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Prehabilitation before major intra-abdominal cancer surgery

A systematic review of randomised controlled trials

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BACKGROUND Although prehabilitation programmes for patients undergoing major intra-abdominal cancer surgery have been shown to improve pre-operative physical fitness, the conclusions regarding any postoperative benefits are inconsistent.

OBJECTIVES The aim of this study was to evaluate the content of and the outcome measures used in studies of prehabilitation programmes for these patients. It was hypothesised that the content of prehabilitation programmes is often therapeutically invalid, and that the postoperative outcomes assessed are inadequate to evaluate the impact of complications.

DESIGN A systematic review of randomised controlled trials.

DATA SOURCES Studies published between January 2009 and January 2019 were retrieved from PubMed, Embase and PEDro.

ELIGIBILITY CRITERIA Studies were included when they investigated the effects of prehabilitation in patients undergoing intra-abdominal surgery for cancer, reported pre-operative and/or postoperative outcome measures and were conducted as a randomised controlled trial. Studies for which the full text was not available were excluded, as were studies of patients undergoing nonabdominal cancer surgery.

RESULTS Eight studies (565 patients) were included. Therapeutic validity was low in five studies. Most studies included low-risk surgical patients and considerable variation was observed between prehabilitation programmes in terms of supervision, training context, frequency, intensity, duration and training type. Objective monitoring of training progression was typically not performed, and most trials did not include nutritional or psychological support. Postoperative complications were reported in seven studies, but no study reported the impact of postoperative complications, nor on long-term postoperative outcomes.

CONCLUSION The content of prehabilitation programmes was heterogeneous. Studies with a high therapeutic validity found unequivocal evidence that prehabilitation had beneficial effects on postoperative outcomes. Future research should focus on adequate selection and inclusion of high-risk surgical patients and provide personalised and probably multimodal (partly) supervised prehabilitation, with objective monitoring of progress. Measuring the incidence and impact of postoperative complications may contribute to demonstrating the clinical value of prehabilitation.

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Introduction

Despite continuing surgical and anaesthetic advances, invasive cancer treatment remains a challenge that requires substantial physiological and psychological resilience from patients, even in the absence of postoperative complications.[1–3] Resilience is defined here as the physical and mental tools and capabilities, which enable patients to cope with the disease and its subsequent treatment. Especially in patients with low physiological

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and psychological reserves, cancer diagnosis and treatment, including surgery, may lead to the deterioration of physical functioning.[4] After treatment, low levels of physical activity by patients result in a further decline in physical functioning, reducing aerobic capacity and muscle function, and these represent obstacles to a swift 'back-to-baseline' recovery of physical functioning.[5,6]

Thus, when psychophysiological reserves are inadequate, as in frail and in less physically fit patients, the risk of postoperative complications increases.[7] The aim of prehabilitation is to improve the pre-operative status of patients in the period between diagnosis and treatment by means of physical exercise training, nutritional interventions, psychological support and/or coaching towards lifestyle changes.[8] Such prehabilitation is thought to result in the faster recovery of physical functioning, a reduction in postoperative complications, shorter hospital stays and an improved long-term prognosis, as well as in lower direct and indirect healthcare costs.[8–10]

Although both unimodal and multimodal prehabilitation programmes have been shown to improve physical fitness before surgery, it is surprising that inconsistent conclusions have been drawn about the postoperative benefits.[11,12] A possible explanation is that the Clavien-Dindo classification, which seems to be the indicator most frequently used to assess the effects of prehabilitation on postoperative outcomes, may underestimate the benefits of prehabilitation because the personal impact of complications probably varies between patients depending on their psychophysiological reserves.[13] Even when complication rates are similar, fitter patients with a higher level of resilience, for example following prehabilitation, may cope better with these stressors and have better postoperative outcomes. This was observed by Hulzebos *et al.*, who reported that postoperative pneumonia had a significantly greater impact on patients in the usual-care-group than patients after prehabilitation: the latter seemed to cope more easily with postoperative hospital-acquired pneumonia.[14] In addition, because of the limited availability of evidence-based guidelines for prehabilitation, the content of prehabilitation programmes found in current literature differs in terms of training frequency, intensity, duration, supervision and the number of modalities targeted. It seems fair to assume that these large differences will also be associated with considerable differences in effectiveness and hence the effect size of studies, and this could account for the overall lack of evidence about the effectiveness of prehabilitation in intra-abdominal cancer surgery in terms of postoperative complications, length of stay and quality of life.[11,12,15]

Many systematic reviews in the current literature have remarked on the heterogeneity of prehabilitation programmes, but there have been no studies that have systematically evaluated the content of pre-operative exercise programmes using clear and predefined criteria. To properly assess the effects of prehabilitation in intra-abdominal cancer surgery, it would seem essential to ensure that the content of prehabilitation programmes is therapeutically valid *and* that there is an optimal assessment of postoperative outcomes. Because both these factors are of crucial importance in demonstrating the clinical benefits of prehabilitation, the present systematic review aims to assess both these factors.

Materials and methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16] and is registered in the PROSPERO register as CRD42018082720. The electronic databases PubMed, Embase and PEDro were searched to find eligible articles published between January 2009 and January 2019. The MeSH headings used included pre-operative care OR operative surgical procedures or pre-operative period AND colorectal neoplasms OR colonic neoplasms OR abdominal neoplasms OR digestive surgical procedure AND exercise OR physical therapy OR resistance training OR physical education and training OR high-intensity interval training. A detailed description of the search can be found in the Appendix (Supplemental Digital File, http://links.lww.com/EJA/A228). Search terms were explored using free text words to avoid the exclusion of recently published articles.

Study selection

Studies were included when they investigated the effects of physical prehabilitation (a pre-operative intervention including physical exercise training with the aim of improving physical fitness) in patients undergoing major intra-abdominal surgery for cancer, reported outcome measures for pre-operative or postoperative levels of physical fitness, postoperative morbidity, postoperative mortality, length of stay and/or quality of life, and were conducted as a randomised controlled trial (RCT). Major surgery was defined here as surgery expected to last more than 2 h, or with an anticipated blood loss greater than 500 ml. Studies for which the full text was not available were excluded, as were studies of patients undergoing nonabdominal cancer surgery.

Data extraction

After the removal of double hits from the search results, two reviewers (GT and RT) independently screened and selected potentially eligible studies. After consensus was reached in this initial selection procedure, both reviewers independently reviewed the full text of the selected studies to determine final suitability for inclusion based on the established inclusion criteria. In order to include additional relevant studies, after full text assessment, reference tracking was performed. A third reviewer

(BB) determined study eligibility if the first two reviewers did not reach agreement.

Data collection process and items

The following information was collected and compared for all included studies: general study information (first author, publication year, country), patient characteristics in the intervention and control group [number of patients, age, treatment and American Society of Anesthesiologists (ASA) classification], elements of prehabilitation (such as physical exercise training, nutritional support, psychological support), content of the physical exercise training programme according to the FITT principles (training frequency, training intensity, training time, training type) and outcome measures (such as postoperative complications, postoperative mortality, length of stay).[17,18]

Assessment of methodological quality and therapeutic validity

Methodological quality was independently assessed by two reviewers (GT and RT) using the Cochrane Collaboration's tool for assessing risk of bias in RCTs, a domain-based evaluation for systematic reviews.[19] Selection, performance, detection, attrition and reporting bias were scored as 'low risk' (√), 'high risk' (×) or 'unclear' (?). If the two authors disagreed, a third evaluator (BB) was consulted as a mediator. To systematically assess the content of prehabilitation programmes, its therapeutic validity was assessed independently by the same reviewers using the Consensus on Therapeutic Exercise Training (CONTENT) scale.[20] Therapeutic validity was defined as the potential effectiveness of a specific physical exercise training intervention given to a specific group of patients.[19] The CONTENT scale assesses the quality of physical exercise training interventions, consisting of nine items covering five critical areas. Patient eligibility, competences and setting, rationale and plausibility of the study, content of the applied intervention and adherence were scored per item as 'adequately performed' (√) or 'not adequately performed' (×). Up till now, physical exercise training programmes have been evaluated on the methodological quality of the studies in which they were evaluated. With help of the CONTENT scale, this is the first thorough attempt to explicitly evaluate the content of the preoperative physical exercise intervention itself. High therapeutic validity was indicated when 'adequately performed' (√) was scored six times or more. Interobserver agreement was calculated by Cohen's Kappa, with poor (<0.20), reasonable (0.21 to 0.40), moderate (0.41 to 0.60), good (0.61 to 0.80) or very good (>0.80) agreement.[21]

Results

Initially, the literature search identified 4372 manuscripts and, eventually, eight RCTs investigating the effects of prehabilitation in major intra-abdominal cancer surgery were included. Sample sizes of the included studies varied from 21 to 144 patients, representing 565 patients in total, with a mean age ranging between 55 and 71 years in the studies.[22–29] Figure 1 shows the PRISMA flow diagram for evidence acquisition. The included studies were published between January 2009 and January 2018 and they investigated prehabilitation in colorectal cancer surgery ($n = 5$), liver cancer surgery ($n = 2$) and a mixed group of patients undergoing major abdominal surgery ($n = 1$). General study characteristics can be found in Table 1.

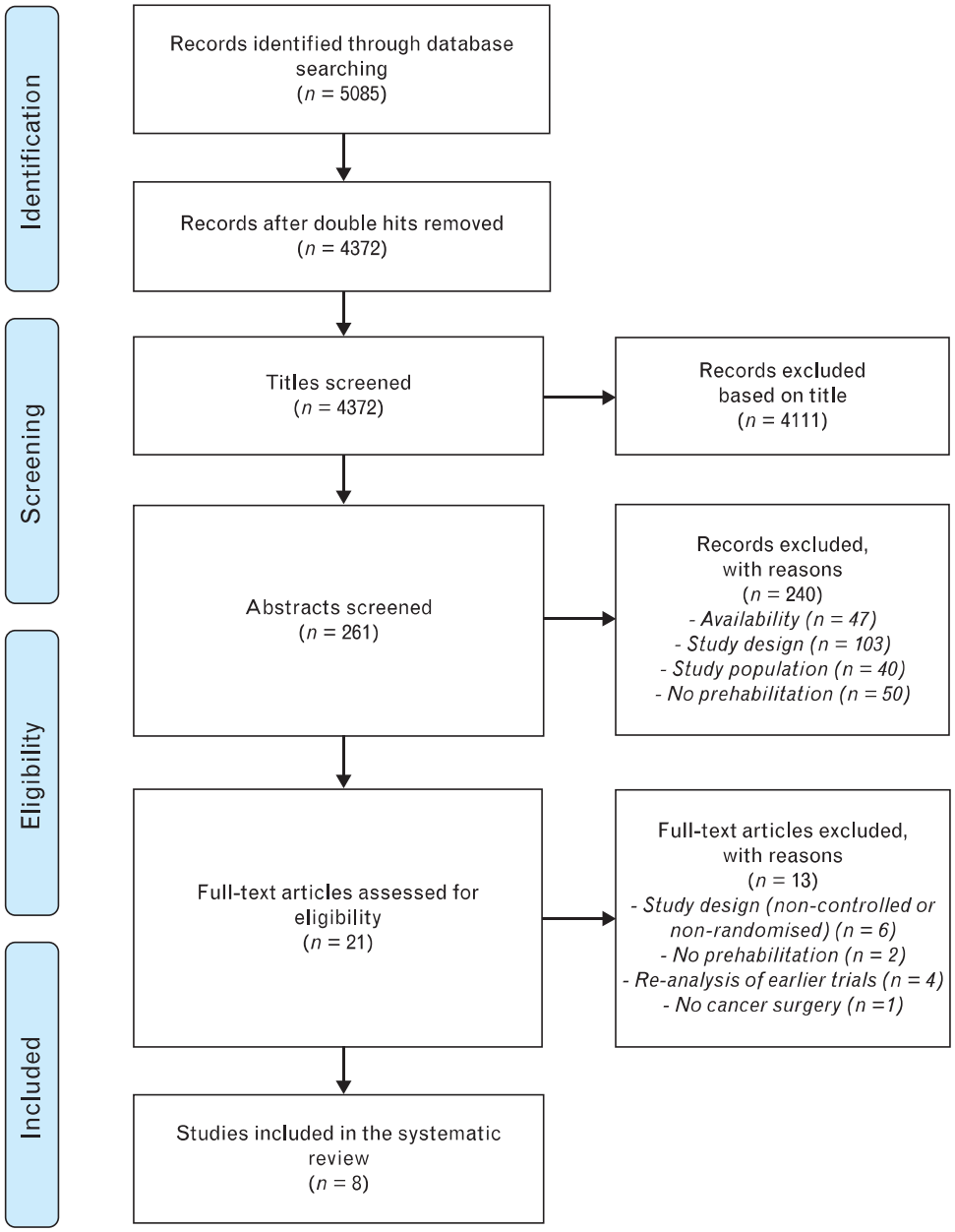
Methodological quality

Table 2 summarises the methodological quality of the included studies for which the interobserver agreement was 'very good' (kappa score of 0.87). None of the studies were blinded. It is noteworthy that the study by Barberan-Garcia *et al.*[28] used a double-informed-consent model in which the control arm was not aware of the existence of an intervention arm and vice versa. Half of the included studies described the blinding of outcome measures in an irreproducible manner or not at all.[22,23,25,26]

Therapeutic validity

Only three of the included studies (Table 2) were found to have high therapeutic validity.[22,24,28] Interobserver agreement for therapeutic validity was 'good' (kappa score of 0.78). Although the selection of patients was described adequately in the majority of the studies, most patients included had low ASA scores and they therefore had a lower risk of postoperative complications. Two studies specifically included high-risk surgical patients, one on the basis of age[24] and the other on the basis of age, ASA classification and Duke activity status index score (Table 1).[28] None of the studies reported inclusion rates, or possible differences between the baseline characteristics of patients who decided not to participate and those who did. In four studies, patients were supervised during the programme by a researcher, exercise physiologist or physiotherapist to a greater or lesser degree[24,27–29]: in the other four trials, patients trained without supervision.[22,23,25,26] However, the degree of supervision varied: in the study by Gillis *et al.*,[26] no researchers or physicians were present during training sessions. Instead, patients received weekly phone calls to evaluate issues related to prehabilitation programme compliance (training frequency, training intensity, amount of whey protein ingested, use of the relaxation methods). On the contrary, in the study by Dunne *et al.*,[27] all sessions were supervised and took place in the hospital. However, in this study and two other included studies, the background of supervising personnel was not described.[24,25,27] In one study in which patients were partly supervised, patients had one supervised session a week at the hospital and were asked to complete the other training sessions unsupervised at home.[29]

Fig. 1



The PRISMA flow diagram for evidence acquisition.

Considerable variation was noted between the prehabilitation programmes in terms of training frequency (ranging from daily to two sessions per week), training intensity (ranging from moderate to high intensity), programme duration (ranging from 2 to 9 weeks) and type of physical exercise (aerobic training, resistance training, high-intensity interval training, stretching exercises, inspiratory muscle training or a combination of these elements) (see Table 3). The personalisation of exercise programmes also varied: the intensity of the aerobic training component was often personalised to some degree using heart rate,[22–24,26,29] ventilatory anaerobic threshold,[25] oxygen uptake at peak exercise[27] or work rate at peak exercise (Table 3).[28] The types and location of training were not personalised in most studies,[23,25–27,29] but personalisation was seen on the basis of physical condition and/or personal circumstances in studies selecting high-risk patients, for example by adjusting the number of hospital visits needed.[24,28] Three studies included hospital-based training.[24,27,29] 'One of these studies combined hospital-based training with home-based training.[29]' One study provided community-based training,[28] and four studies looked at

Table 1 General characteristics of the included studies

Ref.	Year	Country	Sample size	Disease or treatment	Mean ± SD age (years)	ASA score	Targeted high-risk patients
Kim *et al.*[22]	2009	USA	I: 14 C: 7 Total: 21	Colorectal surgery	I: 55 ± 15 C: 65 ± 9	I-III	No
Carli *et al.*[23]	2010	Canada	I: 58 C: 54 Total: 112	Colorectal cancer surgery	I: 61 ± 16 C: 60 ± 15	I-III	No
Dronkers *et al.*[24]	2010	The Netherlands	I: 22 C: 20 Total: 42	Colon cancer surgery	I: 71 ± 6 C: 69 ± 6	NR	Yes[a]
Kaibori *et al.*[25]	2012	Japan	I: 26 C: 25 Total: 51	Liver cancer surgery	I: 68 ± 9 C: 71 ± 9	NR	No
Gillis *et al.*[26]	2014	Canada	I: 38 C: 39 Total: 77	Colorectal cancer surgery	I: 66 ± 14 C: 66 ± 9	I-IV	No
Dunne *et al.*[27]	2016	UK	I: 20 C: 18 Total: 38	Liver cancer surgery	I: 61 [56 to 66] [b] C: 62 [53 to 72] [b]	NR	No
Barberan-Garcia *et al.*[28]	2018	Spain	I: 73 C: 71 Total: 144	Major abdominal surgery	I: 71 ± 10 C: 71 ± 11	II-IV	Yes [c]
Bousquet-Dion *et al.*[29]	2018	Canada	I: 41 C:39 Total: 80	Colorectal cancer surgery	I: 74 [67.5 to 78] [b] C: 71 [54.5 to 74.5] [b]	I-IV	No

ASA, American Society of Anesthesiologists; C, control group; I, intervention group; NR, not reported; SD, standard deviation. [a] Based on: age >60 years. [b] Median and interquartile range. [c] Based on age, ASA score and Dukes classification.

programmes with home-based training only.[22,23,25,26] The monitoring of patient progress throughout the prehabilitation programme and subsequent adjustments to the programme were noted in only two studies: perceived exertion was used in these as a measure for progress.[24,26] No study used objective performance measures to assess training progress (to identify responders and nonresponders) and to adjust the training intensity or training

Table 2 Results of methodological quality according to the Cochrane risk of bias tool and therapeutic validity according to the CONTENT scale

Methodological quality[a] Ref.	Randomisation (selection bias)	Equal groups (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective drop-out (attrition bias)	Selective reporting (reporting bias)	Other sources of bias (other bias)
Kim *et al.*[22]	?	?	X	?	√	?	X
Carli *et al.*[23]	√	?	X	?	√	?	√
Dronkers *et al.*[24]	√	√	X	√	√	?	√
Kaibori *et al.*[25]	?	?	X	?	√	?	X
Gillis *et al.*[26]	√	√	X	?	√	?	√
Dunne *et al.*[27]	√	√	X	√	√	?	√
Barberan-Garcia *et al.*[28]	√	√	X	√	√	√	√
Bousquet-Dion *et al.*[29]	√	√	X	X	√	√	√

Therapeutic validity[b] Ref.	Description patient selection	Adequate patient selection	Eligibility criteria for therapist and setting determined and adequate	Therapeutic exercise based on a priori aims and intentions	Rationale for content and intensity described and plausible	Intensity described	Therapeutic exercise monitored and adjusted when necessary	Exercises personalised and contextualised to individual	Adherence determined and acceptable	Conclusion therapeutic validity [c]
Kim *et al.* [22]	√	X	√	√	√	√	X	√	X	High
Carli *et al.* [23]	√	X	X	X	X	√	X	X	X	Low
Dronkers *et al.* [24]	√	X	X	√	√	√	√	√	√	High
Kaibori *et al.* [25]	√	X	X	X	X	√	X	X	X	Low
Gillis *et al.* [26]	√	X	√	√	X	√	X	√	X	Low
Dunne *et al.* [27]	X	X	X	√	√	√	X	√	√	Low
Barberan-Garcia *et al.* [28]	√	√	√	√	√	√	√	√	√	High
Bousquet-Dion *et al.* [29]	√	X	√	√	X	√	X	√	X	Low

[a] √ = low risk of bias; X = high risk of bias; ? = unclear. [b] √ = adequately performed; X = inadequately performed. [c] High therapeutic validity: ≥6 times √; low therapeutic validity: <6 times √.

Table 3 Prehabilitation characteristics of the included studies

Ref.	Context, location	Supervision	Frequency of training	Method used to set training intensity	Overall intensity of training	Objective monitoring of training progression	Time of a training session	Period of training	Type of physical exercise training, including other prehabilitation modalities
Kim *et al.*[22]	Home-based	Unsupervised	Daily	Aerobic training: at 40 to 65% of HRR based on CPET	Moderate	No	20 to 30 min	4 weeks	Structured aerobic training (20 to 30 min) on a cycle ergometer
Carli *et al.*[23]	Home-based	Unsupervised	Daily	Aerobic training: at 50% of HR_{peak} based on CPET, gradually increased each week by 10%, if tolerable Resistance training: repetitions up to volitional fatigue, with a maximum of 12 repetitions for push-ups, sit-ups and lunges, or up to eight repetitions for biceps, deltoids and quadriceps exercises	Moderate	No	20 to 45 min	3 to 9 weeks	Aerobic training (20 to 30 min) on a cycle ergometer (daily) Resistance training (10 to 15 min): push-ups, sit-ups, and standing strides (three times a week)
Dronkers *et al.*[24]	Hospital-based	Supervised	Two times a week	Aerobic training: at 55 to 75% of HR_{max} or a rating of perceived exertion of 11 to 13 on the Borg scale Resistance training: maximum of one set of eight to15 repetitions, consistent with 60 to 80% of 1RM IMT: breathing against a resistance of 10 to 60% of maximal inspiratory pressure	Moderate to high	No	60 min	2 to 4 weeks	- Aerobic training (20 to 30 min), combined with 15 min of IMT and resistance training of the lower limb extensors (maximum of one set of eight to 15 repetitions) at the outpatient department of the hospital Additional home-based training: participants were asked to perform moderate-intense exercises (minimum of 30 min walking or cycling), five times a week
Kaibori *et al.*[25]	Home-based	Unsupervised	Three times a week	Aerobic training: based on VAT achieved during CPET	Moderate	No	60 min	4 weeks	Aerobic training (30 min), walking [a] Stretching exercises (5 min as warm-up before aerobic training, 20 min of targeted stretching after aerobic training and 5 min as cool-down) Patients also received nutritional support (for patients with hepatitis or liver cirrhosis: daily energy intake was set at 25 to 30 kcal kg body $mass^{-1}$, with a daily protein intake of 1.0 to 1.2 g/kg, and a daily sodium chloride intake of 5 to 7 g/kg; for patients with diabetes or fatty liver disease, daily energy intake was set at 20 to 25 kcal kg body $mass^{-1}$; for patients with hypertension, daily sodium chloride intake was set at 6 kcal kg body $mass^{-1}$)
Gillis *et al.*[26]	Home-based	Unsupervised [b]	Three times a week	Aerobic training: at 40% of HRR, calculated using the Karvonen formula [(220-age) − (resting HR × % intensity) + resting HR], where after intensity was progressed based on perceived exertion, Borg scale >12	Moderate	No	50 min	4 weeks	Trimodal prehabilitation at home, supervised by phone, including: Aerobic (20 min) and resistance (20 min) training, 5 min warm-up and 5 min cool-down Nutritional support (whey protein supplements: 1.2 kcal kg body $mass^{-1}$) Psychological support (relaxation exercises, imagery and visualization, and breathing exercises), 2 to 3 times a week
Dunne *et al.*[27]	Hospital-based	Supervised	Three times a week	HIT: work interval at >90% of VO_{2peak}, rest interval at <60% of VO_{2peak}, based on CPET [c]	High	No	40 min	4 weeks	- HIT (5 min warm-up, 30 min HIT, 5 min cool-down) on a cycle ergometer
Barberan-Garcia *et al.*[28]	Community-based	Supervised	One to three t imes a week [d]	- HIT: 2-min work interval at ≥70% of WR_{peak}, based on CPET, in first 2 weeks, thereafter WR was increased by about 5% every week up to a maximum of 85% of WR_{peak}, 3-min rest interval at ≥40% WR_{peak}, based on CPET, in first 2 weeks, thereafter WR was increased by about 5% every week up to a maximum of 50% of WR_{peak}	High	No	47 min	6 weeks	Personalised HIT (5 min warm-up, 37 min HIT, 5 min cool-down) on a cycle ergometer Nutritional support (patients suffering from iron-deficiency anaemia received intravenous iron and in patients at a high risk of malnutrition (MUST ≥2), a nutritional intervention was done by registered dieticians) Motivational interviewing aiming to realize a more physically active lifestyle and mindfulness Encouraging to be physically active on a daily base
Bousquet-Dion *et al.*[29]	Home and hospital-based [e]	Partly supervised [e]	Three to four times a week	Aerobic training: walking, cycling or jogging based on the rate of perceived exertion (Borg scale) and 6MWT performance at 60 to 70% of HRR calculated from the Karvonen formula Resistance training: based on eight repetitions maximum test to provide a submaximal estimation of maximal strength	Moderate	No	60 min	4 weeks	- Aerobic training (walking, cycling or jogging for 30 min) and resistance training (30 min) Nutritional support (protein intake aiming for 1.2 kcal kg body $mass^{-1}$) and supplementation (whey protein) if patients did not reach this target by diet alone Psychological support (home-based relaxation exercises based on visualisation and breathing exercises (two to three times a week), after 60 min supervised relaxation exercises to instruct patients)

1RM, one-repetition maximum; 6MWT, 6-min walk test; CPET, cardiopulmonary exercise testing; HIT, high-intensity interval training; HR, heart rate; HR_{max}, maximal heart rate; HR_{peak}, peak heart rate; HRR, heart rate reserve; IMT, inspiratory muscle training; MUST, malnutrition universal screening tool; VAT, ventilatory anaerobic threshold; VO_{2peak}, peak oxygen uptake; WR, work rate; WR_{peak}, peak work rate. [a] Walking intensity was based on the AT of each patient. [b] A limited degree of supervision was performed by phone. [c] Duration of work and rest intervals were not reported. [d] The intervention group underwent a personalised prehabilitation programme based on their health conditions and social circumstances. [e] Once a week, a training session was performed in-hospital (supervised by a kinesiologist), and the other sessions were performed at home.

Table 4 Prehabilitation outcomes of the included studies

Ref.	Number of modalities	Physical exercise training	Nutritional support	Psychological support	Personalised	Adherence	Reasons for drop-out in prehabilitation group [a]	Adverse events	Postoperative care	Summary of the effects of the prehabilitation programme
Kim *et al.*[22]	Unimodal	√	X	X	No	74%	Fatigue and malaise	NR	No rehabilitation	In the prehabilitation group, WR_{peak} was the only maximal exercise indicator of aerobic capacity that was responsive to the prehabilitation programme (mean ± SD increase of 26 ± 27%; 95% CI 11 to 41). For submaximal indicators of aerobic capacity, HR (-13 ± 15%; 95% CI -10 to -4) and VO_2 (-7 ± 6%; 95% CI -21.5 to -4.5) during submaximal exercise were most responsive to prehabilitation in the prehabilitation group. There were no changes in maximal and submaximal indicators of aerobic capacity in the control group. 6MWT distance improved in both groups by ~30 m. Postoperative outcomes were not evaluated in this study.
Carli *et al.*[23]	Unimodal	√	X	X	No	59% [b]	Discontinued participation	NR	NR	Adherence was low. There were no differences between the prehabilitation group (aerobic and resistance training) and the control group (walking and breathing exercises) in mean ± SD 6MWT distance over the prehabilitation programme (-10,6 ± 7,3 versus 8,7 ± 6,8 m, respectively; *P* = NR) or at postoperative follow-up (-34.4 ± 9.9 versus -12.2 ± 10.9 m, respectively; *P*-value NR). The proportion showing an improvement in 6MWT distance (≥20 m) was smaller in the prehabilitation group than in the control group after the prehabilitation programme (22 versus 47%, respectively; *P* = 0.051) and after surgery (11 versus 41%, respectively; *P* = 0.019). Anxiety did not change in both groups following prehabilitation, whereas depression significantly improved in the prehabilitation group. There was no significant difference in postoperative complications and mean ± SD length of hospital stay (7.4 ± 6.5 versus 6.5 ± 3.6 days; *P* = NS) between the prehabilitation and control group, respectively.
Dronkers *et al.*[24]	Unimodal	√	X	X	Yes	97%	Death of spouse Unable to combine training with daily work	0	NR	The prehabilitation programme was feasible, with a high compliance and no adverse events. The prehabilitation group increased respiratory muscle endurance preoperatively compared to the control group (from 259 ± 273 to 404 ± 349 J versus 350 ± 299 to 305 ± 323 J, respectively; *P* < 0.01). Estimated aerobic capacity, functional mobility, level of physical activity and QoL did not reveal significant differences between the two groups after the prehabilitation programme. There was no significant difference in postoperative complications (9 versus 8; *P* = 0.650) and mean ± SD length of hospital stay (16.2 ± 11.5 versus 21.6 ± 23.7 days; *P* = 0.310) between the prehabilitation and control group, respectively.
Kaibori *et al.*[25]	Bimodal	√	√	X	Yes	NR	Tumour recurrence Financial reasons Exacerbation of other disease	NR	NR	There were no statistically significant differences in any postoperative outcomes between both groups; however, mean ± SD hospital length of stay of the prehabilitation (physical exercise training and nutritional support) group was shorter than that of the control (nutritional support) group (13,7 ± 4,0 versus 17,5 ± 11,3 days; *P* = 0,120). At 6 months postoperatively, the mean ± SD improvement in VO_2 at the VAT and VO_{2peak} were significantly greater following prehabilitation in a high-frequency exercise (five to six times a week) subgroup compared with a low-frequency (three times a week) subgroup (115 ± 18 versus 102 ± 14%, respectively; *P* = 0.038, and 118 ± 11 versus 103 ± 12%, respectively; *P* = 0,002).

Table 4 (*continued*)

Ref.	Number of modalities	Physical exercise training	Nutritional support	Psychological support	Personalised	Adherence	Reasons for drop-out in prehabilitation group [a]	Adverse events	Postoperative care	Summary of the effects of the prehabilitation programme
Gillis *et al.*[26]	Trimodal	√	√	√	No	78% [c]	Emergency surgery Withdrew consent	0	ERAS, rehabilitation [d]	The prehabilitation group improved 6MWT distance (≥20 m) in a higher proportion compared with the rehabilitation group (53 versus 15%; adjusted $P=0.006$). Complication rates and duration of hospital stay were similar. The mean ± SD difference between baseline and 8-week postoperative 6MWT distance was significantly better in the prehabilitation group than in the rehabilitation group (+23.7 ± 54.8 versus − 21.8 ± 80.7 m, respectively; mean difference 45.4 m; 95% CI 13.9 to 77.0; adjusted $P=0.020$). A higher proportion of the prehabilitation group was also recovered to or above baseline 6MWT distance at 8 weeks postoperatively compared with the rehabilitation group (84 versus 62%, respectively; adjusted $P=0.049$).
Dunne *et al.*[27]	Unimodal	√	X	X	Yes	99%	Insufficient time to complete prehabilitation Distance from tertiary centre	0	ERAS	The prehabilitation group improved in aerobic capacity preoperatively (mean increase in VO_2 at the VAT +1.0 ml kg^{-1} min^{-1}; 95% CI -0.2 to 2.1; $P=0.093$, and mean increase in VO_{2peak} +2.0 ml kg^{-1} min^{-1}; 95% CI 0.4 to 3.6; $P=0.019$). Compared with the control group, the prehabilitation group demonstrated an improvement in VO_2 at the VAT of 1.5 ml kg^{-1} min^{-1} ($P=0.023$) and in VO_{2peak} of 2.0 ml kg^{-1} min^{-1} ($P=0.047$). This was associated with improved preoperative QoL. There were no statistically significant differences in any postoperative outcomes between both groups.
Barberan-Garcia *et al.*[28]	Trimodal	√	√	√	Yes	NR	Incapacity to perform exercise testing Decided to abandon study	0	NR	The prehabilitation group improved in aerobic capacity pre-operatively (mean increase in endurance time +135%; $P<0.001$, versus +12% for the control group; $P=0.118$), whereas 6MWT distance did not change in both groups. Prehabilitation enhanced postoperative clinical outcomes, as it reduced the number of patients with postoperative complications by 51% (relative risk 0.5; 95% CI 0.3 to 0.8; $P=0.001$), reduced the mean ± SD number of complications per patient (0.5 ± 1.0 versus 1.4 ± 1.6; $P=0.001$), reduced mean ± SD hospital length of stay (8 ± 8 versus 13 ± 20; $P=0.078$) and reduced mean ± SD ICU days of stay (1 ± 2 versus 4 ± 13; $P=0.078$).
Bousquet-Dion *et al.*[29]	Trimodal	√	√	√	Yes	98% [e]	Complications Refused to come	NR	ERAS, rehabilitation [d]	Both groups were comparable for baseline mean ± SD 6MWT distance (prehabilitation group: 448 ± 118 m versus rehabilitation group: 461 ± 109 m; $P=0.775$) and included a similar proportion of patients who improved preoperative 6MWT distance ≥20 m (prehabilitation group: 54% versus rehabilitation group: 38%; $P=0.222$). After surgery, changes in 6MWT distance were also similar in both groups. Previously inactive patients were more likely to improve functional capacity due to prehabilitation (OR 7.07; 95% CI 1.10 to 45.51). Length of first stay, emergency department visits and complication rate were similar between both groups. Hospital re-admission and the total duration of hospitalization tended to be higher in the prehabilitation group, but not following intention-to-treat analysis, in which patients who were excluded after surgery due to missing 6MWT at follow-ups were included as well.

6MWT, 6-min walk test; CI, confidence interval; ERAS, enhanced recovery after surgery; HR, heart rate; NR, not reported; NS, not statistically significant (exact *P* value not reported); OR, odds ratio; QoL, quality of life; SD, standard deviation; VAT, ventilatory anaerobic threshold; VO_2, oxygen uptake; VO_{2peak}, peak oxygen uptake; WR_{peak}, peak work rate. [a] Reasons for drop-out other than changes in the surgical plan (timing, other hospital, cancellation). [b] Adherence was defined as the percentage of exercise sessions attended. [c] Adherence was determined using the CHAMPS (community healthy activities model programme for seniors) activities questionnaire for older adults. [d] Eight weeks of rehabilitation for the intervention and control group; however, the exact content of this programme was not specified. [e] Adherence was only described for the supervised in-hospital sessions and determined using the CHAMPS (community healthy activities model programme for seniors) activities questionnaire for older adults and relating this to American Cancer Society guidelines.

programme accordingly. Finally, four trials (50%) investigated a unimodal approach in which physical exercise training was the sole component of prehabilitation,[22–24,27] one study investigated a bimodal programme that also included a nutritional component[25] and two studies investigated a trimodal programme that also included a psychological component (see Table 4).[26,28]

Outcome measures used to evaluate the effects of prehabilitation

Table 5 summarises the outcome measures used to assess the effects of prehabilitation. Postoperative complications were reported in seven of the eight studies included.[23–29] Five of these studies also reported postoperative complications using the Clavien-Dindo

Table 5 Postoperative outcome measures used in the included studies

Authors	Postoperative complications	ICU stay	Length of primary hospital stay	In-hospital mortality	Readmission
Kim *et al.*[22]	NR	NR	NR	NR	NR
Carli *et al.*[23]	I: CD I-II: 16/56 (29%) C: CD I-II: 15/54 (28%) $P=$NS I: CD III-IV: 6/56 (11%) C: CD III-IV: 3/54 (6%) $P=$NS	NR	I: mean ± SD days: 11.9 ± 34.6 C: mean ± SD days: 6.6 ± 3.6 $P=$NS I: mean ± SD days: 7.4 ± 6.5 [a] C: mean ± SD days: 6.5 ± 3.6[a] $P=$NS	NR	NR
Dronkers *et al.*[24]	I: complications: 9/21 (43%) C: complications: 8/20 (38%) $P=0.650$ I: pulmonary complications: 5/21 (24%) C: pulmonary complications: 5/20 (20%) $P=0.930$ I: pneumonia: 1/21 (5%) C: pneumonia: 3/20 (15%) $P=0.270$	NR	I: mean ± SD days: 16.2 ± 11.5 C: mean ± SD days: 21.6 ± 23.7 $P=0.310$	NR	NR
Kaibori *et al.*[25]	I: complications: 2/23 (9%) C: complications: 3/23 (13%) $P=0.671$	NR	I: mean ± SD days: 13.7 ± 4.0 C: mean ± SD days: 17.5 ± 11.3 $P=0.120$	I: 0 (0%) C: 0 (0%)	NR
Gillis *et al.*[26]	I: 30-day CD I-IV: 12/38 (32%) C: 30-day CD I-IV: 17/39 (44%) $P=0.277$	NR	I: median [IQR]: 4 [3 to 5] C: median [IQR]: 4 [3 to 7] $P=0.812$	NR	I: 30-day readmission: 6/38 (16%) C: 30-day readmission: 5/39 (13%) $P=0.780$
Dunne *et al.*[27]	I: CD I-II: 8/19 (42%) C: CD I-II: 7/15 (47%) $P=$NS I: CD III-IV: 3/19 (16%) C: CD III-IV: 1/15 (7%) $P=$NS	I: elective admissions: 8/19 (42%) C: elective admissions: 4/15 (27%) $P=$NS I: median (IQR) days: 1.0 (1 to 2) C: median (IQR) days: 1.5 (1 to 2) $P=$NS	I: median [IQR]: 5 [4.0 to 6.0] C: median [IQR]: 5 [4.5 to 7.0] $P=$NS	NR	I: readmission: 4/19 (21%) C: readmission: 0/15 (0%) P-value NS
Barberan-Garcia *et al.*[28]	I: complications: 19/62 (31%) C: complications: 39/63 (62%) $P=0.001$*	I: mean ± SD days: 1 ± 2 C: mean ± SD days: 4 ± 13 $P=0.078$	I: mean ± SD days: 8 ± 8 C: mean ± SD days: 13 ± 20 $P=0.078$	I: 1 (2%) C: 1 (2%) $P=1.000$	NR
Bousquet-Dion *et al.*[29]	I: 30-day complication: 14/37 (38%) C: 30-day complication: 8/26 (31%) $P=0.562$ I: most severe CD (I: $n=9$; II: $n=3$; III: $n=2$) C: most severe CD (I: $n=4$; II: $n=4$; III: $n=0$) $P=0.269$	NR	I: median [IQR]: 3 [3 to 4] C: median [IQR]: 3 [2 to 4] $P=0.122$	NR	I: 30-day readmission: 5/37 (14%) C: 30-day readmission: 2/26 (8%) $P=0.415$

C, control group; CD, Clavien-Dindo; I, intervention group; IQR, interquartile range; NR, not reported; NS, not statistically significant (exact *P* value not reported); SD, standard deviation. [a]Data minus one outlier. *$P<0.01$.

method (one study using the guidelines of Jammer *et al.*[30] to define complications[23,26–29]); one study reported on the basis of the presence of complications in hospital records[24]; one study did not specify assessment methods.[25] One study with a cohort of 144 high-risk surgical patients reported a reduction in the number of patients with postoperative complications of 51% in the prehabilitation group.[28] None of the other studies reported significant differences in the incidence of postoperative complications.[22–27,29] No study reported anything about the impact of postoperative complications on the patients (such as the effect of complications on length of stay, the use of resources or the patient's physical functioning). Mortality was reported in two studies and, in the time windows used, found no differences between the groups.[25,28] Most studies also reported length of hospital stay: none of them found a statistically significant difference. ICU admission was reported in two studies, and again, there were no statistically significant differences between groups.[27,28] No study reported on long-term postoperative outcomes.

Physical fitness was assessed in the majority of the studies, in five of the eight studies using cardiopulmonary exercise testing. Compared with the controls, two studies found a significant benefit in terms of aerobic capacity after prehabilitation (outcome measures used are provided in the supplementary table, http://links.lww.com/EJA/A210).[22,28] After prehabilitation, one study found significant improvements in multiple variables measuring physical fitness, which were not observed in controls (supplementary table, http://links.lww.com/EJA/A210).[22] Muscle strength, functional mobility and physical activity were also used as outcome measures to evaluate the effects of prehabilitation, and a significant increase in physical activity was seen after multimodal prehabilitation.[28] Data about long-term physical functioning, lifestyle changes or quality of life were not provided in any of the studies.

No adverse events were recorded in any of the studies (Table 4). High adherence to training sessions was reported in the supervised trials (98% on average),[24,27,29] whereas unsupervised training was associated with lower patient adherence (70% on average).[22,23,26] Adherence was determined using either the number of training sessions attended, or the amount of physical exercise performed by patients. Adherence rates were not reported in two studies.[25,28] Adherence during training sessions (as measured by, e.g., prescribed training intensity, unplanned breaks, completion of training sessions) and adherence for other components of a multimodal intervention (such as nutritional or psychological components) were not reported in any of the studies.

Discussion

The aim of this study was to provide a detailed and innovative systematic review of the literature investigating the effectiveness of prehabilitation in patients undergoing major intra-abdominal cancer surgery. By doing so, it should be possible to properly evaluate the effectiveness of prehabilitation trials. More importantly, it should be possible to differentiate between individual trials based on their potential beneficial effects by assessing their content according to the concept of therapeutic validity, as well as by evaluating their use of adequate postoperative outcome measures. The main findings relating to the content of prehabilitation programmes, as assessed using the CONTENT scale for therapeutic validity, were the inclusion of a high proportion of low-risk patients, inadequate monitoring and adjustment of training intensity, and absence of efficient inclusion of prehabilitation in a patient's preexistent living condition (home, nursing home or hospital). Considerable variation was seen in terms of the content of prehabilitation programmes, with many studies focusing exclusively on physical exercise and failing to include other vital components such as nutritional and psychological support. To determine postoperative outcome, most studies used the incidence of postoperative complications as a measure for the effectiveness of prehabilitation, without taking into account the variability in ability of patients to cope with these postoperative complications.

The heterogeneity seen in the design of prehabilitation programmes, and its likely contribution to different conclusions about the postoperative benefits of prehabilitation, confirms findings from earlier systematic reviews.[11,12,15] This variation is not surprising, as the first clinical guideline with recommendations for prehabilitation programmes was published only recently.[31] It is recommended that this heterogeneity should be taken into account when investigating physical exercise training interventions.[32] For the field of prehabilitation research, which is young and therefore lacks extensively validated measurements, the CONTENT scale may be used. This scale was developed in a four-round Delphi study[20] in order to critically evaluate the potential effectiveness of a specific physical exercise training programme given to a potential target group of patients. Although it has been used in various patient populations thus far, it is currently being validated in larger data sets including general and oncological surgery, warranting careful interpretation here. Nevertheless, the present review is the first to provide a systematic evaluation of the therapeutic validity of studies investigating the physical exercise training component of prehabilitation using the CONTENT scale.[20] The therapeutic validity of three studies was high and these studies found significant benefits in terms of clinical outcomes, although not all studies were powered to assess the effect on postoperative complications and outcome. In the other studies, therapeutic validity appeared to be insufficient. Surgical patients at a high risk of postoperative complications and

functional decline after surgery [i.e. generally frail elderly patients and patients undergoing (neo)adjuvant chemoradiotherapy] may benefit most from prehabilitation.[1,31,33,34] The low baseline aerobic capacity and the high incidence of poor nutritional status in these patients means that their capacity to cope with the stressors of disease and treatment is impaired and, consequently, they may need pre-operative optimisation, for example by prehabilitation, to increase their chances of a good outcome after treatment.[11,35] However, as most trials do not select high-risk patients pre-operatively, and even seem to exclude them because high-intensity training is considered to be more challenging or even contra-indicated for these patients, therapeutic validity is impaired. Patient selection should start pre-operatively with an adequate assessment of treatment-associated risks. Assessing pre-operative psychophysiological reserves (e.g. by objectively determining aerobic capacity, muscle mass and nutritional status) may identify patient needs in terms of counselling, physical exercise training, nutritional support, psychological support and smoking cessation, with tailored prehabilitation and personalised and patient-centred care as a result.[36] Inadequate patient selection in many of the trials included in our review may have led to an underestimation of the benefits of prehabilitation: this supposition may be supported by the finding that two studies that completed pre-operative risk stratification and included high-risk patients found significant improvements in patient physiological parameters[24] and in postoperative outcomes.[28] The PREHAB trial, which is currently recruiting, may provide an adequate sample size to perform a subgroup analysis of these high-risk surgical patients.[37] This may further strengthen scientific evidence for a therapeutic window in these patients, eventually leading to the provision of (cost-)efficient prehabilitation in the right patients. Furthermore, in addition to the adequate personalisation of prehabilitation at commencement, the therapeutic validity (and therefore the success) of prehabilitation may also depend on the appropriate and objective monitoring of progress and the subsequent adjustment of treatment throughout the programme. We found large differences between levels of personalisation in prehabilitation programmes. Although training intensity would seem to have been adequately adapted to baseline physical functioning in most studies, progress, which may differ widely between individual subjects, is often not measured objectively. When measured, training intensity can be adjusted in line with training progress, and the appropriate training stimulus can therefore be maintained throughout the programme. Furthermore, the objective monitoring of progress is essential to identify nonresponders or non-compliant individuals, for whom the researcher, exercise physiologist or physiotherapist should reconsider not only the content of training but also nutrition or elements of psychological support.[38] Further personalisation can be achieved when the prehabilitation programme is community or home-based, with patients being taught to train in their own environment with the caregivers and social support already in place being involved. Moreover, high-risk surgical patients are often elderly people who depend on others to get to a hospital and this makes it more difficult for them to participate in a hospital-based prehabilitation programme. Patients who do not live near a hospital are also often unable and/or unwilling to participate in a hospital-based programme.[39,40] In addition to improving pre-operative physical fitness, prehabilitation may provide patients with the skills and awareness needed to start mobilising, practise transfers and to be physically active quickly after surgery, enhancing and accelerating the recovery of physical functioning as a result. Prehabilitation at home or in a community-based setting with adequate supervision allows patients to acquire these skills in their own environment, a setting to which they return after hospital discharge, and this makes it more likely that patients will start exercising again soon after surgery.[41–43] Most of the studies included did not report on the postoperative clinical care pathway, including adequate discharge criteria, the use of a protocol for enhanced recovery after surgery or the content of rehabilitation, even though postoperative care should also be optimised to establish the full potential of prehabilitation. Finally, the modalities in prehabilitation programmes are highly varied. Many programmes are still unimodular, and they focus exclusively on physical exercise training. Multimodal programmes that consider physical exercise training, nutritional support, psychological support and the interaction between these components may be most effective and should be considered in further research.

The second aim of our systematic review was to assess whether the current literature has used optimal postoperative outcome measures to assess the effects of prehabilitation in major intra-abdominal cancer surgery. Although seven out of eight studies assessed postoperative outcome, different assessment methods were used, for example the prevalence of complications, ICU admission or length of stay. These results indicate that no study used an optimal outcome measure to assess the effects of postoperative complications. Although fitter or prehabilitated patients may also have postoperative complications, the impact may not be as severe, as suggested by the results of Hulzebos *et al.*[14] The impact of such complications is not adequately reflected by simply measuring their incidence with scales such as the Clavien-Dindo classification, comprehensive complication index or postoperative morbidity scale. After prehabilitation and the resulting improvement in aerobic capacity, patients may have better short-term and long-term outcomes, even with similar treatment and equal complication rates. Clinicians and researchers involved in prehabilitation should engage in a debate about the development of outcome measures in which the impact of a complication is also considered, for example by

combining a complication with its impact on the use of resources, length of hospital stay or the recovery of a patient's physical functioning. A great step is being made by the COMPAC-stEP group aiming at standardising endpoints in peri-operative trials.[44] Measuring the resilience of patients within such a core outcome set could result in a better picture of the potential benefits of prehabilitation in terms of better outcomes and cost-effective care. Furthermore, alternative concepts in terms of outcome could be explored, for example by using the allostatic load index, which takes psychophysiological reserves of patients into account.[45] These are novel concepts that have not been described or assessed in the current literature about prehabilitation, for example in the context of cancer surgery. Future studies should investigate multidisciplinary, multimodal programmes and use recent scientific insights to design effective/cost-effective programmes for the right patients, in the right setting and using the right outcome measures.

In conclusion, this systematic review found large variation in the content of prehabilitation in studies investigating its effects in intra-abdominal cancer surgery. Studies with a high therapeutic validity found that prehabilitation had beneficial effects on postoperative outcome. Future research in the field of prehabilitation should focus more on the adequate selection of high-risk surgical patients, and provide personalised, and probably multimodal (partly) supervised prehabilitation with objective monitoring of their progress throughout the programme in order to adjust the intervention as required and thereby minimise the risk of nonresponding patients. In addition, there is a need for consensus-defined standardised endpoints for postoperative outcomes, in which the impact of postoperative complications is taken into consideration. Combining all these elements may allow us finally to clarify the value of prehabilitation in major intra-abdominal cancer surgery.

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References

1 West M, Parry M, Lythgoe D, *et al.* Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. *Br J Surg* 2014; **101**:1166–1172.
2 McDermott F, Heeney A, Kelly M, *et al.* Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015; **102**:462–479.
3 Van Leersum N, Snijders H, Henneman D, *et al.* The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; **39**:1063–1070.
4 International Surgical Outcomes Study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle-and high-income countries. *Br J Anaesth* 2016; **117**:601–609.
5 Wilson R, Davies S, Yates D, *et al.* Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010; **105**:297–303.
6 Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol* 2017; **18**:e457–e471.
7 McEwen BS. Stress: homeostasis, rheostasis, allostasis and allostatic load. In: Fink G. Stress science: neuroendocrinology. Oxford: Academic Press, 2010:10–14.
8 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**:715–727.
9 Christensen T, Bendix T, Kehlet H. Fatigue and cardiorespiratory function following abdominal surgery. *Br J Surg* 1982; **69**:417–419.
10 Dimick JB, Chen SL, Taheri PA, *et al.* Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004; **199**:531–537.
11 Moran J, Guinan E, McCormick P, *et al.* The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: a systematic review and meta-analysis. *Surgery* 2016; **160**:1189–1201.
12 Bruns E, Heuvel B, Buskens C, *et al.* The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. *Colorectal Dis* 2016; **18**:O263–277.
13 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**:205–213.
14 Hulzebos EH, Helders PJ, FaviÚ NJ, *et al.* Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. *JAMA* 2006; **296**:1851–1857.
15 Santa Mina D, Clarke H, Ritvo P, *et al.* Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy* 2014; **100**:196–207.
16 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **7**:e1000097.
17 Winters-Stone KM, Neil SE, Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br J Sports Med* 2014; **48**:987–995.
18 Thompson PD, Arena R, Riebe D, Pescatello LS. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription. *Curr Sports Med Rep* 2013; **12**:215–217.
19 Higgins JP, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:d5928.
20 Hoogeboom TJ, Oosting E, Vriezekolk JE, *et al.* Therapeutic validity and effectiveness of preoperative exercise on functional recovery after joint replacement: a systematic review and meta-analysis. *PloS One* 2012; **5**:e38031.
21 Petrie A, Sabin C. *Medical statistics at a glance*. Oxford, UK: Wiley-Blackwell; 2013; 1-180.
22 Kim DJ, Mayo NE, Carli F, *et al.* Responsive measures to prehabilitation in patients undergoing bowel resection surgery. *Tohoku J Exp Med* 2009; **217**:109–115.
23 Carli F, Charlebois P, Stein B, *et al.* Randomized clinical trial of prehabilitation in colorectal surgery. *Br J Surg* 2010; **97**:1187–1197.
24 Dronkers J, Lamberts H, Reutelingsperger I, *et al.* Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clin Rehab* 2010; **24**:614–622.
25 Kaibori M, Ishizaki M, Matsui K, *et al.* Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. *Am J Surg* 2013; **206**:202–209.
26 Gillis C, Li C, Lee L, *et al.* Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* 2014; **121**:937–947.
27 Dunne D, Jack S, Jones R, *et al.* Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg* 2016; **103**:504–512.
28 Barberan-Garcia A, Ubré M, Roca J, *et al.* Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. *Ann Surg* 2018; **267**:50–56.
29 Bousquet-Dion G, Awasthi R, Loiselle S-È, *et al.* Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. *Acta Oncol* 2018; **57**:849–859.

30 Jammer I, Wickboldt N, Sander M, *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015; **32**:88–105.
31 Tew G, Ayyash R, Durrand J, Danjoux G. Clinical guideline and recommendations on preoperative exercise training in patients awaiting major noncardiac surgery. *Anaesthesia* 2018; **73**:750–768.
32 Pinto BM, Floyd A. Methodologic issues in exercise intervention research in oncology. *Semin Oncol Nurs* 2007; **4**:297–304.
33 Levett D, Jack S, Swart M, *et al.* Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth* 2018; **120**:484–500.
34 Richardson K, Levett D, Jack S, Grocott M. Fit for surgery? Perspectives on preoperative exercise testing and training. *Br J Anaesth* 2017; **119**:i34–i43.
35 West M, Asher R, Browning M, *et al.* Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. *Br J Surg* 2016; **103**:744–752.
36 Glance LG, Osler TM, Neuman MD. Redesigning surgical decision making for high-risk patients. *N Engl J Med* 2014; **370**:1379–1381.
37 van Rooijen S, Carli F, Dalton S, *et al.* Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. *BMC Cancer* 2019; **19**:98.
38 Montero D, Lundby C. Refuting the myth of nonresponse to exercise training:'nonresponders' do respond to higher dose of training. *J Physiol* 2017; **595**:3377–3387.
39 Berkel AE, Bongers BC, van Kam M-JS, *et al.* The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial. *BMC Gastroenterol* 2018; **18**:29.
40 Woodfield J, Zacharias M, Wilson G, *et al.* Protocol, and practical challenges, for a randomised controlled trial comparing the impact of high intensity interval training against standard care before major abdominal surgery: study protocol for a randomised controlled trial. *Trials* 2018; **19**:331.
41 Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med* 1994; **38**:1–14.
42 Gill TM, Robison JT, Williams CS, Tinetti ME. Mismatches between the home environment and physical capabilities among community-living older persons. *J Am Geriatr Soc* 1999; **47**:88–92.
43 Siemonsma PC, Blom JW, Hofstetter H, *et al.* The effectiveness of functional task exercise and physical therapy as prevention of functional decline in community dwelling older people with complex health problems. *BMC Geriatr* 2018; **18**:164.
44 Myles P, Grocott M, Boney O, *et al.* Standardizing end points in perioperative trials: towards a core and extended outcome set. *Br J Anaesth* 2016; **116**:586–589.
45 Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev* 2010; **35**:2–16.
46 Whittaker AC, Delledonne M, Finni T, *et al.* Physical Activity and Nutrition INfluences In ageing (PANINI): consortium mission statement. *Aging Clin Exp Res* 2018; **30**:685–692.