Received: 10 May 2024 | Revised: 10 December 2024 | Accepted: 20 January 2025

DOI: 10.1111/codi.70023

META-ANALYSIS

Evaluating the therapeutic quality of prehabilitation programmes in patients scheduled for colorectal surgery: A systematic review and meta-analysis

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Abstract

Aim: The aim of this work was to evaluate whether the therapeutic quality of exercise prehabilitation programmes is associated with their effectiveness to preoperatively improve aerobic fitness and reduce postoperative complications and length of hospital stay in patients scheduled for colorectal surgery.

Method: Three electronic databases (PubMed, Embase and CINAHL) were systematically searched (up to October 2023) for randomized controlled trials that investigated the effects of prehabilitation before colorectal resection. Methodological quality and therapeutic quality were assessed using, respectively, the Cochrane Risk of Bias 2 tool and the i-CONTENT tool. Studies were divided into four subgroups based on the estimated risk of bias and risk of ineffectiveness.

Results: Fourteen studies were included, comprising 986 patients. Meta-analysis showed that, in general, prehabilitation improved preoperative aerobic fitness but did not improve postoperative outcomes. No differences were found between the four subgroups; however, only one study (7%) had a low risk of bias in combination with a low risk of ineffectiveness.

Conclusion: The fact that only one study had a low risk of bias in combination with a low risk of ineffectiveness precluded us from establishing an association between therapeutic quality and the effectiveness of prehabilitation on postoperative outcomes. The quality of future prehabilitation research with exercise interventions should be improved by using an assessment tool during the design phase of prehabilitation programmes.

KEYWORDS
colorectal cancer, exercise programme, preoperative care, preoperative training, presurgical

INTRODUCTION

Despite advances in surgery and care, such as the enhanced recovery after surgery (ERAS) programme [1], the incidence of postoperative complications in colorectal surgery patients remains high (~30%) [2]. Even without the occurrence of postoperative complications, surgical treatment is associated with a functional decline that has an impact on the patient's life [3]. Prehabilitation involves a preventive approach that aims to improve the patient's health preoperatively (e.g. improving physical fitness, improving nutritional status, anxiety reduction, smoking cessation) in order to reduce postoperative complications and enhance postoperative recovery of physical functioning [4].

Recently, several systematic reviews evaluating the effectiveness of prehabilitation on preoperative aerobic fitness and postoperative outcomes in patients undergoing abdominal surgery and colorectal surgery have been published [5–10]. These systematic reviews show inconsistent results, as some indicate that prehabilitation might effectively reduce postoperative complications [5, 6] whereas others do not [7–10]. Heterogeneity in the content and context of the prehabilitation interventions might, at least partially, explain these inconsistent results. That is, in their subgroup analyses, these systematic reviews report that prehabilitation might effectively improve aerobic fitness and improve postoperative outcomes if the duration of the intervention is more than 3 weeks [9], if it contains high-intensity interval training [5], is supervised [8] or is executed in frail (often older) patients [6]. In other words, the inconsistent findings of previous systematic reviews regarding the effectiveness of prehabilitation prior to colorectal surgery might be explained by variations in the therapeutic quality of the studied interventions. The international Consensus ON Therapeutic Exercise aNd Training (i-CONTENT) tool [11] can be used to systematically evaluate the therapeutic quality (i.e. the risk of ineffectiveness) of physical exercise training interventions by assessing their content and context.

To our knowledge, no study has systematically reviewed the effectiveness of prehabilitation interventions prior to colorectal surgery while accounting for their therapeutic quality. Therefore, the primary aim of the current study was to evaluate whether indicators of therapeutic quality are associated with the ability of prehabilitation programmes to preoperatively improve aerobic fitness and reduce postoperative complications and length of hospital stay (LOS) in patients scheduled for colorectal cancer surgery. It was hypothesized that methodologically sound studies investigating prehabilitation programmes with high therapeutic quality would demonstrate greater improvements in preoperative aerobic fitness and reductions in postoperative complications and LOS in patients with colorectal cancer scheduled for surgery compared with prehabilitation programmes with a low therapeutic quality.

What does this paper add to the literature?

There is an ongoing debate on the merit of prehabilitation to optimize the postoperative recovery of patients scheduled for colorectal surgery. With this systematic review we aimed to evaluate whether the content of prehabilitation programmes is associated with their effectiveness to improve a patient's aerobic fitness and subsequently postoperative outcomes.

METHOD

The current systematic review was conducted in accordance with the Cochrane systematic review guidelines [12] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The study protocol was prospectively registered at PROSPERO (CRD42023417172).

Search strategy

The current study is an updated systematic review, including a more in-depth analysis of the content of the included prehabilitation programmes, extending a systematic review and meta-analysis by Falz et al. [9]. A systematic literature search was executed in the databases PubMed, Embase and CINAHL from 2005 until October 2023. The start date of the search was chosen because 2005 was the year the ERAS protocol was introduced for patients undergoing colorectal surgery [14]. The search strategy was constructed in collaboration with a registered librarian. The search strategy included colorectal surgery for population and prehabilitation for intervention. The full PubMed search string is shown in File S1.

Study selection

Randomized controlled trials (RCTs) written in English, German or Dutch including adult patients aged ≥18 years scheduled for colorectal surgery (≥90%) were selected. The prehabilitation programme could be unimodal or multimodal but should at least include a structured form of physical exercise training that aimed to preoperatively improve a patient's aerobic fitness. Control groups consisted of patients who either received no intervention (usual care) or a comparison intervention (e.g. a different physical exercise programme). Studies should include at least one of the following outcome measures: aerobic fitness, overall postoperative complications, severe postoperative complications [Clavien–Dindo score ≥3 or comprehensive complication index (CCI) ≥20] or LOS. Physical exercise training was defined as a structured form of aerobic, interval and/or resistance exercises, based upon validated measurements describing training intensity (e.g. heart rate, rating of perceived exertion, work rate), eventually supplemented with breathing exercises. Studies with patients receiving (neo)adjuvant treatment during the prehabilitation programme were excluded to ensure homogeneity and comparability between studies. Two reviewers (EJ and RF) independently screened titles and abstracts of retrieved records based on inclusion and exclusion criteria using the Rayyan web application [15]. Thereafter, the assessment of full-text articles according to eligibility criteria was performed by the two reviewers (EJ and RF) independently. Any disagreements between reviewers were resolved by reaching consensus after discussion. When no consensus was reached, a third party acted as an adjudicator (MV).

Data extraction

One reviewer (EJ) extracted the following data from the included studies: first author, publication year, number of participants, patient characteristics, type of prehabilitation intervention and main outcomes. In addition, the items of the i-CONTENT tool [11] and characteristics of the physical exercise training programme were extracted using the training frequency, training intensity, training time, training type, training volume and training progression (FITT-VP) principles. Accuracy and completeness of the data extraction was checked randomly by a second reviewer (RF). When outcome data or data needed for the purpose of estimating the risk of ineffectiveness (i-CONTENT) were missing the corresponding author was contacted.

Methodological quality

Risk of bias assessment was undertaken using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs [16]. For all studies that were also included in the original systematic review of Falz et al. [9], risk of bias assessment was adopted from Falz et al. and checked by one reviewer (EJ).

Risk of bias assessment of the additional studies included in the current updated systematic review was assessed by two reviewers (EJ and RF) independently using the RoB2 tool for RCTs. Studies were divided in two groups based on the estimated risk of bias. Studies were considered to be at low risk of bias when all domains of the RoB2 tool were assessed with a low risk of bias. Studies were considered at 'some/high risk of bias' when one or more domains of the RoB2 tool were assessed with 'some/high risk of bias'. Disagreements between the reviewers were resolved by discussion until consensus was reached. When no consensus was reached, a third person (MV) was contacted to resolve the disagreement.

Therapeutic quality

The i-CONTENT tool was used to assess the therapeutic quality of the physical exercise training interventions [11]. The i-CONTENT tool is an internationally developed consensus-based tool that aims to transparently assess the quality of exercise therapy programmes of RCTs [11]. Two assessors (EJ and RF) used the i-CONTENT tool to systematically map and analyse the content of the training programme. To ensure a more consistent assessment, a guideline for the interpretation of the items of the i-CONTENT tool in the context of prehabilitation prior to colorectal cancer surgery was composed by the authors before the start of data extraction (see File S2). The content tool distinguishes between seven binary items based on low risk and high risk of ineffectiveness. Studies were divided into two groups based on the assessed therapeutic quality. Studies were considered to be at low risk of ineffectiveness when all items of the i-CONTENT tool were assessed with a low risk of ineffectiveness. Studies were considered as having any risk of ineffectiveness when one or more items were assessed with a high risk of ineffectiveness.

Statistical analysis

Extracted data were pooled for the outcome measures aerobic fitness, overall postoperative complications, severe postoperative complications (Clavien–Dindo ≥3 or CCI ≥20) and LOS. For pooling purposes, the median and (interquartile) range were converted to mean and standard deviation (SD) using the method by Wan et al. [17] and confidence intervals were converted to SD using the Cochrane Review Manager calculator (RevMan version 5.4, The Cochrane Collaboration, 2020).

A meta-analysis was conducted using the Cochrane Review Manager (RevMan version 5.4, The Cochrane Collaboration, 2020). Random effects models were used to account for clinical heterogeneity between studies. Continuous variables were expressed as mean difference (MD) and 95% confidence interval (CI). Dichotomous variables were expressed as odds ratios (ORs) with CI. Studies were divided in four groups based on the estimated

risk of bias and risk of ineffectiveness (group 1, low risk of bias and low risk of ineffectiveness; group 2, some/high risk of bias and low risk of ineffectiveness; group 3, low risk of bias and any risk of ineffectiveness; group 4, some/high risk of bias and any risk of ineffectiveness). These groups were chosen as the authors of the i-CONTENT tool advise to assess the risk of ineffectiveness in conjunction with the risk of bias [11]. Categorization of the risk of bias (low, some, high) was done according to the criteria of the RoB2 tool. Studies were scored as an overall low risk of ineffectiveness when all items of the i-CONTENT tool scored a low risk of ineffectiveness. If one or more items scored a high risk of ineffectiveness, the study scored as any risk of ineffectiveness. The associations between the ability of prehabilitation to improve aerobic fitness, reduce postoperative complications and LOS were meta-analysed, stratified by the risk of ineffectiveness on the i-CONTENT tool. Heterogeneity was identified using the I^2 statistic and defined as follows: 0%–40%, might not be important; 30%–60%, may represent moderate heterogeneity; 50%–90%, may represent substantial heterogeneity; 75%–100%, considerable heterogeneity [12]. For all statistical analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Study characteristics

A total of 14 studies were included in the current systematic review [18–31], comprising a total of 986 participants (see Figure 1 for a flowchart of study inclusion and Table 1 for characteristics of the included studies). Ten studies (71%) compared prehabilitation with usual care [18,21–23,25–28,30,31], two (14%) compared prehabilitation with rehabilitation [20,24], one (7%) compared prehabilitation plus rehabilitation with rehabilitation alone [19] and one (7%) compared two different exercise prehabilitation interventions (high- and moderate-intensity exercise training) with each other [29]. Eight studies (57%) used a multimodal prehabilitation programme [19,20,22–24,28–30] and six (43%) used a unimodal prehabilitation programme [18,21,25–27,31]. Table 1 also summarizes the characteristics and main outcomes of the studies. Two studies were not eligible for meta-analysis. Of these two studies, one compared two prehabilitation interventions with each other, and therefore did not have a control group that did not perform prehabilitation [29], and one study had only one participant following prehabilitation [23].

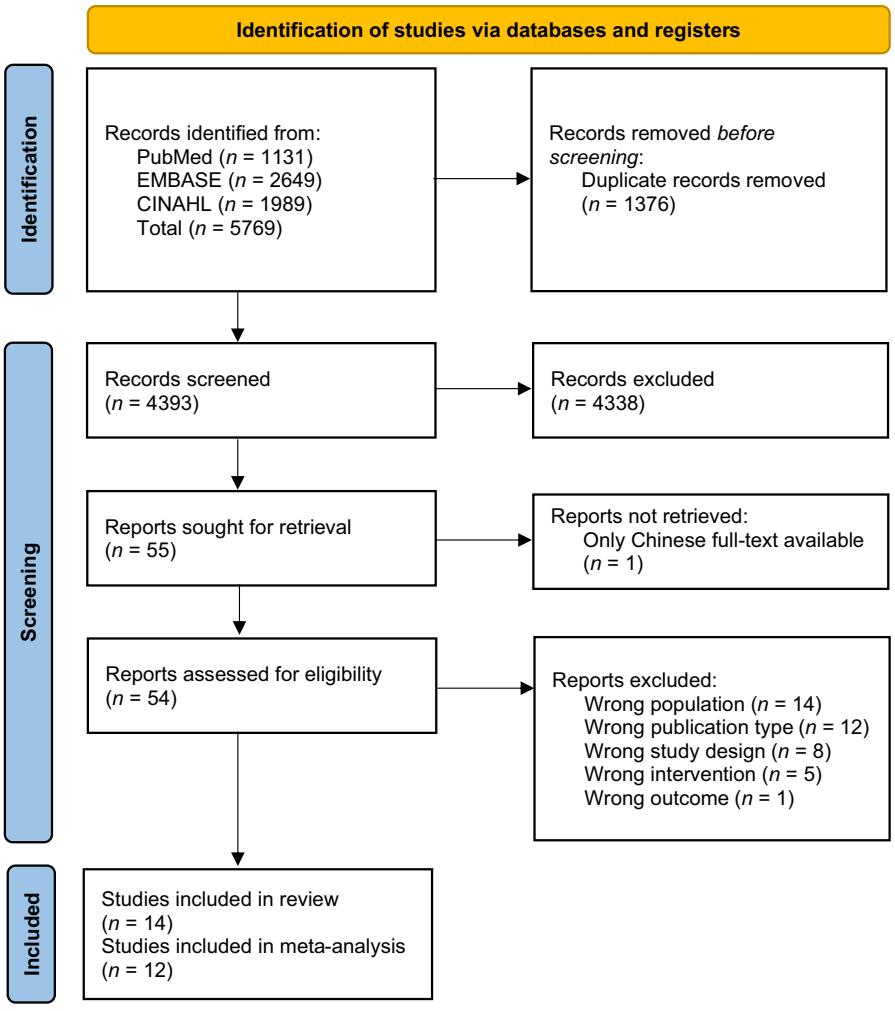

FIGURE 1 PRISMA flow chart of study inclusion.

TABLE 1 General characteristics of the included studies.

Study/country	Intervention/control	Population/patient selection	Sample size (%male)	Laparoscopic surgery (%)	Age (years)	Main outcome	Included in meta-analysis
Berkel et al. (2022)/The Netherlands	Prehab/UC	Colorectal (pre) malignancy/high-risk population	Prehab 28 (57%) UC 29 (48%)	Prehab 82% UC 72%	Prehab 74 (7) UC 73 (6)	Aerobic fitness[b]: VO_{2peak} difference: Prehab +1.3 mL/kg/min ($p=0.051$)[a] VO_2 at the VAT difference: Prehab +0.97 mL/kg/min ($p=0.006$)[a] Postoperative complications: Overall: Prehab 12 (43%); UC 21 (72%) ($p=0.02$) CCI: Prehab 17.3 (26.1); UC 18.4 (16.5) ($p=0.24$) Severe (Clavien–Dindo ≥3): Prehab 4 (14%); UC 4 (14%) LOS: Prehab 8.4 (7.4) days; UC 9.1 (7.0) days ($p=0.14$)	Overall complications Severe complications LOS
Bousquet-Dion et al. (2018)/Canada	Prehab + Rehab/rehab	Colorectal cancer Stage 1–3+/high-risk population	Prehab 37 (81%) UC 26 (62%)	Prehab 84% UC 81%	Prehab 74 [67.5–78] UC 71[54.5–74.5]	Aerobic fitness[b]: 6MWT difference: Prehab 21 m (47); UC 10 m (30) ($p=$n.s) Postoperative complications: Overall: Prehab 14 (38%); UC 8 (31%) ($p=0.562$) Severe (Clavien–Dindo ≥3): Prehab 2 (5%); UC 0 (0%) LOS: Prehab 3 [3–4] days; UC 3 [2–4] days ($p=0.122$)	6MWT Overall complications Severe complications
Carli et al. (2020)/Canada	Prehab/Rehab	Colorectal stage 0–4/low-risk population	Prehab 55 (53%) UC 55 (42%)	Prehab 76% UC 81%	Prehab 78 [72–82] UC 82 [75–84]	Aerobic fitness[b]: 6MWT difference: Prehab 21 m; UC 12 m (MD 11.2, $p=0.37$) LOS: Prehab 4 (3–8) days; UC 4 (3–8) days ($p=0.80$) Postoperative complications: Overall: Prehab 25 (46%); UC 25 (46%) ($p=0.90$) Severe (Clavien–Dindo ≥3): Prehab 7 (13%); UC 11 (20%) ($p=0.23$) CCI: Prehab 12.7 (21.5); UC 15.7 (25.3) ($p=0.45$)	6MWT
Dronkers et al. (2020)/Canada	Prehab/UC	Colorectal (stage not reported)/low-risk population	Prehab 22 (68%) UC 20 (80%)	Not reported	Prehab 69 (6) UC 71 (6)	Aerobic fitness[b]: PWC (O_2 mL/kg/min) difference: Prehab −1.7 (8.4); UC 1.3 (6.4) ($p=0.16$) Overall postoperative complications: Prehab 9 (45%); UC 8 (38%) ($p=0.65$) LOS: Prehab 16.2 (11.5) days; UC 21.6 (23.7) days ($p=0.31$)	Overall complications LOS

(Continues)

TABLE 1 (Continued)

Study/country	Intervention/ control	Population/patient selection	Sample size (%male)	Laparoscopic surgery (%)	Age (years)	Main outcome	Included in meta-analysis
Fulop et al. (2021)/Hungary	Prehab/UC	Colorectal/low-risk population	Prehab 77 (48%) UC 72 (54%)	Prehab 91% UC 90%	Prehab 70 [60–75] UC 70 [64–75]	Aerobic fitness[b]: 6MWT difference: Prehab 85.7 (84) m vs. 23 (49) m[a] Postoperative complications: Overall: Prehab 17 (24%); UC 16 (22%) ($p=0.569$) Severe (Clavien–Dindo ≥3): Prehab 4 (5%); UC 2 (3%) ($p=0.373$) LOS: Prehab 9.8 (6.9) days; UC 8.55 (2.9) days ($p=0.712$)[a]	6MWT Overall complications Severe complications LOS
Furyk et al. (2021)/Australia	Prehab/UC	Colorectal/high-risk population	Prehab 2 (50%) UC 3 (67%)	Not reported	Prehab: P1, 57; P2, 60 UC: P1, 64; P2, 73; P3, 82	Aerobic fitness: 6MWT (baseline; preoperative; follow-up): Prehab ($n=2$): P1 472 m; 488 m; NA. P2 NA; NA; NA Control ($n=3$): P1 380 m; 449 m; 415 m; P2 451 m; 460 m; NA. P3 352 m; NA; NA	Not included
Gillis et al. (2014)/ Canada	Prehab/Rehab	Colorectal/high-risk population	Prehab 38 (55%) UC 39 (69%)	Prehab 97% UC 90%	Prehab 66 (14) UC 66 (9)	Aerobic fitness[b]: 6MWT difference: Prehab 25.2 m (50.2); UC −16.4 m (46.0) ($p<0.001$) Postoperative complications: Overall: Prehab 12 (32%); UC 17 (44%) ($p=0.277$) Severe (Clavien–Dindo ≥3): Prehab 4 (11%); UC 6 (15%) LOS: Prehab 4 [3–5] days; UC 4 [3–7] days ($p=0.812$)	6MWT
Gloor et al. (2022)/ Switzerland	Prehab/UC	Colorectal resection	Prehab 54 (44%) UC 53 (60%)	Prehab 96% UC 98%	Median (range) Prehab 65 (29–86) UC 66 (24–90)	Postoperative complications: Overall: Prehab 52 (96%); UC 45 (85%) Severe (Clavien–Dindo ≥3): Prehab 7 (13%); UC 2 (4%) ($p=0.162$) CCI score, mean (range): Prehab 18 (0–43); UC 15 (0–49) ($p=0.059$)[a] LOS: Prehab median [range] 7 [3–18] days; UC 6 [2–20] days ($p=0.874$)[a]	Severe complications

TABLE 1 (Continued)

Study/country	Intervention/ control	Population/patient selection	Sample size (%male)	Laparoscopic surgery (%)	Age (years)	Main outcome	Included in meta-analysis
Karlsson et al. (2019)/Sweden	Prehab/UC	Colorectal/high-risk population	Prehab 10 (40%) UC 11 (36%)	Prehab 70% UC 73%	Prehab 84 [76–85] UC 74 [73–76]	Aerobic fitness[b]: 6MWT difference, median (95% CI): Prehab 15 (−29 to 46) m; UC −4 (−16 to 20) m ($p=0.64$) Postoperative complications: Overall 6 (60%) vs. 2 (18%) ($p=0.06$) LOS: Prehab 5 (4–6) days; UC 6 (4–7) days ($p=0.57$)	6MWT Overall complications LOS
Kim et al. (2009)/ Canada	Prehab/UC	Colorectal/low-risk population	Prehab 14 (64%) UC 7 (57%)	Not reported	Prehab 55 (15) UC 65 (9)	Aerobic fitness[b]: 6MWT difference: Prehab 31 (61) m; UC 27 (50) m VO_{2peak} difference: Prehab 0.5 (4.2) mL/kg/min; UC −0.4 (1.4) mL/kg/min	6MWT VO_{2peak}
Lopez-Rodriguez-Arias et al. (2021)/ Spain	Prehab/UC	Colorectal/low-risk population	Prehab 10 (60%) UC 10 (70%)	Not reported	Prehab 67 (10) UC 66 (8)	Postoperative complications: Overall: Prehab 2 (20%); UC 5 (50%) ($p=0.16$) LOS: Prehab 4.8 (1) days; UC 7.2 (3.2) days ($p=0.052$)	Overall complications LOS
Minnella et al. (2020)/Canada	Prehab1/Prehab2	Colorectal/low-risk population	HIIT group 21 (48%) MICT group 21 (76%)	Not reported	Prehab1 67 (95% CI 60–72) Prehab2 67 (95% CI 52–76)	Aerobic fitness[b]: 6MWT difference: Prehab1 12.6 m; Prehab2 18.1 m ($p=0.696$) VO_{2peak} difference, mean (95% CI): Prehab1 1.95 (0.71–3.19) mL/kg/min; Prehab2 0.45 (−0.71 to 1.6) mL/kg/min ($p=0.08$) Postoperative complications: Overall: HIIT group 5 (42%); MICT group 8 (38%) ($p=0.449$) Severe (Clavien–Dindo ≥3): Prehab1 0 (0%); Prehab2 0 (0%) LOS: Prehab1 3.5 [3–6] days vs. Prehab2 4 [3–5] days ($p=0.626$)	Not included

(Continues)

TABLE 1 (Continued)

Study/country	Intervention/ control	Population/patient selection	Sample size (%male)	Laparoscopic surgery (%)	Age (years)	Main outcome	Included in meta-analysis
Molenaar et al. (2023)/ international[c]	Prehab/UC	Colorectal cancer Stage I–III/low-risk population	Prehab 123 (50%) UC 128 (59%)	Prehab 118 (96%) UC 116 (91%)	Prehab 69 [60–77] UC 71 [60–76]	Aerobic fitness[b]: 6MWT difference: Prehab 17.5 [−18.0–48.0] m; UC −5.0 [−38.0–34.0] m ($p = 0.06$) VO_{2peak} difference: Prehab 1.0 mL/kg/min; UC Prehab 1.0 mL/kg/min VO_2 at VAT difference: Prehab 1.0 mL/kg/min; UC Prehab 0.0 mL/kg/min Postoperative complications: Overall: Prehab 39 (32%); UC 54 (42%) ($p = 0.07$) Severe (CCI > 20): Prehab 21 (17%); UC 38 (30%) ($p = 0.02$) CCI: Prehab 0 [0–8.7]; UC 0 [0–20.9] LOS: Prehab 3 [3–5] days; UC 3[3–4] days ($p = 0.20$)	Overall complications VO_{2peak}
Northgraves et al. (2020)/United Kingdom	Prehab/UC	Colorectal/low-risk population	Prehab 10 (40%) UC 11 (64%)	Prehab 40% UC 36%	Prehab 64 (11) UC 64 (13)	Aerobic fitness[b]: 6MWT difference: Prehab 68.9 (37.6) m; UC 7.9 (38.6) m LOS: Prehab 10 [5–12] days; UC: 8 [6–27] days	6MWT LOS

Note: Values are presented as mean (standard deviation) or median [interquartile range] unless stated otherwise. Complications until 30 days.

Abbreviations: 6MWT, 6-min walk test; CCI, comprehensive complication index; CI, confidence interval; HIIT, high-intensity interval training; LOS, length of hospital stay; MICT, moderate-intensity continuous training; P1, participant 1; P2, participant 2; P3, participant 3; Prehab, prehabilitation group; PWC, physical work capacity; Rehab, rehabilitation group; UC, usual care group (no intervention); VAT, ventilatory anaerobic threshold; VO_2, oxygen consumption; VO_{2peak}, peak oxygen consumption.

[a]Received after contacting the authors.

[b]Aerobic fitness: illustrates the difference between the baseline and preoperative assessment.

[c]The Netherlands, Canada, Spain, Italy and Denmark.

Methodological quality of the studies

The assessment of the methodological quality is depicted in Table 3. Six out of 14 studies (43%) had a low risk of bias [18,20,22,24,25,30]. Of the remaining studies, one (7%) had a high risk of bias due to missing outcome data [23] and seven (50%) had some concerns due to measurement of the outcome [26,27], selection of the reported result [21,27,29,31], the randomization process [27–29] and deviations from the intended interventions [19,21,26,27].

Characteristics of physical exercise interventions

The physical exercise training interventions of the prehabilitation programmes consisted of aerobic exercise training in all 15 prehabilitation programmes [18–31] and resistance exercises in 13 prehabilitation programmes (87%) [18–21,23–26,28–31]. In three prehabilitation programmes (20%) [21,22,26], breathing exercises were also included. Five prehabilitation programmes (33%) [18,23,25,29,30] used a high-intensity physical exercise intervention and 10 prehabilitation programmes (67%) [19–22,24,26–29,31] used a moderate-intensity physical exercise intervention, of which one compared high-intensity exercise with moderate-intensity exercise [29]. The duration of the physical exercise training interventions varied between 2 and 7 weeks. The frequency of training sessions ranged from two to seven times per week. The duration of training sessions varied between 25 and 60 min per session. A detailed description of the physical exercise training interventions is reported in Table 2.

Therapeutic quality of the exercise prehabilitation interventions

One prehabilitation programme (7%) [18] had a low risk of ineffectiveness on all items of the i-CONTENT tool. All the other prehabilitation programmes (93%) scored a high risk of ineffectiveness on at least one item of the i-CONTENT tool. Of these, 10 prehabilitation programmes (87%) [19–22,24,26–29,31] scored a high risk of ineffectiveness on the i-CONTENT tool item dosing of the exercise prehabilitation programme and nine programmes (60%) [21,22,25,27–31] on patient selection. Six prehabilitation programmes (40%) [19,20,22,24,27,28] scored a high risk of ineffectiveness on the item supervision (i.e. lack of supervised exercise sessions) and four exercise prehabilitation programmes (27%) [20,24,27,30] on adherence to the physical exercise training programme (see Table 3 and File S3).

Effects of prehabilitation on aerobic fitness

Of the studies that were included in the meta-analysis, eight studies used the distance walked on the 6-min walk test (6MWT) as a measure of aerobic fitness [19,20,22,24,26,27,30,31]. The pooled results of all studies showed that prehabilitation improved the distance walked on the 6MWT (MD +31.45 m, 95% CI 11.97–50.93 m; $I^2 = 69\%$). None of these studies scored a low risk of bias in combination with a low risk of ineffectiveness. Figure 2 shows the pooled results of the 6MWT of all studies combined and stratified for the risk of bias and risk of ineffectiveness. There were no statistically significant differences found between the subgroups with a low risk of ineffectiveness and a high risk of ineffectiveness for the individual items of the i-CONTENT tool (see File S4).

Two studies [27,30] reported on the difference in oxygen uptake at peak exercise (VO_{2peak}) between the prehabilitation and control group. One study [30] scored a low risk of bias in combination with any risk of ineffectiveness and showed that prehabilitation improved the VO_{2peak} (MD +0.80, 95% CI 0.13–1.47). The other study [27] scored some or high risk of bias and any risk of ineffectiveness and showed that prehabilitation did not improve the VO_{2peak} statistically significantly (MD +0.90, 95% CI −1.53 to 3.33).

Effects of prehabilitation on postoperative complications

Overall postoperative complications were assessed in 11 studies [18–22,24–26,28–30]. Four studies [20,24,25,29] were excluded from the meta-analysis. The reasons for exclusion were an extremely high proportion of overall postoperative complications (91%) [25] that was not consistent with other studies (average of 34%) or that the control group performed a different prehabilitation programme [29]. When the control group performed rehabilitation [24,32], the studies were also excluded to prevent confounding from an additional postoperative intervention (i.e. the initiation of any rehabilitation interventions falls within the follow-up period for the evaluation of postoperative complications). The pooled results of all studies reporting postoperative complications did not show a significant difference in overall postoperative complications in patients receiving prehabilitation compared with patients receiving usual care (OR 0.89, 95% CI 0.54–1.46; $I^2 = 50\%$; Figure 3).

When stratifying for the risk of ineffectiveness and risk of bias, only the study that scored a low risk of bias in combination with a low risk of ineffectiveness [18] showed that prehabilitation reduced overall postoperative complications (OR 0.29, 95% CI 0.09–0.85; Figure 3). There were no statistically significant differences found between the subgroups with a low risk of ineffectiveness and a high risk of ineffectiveness for the individual items of the i-CONTENT tool (see File S4).

Severe postoperative complications were reported in eight studies [18,19,22,24,25,29,30,32]. Three studies were excluded in the meta-analysis due to the control group performing a different prehabilitation programme [29] or performing rehabilitation [24,32]. The pooled results of all studies reporting on severe

TABLE 2 Characteristics of prehabilitation programmes.

Study	Prehabilitation modules	Description of physical exercise intervention	Duration of exercise intervention	Training frequency	Training intensity	Time	Adherence training sessions/adverse events
Berkel et al. (2022)/The Netherlands	Physical exercise training	(a) Supervised community-based cycle ergometer interval training (b) Supervised community-based resistance training	3 weeks	3 times per week	(a) Moderate- to high-intensity, intervals at 120% of the work rate achieved at the VAT and adapted based on Borg scale (b) 70%–80% of one-repetition maximum	(a) 40 min (b) 20 min	Adherence: 90% of supervised training sessions were attended No adverse events
Bousquet-Dion et al. (2018)/ Canada	Physical exercise training Nutritional support Psychological intervention	(a) Unsupervised home-based endurance training and resistance training (b) Supervised in-laboratory stepper and resistance training	4 weeks	(a) 3–4 times per week (b) Once per week	(a) Moderate intensity, 60%–70% of maximum heart rate (b) 6–20 Borg scale >12	(a) 30 min (b) 60 min	Adherence: 98% of supervised training sessions were attended Adverse events: NR
Carli et al. (2020)/ Canada	Physical exercise training Nutritional support Psychological intervention	(a) Unsupervised home-based whole-body exercise (endurance training and resistance training) (b) Supervised in-laboratory stepper and resistance training	4 weeks	(a) 3–4 times per week (b) Once per week	(a) Moderate intensity, 60%–70% of maximum heart rate (b) 6–20 Borg scale >12	(a) 30 min (b) 60 min	Adherence: 68% of supervised in-hospital exercise sessions were attended No adverse events
Dronkers et al. (2010)/Canada	Physical exercise training	(a) Supervised resistance, endurance and inspiratory muscle training (b) Home-based walking or cycling	2–3 weeks	(a) Twice per day (b) 7 times per week	(a) Moderate intensity, 55%–75% maximum heart rate or Borg scale 11–13 (b) Not reported	(a) 35–45 min (b) 30 min	Adherence: 97% of training sessions attended No adverse events
Fulop et al. (2021)/Hungary	Physical exercise training Nutritional support Psychological intervention	(a) Home-based endurance training and breathing exercises (b) Supervised in-hospital endurance training and breathing exercises	4 weeks	7 times per week	According to patient's ability	(a) 30 min	Adherence: NR Adverse events: NR
Furyk et al. (2021)/Australia	Physical exercise training Nutritional support	(a) High-intensity interval walking (b) Supervised strength training and core balance	4 weeks	3 times per week	(a) Moderate- to high-intensity interval training Intensity not further defined (b) 50% predicted maximum	(a) 20 min (b) 30 min	Adherence: one participant attended 42% of training sessions No adverse events

TABLE 2 (Continued)

Study	Prehabilitation modules	Description of physical exercise intervention	Duration of exercise intervention	Training frequency	Training intensity	Time	Adherence training sessions/adverse events
Gillis et al. (2014)/ Canada	Physical exercise training Nutritional support Psychological intervention	Home-based unsupervised endurance training and resistance training	3.5 weeks	At least 3 times per week	Moderate intensity, starting at 40% of heart rate reserve, Borg scale >12, repetition maximum	50 min	Adherence: during preoperative period 78% Adverse events: NR
Gloor et al. (2022)/ Switzerland	Physical exercise training	Partly supervised: (a) Aerobic high intensity interval training, cycling (b) Resistance training of large muscle groups (arms, legs and trunk)	3–6 weeks	Twice per week supervised. Once per week at home unsupervised	(a) High-intensity interval on 85%–90% of maximum training capacity measured with SRT (b) Not reported	(a) 32 min, work interval (4×4 min) (b) 35 min	Adherence: 87% of participants completed full intervention programme and overall 84.4% of all planned sessions were conducted[a] Adverse events: 1× training break due to dizziness[a]
Karlsson et al. (2019)/Sweden	Physical exercise training	Supervised home-based training including inspiratory muscle training, high-intensity functional strength training and endurance training	2–3 weeks	2–3 times per week	Borg scale (CR-10) (7, 8)	60 min	Adherence: overall 97% of all planned sessions were performed Adverse events: 2× pain and 1× dizziness
Kim et al. (2009)/ Canada	Physical exercise training	Home-based aerobic cycle ergometer training	3.8 weeks	7 times per week	Moderate intensity, %HRR (40%–65%) and 6–20 Borg scale (12–16)	20–30 min	Adherence: during preoperative period 74% Adverse events: 2× fatigue and malaise
Lopez-Rodriguez-Arias et al. (2021)/ Spain	Physical exercise training Nutritional support Relaxation and breathing exercise	Endurance training and resistance video training	4.1 weeks	7 times per week	NR	30–45 min	Adherence: NR Adverse events: NR
Minnella et al. (2020)/Canada (excluded from meta-analysis)	Physical exercise training Nutritional support Relaxation	Prehab1: (a) High-intensity interval training (HIIT) (b) Resistance training Prehab2: (c) Moderate-intensity continuous training (MICT) (b) Resistance training	4 weeks	3 times per week	(a) High-intensity, work interval 85%–90% of peak power; rest interval 80%–85% of PAT (b) Moderate level using the OMNI-RES (c) Moderate intensity, 80%–85% of PAT	(a) HIIT: 4× work interval 2 min, 4× rest interval 3 min (b) NR (c) MICT: 30 min	Adherence: overall 89% adherence in the HIIT group and 93% in the MICT group No adverse events

TABLE 2 (Continued)

Study	Prehabilitation modules	Description of physical exercise intervention	Duration of exercise intervention	Training frequency	Training intensity	Time	Adherence training sessions/adverse events
Molenaar et al. (2023)/international[b]	Physical exercise training Nutritional support Psychological support Smoking cessation	Supervised: (a) High intensity interval training (cycle ergometer) (b) Resistance training major muscle groups	4 weeks	3 times per week	(a) High intensity, work interval at 85%–90% of peak power CPET; rest interval: 30% peak power CPET (b) 65%–70% of one-repetition maximum	Total 60 min: (a) 4× work interval 2 min, rest interval 4 min (b) 2×10 repetitions	Adherence: 77.2% of the patients completed 9 out of 12 sessions/ No serious adverse events
Northgraves et al. (2020)/United Kingdom	Physical exercise	Individualized: (a) Aerobic training (b) Functional resistance training	3 weeks	3 times per week	Moderate intensity, HRR (40%–60%) and 6–20 Borg scale (11–13)	(a) 25 min (b) 25 min	Adherence: overall 89.6% of all planned sessions were conducted Adverse events: NR

Abbreviations: 6MWT, 6-min walk test; ASA, American Society of Anesthesiologists; CPET, cardiopulmonary exercise test; HIIT, high-intensity interval training; HRR, heart rate reserve; LOS, length of hospital stay; MICT, moderate-intensity continuous training; NR, not reported; OMNI-RES, OMNI Perceived Exertion Scale for Resistance Exercise; PAT, power output at the ventilatory anaerobic threshold; Prehab, prehabilitation; SRT, steep ramp test.

[a]Received after contacting the authors.

[b]The Netherlands, Canada, Spain, Italy, and Denmark.

postoperative complications showed that prehabilitation did not reduce severe postoperative complications (OR 1.26, 95% CI 0.50–3.18; $I^2 = 50\%$; Figure 4). There was one study [18] that scored a low risk of bias in combination with a low risk of ineffectiveness that showed that prehabilitation did not reduce severe postoperative complications (OR 1.04, 95% CI 0.23–4.46; Figure 4). There were no statistically significant differences found between the subgroups with a low risk of ineffectiveness and a high risk of ineffectiveness for the individual items of the i-CONTENT tool (see File S4).

Effects of prehabilitation on length of hospital stay

LOS was assessed in 12 of the studies assessed [18–22,24–26,28–31]. No significant difference in LOS was observed in patients receiving prehabilitation compared with patients receiving usual care (MD −0.20, 95% CI −1.16 to 0.76; $I^2 = 45\%$; Figure 5) in all studies combined or when stratified for risk of ineffectiveness and risk of bias. There were no statistically significant differences found between the subgroups with a low risk of ineffectiveness and a high risk of ineffectiveness for the individual items of the i-CONTENT tool (see File S4).

DISCUSSION

The aim of the current systematic review was to evaluate whether therapeutic quality is associated with the ability of prehabilitation programmes to preoperatively improve preoperative aerobic fitness and reduce postoperative complications and LOS in patients scheduled for colorectal cancer surgery. Pooled results of 12 studies [18–22,24–28,30,31] included in the meta-analysis showed that prehabilitation improved preoperative aerobic fitness but did not reduce overall postoperative complications or LOS. Of the 14 studies that were evaluated, 13 scored a high-risk of ineffectiveness on one or more items of the i-CONTENT tool. Only one study had a low risk of bias in combination with a low risk of ineffectiveness on all items of the i-CONTENT tool. This study, by Berkel et al. [18], showed a reduction in overall postoperative complications of ~50% but not in LOS. The pooled results of all other studies showed an improvement in aerobic fitness and a reduction in overall postoperative complications and LOS.

Our result that prehabilitation improves aerobic fitness before surgery is in line with previous research [5–9]. For overall postoperative complications, previous literature shows inconsistent results, as some studies show that prehabilitation effectively reduced postoperative complications [5, 6] whereas others do not [7–10]. These inconsistent results could partially be explained by differences in study populations and the training volume reported in these studies. For LOS, previous research shows that prehabilitation does not effectively reduce LOS [5, 6, 9, 10], which is in line with our results.

The aim of the current study, to evaluate whether the therapeutic quality of the physical exercise training intervention (i.e. the anticipated

TABLE 3 Risk of bias according to the Cochrane Risk of Bias 2 (RoB2) assessment and therapeutic quality assessed with i-CONTENT tool.

	RoB2 assessment						i-CONTENT tool						
First author	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias	Patient selection	Dosage of the training programme	Type of the training programme	Qualified supervisor	Type and timing of outcome assessment	Safety of the training programme	Adherence to the training programme
Berkel (2022)	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
Bousquet-Dion (2018)	LR	SC	LR	LR	LR	SC	LR	HR	LR	HR	LR	LR	LR
Carli (2020)	LR	LR	LR	LR	LR	LR	LR	HR	LR	HR	LR	LR	HR
Dronkers (2020)	LR	SC	LR	LR	SC	SC	HR	HR	LR	LR	LR	LR	LR
Fulop (2021)	LR	LR	LR	LR	LR	LR	HR	HR	LR	HR	LR	LR	NI
Furyk (2021)	SC	SC	HR	LR	LR	HR	LR	LR	LR	LR	LR	LR[a]	HR[a]
Gillis (2014)	LR	LR	LR	LR	LR	LR	LR	HR	LR	HR	LR	LR	HR
Gloor (2022)	LR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR	LR	LR
Karlsson (2019)	LR	SC	LR	SC	LR	SC	LR	HR	LR	LR	LR	LR	LR
Kim (2009)	SC	SC	LR	SC	SC	SC	HR	HR	LR	HR	LR	LR	HR
Lopez-Rodriguez-Arias (2021)	SC	LR	LR	LR	LR	SC	HR	HR	LR	HR	LR	LR	NI
Minnella (2020) Prehab	SC	LR	LR	LR	SC	SC	HR	LR	LR	LR	LR	LR	LR
HITT Prehab MICT	SC	LR	LR	LR	SC	SC	HR	HR	LR	LR	LR	LR	LR
Molenaar (2023)	LR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR	LR	HR
Northgraves (2020)	LR	LR	LR	LR	SC	SC	HR	HR	LR	LR	LR	LR	LR

Note: ROB2 assessment: HR, high risk of bias (red); LR, low risk of bias (green); SC, some concerns (yellow). i-CONTENT tool: HR, high risk of ineffectiveness (red); LR, low risk of ineffectiveness (green); NI, no information reported nor provided after contacting the corresponding author. See File S3 for a detailed explanation of the therapeutic quality assessment with the i-CONTENT tool.

[a]Please interpret with caution due to the extremely low number of participants.

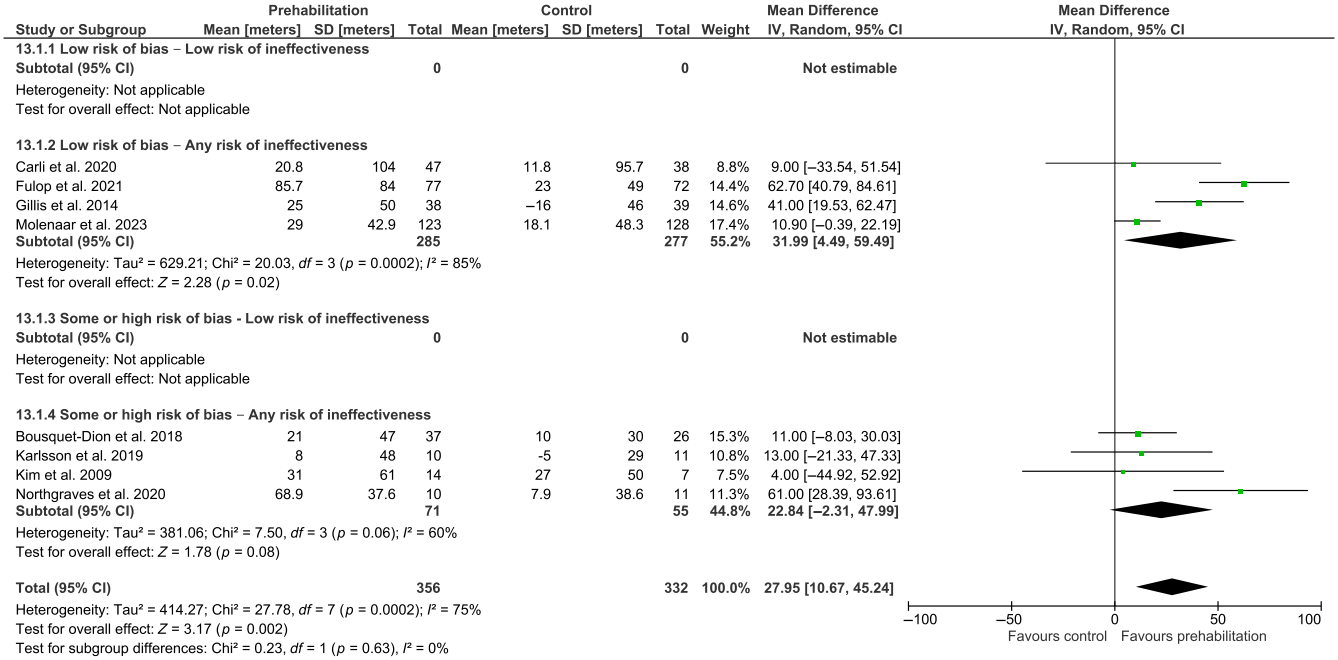

FIGURE 2 Meta-analysis of the effect of prehabilitation versus usual care for the outcome preoperative 6-min walk test distance, stratified for risk of ineffectiveness.

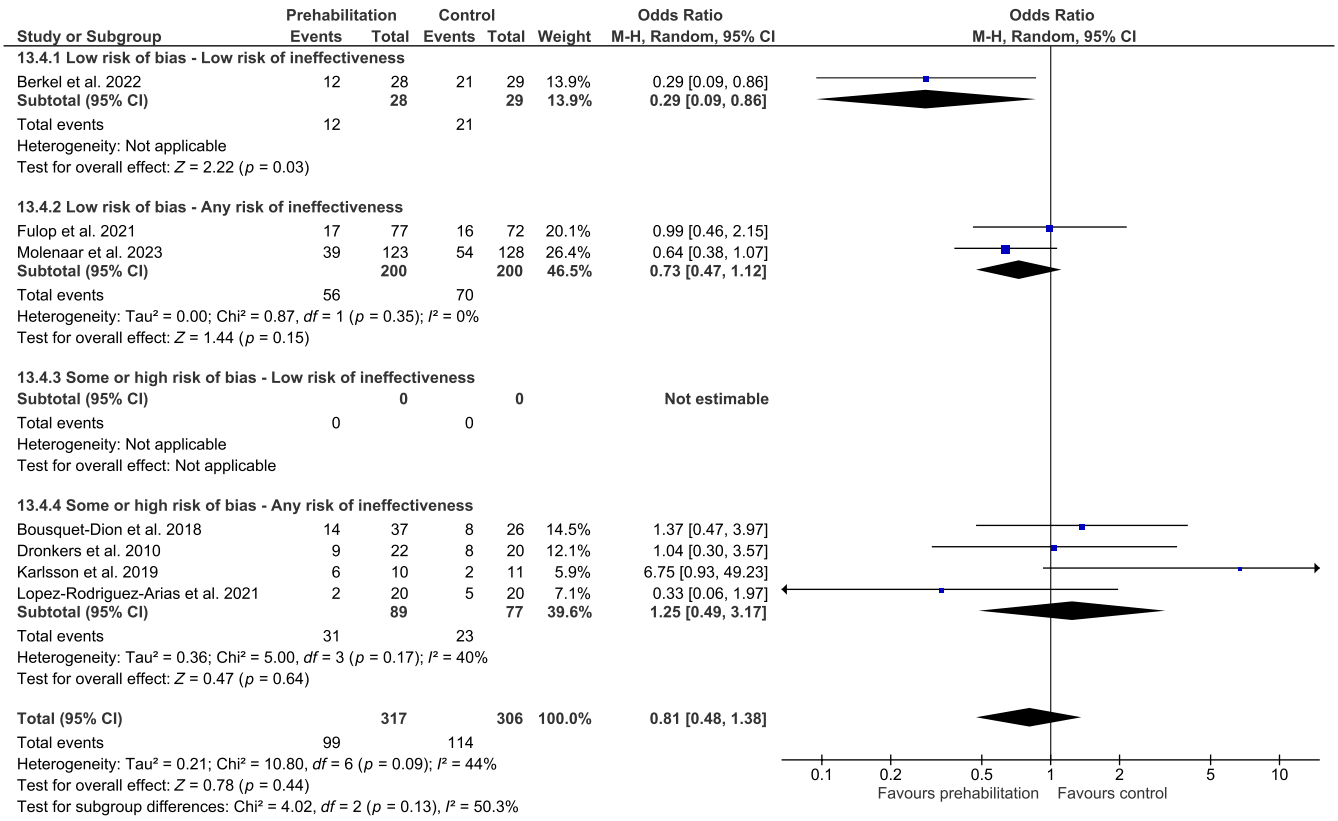

FIGURE 3 Meta-analysis of the effect of prehabilitation versus usual care on the outcome overall postoperative complications, stratified for risk of ineffectiveness.

risk of ineffectiveness) is related to the effectiveness of prehabilitation to improve postoperative outcomes, might have been too optimistic as (reporting of) therapeutic quality in most studies (93%) was suboptimal. Only one study [18] had a low risk of bias in combination with a low risk of ineffectiveness, because the physical exercise training intervention had adequate patient selection, adequate dosage, a

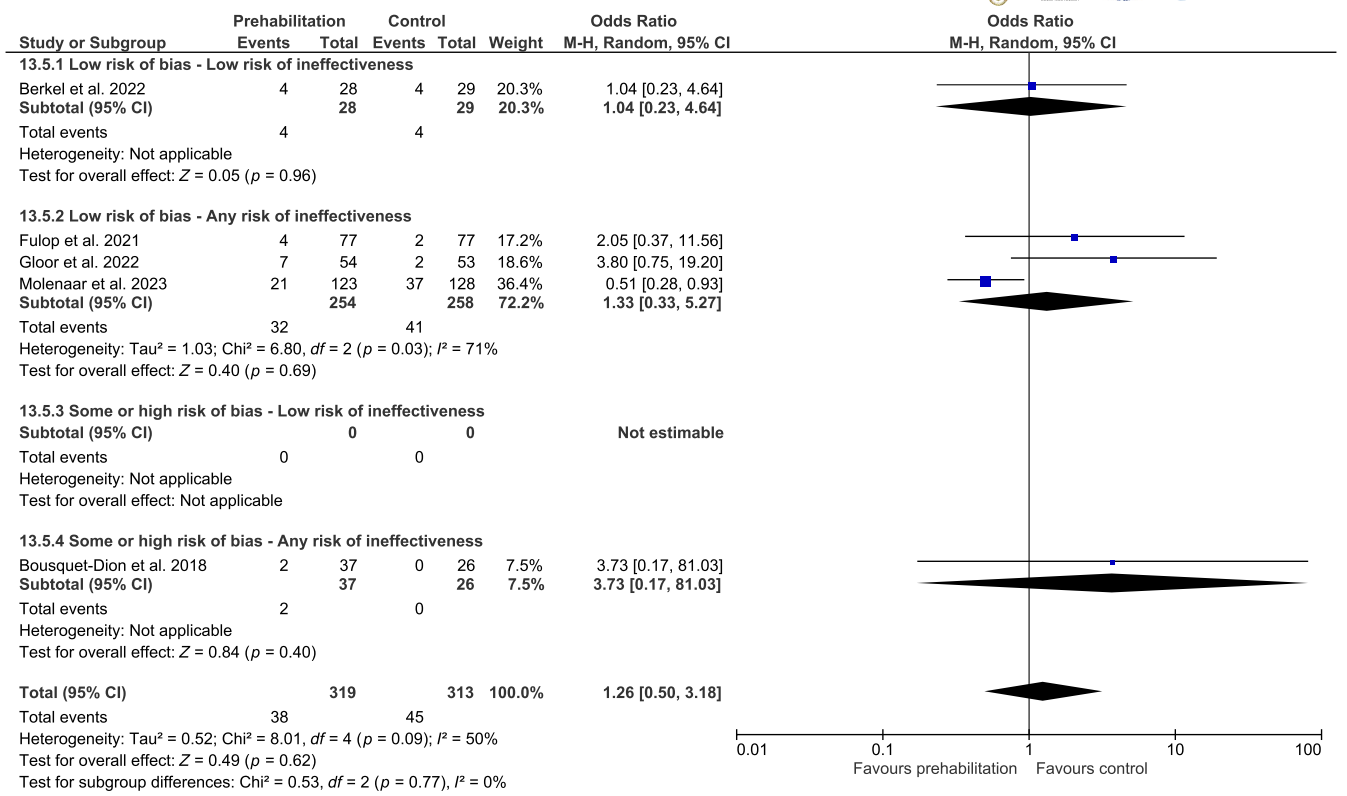

FIGURE 4 Meta-analysis prehabilitation versus usual care for the outcome severe postoperative complications, stratified for risk of ineffectiveness.

qualified supervisor, and there was a high adherence to the training programme. It is not surprising that this study scored a low risk of bias and low risk of ineffectiveness, because in their discussion the authors state that the trial methodology and experimental intervention were designed using the Cochrane Risk of Bias tool and the CONTENT tool [33]. In addition, comparable reductions in postoperative complications were reported in a Spanish study [34] investigating prehabilitation in patients undergoing different types of abdominal surgery. That study [34] also scored a high therapeutic quality in a previous systematic review [35]. Although these two studies with a high therapeutic quality [18,34] show promising results it is hard to reach definitive conclusions based on the results of just two studies. Therefore, their results should be confirmed in future research including prehabilitation interventions with a high therapeutic quality.

When stratifying the studies on the basis of their risk of ineffectiveness based on the individual items of the i-CONTENT tool there were no significant differences between the groups who had a low risk of ineffectiveness comparison with the groups that had a high risk of ineffectiveness (see File S4). This could be due to a lack of contrast within these individual items, as most of the studies either collectively scored a high or low risk of ineffectiveness for most items of the i-CONTENT tool. This is in line with a recent review [36] evaluating prehabilitation programmes for lung cancer patients where they also reported that most of the included studies had a high risk of ineffectiveness on one or multiple items and therefore lacked contrast between studies.

Poor reporting of the physical exercise interventions might have contributed to the fact that most studies scored a high risk of ineffectiveness on multiple items of the i-CONTENT tool. In the current systematic review, 10 prehabilitation programmes (67%) [19–22,24,26–29,31] scored a high risk of ineffectiveness due to inadequate reporting of the dose or due to inadequate dosing of the exercise prehabilitation programme. This observation is not new, as reporting of the physical exercise training interventions within prehabilitation programmes usually only includes reporting of the prescribed physical exercise training dose, whereas full reporting of the actually performed physical exercise training dose, other than training session attendance (i.e. training frequency), is often missing [37]. Full reporting of the training dose actually performed according to the FITT-VP principles is essential to be able to estimate the performed training volume and subsequent risk of ineffectiveness. When evaluating the risk of ineffectiveness, the performed training dose might be more important than the prescribed dose. However, the latter was not feasible in the current study due to inadequate reporting.

With regard to the chosen outcome measures, 10 out of 14 studies used the 6MWT to assess aerobic fitness. Previous research has indeed shown that the outcomes of the 6MWT are associated with aerobic fitness [38]. However, it is also well known that results of the 6MWT are affected by many factors that are not related to cardiopulmonary status, such as sex, body height and body mass [39]. There are more appropriate exercise tests for measuring or estimating aerobic capacity [e.g.

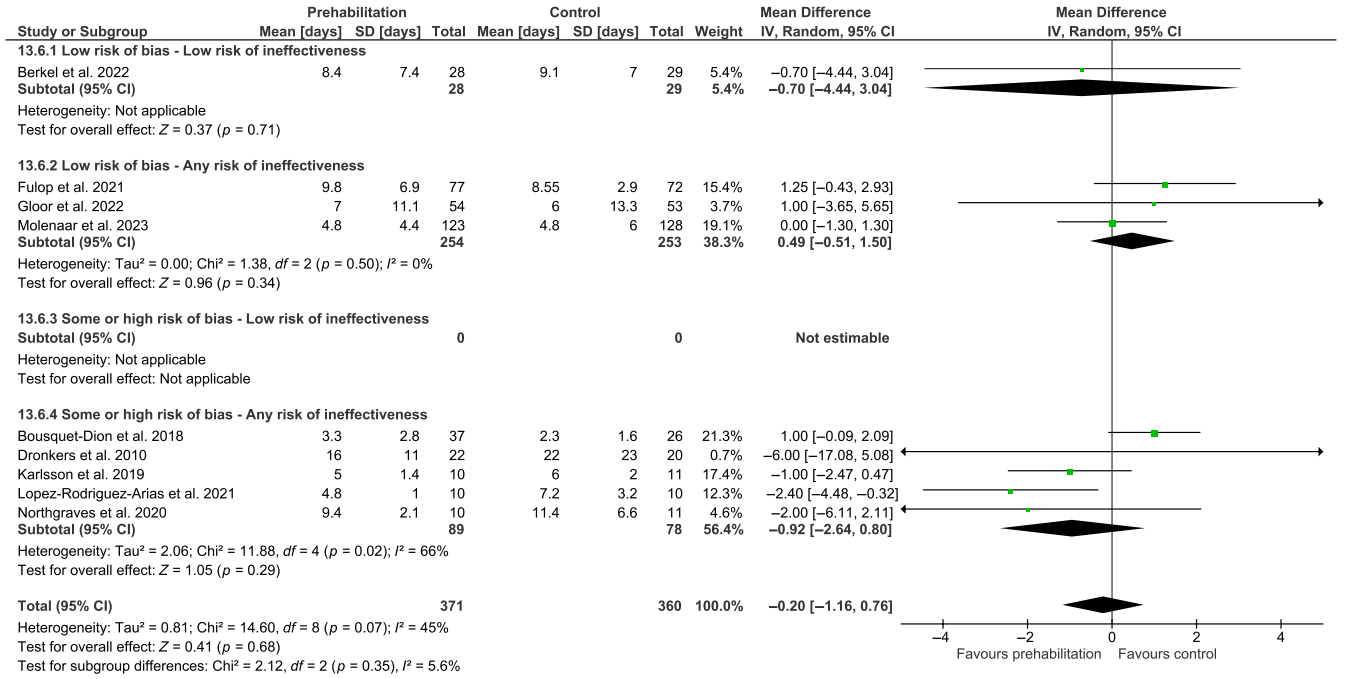

FIGURE 5 Meta-analysis prehabilitation versus usual care for the outcome length of hospital stay, stratified for risk of ineffectiveness.

the (modified) steep ramp test [40] or cardiopulmonary exercise testing (CPET) [41]—CPET is the gold standard for measuring aerobic fitness [42]]. Only four studies used outcomes from CPET (e.g. VO_{2peak}) to assess aerobic fitness. Of these studies, only two [27,30] reported on the difference in VO_{2peak} between the prehabilitation and control group, which precluded us from stratification based on risk of ineffectiveness using VO_{2peak} as an outcome. Furthermore, current literature solely reports the incidence and severity of complications (e.g. Clavien–Dindo classification). It can be imagined that a prehabilitation intervention would have a greater impact on how patients cope with a complication than on the incidence and severity of complications [43]. Therefore, a composite measure that considers the impact of complications (e.g. the impact of complications on time to recovery of physical functioning) might be a better outcome measure for evaluating an association between therapeutic quality and the effectiveness of exercise prehabilitation.

A strength of the current study is the in-depth assessment of the content of the prehabilitation programmes using the i-CONTENT tool. The structured assessment of the i-CONTENT tool provides insight in the weaknesses in (reporting of) physical exercise interventions of prehabilitation programmes. Furthermore, prior to the start of the study assessment, the research team developed operationalization of terms of the i-CONTENT tool. By using this operationalization of terms, i-CONTENT assessment was facilitated and reliability and validity of the assessment was improved. Besides these strengths, the current systematic review also has some limitations. As discussed before, the score on the i-CONTENT tool is strongly associated with the quality of reporting. If the authors did not report certain aspects of the i-CONTENT tool it is probably more likely to be scored with a high risk of ineffectiveness. Furthermore, the i-CONTENT tool is only capable of assessing the physical exercise intervention and not the other modalities in the prehabilitation programme (e.g. nutritional or psychological intervention). The authors strongly believe that prehabilitation should be tailored to an individual's risks and that effectiveness probably depends on the synergistic effect of all prehabilitation modules.

Outcome measures of prehabilitation trials should not be limited to the incidence and severity of postoperative complications but should include composite measures that also take the impact of a complication into account. In addition, for an accurate evaluation of exercise prehabilitation studies and the relation to therapeutic quality, full reporting of prescribed as well as performed exercise (i.e. training volume) is essential. Lastly, the quality of prehabilitation programmes as well as the reporting of future prehabilitation studies should be improved by using the i-CONTENT or a similar tool [44] for the design of prehabilitation programmes and their reporting.

CONCLUSION

An association between therapeutic quality and the effectiveness of prehabilitation in patients scheduled for colorectal surgery could not be established as only one study had a low risk of bias and a low risk of ineffectiveness of the physical exercise training intervention. The quality of physical exercise training interventions within future prehabilitation research should be improved by using i-CONTENT or a similar tool during the design phase of prehabilitation programmes.

AUTHOR CONTRIBUTIONS

Evy E. J. Jetten: Writing – original draft; writing – review and editing; project administration; formal analysis; methodology; conceptualization. **Ruud F. W. Franssen:** Writing – original draft; writing

– review and editing; formal analysis; methodology; conceptualization. **Melissa J. J. Voorn:** Writing – review and editing; formal analysis. **Roberto Falz:** Writing – review and editing. **Martin Busse:** Writing – review and editing. **Bart C. Bongers:** Writing – review and editing. **Maryska L. G. Janssen-Heijnen:** Writing – review and editing; conceptualization. **Thomas J. Hoogeboom:** Writing – review and editing; conceptualization; methodology.

ACKNOWLEDGEMENTS

We are grateful for the assistance provided by the senior librarian, Quinten de Bakker MSc, with the search strategy.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

Thomas J. Hoogeboom was involved in the development of the i-CONTENT tool. The other 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

No ethical approval was required for this systematic review and meta-analysis of previously published research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Inforation section at the end of this article.

How to cite this article: Jetten EEJ, Franssen RFW, Voorn MJJ, Falz R, Busse M, Bongers BC, et al. Evaluating the therapeutic quality of prehabilitation programmes in patients scheduled for colorectal surgery: A systematic review and meta-analysis. Colorectal Dis. 2025;27:e70023. https://doi.org/10.1111/codi.70023