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Review Article

Real-life effectiveness of prehabilitation to improve postoperative outcomes in patients with colorectal cancer approaching surgery: A systematic review and meta-analyses of observational studies versus randomized controlled trials

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ABSTRACT

Introduction: Current evidence synthesis of prehabilitation studies in colorectal surgery is based on results of randomized controlled trials (RCT). Although RCTs are the gold standard for effectiveness research, observational studies probably better reflect real-life practice. The aims of the current study were to compare observational studies to RCTs regarding the association between prehabilitation and postoperative outcomes, and characteristics of included patients and interventions.

Methods: A systematic search was conducted in PubMed, Embase, and CINAHL (until September 2023). Observational studies and RCTs investigating prehabilitation before colorectal surgery and reporting postoperative complications and/or length of stay (LoS) were included. Two reviewers independently assessed the risk of bias using the Cochrane Risk of Bias 2 tool for RCTs and the Cochrane ROBINS-I tool for observational studies. Meta (regression)-analyses were performed for postoperative complications and LoS.

Results: Pooled results showed a statistically significant reduction in postoperative complications (OR 0.54; 95 % confidence interval (CI) 0.40 to 0.72) and LoS (mean difference (MD) −1.34 CI -2.57 to −0.12) after prehabilitation in observational studies but not in RCTs (complications OR 0.95; CI 0.53 to 1.72; LoS MD 0.16 CI -0.52 to 0.83). Patients included in observational studies were older and more often had an ASA score ≥3. In a meta-regression analysis, these characteristics were not statistically significantly associated with the main outcomes.

Conclusion: Observational studies in a real-life setting showed that prehabilitation can reduce postoperative complications and LoS. To further explore the real-life effectiveness of prehabilitation, specific observational study designs, like a target emulation trial could be used.

1. Introduction

Implementation of routine preventive interventions are of major importance to allow for sustainable healthcare that is affordable and accessible for everyone [1]. Prehabilitation is such a preventive intervention that aims to prepare patients for surgery by increasing their

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resilience preoperatively in order to improve postoperative outcomes and enhance recovery [2]. As such, prehabilitation is an intervention that might reduce healthcare costs [3,4] and improve a patient's well-being [5].

Within the domain of colorectal surgery, several systematic reviews and meta-analyses have been published [6] of which some show that prehabilitation can effectively improve preoperative cardiorespiratory fitness [7–9] and might reduce postoperative complications and length of hospital stay (LoS) [8,9]. However, the conclusions of these systematic reviews are predominantly based on the findings from randomized controlled trials (RCTs). Although it is generally accepted that an RCT is the gold standard study design to assess efficacy of an intervention, there are also downsides associated with this study design in the setting of prehabilitation research [10]. Generalizability of RCTs to real-life practice is often complex due to factors associated with the randomized design, such as low willingness to participate and strict inclusion criteria [10]. Therefore, outcomes of an RCT might not always mimic real-life practice. Observational cohort studies investigating prehabilitation often represent a greater volume of included patients and probably better reflect real-life practice, but are also more prone to (unobserved) bias [11].

It is currently unknown if, and how, outcomes of RCTs can be translated into real-life practice. Therefore, the primary aim of the current systematic review and meta-analysis was to compare RCTs to observational studies investigating prehabilitation in patients undergoing colorectal surgery regarding the association between prehabilitation and postoperative complications and LoS.

The secondary aim was to compare RCTs to observational studies regarding participation rates, characteristics of included patients and characteristics of their prehabilitation interventions.

2. Methods

The current study was performed and reported according to "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews" [12] and was prospectively registered at the International prospective register of systematic reviews (PROSPERO) under registration ID CRD42023459763.

2.1. Systematic search

A systematic literature search was conducted in the databases PubMed, Embase, and CINAHL from 2005 until September 2023. The start date of 2005 was chosen as this was the year of the first enhanced recovery after surgery (ERAS) guidelines in colorectal surgery [13]. Search items included elective curative colon or rectal surgery for population and prehabilitation as intervention. A full search string for each database can be found in Supplementary file 1.

2.2. Eligibility criteria

Observational studies and RCTs investigating prehabilitation in adult patients (age ≥18 years) before colorectal surgery written in English were included. A minimum of 90 % of the included patients in the original study should undergo colon or rectal surgery. Prehabilitation interventions during neoadjuvant chemotherapy or radiotherapy were excluded. The intervention group (prehabilitation) should at least receive a structured form of physical exercise training that aimed to preoperatively improve a patient's cardiorespiratory fitness. The control group consisted of patients who either received no intervention (usual care) or a comparison intervention (e.g., a different preoperative physical exercise program). In order to be eligible, studies should have focused on postoperative complications and/or postoperative LoS as outcome measures. Conference papers, case series, case reports, opinion studies (non-original research), and systematic reviews were excluded. Reference lists of systematic reviews and included studies were screened for additional potentially eligible studies.

2.3. Study selection

Study selection based on title and abstract was performed by two reviewers (RF and MV) independently using the web application Rayyan [14]. All studies meeting the eligibility criteria were reviewed by reading the full text by two independent reviewers (RF and MV). Any issues with eligibility were resolved by discussion between reviewers (RF and MV). When no consensus could be reached after discussion by contacting a third researcher (EJ).

2.4. Data extraction

Study data from the original studies were extracted by the first author (RF) onto predefined data tables and checked for consistency and completeness by two reviewers (EJ for RCTs and MV for observational studies). Extracted data included author, publication year, number of participants, participation rates, study exclusion criteria, patient characteristics, type of prehabilitation intervention, modules of the prehabilitation intervention, supervision (guidance of a physical therapist who is specialized in supervising adult clinical populations), and main and additional outcomes. Characteristics of the physical exercise training intervention were extracted using the training frequency, training intensity, training time, training type, training volume, and training progression (FITT-VP) principles.

Risk of Bias assessment Risk of bias assessment of RCTs (EJ and RF) and observational studies (RF and MV) was done by two reviewers independently using the Cochrane Risk of Bias 2 (RoB2) tool and the Cochrane ROBINS-I tool, respectively. Any disagreement between assessors after discussion was resolved by contacting a third reviewer (MV for RCTs and EJ for observational studies).

2.5. Statistical analyses

Outcome data were presented as reported in the original study. If median and interquartile range [IQR] or median and range were reported in the original study, these data were converted to mean and standard deviation (SD) for pooling purposes according to the method described by Wan et al. [15]. If confidence intervals were reported, the standard deviation of the mean (SD) was calculated using the Cochrane RevMan calculator [16]. Continuous outcome data between studies were pooled per group (intervention and control groups) using the Cochrane formula for combining groups [17]. Comparison between groups was done by using an unpaired samples t-test for continuous variables and Chi-squared test for categorical variables. Meta-analyses were performed using Review Manager (RevMan Version 5.4, The Cochrane Collaboration, 2020). A random effects model was applied to account for heterogeneity in both outcome assessment and measurement of exposure between studies. Continuous variables were expressed as mean difference (MD) and 95 % confidence interval (CI). Dichotomous variables were expressed as odds ratios (OR) with CI. Subgroups were made based on study type (observational and RCT) for the outcomes postoperative complications, severe postoperative complications (Clavien-Dindo ≥3 or Comprehensive Complication Index (CCI) ≥20), and postoperative LoS. Additional subgroups were considered based on heterogeneity between studies. Heterogeneity was identified using I^2 statistic and was defined as "might not be important" (0 %–40 %), "may represent moderate heterogeneity" (30 %–60 %), "may represent substantial heterogeneity" (50 %–90 %), and "considerable heterogeneity" (75 %–100 %) [18]. A meta-regression analysis was considered for patient or intervention characteristics that were significantly different between observational studies and RCTs in order to investigate a possible association between these characteristics and the main outcomes. For all statistical tests, a p-value <0.05 was considered statistically significant.

3. Results

A total of eight observational studies [19–26] and eleven RCTs [5, 27–36] including 6214 patients (observational studies n = 5393 and RCTs n = 821) were included in the current systematic review. Open surgery had been performed in 30.8% of patients in the observational studies and 10% of patients in the RCTs. Minimally invasive surgery had been performed in 69.2% of patients in the observational studies and 90% in the RCTs. See Fig. 1 for a flowchart of inclusion and Table 1 for the characteristics of the included studies. Of the 19 included studies, 14 studies [5,21–27,29,30,32–34,36] (six observational studies, and eight RCTs) investigated the effect of prehabilitation compared to usual care and reported on (general) postoperative complications and/or LoS and were included in the meta-analyses. Of these six observational studies, five studies [22–26] were retrospective cohort studies that were initiated as an evaluation of "usual care", which included a prehabilitation program. For comparison, a usual care group of patients who underwent colorectal surgery before the initiation of the prehabilitation intervention (i.e., a historical cohort) was used. One study was a set up as a prospective pragmatic non-randomized trial [21].

Of the five studies that were not included in the meta-analyses, one observational study [20] only reported medical and surgical complications and one observational study [19] only reported on postoperative ileus. Of the RCTs, two studies compared prehabilitation versus rehabilitation [28,31] whereas one study compared two prehabilitation interventions with each other and did not have a usual care group [35]. These three studies were not included in the meta-analysis.

Methodological quality assessment Of the eight observational studies, four studies [22–25] (50 %) had a low risk of bias, one study [19] (13 %) had a serious risk of bias, and three studies [20,21,26] (38 %) had a critical risk of bias. Of the six studies included in the meta-analyses, four studies [22–25] (67 %) had a low risk of bias and two [21,26] (33 %) had a critical risk of bias. Of the eleven included RCTs, six studies [5,28, 30–32,36] (55 %) had a low risk of bias and five studies [27,29,33–35]

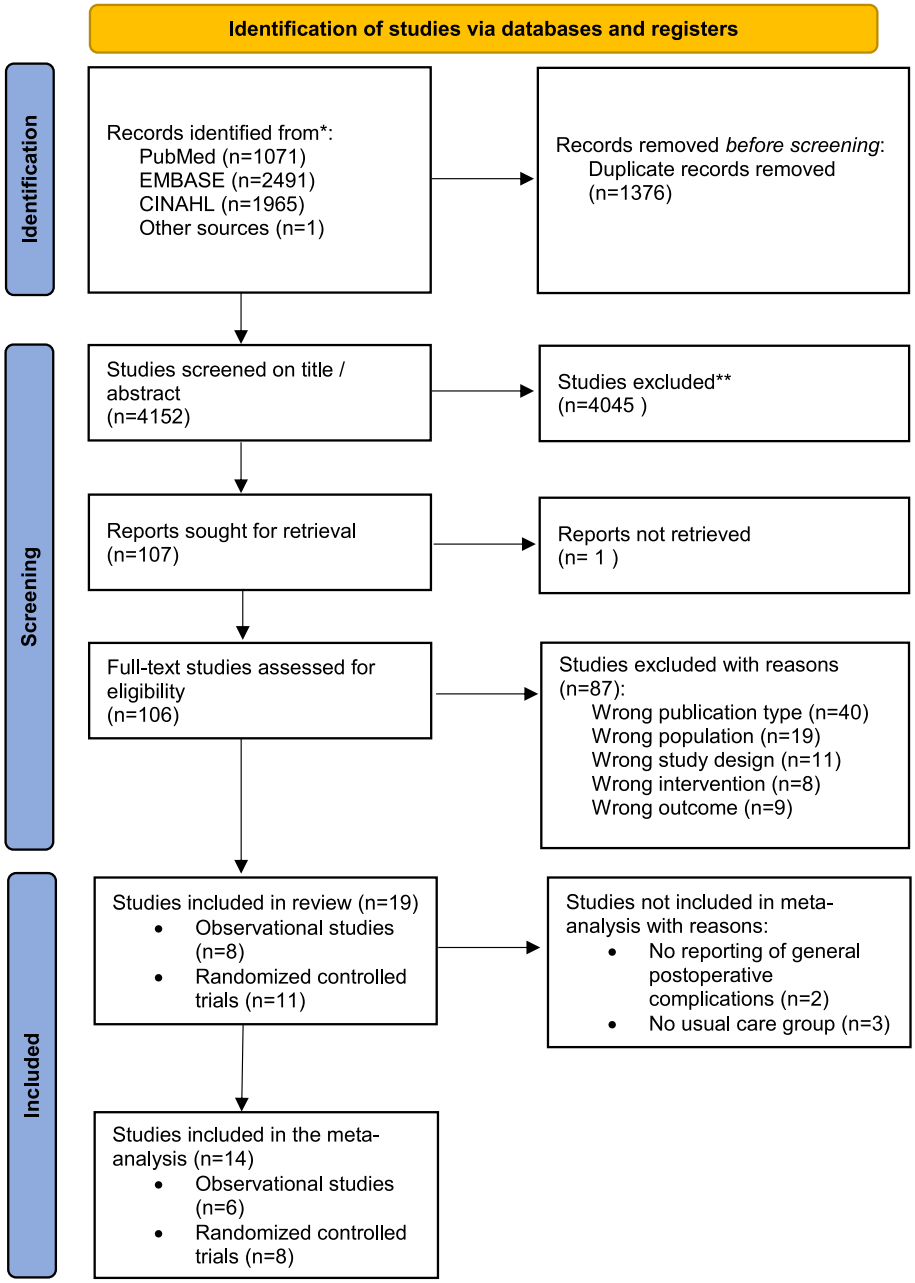

Fig. 1. Prisma flowchart of study inclusion A.

Table 1
Characteristics of the included studies.

Observational studies						
Study (year)/ country	Study design	Intervention/control	Population and patient selection	Patient-related exclusion criteria	Sample size (n)	Main outcomes
Cerdan Santacruz et al. (2022) / Spain	Retrospective cohort study	Prehab / ERAS and Conventional care (historical cohort 2016-2019)	Colon cancer Stage 1-3 Age ≥ 65 years, and ≤ 14 on G8 scale (A)	- Inability to understand instructions (C) - Disabled patients unable to do any physical activity (B)	Prehab: 51 UC[a]: 103	*Postoperative complications:* Prehab: UC: 17 (33.3%) 42 (40.7%) *Clavien Dindo ≥3:* Prehab: UC: : 7 (13.7%) 8 (7.8%) *LoS (days)* Prehab: UC: 7.8 (6.7) 7.7 (5.2)
Heil et al. (2022) / the Netherlands	Retrospective cohort study	Prehab (2018-2021) / UC (historical cohort 2016-2017)	Colorectal cancer stage 1-3 Age ≥ 65 years, and/or ASA III-IV (A)	- None (G)	Prehab: 123 UC: 128	***Unweighted outcomes:*** *Postoperative complications:* Prehab: UC: 51 (41.5%) 85 (66.4%) *LoS (days)* Prehab: UC: 4 (1.5) 6 (2.9) ***Weighted outcomes:*** *Postoperative complications (weighted complication risk)* Prehab: UC: 0.39 0.67 ARD -0.28 (-0.42 to -0.15) *Expected LoS (days)* Prehab: UC: 4.9 7.3
Hulst et al. (2021) / the Netherlands [b]	Retrospective cohort study	Prehab (2014-2019 /	Colorectal Stage 1-3	- Not able to exercise (B) - (Partial) obstructive tumors (E)	Prehab 124 UC: 210	*Medical complication:* Prehab: UC: 33 (26.6%) 43 (20.5%) p 0.20
		UC (2014-2019)	Age ≥ 70 years And unfit based on clinical impression (A)			*Surgical complication:* Prehab: UC: 24 (19.4%) 30 (14.3%) p 0.22
Klerk et al. (2021) / the Netherlands	Retrospective cohort study	Prehab (2019-2020) / UC (historical cohort 2017-2018)	Colorectal cancer stage 1-3 Age ≥ 65 years, and/or ASA III-IV (A)	None (G)	Prehab 84 UC: 275	*Postoperative complications:* Prehab: UC: 20 (26.3%) 110 (40.0%) p 0.03 *Clavien Dindo ≥3a: (n= prehab 76 UC 250)* Prehab: UC: *8 (10.5%)* *40 (16.0%)* *Medical complication:* Prehab: UC: 5(6.6%) 21 (7.6%) p 1.00 *Surgical complication:* Prehab: UC: 2 (2.6%) 9 (3.3%) *LoS (days):* Prehab: UC: 6.5 (5.0) 7.3 (SD 5.8)
Koh et al (2022) / Singapore	Prospective cohort	Prehab (2017) / UC (historical cohort before 2017)	Colorectal Stage 1-3 Age ≥ 70 years	- partial) obstructive tumors which precluded a 2- to 4-week intervention (E)	Prehab: 58 UC: 23	Postoperative complications: Prehab: UC: 24 (41.3%%) 11 (47.8%) p 0.60 *Clavien Dindo 3:* Prehab: UC: 3 (5.2%) 3 (13%) p 0.02 *Clavien Dindo 4:* Prehab: UC: 2 (3.4%) 1 (4.5%) p 0.85 *LoS (days):* Prehab: UC: 13 (6.1) 16 (8.6)

Li et al (2012) / Canada	Prospective cohort, retrospective control	Prehab (2010-2011)/ UC (historical cohort 2009-2010)	Colorectal Stage 1-3	- Medical condition precluding exercise (A,B) - Inability to understand French / English (D)	Prehab 43 UC: 45	*Postoperative complications:* Prehab: UC: 15 (36.0%) 20 (43.0%) p 0.07 *Clavien Dindo ≥3:* Prehab: UC: 2 (5%) 1 (2%) *LoS (days):* Prehab: UC: 4.3 (2.3) 4.3 (2.3)
Rooijen, van et al. (2019) / the Netherlands	Non-randomized trial	Prehab (2016-2017 / UC (2016-2017)	Colorectal cancer stage 1-3	- Chronic renal failure (A) - ASA score IV or V (A) - Paraplegia, orthopedic impairment precluding exercise (B)	Prehab: 20 UC: 30	*Postoperative complications:* Prehab: UC: 15 (36.0%) 25 (43.0%) *LoS (days):* Prehab: UC: 7.3 (3.5) 13.2 (9.6)
Ushida (2023) / Japan[b]	Retrospective cohort	Prehab (2014-2020_ / UC (2014-2020)	Colorectal cancer stage 1-3 And Determined by physician preference	None (G)	Prehab: 1914 UC: 2162	*Postoperative ileus:* Prehab: UC: 5 (25%) 7 (23.0%)
Combined			A) High risk n= 4 (50%)	A) Comorbidity: n= 2 (25%) B) Physical inabilities n=4 (50%) C) Cognitive impairments n=1 (12.5%) D) Language n= 1 (12.5%) E) Tumor related n= 2 (25%) F) Other G) No exclusion n=2 (25%)		*Postoperative complications:* *Prehab: UC:* *130 (35%) 277 (46%)* *Severe complications (CCI>20 or Clavien-Dindo ≥3)* *Prehab: UC:* *22 (10%) 53 (13%)*
Randomized controlled trials (RCTs)						

Study (year)/ country	Study design	Interventio n/control	Population and patient selection	- Patient-related exclusion criteria	Sample size (n)	Main outcomes
Bousquet-Dion et al. (2018)/ Canada	RCT	Prehab + rehab (2013-2015) / Rehab (2013-2015; UC in preoperative period)	Colorectal cancer stage 1-3	- Inability to understand French / English (D) - medical conditions that contraindicated exercise (A)	Prehab + rehab: 37 Rehab: 26	*Postoperative complications:* *Prehab + rehab Rehab:* *14 (38%) 8 (31%) p 0.56* *Clavien Dindo ≥3a:* *Prehab + rehab Rehab:* *2 (5%) 0 (0%)* *LoS (days):* *Prehab + rehab Rehab:* *3.3 (0.8) 2.3.(1.6)*
Carli et al. (2020) / Canada[b]	RCT	Prehab / (2015-2019) Rehab (2015-2019; UC in preoperative period)	Colorectal surgery And ≥ 65 years and frail (A)	- Inability to understand French / English (D) - Premorbid conditions prohibiting exercise (A)	Prehab:55 Rehab:55	*Postoperative complications:* *Prehab: Rehab:* *25 (46%) 25 (46%) p 0.90* *Clavien Dindo ≥3a:* *Prehab: Rehab:* *7 (13%) 11 (20%) p 0.23* *LoS (days):* *Prehab: Rehab:* *4 (3-8) 4.1 (3-8) p 0.80*
Dronkers et al. (2020)/ the Netherlands	RCT	Prehab / UC	Colorectal cancer stage 1-3 And ≥ 60 years	- Inadequate cognitive functions (C) - Heart disease prohibiting exercise (A) - Sever systemic illness (A) - Recent embolism (A) - Uncontrolled diabetes (A) - Orthopedic conditions that impede exercise (A) - Wheelchair dependence (B)	Prehab: 22 UC: 20	*Postoperative complications:* *Prehab: UC:* *17 (24%) 16 (22%) p 0.57* *LoS (days):* *Prehab: UC:* *16.2 (11.5) 21.6 (23.5) p 0.31*

Fulop et al. (2021)/ Hungary	RCT	Prehab (2017-2019) / UC (2017-2019)	Colorectal surgery And > 18 years	None (G)	Prehab:77 UC: 72	*Postoperative complications:* *Prehab:* *17 (24%)* *Clavien Dindo ≥3:* *4 (5%)* *LoS (days):* *Prehab:* *9.8 (6.9)*	*UC:* *16 (22%)* *2 (3%)* *UC:* *8.6 (2.9)*	*p 0.57* *p 0.37* *p 0.71*
Gillis et al. (2014)/ Canada[b]	RCT	Prehab (2011-2013)/ Rehab (2011 – 2013; UC in preoperative period)	Colorectal cancer stage 1-3	- Inability to understand French / English (D) - Premorbid conditions that contraindicated exercise (A).	Prehab: 38 Rehab: 39	*Postoperative complications:* *Prehab:* *12 (32%)* *Clavien Dindo ≥3a:* *Prehab:* *4 (11%)* *LoS (days):* *Prehab:* *4.0 (1.5)*	*Rehab:* *17 (44%)* *Rehab:* *6 (15%)* *Rehab:* *4.7 (3.1)*	*p 0.28* *p 0.57*
Gloor et al. (2022)/ Switzerland	RCT	Prehab (2016-2019) / UC (2016-2019)	Colorectal resection (elective) And ≥ 18 years	- (Partially) obstructive tumor (E) - Inability to exercise (B)	Prehab:54 UC:53	*Postoperative complications:* *Prehab:* *52 (96%)* *Clavien Dindo ≥3a:* *Prehab:* *7 (13%)* *LoS (days):* *Prehab:* *8.8 (3.3)*	*UC:* *45 (85%)* *UC* *2 (4%)* *UC:* *8.5 (4.5)*	*p 0.16*
Karlsson et al. (2019)/ Sweden	RCT	Prehab (2016-2018) / UC (2016-2018)	Colorectal stage I-III And ≥ 70 years	- Inability to understand Swedish (D) - health status that prohibits physical exercise, such as unstable heart disease, severe systematic illness or severe orthopedic conditions (A)	Prehab:10 UC:11	*Postoperative complications:* *Prehab:* *6 (60%)* *LoS (days):* *Prehab:* *5.0 (1.4)*	*UC:* *2 (18%)* *UC:* *6.0 (2.0)*	*p 0.06* *p 0.57*

Lopez-Rodriguez-Arias et al. (2021)/ Spain	RCT	Prehab (2020) / UC (2020)	Colorectal cancer stage I-III	- a minimum physical condition (B) - and/or autonomy (C) allowing the patient to safely perform the intervention exercises was required	Prehab:10 UC: 10	*Postoperative complications:* *Prehab:* *UC:* *2 (20%)* *5 (50%)* *p 0.16* *LoS (days):* *Prehab:* *UC:* *4.8 (1.0)* *7.2 (3.1)* *p 0.57*
Minnella et al. (2020)/ Canada[b]	RCT	Prehab (HIIT; 2016-2017)/ Prehab (MIET;2016 -2017))	Colorectal I-III And ≥ 18 years	- ASA score >3 (A) - comorbid conditions that contraindicated oral nutrition or exercise such as unstable cardiovascular disease, disabling physical (A) and cognitive impairment (C), and end-stage organ dysfunction - Inability to understand French / English (D)	Prehab (HIIT): 21 Prehab (MIET) 21	*Postoperative complications:* *Prehab (HIIT):* *Prehab (MIET):* *39 (32%)* *54 (42%)* *p 0.07* *Clavien Dindo ≥3a:* *Prehab (HIIT):* *Prehab (MIET):* *0 (0%)* *0 (0%)* *LoS:* *Prehab (HIIT):* *Prehab (MIET):* *4.1 (2.4)* *4 .0 (1.6)*
Molenaar et al. (2023)/ International	RCT	Prehab (2017-2020) / UC (2017-2020)	Colorectal cancer stage I-III	- ASA score >3 (A) - chronic kidney failure (A) - medical conditions (A,B) and/or cognitive impairments (C) that contraindicated the intervention - illiteracy or language barriers (D)	Prehab: 62 UC: 71	*Postoperative complications:* *Prehab:* *UC:* *39 (32%)* *54 (42%)* *p 0.07* *Severe complications (CCI>20):* *Prehab:* *UC:* *21 (17%)* *38 (30%)* *p 0.02* *LoS (days):* *Prehab:* *UC:* *3.7 (1.5)* *3.3 (0.8)*
Combined			A) High risk n=2 (18%)	A) Comorbidities n=5 (46%) B) Physical inabilities n=5 (46%) C) Cognitive impairments n=3 (27%) D) Language n=6 (55%) E) Tumor related n=2 (18%) F) Other n=1 (9%) G) No exclusion n=1 (9%)		*Postoperative complications:* *Prehab:* *UC:* *99 (31%)* *114 (37%)* *Severe complications (CCI>20 or Clavien-Dindo ≥3)* *Prehab:* *UC:* *38 (11%)* *45 (13%)*

[a] ERAS group and conventional care group of the original study were combined

[b] Study not included in meta-analyses

Abbreviations: American Society of Anesthesiologists score, CCI = Comprehensive Complication Index, UC = usual care, HIIT = high-intensity interval training, LoS = Length of hospital stay, MIET = moderate-intensity endurance training, Prehab = prehabilitation, RCT= randomized controlled trial, Rehab = rehabilitation.

(45 %) had some risk of bias. When evaluating the seven studies included in the meta-analyses, three had a low risk of bias [5,30,36] (43 %) and four [27,29,33,34] (47 %) had some risk of bias. Fig. 2 depicts the risk of bias assessment in observational studies (A) and RCTs (B).

Postoperative outcomes In observational studies, a lower percentage of postoperative complications was observed in the prehabilitation group compared to the usual care group (OR 0.54; 95 % confidence interval (CI) 0.40 to 0.72; I^2 0 %), but not in RCTs (OR 0.95; 95 % CI 0.53 to 1.72; I^2 56 %) (Fig. 3A). There were no differences in the percentage of severe postoperative complications in either observational studies or RCTs (Fig. 3B). LoS was shorter in patients undergoing prehabilitation in observational studies (mean difference (MD) −1.34; 95 % CI -2.57 to −0.12; I^2 78 %) but not in RCTs (MD 0.16; 95 % CI -0.52 to 0.83; I^2 57 %) (Fig. 3C).

Characteristics of included patients and intervention characteristics Respectively 50 % (n = 4) and 18 % (n = 2) of the observational studies and RCTs explicitly focused on including patients with a high risk for postoperative complications. Observational studies excluded patients based on comorbidity (25 %), physical inabilities (50 %), cognitive impairments (13 %), language (13 %), and tumor-related criteria (25 %). Two observational studies (25 %) did not have any patient-related exclusion criteria. Patient-related exclusion criteria in RCTs were based on comorbidity (46 %), physical inabilities (46 %), cognitive impairments (27 %), language (55 %), and/or tumor-related criteria (i.e., bowel obstruction) (18 %). One RCT did not report any patient-related exclusion criteria (Fig. 4).

Patients included in the observational studies were on average of older age compared to patients in the RCTs (mean age prehabilitation group 75.3 years versus 69.4 years, respectively; $p < 0.001$, and mean age control group 75.1 years versus 69.8 years, respectively; $p < 0.001$). In addition, the proportion of patients with an American Society of Anesthesiologists (ASA) score ≥3 was higher in patients included in the prehabilitation group of the observational studies compared to patients included in RCTs (40.8 % vs. 30.4 %; $p < 0.002$). For the control group, these figures were 34.6 % in observational studies and 35.1 % in RCTs ($p = 0.800$)

For studies included in the meta-analyses [5,21–27,29,30,32–34,36], mean age was also higher in observational studies compared to RCTs (mean age prehabilitation group 75.5 years versus 68.9 years; $p < 0.001$, and mean age usual care group 73.3 years versus 68.5 years; $p < 0.001$). The proportion of patients with an ASA score ≥3 for observational studies compared to RCTs was 42.0 % versus 25.2 % ($p < 0.001$) in the prehabilitation group and 39.1 % versus 26.5 % ($p < 0.001$) in the usual care group. No statistically significant differences between observational studies and RCTs were found for the variables sex, and invasiveness of the surgical procedure. When controlling for mean age and the proportion of ASA score ≥3 in a meta regression analysis, both variables did not significantly influence the pooled estimates for postoperative complications (mean age coefficient −0.42; $p = 0.680$, and ASA ≥3 coefficient 0.009; $p = 0.260$) or LoS (mean age coefficient −0.13; $p = 0.410$, and ASA ≥3 coefficient 0.05; $p = 0.430$). An overview of patient and surgical characteristics in observational studies an RCTs can be found in Table 2 and Supplementary file 2, Table 1.

Seven out of eight observational studies (88 %) used a multimodal

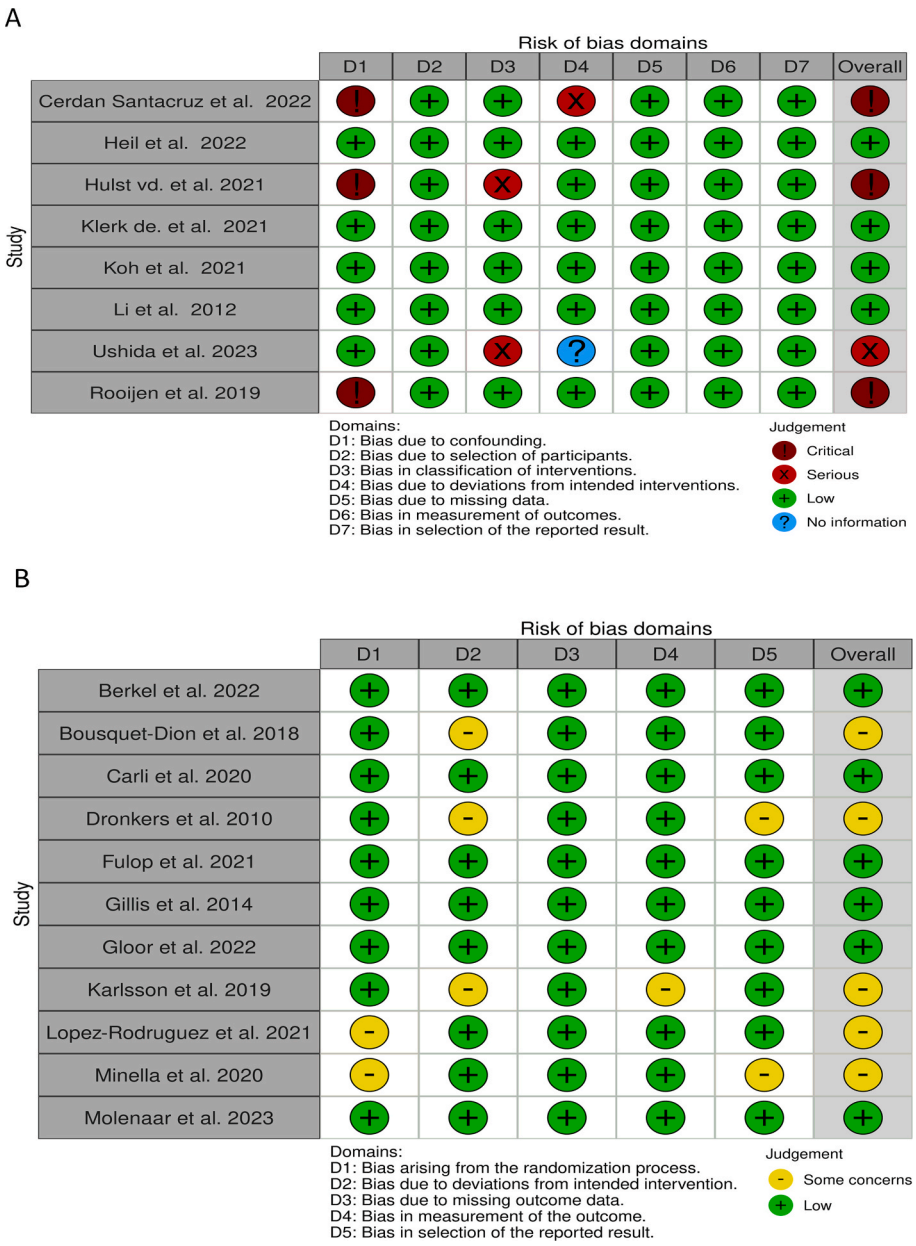

Fig. 2. Risk of Bias assesment of observational studies (A) and randomized controlled trials (B).

prehabilitation intervention compared to 63 % (seven out of 11) of the RCTs. See Supplementary file 2, Table 2, for an overview of the included modules per study. In observational studies, six interventions (75 %) were supervised, one was partly supervised (13 %) and one (13 %) was unsupervised, compared to 5 supervised (45 %), four partly supervised (36 %) and two unsupervised (18 %) interventions in RCTs. Of the observational studies, five (63 %) were hospital-based, one (13 %) was home-based, and one (13 %) was community-based. In RCTs, five interventions (45 %) were hospital-based, five (45 %) were home-based and one (10 %) was community-based. Full reporting of the prescribed and performed physical exercise intervention according to the training frequency, intensity, time, type, volume and progression (FIIT-VP) principles was lacking in seven out of eight observational studies and nine out of eleven RCTs. See Supplementary file 2, Table 2, for an overview of the physical exercise intervention characteristics.

4. Discussion

The current systematic review is the first study that systematically reviewed the results of observational studies and RCTs investigating prehabilitation in patients who underwent colorectal surgery. In addition, the current study is the first study that compared observational studies and RCTs based on the patient characteristics and the prehabilitation intervention characteristics. It was assumed that observational studies would be a good reflection of real-life practice while RCTs are generally considered to be the gold standard to estimate effectiveness of interventions. Pooled results of the observational studies showed that the odds for postoperative complications were ~50 % lower, and LoS was 1.34 days shorter in the prehabilitation group compared to the usual care group. Combined results of RCTs did not show a significant reduction in postoperative complications or LoS. Patients included in observational studies were on average of older age and more often had an ASA score ≥3. In a meta-regression analysis, these patient characteristics (age and ASA classification) were not associated with the effect

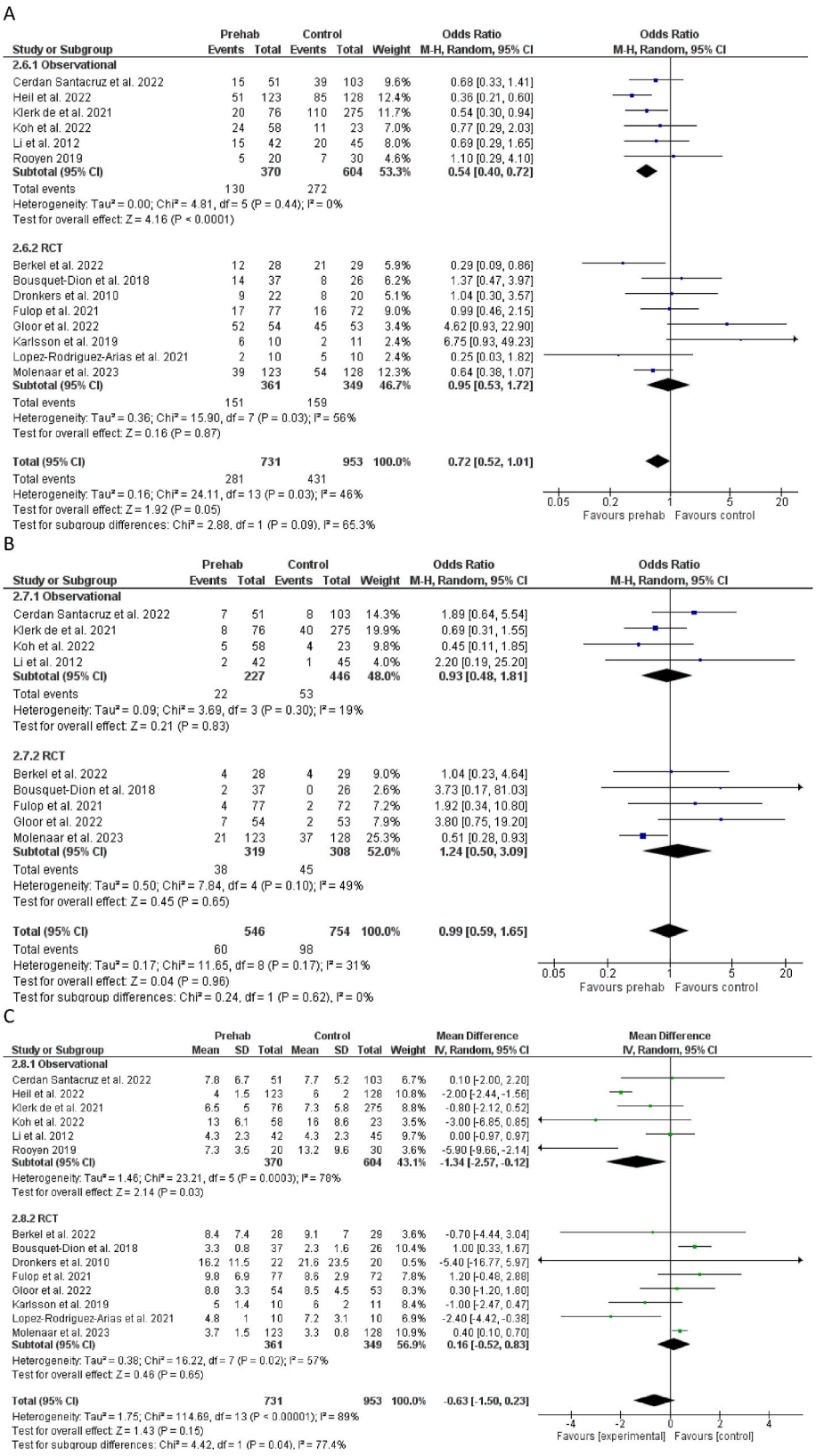

Fig. 3. The effect of exercise prehabilitation compared to usual care on postoperative complications (A), severe (Clavien-Dindo ≥3) postoperative complications (B) and length of hospital stay (C).

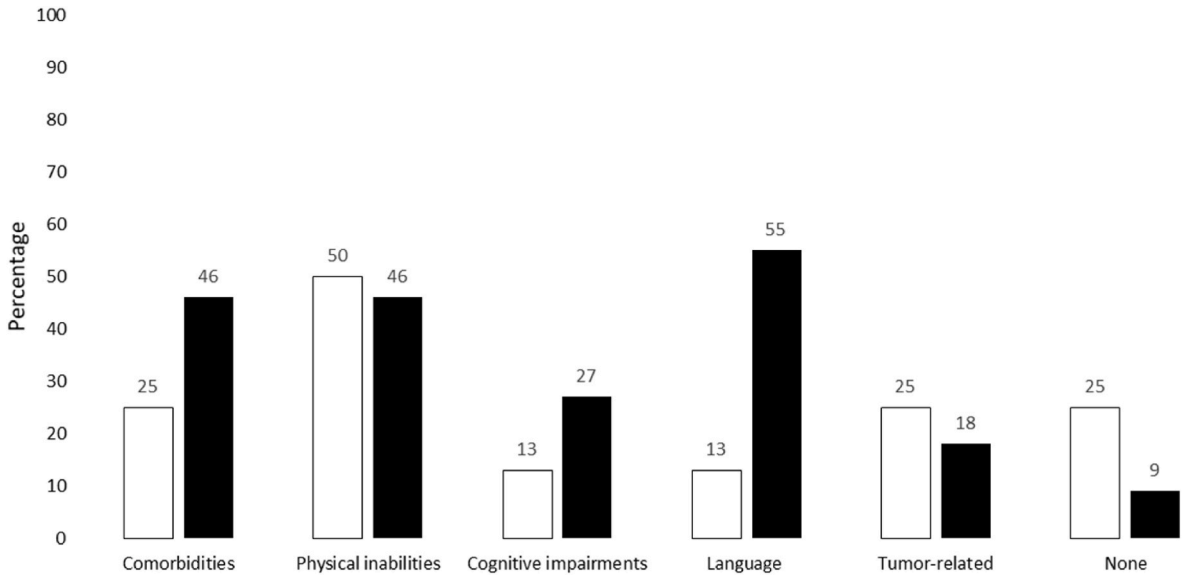

Fig. 4. Percentage of observational studies (white bars) and RCTs (black bars) reporting patient-related exclusion criteria.

of prehabilitation on postoperative complications and LoS.

When evaluating pooled postoperative complications and LoS outcomes of the included RCTs, results of the current study are in line with previous research that did not show a statically significant improvement in postoperative outcomes following prehabilitation [6,8,9]. On the contrary, when evaluating observational studies alone, a statistically significant reduction in postoperative complications and LoS following prehabilitation was observed.

As five [22–26] out of six observational studies that were included in the meta-analyses used a historical cohort as a reference population, one could easily argue that differences between observational studies and RCTs regarding complications and LoS are impacted by other healthcare innovations that might have been introduced during the study period. The two most impactful healthcare innovations in recent years that are expected to decrease the occurrence of postoperative complications and LoS [37–39] are minimally invasive surgery and enhanced recovery after surgery (ERAS, introduced in ~2005). Although unobserved bias can never be ruled out completely, reference populations within the five studies with a historical cohort [22–26] included in the meta-analysis were based on data of patients who underwent surgery in the one or two years directly preceding the start of the prehabilitation programs. In addition, three [22,24,26] out of five studies with a historical cohort explicitly reported that all patients were treated according to the ERAS guidelines and one study [25] was performed using data from 2017 onwards, which is well after the introduction and implementation of ERAS [40]. In the remaining study [23], it was unclear whether ERAS had been implemented in both the prehabilitation and the control group. As sensitive analyses without this one study [23] only marginally altered the OR for postoperative complications from 0.54 to 0.53. Moreover, no differences were found between observational studies and RCTs regarding the proportion of patients receiving minimally invasive surgery (Table 2). Therefore, differences in effectiveness of prehabilitation on postoperative outcomes between observational studies and RCTs as observed in the current systematic review and meta-analyses are unlikely to be fully explained by healthcare innovations that might have been introduced alongside or directly preceding the prehabilitation interventions. The observation that no reductions in severe postoperative complications were seen after prehabilitation might be due to a low total number of events (75 events in observational studies (11.6 %) and 83 events in RCTs (12.3 %); see Fig. 3B).

In the current systematic review, patients included in observational studies were of older age and had more (severe) systemic comorbidities (i.e., ASA score ≥3) compared to patients included in RCTs. This could mean that there is a mismatch between the populations included in RCTs and those included in prehabilitation in real-life practice (i.e., in observational studies). However, in meta-regression analysis, the differences in age and ASA score between included studies were not associated with the ability of prehabilitation to improve postoperative outcomes. This lack of association seems to be in contrast with previous research that has shown that adequate patient selection (i.e., focus on high-risk patients, often of older age with more co-morbidities) might be important for a prehabilitation program to be effective [41]. However, we were only able to adjust the analyses for chronological age instead of functional (physiological) age. Previous research has shown that a patient's aerobic fitness (as a marker of physiological age) is a stronger predictor of postoperative complications than chronological age [42]. In addition, the lack of association could also infer that patient selection cannot be seen in isolation of other content-related factors, such as prescribed and performed physical exercise training load, the amount of supervision and the adherence to the prehabilitation program, regardless of the study design (i.e., RCTs or observational studies).Regarding intervention characteristics, observational studies seemed to be more often multimodal (88 % versus 63 %) and fully supervised (75 % versus 45 %) compared to RCTs. High heterogeneity existed in the content of prehabilitation programs, which was also previously observed by Hijazi et al. [43]. In addition, reporting of prescribed and performed physical exercise training was rather incomplete, which precluded a comparison between interventions of observational studies and RCTs. As with the elements of ERAS, adherence to all individual items of an intervention are of a major importance for its combined effectiveness [38]. Studies included in the current review did not only lack adequate reporting of the received intervention dose (i.e., adherence); they also failed to report the prescribed prehabilitation interventions to sufficient detail (especially in observational studies). Poor reporting of physical exercise training interventions is not new [44], but does form a major barrier for the comparison of prehabilitation programs, as well as the implementation of prehabilitation programs [45].

The current systematic review showed that, in general, RCTs had more stringent inclusion criteria compared to observational studies. In addition, it is well known that including patients in randomized studies is difficult as is evidenced by the often very long period needed to include a relatively small number of participants [5]. These factors, along with the fact that observational studies more often focus on high-risk patients (50% versus 18%), might partially explain the

Table 2
Comparison of patient-related factors between and within observational studies and randomized controlled trials.

Studies included in the meta-analyses										
	Prehabilitation group				Usual care group[a]				Observational	RCT
	Observational (n = 370)	RCT (n = 361)	Mean difference (95 % CI)	p-value	Observational (n = 604)	RCT (n = 359)	Mean difference (95 % CI)	p-value	Prehab vs. UC p-value	Prehab vs. UC p-value
Age	75.5 (15.9)	68.9 (7.5)	6.6 (4.8–8.4)	**<0.001**	73.3 (9.7)	68.5 (7.5)	4.8 (3.7–5.9)	**<0.001**	0.11	0.38
Sex										
Male	226 (55.5 %)	202 (55.5 %)		1.0	327 (54.1 %)	206 (57.4 %)		0.40	0.94	0.42
Female	144 (45.5 %)	169 (45.5 %)			277 (45.9 %)	153 (42.6 %)				
ASA score I-II	181 (58.0 %)	196 (74.8 %)		**<0.001**	353 (60.9 %)	188 (73.4 %)		**<0.001**	0.40	0.72
ASA score ≥ III	131 (42.0 %)	66 (25.2 %)			227 (39.1 %)	68 (26.6 %)				
Missing[b]	58	99			24	103				
Surgery										
Open	43 (11.6 %)	28 (8.5 %)		0.17	55 (9.1 %)	36 (11.3 %)		0.55	0.20	0.23
Minimal invasive	327 (88.4 %)	301 (91.5 %)			548 (90.9 %)	283 (88.7 %)				
Missing[b]	–	32			1	40				
Smoking										
No/former	184 (95.4 %)	263 (78.7 %)		**<0.001**	242 (93.1 %)	238 (73.7 %)		**<0.001**	0.32	0.30
Current	9 (4.6 %)	71 (21.3 %)			18 (6.9 %)	85 (26.3 %)				
Missing[b]	177	54			344	36				

All studies										
	Prehabilitation group				Control group[c]				Observational	RCT
	Observational (n = 2408)	RCT (n = 496)	Mean difference (95 % CI)	p-value	Observational (n = 2976)	RCT (n = 464)	Mean difference (95 % CI)	p-value	Prehab vs. control p-value	Prehab vs. control p-vale
Age	75.3 (12.0)	69.4 (8.5)	6.0 (4.9–7.1)	**<0.001**	75.1 (11.6)	69.8 (8.5)	6.3 (5.2–7.4)		0.54	0.72
Sex										
Male	1352 (56.1 %)	278 (56.0 %)		0.97	1664 (55.9 %)	256 (55.2 %)		0.76	0.86	0.78
Female	1056 (43.9 %)	218 (44.0 %)			1312 (44.1 %)	208 (44.8 %)				
ASA score I-II	258 (59.2 %)	276 (69.5 %)		**0.002**	517 (65.4 %)	227 (64.8 %)		0.80	**0.03**	0.17
ASA score ≥ III	178 (40.8 %)	121 (30.5 %)			273 (34.6 %)	123 (35.1 %)				
Missing[b]	1972	99			2186	114				
Surgery										
Open	641 (30.8 %)	42 (10.0 %)		**<0.001**	625 (21.0 %)	50 (12.1 %)			**<0.001**	0.32
Minimal invasive	1667(69.2 %)	380 (90.0 %)			2351(79.0 %)	363 (87.9 %)				
Missing[b]	100	74			–	51				
Smoking										

(*continued on next page*)

Table 2 (*continued*)

All studies								
No/former	184 (95.4 %)	346 (80.3 %)	**<0.001**	242 (93.1 %)	288 (76.2 %)	**<0.001**	0.32	0.16
Current	9 (4.6 %)	85 (19.7 %)		18 (6.9 %)	90 (23.8 %)			
Missing[b]	2031	65		2716	84			

Numbers are reported as mean and standard deviation (SD) or numbers and percentage (%) unless stated otherwise. Bold numbers represent statistically significance at level $p < 0.05$. Abbreviations: CI = confidence interval, ASA = American Society of Anesthesiologists, UC = usual care.

[a] only includes studies that used a usual care group (no intervention) as reference population.

[b] missing was not included in statistical analyses.

[c] also includes studies that used patients receiving (postoperative) rehabilitation as a reference population.

differences found in populations included in RCTs and observational studies. Also, as a placebo is lacking in prehabilitation studies, it is very well imaginable that participants who were not included in the intervention group had become more active, or paid more attention to a healthy diet, which might have negatively influenced the magnitude of effect between the intervention and control group and might partially explain differences seen between observational studies and RCTs in the current systematic review.

The current study has several limitations. First, we were unable to achieve all aims since reporting of the intervention characteristics was poor and incomplete. Therefore, we were unable to compare observational studies and RCTs regarding the used prehabilitation interventions. Secondly, one of the main outcomes (LoS) was expressed as mean (SD). However, LoS is probably not normally distributed in most studies as evidenced by frequent reporting of a median and interquartile range. For pooling purposes (transformed) mean values were used as it was assumed that the differences between groups would show a normal distribution. Third, studies that included patients who underwent neoadjuvant chemotherapy or radiotherapy were excluded to ensure homogeneity. As chemotherapy and radiotherapy are part of real-life practice caution is warranted by extrapolation of the current results to this population.

Strengths of the current systematic review are that both observational studies as well as RCTs were included. In addition, the current study provides an elaborate evaluation of the current prehabilitation literature and provides an in-depth evaluation of the characteristics of patients included and intervention characteristics of prehabilitation studies.

To effectively evaluate prehabilitation interventions, future research should more closely reflect real-world practice by considering patient characteristics, including neoadjuvant treatments, and the types of interventions used. A study design such as a target emulation trial [46] could be an attractive approach, combining the advantages of observational studies (e.g., large sample sizes and closer alignment with clinical practice) with those of randomized controlled trials (e.g., high control and causal inference between interventions and outcomes). Additionally, more comprehensive reporting of both prescribed and performed interventions, using tools such as the i-CONTENT scale [47] or prehabilitation-specific measures [44], or prehabilitation-specific measures [44], is crucial to enable comparison across interventions and to facilitate effective implementation. While previous research has shown that partially supervised prehabilitation is feasible [48], further studies are necessary to evaluate its (cost-)effectiveness. Lastly, the variability observed in prehabilitation research may be driven by the fact that it is still unclear why some patients benefit from prehabilitation while others do not. Therefore, more fundamental and mechanistic studies are required, focusing on variables such as different exercise modalities, patient or tumor characteristics, or metabolic profiles,. in order to guide the contents of prehabilitation interventions.

5. Conclusions

Pooled results of observational studies in a real-life setting showed that prehabilitation can lower the odds for postoperative complications and reduce LoS, whereas no association between prehabilitation and postoperative outcomes was found in RCTs. Patient characteristics of patients included in RCTs did not seem to reflect real-life practice as patients included in observational studies were of older age and had more (severe) comorbidities compared to patients in RCTs. Specific observational study designs, like a target emulation trial, that better reflect real-life practice could be used to evaluate real-life effectiveness of current and future prehabilitation interventions.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://do

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References

[1] Ministerie van Volksgezondheid, W.e.S. Integraal Zorg Akkoord. Samen werken aan gezonde zorg [cited October 14, 2023; Available from: https://www.rijksoverheid.nl/documenten/rapporten/2022/09/16/integraal-zorgakkoord-samen-werken-aan-gezonde-zorg; September 2022.

[2] Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. Am J Phys Med Rehabil 2013;92(8):715–27.

[3] Davis JF, van Rooijen SJ, Grimmett C, West MA, Campbell AM, Awasthi R, et al. Davis JF, et al. From theory to practice: an international approach to establishing prehabilitation programmes. Curr Anesthesiol Rep 2022;12(1):129–37.

[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(4):450–6.

[5] 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(2):e299–306.

[6] Zhang X, Wang S, Ji W, Wang H, Zhou K, Jin Z, et X, et al. The effect of prehabilitation on the postoperative outcomes of patients undergoing colorectal surgery: a systematic review and meta-analysis. Front Oncol 2022;12:958261.

[7] Bruns ER, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. Colorectal Dis 2016;18(8):O267–77.

[8] Falz R, Bischoff C, Thieme R, Lassing J, Mehdorn M, Stelzner S, et al. Effects and duration of exercise-based prehabilitation in surgical therapy of colon and rectal cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2022;148(9):2187–213.

[9] Molenaar CJ, van Rooijen SJ, Fokkenrood HJ, Roumen RM, Janssen L, Slooter GD. Prehabilitation versus no prehabilitation to improve functional capacity, reduce postoperative complications and improve quality of life in colorectal cancer surgery. Cochrane Database Syst Rev 2022;5(5):CD013259.

[10] Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: study design: randomised controlled trials. BJOG 2018;125(13):1716.

[11] Hannan EL. Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations. JACC Cardiovasc Interv 2008;1(3):211–7.

[12] 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. Int J Surg 2021;88:105906.

[13] Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr 2005;24(3):466–77.

[14] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.

[15] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.

[16] Cochrane. RevMan Calculator. [cited October 10, 2023; Available from: https://training.cochrane.org/resource/revman-calculator.

[17] Cochrane. [cited October 10, 2023; Available from: https://handbook-5-1.cochrane.org/chapter_7/7_7_3_8_combining_groups.htm.

[18] Cochrane. [cited October 15, 2023; Available from: https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm.

[19] Ushida K, Yamamoto Y, Hori S, Shimizu M, Kato Y, Toiyama Y, et al. The effect of preoperative rehabilitation on the prevention of postoperative ileus in colorectal cancer patients. Support Care Cancer 2023;31(2):123.

[20] 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(11):2830–40.

[21] van Rooijen SJ, Molenaar CJL, Schep G, van Lieshout R, Beijer S, Dubbers R, et al. Making patients fit for surgery: introducing a four pillar multimodal prehabilitation program in colorectal cancer. Am J Phys Med Rehabil 2019;98(10):888–96.

[22] 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(3):645–53.

[23] Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc 2013;27(4):1072–82.

[24] Heil TC, Verdaasdonk EGG, Maas H, van Munster BC, Rikkert M, de Wilt JHW, et al. Improved postoperative outcomes after prehabilitation for colorectal cancer surgery in older patients: an emulated target trial. Ann Surg Oncol 2023;30(1):244–54.

[25] 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(11):2849–56.

[26] Cerdan Santacruz C, Merichal Resina M, Gomez Baez FD, Milla Collado L, Sanchez Rubio MB, Cano Valderrama O. et al."Optimal recovery" after colon cancer surgery in the elderly, a comparative cohort study: conventional care vs. enhanced recovery vs. prehabilitation. Cir Esp 2023;101(6):426–34.

[27] Bousquet-Dion G, Awasthi R, Loiselle SE, Minnella EM, Agnihotram RV, Bergdahl A. et al Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. Acta Oncol 2018;57(6):849–59.

[28] 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(3):233–42.

[29] Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM, Veldman A, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. Clin Rehabil 2010;24(7):614–22.

[30] 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(1):82–90.

[31] Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology 2014;121(5):937–47.

[32] Gloor S, Misirlic M, Frei-Lanter C, Herzog P, Muller P, Schafli-Thurnherr J, et al. Prehabilitation in patients undergoing colorectal surgery fails to confer reduction in overall morbidity: results of a single-center, blinded, randomized controlled trial. Langenbeck's Arch Surg 2022;407(3):897–907.

[33] 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(7):e0219158.

[34] Lopez-Rodriguez-Arias F, Sanchez-Guillen L, Aranaz-Ostariz V, Triguero-Canovas D, Lario-Perez S, Barber-Valles X, et al. Effect of home-based prehabilitation in an enhanced recovery after surgery program for patients undergoing colorectal cancer surgery during the COVID-19 pandemic. Support Care Cancer 2021;29(12):7785–91.

[35] Minnella EM, Ferreira V, Awasthi R, Charlebois P, Stein B, Liberman AS, et al. Effect of two different pre-operative exercise training regimens before colorectal surgery on functional capacity: a randomised controlled trial. Eur J Anaesthesiol 2020;37(11):969–78.

[36] Molenaar CJL, Minnella EM, Coca-Martinez M, Ten Cate DWG, Regis M, Awasthi R, et al. Effect of multimodal prehabilitation on reducing postoperative complications and enhancing functional capacity following colorectal cancer surgery: the PREHAB randomized clinical trial. JAMA Surg 2023;158(6):572–81.

[37] Turaga AH. Enhanced recovery after surgery (ERAS) protocols for improving outcomes for patients undergoing major colorectal surgery. Cureus 2023;15(7):e41755.

[38] Pache B, Hubner M, Jurt J, Demartines N, Grass F. Minimally invasive surgery and enhanced recovery after surgery: the ideal combination? J Surg Oncol 2017;116(5):613–6.

[39] Ni X, Jia D, Chen Y, Wang L, Suo J. Is the enhanced recovery after surgery (ERAS) program effective and safe in laparoscopic colorectal cancer surgery? A meta-analysis of randomized controlled trials. J Gastrointest Surg 2019;23(7):1502–12.

[40] Gillissen F, Hoff C, Maessen JM, Winkens B, Teeuwen JH, von Meyenfeldt MF, et al. Structured synchronous implementation of an enhanced recovery program in elective colonic surgery in 33 hospitals in The Netherlands. World J Surg 2013;37(5):1082–93.

[41] Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: a systematic review of randomised controlled trials. Eur J Anaesthesiol 2019;36(12):933–45.

[42] West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. Br J Surg 2016;103(6):744–52.

[43] Hijazi Y, Gondal U, Aziz O. A systematic review of prehabilitation programs in abdominal cancer surgery. Int J Surg 2017;39:156–62.

[44] Engel D, Testa GD, McIsaac DI, Carli F, Santa Mina D, Baldini G, et al. Reporting quality of randomized controlled trials in prehabilitation: a scoping review. Perioper Med (Lond) 2023;12(1):48.

[45] Franssen RFW, Janssen-Heijnen MLG, Barberan-Garcia A, Vogelaar FJ, Van Meeteren NLU, Bongers BC. Moderate-intensity exercise training or high-intensity interval training to improve aerobic fitness during exercise prehabilitation in patients planned for elective abdominal cancer surgery? Eur J Surg Oncol 2022;48(1):3–13.

[46] Hernan MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. JAMA 2022;328(24):2446–7.

[47] Hoogeboom TJ, Kousemaker MC, van Meeteren NL, Howe T, Bo K, Tugwell P, et al. i-CONTENT tool for assessing therapeutic quality of exercise programs employed in randomised clinical trials. Br J Sports Med 2021;55(20):1153–60.

[48] Franssen RFW, Bongers BC, Vogelaar FJ, Janssen-Heijnen MLG. Feasibility of a tele-prehabilitation program in high-risk patients with colon or rectal cancer undergoing elective surgery: a feasibility study. Perioper Med (Lond) 2022;11(1):28.