



Impact of Multidisciplinary Prehabilitation Interventions on Postoperative Hospital Length of Stay and Functional Capacity in Patients Undergoing Resection of Colorectal Cancer: A Systematic Review and Meta-analysis

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BACKGROUND: Although surgery is commonly regarded as the primary curative treatment for colorectal cancer, it could potentially be associated with postoperative morbidity and mortality.

OBJECTIVE: To determine the pooled effect of exercise and multidisciplinary prehabilitation interventions on postoperative hospital length of stay and functional capacity in patients undergoing resection of colorectal cancer.

DATA SOURCES: A systematic search was conducted in MEDLINE (via PubMed) and Web of Science databases from inception to November 2022.

STUDY SELECTION: The original systematic search retrieved 2005 studies. After the removal of duplicates and screening by title and abstract, 77 eligible full-text documents were evaluated for final inclusion in the meta-analysis. A total of 12 randomized controlled trials, 5 nonrandomized controlled trials, and 3 uncontrolled before-and-after studies were selected.

MAIN OUTCOME MEASURES: Postoperative hospital length of stay (in days) and functional capacity (assessed with the peak of oxygen consumption [VO₂ peak] and 6-minute walking test) were the outcome measures.

RESULTS: The meta-analysis was conducted on 20 studies (3805 participants). Randomized controlled trials and

nonrandomized controlled trials showed significant reductions in postoperative hospital length of stay ($d = -0.10$, nearly 2 days) and significant incremental improvements in VO_2 peak ($d = 0.27$) and 6-minute walking test ($d = 0.31$). Regarding the before-and-after studies, the pooled effect of multidisciplinary prehabilitation interventions was positively significant for VO_2 peak ($d = 0.29$) and 6-minute walking test ($d = 0.29$). There was no risk of publication bias (Egger test: $p > 0.05$), with a score of 0.71 (0–1) on average.

LIMITATIONS: There was a high between-studies heterogeneity, and several outcomes did not have the required number of studies for a desirable statistical power.

CONCLUSIONS: These findings suggest that multidisciplinary prehabilitation interventions might be effective at decreasing postoperative hospital length of stay (nearly 2 days) and improving functional capacity.

REGISTRATION: PROSPERO registration number CRD42022373982.

KEY WORDS: Fitness; Multimodal; Operation; Recovery; Training.

Colorectal cancer is currently the second leading cause of cancer death (estimated 600,000 deaths; 9.4%).¹ Although surgery is widely considered the primary curative treatment for this pathological condition,² it is a stressful procedure that may involve numerous health-related conditions.³ Considering that the mean age of colorectal cancer diagnosis is just younger than 70 years,¹ these patients mostly present with several comorbidities that increase the postoperative hospital length of stay and physical disturbances.⁴

Higher cardiorespiratory fitness is associated with high rates of survival among patients with cancer.^{5,6} Indeed, extensive evidence has strongly established that cardiorespiratory fitness is associated with a lower risk of cardiovascular disease, all-cause mortality, and mortality rates attributable to various cancers.^{5,6} Moreover, unhealthy dietary habits and psychological disturbances are remarkable contributors to subsequent increments of avoidable postoperative complications.⁷ Previous evidence has shown that the implementation of multidisciplinary prehabilitation interventions, including physical, dietary, and psychological programs, might counteract age-related patients' vulnerability before surgery, and therefore, it becomes a potential strategy to avoid postoperative comorbidities.^{8–10} Interestingly, a recent meta-analysis highlighted the effectiveness of these interventions in patients with breast, prostate, lung, and bladder cancer.¹¹ However, the study did not include multidisciplinary prehabilitation interventions before colorectal cancer resection. In

patients undergoing resection of colorectal cancer, a recent study analyzed the effect of an exercise-based prehabilitation intervention, observing no differences in postoperative hospital length of stay but significant improvements in functional capacity.¹² Hence, the effectiveness of multidisciplinary prehabilitation interventions in reducing the duration of postoperative hospital stays and enhancing the functional capacity of patients undergoing colorectal cancer resection remains uncertain.

This systematic review and meta-analysis aimed to examine the effect of exercise and multidisciplinary prehabilitation interventions on postoperative hospital length of stay and functional capacity in patients undergoing resection of colorectal cancer. We hypothesized that multidisciplinary prehabilitation interventions would positively affect both postoperative hospital length of stay and functional capacity.

MATERIALS AND METHODS

Identification and Selection of Studies

Search Strategy, Information Sources, and Selection Process. This systematic review and meta-analysis was registered in the International Prospective Register for Systematic Reviews (PROSPERO registration No. CRD42022373982). The recommendations of the Cochrane Collaboration Handbook for conducting systematic reviews and meta-analyses were strictly followed.¹³ Findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1; see Supplemental Table S1 at <http://links.lww.com/DCR/C347>).^{14,15}

A systematic search of eligible studies was conducted using the MEDLINE (via PubMed) and Web of Science databases from inception to November 2022. Intervention studies addressing the effect of exercise or different types of multidisciplinary prehabilitation programs on postoperative hospital length of stay and functional capacity in patients undergoing resection of colorectal cancer were considered eligible. Moreover, we contacted authors for missing information when necessary. Combinations of keywords used in the searches are available in Supplemental Table S2 at <http://links.lww.com/DCR/C347>.

Eligibility Criteria. Study inclusion criteria were as follows: 1) participants: patients undergoing resection of colorectal cancer, 2) study design: intervention studies (randomized controlled trials [RCTs], non-RCTs, and before-and-after studies), 3) exposure: exercise or multidisciplinary prehabilitation programs including exercise and dietary and/or psychological components, and 4) outcome: postoperative hospital length of stay and functional capacity (ie, peak of oxygen consumption [VO_2 peak]) and 6-minute walking test (6MWT). Exclusion criteria were as follows: 1) patients younger than 18 years, 2) noneligible

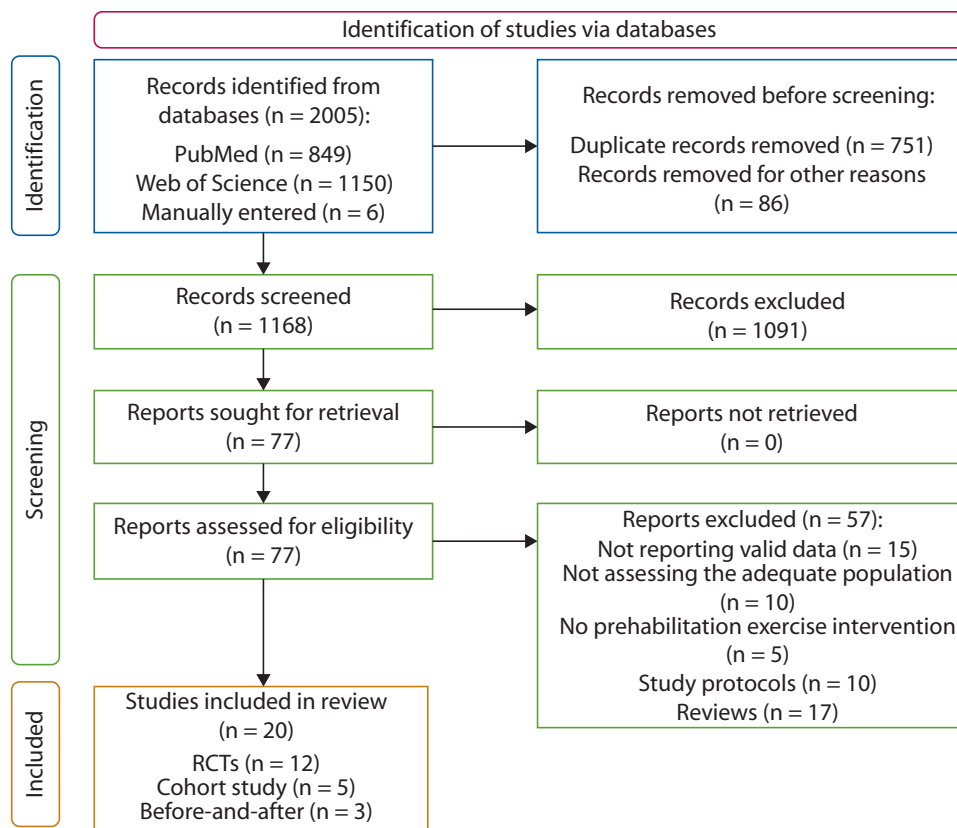


FIGURE 1. Flow chart of the search and selection of studies. RCT = randomized controlled trial.

publications (ie, review articles or case reports), and 3) postoperative exercise or multidisciplinary interventions. Two researchers independently screened all studies for their inclusion, and disagreements were resolved by consensus or by involving a third researcher.

Data Extraction and Outcomes Measures. We retrieved the following information from the original reports: 1) authors and year of publication, 2) country from which the data were collected and title, 3) study design, 4) sample characteristics (ie, age, sex, sample size, BMI, type of cancer), 5) postoperative hospital length of stay (in days), and 6) functional capacity (assessed with the VO_2 peak and the 6MWT). Furthermore, the following data concerning exercise programs were extracted from the original articles: 1) frequency, 2) intensity, 3) time, 4) type, 5) volume, 6) progression, 7) intervention duration, and 8) other characteristics regarding the physical, dietary, and psychological programs.

Study Quality Assessment

All studies were assessed for methodological quality using the relevant items from the Cochrane risk-of-bias tool¹³ and the Physiotherapy Evidence Database scale.¹⁶ The quality assessment of controlled studies consists of 9 items or criteria, each referring to a relevant methodological aspect of the study including 1) specification of eligibility criteria, 2) random allocation to groups, 3) concealed allocation, 4)

intergroup similarity in outcomes at baseline, 5) blinding (including outcome assessors, data analysts, participants, and researchers), 6) sample dropout rate ($\leq 15\%$), 7) intention to treat analysis, 8) reported comparisons between groups, and 9) report of effect-size coefficients or other parameters, which make the calculation of them possible. Plausible scores were “no” (0 points) when the study did not meet the criteria, “unclear” (0 points) when the study reported no information on the scored item, 0.5 points when the study met the criteria for some outcomes but not all, and “yes” (1 point) when the study met the criteria.

Statistical Analysis

RCTs and uncontrolled before-and-after studies were separately analyzed. Nevertheless, RCT intervention groups and non-RCTs were additionally included in the meta-analysis of the before-and-after studies. RCTs' standardized effect-size coefficients were calculated, from baseline to postintervention, as the mean difference between the mean change in intervention and control groups divided by mean baseline SD ¹⁷: $d = c(df_{E,C}) \cdot [((\bar{X}_{pre,E} - \bar{X}_{post,E}) - (\bar{X}_{pre,C} - \bar{X}_{post,C})) / S_{pre}]$. Concerning uncontrolled before-and-after studies, standardized effect-size coefficients were calculated for each intervention group as the mean change from baseline to postintervention divided by baseline SD ¹⁸: $d = c(df) \cdot [(\bar{X}_{pre,E} - \bar{X}_{post,E}) / S_{pre}]$. Both

coefficients included $c(df_{E,C})$ and $c(df)$ correction factors for small samples¹⁹ (see Supplemental Table S3 at <http://links.lww.com/DCR/C347>). The inverse variance method was used in both cases for the weighting of studies. In addition, we computed the raw (unstandardized) mean difference for before-and-after studies ($\bar{X}_{pre,E} - \bar{X}_{pos,E}$) and RCTs ($(\bar{X}_{pre,E} - \bar{X}_{pos,E}) - (\bar{X}_{pre,C} - \bar{X}_{pos,C})$) using the weights calculated in our standardized meta-analysis.

We combined effect-size coefficients from studies and outcomes. They were analyzed via the DerSimonian and Laird's random-effects model.²⁰ Data for meta-analyses were extracted directly from each study or computed from the weighted standardized mean changes, variance 95% CIs, or medians (interquartile ranges).²¹⁻²³ We estimated potential statistical heterogeneity with the Cochran Q test and I^2 index (moderate heterogeneity if $I^2 \geq 50\%$, $p < 0.05$). Heterogeneity was classified depending on the I^2 index as follows: 0% to 40%, might not be important; 30% to 60%, may be moderate; 50% to 90%, substantial; and 75% to 100%, considerable.²⁴ Potential moderators of the effect sizes were evaluated by meta-regression analyses for continuous variables and ANOVA for qualitative variables. Additional sensitive analyses were performed to assess the influence of each individual study on the pooled effect sizes. Potential publication bias was also analyzed using the Egger test²⁵ and Rosenthal method.²⁶ Risk of bias/methodological quality was evaluated as a potential moderator variable to analyze its moderation on effect sizes for postoperative hospital length of stay and functional capacity outcomes. The statistical analyses were performed using metaphor package²⁷ from the R statistic program.

RESULTS

Overview of Included Studies

The systematic search identified 2005 studies. After the removal of duplicates and screening by title and abstract, 77 eligible full-text documents were evaluated for final inclusion in the meta-analysis. The flow chart of the search and selection of studies is shown in Figure 1. We included a total of 12 RCTs,²⁸⁻³⁹ 5 non-RCTs,⁴⁰⁻⁴⁴ and 3 uncontrolled before-and-after studies.^{9,45,46}

Description of Study Participants

Participant descriptive and intervention characteristics of all included studies are summarized in Table 1. The total sample was composed of 3805 participants ($n = 1013$ intervention and $n = 1432$ control from RCTs and non-RCTs; $n = 1360$ from before-and-after studies), with 45.6% of the sample being women. The mean age of the total sample was 69 years ($SD = 11$). The mean postoperative hospital length of stay was 9.1 days ($SD = 5.2$), the mean VO_2 peak was 21.7 mL/kg/min ($SD = 5.6$) at baseline, and the mean

walked distance in the 6MWT was 382.5 m ($SD = 94.4$) at baseline. Most studies were originally from Canada ($n = 6$), The Netherlands ($n = 4$), United Kingdom ($n = 4$), and Spain ($n = 3$), and the others were conducted in Sweden, Singapore, and Australia. Components of multidisciplinary prehabilitation interventions included only exercise training ($n = 10$); exercise training and nutritional intervention ($n = 2$); and exercise training, nutritional intervention, and psychological intervention ($n = 9$). Interventions had a mean duration of 4.9 weeks and were mostly performed in groups rather than individually.

Meta-analysis

Effects of Multidisciplinary Prehabilitation Interventions. The effects of these interventions on postoperative hospital length of stay are displayed in Figure 2. Concerning postoperative hospital length of stay, the overall pooled effect size of RCTs was -0.10 (95% CI, -0.20 to 0.00), meaning that the postoperative hospital length of stay was significantly reduced by multidisciplinary prehabilitation interventions by nearly 2 days ($p < 0.05$). Differences between RCTs showed substantial heterogeneity ($Q_{(7)} = 35.91$, $p < 0.001$; $I^2 = 63.80\%$). Raw data of each included study on primary postoperative hospital length of stay outcome are provided in Supplemental Tables S4 and S5 at <http://links.lww.com/DCR/C347>. The assessment of potential publication bias for RCTs when evaluating the length of hospital stay is presented in Supplemental Figure S1 at <http://links.lww.com/DCR/C347>.

Effects of multidisciplinary prehabilitation interventions on functional capacity are presented in Figures 3 and 4. VO_2 peak ($d = 0.27$) and 6MWT ($d = 0.31$) were significantly increased by multidisciplinary prehabilitation interventions in RCTs. Concerning the before-and-after studies, the pooled effects of multidisciplinary prehabilitation interventions were significant on VO_2 peak ($d = 0.29$) and 6MWT ($d = 0.29$). Differences between studies showed some heterogeneity: VO_2 peak ($Q_{(7)} = 10.66$, $p < 0.05$; $I^2 = 81.24\%$) and 6MWT ($Q_{(7)} = 12.43$, $p < 0.05$; $I^2 = 59.78\%$) from RCTs and VO_2 peak ($Q_{(7)} = 15.85$, $p < 0.05$; $I^2 = 55.83\%$) and 6MWT ($Q_{(7)} = 23.88$, $p < 0.05$; $I^2 = 49.75\%$) from before-and-after studies. Raw data from each included study on secondary functional capacity outcomes are provided in Supplemental Tables S6 to S9 at <http://links.lww.com/DCR/C347>. The assessment of potential publication bias for RCTs and before-and-after studies when evaluating the VO_2 peak and the 6MWT are presented in Supplemental Figures S2 to S5 at <http://links.lww.com/DCR/C347>.

Analyses of Potential Moderator Variables. Considering the large heterogeneity found in the meta-analyses of multidisciplinary prehabilitation intervention effects on postoperative hospital length of stay, VO_2 peak, and 6MWT

TABLE 1. Summary of characteristics and outcomes of included studies

Study	Study design	N (prehab/control)	Sex, % women	Age, y, mean (SD)	Cancer (colon/rectal)	Participants receiving neo-adjuvant therapy, %	Type of intervention	Exercise intervention description	Nutritional intervention description	Psychological intervention description	Measured outcomes
Onerup et al ¹⁹	Randomized controlled trial	317/351	40.1	68.0 (11.0)	335/333	36.0	Exercise intervention	Home based, 2 wk, daily aerobic training and inspiratory muscle training	NA	NA	Hospital length of stay
Carli et al ³⁰	Randomized controlled trial	55/55	52.7	78.8 (7.0)	79/31	11.9	Exercise + nutritional + psychological intervention	Home based and once per week supervised, 4 wk, 7x per week walking, 3-4x per week resistance training	Baseline assessment by nutritionist, counseling, when appropriate supplementation (if needed)	Anxiety reduction strategies and alcohol cessation strategies	Hospital length of stay, 6MWT
Gillis et al ²²	Randomized controlled trial	38/39	37.7	65.9 (11.3)	47/30	23.4	Exercise + nutritional + psychological intervention	Home-based, 4 wk, 3x per week, concurrent training	Baseline assessment by nutritionist, counseling, when appropriate supplementation (if needed)	Anxiety reduction strategies	Hospital length of stay, 6MWT
Bousquet-Dion et al ²⁹	Randomized controlled trial	37/26	27.0	70.3 (10.7)	44/18	14.2	Exercise + nutritional + psychological intervention	Home based and once per week supervised, 4 wk, 3-4x per week, concurrent training	Baseline assessment by nutritionist, counseling, when appropriate supplementation (if needed)	Anxiety reduction strategies	Hospital length of stay, 6MWT
Berkel et al ²⁸	Randomized clinical trial	28/29	47.4	73.6 (6.1)	54/3	3.5	Exercise intervention	Supervised, 3 wk, 3 sessions per week, concurrent training	NA	NA	Hospital length of stay, VO ₂ peak
Moug et al ³⁸	Randomized controlled trial	24/24	35.4	65.9 (10.5)	0/48	100.0	Exercise intervention	12-14 total weeks of aerobic training; 6 supervised weeks, 3 sessions per week, then 6-8 home-based intervention, 3x per week	NA	NA	Hospital length of stay, 6MWT

(Continued)

TABLE 1. Continued

Study	Study design	N (prehab/control)	Sex, % women	Age, y, mean (SD)	Cancer (colon/rectal)	Participants receiving neo-adjuvant therapy, %	Type of intervention	Exercise intervention description	Nutritional intervention description	Psychological intervention description	Measured outcomes
Dronkers et al ³¹	Randomized controlled trial	20/22	26.2	69.9 (6.4)	42/0	0.0	Exercise intervention	Home based and supervised 2x per week, 2-4wk, 2x per week concurrent training and inspiratory muscle training; aerobic exercise the other 5 d	NA	NA	Hospital length of stay, VO ₂ peak
Minnella et al ³⁷	Randomized controlled trial ^a	21/21 ^a	38.1	67.0 (22.2)	31/11	14.3	Exercise intervention	Supervised, 4 wk, 3 sessions per week, concurrent training ^a	NA	NA	VO ₂ peak, 6MWT
Loughney et al ³⁵	Randomized controlled trial	17/16	21.2	60.6 (12.1)	0/33	100.0	Exercise intervention	Supervised, 9 wk, 3 sessions per week, aerobic training	NA	NA	VO ₂ peak
Karlsson et al ³³	Randomized controlled trial	10/11	61.9	77.8 (8.1)	18/3	14.3	Exercise intervention	Supervised, 2-3 wk, 2-3 sessions per week, concurrent training, and inspiratory muscle training	NA	NA	Hospital length of stay, 6MWT
Northgraves et al ³⁶	Randomized controlled trial	10/11	45.5	63.8 (11.5)	7/12	36.8	Exercise intervention	Supervised, 2-4wk, 3 sessions per week, concurrent training	NA	NA	Hospital length of stay, 6MWT
López-Rodríguez-Arias et al ³⁴	Randomized controlled trial	10/10	35.0	66.5 (9.4)	15/5	25.0	Exercise + nutritional + psychological intervention	Home based, 4 wk, every day, concurrent training	Dietary advice and protein supplementation (if needed)	Anxiety reduction and smoking and alcohol cessation strategies	Hospital length of stay
Mora López et al ⁴²	Nonrandomized controlled trial (historical control group)	119/530	63.8	69.2 (28.0)	464/185	NA	Exercise + nutritional + psychological intervention	Home based, 4 wk, daily walking program	Assessment of nutritional status, tips for high-protein shakes, phone reinforcement	A link to a mindfulness resource, phone reinforcement	Hospital length of stay

(Continued)

TABLE 1. Continued

Study	Study design	N (prehab/control)	Sex, % women	Age, y, mean (SD)	Cancer (colon/rectal)	Participants receiving neo-adjuvant therapy, %	Type of intervention	Exercise intervention description	Nutritional intervention description	Psychological intervention description	Measured outcomes
Li et al ⁴¹	Nonrandomized controlled trial (historical control group)	42/45	41.4	66.9 (11.5)	33/54	NA	Exercise + nutritional + psychological intervention	Home based, 3 to 5 wk, 3x per week, concurrent training	Baseline assessment by nutritionist, counseling, whey protein supplementation (if needed)	Anxiety reduction strategies	Hospital length of stay, 6MWT
van Rooijen et al ⁴³	Nonrandomized controlled trial	20/30	46.0	68.5 (31.9)	37/13	0.0	Exercise + nutritional + psychological intervention	Supervised, 4 wk, 3 sessions per week, concurrent training	Dietary advice, protein supplementation (if needed)	Anxiety reduction strategies, phone reinforcement	Hospital length of stay, 6MWT
West et al ⁴⁴	Nonrandomized controlled trial	13/22	34.3	69.0 (6.9)	0/35	100.0	Exercise intervention	Supervised, 6 wk, 3 sessions per week, aerobic training	NA	NA	VO ₂ peak
Suen et al ⁹	Pre-post	22/0	45.5	73.6 (7.8)	Not reported	NA	Exercise + nutritional + psychological intervention	Home based and supervised 2-4 wk intervention; 2 sessions supervised per week, concurrent training, home-based aerobic training 3x per week	Written information on healthy nutrition before surgery	Nurse-led phone general support and encouragement	6MWT
Morielli et al ⁴⁶	Pre-post	13/0	46.2	57.5 (10.4)	0/13	100.0	Exercise intervention	Supervised, 6 wk, 3 sessions per week, aerobic training	NA	NA	VO ₂ peak, 6MWT
Alejo et al ⁴⁵	Pre-post	12/0	75.0	61.0 (7.0)	0/12	100.0	Exercise intervention	Educational sessions, 6 sessions in 5 wk, concurrent training	NA	NA	VO ₂ peak
Koh et al ⁴⁰	Comparative prospective cohort study	58/23	44.4	80.2 (16.4)	62/19	NA	Exercise + nutritional intervention	3 wk with weekly review, resistance exercise	Oral nutrition supplementation as recommended by the dietetics team	NA	Hospital length of stay, 6MWT

6MWT = 6-min walk test; NA = not applicable; prehab = prehabilitation; VO₂ peak = maximal oxygen uptake.

^aThe study by Minnella et al¹⁷ was a randomized clinical trial, but there was not a control group. Instead, there were 2 different intervention groups (the difference between groups was the type of aerobic training performed during the intervention: moderate-intensity continuous training vs high-intensity interval training). Therefore, in this meta-analysis, both groups were included separately, treating this study, for statistical purposes, as 2 pre-post studies.

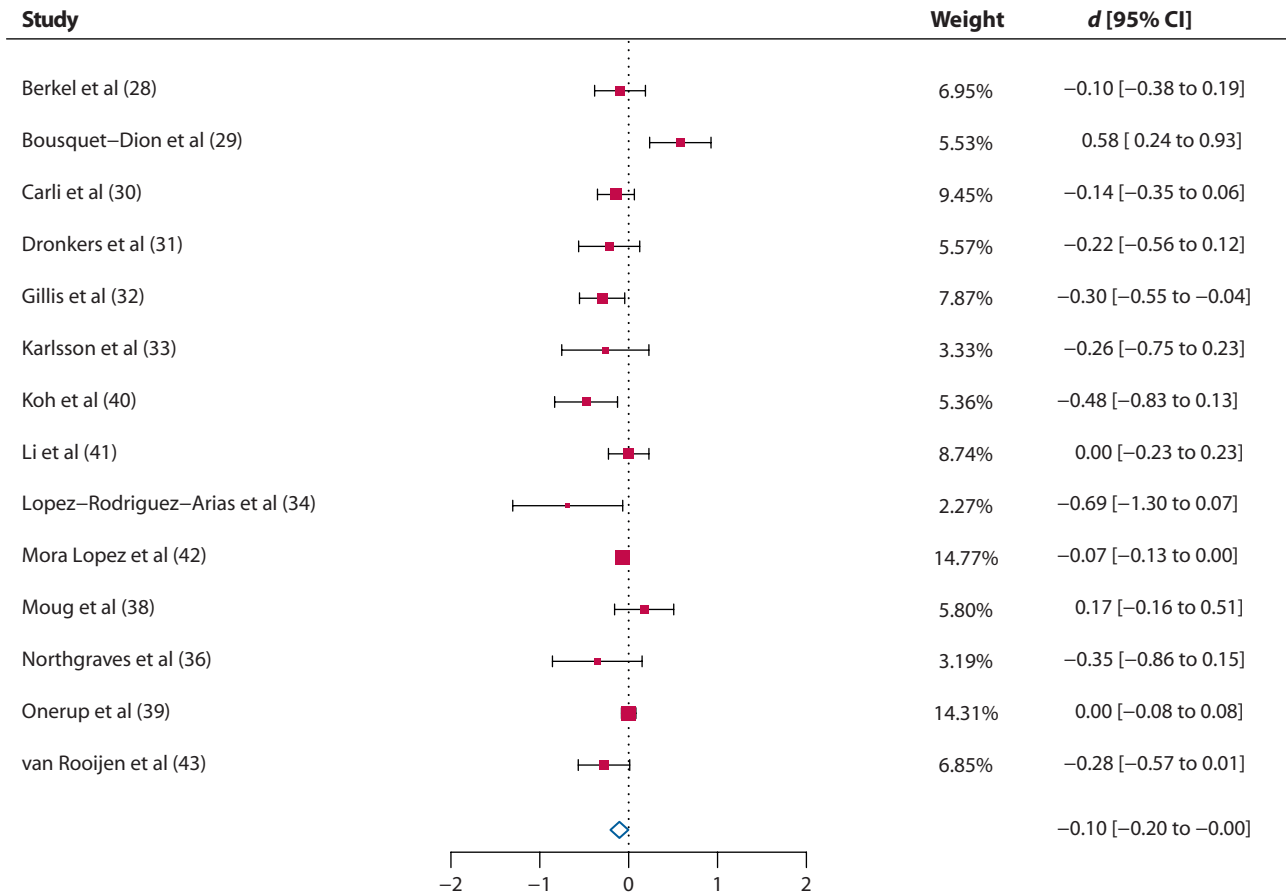


FIGURE 2. Forest plot of the standardized mean differences (*d*) for the postoperative hospital length of stay, by RCTs and non-RCTs. Negative values mean that the outcome after intervention has been reduced. RCT = randomized controlled trial.

outcomes, we conducted additional analyses considering the main characteristics of the participants (ie, sex, age, BMI) and interventions (ie, intervention type, exercise type, supervision, intervention duration), all of them factors that may contribute to the effect-size variability.

Concerning RCTs, 14 studies reported data on postoperative hospital length of stay. The intervention modality (exercise and nutrition; *d* = -0.48, *p* < 0.05), the intervention type (resistance training and concurrent training; *d* = -0.48, *p* < 0.05 and *d* = -0.13, *p* < 0.05, respectively), and the supervision of sessions (supervised; *d* = -0.28, *p* < 0.01) significantly moderated the effects on postoperative hospital length of stay. Exercise and nutrition modality and resistance training had a larger effect than concurrent training and the supervision of sessions on reduction of postoperative hospital length of stay. Concerning VO₂ peak, 3 studies showed data on this dimension. The intervention type (aerobic training; *d* = 0.61, *p* < 0.05), the supervision of sessions (supervised; *d* = 0.61, *p* < 0.05), and the cancer type (colon; *d* = -0.001, *p* < 0.05) significantly moderated the effects on VO₂ peak. Aerobic training and the supervision of sessions also had more of an effect than the cancer type (colon) on increasing VO₂ peak. Regarding the

walked distance in the 6MWT, 6 studies reported data on this dimension. The intervention modality (exercise; *d* = 0.51, *p* < 0.05), the intervention type (aerobic training; *d* = 1.09, *p* < 0.001), the supervision of sessions (home based; *d* = 0.65, *p* < 0.01), and the cancer type (colon; *d* = -0.013, *p* < 0.05) had a significant moderation on the walked distance in the 6MWT. Aerobic training had a larger effect than exercise modality, the supervision of sessions, and the cancer type (colon) on increasing the walking distance in the 6MWT. In the case of before-and-after studies, 7 studies presented data on VO₂ peak. The intervention modality (exercise; *d* = 0.34, *p* < 0.05), the intervention type (aerobic; *d* = 0.34, *p* < 0.01), and the supervision of sessions (supervised; *d* = 0.49, *p* < 0.001) were statistically significant moderators of VO₂ peak. The supervision of sessions had more of an effect than exercise modality and aerobic training on increasing VO₂ peak. Regarding 6MWT, 12 studies showed data on this outcome. The intervention modality (exercise, nutritional, and psychological intervention *d* = 0.32, *p* < 0.001), the intervention type (concurrent training; *d* = 0.32, *p* < 0.001), and the supervision of sessions (supervised, home based, and mixed; *d* range from 0.27 to 0.32, *p* values range from 0.004 to 0.036) were also significant

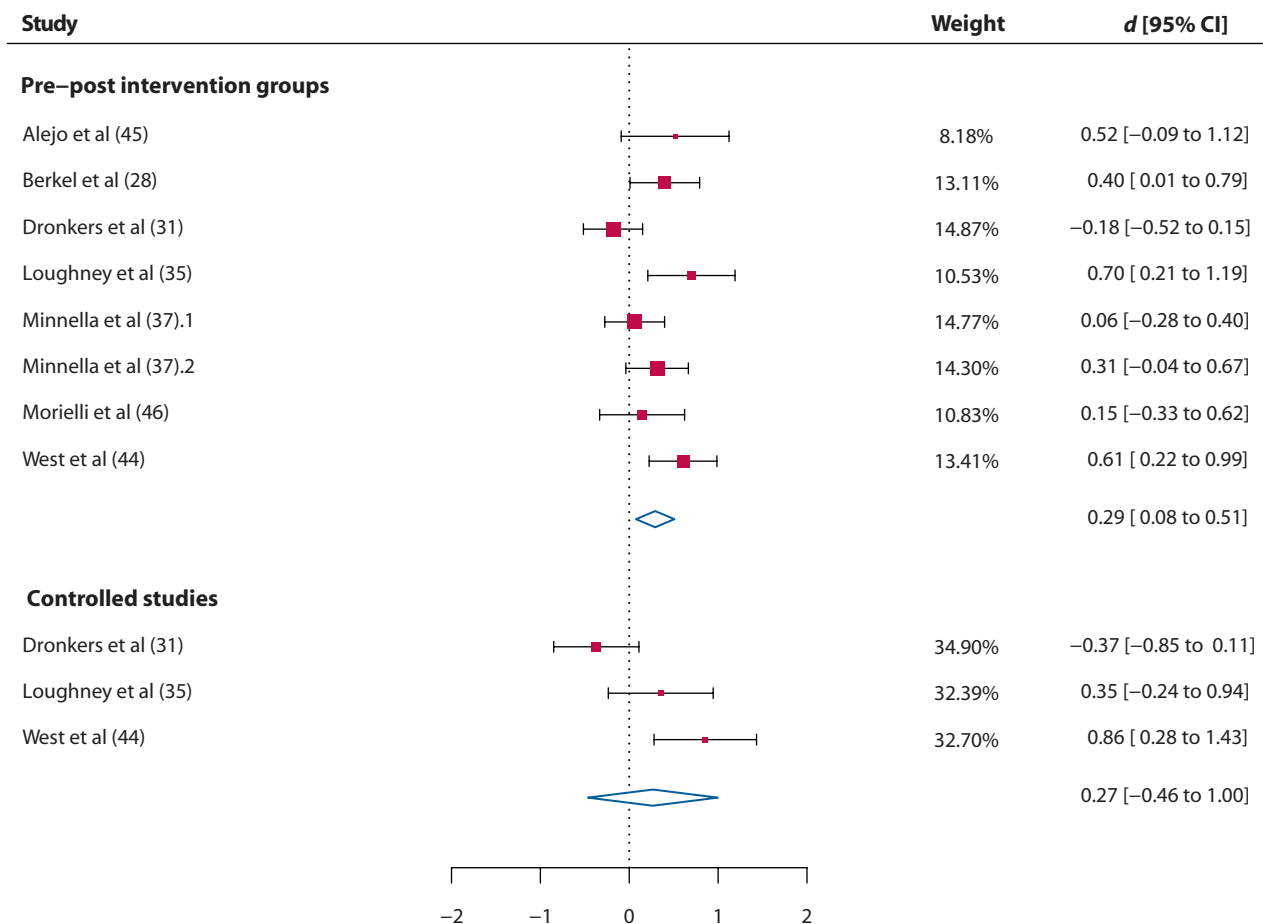


FIGURE 3. Forest plot of the standardized mean differences (*d*) for the VO_2 peak, by uncontrolled before-and-after studies and RCTs and non-RCTs. Negative values mean that the outcome after intervention has been reduced. RCT = randomized controlled trial. Minnella et al (37).1 refers to moderate intensity continuous training group, and Minnella et al (37).2 refers to high-intensity interval training group.

moderators. The supervision of sessions (and home based) had more effect than the multidisciplinary intervention modality and concurrent training on increasing the walked distance in the 6MWT. Concerning continuous variables, the methodological quality of studies significantly moderated postoperative hospital length of stay from RCTs ($d = 0.12$, $p = 0.059$). Similarly, BMI obtained at baseline was a significant moderator of VO_2 peak ($d = -5.78$, $p < 0.01$). Finally, the moderation of interventions' duration (in weeks) was significant for 6MWT ($d = 0.03$, $p < 0.00$). For before-and-after studies, no potential moderators reached a statistical significance.

Risk of Bias. Potential publication bias was evaluated by Egger test and was an indicator of statistical significance in primary and secondary outcomes of RCTs and before-and-after studies. We did not find the risk of publication bias (Egger test: $p > 0.05$). The risk of bias/methodological quality of primary studies was 0.71 (from 0 to 1) on average (see Supplemental Table S10 at <http://links.lww.com/DCR/C347>). This variable yielded nonsignificant results ($p \geq 0.05$ for both RCTs and before-and-after studies).

DISCUSSION

The present systematic review and meta-analysis synthesizes the effect of exercise and multidisciplinary prehabilitation interventions on postoperative hospital length of stay and functional capacity in patients undergoing resection of colorectal cancer. We also aimed to examine those intervention and participant characteristics that could moderate the effect of the previously mentioned interventions. The main findings indicate that postoperative hospital length of stay was reduced by nearly 2 days after approximately 4 weeks of exercise and multidisciplinary prehabilitation programs, while functional capacity was improved in response to these interventions. These results suggest that a well-designed multidisciplinary prehabilitation intervention might be effective in reducing postoperative hospital length of stay and improving functional capacity.

According to the present meta-analysis, multidisciplinary prehabilitation interventions exhibited a significant reduction of postoperative hospital length of stay (nearly 2 days), with the associated economic cost savings,

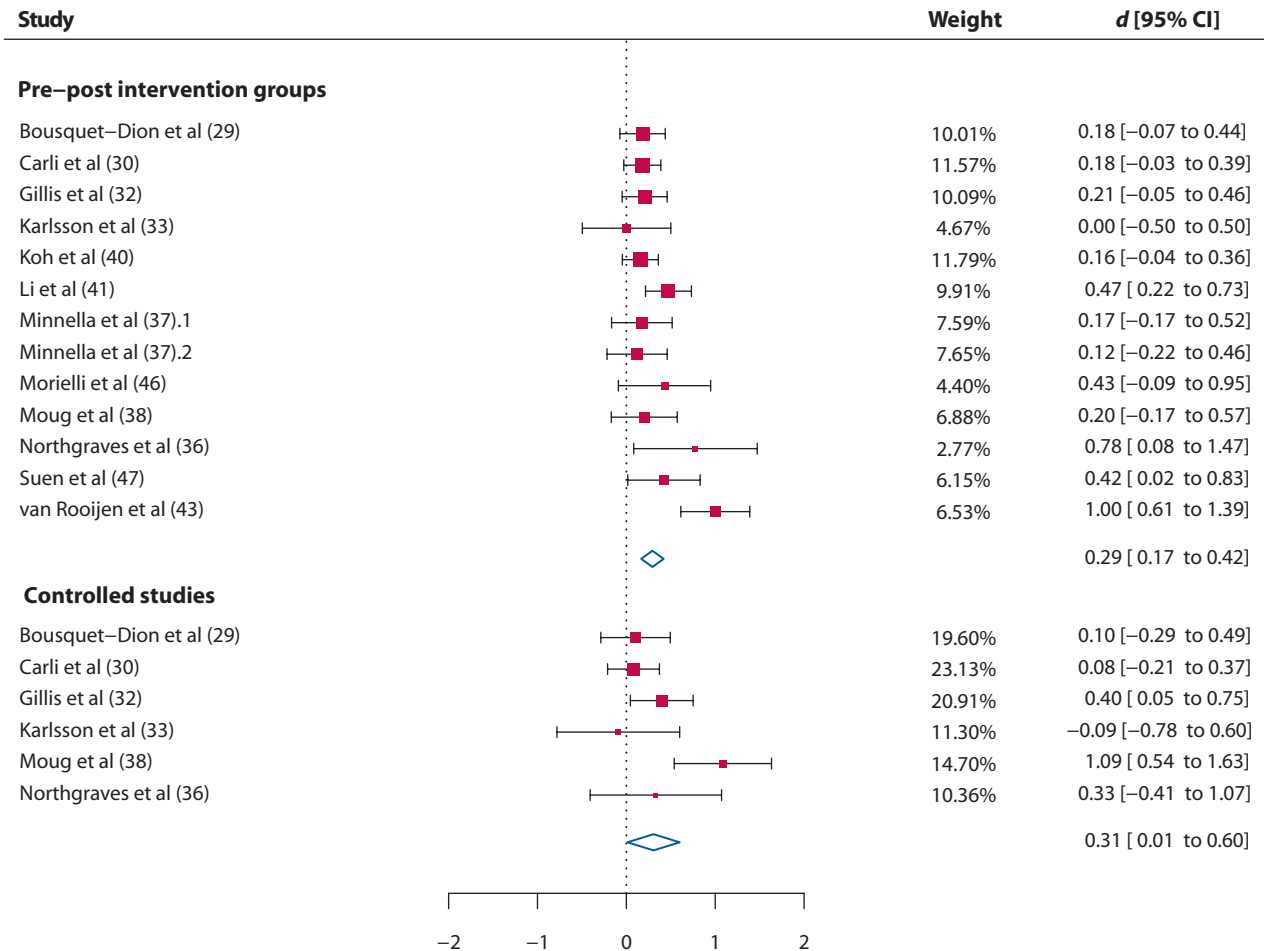


FIGURE 4. Forest plot of the standardized mean differences (*d*) for the 6MWT, by uncontrolled before-and-after studies and RCTs and non-RCTs. Negative values mean that the outcome after intervention has been reduced. RCT = randomized controlled trial; 6MWT = 6-min walking test. Minnella et al (37).1 refers to moderate intensity continuous training group, and Minnella et al (37).2 refers to high-intensity interval training group.

as previously reported.⁴⁷ From a clinical perspective, this is highly relevant because the number of colorectal cancer diagnoses continuously rises worldwide, while the hospital capacity to allocate resources could be largely improved. First, the combination of exercise and nutrition programs, which has been widely recommended by the European Society of Parenteral and Enteral Nutrition guidelines,⁴⁸ moderated this positive effect concurring with previous literature.⁴⁹ Second, concurrent training has been another significant and remarkable moderator of the reduction of the length of stay in postoperative hospitals. This result agrees not only with the purpose of far-reaching entities such as the World Health Organization⁵⁰ and the American Cancer Society⁵¹ but also with the guidelines for Perioperative Care in Elective Colorectal Surgery (enhanced recovery after surgery [ERAS])⁵² because concurrent training in rehabilitation has shown promising results in recovery of functional capacity. However, further research is needed before considering this as a mandatory item in the ERAS protocol. To the best of our knowledge,

it remains unknown whether the inclusion and implementation of a psychological support component during the prehabilitation phase—in addition to exercise and nutrition based on the previously mentioned premises—could reduce the postoperative hospital length of stay.⁵³ However, it should be noted that the implementation of exercise prehabilitation interventions (without nutrition or psychological support) did not modify postoperative hospital length of stay in this population.¹² Future RCTs will shed more light on this sense.⁵⁴⁻⁵⁶

Given that the period between the diagnosis and surgery is usually short (around 4 weeks), the increment in the exercise intensity could potentially provide additional benefits from a clinical point of view. Therefore, the implementation of high-intensity interval training (HIIT) methodology may result in even greater improvements in functional capacity.³⁷ There is strong scientific evidence supporting the fact that HIIT is an effective and feasible method to improve several health-related physiological parameters in healthy individuals, patients with cancer,

and frail/geriatric populations.^{57–63} Nevertheless, when attempting prehabilitation with frail patients, some modifications should be implemented, such as 1) performing exercises while seated or using a chair for support, 2) low-impact aquatic exercises in heated pools, 3) body weight exercises, 4) gradual progressions with extended rest periods, and 5) reduced exercise set durations. In this regard, more research is needed to elucidate whether HIIT could add additional improvements in comparison with moderate-intensity interventions.

The current results suggest that studies implementing multidisciplinary prehabilitation interventions significantly improved VO_2 peak and 6MWT. Remarkably, this increment in functional capacity has shown consistent health-related associations with better survival among patients with cancer.⁵ The intervention modality (exercise), the intervention type (aerobic training), and being supervised were significant moderators of functional capacity. It is well known that aerobic training improves cardiorespiratory fitness in adults in medium and long terms.⁶⁴ However, less scientific evidence is available regarding its effects in the short term (ie, around 4 weeks). Therefore, the inclusion of HIIT as the prehabilitation exercise intervention could also be a clinically interesting alternative for improving functional capacity in such a short period between diagnosis and surgery.⁶⁴

Importantly, we did not identify enough original studies addressing the effects of multidisciplinary prehabilitation interventions on muscular fitness in patients undergoing resection of colorectal cancer to include the results in our meta-analysis. However, a few studies showed promising findings, presenting improvements in muscular fitness, assessed by the stair climb test, after these types of interventions before surgery.³⁶ This factor could be improved in response to this kind of interventions⁵⁰ and that has been robustly and negatively associated with morbidity and mortality risk.⁶⁵

Limitations

This systematic review and meta-analysis should be interpreted with caution because of some limitations. First, there was a high between-studies heterogeneity, both in the types of intervention and in the inclusion/exclusion criteria, and several outcomes did not have the required number of studies for a desirable statistical power. Therefore, uncontrolled pre–post intervention groups were included, although these could bias the obtained effect sizes because of their inherent limitations. Second, numerous studies failed to precisely describe the exercise intervention programs following evidence-based frequency, intensity, time, and type prescriptions.⁶⁶ This poor reporting of the intervention programs did not facilitate the required number of studies for some characteristics. Third, although we tried to homogenize the sample of patients with colorectal

cancer, the heterogenous inclusion/exclusion criteria of the included studies may have affected the calculated effect sizes. Thus, the results may not be generalizable beyond this population. Indeed, data were not collected by the study regarding the proportion of new ostomates, while this would likely factor into postoperative hospital length of stay. Moreover, few studies reported that followed the ERAS protocol, and hence, this was not possible to be accounted for, yet it should have been appropriate given the long mean length of stay (9.0 ± 5.2 days). Finally, given the great relevance of clinical results in this population, the nonsignificant findings of the included studies may be underrepresented in the present systematic review and meta-analysis.

CONCLUSIONS

Our findings suggest that multidisciplinary prehabilitation interventions may effectively decrease postoperative hospital length of stay and improve functional capacity. Future research on the postoperative prognosis of colorectal cancer should consider the inclusion of multidisciplinary approaches based on exercise, nutrition, and psychology, accounting for those who receive neoadjuvant therapies, such as patients with rectal cancer. Additionally, the inclusion of higher-intensity exercise such as HIIT in this type of intervention should be investigated to determine whether they could optimize improvements because of the relatively short period between the diagnosis and the surgery in these patients.

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