ($P = 0.024$) → Hospital readmission rates between the groups	↑ Aerobic fitness in the prehabilitation group presurgery (by 10.1 %, $P = 0.006$]	–
Bojesen et al., 2022 [40]	A hospital stay more than 10 days	Mortality within 30 days, unplanned admission to intensive care, readmission within 30 days, complication with a Clavien-Dindo complication grade ≥3, within 30 days, comprehensive complication index	→ Mortality between the groups → LOS between the groups ↓ Postoperative complications in prehabilitation group ($P = 0.001$) ↓ Readmission rates in prehabilitation group ($P = 0.04$) ↑ 30-days alive and out of hospital median in prehabilitation group ($P = 0.001$	–	–
Carli et al., 2020 [41]	Comprehensive complication index	Primary LOS, total LOS, readmissions, emergency department visits within 30 days postsurgery, 6MWT distance assessed at baseline, presurgery, 4 weeks postsurgery, short form health survey (SF-36), HAD, Community Healthy Activities Model Program for Seniors questionnaire	→ Comprehensive complication index (12.7 versus 15.7, $P = 0.45$) → Severe complications (7 (12.7 %) versus 11 (20.0 %), $P = 0.23$) → LOS (4 versus 5), $P = 0.32$) → Emergency department visit (3 (5.5 %) versus 6 (10.9 %), $P = 0.21$) → Hospital readmission (2 (3.6 %) versus 5 (9.1 %), $P = 0.18$)	→ 6MWT (presurgery 346.1 m versus 315.8 m, $P = 0.37$) → 6MWT at 4 weeks postsurgery (336.4 m versus 286.1 m, $P = 0.34$) metres	→ Self-reported generic health status (SF-36) → Anxiety and depression scale (HAD) → Energy expenditure (Community Healthy Activities Model Program for Seniors questionnaire)
Chen et al., 2017 [43]	The amount and intensity of physical activity performed using a physical activity questionnaire	6MWT	–	↑ Moderate and vigorous physical activities presurgery in the prehabilitation group compared to the control group (5 h versus 1.33 h, $P = 0.001$) ↑ 6MWT baseline to presurgery in the prehabilitation group compared to the control group (+23.7 m versus −5.4 m, $P = 0.002$)	–
Chia et al., 2016 [44]	LOS	A Clavien-Dindo complication grade ≥3, 30-day mortality, recovery of functional status as measured by a modified Barthel Index at 6 weeks postsurgery	↓ LOS in prehabilitation group (8.4 versus 11.0 days, $P = 0.029$). → Severe complications (8.3 versus 11, $P = 0.511$) → Mortality (1.7 versus 3.3, $P = 0.579$)	→ Functional recovery at 6 weeks postsurgery (98.2 % versus 93.3 %, $P = 0.189$)	–

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Table 4 (*continued*)

Study, year	Primary endpoint	Secondary endpoint	Postoperative outcomes	Functional outcomes	Psychological outcomes
de Klerk et al., 2021 [46]	Postoperative complications	Unplanned readmissions, length of hospital stay, mortality	↓ Number of patients with any type of complication (13.2 % ($n = 10$) versus 26.5 % ($n = 73$), $P = 0.015$) ↓ LOS in prehabilitation group (4 versus 5, $P = 0.004$) ↓ Unplanned readmissions (5.3 % ($n = 4$) versus 16.4 % ($n = 45$), $P = 0.014$) → Prolonged LOS (10.5 % versus 10.9 %, $P = 1.00$) → Mortality (0 % versus 1.8 %, $P =$ not significant)	↑ 6MWT presurgery in prehabilitation group (+36 m (+8.3 %) ↑ Leg press one repetition maximum in prehabilitation group (19 kg (+17 %))	–
Karlsson et al., 2019 [45]	Process feasibility (recruitment rate, exercise compliance, and acceptability)	The 17-item postoperative recovery profile, 6MWT, gait speed, functional leg strength, maximal inspiratory pressure, postoperative complications (Clavien–Dindo), length of stay, adverse events, scientific feasibility	→ Number of complications in prehabilitation group versus control group (6 versus 2, $P = 0.06$) → LOS in prehabilitation group versus control group (5 versus 6, $P = 0.57$)	→ Patient reported recovery in prehabilitation group versus control group (5.5 versus 2, $P = 0.22$) ↑Maximal inspiratory pressure presurgery in prehabilitation group ↓ T and habitual gait speed in prehabilitation group postsurgery → In any of the physical performance test in control group presurgery ↓ 6MWT, maximal gait speed, leg strength in control groups postsurgery	–
Koh et al., 2022 [6]	LOS, 30-day morbidity, 30-day mortality	Physical and functional measures, grip strength, gait speed, 30-s chair rise, functional reach, 6MWT, Quality of life	↓ LOS in prehabilitation group (9 versus 11 days, $P = 0.01$), → Clavien-Dindo grade III and more (8.6 % versus 17.4 %, $P = 0.26$) → 30-day mortality (0 % versus 0 %, $P = 1.00$) → 30-day morbidity (41.3 % versus 47.8 %, $P = 0.60$)	↑ 30-s chair rise repetition in prehabilitation group presurgery versus control group (−4 to 10, $P = 0.06$) → Grip strength, 6MWT, gait speed, functional reach presurgery between the groups	↑ EuroQol-5 Dimension Health Questionnaire at 6 months in prehabilitation group
Mazzola et al., 2017 [47]	30-day mortality, 3-months mortality	Overall and severe postoperative complications, LOS, referral to post-discharge institutionalization, hospital re-admission	↓ 30-day mortality (0 % versus 14 %, $P = 0.01$) ↓ 3-month mortality (0 % versus 28 %, $P = 0.001$) ↓ Overall complications (41 % versus 74 %, $P = 0.005$) ↓ Severe complications (17 % versus 43 %, $P = 0.02$) ↓ All complications (17 of 41 versus 26 of 35, $P = 0.005$) ↓ CDC grade ≥ III (7 of 41 versus 15 of 35, $P = 0.02$) → LOS (17 versus 27, $P = 0.08$) → Readmission or discharge institutionalization (7 % versus 16 %, $P = 0.41$)	–	–
Nakajima et al., 2019 [48]	90-Day mortality	Overall morbidity (Clavien-Dindo grade ≥3), infectious complication, pneumonia, bile leakage grade ≥ B, pancreatic fistula grade ≥ B, liver failure grade ≥ B, delayed gastric emptying grade ≥ B, median postoperative hospital stay, 6MWT, knee extension strength, grip strength, 10-m usual walking speed	→ 90-day mortality → Overall morbidity (42 % versus 50 %, $P = 0.329$) ↓ LOS in prehabilitation group (23 versus 30 days, $P = 0.045$) ↓ Bile leakage grade ≥ B in prehabilitation group (8 versus 19, $P = 0.020$)	↑ 6MWT presurgery in prehabilitation group (from 530 m to 554 m, $P = 0.001$) → Knee extension strength, grip strength, 10-m usual walking speed	–

Souwer et al., 2018 [49]	1-Year overall mortality	Postoperative complication rates, readmission rates, 30-day mortality	→ 1-year mortality → 30-day mortality ↓ Severe complications in prehabilitation group ($P = 0.03$) ↓ Number of patients with a prolonged (14 days) LOS in prehabilitation group ($P = 0.001$) → Readmission rates	–	–
Pang et al., 2021 [50]	Postoperative complications	LOS, 30-day readmission rate, institutional care after surgery	→ Postoperative complications → Comprehensive complication index → LOS → 30-day readmission rates → Step down care needed	↑ Postoperative ambulation distance in prehabilitation group up to day 4 in metres (30.6 versus 16.2, day 1, $P = 0.001$), → no significant difference on day 5 (74.8 versus 65.3, $P = 0.321$)	→ Pain score at rest or on movement
van der Hulst et al., 2021 [42]	Postoperative complications	The rate of readmissions in the first 90 days after surgery, 1-year mortality	→ Medical complications (26.6 % versus 20.5 %, $P = 0.20$) → Surgical complications (19.4 % versus 14.3 %, $P = 0.22$) → Readmission rates (11.6 % versus 8.1 %, $P = 0.30$) → 1-year mortality (4.0 % versus 1.9 %, $P = 0.25$)	–	–
Wada et al., 2022 [51]	Postoperative complication	Postoperative LOS	↓ Severe complications in prehabilitation group (6.7 % versus 18.6 %, $P = 0.03$) ↓ LOS in prehabilitation group (13 versus 15.9 days, $P = 0.03$)	–	–

↑ – increase (higher, better), prehabilitation group versus control group; ↓ – decrease (lower), prehabilitation group versus control group; → – no difference between the groups, prehabilitation group versus control group; CCI – Comprehensive Complication Index; HAD – Hospital Anxiety and Depression scale; ICU – intensive care unit; LOS – length of stay (days); 6MWT – 6-minute walk test; SF-36 – Short Form Health Survey.

undergoing elective abdominal surgery found that 70 % of frail patients recovered to preoperative activities of daily living (bathing, dressing, feeding, transferring) after 6 months of recovery compared with 92 % of pre-frail patients and 100 % of those without frailty [56]. Contrary to these findings, a study of patients over 70 years of age who underwent surgery for colorectal cancer found improvement in quality of life scores 3 months after surgery without differences between non-frail and frail patients [57]. Nevertheless, across all noncardiac surgical specialties, frailty is associated with postoperative mortality regardless of disease [58]. Variations in definitions of frailty, study aims or the surgical population can all lead to a difficulty in directly comparing studies.

Quality of life is a notable patient-oriented postoperative outcome, perhaps even more so for older frail patients. Prehabilitation has potential to optimise postoperative functional recovery [11,53], which is in accordance with our findings in this vulnerable group of patients. Regarding prehabilitation of older adults and frail patients, studies and reviews are inconsistent and lacking. The risks and side effects of individual prehabilitation regimens [10], as well as their cost-effectiveness [4,6], are also not thoroughly explored. In a study performed by Carli et al., 110 frail patients received either four weeks of multimodal prehabilitation or four weeks of rehabilitation following colorectal surgery [41]. The 30-day CCI, overall and severe complications at 30 days, LOS, readmission, recovery of walking capacity, and patient-reported outcome indicators did not differ, suggesting that rehabilitation may be equally as effective as prehabilitation [10,41]. In similar high-risk patients (older than 70 years with or without ASA physical status III or IV; $n = 144$) awaiting major abdominal surgery, a prehabilitation programme that included high-intensity endurance training, motivational interview, and promotion of physical activity showed 51 % reduction in the number of patients developing postoperative complications (31 % versus 62 %) [17]. In 2018, at a time when the evidence to support prehabilitation was limited, Milder et al. [59] conducted the first review on the effects of prehabilitation in frail surgical patients and included only two studies with multimodal prehabilitation. These studies showed the potential for prehabilitation to reduce mortality and LOS but had low-quality evidence [44,47]. An additional meta-analysis suggested that prehabilitation was effective in improving the postoperative outcomes in high-risk patients with cancer [60]. Patients ($n = 674$) had a mean age of 78 years and were at high-risk for adverse oncologic surgical events (defined as frail and/or age 70 years and/or with an ASA score ≥ III). Prehabilitation was associated with a decreased risk of major complications (RR −0.09, 95 % CI: −0.15 to −0.03, $P = 0.005$; $I^2 = 27$ %, $P = 0.24$) and surgical complications (RR 0.62, 95 % CI: 0.43 to 0.89, $P = 0.01$; $I^2 = 33$ %, $P = 0.22$) compared with standard care. In addition, prehabilitation lowered LOS (mean difference −2.7, 95 % CI: −5.37 to −0.17, $P = 0.04$) and enhanced functional recovery as measured by the distance covered in 6MWT (mean difference 29.06 m, 95 % CI: 26.55 to 31.06, $I^2 = 42$ %, $P = 0.001$) [60]. In a more recent analysis of the impact of multimodal prehabilitation in older adults (≥ 65 years) before major abdominal surgery which included nine RCTs with a total of 823 patients, the prehabilitation group had significantly fewer postoperative complications than the control group (OR 0.67; 95 % CI: 0.46 to 0.99; $I^2 = 32$ %; $P = 0.04$). Nevertheless, this meta-analysis has some limitations; the researchers concluded only an average or median age from characteristic tables. Consequently, a proportion of participants were younger and did not meet the criteria for old age. Additionally, in contrast to our review, the authors did not include frail younger patients. Our review thus demonstrates the impact of prehabilitation on high-risk patients of all age categories, including those who were frail and/or old.

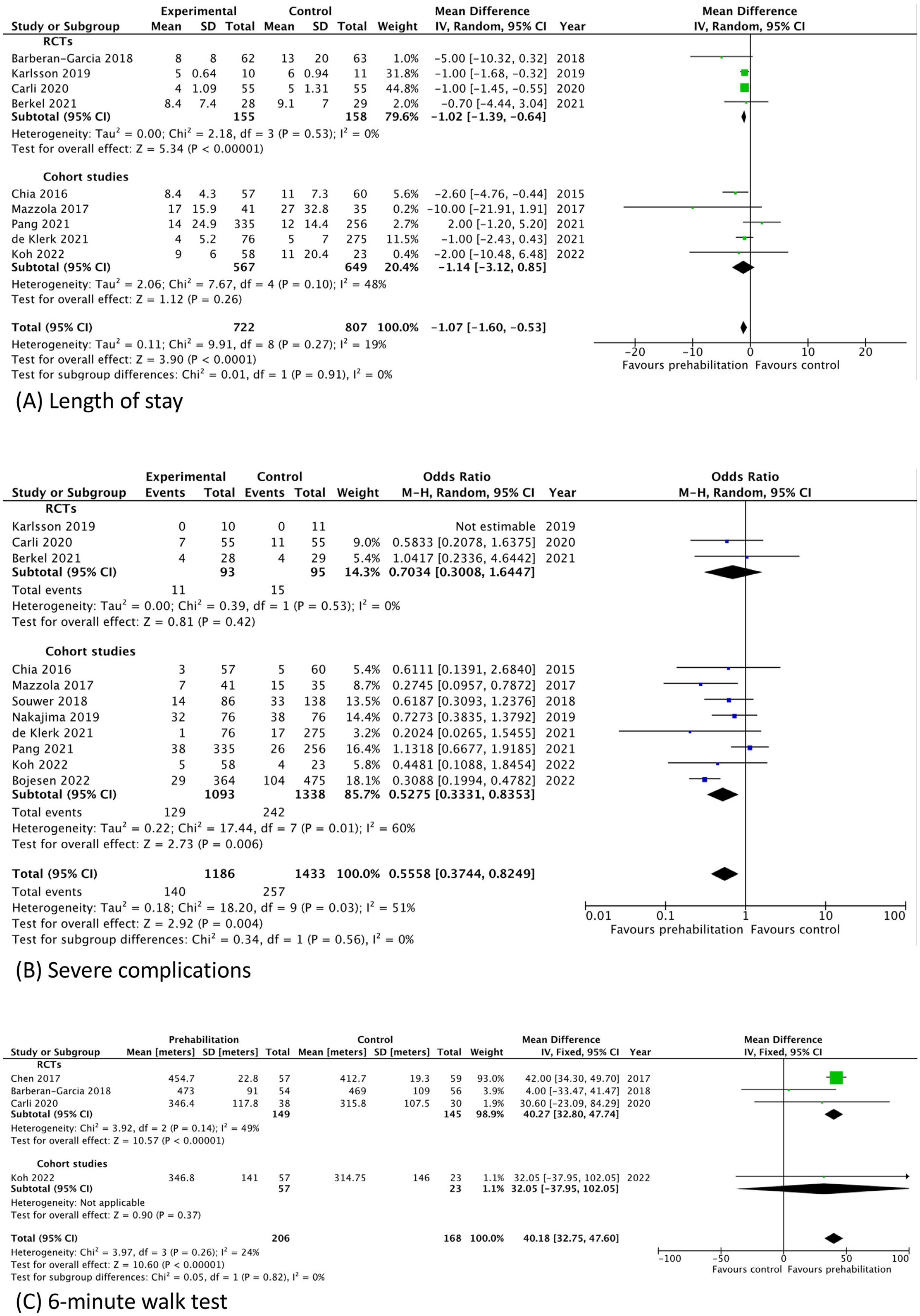

Fig. 2. Forest plots of outcomes for RCTs, cohort studies and combined RCTs and cohort studies. A) Length of stay, B) Severe complications and C) 6-minute walk test.

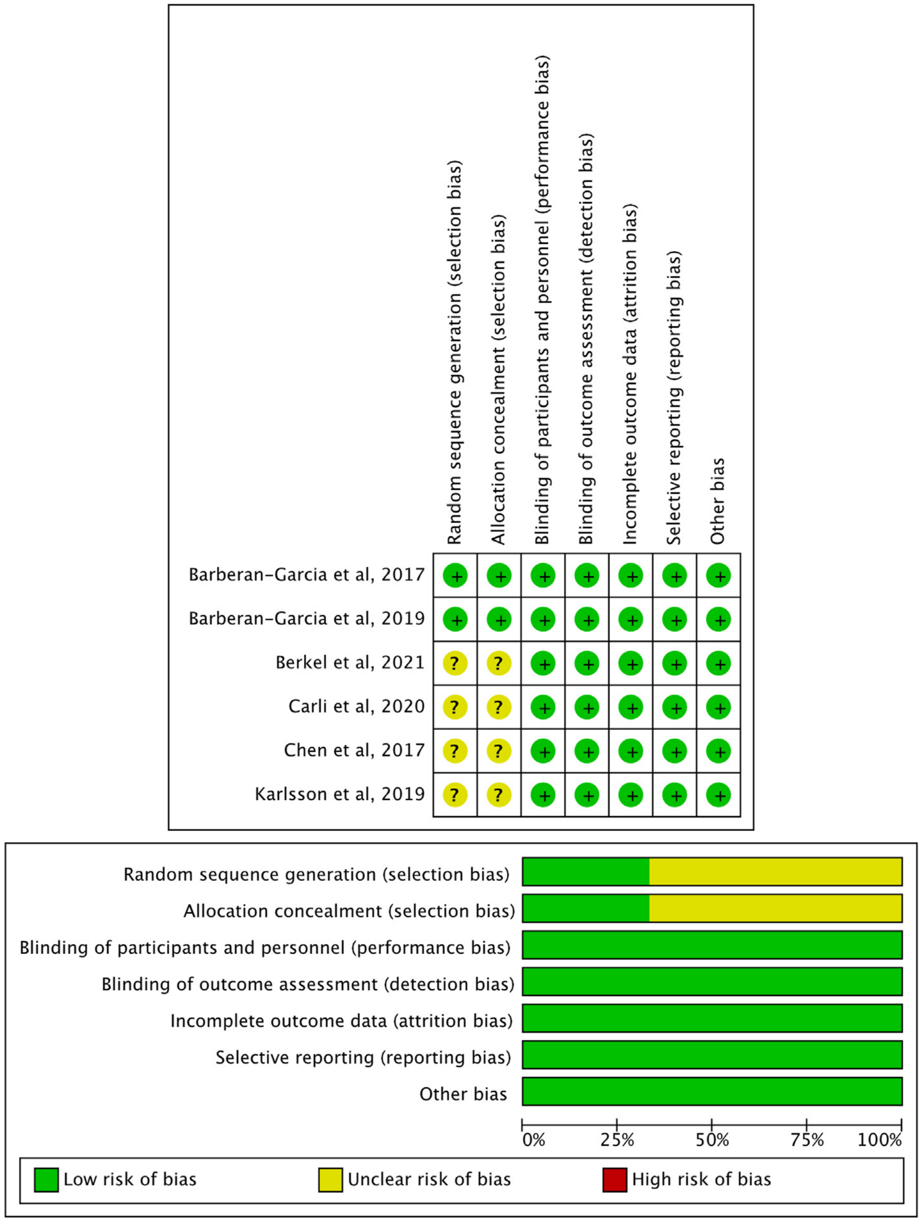

Fig. 3. Risk of bias for the RCTs.

Several studies were excluded from our meta-analysis due to differences in the classification of severe complications (other than Clavien–Dindo classification ≥ Grade 3). In one study investigating the impact of preoperative nutrition and exercise intervention on frail patients with gastric cancer undergoing gastrectomy, the rate of postoperative complications (Clavien–Dindo classification ≥ Grade 2) was 6.7 % (1/15) in the prehabilitation group and 18.6 % (8/43) in the control group ($P = 0.08$) [51]. In another study, the severity of complications was not specified, however, the prehabilitation group showed a lower rate of complications (medical and surgical) than the control group, 31 % versus 62 % ($P = 0.001$) [17]. Accordingly, the estimated RR of 0.5 (95 % CI, 0.3 to 0.8) for complications demonstrated that prehabilitation intervention protects against postoperative complications. An additional study conducted by Souwer et al. on older patients with colorectal cancer showed that when prehabilitation programmes were implemented, the proportion of patients with serious complications decreased from 32 % in 2010–2011 to 16 % in 2014–2015 (OR 0.4, 95 % CI 0.2 to 0.9, $P = 0.03$) [49]. In another study of 182 older (> 60 years old), frail patients who underwent curative cancer surgery, including thoracic, urological, colorectal and hepatobiliary procedures and underwent home-based prehabilitation, neither the primary outcome (6MWT), nor the secondary outcomes (LOS, quality of life, 30-day readmission), showed any significant differences [61]. A different trial measured the impact of a supervised preoperative walking intervention using an activity tracker on postoperative stamina (6MWT), and mobility (steps walked the day after surgery using a thigh-worn monitor) in older adults with frailty in mixed surgical population (colorectal, thoracic, urological, oncology, vascular and transplant) and found no difference in intervention versus control in the postoperative 6MWT distance (median 72 vs. 74 m, $P = 0.54$) or postoperative steps taken (median 128 vs. 51 steps, $P = 0.76$) [62]. Although preoperative levels of physical activity were much higher, the intervention had no impact

Table 5
Risk of bias assessment for cohort studies using Newcastle Ottawa Scale.

Study	Risk of bias assessment			
	Selection	Comparability	Outcome/exposure	Overall score
Bojesen et al., 2022 [40]	★★★	–	★★	5
Chia et al., 2016 [44]	★★	★★	★	5
de Klerk et al., 2021 [46]	★	–	★★★	4
Koh et al., 2022 [6]	★★★	–	★★	5
Mazzola et al., 2017 [47]	★★★	★	★★	6
Nakajima et al., 2019 [48]	★★	★★	★	5
Pang et al., 2021 [50]	★★	–	★	4
Souwer et al., 2018 [49]	★★★	★	★★★	7
van der Hulst et al., 2021 [42]	★★★★	★	★★★	8
Wada et al., 2022 [51]	★★★	★	★★	6

Risk of bias.
6 or above: low risk.
4 to 5: medium risk.
1 to 3: high risk.

on postoperative mobility or endurance. However, they did not record the number of steps taken by the control group prior to surgery. Another prospective cohort study by Risco et al. focused on patients who were at high risk for postoperative complications, as defined by age > 70 years, ASA risk scale 3–4, severe cancer-related deconditioning, and/or highly aggressive surgeries (major digestive, cardiac, thoracic, gynaecology, or urologic surgery), and whose preoperative schedule allowed for at least 4 weeks of prehabilitation [63]. No difference in outcomes between the prehabilitation and control groups (each containing 328 patients) were observed. The per-protocol analysis, which included only patients who completed the programme ($n = 112$, 34 %), revealed a reduction in the average LOS (9.9 *vs.* 12.8 days; $P = 0.035$). Completers undergoing highly aggressive surgical procedures ($n = 60$) also demonstrated a reduction in mean intensive care unit stay (2.3 *vs.* 3.8 days, $P = 0.021$) and a 32 % cost reduction per patient ($P = 0.007$). A recent RCT on prehabilitation in patients aged ≥ 18 years undergoing elective cardiac surgery revealed that the combination of exercise and inspiratory muscle training was not superior to standard care in terms of improving functional exercise capacity as measured by the 6MWT distance pre-operatively (mean difference −7.8 m, 95 % CI−30.6 to 15.0, $P = 0.503$) [64]. Furthermore, there were no significant differences in postoperative mortality, surgical or pulmonary complications [64]. Subgroup analyses based on interaction tests revealed that sarcopenic patients in the prehabilitation group improved more in the six-minute walk test distance ($P = 0.004$) [64]. According to the findings of previous trials and based on our review, prehabilitation should be focused on frail and high-risk patients and this strategy should be universally applicable to all types of operations, including but not limited to major abdominal surgery.

4.4. Adherence to prehabilitation and risk of injury

Patient adherence is vital to the success of a prehabilitation programme. Difficulties with adhering to a prehabilitation programme appears to be even greater for patients with frailty due to difficulties with regular transportation to exercise sessions, resulting from their decreased mobility [10]. We monitored adherence in individual studies for this purpose (Table 2), however, it was not reported at all in 9 studies [4,6,17,40,43,47,48,50,51]. Consequently, low adherence may diminish the efficacy of prehabilitation. In the other included studies, adherence ranged from 68 % [41] to 97 % [45], whereas one study only reported on patients who were 100 % adherent to the programme [42]. In a qualitative study on adherence to prehabilitation prior to major surgery, adherence was facilitated by the intervention being perceived as beneficial [65]. Although some participants faced challenges or avoided certain recommended exercises, recognising the importance of physical activity in their treatment prompted them to tailor the exercises to meet their personal goals [65].

Physical activity is not without risk of injury, particularly for older and frail patients with lower levels of physical function [66]. Overall, it is anticipated that the risk of injury will be low [10], which is supported by the small number of adverse events observed in studies included herein (Table 2). Preoperative patient education appears to have a positive effect on the postoperative course [67], furthermore participants reported that knowing what to anticipate from physically preparing the body increased feelings of control and, as a result, decreased apprehension regarding surgery [68]. Appropriate education and supervision can further reduce the risk of injury. However, after providing instructions for exercise interventions, many participants in a prehabilitation study for cardiac surgery were hesitant to engage in home-based exercise without the security of a hospital-based setting [69]. Repeatedly, those assigned to the prehabilitation group expressed a desire to continue supervised exercise up until the day of their surgery [69]. Also, patients highlighted the significance of education in improving quality of life and placed a high value on the time they spent interacting with staff, raising questions about the relative effectiveness of the unsupervised home-based component of the programme [69]. The same may apply to elective abdominal surgery in older frail patients. Findings suggest that strenuous exercise is inappropriate for frail patients who have not received adequate guidance or support.

4.5. Strengths and limitations

The validity of a review is determined by the quality of included original papers. The inclusion of both RCTs and cohort studies is the main weakness of this meta-analysis. The number of RCTs was smaller than the number of observational studies. To provide a more robust interpretation of the data, each analysis was conducted separately utilising evidence from RCT and cohort studies alone, as well as a summative analysis. The difficulty in interpretation is due to the differences between the various prehabilitation programmes; therefore, we have attempted to describe their specifics (Table 3). As postoperative rehabilitation is a typical component of postoperative care, several studies lacked information about interventions in the control group, or the control group received supervised rehabilitation or physical activity recommendations (Table 3). This may have reduced the magnitude of the differences between the intervention and control groups in our meta-analysis. It may also appear that a combination of prehabilitation and rehabilitation may be the most effective method, but further research is needed. Patients with malignancies or receiving adjuvant chemotherapy were also represented differently, which may contribute to higher heterogeneity. Also, some abdominal surgical procedures are associated with much longer hospital stays than others. However, the results are more interpretable because of the emphasis on different areas of major abdominal surgery and cancer or non-cancer surgery. Therefore, the impact of these variations on LOS may be more pronounced in smaller studies. Despite this, this meta-analysis has evaluated prehabilitation interventions comprehensively, concentrating solely on their preoperative use in abdominal surgery. Results are generalisable to at-risk patients who are frail and at high-risk. Given the choice of exercise intervention (i.e., setting, frequency, intensity, duration), nutritional support, and type of psychological intervention, a degree of methodological heterogeneity is to be anticipated; this was accounted for by conducting a random-effects analysis. Finding low to moderate I^2 values (which is a measure of the quantity of heterogeneity) even when all of this variation is accounted for validates the significance of our findings.

4.6. Further perspectives

Several ongoing studies should provide additional insight into the effects of prehabilitation on patients at risk of developing postoperative complications. Many combine nutritional and exercise interventions in pre-frail or frail older adults [70]. It will be intriguing to observe the results of a prospective, randomised study focused solely on patients with frailty (with 1400 planned participants) undergoing elective surgery, with the primary outcome being the level of dependency 12 months after the operation [68]. This could also be accompanied by a justification for the overall cost-effectiveness of the process. Prehabilitation does not appear to increase the cost of overall care [4,10]. In a study conducted on frail patients by Barberan-Garcia et al., however, the prehabilitation programme did not demonstrate statistically significant cost reductions at 30 days (€812; CI 95 %: −878 to 2642, $P = 0.365$) [4]. Similarly, there were no statistically significant differences in costs between study groups when stratified by surgical aggression level or surgical risk. Additional research will be required to elucidate the financial costs in frail patients. Also qualitative findings (including psychological benefits and those pertaining to recovery, change in anxiety level, motivation to improve quality of life, greater happiness during preparation period, with reduced frequency of periods of depression) revealed potential non-physical benefits of prehabilitation that are difficult to capture with conventional outcome measures [69].

In view of the benefits of prehabilitation, we recognise the critical need for standardised protocols across its key components: exercise, nutritional optimisation, and psychological preparation (Fig. 4). While we have presented a number of interventional approaches, the current lack of universally accepted standards underscores a significant opportunity for advancement in patient care.

To bridge this gap, we advocate for combined, international efforts toward the establishment of comprehensive prehabilitation standards. Future research endeavours should be directed at developing a consensus on prehabilitation protocols, informed by multidisciplinary expertise and targeted to the

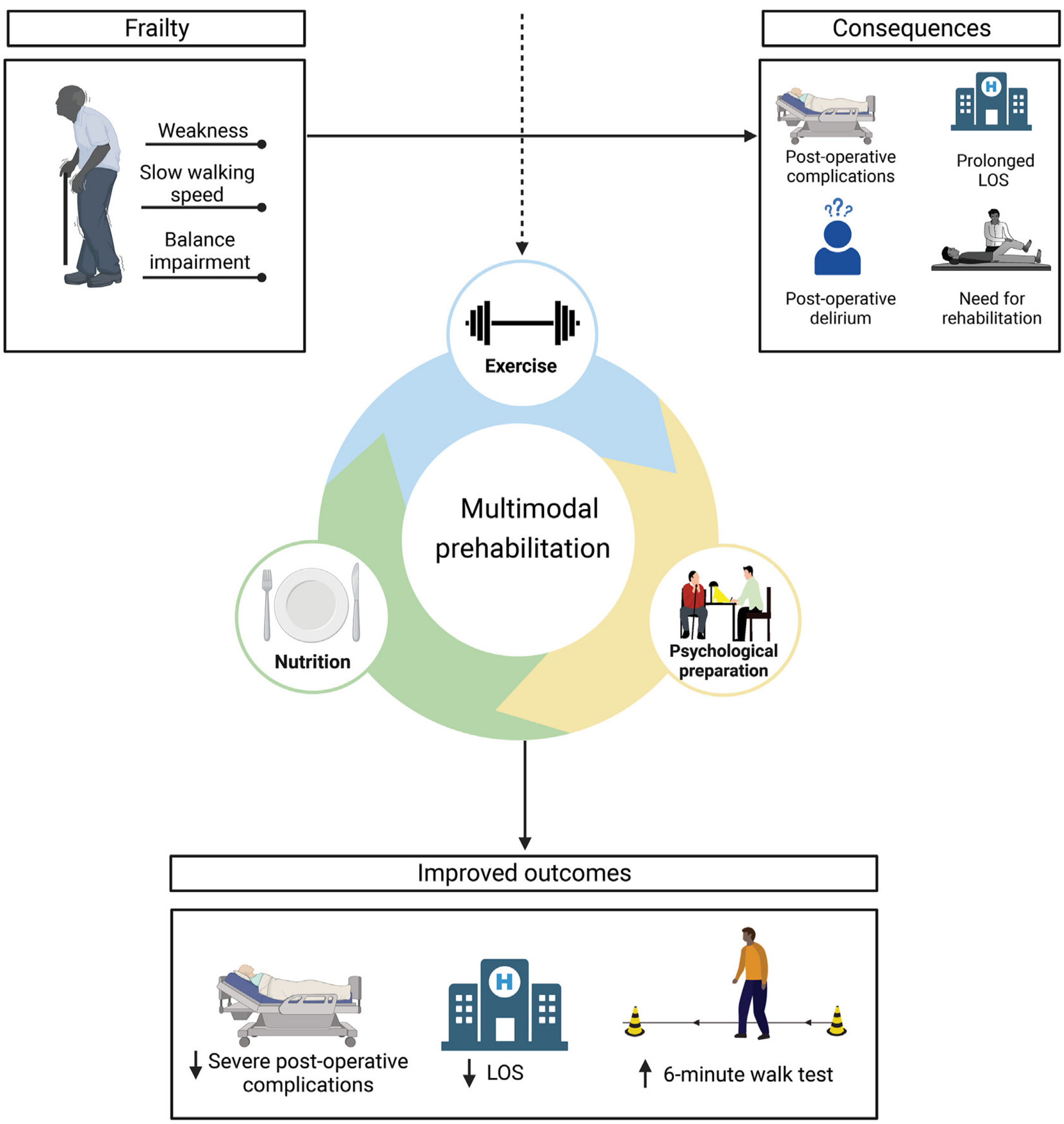

Fig. 4. Selected outcomes of frailty and the benefits of multimodal prehabilitation interventions. While not every study in the meta-analysis employed a multimodal intervention, it is the optimal approach. The improved outcomes in the figure correspond to those identified in our study. LOS = length of hospital stay.

unique requirements of each patient. The implementation of standardised guidelines could contribute to greater consistency in multimodal prehabilitation programmes and may extend their reach, offering the possibility of improved patient outcomes after surgical interventions.

5. Conclusion

This systematic review and meta-analysis of the effect of prehabilitation in frail and high-risk patients undergoing major abdominal surgery found a 1-day reduction in LOS and a decrease in severe complications. Results demonstrate that it is possible to increase the likelihood of successful treatment and, consequently, the indispensable role of prehabilitation in the ageing population. Prehabilitation was also found to be feasible, safe, and posed a minimal risk of complications. This is the only comprehensive review to date that has focused on this high-risk population, and it demonstrates arguments for enhancing perioperative care and incorporating prehabilitation into daily clinical practice.

Author contributions

Study design: PS, KF, AA, DO'C, CMP, DG, DNL.
Data collection: PS, KF.
Data-analysis: PS, KF, AA, DNL.
Data-interpretation: PS, KF, AA, DO'C, CMP, DG, DNL.
Writing of the manuscript: PS, KF, DNL.
Critical review of the manuscript: PS, KF, AA, DO'C, CMP, DG, DNL.
Final approval: PS, KF, AA, DO'C, CMP, DG, DNL.
All authors had access to the data.

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Data sharing

No original data to share.

Ethical statement

As this was a systematic review and meta-analysis, ethical approval was not necessary.

Protocol registration

The protocol was registered with the PROSPERO database (Registration number: CRD42022340986 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=340986).

Conference presentation

A preliminary version of this paper was presented to the Annual Meeting of the Surgical Research Society, Nottingham, March 2023 and has been published in abstract form – Br J Surg. 2023; 110(Suppl 3):znad101.148.

Conflict of interest

None of the authors has a direct conflict of interest to declare. DNL has received an unrestricted educational grant from B. Braun for unrelated work. He has also received speaker's honoraria for unrelated work from Abbott, Nestlé and Corza. KF has received honoraria for unrelated work from Abbott Nutrition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.01.020.

References

[1] Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242:326–41. discussion 341–343.
[2] Freundlich RE, Maile MD, Sferra JJ, Jewell ES, Kheterpal S, Engoren M. Complications associated with mortality in the National Surgical Quality Improvement Program Database. Anesth Analg 2018;127:55–62.
[3] Fulop A, Lakatos L, Susztak N, Szijarto A, Banky B. The effect of trimodal prehabilitation on the physical and psychological health of patients undergoing colorectal surgery: a randomised clinical trial. Anaesthesia 2021;76:82–90.
[4] Barberan-Garcia A, Ubre M, Pascual-Argente N, Risco R, Faner J, Balust J, et al. Post-discharge impact and cost-consequence analysis of prehabilitation in high-risk patients undergoing major abdominal surgery: secondary results from a randomised controlled trial. Br J Anaesth 2019;123:450–6.
[5] Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, et al. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Ann Surg 2011;254:907–13.
[6] Koh FH, Loh CH, Tan WJ, Ho LML, Yen D, Chua JMW, et al. Structured presurgery prehabilitation for aged patients undergoing elective surgery significantly improves surgical outcomes and reduces cost: a nonrandomized sequential comparative prospective cohort study. Nutr Clin Pract 2022;37:645–53.
[7] Looijaard S, Slee-Valentijn MS, Otten RHJ, Maier AB. Physical and nutritional prehabilitation in older patients with colorectal carcinoma: a systematic review. J Geriatr Phys Ther 2018;41:236–44.
[8] Sinclair DR, Maharani A, Chandola T, Bower P, Hanratty B, Nazroo J, et al. Frailty among older adults and its distribution in England. J Frailty Aging 2022;11:163–8.
[9] Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care 2005;8:23–32.
[10] Lobo DN, Skorepa P, Gomez D, Greenhaff PL. Prehabilitation: high-quality evidence is still required. Br J Anaesth 2023;130:9–14.
[11] Perry R, Herbert G, Atkinson C, England C, Northstone K, Baos S, et al. Preadmission interventions (prehabilitation) to improve outcome after major elective surgery: a systematic review and meta-analysis. BMJ Open 2021;11:e050806.
[12] McIsaac DI, Gill M, Boland L, Hutton B, Branje K, Shaw J, et al. Prehabilitation in adult patients undergoing surgery: an umbrella review of systematic reviews. Br J Anaesth 2022;128:244–57.
[13] Pang NQ, Tan YX, Samuel M, Tan KK, Bonney GK, Yi H, et al. Multimodal prehabilitation in older adults before major abdominal surgery: a systematic review and meta-analysis. Langenbecks Arch Surg 2022;407:2193–204.
[14] Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer 2012;107:931–6.
[15] Prado CM, Ford KL, Gonzalez MC, Murnane LC, Gillis C, Wischmeyer PE, et al. Nascent to novel methods to evaluate malnutrition and frailty in the surgical patient. J Parenter Enteral Nutr 2023;47(Suppl. 1):S54–68.
[16] Ford KL, Prado CM, Weimann A, Schuetz P, Lobo DN. Unresolved issues in perioperative nutrition: a narrative review. Clin Nutr 2022;41:1578–90.
[17] Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg 2018;267:50–6.

[18] Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, et al. Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial. Ann Surg 2022;275: e299–306.
[19] Gillis C, Gill M, Gramlich L, Culos-Reed SN, Nelson G, Ljungqvist O, et al. Patients' perspectives of prehabilitation as an extension of enhanced recovery after surgery protocols. Can J Surg 2021;64:E578–87.
[20] Dhesi JK, Lees NP, Partridge JS. Frailty in the perioperative setting. Clin Med 2019;19:485–9.
[21] Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26:1091–101.
[22] Bagshaw M, Majumdar SR, Rolfson DB, Ibrahim Q, McDermid RC, Stelfox HT. A prospective multicenter cohort study of frailty in younger critically ill patients. Crit Care 2016;20:175.
[23] Yao X, Li H, Leng SX. Inflammation and immune system alterations in frailty. Clin Geriatr Med 2011;27:79–87.
[24] Espaulella-Ferrer M, Espaulella-Panicot J, Noell-Boix R, Casals-Zorita M, Ferrer-Sola M, Puigoriol-Juvanteny E, et al. Assessment of frailty in elderly patients attending a multidisciplinary wound care centre: a cohort study. BMC Geriatr 2021;21:727.
[25] Howell SJ, Nair S. Measuring frailty in the older surgical patient: the case for evidence synthesis. Br J Anaesth 2021;126:763–7.
[26] Rothenberg KA, Stern JR, George EL, Trickey AW, Morris AM, Hall DE, et al. Association of frailty and postoperative complications with unplanned readmissions after elective outpatient surgery. JAMA Netw Open 2019;2:e194330.
[27] Suzuki Y, Tei M, Ohtsuka M, Mikamori M, Furukawa K, Imasato M, et al. Effectiveness of frailty screening and perioperative team management of colectomy patients aged 80 years or more. Am J Surg 2022;223:346–52.
[28] Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Available from: https://training.cochrane.org/handbook.
[29] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.
[30] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[31] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[32] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1–7.
[33] UN Population Division. World population ageing, 2013. New York: United Nations; 2013. Available from: https://digitallibrary.un.org/record/826632?ln=en.
[34] Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 2016;104:240–3.
[35] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
[36] Review Manager (RevMan) [Computer program]. The Cochrane Collaboration; 2020. Version 5.4.
[37] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2021.
[38] Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014;20:123–9.
[39] Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions version 6.3: Cochrane; 2022. Available from: https://training.cochrane.org/handbook/current/chapter-10.
[40] Bojesen RD, Grube C, Buzquurz F, Miedzianogora REG, Eriksen JR, Gogenur I. Effect of modifying high-risk factors and prehabilitation on the outcomes of colorectal cancer surgery: controlled before and after study. BJS Open 2022;6: zrac029.
[41] Carli F, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, et al. Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial. JAMA Surg 2020;155: 233–42.
[42] van der Hulst HC, Bastiaannet E, Portielje JEA, van der Bol JM, Dekker JWT. Can physical prehabilitation prevent complications after colorectal cancer surgery in frail older patients? Eur J Surg Oncol 2021;47:2830–40.
[43] Chen BP, Awasthi R, Sweet SN, Minnella EM, Bergdahl A, Santa Mina D, et al. Four-week prehabilitation program is sufficient to modify exercise behaviors and improve preoperative functional walking capacity in patients with colorectal cancer. Supp Care Cancer 2017;25:33–40.
[44] Chia CL, Mantoo SK, Tan KY. 'Start to finish trans-institutional transdisciplinary care': a novel approach improves colorectal surgical results in frail elderly patients. Colorect Dis 2016;18:O43–50.
[45] Karlsson E, Farahnak P, Franzen E, Nygren-Bonnier M, Dronkers J, van Meeteren N, et al. Feasibility of preoperative supervised home-based exercise in older adults undergoing colorectal cancer surgery – a randomized controlled design. PLoS One 2019;14:e0219158.
[46] de Klerk M, van Dalen DH, Nahar-van Venrooij LMW, Meijerink W, Verdaasdonk EGG. A multimodal prehabilitation program in high-risk patients undergoing elective resection for colorectal cancer: a retrospective cohort study. Eur J Surg Oncol 2021;47:2849–56.
[47] Mazzola M, Bertoglio C, Boniardi M, Magistro C, De Martini P, Carnevali P, et al. Frailty in major oncologic surgery of upper gastrointestinal tract: how to improve postoperative outcomes. Eur J Surg Oncol 2017;43:1566–71.
[48] Nakajima H, Yokoyama Y, Inoue T, Nagaya M, Mizuno Y, Kadono I, et al. Clinical benefit of preoperative exercise and nutritional therapy for patients undergoing hepato-pancreato-biliary surgeries for malignancy. Ann Surg Oncol 2019;26:264–72.
[49] Souwer ETD, Bastiaannet E, de Bruijn S, Breugom AJ, van den Bos F, Portielje JEA, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "from prehabilitation to independence". Eur J Surg Oncol 2018;44:1894–900.
[50] Pang NQ, He SS, Foo JQX, Koh NHY, Yuen TW, Liew MN, et al. Multimodal prehabilitation before major abdominal surgery: a retrospective study. Ann Acad Med Singap 2021;50:892–902.
[51] Wada Y, Nishi M, Yoshikawa K, Takasu C, Tokunaga T, Nakao T, et al. Preoperative nutrition and exercise intervention in frailty patients with gastric cancer undergoing gastrectomy. Int J Clin Oncol 2022;27:1421–7.
[52] Argillander TE, Heil TC, Melis RJF, van Duijvendijk P, Klaase JM, van Munster BC. Preoperative physical performance as predictor of postoperative outcomes in patients aged 65 and older scheduled for major abdominal cancer surgery: a systematic review. Eur J Surg Oncol 2022;48:570–81.
[53] Minnella EM, Awasthi R, Loiselle SE, Agnihotram RV, Ferri LE, Carli F. Effect of exercise and nutrition prehabilitation on functional capacity in esophagogastric cancer surgery: a randomized clinical trial. JAMA Surg 2018;153: 1081–9.
[54] Minnella EM, Liberman AS, Charlebois P, Stein B, Scheede-Bergdahl C, Awasthi R, et al. The impact of improved functional capacity before surgery on postoperative complications: a study in colorectal cancer. Acta Oncol 2019;58:573–8.
[55] Adiamah A, Skorepa P, Weimann A, Lobo DN. The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer: a systematic review and meta-analysis. Ann Surg 2019;270:247–56.
[56] Sikder T, Sourial N, Maimon G, Tahiri M, Teasdale D, Bergman H, et al. Postoperative recovery in frail, pre-frail, and non-frail elderly patients following abdominal surgery. World J Surg 2019;43:415–24.
[57] Rønning B, Wyller TB, Nesbakken A, Skovlund E, Jordhøy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer – a follow-up study. J Geriatr Oncol 2016;7:195–200.
[58] George EL, Hall DE, Youk A, Chen R, Kashikar A, Trickey AW, et al. Association between patient frailty and postoperative mortality across multiple noncardiac surgical specialties. JAMA Surg 2021;156:e205152.
[59] Milder DA, Pillinger NL, Kam PCA. The role of prehabilitation in frail surgical patients: a systematic review. Acta Anaesthesiol Scand 2018;62:1356–66.
[60] Teixeira-Oliveira F, Silva G, Santos F, Martins PC, Moreira-Gonçalves D. Pré-habilitação e prognóstico pós-operatório em doentes oncológicos de alto risco: uma revisão sistemática e meta-análise. Rev Portug Cirurg 2021;51: 99–114.
[61] McIsaac DI, Hladkowicz E, Bryson GL, Forster AJ, Gagne S, Huang A, et al. Home-based prehabilitation with exercise to improve postoperative recovery for older adults with frailty having cancer surgery: the PREHAB randomised clinical trial. Br J Anaesth 2022;129:41–8.
[62] Rampam S, Sadiq H, Patel J, Meyer D, Uy K, Yates J, et al. Supervised preoperative walking on increasing early postoperative stamina and mobility in older adults with frailty traits: a pilot and feasibility study. Health Sci Rep 2022;5:e738.
[63] Risco R, Gonzalez-Colom R, Montane-Muntane M, Cano I, Vela E, Sebio R, et al. Actionable factors fostering health value generation and scalability of prehabilitation: a prospective cohort study. Ann Surg 2023;278:e217–25.
[64] Akowuah EF, Wagnild JM, Bardgett M, Prichard JG, Mathias A, Harrison SL, et al. A randomised controlled trial of prehabilitation in patients undergoing elective cardiac surgery. Anaesthesia 2023;78:1120–8.
[65] Cooper M, Chmelo J, Sinclair RCF, Charman S, Hallsworth K, Welford J, et al. Exploring factors influencing uptake and adherence to a home-based prehabilitation physical activity and exercise intervention for patients undergoing chemotherapy before major surgery (ChemoFit): a qualitative study. BMJ Open 2022;12:e062526.
[66] Laurence BD, Michel L. The fall in older adults: physical and cognitive problems. Curr Aging Sci 2017;10:185–200.
[67] Brodersen F, Wagner J, Uzunoglu FG, Petersen-Ewert C. Impact of preoperative patient education on postoperative recovery in abdominal surgery: a systematic review. World J Surg 2023;47:937–47.
[68] Schaller SJ, Kiselev J, Loidl V, Quentin W, Schmidt K, Mörgeli R, et al. Prehabilitation of elderly frail or pre-frail patients prior to elective surgery

(PRAEP-GO): study protocol for a randomized, controlled, outcome assessor-blinded trial. Trials 2022;23:468.
[69] Harrison SL, Loughran KJ, Trevis J, Witharana P, Maier R, Hancock H, et al. Experiences of patients enrolled and staff involved in the prehabilitation of elective patients undergoing cardiac surgery trial: a nested qualitative study. Anaesthesia 2023;78:1215–24.
[70] Orsso CE, Montes-Ibarra M, Findlay M, van der Meij BS, de van der Schueren MAE, Landi F, et al. Mapping ongoing nutrition intervention trials in muscle, sarcopenia, and cachexia: a scoping review of future research. J Cachexia Sarcop Muscle 2022;13:1442–59.