



# Moderate-intensity exercise training or high-intensity interval training to improve aerobic fitness during exercise prehabilitation in patients planned for elective abdominal cancer surgery?

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## ABSTRACT

Low preoperative aerobic fitness is associated with an increased risk of postoperative complications and delayed recovery in patients with abdominal cancer. Surgical prehabilitation aims to increase aerobic fitness preoperatively to improve patient- and treatment-related outcomes. However, an optimal physical exercise training program that is effective within the short time period available for prehabilitation (<6 weeks) has not yet been established. In this comparative review, studies (n = 8) evaluating the effect of short-term (<6 weeks) moderate-intensity exercise training (MIET) or high-intensity interval training (HIIT) on objectively measured aerobic fitness were summarized. The content of exercise interventions was critically appraised regarding the frequency, intensity, time, type, volume, and – monitoring of – progression (FITT-VP) principles. Three out of four studies evaluating HIIT showed statistically significant improvements in oxygen uptake at peak exercise (VO<sub>2peak</sub>) by more than 4.9%, the coefficient of variation for VO<sub>2peak</sub>. None of the two studies investigating short-term MIET showed statistically significant pre-post changes in VO<sub>2peak</sub>. Although short-term HIIT seems to be a promising intervention, concise description of performed exercise based on the FITT-VP principles was rather inconsistent in studies. Hence, interpretation of the results is challenging, and a translation into practical recommendations is premature. More emphasis should be given to individual responses to physical exercise training. Therefore, adequate risk assessment, personalized physical exercise training prescription using the FITT-VP principles, full reporting of physical exercise training adherence, and objective monitoring of training progression and recovery is needed to ensure for a personalized and effective physical exercise training program within a multimodal prehabilitation program.

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## 1. Introduction

There is a clear body of evidence showing that lower preoperative aerobic fitness is consistently and independently associated with a higher risk for postoperative complications following major abdominal cancer surgery [1–4]. Surgical prehabilitation involves targeted preventive interventions to improve a patient's health between the time of cancer diagnosis and the surgical procedure [5], in order to reduce the incidence, severity, and impact of postoperative complications, thereby accelerating and improving recovery [6]. The effectiveness of prehabilitation relies on the assumptions that 1) a patient's health status (not limited to, but also including aerobic fitness) can be improved in an often time-constrained preoperative setting, and 2) an improved health status translates into a reduced risk of postoperative complications and enhanced recovery.

Prehabilitation interventions should be designed using a multimodal perspective, thereby encompassing modalities such as physical exercise training, nutritional support, psychosocial support, alcohol consumption and/or smoking cessation [7], and anemia correction [8]. Physical exercise training is considered to be the main driver to improve aerobic fitness preoperatively. Intuitively, the process of increasing aerobic fitness seems to be straightforward; however, an effective physical exercise training program involves a complex interplay between sufficient overload and post-exercise recovery in order to promote supercompensation to subsequently improve aerobic fitness. To date, there is large heterogeneity between preoperative physical exercise training programs regarding program composition, mode of administration, and outcome measures of aerobic fitness [9], while the content of the programs seems to be based on a “one-size-fits-all” approach. Variation in the design and the quality of administering preoperative physical exercise training interventions may (partly) explain the variability in between-study estimates of effects.

As the period between cancer diagnosis and surgery is often time constrained (e.g., maximal 34 days in colorectal cancer) due to current treatment guidelines [10,11], a preoperative physical exercise training program that is effective in a short time period is needed. Although aerobic fitness can be improved by moderate-intensity exercise training (MIET), high-intensity interval training (HIIT) has been introduced as a type of training that can improve aerobic fitness faster and more time-efficient [12]. As such, HIIT might on average be a physiologically more feasible option with respect to the effectiveness for a short-term preoperative optimization of aerobic fitness compared to MIET. The aim of the current comparative review is to provide evidence-based decision-support for choosing short-term MIET or HIIT as part of a multimodal prehabilitation program in patients scheduled for elective abdominal cancer surgery.

To achieve this aim, a literature search (online Supplemental file 1) in the databases PubMed, CINAHL, and Embase (up to December 2020) has been conducted. Studies in patients with abdominal cancer or abdominal cancer survivors, in which short-term (defined as  $\leq 6$  weeks) unimodal MIET or HIIT were compared to either usual care or to each other, with the main outcome being aerobic fitness as measured by means of a cardiopulmonary exercise test (CPET), were included. The rationale to also include studies in abdominal cancer survivors was based on the expected low number of prehabilitation studies and the fact that the short time period between diagnosis and surgery is the main challenge in improving aerobic fitness. As such, we focused on short-term physical exercise training programs in populations with comparable subject characteristics with regard to age, comorbidities, and lifestyle. Studies investigating multimodal prehabilitation interventions, studies that combined MIET or HIIT with another type of training (e.g.,

resistance training, functional exercise training) and studies investigating physical exercise training programs during active cancer treatment (e.g., neoadjuvant chemo and/or radiation therapy) were excluded. Moderate intensity was defined as exercise intensities between 64 and 76% of maximal heart rate ( $HR_{max}$ ) [13], whereas high intensity was defined as efforts  $\geq 80\%$  of  $HR_{max}$  or equivalent [14].

The search identified eight studies of which six randomized controlled trials [15–20], one non-randomized controlled trial [21], and one single-arm pre-post study [22]. Six of these eight studies were prehabilitation studies [15–17,20–22]. Three studies were performed in patients with colorectal cancer or colorectal cancer survivors [18,19,22], one study in patients with rectal cancer [21], two studies in patients with urological cancer [15,17], and one study in patients with colorectal liver metastasis undergoing elective surgery [16]. Table 1 depicts relevant study characteristics. In order to add context to the included studies, subsequent sections are used to summarize basic background information concerning physical exercise training and program design. In addition, study results, study limitations, and future directions are discussed in the final sections.

## 2. Significance of maximal oxygen uptake for the quantification of preoperative aerobic fitness

Maximal oxygen uptake ( $VO_{2max}$ ) as assessed during a progressive maximal CPET is generally considered as the gold standard for quantifying aerobic fitness [23].  $VO_{2max}$  is determined by the integrative capacity of the pulmonary, cardiovascular, and muscular system to take in, transport, and utilize oxygen during maximal effort [24]. A true  $VO_{2max}$  requires a plateau in oxygen uptake ( $VO_2$ ) despite an increasing exercise intensity, which is seldom seen [25]. Therefore, derivative indicators of aerobic fitness are often used. These indicators of aerobic fitness include 1) the highest achieved oxygen uptake ( $VO_2$ ) at peak exercise ( $VO_{2peak}$ ), which also requires a maximal effort but no  $VO_2$  plateau, and 2) the submaximal  $VO_2$  at the ventilatory anaerobic threshold (VAT) [3,21,26,27]. The VAT demarks the transition from an almost entirely aerobic metabolism to anaerobic metabolism as an additional source of energy production to meet an increasing metabolic demand. It is assumed that an adequate preoperative aerobic fitness level is required to be able to cope with the surgically induced stress response, and the associated increased metabolic demands following major abdominal cancer surgery [28]. Therefore, patients with a low aerobic fitness have a higher risk for complications. In abdominal cancer surgery, patients with an  $VO_2$  at the VAT  $< 11$  mL/kg/min are generally classified as high risk, although exact thresholds for identifying patients with a high risk for complications differ depending on type of surgery and type of outcome measure and are summarized by Older and Levett [1]. Particularly patients with a low preoperative aerobic fitness as determined by these CPET derived thresholds, who consequently have a high risk for postoperative complications, might benefit the most from preoperative interventions that improve their aerobic fitness.

## 3. Principles of physical exercise training prescription and adjustment

The process of developing a physical exercise training prescription consists of 1) assessing health and aerobic fitness levels, 2) interpretation of the assessment, 3) performing adequate risk assessment, 4) formulating a personalized and feasible exercise prescription based on previously selected aims, and 5) regular and structured assessment of progression and subsequent consideration of program adjustments [29,30]. Training frequency, intensity,

**Table 1**  
General study characteristics.

Authors (year)	Study Design	Intervention versus control	Exercise training program duration	Study population/ study period	Sample size		Age (years) <sup>a</sup>	Sex (% male)	Mean ± SD baseline VO <sub>2</sub> at the VAT (mL/kg/min)	Mean ± SD baseline VO <sub>2peak</sub> (mL/kg/min)
Boereboom et al. (2016) [22]	Pre-post intervention study	HIIT (no control)	4 weeks	Colorectal cancer/ preoperative	HIIT n = 18	HIIT 67 ± 8		HIIT 72%	HIIT 14.0 ± 3.4	HIIT 23.9 ± 7.0
Blackwell et al. (2019) [17]	RCT	HIIT versus UC	4 weeks	Urological cancer/ preoperative	HIIT n = 19 UC n = 21	HIIT 71 ± 2 UC 72 ± 4		HIIT 100% UC 95%	HIIT 13.2 ± 1.9 UC 13.8 ± 2.8	HIIT 24.8 ± 5.2 UC 26.4 ± 5.7
Dunne et al. (2016) [16]	RCT	HIIT versus UC	4 weeks	Liver cancer/ preoperative	HIIT n = 20 UC n = 17	HIIT Median 61 (IQR 56–66) UC Median 62 (IQR 53–72)		HIIT 65% UC 76%	HIIT 11.2 ± 1.5 UC 11.4 ± 1.8	HIIT 17.6 ± 2.3 UC 18.6 ± 3.9
West et al. (2015) [21]	NRCT	HIIT versus UC	6 weeks	Rectal cancer/ post-NACRT, preoperative	HIIT n = 22 UC n = 13	HIIT 64 (range 45–82) UC 72 (range 62–84)		HIIT 64% UC 69%	HIIT 10.2 (95% CI 9.15 to 11.37) UC 10.1 (95% CI 8.7 to 11.6)	HIIT 16.1 (95% CI 14.1 to 17.9) UC 15.7 (95% CI 13.2 to 18.2)
Banerjee et al. (2018) [15]	RCT	MHIIT versus UC	3–6 weeks	Bladder cancer/ preoperative	MHIIT n = 30 UC n = 30	MHIIT 71.6 ± 6.8 UC 72.5 ± 8.4		MHIIT 90% UC 87%	MHIIT 11.5 ± 2.1 UC 11.4 ± 2.6	MHIIT 19.2 ± 4.8 UC 20.4 ± 5.6
Kim et al. (2009) [20]	RCT	MIET versus UC	4 weeks	Colorectal cancer/ preoperative	MIET n = 14 UC n = 7	MIET 55 ± 15 UC 65 ± 9		MIET 64% UC 57%	MIET 21.5 ± 10.1 UC 20.3 ± 4.6	MIET 21.5 ± 10.1 UC 20.3 ± 4.6
Devin et al. (2016) [19]	RCT	HIIT versus MIET	4 weeks	Colorectal cancer/ post-treatment	HIIT n = 30 MIET n = 17	HIIT 61.4 ± 11.1 MIET 61.6 ± 10.8		HIIT 60% MIET 47%	HIIT Median 22.8 (IQR 6) MIET Median 21.5 (IQR 8)	HIIT Median 22.8 (IQR 6) MIET Median 21.5 (IQR 8)
Devin et al. <sup>b</sup> (2018) [18]	RCT	HIIT <sup>2</sup> versus MIET	4 weeks	Colorectal cancer/ post-treatment	HIIT1 n = 18 HIIT2 n = 20 MIET n = 19	HIIT1 60.7 ± 11.7 HIIT2 61.5 ± 10.2 MIET 59.8 ± 11.4		HIIT1 72% HIIT2 50% MIET 47%	HIIT1 23.2 (95% CI 21.8 to 24.5) HIIT2 23.5 (95% CI 22.2 to 24.8) MIET 23.4 (95% CI 22.1 to 24.7)	HIIT1 23.2 (95% CI 21.8 to 24.5) HIIT2 23.5 (95% CI 22.2 to 24.8) MIET 23.4 (95% CI 22.1 to 24.7)

Abbreviations: CI = confidence interval; HIIT = high-intensity interval training; IQR = interquartile range; MHIIT = moderate- to high-intensity interval training; MIET = moderate-intensity exercise training; NACRT = neoadjuvant chemoradiotherapy; NRCT = non-randomized controlled trial; RCT = randomized controlled trial; SD = standard deviation; UC = usual care (no exercise intervention).

<sup>a</sup> Values are presented as mean ± SD, unless stated otherwise.

<sup>b</sup> The study of Devin et al., 2018 consisted of two groups receiving HIIT: the two HIIT protocols were equal for the first 4 weeks of training; thereafter, in a second cycle of 4 weeks, one group (HIIT1) continued to exercise three times per week, whereas group two (HIIT2) only trained once a week (only results of the first four weeks of training are displayed for both groups).

time, type, volume, and progression (FITT-VP principles) should be well-considered [29], along with recommendations as described by Hoozeboom et al. [31] in the international Consensus on Therapeutic Exercise and Training (i-CONTENT) tool.

Training **frequency** is typically described as the number of training sessions per week. Exact timing of training should be individualized, as it depends on several factors such as training intensity, training duration, recovery potential, training goals, and baseline aerobic fitness and periodization. Training **intensity** describes the effort that is associated with exercise that can be estimated using physiological performance parameters, preferably associated by using perception parameters. Ideally, training intensity is physiologically estimated based on the work rate at a given percentage of  $\text{VO}_{2\text{peak}}$  (or  $\text{VO}_2$  at the VAT) as measured during a CPET [32]. However, work rate-based prescription will only be feasible when using specialized and calibrated fitness equipment. Other means involve heart rate monitoring, either using heart rate zones as derived from a CPET, a percentage of  $\text{HR}_{\text{max}}$  or heart rate reserve (HRR), and rating of perceived exertion (e.g., Borg scale) [12]. When using interval training with short intervals, work rate or rating of perceived exertion-based prescription is recommended as heart rate monitoring is less useful when work intervals are <3 min due to the delayed cardiac response to exercise. According to the American College of Sports Medicine (ACSM), a minimal exercise intensity of 40% of HRR (maximal heart rate minus resting heart rate as measured after sitting for 5 min) is the threshold that should be exceeded for exercise to provide sufficient overload to improve aerobic fitness in deconditioned individuals (probably the majority of patients in need for prehabilitation). Training **time** indicates the duration of a single exercise training session, including warm-up and cool-down. In case of interval training, special consideration should be given to reporting the duration of the work and rest intervals separately. Training **type** defines the training modality, such as cycling, walking, running, continuous or interval exercise, functional exercises, or resistance training.

The product of training period (weeks), frequency (training sessions per week), intensity (e.g., percentage of  $\text{VO}_2$  at the VAT or at peak exercise), and time (training session duration) is called training **volume**, which is usually expressed as the energy (in Kilojoules or Kilocalories) that is expended during an entire training program episode. Due to improvements in aerobic fitness as a result of training adaptations, training volume should be increased (by either increasing training frequency, intensity, and/or training time) to make sure an adequate overload is maintained throughout the complete program. This is known as **progression** of training. As sufficient progress in aerobic fitness should be the main outcome parameter of exercise prehabilitation, progression of training should frequently be assessed (referred to as “titration” [33]), preferably on a weekly base using a formal performance test [34]. Quantification of progression is essential to motivate responders, to timely identify non-responders, and to subsequently make necessary program adjustments concerning training frequency, intensity, and duration [34]. Based on the law of diminishing returns, the adaptive potential of physiologic function will diminish when training progresses, and improvements in aerobic fitness will plateau at some point [29]. This asymptotic response to exercise emphasizes another necessity for frequent formal monitoring of progression. The point at which improvements level-off despite progression of training might be important when considering optimal timing of surgical interventions.

In addition to the FITT-VP principles, **auto-regulation** is an important aspect of an individualized training program [35]. Auto-regulation refers to possibility of a patient to adjust a training session based on his state of recovery. Time needed to recover from

a training session is highly individual and depends on factors as training volume, stress levels, sleep quality, nutrition, neuroendocrine- and immune system resilience, and environment. By using autoregulation, training load can be adjusted accordingly, allowing for higher training loads on days the patient is recovered well, whereas lower training loads or rest could be prescribed on days the patient is still fatigued. To monitor recovery, several questionnaires exist, such as the perceived recovery status scale [36] and the wellbeing review [37]. These can be applied before every training session to give insight into the patient's preparedness to perform exercise.

#### 4. How are high- and moderate-intensity exercise defined?

HIIT encompasses a broad spectrum of physical exercise training modalities characterized by brief periods of high-intensity exercise (work interval) interspersed with periods of (active) rest at a low intensity (recovery interval). High-intensity intervals are defined as near maximal efforts that elicits heart rate to rise  $\geq 80\%$  of its maximum or equivalent [14]; however, this definition is imperfect, as perceived intensity of exercise is dependent on intensity multiplied by time. Duration of the work and rest intervals can vary significantly and are typically between 30 s and 4 min [38].

The term MIET involves types of exercise with intensities lower than HIIT that is usually performed in a continuous manner [14]. Though, several interval types are also possible. In order to improve aerobic fitness, a minimal duration of 20 min of continuous MIET is recommended [29].

There is evidence that especially skeletal muscle adaptations largely depend on exercise intensity, with higher intensities leading to more pronounced training effects. The rationale behind this is that cellular stress caused by higher intensities leads to greater mitochondrial biogenesis and subsequent increased mitochondrial content [14]. By this cascade of events, oxidative capacity of the muscle is increased. There is less evidence available regarding the role of exercise intensity in mediating changes in skeletal muscle capillary density, maximal stroke volume, maximal cardiac output, and blood volume [14].

Evidence suggests that skeletal muscle mitochondrial adaptations [14] and improvements in  $\text{VO}_{2\text{peak}}$  in healthy individuals [14,39], as well as clinical populations [38], are greater for HIIT than MIET with equal training volumes (the product of training frequency, intensity, and time). Hence, improvements in  $\text{VO}_{2\text{peak}}$  are comparable when the training volume of HIIT is lower. Especially in time-constrained periods, such as the period before abdominal cancer surgery, high training volumes might not always be feasible. HIIT therefore provides an attractive alternative to achieve training adaptations that improve aerobic fitness fast and more time efficient. A recent systematic review on HIIT in patients with cancer across all stages of therapy and aftercare, however not limited to exercise interventions <6 weeks (mean (SD) duration of 6 (3) weeks), was less conclusive. Although the authors found that HIIT was superior in improving aerobic fitness compared to usual care, they found no evidence for additional benefits of HIIT above MIET for improvements in aerobic fitness [40]. In a recent randomized controlled trial comparing a multimodal 4-week prehabilitation program containing either MIET or HIIT [41], both groups increased their preoperative  $\text{VO}_2$  at the VAT with respectively 1.71 mL/kg/min (+12.4%) and 1.97 mL/kg/min (+16.0%), with no significant between-group differences. Improvements in  $\text{VO}_{2\text{peak}}$  were statistically significant after HIIT (+1.95 mL/kg/min, +10.5%) but not after MIET (+0.45 mL/kg/min, +2.1%) with no significant difference between groups ( $p = 0.080$ ) [41].



## 5. What is the ability of short-term HIIT or MIET to improve preoperative aerobic fitness in patients with abdominal cancer?

### 5.1. The effect of short-term HIIT on short-term improvement of preoperative aerobic fitness

Three studies [16,17,21] evaluating the effect of short-term HIIT compared to usual care (no exercise intervention) on aerobic fitness found significant improvements in  $\text{VO}_2$  at the VAT and/or  $\text{VO}_{2\text{peak}}$  after 4–6 weeks of HIIT. One study without a control group [22] did not find significant changes in  $\text{VO}_2$  at the VAT or  $\text{VO}_{2\text{peak}}$  after 4 weeks of HIIT. In the latter study, an uncontrolled pre-post intervention study, patients with colorectal cancer trained for 4 weeks prior to elective surgery. No significant improvements in aerobic fitness were found on the group level. However, there was a large heterogeneity in response to training between participants. A limitation of this study was the low adherence. Participants only attended a median of eight out of twelve intended exercise sessions. This low amount of attended HIIT sessions (40 min of HIIT with an estimated energy expenditure of 343 Kcal) might not have been a sufficient training volume to improve  $\text{VO}_2$  at the VAT or  $\text{VO}_{2\text{peak}}$  [42]. This is further emphasized by the fact that essentially the same HIIT exercise prescription, though with higher exercise session attendance rates (and therefore higher training volumes), did manage to increase  $\text{VO}_2$  at the VAT and  $\text{VO}_{2\text{peak}}$  in healthy adults (60 min of HIIT, with an estimated energy expenditure of 491 Kcal) [43] and in patients with urological cancer (55 min of HIIT with an estimated energy expenditure between 417 and 479 Kcal) [17]. In the latter study, four weeks of HIIT increased  $\text{VO}_2$  at the VAT by 2.3 mL/kg/min (+17.4%) and  $\text{VO}_{2\text{peak}}$  by 2.2 mL/kg/min (+8.9%). Two other studies [16,21] also showed beneficial effects of HIIT on aerobic fitness after 4 and 6 weeks of training. In patients awaiting liver resection for colorectal liver metastasis, a 4-week HIIT program improved  $\text{VO}_{2\text{peak}}$  by 2.0 mL/kg/min (+11.4%) [16]. West et al. [21] studied the effect of preoperative HIIT between neoadjuvant chemoradiotherapy (NACRT) and surgery in patients with rectal cancer. The HIIT group showed an improvement in  $\text{VO}_2$  at the VAT and  $\text{VO}_{2\text{peak}}$  of respectively 2.1 mL/kg/min (+20.6%) and 2.7 mL/kg/min (+17.1%) after six weeks of training. In the study of Dunne et al. [16], 18 out of 19 participants (~95%) in the exercise arm of the study attended all prescribed exercise sessions, whereas ~96% attended all 18 prescribed exercise sessions in the latter study of West et al. [21]. An overview of exercise prescription, performed physical exercise training, and outcomes of the studies can be found in Table 2, Table 3, and Fig. 1 (graph A and B), respectively, as well as in online Supplemental file B.

### 5.2. The effect of short-term MIET or moderate- to high-intensity interval training on short-term improvement of preoperative aerobic fitness

Two studies investigated the effect of short-term MIET [20], or moderate- to high-intensity interval training [15] on objectively measured preoperative aerobic fitness in patients with abdominal cancer. In the study of Banerjee et al. [15], patients with bladder cancer followed a 3- to 6-week moderate- to high-intensity interval training program. Kim et al. [20] studied patients with colorectal cancer who participated in a 4-week daily, partly-supervised MIET program (Table 2). In both studies [15,20], no significant improvements in  $\text{VO}_2$  at the VAT or  $\text{VO}_{2\text{peak}}$  at the group level were found (Fig. 1, graph A and B, and online Supplemental file B). However, the median number of attended sessions in the study of Banerjee et al. [15] was low and varied greatly between participants (median 8 sessions, range 1–10 sessions) (Table 3). This low amount and large

range of attended exercise sessions, in combination with a training frequency of only 2 sessions per week, might not have provided sufficient overload to improve  $\text{VO}_2$  at the VAT and  $\text{VO}_{2\text{peak}}$  rapidly. In the study of Kim et al. [20], merely ~74% of the sessions were attended, and attendance rates were based on self-report. Furthermore, the exercise intensity of 40% of the HRR was at the lower end of the minimal intensity needed to elicit improvements in aerobic fitness as recommended by the ACSM [29]. Although some progression was intended over the course of the 4-week exercise program, this progression was not based on objectively monitored training progression and recovery at the individual level, and the authors did not report actual adherence to the exercise prescription. Hence, the combination of low attendance rates in combination with the relatively low training intensity (low training volume) might not have led to sufficient overload.

## 6. The effect of short-term HIIT versus short-term MIET on short-term improvement of aerobic fitness

Currently, there seem to be no unimodal studies directly comparing short-term HIIT with short-term MIET in the preoperative setting. However, two studies evaluated the effect of short-term HIIT compared to MIET in colorectal cancer survivors (Table 2). In the first study performed in 2016, 4 weeks of HIIT was compared to 4 weeks of MIET. The HIIT group significantly increased  $\text{VO}_{2\text{peak}}$  with 3.5 mL/kg/min (+14.6%) after 4 weeks of training, whereas the MIET group did not significantly improve  $\text{VO}_{2\text{peak}}$  (+4.3%) [19] (Fig. 1, graph C). In a second study performed in 2018, Devin et al. [18] compared two HIIT training protocols with MIET. The two HIIT protocols were identical for the first four weeks of training. Thereafter, a subgroup (HIIT1) continued to exercise three times per week, whereas another subgroup (HIIT2) only trained once a week (Table 2). As the aim of the current review was to evaluate the effect of short-term HIIT or MIET (i.e. within the available time period for prehabilitation), results displayed here only comprise the first 4 weeks of the exercise program. After the first 4 weeks of training,  $\text{VO}_{2\text{peak}}$  in both HIIT groups increased significantly (HIIT1  $\text{VO}_{2\text{peak}}$  +4.2 mL/kg/min (+18.1%); HIIT2  $\text{VO}_{2\text{peak}}$  +3.3 mL/kg/min (+14.1%)), whereas no significant changes in  $\text{VO}_{2\text{peak}}$  were seen in the group receiving MIET (+4.7%) [18] (Fig. 1, graph C). Attendance rates in both studies of Devin et al. [18,19] were >97% for HIIT and MIET.

## 7. Clinical relevance of preoperatively increasing aerobic fitness in abdominal cancer surgery

Exercise prehabilitation in high-risk patients (those with a low preoperative aerobic fitness) aims to preoperatively increase a patient's aerobic fitness, thereby increasing the adaptive capacity to cope with the surgical stress response and reducing the risks of postoperative complications, a delayed recovery, and the associated socio-economic impact [28,45]. A higher preoperative aerobic fitness has been found to be associated with a lower incidence of postoperative complications [4,27]. Moreover, a higher preoperative aerobic fitness might reduce the impact of postoperative complications [6,46]. This is confirmed by a randomized controlled trial investigating the effect of a 3-week community-based supervised preoperative HIIT program and resistance training on postoperative complications in high-risk patients (preoperative  $\text{VO}_2$  at the VAT <11 mL/kg/min) undergoing colorectal surgery [47]. In this study, an increase in  $\text{VO}_2$  at the VAT of 1.0 mL/kg/min (+10.1%) and  $\text{VO}_{2\text{peak}}$  of 1.3 mL/kg/min (+8.8%) led to a reduction in postoperative complications of ~50%. In an RCT in patients scheduled for major abdominal surgery, a similar reduction of ~50% in postoperative complications was seen after a six-week prehabilitation program including HIIT [48].

**Table 2**  
Exercise prescription according to the FITT-VP principles.

Authors (year)	Exercise protocol (FITT-VP principles)					
	F	I	T	T	V	P
Boereboom et al. (2016) [22]	3–4 times a week	<b>HIIT</b> Work interval: 100–120% $WR_{peak}$ Rest interval: unloaded cycling	<b>HIIT</b> Work interval: $5 \times 1$ min Rest interval: $5 \times 1.5$ min	Cycling		Not reported
Blackwell et al. (2019) [17]	3–4 times a week	<b>HIIT</b> Work interval: 110–120% $WR_{peak}$ Rest interval: unloaded cycling	<b>HIIT</b> Work interval: $5 \times 1$ min Rest interval: not reported	Cycling		Increase in WR after 6 sessions
Dunne et al. (2016) [16]	3 times a week	<b>HIIT</b> Work interval: $>90\%$ $VO_{2peak}$ Rest interval: $<60\%$ $VO_{2peak}$	<b>HIIT</b> Total: 30 min Work interval: not reported Rest interval: not reported	Cycling		Not reported
West et al. (2015) [21]	3 times a week	<b>HIIT</b> Work interval: 50% of WR between $VO_2$ at the VAT and $VO_{2peak}$ Rest interval: WR at 80% of $VO_2$ at the VAT	<b>HIIT</b> <i>First two sessions</i> Work interval: $4 \times 2$ min Rest interval: $4 \times 3$ min <i>After two sessions</i> Work interval: $6 \times 2$ min Rest interval: $6 \times 3$ min	Cycling		Responsive to exercise test in week 3
Banerjee et al. (2018) [15]	2 times a week	<b>MHIIT</b> Work interval: 70–85% of predicted $HR_{peak}$ Rest interval: light resistance (50 W)	<b>MHIIT</b> Work interval: $6 \times 5$ min Rest interval: $6 \times 2.5$ min	Cycling		Not reported
Kim et al. (2009) [20]	7 times a week	<b>MIET</b> 40–65% HRR	<b>MIET</b> 50 min	Cycling (partially supervised)		Not reported
Devin et al. (2016) [19]	<b>HIIT</b> 3 times a week <b>MIET</b> 3 times a week	<b>HIIT</b> Work interval: 85–95% $HR_{peak}$ Rest interval: 50–70% $HR_{peak}$ <b>MIET</b> 70% $HR_{peak}$	<b>HIIT</b> Work interval: $4 \times 4$ min Rest interval: $4 \times 3$ min <b>MIET</b> 50 min	Cycling		<b>HIIT</b> Not reported <b>MIET</b> Not reported
Devin et al. (2018) <sup>a</sup> [18]	<b>HIIT</b> 3 times a week <b>MIET</b> 3 times a week	<b>HIIT</b> Work interval: 85–95% $HR_{peak}$ Rest interval: 50–70% $HR_{peak}$ <b>MIET</b> 70% $HR_{peak}$	<b>HIIT</b> Work interval: $4 \times 4$ min Rest interval: $4 \times 3$ min <b>MIET</b> 50 min	Cycling		<b>HIIT</b> Not reported <b>MIET</b> Not reported

Abbreviations: FITT-VP = frequency, intensity, time, type, volume, and progression; HIIT = high-intensity interval training; HR = heart rate; HRR = heart rate reserve;  $HR_{peak}$  = heart rate at peak exercise;  $HR_{max}$  = maximal heart rate; MHIIT = moderate- to high-intensity interval training; MIET = moderate-intensity exercise training; VAT = ventilatory anaerobic threshold;  $VO_2$  = oxygen uptake;  $VO_{2peak}$  = oxygen uptake at peak exercise; WR = work rate;  $WR_{peak}$  = work rate at peak exercise.

<sup>a</sup> the study of Devin et al., 2018 consisted of two groups receiving HIIT: the two HIIT protocols were equal for the first 4 weeks of training; thereafter, in a second cycle of 4 weeks, one group (HIIT1) continued to exercise three times per week, whereas group two (HIIT2) only trained once a week (only results of the first four weeks of training are displayed for both groups).

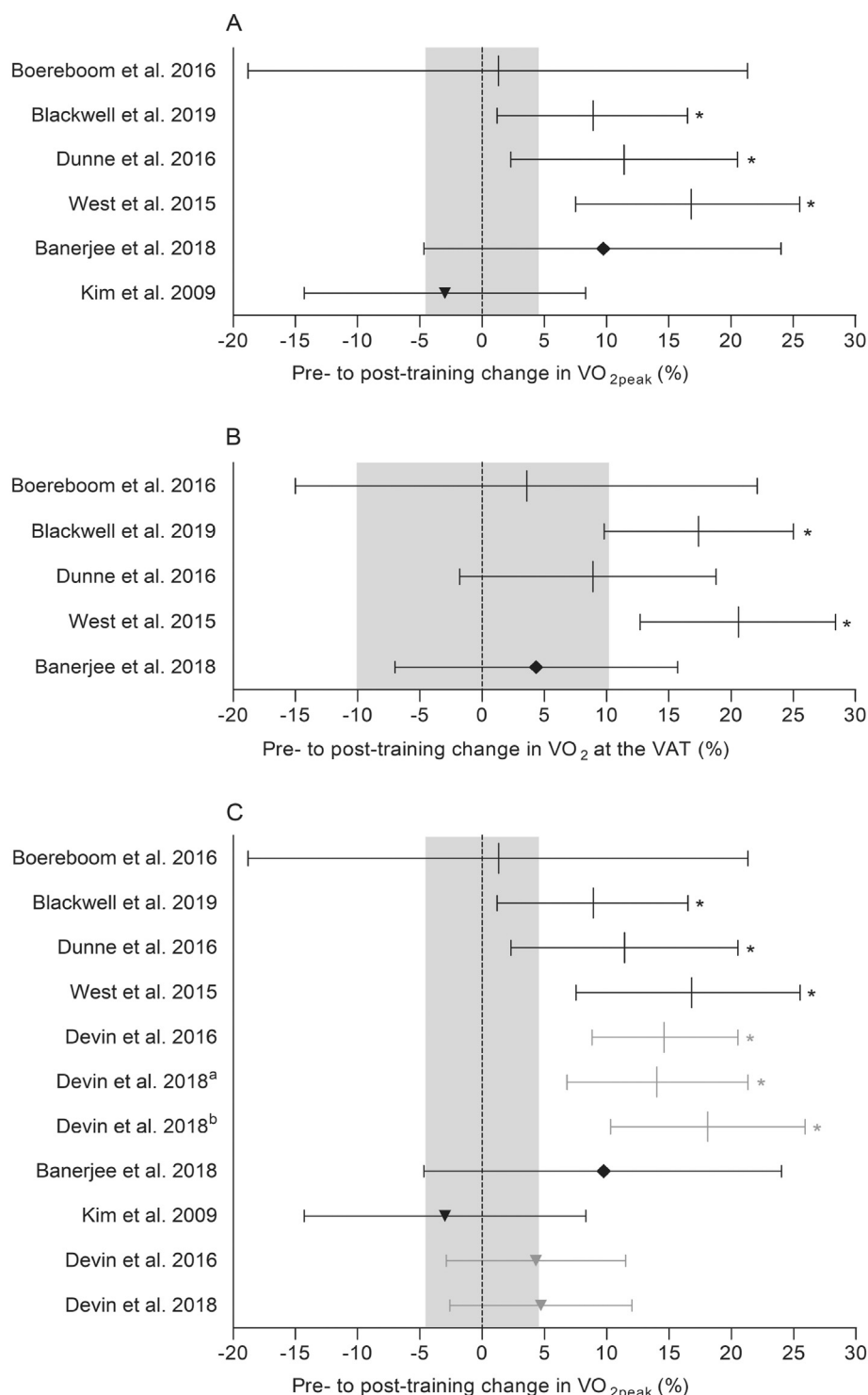
**Table 3**  
Performed exercise according to the FITT-VP principles.

Authors (year)	Performed exercise (FITT-VP principles)					
	F	I	T	T	V	P
Boereboom et al. (2016) [22]	<b>HIIT</b> Sessions per week: not reported Total number of sessions: median 8 (range 6–14)	<b>HIIT</b> Not clearly reported; mean training work rate $155 \pm 55^a$ W, 100% of patients between 100 and 120% of $WR_{peak}$	<b>HIIT</b> Work interval: not clearly reported Rest interval: not clearly reported	Cycling	<b>HIIT</b> Not reported	
Blackwell et al. (2019) [17]	<b>HIIT</b> Sessions per week: not reported Total number of sessions: median 11 (IQR 10–12)	<b>HIIT</b> All participants achieved >85% of predicted $HR_{max}$ during the sessions	<b>HIIT</b> Work interval: not reported Rest interval: not reported	Cycling	<b>HIIT</b> 89% of the participants increased WR with 10% after 6 sessions	
Dunne et al. (2016) [16]	<b>HIIT</b> Sessions per week: not reported Total number of sessions: 94% of participants attended all (12) sessions	<b>HIIT</b> Not reported	<b>HIIT</b> Work interval: not reported Rest interval: not reported	Cycling	<b>HIIT</b> Not reported	
West et al. (2015) [21]	<b>HIIT</b> Sessions per week: not reported Total number of sessions: 96% $\pm$ 5% of participants attended all (18) sessions	<b>HIIT</b> Not reported	<b>HIIT</b> Work interval: not reported Rest interval: not reported	Cycling	<b>HIIT</b> Progression measured by interim CPET; a subsequent adjustments to the training program not clearly reported	
Banerjee et al. (2018) [15]	<b>MHIIT</b> Sessions per week: not reported Total number of sessions: median 8 (range 1–10)	<b>MHIIT</b> Average HR between 85% and 87% of predicted $HR_{peak}$ or 90 and 92% of measured $HR_{max}$ during CPET	<b>MHIIT</b> Work interval: in week 1, an average of 5.5 intervals achieved (range 3.5–6.0), in week 4, all patients achieved 6 intervals Rest interval: not reported	Cycling	<b>MHIIT</b> Training load increased from $111 \pm 5.5^a$ W to $122 \pm 5.8^a$ W	
Kim et al. (2009) [20]	<b>MIET</b> Sessions per week: not reported Total number of sessions: mean $27 \pm 9$ , compliance $74 \pm 16\%$	<b>MIET</b> Not reported	<b>MIET</b> Not reported	Cycling (partially supervised)	<b>MIET</b> Not reported	
Devin et al. (2016) [19]	<b>HIIT</b> Sessions per week: not reported Total number of sessions: on average, 97% of prescribed sessions were attended <b>MIET</b> Sessions per week: not reported Total number of sessions: on average, 97% of prescribed sessions were attended	<b>HIIT</b> $91.7 \pm 4.2\%^a$ of $HR_{peak}$ <b>MIET</b> $73.4\% \pm 4.2^a$ of $HR_{peak}$	<b>HIIT</b> Work interval: total $15.9 \pm 0.1^a$ min (97%) <b>MIET</b> $50 \pm 0^a$ min (100%)	Cycling	<b>HIIT</b> Not reported <b>MIET</b> Not reported	
Devin et al. (2018) <sup>b</sup> [18]	<b>HIIT</b> Sessions per week: not reported Total number of sessions: $99.3 \pm 2.2\%^a$ and $99.9 \pm 0.5\%^a$ of prescribed sessions were attended <b>MIET</b> Sessions per week: not reported Total number of sessions: $100 \pm 0\%^a$ of prescribed sessions were attended	<b>HIIT</b> <i>Subgroup HIIT1</i> $90.6 \pm 3.7\%^a$ of $HR_{peak}$ and <i>Subgroup HIIT2</i> $90.7 \pm 4.3\%^a$ of $HR_{peak}$ <b>MIET</b> $71.4 \pm 8.3\%^a$ of $HR_{peak}$	<b>HIIT</b> Work interval: <i>Subgroup HIIT1</i> $99.8 \pm 0.4\%^a$ of prescribed <i>Subgroup HIIT2</i> $100 \pm 0\%^a$ of prescribed <b>MIET</b> $100 \pm 0.0\%^a$ of prescribed	Cycling	<b>HIIT</b> Not reported <b>MIET</b> Not reported	

Abbreviations: FITT-VP = frequency, intensity, time, type, volume, and progression; HIIT = high-intensity interval training; HR = heart rate;  $HR_{peak}$  = heart rate at peak exercise;  $HR_{max}$  = maximal heart rate; IQR = interquartile range; MHIIT = moderate- to high-intensity interval training; MIET = moderate-intensity exercise training; WR = work rate;  $WR_{peak}$  = work rate at peak exercise.

<sup>a</sup> Values are presented as mean  $\pm$  SD.

<sup>b</sup> The study of Devin et al., 2018 consisted of two groups receiving HIIT: the two HIIT protocols were equal for the first 4 weeks of training; thereafter, in a second cycle of 4 weeks, one group (HIIT1) continued to exercise three times per week, whereas group two (HIIT2) only trained once a week (only results of the first four weeks of training are displayed for both groups).



**Fig. 1.** Relative pre- to post-training changes in  $VO_{2peak}$  (graph A) and  $VO_2$  at the VAT (graph B) in studies evaluating short-term preoperative HIIT or MIET, as well as relative pre- to post-training changes in  $VO_{2peak}$  (graph C) in studies evaluating preoperative short-term HIIT or MIET (black bars) and in studies evaluating short-term HIIT and MIET in abdominal cancer survivors (grey bars).

Abbreviations: VAT = ventilatory anaerobic threshold;  $VO_2$  = oxygen uptake;  $VO_{2peak}$  = oxygen uptake at peak exercise.

| = high-intensity interval training; ♦ = moderate- to high-intensity interval training; ▼ = moderate-intensity exercise training. \* = statistically significant ( $P < 0.05$ ). Error bars represent the 95% confidence interval. Grey area demarks the coefficient of variation of 4.9% for  $VO_{2peak}$  and 10.4% for  $VO_2$  at the VAT [44]. <sup>a, b</sup>: Devin et al. 2018<sup>a</sup> and Devin et al. 2018<sup>b</sup> represent two subgroups within the same study that both performed HIIT, in which the two HIIT protocols were identical for the first four weeks of training: results displayed here only comprise the first 4 weeks of the exercise program.

Based on the law of diminishing returns, which states that improvements will level off when fitness levels improve, patients at high risk for complications (low preoperative aerobic fitness), as defined by a

$VO_2$  at the VAT  $\leq 11$  mL/kg/min or an oxygen uptake at peak exercise  $VO_{2peak} \leq 18$  mL/kg/min, are likely to benefit most [34]. This holds especially true when preoperative aerobic fitness can be increased



above these thresholds in high-risk patients [16]. Only one study in this review specifically included high-risk patients [21] and one study [16] separately reported on high-risk patients as a subgroup. In the RCT of Dunne et al. [16], patients trained before liver resection, of which five of the nine patients (56%) who met the definition of high-risk ( $\text{VO}_2$  at the VAT  $\leq 11$  mL/kg/min) at baseline were no longer considered to be high-risk patients after a 4-week HIIT, as their aerobic fitness improved above the risk threshold. Nevertheless, although HIIT seems to be able to increase aerobic fitness in a training episode as short as 4 weeks, longer training episodes will probably elicit greater improvements in aerobic fitness before the asymptotic response will start to level off, especially in patients with a low aerobic fitness. In patients with rectal cancer who participated in a 6-week preoperative physical exercise training after NACRT,  $\text{VO}_2$  at the VAT and  $\text{VO}_{2\text{peak}}$  rapidly increased in the first three weeks following NACRT [21]. Despite a slightly less steep increase, aerobic fitness continued to increase between week 3 and 6 post-NACRT [21]. Although longer training episodes will lead to greater improvements, to date, optimal duration of individual preparation episodes are impossible to determine, as sufficient data is lacking. Nevertheless, future surgical planning should be a tradeoff between the medical urgency to operate and the time that is needed for optimal patient preparation in order to improve postoperative outcome.

## 8. Main limitations of the current literature and future perspectives

This comparative review aimed to evaluate current evidence concerning the effect of short-term ( $\leq 6$  weeks) MIET and/or HIIT on objectively measured aerobic fitness. On the group level, short-term HIIT should probably be considered as more effective than MIET in the short preoperative period, as three out of four studies showed statistically significant improvements in  $\text{VO}_{2\text{peak}}$  after HIIT training as of  $>4.9\%$ , the coefficient of variation of  $\text{VO}_{2\text{peak}}$  [44] (Fig. 1, graph A). In contrast, the two studies that evaluated short-term preoperative MIET, pre-post changes in  $\text{VO}_{2\text{peak}}$  were not statistically significant and consistently smaller than the coefficient of variation (Fig. 1, graph A). Although not performed in the preoperative period, the studies of Devin et al. in colorectal cancer survivors [18,19] showed significant improvements in  $\text{VO}_{2\text{peak}}$  after short-term HIIT, but not after short-term MIET (Fig. 1, graph C). Improvements in  $\text{VO}_{2\text{peak}}$  of the MIET group only became significant after 8 weeks of training (data not shown), meaning that it might take longer to improve aerobic fitness by means of MIET [18]. Nevertheless, the available studies mainly consisted of small (pilot) randomized controlled and/or single-arm trials. The largest study in this review included only 30 participants. As the aim of these small studies was probably more focused at feasibility than effectiveness of the physical exercise training intervention, studies seem inaccurate with regard to adequately reporting 1) all FITT-VP components of the physical exercise training prescription, 2) adherence to FITT-VP components of the physical exercise training program, and 3) objectively monitoring of individual (interim) training responses.

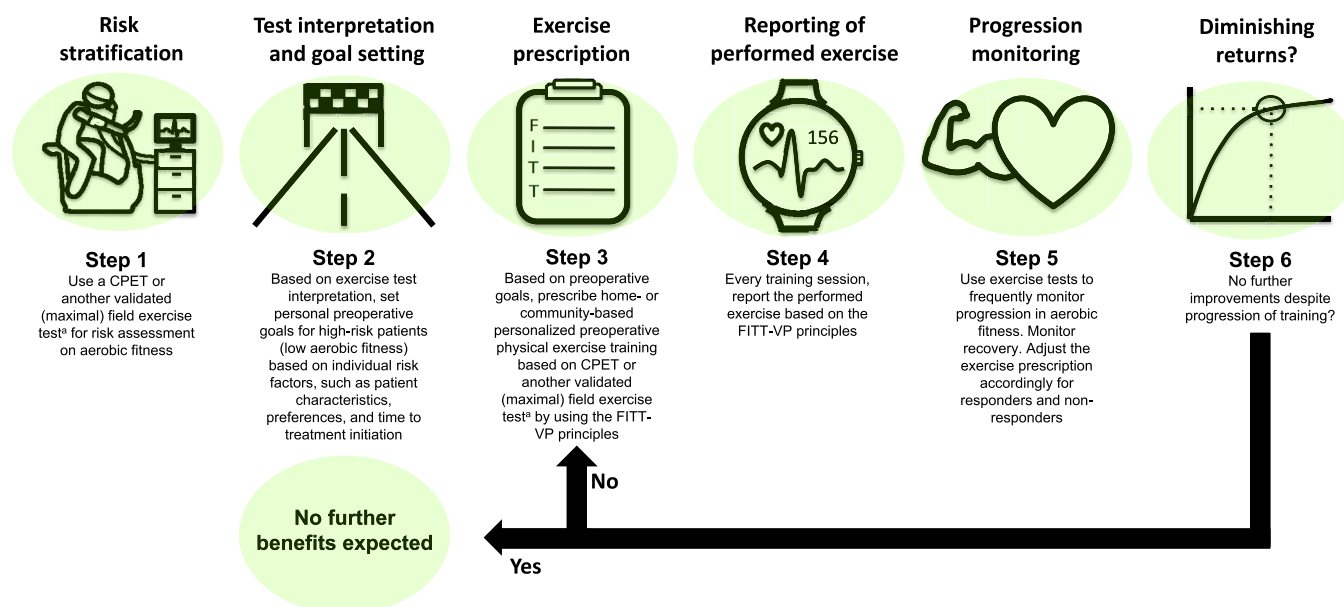
With regard to physical exercise training prescription (Table 2), all studies described their protocol in terms of frequency, intensity, time, and type. Except for MIET or HIIT, no variation existed with respect to type of training, as all included studies used a cycle ergometer to perform MIET and/or HIIT. Progression of training was merely reported in two studies [17,20]. Only one study [21] used intermediate formal exercise testing in order to objectively monitor individual training responses and adjusted the exercise prescription accordingly. Reporting of the actual performed exercise was rather incomplete as shown in Table 3. Applying training progression was only clearly reported in two studies (25%) [15,17], and reported progression was rather generic instead of based on

objectively measured individual training responses. None of the studies reported whether the exercise prescription was adjusted based on the recovery status of the patient. Overall, reporting of adherence to the exercise prescription was incomplete. As an adequate quantification of the actually performed FITT-VP is incomplete in most studies, the actual training dose, performed by the participants during the entire episode cannot be calculated. To allow for a better understanding between the performed dose of exercise and the response to exercise (e.g., improvement in aerobic fitness), as well as for an easier translation of scientific research into clinical practice, completely reporting the prescribed physical exercise training program, as well as adherence to its FITT-VP components on an individual patient's level is imperative.

Furthermore, by primarily focusing on group averages (e.g., mean increase in  $\text{VO}_{2\text{peak}}$ ), the variability in individual physical exercise training response is obscured. Although true non-responders to exercise do not exist [49], it is well known that there is large between-subject variation in response to physical exercise training [49,50] and recovery [35]. Responders and non-responders among patients with colorectal cancer were briefly discussed in the study of Boereboom et al. [22]. Although 50% of the participants responded by improving their  $\text{VO}_{2\text{peak}}$ , the other half did not respond. The same trend was observed in the study of Dunne et al. [16], in which only 40% of the participants improved their  $\text{VO}_2$  at the VAT. It was not reported whether variability in response to HIIT was affected by the performed total training volume, and therefore by the completed training dose, nor was the exercise prescription adjusted in accordance with the training response. Non-responders might actually become responsive to exercise when training volume (either training frequency, intensity, and/or time) is altered [49] or when another training type is applied [51]. To enable for timely identification of non-responders and to motivate responders, objective and frequent monitoring and quantification of training progression (titration) using performance tests is essential to be able to manipulate the components of the FITT-VP principles in such a way that it leads to an individualized effective physical exercise training program [34].

With regard to patient selection, most studies in this comparative review included relatively fit patients, and therefore estimates of effects might be attenuated. Considering the law of diminishing returns, as well as based on the a priori risk for postoperative complications, patients with a low aerobic fitness, as identified by CPET and quantified by a  $\text{VO}_2$  at the VAT  $\leq 11$  mL/kg/min and/or  $\text{VO}_{2\text{peak}} \leq 18$  mL/kg/min, are expected to have the greatest preoperative improvements in aerobic fitness and the greatest reduction in postoperative complication risk. Based on these criteria for determination of low aerobic fitness, only two [16,21] out of the six included prehabilitation studies (two studies were performed in colorectal cancer survivors) included an, on the group level, high-risk patient group. In addition, self-selection bias seems an issue in prehabilitation trials, as there are indications that patients that are able and motivated to participate in exercise interventions are younger, have less comorbidities, and are more physically active (selection bias) compared to patients not willing to participate [52]. Therefore, those patients that need it most are probably the hardest to reach.

All physical exercise programs included in this review were executed in the hospital. This inevitably excludes patients that are in greatest need for prehabilitation, as the most vulnerable patients are probably less mobile and therefore less likely to be able to attend hospital-based training sessions. Indeed, in the three studies [15–17] that reported on reasons for non-enrollment, between 26% and 73% of the participants declined participation due to travel distance to the hospital and therewith-associated costs. Evidence in sedentary middle-aged subjects suggests home-based HIIT is safe and can significantly increase aerobic fitness within 4 weeks [53].



**Fig. 2.** Proposed steps for the development and execution of a preoperative physical exercise training program to increase aerobic fitness.

Abbreviations: CPET = cardiopulmonary exercise test; FITT-VP = frequency, intensity, time, type, volume, and progression.

<sup>a</sup> E.g., the steep ramp test, a short maximal exercise test on a cycle ergometer, or incremental shuttle walk test.

Therefore, home- or community-based HIIT, possibly in combination with modern tele-monitoring techniques, could be a tempting alternative that might be able to ensure that patients are willing and able to participate in an efficient and effective preoperative physical exercise training program to improve their aerobic fitness, especially for high-risk patients with a low aerobic fitness.

Future development and reporting of preoperative physical exercise programs might be improved by using the i-CONTENT tool [31], by focusing on patients with a low aerobic fitness, by using individualized exercise prescriptions based on formal baseline assessments (i.e. CPET), by monitoring adherence to all FITT-VP principles, and by formally measuring training progression and recovery. The steps that can be taken to come to such an individualized approach are depicted in Fig. 2. Substantial new data concerning preoperative optimization of aerobic fitness is expected in the near future. Within the domain of colorectal cancer alone, at least three prehabilitation trials are currently ongoing or have just finished [54–56]. Nevertheless, as randomized controlled trials in general have an excellent internal validity, their external validity or generalizability is often limited. Therefore, there is an urgent need for studies using real-life data to evaluate the effectiveness of different preoperative exercise training programs. In addition, studies investigating the feasibility and effectiveness of home-based HIIT with or without tele-monitoring for prehabilitation are needed.

## 9. Conclusion

Despite limited evidence in the preoperative period, HIIT seems to be a powerful stimulus to increase aerobic fitness at the group level within the often limited 4- to 6-week preoperative time window prior to abdominal cancer surgery. No evidence was found that short-term MIET alone could effectively improve aerobic fitness within this short time period. Nevertheless, one size does not fit all, and there is large heterogeneity in the response to physical exercise training. Therefore, adequate patient selection, personalized physical exercise training prescription using the FITT-VP principles, full reporting of physical exercise training adherence,

and formal monitoring of training progression and recovery is needed to ensure for a personalized and effective short-term physical exercise training program embedded within a multi-modal prehabilitation program.

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## CRediT authorship contribution statement

**Ruud F.W. Franssen:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Maryska L.G. Janssen-Heijnen:** Conceptualization, Writing – review & editing, Supervision. **Anael Barberan-Garcia:** Writing – review & editing. **F. Jeroen Vogelaar:** Writing – review & editing. **Nico L.U. Van Meeteren:** Conceptualization, Writing – review & editing. **Bart C. Bongers:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Supervision.

## Declaration of competing interest

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

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejso.2021.08.026>.

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