Maximal oxygen uptake in patients exercising during cancer treatment – an evaluation of test criteria and the impact of exercise intensity
Maximal oxygen uptake in patients exercising during cancer treatment – an evaluation of test criteria and the impact of exercise intensity

A sub-study within the Phys-Can consortium: investigating criteria for maximal oxygen uptake testing and how prescribing different exercise characteristics impacts patients undergoing cancer treatment

Dissertation for the degree of Doctor of Philosophy (Ph.D.)

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Ann Christin Helgesen Bjørke
To Marie, Vilde and Lars – for being you!

IX
SUMMARY

Background and objectives: An increasing number of people are living with short- and long-term adverse effects of cancer and cancer treatment. Maximal oxygen uptake (\(\dot{V}O_2\text{max}\)) is a measure of cardiorespiratory fitness often used to monitor changes in fitness during and after treatment for cancer. There is, however, limited knowledge regarding how standard criteria verifying \(\dot{V}O_2\text{max}\) in healthy populations work for patients newly diagnosed with cancer. Patients with cancer are recommended to be as physically active as their abilities and condition allow them to be before, during and after cancer treatment. Still, there is a lack of tailored exercise recommendations, i.e. how the exercise characteristics frequency, intensity, time/duration and type (the FITT factors) should be prescribed, for patients that are undergoing treatment for different types of cancer.

One objective in this study was to increase the validity of cardiorespiratory fitness tests among patients diagnosed with cancer. However, the overarching aim was to address how exercise at different intensity levels may affect cardiorespiratory fitness from time of diagnosis until post-treatment. An additional objective was to study the overall exercise-induced effect on cardiorespiratory fitness, and to investigate whether the FITT factors individually could affect this response in cardiorespiratory fitness in patients undergoing treatment for cancer.

Methods: Paper I. Medline and Embase through OvidSP were searched to identify randomized controlled trials examining the effects of aerobic exercise on \(\dot{V}O_2\text{max}\) in adult patients with cancer receiving (neo-)adjuvant treatment. Only studies using maximal tests, directly or indirectly measuring \(\dot{V}O_2\text{max}\) were included. Two independent reviewers extracted data, and assessment of study quality was performed using TESTEX. Effect sizes and differences across intervention characteristics were calculated using Comprehensive Meta-Analysis software. Exercise duration and exercise volume was analysed with meta-regression.

Paper II. From the Phys-Can randomized controlled trial, 535 patients newly diagnosed with breast, prostate or colorectal cancer performed an incremental \(\dot{V}O_2\text{max}\) test on a treadmill before starting their cancer treatment and an exercise intervention. Fulfilment of different cut-points within typical criteria verifying \(\dot{V}O_2\text{max}\) was described. The dependent key variables included in the initial bivariate analysis were achievement of a \(\dot{V}O_2\) plateau, peak values for maximal
heart rate, respiratory exchange ratio (RER), the patients’ rating of perceived exertion on Borg’s scale6-20, and peak breathing frequency ($f_R$). A receiver operating characteristic analysis was performed to establish cut-points for variables associated with the test leader’s evaluation. Last, a cross-validation of the cut-points found in the receiver operating characteristic analysis was performed on a comparable sample of cancer patients (n=80).

**Paper III.** The Phys-Can study was a multicentre, randomised controlled trial with a 2x2 factorial design performed in Uppsala, Lund and Linköping in Sweden. Patients newly diagnosed with breast, prostate or colorectal cancer undergoing (neo-)adjuvant treatment were randomised to high intensity (HI) or low-to-moderate intensity (LMI) exercise, with or without additional behavioural change support. The six-month exercise intervention consisted of supervised resistance training and home-based endurance training. The main outcome was cancer-related fatigue, and one of the secondary outcomes was cardiorespiratory fitness, measured by a $\dot{V}O_2\max$ test. Regarding this thesis, $\dot{V}O_2\max$ was the main outcome of interest. Main results are based on multiple linear regression analysis performed per intention-to-treat (ITT) principles. In addition, a complete-case analysis (n=331) was performed, and in the present thesis, adherence to the endurance training was included as a covariate in the analyses.

**Results:** From Paper II, criteria of RERpeak, Borg’s RPE and $f_R$ peak were associated with the test leader’s evaluation of whether a test was defined as ‘to exhaustion’. Within these three criteria variables, the cut-points found to have the highest sensitivity and specificity for predicting the test leader’s evaluation were RER $\geq$1.14, RPE $\geq$18 and $f_R$ $\geq$40 breaths/min.

The results from the systematic review and meta-analysis of 13 studies (Paper I) demonstrate that exercise interventions with an aerobic component during (neo-)adjuvant cancer treatment positively impacted $\dot{V}O_2\max$ compared with controls that did not perform any exercise. The beneficial effect of aerobic exercise on $\dot{V}O_2\max$ was defined as ‘moderate’ (ES: 0.46, 95%CI, 0.23 to 0.69). Furthermore, the duration of each exercise session, weekly exercise duration and volume (combination of duration and intensity) were associated with changes in $\dot{V}O_2\max$. Neither frequency nor intensity was per se associated with improvements in $\dot{V}O_2\max$. However, since weekly exercise duration and volume are a function of frequency, intensity and session duration, the combination of these variables seems important.
The Phys-Can results from the main ITT analysis reveal a positive effect on changes in $\dot{V}O_2\text{max}$ by exercising at HI vs. LMI, finding the difference between intensity groups to be 1.60 (95% CI; 0.12 to 3.07) ml/kg/min (Paper III). The complete-case analysis showed that participants exercising at high vs. low-to-moderate intensity had significantly larger relative improvements (or less decline) in $\dot{V}O_2\text{max}$, when adjusting for adherence to the endurance training.

**Conclusions:** When verifying $\dot{V}O_2\text{max}$ in newly diagnosed cancer patients, we suggest applying a ‘two-out-of-three approach’, including 1) the test leader’s evaluation (‘to exhaustion’); 2) RER $\geq1.1$ – 1.15; and 3) an RPE of $\geq17$ or $\geq18$. Compared to no exercise during (neo-)adjuvant cancer treatment, exercise including an aerobic component (independently of intensity, frequency and duration) is ‘moderately’ effective in improving $\dot{V}O_2\text{max}$. Exercise intensity seems important to positively affect $\dot{V}O_2\text{max}$. When abilities and conditions allow for it, HI exercise should be recommended to maintain or increase cardiorespiratory fitness during cancer treatment. However, since larger exercise volumes and longer durations also seem to be decisive to affect $\dot{V}O_2\text{max}$, the combination of frequency, intensity and duration should be considered carefully for sufficient exercise volume in patients undergoing treatment for cancer.
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This thesis is based upon three papers:


Which exercise prescriptions optimize $\dot{V}O_2$max during cancer treatment? – A systematic review and meta-analysis.


Criteria to define maximal oxygen uptake in patients newly diagnosed with cancer: Baseline data from the randomized controlled trial of physical training and cancer (Phys-Can).

Accepted by Plos One, June 1st 2020.


Does exercise intensity matter for fatigue during (neo-)adjuvant cancer treatment? The Phys-Can RCT

Submitted to British Journal of Sports Medicine, May 26th 2020
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AET</td>
<td>aerobic exercise training</td>
</tr>
<tr>
<td>ADT</td>
<td>androgen deprivation therapy</td>
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<tr>
<td>BCS</td>
<td>behavioural change support</td>
</tr>
<tr>
<td>BLa′</td>
<td>blood lactate</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>ES</td>
<td>effect size</td>
</tr>
<tr>
<td>FITT</td>
<td>frequency, intensity, type, time</td>
</tr>
<tr>
<td>fR</td>
<td>breathing frequency</td>
</tr>
<tr>
<td>HI</td>
<td>high intensity</td>
</tr>
<tr>
<td>HIIT</td>
<td>high intensity interval training</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>HRR</td>
<td>heart rate reserve (HRmax - HRrest)</td>
</tr>
<tr>
<td>HRmax</td>
<td>maximal heart rate</td>
</tr>
<tr>
<td>HRrest</td>
<td>resting heart rate</td>
</tr>
<tr>
<td>LMI</td>
<td>low-moderate intensity</td>
</tr>
<tr>
<td>MET</td>
<td>metabolic equivalents of task</td>
</tr>
<tr>
<td>V̇O₂max</td>
<td>maximal oxygen uptake; the highest rate at which an individual can consume oxygen during exercise (ml/kg/min)</td>
</tr>
<tr>
<td>V̇O₂peak</td>
<td>peak oxygen uptake; highest recorded oxygen consumption during an exercise test (ml/kg/min)</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RER</td>
<td>respiratory exchange ratio</td>
</tr>
<tr>
<td>RET</td>
<td>resistance exercise training</td>
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<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>RPE</td>
<td>ratings of perceived exertion</td>
</tr>
<tr>
<td>RT</td>
<td>radiotherapy</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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1 INTRODUCTION

Cancer is a disease that massively impacts those it affects and is also a burden for the society [1]. Although improved diagnostic techniques and treatments have increased survival rates in recent decades [2, 3], individuals with a history of cancer struggle with reduced physical function and quality of life due to various side effects [4]. Patients treated for cancer often experience impaired cardiorespiratory fitness [5, 6]. Cardiorespiratory fitness is an important clinical outcome predicting mortality in both healthy individuals and in patients with cardiovascular disease [7-9]. In patients with breast cancer, impaired cardiorespiratory fitness is associated with increased cardiovascular mortality [5, 10]. Furthermore, cardiorespiratory fitness has been proven to be an independent predictor of cancer mortality risk when comparing individuals with poor cardiorespiratory fitness with individuals with moderate and high cardiorespiratory fitness in six prospective studies [11].

Historically, patients with cancer were told to rest and to avoid strenuous physical activity (PA) following diagnosis [12]. Fortunately, this recommendation has changed, and patients are now encouraged to perform 150 minutes of moderate-to-vigorous PA per week and generally to be as physically active as possible [13]. However, individually tailored PA and exercise guidelines are lacking [14].

From the first randomised controlled trial (RCT) published in the mid-to-late 1980s, in which patients with breast cancer performed interval training on bicycles during chemotherapy treatment [15], there has been an exponential increase in published studies within the exercise-oncology field [12]. A literature search performed by Christensen et al. (2018) found that 292 exercise training intervention studies have been published [12]. In the early studies, researchers focused on the effect of PA on various side effects, such as cancer-related fatigue and health-related quality of life [16]. In the late 1990s, the effect of hospital-based aerobic exercise during high-dose chemotherapy and stem-cell transplantation was studied in relation to important clinical outcomes and physical function [17]. The landmark study by Segal et al. (2001) was the first of many studies focusing on ameliorating more indirect symptoms/side effects of cancer treatment (e.g. physical functioning/cardiorespiratory fitness and weight management) [18]. In a publication by Wahnefried et al. (2001), the importance of PA and weight management was further highlighted [19]. Due to large epidemiological studies with encouraging preliminary evidence that being
physically active after a cancer diagnosis is associated with increased survival time and reduced risk of disease progression [20], interest in the underlying biological mechanisms arose from around the mid-2000’s [21]. In addition to the emerging evidence on how exercise can improve cancer outcomes, questions related to how patients should exercise appeared. In the START trial, which involved breast cancer patients during chemotherapy treatment, resistance exercise training (RET), aerobic exercise training (AET) and a control group were compared (in the time between 2003 and 2005) [22]. In 2014, follow-up data regarding survival after the START trial were published, and a 25% reduced risk of death was evident in patients who had been randomly assigned to the two exercise groups compared with the control group, although it should be mentioned that the study did not have sufficient power to detect significant differences between the two exercise groups [23].

Today, we know that exercise can be beneficial in managing a variety of cancer disease- and treatment-related side effects [24]. What is not known, however, is how we should prescribe tailored PA and exercise in terms of frequency, intensity, type and time to improve cancer-related side effects and prognosis to patients in different phases of their cancer trajectory [14, 25-27]. To our knowledge, regarding exercise intensity, no studies have been designed to justify whether higher exercise intensity may result in improved changes in cardiorespiratory fitness during cancer treatment when controlling for exercise volume.

When prescribing aerobic exercise, the intensity is normally specified using percentages of either maximal oxygen uptake ($\dot{V}O_{2\text{max}}$), maximal heart rate (HRmax) or heart rate reserve (HRR). To prescribe precise exercise intensity and to be able to evaluate the effect on cardiorespiratory fitness post-intervention, a valid measure of cardiorespiratory fitness is important. $\dot{V}O_{2\text{max}}$ is often used to monitor changes in cardiorespiratory fitness during and after treatment in cancer patients. There is, however, no consensus on how criteria verifying $\dot{V}O_{2\text{max}}$ should be applied to patients newly diagnosed with cancer. Consequently, there is a need to study how criteria and their cut-point verifying $\dot{V}O_{2\text{max}}$ works in cancer patients. The test leader’s evaluation regarding whether the test has been performed to exhaustion may be important as part of this investigation.
2 BACKGROUND

2.1 What is cancer?

Cancer is a general term for a large group of diseases that can originate almost anywhere in the body. One characteristic of cancer is that a rapidly created group of abnormal cells grows beyond its usual boundaries and can invade adjoining parts of the body and spread to other organs [28, 29]. This latter process is referred to as metastasising, which is the major cause of death from cancer. Normal cells in the body grow and divide to form new cells as the body needs them, and when they get old or damaged, they die, and new cells take their place. However, when cancer develops, old or damaged cells do not die as they usually would, and abnormal cells act differently than they usually do [28]. New cells are then formed even when they are not needed, and this uncontrolled cell development may eventually form tumours. Cancerous tumours are malignant, which means that they can invade nearby tissues and travel through the blood or the lymph system and form new tumours at other locations in the body. Benign tumours do not spread or invade other tissues, unlike malignant tumours, in which cancer recurrence after removal is common [28, 30].

2.2 Prevalence, incidence and burden

Worldwide, an estimated 18.1 million new cases and 9.6 million cancer deaths occurred in 2018 [31]. In the 21st century, cancer is expected to be the leading cause of death in every country of the world, according to estimates from the World Health Organization (WHO)[31]. The trends for cancer incidence in Norway in recent years have been relatively stable for men (+0.3%), with a small increase of 5.6% in women when compared with the previous five-year period (2014-2018) [32]. In Norway, there was a total of 34,190 new cancer cases reported in 2018, which is estimated to increase to 40,000 by 2030. In 2017, there were 11,016 deaths from cancer in Norway, of which 5,837 were men, and 5,179 were women [32]. On a population level, about 36% of men and 30% of women will be diagnosed with cancer before the age of 75 [32].

Survival rates are improving due to better diagnostics and treatment strategies [33]. Consequently, the number of individuals living with previous or current cancer is increasing. In December 2018, a total of 283,894 individuals were living with or had received a diagnosis of cancer in Norway [32]. The most common new cancer cases in 2018 were located in the prostate, female breast, lung and colorectum (accounting for 43% of new cases) [32]. Each year, 4,848 men are diagnosed with prostate cancer, 3,568 women are diagnosed with breast
cancer and 4,428 persons (men and women in total) are diagnosed with colorectal cancer in Norway [32].

The burden related to cancer is expected to increase in the future [1]. This burden is evident on several levels, affecting the large-scale economy, the healthcare system and individual patients (as well as their family and friends) [1]. Cancer and the related treatments may cause various symptoms and signs that can be acute, chronic or appear later in life, such as fatigue, reduced physical function, lymphedema, pain, neuropathies, diabetes, hypertension or osteoporosis [34, 35]. In addition, cancer survivors have an increased risk of recurrence and secondary tumours [36]. These challenges all undermine the health and quality of life of cancer survivors. Employed cancer survivors in Norway have been found to struggle with their ability to work five years after diagnosis, and 75% of long-term cancer survivors took sick leave (defined as >16 days in one year) within the first 12 months’ post-diagnosis [37]. Employees previously diagnosed with cancer had higher sick leave compared with a cancer-free control group [37].

2.3 Prevention and risk factors

Some argue that the lifetime cancer risk is mostly due to ‘bad luck’, and that only one-third can be attributed to environmental factors or inherited predispositions [38]. This ‘bad luck’ explanation is criticised by others [39]. Some report that only 5 to 10% of cancer cases are developed due to inherited factors only [40], and that cancer occurrence is heavily influenced (>70-90%) by lifestyle- and environmental factors [41]. In addition, some chronic infections have a major relevance for some specific cancer types [42]. Increasing age is known as the largest risk factor for cancer [43], and obesity is also a known risk factor for many cancer types [44]. There are some risk factors particularly related to different cancer types. Regarding breast cancer, family history of breast cancer, reproductive factors (early menarche, late menopause, late age at first pregnancy and low parity can increase the risk), oestrogen, alcohol consumption, tobacco use and a diet including a high intake of saturated fat are important risk factors [45]. The main risk factors for prostate cancer incidence or advanced prostate cancer are suggested to be cigarette smoking history, race, family history of prostate cancer, physical inactivity, body mass index (BMI), height, total energy consumption, and intakes of calcium, tomato sauce and α-linolenic acid [46]. Furthermore, obesity, physical inactivity, red meat consumption, and alcohol and tobacco use are considered the driving factors behind the growth of colorectal cancer, although family history of colorectal cancer and inflammatory bowel disease also are known risk factors [47, 48]. Although there is disagreement
related to the magnitude such lifestyle and environmental risk factors may play in cancer development [49], we know that reducing the intake of tobacco, alcohol and an unhealthy diet in combination with increasing PA levels may prevent cancer [40, 42].

In a large study of pooled data, including 1.44 million participants, Moore et al. (2016) found that a higher level of leisure-time PA (above the 90th percentile) was associated with lower risk for 13 of the 26 types of cancer studied, compared with the lower levels (below the 10th percentile). The risk reductions were found to be 20% or more for seven of the cancer types (oesophageal adenocarcinoma, cancers of the liver, lung, kidney, gastric cardia, and endometrium, and myeloid leukaemia). The risk was found to be moderately (10-20%) reduced for myeloma, colon-, head and neck-, rectal-, bladder- and breast cancer. The risk reduction was reported to be 7% when combining all 26 cancer types. Furthermore, the results from this large study support the notion that the associations between leisure-time PA and cancer risk are broadly generalizable to different populations, including overweight or obese individuals, or those with a history of smoking [29].

2.3.1 Physiological mechanisms linking exercise to cancer prevention

Exercise may have important implications for cancer control across the entire cancer trajectory, from pre-diagnosis (i.e. pre-screening and screening/diagnosis) to post-diagnosis (i.e. pre-treatment, treatment, post-treatment and recurrence) [51]. Regular exercise reduces the risk of numerous chronic diseases, not only by affecting the contracting skeletal muscle, but also through systemic changes [50]. The exact mechanisms driving these more systemic changes have yet to be resolved, but exercise factors (in which proteins serve a signalling role) are thought to be important [50, 52].

Within the exercise-oncology field, in human observational studies and from smaller randomised clinical trials, several biological mechanisms have been suggested to be important in affecting cancer risk and tumour progression. Exercise-dependent regulation of the systemic levels of sex hormones, insulin, inflammatory markers and immune cell function were proposed by McTiernan in 2008 [21]. Such alterations in the blood profile take place in conjunction with improved fitness level, reduced adiposity and improved lean body mass [53].

However, there are also other alterations in the blood profile resulting from single exercise bouts [53]. During acute exercise, transient but marked increases in a wide range of circulating hormones, cytokines and immune cells occur [54-
These short-lasting alterations are, in magnitude, much more evident than the adaptations seen with long-term exercise [53, 57], which highlights the important protective effect of regularly exercise [57].

Tumour infiltration by natural killer (NK) cells has been associated with prolonged survival in cancer patients [58-60], and high NK-cell cytotoxic activity has been linked to a decreased risk of cancer [61]. In 2016, one study of mice gained attention in the exercise-oncology field; the results linked exercise, epinephrine and interleukin-6 (IL-6) to NK-cell mobilisation and redistribution, and ultimately to the control of tumour growth [62]. Pedersen et al. demonstrated a >60% reduction in tumour growth in five different mice tumour models in which mice performed voluntary wheel running after being injected with different tumour types [62]. It is important to highlight that, to induce a stress-reaction that releases epinephrine, a certain level of exercise intensity and/or duration is necessary, and the magnitude of activation depends on training status [56], suggesting that exercise duration and intensity should be individualised to induce this protective effect.

Two recognised hallmarks of cancer that are both involved in cancer initiation and progression are evasion of immune surveillance and tumour-associated inflammation [63]. Exercise may regulate these processes, as it can mobilise and activate cytotoxic immune cells, restrict inflammatory signalling pathways in immune cells, and regulate acute and chronic systemic inflammatory responses. Pernille Højman concluded in her review study from 2017: ‘These regulatory effects can result in lower tumor incidence and cancer progression, linking exercise training with control of immune function, inflammation, and ultimately cancer’ [64].

2.4 Adverse effects related to cancer treatments

The traditional and most widely used cancer treatment methods are surgery, chemotherapy and radiotherapy [28]. In addition, there are biological treatments or targeted therapies involving more modern modalities (hormone-based therapy, anti-angiogenic modalities, signal transduction inhibition and various types of immunotherapy) [28]. It is important to distinguish between treatments in relation to the prognosis for the patient, with some treatments being delivered with a curative intention and some with a palliative intention. A curative treatment aims to cure and make the person cancer-free; whereas, a treatment with a palliative intention aims to slow the disease development, to help the patient to obtain symptom relief, and to prolong the time left with the best
possible quality of life [65]. In this present thesis, the focus is on patients in the curative setting.

2.4.1 Short-term adverse effects from treatment

Cancer treatments and their cytotoxic effects can damage healthy tissues within the heart, lung, skeletal muscle, circulatory system, bone marrow and nervous system [66-68]. Such damage can lead to cardiac dysfunction [69, 70], myelosuppression or pancytopenia [71, 72], pulmonary dysfunction [73], peripheral neuropathy [74], muscular weakness [75] and postural instability [76]. Furthermore, these alterations can all impair cardiorespiratory fitness [70].

Generally, the most common and distressing side effect, regardless of type of cancer and treatment, is cancer-related fatigue [77, 78]. Such fatigue is defined as a distressing, persistent sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent activity and that interferes with normal functioning [79]. Between 30% and 60% of patients experience cancer related fatigue during treatment for cancer, but the prevalence depends on the patient population, type of treatment and method of assessment [80]. Clinically relevant levels of cancer related fatigue have been reported in one-third of patients up to six years after treatment [81]. The aetiology of cancer related fatigue is not fully understood but depends, most likely, on a variety of factors [80]. One plausible biological mechanism is disease- and treatment-induced activation of pro-inflammatory cytokines, signalling the nervous system to generate fatigue symptoms [80]. The prevalence and severity of fatigue seem to depend on the time that has elapsed since treatment completion, with fatigue prevalence at its highest at the end of breast cancer treatment, and then slowly declining [82]. The meta-analysis by Abrahams et al. (2016) found that more severe disease, chemotherapy alone and receiving a combination of surgery, radiotherapy and chemotherapy, both with and without additional hormone therapy, increased the risk of severe fatigue [82].

2.4.1.1 Chemo-, hormone- and radiation therapy

Chemotherapy (especially if it contains anthracyclines) has been demonstrated to cause short- and long-term toxic side effects [12]. Such toxicities may cause changes in the haematology profile (e.g. anaemia) and organ damage, which again may lead to cardiomyopathy or impaired pulmonary function [12]. These impairments can directly cause negative effects on the cardiovascular and respiratory systems, consequently impairing cardiorespiratory fitness [70]. Furthermore, hormone therapy, such as androgen deprivation therapy (ADT),
may induce changes in body composition, with increased fat body mass (FBM), decreased lean body mass (LBM) and decreased bone mineral density [67, 83-85]. Increased FBM, decreased LBM and sarcopenia are also side effects often observed in women treated for breast cancer, especially among those receiving endocrine therapy [86]. Radiation therapy may cause fatigue shortly after the start of the treatment, and is often more severe when combined with chemotherapy [28]. Other side effects from radiotherapy result from damage to the nearby tissue and cells being treated [28]. For example, damage to the cells in the alveolar space may develop into inflammation in the lung, occurring 4-12 weeks after radiotherapy completion [87]. Regarding radiation for prostate cancer, early and late toxicities can occur and, depending on the radiation dosages, may cause complications appearing in the gastrointestinal tract, in the rectum or in the urinary and genital organs [88].

Structural exercise and PA may counteract some of these negative effects on the cardiovascular and respiratory systems and level of fatigue [89]. Furthermore, PA, endurance training and RET help preserve or even increase bone mass, muscle mass and function while undergoing ADT [90-93].

2.4.2 Long-term adverse effects of treatment

Systemic cancer treatments may induce permanent injuries to the cardiovascular system, leading to, for example, cardiac dysfunction, cardiomyopathy, reduced left ventricular ejection fraction, myocyte cell death (either by apoptosis or necrosis) and heart failure [68, 89, 94-96]. Radiation, chemotherapy and biological agents, independently and in combination, increase the risk of cardiovascular disease (CVD) in people who have survived cancer [97]. Furthermore, radiotherapy in combination with chemotherapy may cause a significant reduction in pulmonary function (forced vital capacity, forced expiratory volume and carbon monoxide diffusing capacity) three months after radiotherapy completion without seeing a reduction in cardiorespiratory fitness, measured as \(\hat{V}O_2\text{max}\) [87]. Up to 10 years after locoregional breast radiotherapy, an important reduction in pulmonary function has been observed, but this may also be explained by the use of endocrine treatment (Tamoxifen) [98]. Tamoxifen enhances the risk of radiation-induced lung fibrosis through the induction of transforming growth factor-beta (TGF-beta) secretion, which has been implicated in the pathogenesis of radiation-induced fibrosis [99].
2.5 Physical activity and exercise guidelines for patients with curative cancer

Physical activity is defined as ‘…any bodily movement produced by skeletal muscles that requires energy expenditure’; whereas, ‘exercise is a subset of PA that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness’ [100]. Although the focus on PA and structured exercise for cancer patients has increased excessively in recent decades, the current PA guidelines are still rather general [27]. People with cancer should try to be as physically active as their abilities and conditions allow before, during and after cancer treatment [13, 101, 102]. Physical activity guidelines for patients with cancer do not differ much from the recommendations presented for the healthy population [103]. The PA guidelines for cancer survivors by The American Cancer Society [13] are to engage in regular PA and,

- Avoid inactivity and return to daily activities as soon as possible following diagnosis.
- Aim to exercise at least 150 minutes per week of moderate intensity, or 75 minutes per week of vigorous intensity, or a combination of moderate and vigorous intensity.
- Include strength training exercises at least two days per week.

Evidence strongly suggests that exercise during and after cancer treatment is safe and feasible [13], and the recommendations are clear: patients undergoing or ending cancer treatment should be regularly physically active [13]. Health professionals involved in the care of people with cancer are encouraged to discuss the role of exercise in cancer recovery and to recommend that their patients adhere to the PA guidelines [104]. In addition, patients should be referred to a health professional who is specialist in the prescription and delivery of exercise [104].

However, there is a lack of studies investigating specific components of exercise prescriptions (e.g. exercise frequency, intensity, type and time/duration) referred to as FITT factors. Consequently, the knowledge base is insufficient to make specific and tailored exercise recommendations to patients with different cancer types, severities and in different phases of their cancer trajectory [14, 25-27].

As with the healthy population, patients with cancer struggle to fulfil the PA guidelines, and cancer survivors are even less likely to engage in PA than healthy individuals [105, 106]. In the United States (US), only 9% of cancer survivors
and 19% of people with no history of cancer meet both PA guidelines [106]. Although cancer survivors in Scotland were found to be more likely to eat more healthily and to stop smoking, they were less likely to perform at least two hours of PA each week than individuals without a history of cancer [105]. It must be noted, however, that the results were based on self-reported health behaviours [105].

2.6 Cardiorespiratory fitness

Cardiorespiratory fitness reflects the ability to transport oxygen from the air to the mitochondria in working muscles [107]. The gold standard for verifying cardiorespiratory fitness is direct measurement of maximal oxygen uptake ($\dot{V}_\text{O}_2\text{max}$) [108]. The definition of $\dot{V}_\text{O}_2\text{max}$ is ‘the highest oxygen uptake obtainable for a given form of ergometry despite further work rate increases and effort by the subject’ [109], and the Fick equation is used to define $\dot{V}_\text{O}_2\text{max}$ [110]:

$$\dot{V}_\text{O}_2\text{max} = \text{cardiac output (Q) } \times \text{ arterio-venous (a-v) O}_2$$

*In the Fick equation, cardiac output is the amount of blood pumped from the heart in one minute, and the arterio-venous O$_2$ difference is the difference in the amount of oxygen in arterial blood compared with venous blood (representing how much of the O$_2$ was used by the muscles).

Estimated energy expenditure and measured $\dot{V}_\text{O}_2$ can be obtained using indirect calorimetry. The equipment and methods used to calculate $\dot{V}_\text{O}_2$ during incremental exercise originates from the classic bag system, in which expired air is collected in plastic or canvas Douglas bags, and the composition of O$_2$ and CO$_2$ are measured [111]. Today, we have more advanced equipment and computers, enabling the rapid measuring of metabolic and physiologic responses to exercise.

There are many systems that form part of the process of transporting O$_2$ from the air to the working muscles: pulmonary ventilation and diffusion, right and left ventricular function, ventricular-arterial coupling, the ability of the vascular system to efficiently transport blood from the heart and match the oxygen requirements, and the ability of the muscle cells to receive and use the oxygen and nutrients delivered by the blood, as well as to communicate these metabolic demands to the cardiovascular control centre [107].
About half the variance observed in cardiorespiratory fitness level after performing regular AET is considered to be inheritable factors [112]. Other important factors affecting \( \dot{V}O_2 \text{max} \) are age, gender, sex hormones, body size and LBM [109, 112].

With increasing age, both cardiac and vascular systems undergo significant functional and structural changes that impair cardiorespiratory fitness [113]. In the third and fourth decades, the decline in maximal aerobic capacity is 3 to 6% each decade, and from the age 70, the decline in each decade is larger (>20%) [114, 115].

### 2.7 Cardiorespiratory fitness in patients with cancer

Patients newly diagnosed with cancer (before treatment) [5, 6, 116, 117], patients undergoing treatment [5, 117] and cancer survivors (finished with their treatment) [5, 6, 117-119] have all been found to have lower cardiorespiratory fitness than healthy age-matched individuals.

In a 2012 study by Jones et al., \( \dot{V}O_2 \text{max} \) was measured in 248 women (~55 years) distributed in four different samples of patients with breast cancer, 1) before, 2) during and 3) after treatment for non-metastatic cancer, and 4) during therapy in metastatic disease [5]. Jones et al. (2012) found \( \dot{V}O_2 \text{max} \) markedly reduced across all patient samples, with an average \( \dot{V}O_2 \text{max} \) of ~18 ml/kg/min, which is 27% lower than healthy, physically inactive women of the same age [120]. When comparing the findings from Jones et al. (2012) with \( \dot{V}O_2 \text{max} \) in 140 healthy Norwegian women in the age groups 50-59 (~30 ml/kg/min) and 60-69 years old (~29 ml/kg/min), the difference was approximately 40% [121]. Furthermore, when comparing Jones et al. (2012) with another reference study from Norway – the HUNT 3 Fitness, including 428 women in the age group 50-59 years old – the difference was even larger (\( \dot{V}O_2 \text{max} \): ~34 ml/kg/min): 48% [122]. It is notable that, in the study by Fitzgerald et al. [120], they separated the physically inactive and active women, and in the Norwegian studies there was a mix of inactive and physically active adults in the analyses. It should also be highlighted that the study by Jones et al. (2012) included American women, and the tests were performed on a cycle ergometer; whereas, treadmills were used in the Norwegian studies [121, 122]. \( \dot{V}O_2 \text{max} \) tests performed on a treadmill yield up to 20% higher \( \dot{V}O_2 \text{max} \) results compared with tests performed on a cycle ergometer, which is often explained by quadricep fatigue [123-125].
2.7.1 Cardiorespiratory fitness before treatment

In the systematic review by Steins Bisschop et al. (2012), in which $\dot{V}O_2\text{max}$ levels were investigated in studies including different cancer populations (breast cancer, lung cancer, lymphoma, haematological cancer, prostate cancer and mixed cancer types), the percentage of reference values (compared with healthy individuals) varied between 65% and 89% before treatment [117]. However, it should be mentioned that Steins Bisschop et al. used the mean $\dot{V}O_2\text{max}$ values for the total study populations in their calculations of percentage related to healthy persons [117]. In a review by Peel et al. from 2014, in which cardiorespiratory fitness was measured in 493 women before breast cancer treatment, the mean $\dot{V}O_2\text{max}$ was approximately 25 ml/kg/min [6], which is 17% lower than age-matched, physically inactive healthy controls [120]. This finding supports the results in the review by Steins Bisschop et al. Furthermore, in a recently published small case-control study including $\dot{V}O_2\text{max}$ results from 29 women newly diagnosed with breast cancer, similar values were reported: ~29% lower than the healthy, inactive women in the control group (n=10) [116].

2.7.2 Cardiorespiratory fitness during treatment

In women with breast cancer scheduled to undergo chemotherapy, a reduction in cardiorespiratory fitness from pre- to post-treatment is expected. In a study by Klassen et al. (2014), breast cancer patients (~54 years old) who had just begun their chemotherapy treatment (finished with one or two cycles) were found to have a mean $\dot{V}O_2\text{max}$ of 23 ml/kg/min [126]. Furthermore, $\dot{V}O_2\text{max}$ measured after adjuvant chemotherapy treatment was observed to be much lower: 15.5 ml/kg/min (a 30% reduction) [126].

Regarding prostate cancer patients on ADT, 112 men were stratified according to how long they had been receiving ADT (‘acute’: <3 months and ‘chronic’: >3 months), and cardiorespiratory fitness was measured in both groups. Wall et al. found the ‘chronic’ group (23.2 ml/kg/min) to have 11% lower $\dot{V}O_2\text{max}$ values than the ‘acute’ group (26.1 ml/kg/min) [119].

In a study by Cramer et al. (2014), $\dot{V}O_2\text{max}$ was found to be severely impaired in ~60-year-old patients who had undergone chemotherapy for colorectal cancer (20.4 ml/kg/min) and in colorectal patients who had not yet begun chemotherapy after their surgery (23.4 ml/kg/min). Compared with the healthy age-matched controls used in the study by Cramer et al. (28 ml/kg/min), a 27% reduction in
\( \dot{V}O_{2\text{max}} \) may be expected in this group of patients following chemotherapy [127].

In summary, both chemotherapy and ADT may impair cardiorespiratory fitness, but chemotherapy seems to have the most toxic effect.

### 2.7.3 Cardiorespiratory fitness after treatment

Again, in the review by Steins Bisschop et al. (2012), the percentage of \( \dot{V}O_{2\text{max}} \) compared with healthy persons was found to vary between 52% and 117% (of healthy individuals) for tests performed after various cancer treatments [117]. Furthermore, Klassen et al. (2014) included \( \dot{V}O_{2\text{max}} \) measurements four weeks after finished chemotherapy treatment for breast cancer and found a mean \( \dot{V}O_{2\text{max}} \) of \(~15.5\) ml/kg/min [126], consistent with the \(~70\%\) of age-expected level in women who were tested \(~27\) months after adjuvant therapy[5]. In 703 American survivors of mixed cancers (78% females, \(~57\) years old), among whom nearly 80% finished their cancer treatment (mostly chemotherapy) about 7.5 \((\pm9.8)\) months previously, age-specific \( \dot{V}O_{2\text{max}} \) was strikingly lower (27-41%) than in healthy Americans [118]. Similar findings were evident when 21 studies involving women (\(~52\) years old) with breast cancer post-treatment were reviewed, with a mean \( \dot{V}O_{2\text{max}} \) (\(~22\) ml/kg/min) of 25% lower than healthy, age-specific inactive women [6]. In women previously treated for breast cancer 7.4 \(\pm\) 6.2 years previously, reductions were also observed in estimated \( \dot{V}O_{2\text{max}} \) (5% below age-matched women), and the impairment was found to be largest in women treated with more than one adjuvant therapy [95]. Moreover, in a study including patients treated with ADT for prostate cancer, lower \( \dot{V}O_{2\text{max}} \) values (\(~25\) ml/kg/min) were reported than in healthy males in the same age group, and the researchers found that men treated with ADT for a longer vs a shorter time had the largest decrements in \( \dot{V}O_{2\text{max}} \) [119]. It is important to acknowledge that the percentages of healthy individuals may be affected by many factors related to how the implementation of the maximal test was conducted and the group of healthy individuals used for comparison.
2.8 Why is cardiorespiratory fitness often impaired in patients with cancer?

Level of PA is reported to decline during treatment and then increase to pre-treatment levels afterwards [128]. Since level of PA and exercise are important for cardiorespiratory fitness [129], low PA levels [106] may potentially explain some of the impairment observed in patients with cancer before, during and after cancer treatment.

2.8.1 Why may cardiorespiratory fitness be impaired in newly diagnosed patients before starting cancer treatment?

Whether lower $\dot{V}O_2\text{max}$ in newly diagnosed cancer patients is a result of lower levels of PA or directly related to the disease is unclear, but there are some indications that the cancer itself can have direct negative effects. In a review from 2009, Jones et al. [70] explain that certain cancers might directly affect the functionality or the structural integrity of components that are part of the oxygen cascade. Changes in any step of the oxygen transport process can cause predictable changes in the body’s ability to consume and use oxygen [130]. For example, a tumour in the lungs, from either primary or metastatic lung cancer, may disrupt pulmonary mechanisms and gas exchange [131], and are often accompanied by weight loss, anaemia, protein catabolism and muscle wasting. Tumour-derived factors (e.g. proteolysis-inducing factor and cytokines; tumour necrosis factor α and different interleukins) may cause muscle atrophy and the inhibition of muscle regeneration, consequently causing muscle wasting (cachexia) [132, 133]. Cachexia is often characterised by a large reduction in the mitochondria capacity, which again leads to a reduced oxidative capacity [70]. It should be noted that there is still a lack of clarity regarding how cachexia is mediated, as well as the aetiology for the underlying factors to drive the interactions between tumours and the muscle tissue [133].

Both the right and left ventricle end-diastolic volumes were reduced in women newly diagnosed with breast cancer (before treatment) compared with healthy controls [116]. Since ‘only’ 45% of the variance in $\dot{V}O_2\text{max}$ could be explained by cardiac output, it was suggested that peripheral factors (e.g. muscle blood flow and/or $O_2$ extraction) may also play a prominent role in limiting $\dot{V}O_2\text{max}$ prior to chemotherapy treatment [116].

In summary, in addition to tumours that directly affect the $O_2$ cascade due to the location of the tumour, tumours can also influence $\dot{V}O_2\text{max}$ systemically by, for
example, affecting the muscles (muscle wasting and lower mitochondria density) and their ability to extract and utilise $O_2$.

2.8.2 Why may cardiorespiratory fitness be impaired due to cancer treatments?

To date, few studies have directly investigated the mechanisms behind why cardiorespiratory fitness is often reduced in patients with cancer [134]. In a review article by Christensen et al. (2018), the authors summarise three factors that limit exercise adaptations (to increase $\dot{V}O_2\text{max}$) in cancer patients: reduced blood cells, blood volume and muscular impairment [12]. These three factors are all essential for determining cardiac output (blood volume) and the arterial-venous difference (reduced blood cells and muscular impairment), which further determine $\dot{V}O_2\text{max}$.

Adding one or several cancer treatment therapies to an already diseased body further complicates the question of why people with a current or previous cancer diagnosis often have impaired $\dot{V}O_2\text{max}$ compared with healthy individuals.

**Surgery**

Except for malignant lung cancer, for which a pulmonary resection may be performed, surgical removal of other types of tumours does not directly affect the $O_2$ cascade [70]. However, functional limitations, pain and long periods of bedrest and inactivity often follow surgery, and these factors are important consequences affecting cardiorespiratory fitness [70, 135].

**Radiation**

Ionising radiation causes fibrosis or a non-healing wound response, leading to a pro-inflammatory cascade in tissues, which disturbs the homeostatic control [136]. Together with the resulting excessive deposition of extracellular matrix and collagen, these events cause vascular damage and restrict blood supply (ischaemia) [70]. Moreover, off-target radiation to the heart and lungs may directly affect these systems, which are decisive for cardiorespiratory fitness [137]. Together, these adverse effects might contribute to reduced exercise tolerance by impairing pulmonary diffusion capacity and convective oxygen delivery [70].

**Systemic therapy**
Systemic therapy includes all therapies that affect the whole body (traditional chemotherapy drugs, targeted chemotherapy, hormonal therapies and biological therapies/immunotherapy).

Central roles for the underlying mechanisms for the chemotherapy-induced toxicity are the generation of reactive oxygen species and the induction of cardiac myocyte apoptosis or necrosis [68, 138, 139]. Bone-marrow damage and the lowered production of red blood cells, because of chemotherapy, can further cause anaemia. The number of red blood cells is commonly reduced as a consequence of cancer treatment (especially chemotherapy), thereby reducing the oxygen-carrying capacity of the blood [12]. This factor has been proven in clinical practice, in which people with anaemia have been given a blood transfusion or bone-marrow stimulating agents, observing an increased $\dot{V}O_2$max afterwards [70]. We know that total blood volume, including red blood cells (after ~2-3 weeks) and plasma volume (initial 2 weeks), is an early adaptation to exercise [129]. Increased blood volume leads to a higher venous return to the heart, higher cardiac filling and, consequently, a larger cardiac output [140], which again is the main contributor affecting $\dot{V}O_2$max. Dehydration is common in patients with cancer, which is explained by the saline content in several chemotherapy drugs or due to the use of steroid hormones [70]. Moreover, diarrhea, infections and bleeding can also lead to dehydration [70].

The final step of the $O_2$ delivery chain is the $O_2$ extraction from the blood to the muscles, which is controlled by intracellular capillary density and mitochondrial content. Regarding exercise adaptations at the muscular level, few studies have been published [12]. In a study by Mijwel et al., women with breast cancer were randomly assigned to either high-intensity AET (interval training), high-intensity RET or usual care for 16 weeks, and muscle biopsies were analysed. Over the intervention, citrate synthase activity (representing mitochondrial content), muscle fibre cross-sectional area, capillaries per fibre, and myosin heavy chain isoform type I were reduced in the usual care group; whereas, high-intensity RET and AET could counteract these declines [141]. The high-intensity AET was superior to the usual care and RET groups regarding the protein levels of the electron transport chain [141]. The authors explain the observed difference between exercise groups by the extra 20 minutes of moderate-intensity AET in this group, which indicates the importance of training volume and type of training in improving mitochondrial content [141], which has also been reported in healthy individuals [142]. In addition to negative effects on the $O_2$ transport capacity of the heart and the circulating system, direct consequences of chemotherapy to the skeletal muscles have been found as well [143].
Chemotherapy-induced muscle wasting may be induced through activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway [144]. Hormone therapy may also be associated with physiological consequences involving the oxygen cascade [70]. In women, unfavourable conditions (changes in lipid profile, insulin, glucose and C-reactive protein) supposedly affect cardiorespiratory fitness (e.g. by impairing convective oxygen delivery) in addition to increasing the risk of CVD [145]. For men receiving ADT, reduced LBM and increased fat mass are common [146]. Low levels of muscle mass are associated with low levels of cardiorespiratory fitness [147, 148]. Consequently, decreased muscle mass and, therefore, also reduced mitochondrial size and number, affects the final steps of the O₂ transport cascade. Among untrained individuals, V̇O₂max is suggested to be limited by the capacity of the mitochondria to consume oxygen, despite an excess of oxygen supply [149]. The effects of ADT on cardiac function in humans are unclear [70], but in a study in which male mice received ADT, these mice were found to have an impaired cardiac function compared with control animals [150].

Inhibition of tumour angiogenesis is one established cancer therapy. In addition to other essential functions, such as organ growth, wound healing and vascular repair, the inhibition of angiogenesis affects the exercise-induced vascular adaptations in skeletal muscles [151]. Inhibiting the vascular endothelial growth factor (VEGF) and related proteins may potentially have direct consequences on both convective and diffusive O₂ delivery within the O₂ cascade [70]. This therapy may lead to capillary damage in the skeletal muscle, contributing to poor exercise tolerance.

2.9 How exercise may affect cardiorespiratory fitness in patients with cancer – a focus on exercise frequency, intensity, type and time

We know that AET produces significant and clinically relevant beneficial changes in cardiorespiratory fitness in patients both during and after curative cancer treatment compared with non-exercising control groups [152, 153]. However, there is limited knowledge regarding how exercise should be prescribed (i.e. the FITT factors, Table 1) to induce beneficial changes in cardiorespiratory fitness during and after cancer treatment.
Table 1. Explanations of the FITT factors (from Hecksteden et al., 2018 [154]).

<table>
<thead>
<tr>
<th>Training characteristics</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Number of training sessions per day or week</td>
</tr>
<tr>
<td>Intensity</td>
<td>Absolute (velocity, weight and power output) and relative (percentage of ( \dot{V}O_{2\text{max}} ), HRR, HRmax, 1RM) load</td>
</tr>
<tr>
<td>Type</td>
<td>Movement execution and position, as well as functional domains (e.g. cardio-circulatory or/and neuromuscular)</td>
</tr>
<tr>
<td>Time (duration)</td>
<td>Duration and repetitions of one or multiple training stimuli and exercises (Volume = Frequency x Time)</td>
</tr>
</tbody>
</table>

Abbreviations: \( \dot{V}O_{2\text{max}} \) = maximal oxygen uptake; HRmax = maximal heart rate; HRR = heart rate reserve; 1RM = one repetition maximum.

There is considerable methodological heterogeneity in aspects related to study design and outcomes in studies published within the exercise-oncology field [153, 155]. The high heterogeneity makes it difficult to disentangle how each exercise characteristic potentially impacts an outcome (e.g. cardiorespiratory fitness). In the following sections, relevant studies suitable within each exercise characteristic are presented. However, since most studies investigating one or two of the FITT factors did not control for the other characteristics, especially total exercise volume, many studies could potentially have been presented under two or more of these four sections.

2.9.1 Frequency

Generally, there are few studies in which different exercise frequencies have been exclusively investigated in relation to the effect on changes in cardiorespiratory fitness in cancer patients. However, in a meta-analysis including 41 clinical trials in healthy adults (60-85 years old), measures of intensity, frequency and duration and their effect on \( \dot{V}O_{2\text{max}} \) were reported [156]. Huang et al. (2016) found that the peak \( \dot{V}O_{2\text{max}} \) adaptation from training was evident around a training frequency of 3.5 days/week. Both more and fewer exercise sessions per week produced smaller changes in \( \dot{V}O_{2\text{max}} \) [156].

Frequency depends on exercise duration and intensity, as illustrated by the PA recommendations for healthy individuals by the American College of Sports Medicine (ACSM) [103]. In the latest exercise guidelines for cancer survivors specified to affect different clinical outcomes positively (anxiety, depressive symptoms, fatigue, health-related quality of life, lymphedema and physical
function), the recommendations are generally three or two to three exercise sessions per week [102].

2.9.2 Intensity

There are few studies in which different exercise intensities have been directly compared in cancer populations. In the PACES study by van Waart et al. (2015), 230 women were randomly assigned to either moderate- to high-intensity combined supervised RET and AET (50-80% of estimated maximal workload), low- to moderate-intensity home-based PA (12-14 rating of perceived exertion [RPE] on the Borg scale), or usual care during treatment for breast cancer for six months [157]. The improvements in cardiorespiratory fitness, measured by a submaximal test, were larger in the combined, supervised exercise group (ES 0.45 vs ES 0.32 in the home-based AET group) compared with usual care [157]. Importantly, however, conclusions on the effect of exercise intensity per se could not be made.

In the REACT study by Kampshoff et al. (2015), 277 adults previously treated for different cancer diseases either performed AET (interval training) and RET at high intensity (HI) (≥80% of HRR) or at low-to-moderate intensity (LMI) (≥40-50% of HRR), or they were randomly assigned to a waiting list for 12 weeks [158]. Larger improvements in \( \dot{V}O_2 \) max were found in subjects performing AET and RET at HI compared with LMI, but the difference between the two intensity groups was not significant (0.90 [95% CI: -0.1 to 1.9] ml/kg/min) [158]. In Burnham et al. (2002), 18 breast cancer survivors were randomly assigned to either continuous AET at low (25-35% HRR) or moderate (40-50% HRR) intensity after finishing their treatment. The researchers found no differences in effect on cardiorespiratory fitness between exercise groups [159]. In Martin et al. (2015), 87 prostate cancer survivors and 72 breast cancer survivors (34-76 years old) were randomly assigned to either usual care or continuous AET at low intensity (60-65% of \( \dot{V}O_2 \) max) or HI (75-80% \( \dot{V}O_2 \) max), and no differences in \( \dot{V}O_2 \) max between intensity groups after 10 weeks of training were found [160]. However, a positive effect of HI exercise in the more long term was observed: \( \dot{V}O_2 \) max assessments four months post-intervention revealed that the HI group had preserved their positive training-induced change in \( \dot{V}O_2 \) max better than in the low-intensity group [160]. Dolan et al. (2016) found no differences in cardiorespiratory fitness between women treated for breast cancer performing either HIIT (70-100% \( \dot{V}O_2 \) max) or continuous moderate-intensity training (60-70% \( \dot{V}O_2 \) max) for six weeks [161]. In an RCT lasting only three weeks, female cancer survivors exercising at LMI (two weekly sessions of 75 min of 60%
HR_{peak}) were found to have significantly larger improvements in $\dot{V}O_2$max than the group performing HIIT (three weekly sessions, eight intervals of one min at >95% HR_{peak}) [162]. It is notable that the total exercise volume was largest in the LMI group, potentially explaining these findings [162]. In two publications by Devin et al. from 2016 (n=39) and 2018 (n=57), colorectal cancer survivors were randomly assigned to either HIIT (85-95% HR_{peak}) or moderate-intensity (70% HR_{peak}) AET for four (2016) or eight weeks (2018), with a mean start-up of approximately 1.5 to 3.5 years post-treatment [163, 164]. In both publications, cardiorespiratory fitness was found to increase significantly more when performing HIIT compared with LMI [163, 164]. Devin et al. mention that they did not have full control of total exercise volume, but that they assumed this to be similar across the two groups [163].

In a recent meta-analysis, patients or survivors from mixed cancer diagnoses in different phases of the cancer trajectory (before surgery, during or after treatment) were investigated [165]. In four studies (described above), HIIT was compared with LMI continuous exercise [161-164], and in five studies, HIIT was compared with usual care [161, 166-169]. Unsurprisingly, the meta-analysis results revealed that HIIT produces significantly positive changes in $\dot{V}O_2$max compared with usual care [165]. The authors found no additional benefit of HIIT in the four studies in which HIIT was compared with moderate intensity exercise, but suggest that HIIT is more time-efficient for producing improvements in $\dot{V}O_2$max [165]. However, in this meta-analysis, Mugele et al. (2019) did not differentiate between cancer types or the timing of exercise intervention in relation to treatment, which should be remembered when interpreting the results.

In healthy elderly people with a mean age of 67.6 ± 5.3, Huang et al. (2016) found that the degree of improvements in cardiorespiratory fitness increased with increasing exercise intensity [156]. However, an intensity ceiling was found around 70 to 73% of HRR, and higher intensities did not induce further enhancements in $\dot{V}O_2$max [156].

In summary, there seems to be a dose-response relationship between exercise intensity and improvements in cardiorespiratory fitness in patients who have finished their treatment [158, 163, 164]. For patients exercising during chemotherapy, a beneficial effect of increasing intensity has been suggested [157]. However, the knowledge base is very limited, and more insight into the relationship between intensity and changes in $\dot{V}O_2$max is needed, with a focus on controlling for exercise volume.
2.9.3 Type

Exercise interventions aiming to affect cardiorespiratory fitness positively consist primarily of AET, either alone or in combination with RET. To our knowledge, within the exercise-oncology field, there are no studies in which different endurance types or modalities (e.g. cycling, walking/running, skiing and swimming) are compared. Moreover, it is difficult to summarise the studies that have compared continuous vs interval AET, since these studies naturally differ in relation to exercise intensity, duration and frequency as well. Therefore, the potential studies suitable for this particular ‘type’ section are described under the ‘intensity’ section [161-164] and summarised in the meta-analysis by Mugele et al. (2019) [165].

Under this ‘type’ section, another definition of type of training is interesting to elucidate: RET and AET have been compared in some studies involving cancer patients. In Courneya et al. (2007), 242 patients undergoing treatment for breast cancer were randomly assigned to either AET or RET. Not surprising, a more beneficial change in cardiorespiratory fitness was observed in women performing AET, compared to RET [22]. Interestingly, in men receiving ADT for prostate cancer (n=121), both 24 weeks of RET (+1.5 ml/kg/min) and AET (+1.4 ml/kg/min) mitigated the decline in VO₂max observed in the usual care group [93].

2.9.4 Time (duration)

Few studies have investigated the exercise characteristic time, in general, and particularly within the exercise-oncology field. Again, in the meta-analysis by Huang et al. (2016), in which FITT factors were investigated in healthy older adults, it was found that approximately 45 minutes was the most effective session duration to induce VO₂max gain. Exercise sessions lasting longer than 50 min provided no more benefits but led to a decline in VO₂max gain [156].

In 2013, Courneya et al. investigated the effect of RET vs AET and the total exercise volume (combination of intensity and duration) among 301 women undergoing chemotherapy treatment for breast cancer. The exercise intensity (70-75% of VO₂peak) was the same for all three groups. The STAN group exercised 75 min/week AET spread over three days/week. In the HIGH group, the duration was doubled (150 min/week), and for the COMB group, RET was included three days/week in addition to AET 75 min/week. The authors found that the HIGH exercise group preserved VO₂max better (-2.5 ml/kg/min) than the STAN exercise group (-3.4 ml/kg/min) [170].
2.10 Challenges by performing maximal testing on patients with cancer

One important challenge with exercise testing in general is that we can never be completely certain that the subjects being tested have performed to their exhaustion and thereby reached their physiological limits. Additionally, when we perform maximal tests in various patient groups and among the elderly, this uncertainty is possibly even more prominent than in healthy young adults [171]. Due to individual experiences with exercise, in addition to how exertion and effort are perceived in both healthy and diseased populations, objective criteria verifying $\dot{V}O_2$max are important to include when performing such tests [172].

Physically inactive individuals with little or no previous experience with exercise may have more difficulties motivating and pushing themselves than those familiar with exercise, and they are also more likely to reach their perceived maximal exertion before they actually attain their ‘true’ $\dot{V}O_2$max [175]. In a selection of patients diagnosed with cancer, heterogeneity may be especially large as they are often old [173], unfit [6] and may suffer from comorbidities and side effects such as fatigue or pain [66, 174].

2.10.1 Considerations before initiating maximal oxygen uptake tests

To ensure the high validity and reliability of a $\dot{V}O_2$max test (i.e. capable of being replicated), accurate instruments and experienced personnel are important in all aspects related to conducting the test. Regular equipment calibration is critical to ensure that exercise test data are reliable and valid [130], and, optimally, calibrations should be performed prior to each test [176]. Before commencing the test, the participants should be familiarised with the equipment (e.g. wearing the mask and walking on the treadmill). The choice of test protocol and test modality should be made based on the individual/population being tested. The participants should not perform strenuous physical activity on the test day or the day before, or drink much or eat anything two hours before the test, and they should wear suitable clothes and shoes.

2.10.2 Test protocol, data acquisition and treadmill vs cycle tests

In addition to the aforementioned higher $\dot{V}O_2$max results generally found in treadmill vs cycle tests, protocol design variables such as stage length, workload increment per stage, and total test duration may individually affect the result variables [177]. Shorter and faster test protocols result in higher RERpeak values compared with ramp tests of longer durations [178]. Commonly used maximal treadmill stress tests are Balke, Bruce, Ellestad and a continuous multistage
running protocol, and these have been found to correlate highly [179]. There are different increases in energy requirements (from one stage to the next) across these protocols, with Balke having the most gradual rate of progression (~1 Metabolic equivalents (MET) per minute) [180]. The test protocol should be chosen based on the test persons’ assumptions, but in clinical trials it is practical and more feasible to standardise one protocol for the entire sample. The modified Balke protocol is popular in clinical settings in which patients with low functional capacities are being tested, since the MET values in the initial stages are very low [180]. The protocol should be adapted so that the test duration is 8 to 12 minutes following a warm-up period of about five minutes [176, 180].

In a study by Robergs et al. (2010)[181], 75 responders experienced with performing exercise tests using indirect calorimetry answered a questionnaire. Methods of processing to remove the variability in sequential $\dot{V}O_2$ measurements varied widely, and consisted of time averages (30 sec [38%], 60 sec [18%], 20 sec [11%], 15 sec [8%]), a moving average of 5 to 11 breaths (10%), and the middle five of seven breaths (7%). The remaining 8% of respondents used even shorter durations or rolling averages of breath-by-breath data. These findings illustrate that there is a broad variety of methods being used. The majority of respondents reported that they used between 0.5- and 1-minute time averages [181].

2.10.3 The test leader

The results from a $\dot{V}O_2$max test rely heavily on the willingness to allow the participant to exercise to exhaustion [182]. The test leader’s subjective evaluation of whether a $\dot{V}O_2$max test is performed to exhaustion is an important aspect when considering the validity of $\dot{V}O_2$max tests. Although evaluations are based on predefined observations of body language and facial expressions, subjectivity remains part of the test leader’s evaluation. Supposedly, in practice, there are different approaches to how test leaders behave towards the person being tested before and during the test. How test personnel verbally encourage the person being tested is an example of possible bias that may affect the test results [183-185]. Importantly, experience with and qualifications in performing exercise tests are crucial for understanding the response variables presented by the software program during the test, and at the same time manage to observe the body and facial language of the person on the treadmill/cycle [186]. Submaximal results may occur if the test leader is inexperienced and acts too ‘kind’; meaning that he/she does not push the exercising person thoroughly enough or even terminates the test before a maximal effort has been reached, of various reasons (e.g. the
cancer diagnosis, comorbidities or age). Maybe speculative, but the test-leader may be even more afraid to push their patient when they have a cancer diagnosis.

2.10.4 $\text{VO}_2\text{peak} \text{ vs } \text{VO}_2\text{max}$

The terms $\text{VO}_2\text{peak}$ and $\text{VO}_2\text{max}$ are often used interchangeably in the literature, causing difficulties for the reader to interpret the results, both in relation to pre- and post-exercise intervention testing and the results between studies. A common definition of the two terms is that $\text{VO}_2\text{peak}$ is the highest value attained during exercise and represents an individual’s exercise tolerance; whereas, $\text{VO}_2\text{max}$ represents the highest physiologically attainable value [187]. Hence, ‘a $\text{VO}_2\text{max}$ is always a peak, but a peak is not always maximal’ [177].

If results from submaximal tests (i.e. a maximal effort was not achieved) are used in the planning of and in prescribing exercise, a consequence of this is that exercise intensity prescriptions are too low. Thus, the effect of the planned intensity is not properly evaluated. Furthermore, if the aim of an exercise intervention study is to compare the effect on $\text{VO}_2\text{max}$ and other clinical outcomes in two groups exercising at different intensities, the invalid data would introduce biased results [175].

Moreover, comparisons of results across studies are complicated if we rely on invalid data regarding cardiorespiratory fitness. To be able to state that a subject has reached his/her highest physiologically attainable value, certain objective criteria need to be defined prior to the exercise test.

2.10.5 Criteria for verifying $\text{VO}_2\text{max}$

When evaluating whether a maximal effort has been made during a $\text{VO}_2\text{max}$ test, a set of markers (criteria and cut-points) of exhaustion is often applied. The most widely used objective criterion, a plateau or levelling off in $\text{VO}_2$ with increasing workload, has been the subject of extensive debate over the past 20 to 30 years. The debate has especially concerned the definition of the $\text{VO}_2$ plateau, whether a plateau exists and the general validity in using this criterion to determine ‘true’ $\text{VO}_2\text{max}$ [179, 188-192]. Due to these controversies and the fact that there are enormous variations in the number of subjects fulfilling this plateau criterion in different studies [193], secondary criteria are used in the evaluation of $\text{VO}_2\text{max}$ tests.
Among these secondary criteria, estimated peak HR, peak respiratory exchange ratio (RER), blood lactate (BLa) and self-reported Borg’s RPE Scale6-20 with a variety of cut-offs are reported in the literature [178, 194]. How well these secondary end-criteria are associated with VO₂max is not well validated; they all have pros and cons; hence, the criteria and their cut-points have been discussed in the literature [172, 178, 194, 195]. Furthermore, there is no consensus on how to apply these criteria in various populations, including cancer patients [172], but some suggestions have been made for healthy athletes [194], healthy adult subjects between 20 and 85 years old [196], and for overweight, obese adults [197, 198]. Based on 861 healthy individuals performing an exercise test on a treadmill until exhaustion, Edvardsen et al. recommend the following specific RER cut-points to use in the validating of maximal effort for different age groups: RER ≥ 1.10 (20–49 years old), RER ≥ 1.05 (50–64 years old) and RER ≥ 1.00 (≥ 65 years old). In addition to the mentioned criteria, respiratory frequency (f_R) has been suggested to be a valid variable for defining maximal effort [199], but to our knowledge, f_R has not been used as a criterion in VO₂max testing.
3 GAPS IN THE LITERATURE

In the exercise-oncology field, there are several RCTs in which the effect of exercise on cardiorespiratory fitness has been evaluated. Nevertheless, there remains a lack of tailored recommendations (i.e. how the exercise characteristics of frequency, intensity, time/duration and type [the FITT factors] should be prescribed) for patients undergoing treatment for different types of cancer. Single studies cannot individually provide answers to how exercise should be prescribed most efficiently to induce beneficial changes in cardiorespiratory fitness, especially controlling for all the other FITT factors. However, by pooling data from single studies, it is possible to investigate each of these exercise characteristics and their ability to induce beneficial changes to cardiorespiratory fitness.

Although there are some RCTs that investigated the effect of one exercise intervention compared with a control group, there is a lack of studies in which the design enables the comparison of one exercise characteristic (isolated, controlling for other exercise characteristics) with different outcomes. Hence, there is a need for studies in which the effects of exercising at different intensities on cardiorespiratory fitness are investigated. The randomised multicentre clinical trial of Phys-Can (Physical training and Cancer) examined the effect of low-to-moderate vs. high-intensity exercise on cardiorespiratory fitness, in addition to a variety of clinical outcomes, contributing to an increase in the knowledge base within the exercise-oncology field.

When assessing cardiorespiratory fitness, a maximal oxygen uptake (VO$_2$max) test is acknowledged as the gold standard. When verifying that VO$_2$max has been reached, the typical criteria applied are a plateau in oxygen uptake and certain thresholds within peak values of RER, predicted HR$_{max}$, RPE and post-exercise Bla'. Both within clinical populations and among healthy individuals, no consensus has been agreed regarding which criteria and cut-points to apply when verifying VO$_2$max. To our knowledge, there are no published studies in which criteria verifying VO$_2$max within a population of cancer patients have been investigated; consequently, there is a need to elucidate this matter.
4 AIMS AND OBJECTIVES

The overall aim of this present thesis is to address how exercise at different intensity levels may affect cardiorespiratory fitness from the time of diagnosis until post-treatment. A secondary aim is to increase the validity of cardiorespiratory fitness tests among patients diagnosed with cancer.

More specifically, the objectives are as follows:

1. Describe the peak values and fulfilment of various \( \dot{V}O_2 \text{max} \) criteria in a population of newly diagnosed patients with breast, prostate and colorectal cancer (Paper II).

2. Determine which criteria and cut-points are best associated with the test leader’s subjective evaluation of whether the cardiorespiratory fitness tests were defined as ‘to exhaustion’ (Paper II).

3. Investigate the exercise-induced effect on \( \dot{V}O_2 \text{max} \) during cancer treatment (Paper I).

4. Study how exercise frequency, intensity and duration can influence training-induced changes in \( \dot{V}O_2 \text{max} \) among patients with cancer who are receiving (neo-)adjuvant treatment (Paper I), with an extra focus on intensity and how adherence to the exercise may affect the results (Paper III).
5 METHODS AND MATERIALS

As basis for the present PhD thesis, a systematic review with a meta-analysis was first conducted, representing Paper I. Further, in Paper II, baseline-data from the Phys-Can intervention study were used to describe the fulfilment of different criteria cut-points and to find ‘new’ criteria verifying \( \dot{V}O_2 \text{max} \) in this population. The results were applied on a control sample; participants from the Phys-Can cohort study. Last, \( \dot{V}O_2 \text{max} \) results from pre- and post-exercise in Phys-Can intervention study were analysed and presented in Paper III (as one of the secondary outcomes investigated).

5.1 Systematic review (Paper I)

The systematic review was performed according to the PRISMA 2009 checklist [200]. A systematic search based on predefined inclusion and exclusion criteria was performed, followed by data extraction and risk-of-bias assessment of included studies. Further, studies eligible for the systematic review were also included in the meta-analysis if adequate data were possible to extract.

5.1.1 Subjects and search strategy

*Inclusion and exclusion criteria*

The meta-analysis included RCTs of adult (>18-year old) patients with cancer where the effects of an exercise intervention with an AET component during treatment compared with a usual care control group was evaluated. Studies in patients with all cancer types during (neo-)adjuvant treatments (radiotherapy, chemotherapy, radio chemotherapy, or hormone therapy) with curative intent were included. Furthermore, studies were included if the cardiorespiratory fitness test was conducted pre- and post-exercise intervention, directly through measures of maximal oxygen uptake or indirectly by estimating \( \dot{V}O_2 \text{max} \) from a maximal exercise test. We excluded studies in which patients participated in an exercise intervention before or after surgery and did not receive any concurrent adjuvant cancer treatment, studies evaluating combined lifestyle interventions, for example interventions focusing on exercise and diet or other medical/dietary supplements, studies investigating patients both during and after treatment, and studies that examined cardiorespiratory fitness using a submaximal exercise test.

If relevant information regarding FITT factors and \( \dot{V}O_2 \text{max} \) in both patients randomised to the exercise group and the control group could be collected from the published paper, or via correspondence with the author, they were included in
the meta-analysis. If this information could not be derived, the study was only included in the systematic review.

Search strategy

Through OvidSP, an electronic search in the databases Medline and Embase was performed (Table 2). To identify relevant papers, the search was based on predefined terms regarding population, intervention, comparison, and outcome (PICO terms) using MeSH terms and free text: Population (P): patients with cancer who are undergoing (neo-)adjuvant cancer treatment; Intervention (I): supervised and unsupervised physical exercise interventions involving an aerobic component; Comparison (C): patients receiving standard care, on a waiting list, or on attention control; and Outcome (O): cardiorespiratory fitness. The literature search was conducted in April 2016 and updated in January 2019. Reviews and references of relevant papers were searched for additional studies.
Table 2. The search string for the systematic search.

| 1. exp neoplasms/                      |
| 2. (cancer or neoplasm* or tumor*).ti,ab. |
| 3. 1 or 2                              |
| 4. exp exercise/ or exercise*.ti,ab.    |
| 5. exertion*.ti,ab.                     |
| 6. training.ti,ab.                      |
| 7. running.ti,ab.                       |
| 8. (physical adj1 activ*).ti,ab.        |
| 9. (workout or work out).ti,ab.         |
| 10. 4 or 5 or 6 or 7 or 8 or 9          |
| 11. exercise test/                      |
| 12. ((o2 or oxygen) adj (uptake or consumption*)).ti,ab. |
| 13. vo2max.ti,ab,hw.                   |
| 14. fitness/                           |
| 15. fitness.ti,ab.                      |
| 16. aerobic capacity/                   |
| 17. aerobic capacit*.ti,ab.             |
| 18. physical endurance/                 |
| 19. physical fitness/                   |
| 20. fitness.ti,ab,hw                    |
| 21. exp oxygen consumption/             |
| 22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 |
| 23. 3 and 10 and 22                     |
| 24. clinical trial/ or controlled study/ or randomized controlled trial/ |
| 25. (intervention* or rct or trial or trials or randomized).ti,ab,hw. |
| 26. 24 or 25                            |
| 27. 23 and 26                           |

The electronic search-string in the databases Medline and Embase, through OvidSP

5.1.2 Study selection

While only one reviewer removed duplicates and screened titles and abstracts for eligibility, we were two researchers conducting the full-text assessments. After evaluating eligible studies for the meta-analysis, two additional reviewers also reviewed and accepted the decisions regarding inclusion of studies. Details concerning study inclusion are provided in the following flow-chart (Fig. 1).
As displayed in Fig. 1, 14 RCTs were included in the systematic review according to the predefined criteria. Five studies did not present sufficient data to calculate effect sizes, but we obtained data from four studies [201-204] through author correspondence. For one study, we were unable to obtain data to calculate effect sizes [15], resulting in a total of 13 studies included in the meta-analysis. One study [204] presented results for female and male patients separately and was included separately, thus resulting in 14 comparisons in the meta-analysis.
5.1.3 Extraction of data

Two reviewers independently extracted information regarding the study population: country, cancer site, disease stage, medical treatment, number of patients at baseline and at follow-up, age, and sex. Both reviewers also independently extracted the characteristics of the exercise interventions, methods of $\dot{V}O_2$max testing, and post-intervention $\dot{V}O_2$max scores or changes from baseline (in l/min, ml/min, ml/min/kg, or metabolic equivalents of task [METs]). The outcomes of patients randomised to the exercise and control groups were derived via correspondence with the author if this information could not be retrieved from the papers.

5.1.4 Study characteristics

The 14 studies included in the systematic review [15, 22, 90, 93, 201-210] involved 1332 patients (range, 14–269 patients per study), with 751 in the intervention group and 581 in the control group (Table 3). The patients’ mean age varied from 45 to 69 years, and 70% of the participants were women. Various cancer types and (neo-)adjuvant treatments were represented (Table 3).
Table 3. Overview of the study characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cancer site</th>
<th>Disease stage</th>
<th>Treatment</th>
<th>No, baseline/follow-up</th>
<th>Age (mean)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamsen et al., 2009</td>
<td>Denmark</td>
<td>Mixed</td>
<td>all</td>
<td>Adj Ch</td>
<td>AET+RET: 135/118, CO: 134/117</td>
<td>47</td>
<td>73</td>
</tr>
<tr>
<td>Alibhai et al., 2015</td>
<td>Canada</td>
<td>AML</td>
<td>all</td>
<td>Adj Ch</td>
<td>AET+RET: 57/43, CO: 24/19</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>Al-Majid et al., 2015</td>
<td>USA</td>
<td>Breast</td>
<td>I-II</td>
<td>Adj Ch</td>
<td>AET: 7/6, CO: 7/6</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>Courneya et al, 2007</td>
<td>Canada</td>
<td>Breast</td>
<td>I - IIIa</td>
<td>Adj Ch</td>
<td>AET: 78/71, CO: 82/73</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>Drouin et al., 2005</td>
<td>Canada</td>
<td>Breast</td>
<td>I - IIIc</td>
<td>RT</td>
<td>AET:13/13, CO:10/7</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>Griffith et al., 2009</td>
<td>USA</td>
<td>Mixed</td>
<td>I-III</td>
<td>RT, Ch or BT</td>
<td>AET: 73/68, CO: 65/58</td>
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<td>61</td>
</tr>
<tr>
<td>Hornsby et al., 2014</td>
<td>USA</td>
<td>Breast</td>
<td>IIB-IIIC</td>
<td>Neoadj Ch</td>
<td>AET: 10/9, CO: 10/10</td>
<td>49</td>
<td>100</td>
</tr>
<tr>
<td>Kim et al., 2006</td>
<td>USA</td>
<td>Breast</td>
<td>I-IIB</td>
<td>Adj Ch and/or RT</td>
<td>AET: 37/22, CO: 37/19</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>MacVicar et al., 1989</td>
<td>USA</td>
<td>Breast</td>
<td>II</td>
<td>Adj Ch</td>
<td>AET: 18, CO: 16</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>Monga et al., 2007</td>
<td>USA</td>
<td>Prostate</td>
<td>all</td>
<td>RT</td>
<td>AET: 11, CO: 10</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>Segal et al., 2009</td>
<td>Canada</td>
<td>Prostate</td>
<td>I-IV</td>
<td>RT, some ADT</td>
<td>AET: 40/40, CO: 41/41</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td>Travier et al, 2015</td>
<td>Netherland</td>
<td>Breast</td>
<td>M0</td>
<td>Adj Ch</td>
<td>AET: 102/87, CO: 102/77</td>
<td>49</td>
<td>100</td>
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<tr>
<td>Uth et al, 2014</td>
<td>Denmark</td>
<td>Prostate</td>
<td>all</td>
<td>ADT</td>
<td>AET: 29/26, CO: 28/23</td>
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<tr>
<td>Van Vulpen et al, 2016</td>
<td>Netherland</td>
<td>Colon</td>
<td>M0</td>
<td>Adj Ch</td>
<td>AET: 17/15, CO: 16/13</td>
<td>58</td>
<td>41</td>
</tr>
</tbody>
</table>

Abbreviations: Adj, adjuvant; AET, aerobic exercise training; ADT, androgen deprivation therapy; AML, acute myeloid leukemia; BT, brachytherapy; Ch, chemotherapy; CO, control; M0, no distant metastasis, Neoadj, neoadjuvant; RET, resistance exercise training; RT, radiotherapy
5.1.5 Exercise intervention characteristics

The classification of prescribed exercise intensity was based on the American College of Sports Medicine guidelines [211], and the input for classification was information on the prescribed intensity. If the prescribed exercise intervention in a study had an intensity range that overlapped two intensity levels (i.e., low and moderate), the study was referred to by these two intensities (i.e., low–moderate intensity). Consequently, five categories were defined: low, low–moderate, moderate, moderate–high, and high intensity. Exercise intensity was indicated by the value of METs; we used a value of 1.5 METs to indicate low intensity, 3.0 METs to indicate low–moderate intensity, 4.5 METs to indicate moderate intensity, 6.0 METs to indicate moderate–high intensity, and 7.5 METs to indicate high intensity exercise [212]. We calculated the weekly exercise volume as follows: exercise intensity (MET value) × duration × frequency.

See Table 4 for detailed exercise intervention characteristics. The median frequency of exercise was 3 days/week (range: 2–5 days/week); seven studies prescribed ‘high’ intensity exercise [15, 22, 93, 205, 208-210], five ‘moderate–high’ [90, 201, 203, 204, 206], and two ‘low–moderate’ [202, 207] intensity exercise. The median duration of exercise sessions was 35 min (range, 27–90 min) and the median duration of the interventions was 11.5 weeks (range, 5–24 weeks). The median weekly exercise duration was 120 min (range, 80–270 min), and the median weekly exercise volume was 720 MET min/week (range: 390–2025 MET min/week).
Table 4. Characteristics of the exercise interventions and methods for testing cardiorespiratory fitness.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Freq./wk</th>
<th>Intended int. range</th>
<th>Int. cat.</th>
<th>Int. monitoring</th>
<th>Duration range/session, in min.</th>
<th>Mean, in min.</th>
<th>Modality (cont. / interval.)</th>
<th>Weekly min. and MET’s</th>
<th>Fitness test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamsen et al., 2009</td>
<td>6 wk AET+RET Superc.</td>
<td>6</td>
<td>85-95% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>High</td>
<td>HR</td>
<td>90 **</td>
<td>90</td>
<td>CE (interval)</td>
<td>270 min 2025 MET’s</td>
<td>CE Indirect</td>
</tr>
<tr>
<td>Alibhai et al., 2015</td>
<td>5 wk AET+RET Superc.</td>
<td>2-3</td>
<td>50-75% HRR</td>
<td>Mod-High</td>
<td>HR, BORG</td>
<td>30-60 **</td>
<td>45</td>
<td>CE, TM, Walk. (cont.)</td>
<td>203 min 1215 MET’s</td>
<td>TM Indirect</td>
</tr>
<tr>
<td>Al-Majid et al., 2015</td>
<td>11 wk AET Superc.</td>
<td>2-3</td>
<td>50-80% HRR</td>
<td>Mod-High</td>
<td>HR</td>
<td>30-40</td>
<td>33</td>
<td>TM (cont.)</td>
<td>82 min 494 MET’s</td>
<td>TM Direct</td>
</tr>
<tr>
<td>Courneya et al., 2007</td>
<td>17 wk AET Superc.</td>
<td>2-3</td>
<td>60-80% VO&lt;sub&gt;2max&lt;/sub&gt;</td>
<td>High</td>
<td>NA</td>
<td>15-45</td>
<td>27</td>
<td>CE, TM, ET (cont.)</td>
<td>80 min 603 MET’s</td>
<td>TM Direct</td>
</tr>
<tr>
<td>Drouin et al., 2005</td>
<td>7 wk AET Unsup.</td>
<td>3-5</td>
<td>50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Low-Mod</td>
<td>HR</td>
<td>20-45</td>
<td>33</td>
<td>Walk. (cont.)</td>
<td>130 min 390 MET’s</td>
<td>TM Direct</td>
</tr>
<tr>
<td>Griffith et al., 2009</td>
<td>13 wk AET Unsup.</td>
<td>5</td>
<td>50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Low-Mod</td>
<td>NA</td>
<td>25-35</td>
<td>30</td>
<td>Walk. (cont.)</td>
<td>150 min 450 MET’s</td>
<td>TM Direct</td>
</tr>
<tr>
<td>Hornsby et al., 2014</td>
<td>12 wk AET Superc.</td>
<td>3</td>
<td>60-100% VO&lt;sub&gt;2peak&lt;/sub&gt;</td>
<td>High</td>
<td>HR</td>
<td>20-45</td>
<td>31</td>
<td>CE (cont. + interval)</td>
<td>92 min 686 MET’s</td>
<td>CE Direct</td>
</tr>
<tr>
<td>Kim et al., 2006</td>
<td>8 wk AET Superc.</td>
<td>3</td>
<td>60-70% VO&lt;sub&gt;2peak&lt;/sub&gt;</td>
<td>High</td>
<td>HR</td>
<td>35</td>
<td>35</td>
<td>CE, TM, Walk. (cont.)</td>
<td>105 min 788 MET’s</td>
<td>TM Direct</td>
</tr>
<tr>
<td>MacVicar et al., 1989</td>
<td>10 wk AET Superc.</td>
<td>3</td>
<td>60-85% HRR</td>
<td>High</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CE (interval)</td>
<td>NA NA NA NA NA NA</td>
<td>NA NA NA NA NA</td>
</tr>
<tr>
<td>Monga et al., 2007</td>
<td>8 wk AET Superc.</td>
<td>3</td>
<td>65% HRR</td>
<td>High</td>
<td>HR</td>
<td>45-50</td>
<td>48</td>
<td>Walk. on TM (cont.)</td>
<td>143 min 1069 MET’s</td>
<td>TM Indirect</td>
</tr>
</tbody>
</table>

36
Table 4 continues

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Intervention</th>
<th>Frequency</th>
<th>HR max (%)</th>
<th>VO2peak</th>
<th>HRR</th>
<th>Intensity</th>
<th>Heart Rate</th>
<th>Duration</th>
<th>MET's</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segal et al., 2009</td>
<td>24 wk</td>
<td>AET Superv.</td>
<td>3</td>
<td>60-75%</td>
<td>High</td>
<td>HR</td>
<td>20-45</td>
<td>33</td>
<td>98 min</td>
<td>731 MET's</td>
<td>TM Direct</td>
</tr>
<tr>
<td>Travier et al., 2015</td>
<td>18 wk</td>
<td>AET+RET Superv.</td>
<td>2</td>
<td>70-90%</td>
<td>Mod-High</td>
<td>HR,</td>
<td>60</td>
<td>** NA (interval)</td>
<td>120 min</td>
<td>720 MET's</td>
<td>CE Direct</td>
</tr>
<tr>
<td>Uth et al., 2014</td>
<td>12 wk</td>
<td>AET Superv.</td>
<td>2-3</td>
<td>70-100%</td>
<td>Mod-High</td>
<td>HR</td>
<td>45-60</td>
<td>56</td>
<td>140 min</td>
<td>837 MET's</td>
<td>CE Direct</td>
</tr>
<tr>
<td>VanVulpen et al., 2016</td>
<td>18 wk</td>
<td>AET+ RET Superv.</td>
<td>2</td>
<td>70-90%</td>
<td>Mod-High</td>
<td>HR</td>
<td>60</td>
<td>** NA (interval)</td>
<td>120 min</td>
<td>720 MET's</td>
<td>CE Direct</td>
</tr>
</tbody>
</table>

*Reported post-intervention, with HR registrations. **minutes including both AET and RET. ***Intensity categories based on intended intensity (range) and ACSM’s guidelines. #Informed through author correspondence. Weekly duration: session duration x frequency. Weekly MET’s: weekly duration x MET value representing target intensity. Abbreviations: AET, aerobic exercise training; BORG, perceived exertion (6-20/1-10); cat, categories; CE, cycle ergometry; cont., continuous exercise; ET, elliptical trainer; Freq., frequency; HR, heart rate; HR max, heart rate maximum; HRR, heart rate reserve; int., intensity; MET’s, Metabolic equivalents; min., minutes; NA, not available; RET, resistance exercise training; Superv., Supervised exercise; TM, treadmill; VO2max/peak, maximum/peak oxygen consumption; Unsup., Unsupervised exercise; wk., weeks; Walk., Walking.
5.2 Phys-Can, design (Paper II and III)

The Phys-Can study was a multicentre, stratified, randomised controlled trial. Participants were recruited from three University hospitals in Sweden; Uppsala, Lund/Malmö and Linköping. The study was performed between March 2015 and November 2018 [213].

The study had a 2x2 factorial design, where both main effects and interactions between factors could be studied. Patients with newly diagnosed breast, colorectal or prostate cancer were randomised to one of the following four groups; A) individually tailored high intensity training twice a week with (H+BM) or without behavioural change support (BCS) strategies (H), or B) individually tailored low-moderate intensity training twice a week with (LM+BM) or without BCS strategies (LM).

The main aim of the Phys-Can intervention study was to determine the effects of low-to-moderate vs. high intensity exercise with or without supplementary BCTs on cancer-related fatigue in people undergoing cancer treatment. Secondarily, to determine the effects on health-related quality of life, anxiety/depression, function in daily life, cardiorespiratory fitness, muscle strength, PA, sedentary time, sleep and chemotherpay/radiotherapy completion rates.

Cancer related fatigue (main outcome in Paper III) was found to be lower in patients randomised to exercise at HI, compared with LMI (adjusted mean difference -1.11 95% CI -1.91 to -0.30) (Tables 4 and 6 in Paper III) after the six-months exercise intervention. This group difference was not clinically significant. However, the responder analysis indicated a clinically important improvement in physical fatigue in ~55% of patients in the HI exercise groups, compared with ~46% in the LMI exercise groups (Table 7 in Paper III).

For the present thesis, the focus is directed towards one of the secondary outcomes; cardiorespiratory fitness assessed by a maximal oxygen uptake ($\dot{V}O_2$max).

Since the focus in the present thesis is on the effect of exercise intensity on $\dot{V}O_2$max, and not on the influence of BCS, the four exercise groups are merged into two (‘High intensity’ and ‘Low-Moderate intensity’) in the consort diagram of flow of participants through the Phys-Can study (Fig. 2).

In addition, a group of patients was included in a control cohort (usual care only, for six months) to test out the cut-points derived through the ROC analysis.
Patients allocated for the control cohort were recruited between September 2014 and February 2015, thus before the inclusion of patients to the intervention study started.

Figure 2. CONSORT diagram of flow of participants through the Phys-Can study. Numbers with (in)complete baseline and follow-up data are based on VO\textsubscript{2}max assessment. Follow-up refers to data collected at the end of the 6-month intervention. HI: High intensity exercise; LMI: Low-to-moderate intensity exercise, BCS; additional behaviour change support.
5.2.1 Inclusion criteria

Eligible participants were adults (≥18 years) who could understand and speak Swedish and were newly diagnosed with breast, prostate or colorectal cancer. They were scheduled to begin neoadjuvant chemotherapy (breast cancer) or adjuvant chemotherapy (breast and colorectal cancer) and/or adjuvant radiotherapy (breast cancer) and/or adjuvant endocrine therapy (breast cancer) or radiotherapy with curative intent with or without additional endocrine therapy (prostate cancer).

5.2.2 Exclusion criteria

Persons were not eligible if they had stage IIIb-IV breast cancer, were not able to perform basic activities of daily living, showed cognitive disorders or severe psychiatric disease, suffered from other disabling co-morbid conditions that might contraindicate high intensity physical exercise (e.g. severe heart failure, severe chronic obstructive pulmonary disease, orthopaedic conditions, neurological disorders or fibromyalgia), had an additional ongoing malignant disease, had BMI<18.5kg/m\(^2\) or were pregnant.

All persons evaluated as eligible by a cancer specialist were contacted by a member of the research staff who provided verbal and written information about the study. Those who agreed to participate in the study gave their written informed consent before baseline data collection.

5.2.3 Cardiorespiratory fitness test

The participants were told not to eat and drink else than water the last 2 hours before the maximal oxygen uptake (\(\dot{V}O_2\)max) test measuring cardiorespiratory fitness. Before the test, at the test-location, height and body mass were measured to the nearest 0.5 cm and 0.1 kg, respectively, while wearing light clothes and no shoes [213]. Participants performed a graded exercise test on a motorized treadmill (see Table 5 for the different treadmills) using a modified Balke protocol. Following a 5-min warm-up with increasing workload, participants started at 4 km/h with an inclination of 2%. The inclination increased with 1% each minute until reaching 12%, from which only the speed increased 0.5 km/h per minute until exhaustion [213] (Table 6). Expired gas was collected continuously using the different gas-analysers and software-programs presented in Table 5.
To assess rate of perceived exertion (RPE), Borg scale 6-20 was applied during and at the end of the \( \dot{V}O_2 \text{max} \) test [214]. Instructions in the use of this scale were given before the test. During the tests, HR was measured using the equipment presented in Table 5. The peak average over 5 or 15 seconds was used when presenting HRpeak. Regarding \( \dot{V}O_2 \), RER and breathing frequency (\( f_R \)), the highest mean minute (independent of each other) within the duration of the test was reported as peak values.

**Table 5.** The equipment used at the three hospital sites in Phys-Can.

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Uppsala</th>
<th>Lund</th>
<th>Linköping</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treadmill</strong></td>
<td>SportsArt Fitness Tr32</td>
<td>Rodby RL2500E</td>
<td>Until Dec 2015: GE T2100 (Helsinki, Finland)</td>
</tr>
<tr>
<td></td>
<td>(Washington, USA)</td>
<td>(Vänge, Sweden)</td>
<td>For the remaining study period:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rodby RL2000, (Vänge, Sweden)</td>
</tr>
<tr>
<td><strong>Gas-analysys</strong></td>
<td>Sensor Medics Vmax 29, Care</td>
<td>Jaeger Oxycon Pro, CareFusion</td>
<td>Until Dec 2015: Jaeger Oxycon Pro, CareFusion (Germany, Hoechberg)</td>
</tr>
<tr>
<td></td>
<td>Fusion (San Diego, USA)</td>
<td></td>
<td>For the remaining study period: Cosmed Quark CPET (Rome, Italy)</td>
</tr>
<tr>
<td><strong>Software</strong></td>
<td>Vmax Encore and Cardiosoft</td>
<td>LabManager version 5.31.0, Jlab, CareFusion (Germany, Hoechberg)</td>
<td>Until Dec 2015: LabManager, Jlab, CareFusion, version 5.31.0.83, (Hoechberg, Germany)</td>
</tr>
<tr>
<td></td>
<td>ECG Version 6.7 (San Diego, USA)</td>
<td></td>
<td>For the remaining study period: Cosmed Quark PFT Ergo was (Rome, Italy)</td>
</tr>
<tr>
<td><strong>Heart rate monitoring</strong></td>
<td>Polar RS400 heart rate watch</td>
<td>A Coded Polar receiver 4208</td>
<td>Until Dec 2015: A heart rate receiver in the EKG equipment (GE Healthcare, CASE GE connected to the Oxycon Pro)</td>
</tr>
<tr>
<td>during exercise tests</td>
<td></td>
<td>(connected to Oxycon Pro)</td>
<td>For the remaining study period: A Cosmed SZ990 sensor (connected to the Cosmed Quark CPET)</td>
</tr>
<tr>
<td><strong>Number of ( \dot{V}O_2 \text{max} ) test</strong></td>
<td>136</td>
<td>135</td>
<td>60</td>
</tr>
<tr>
<td>(complete pre- and post-</td>
<td></td>
<td></td>
<td>intervention)</td>
</tr>
<tr>
<td>intervention)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Criteria verifying $\dot{V}O_2\text{max}$ in Paper III

In Paper III, the criteria verifying $\dot{V}O_2\text{max}$ were two out of the following three; 1) if the test-leader judged the test as maximal by observing breathing and body/facial expressions, 2) a Borg RPE rating $\geq 17$ or 3) a respiratory exchange ratio (RER) $\geq 1.1$.

Performing the $\dot{V}O_2\text{max}$ test

During the $\dot{V}O_2\text{max}$ test, the participants had to be able to walk freely with their arms and hands; not hold on to the handles or anything else. If the patient could not manage to walk alone, without holding on to something, or for other reasons could not manage to perform the test on a treadmill (e.g. dizziness or severe instability), a bicycle could be used instead. This option was only considered if the test person could not manage to walk on the treadmill after 15-30 minutes’ warm-up, or if there were any obvious indicator that the test should have been done on a bicycle.

The test-personnel were instructed to motivate and encourage to keep on walking or running until exhaustion, but the patient decided and gave his/her signal to stop when he/she could not manage to keep on exercise. After the test was completed, the patient was told to cool down on the treadmill for a few minutes, until the heart rate had normalised. Afterwards, the test person was offered something to drink and if wanted, something to eat.

Test protocol

The $\dot{V}O_2\text{max}$ testing was performed using a standardised protocol (Table 6); a modified Balke protocol starting easy with an inclination of 2\% and a speed of 4 km/h. Since not all the three treadmills used in Phys-Can could be elevated above 12\%, only the speed was increased by 0.5 km/h from 12\%. 

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Table 6. The modified Balke protocol used in Phys-Can.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Speed (km/h)</th>
<th>Incline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>4.5</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>5.5</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>6.0</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>6.5</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>7.0</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>7.5</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>8.0</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>8.5</td>
<td>12</td>
</tr>
</tbody>
</table>

The speed was increased by 0.5 km/h every minute, until exhaustion.

5.2.4 Baseline characteristics and results related to cancer related fatigue

In Table 7, baseline characteristics of all Phys-Can participants performing a \( \dot{V}O_2 \)\(_{\text{max}} \) test at baseline, in both the intervention (n=535) and in the cohort study (n=80), are presented. Information regarding living situation, education, sick-leave and smoking status were retrieved through questionnaires. The questionnaires Multidimensional Fatigue Inventory (MFI)[215] and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer patients (EORTC QLQ C30)[216] were used to retrieve information regarding physical fatigue, global health status and physical function. Diagnosis was gathered from medical journals and hours in moderate to vigorous intensity PA per day was retrieved from the PA monitor SenseWear Armband Mini (BodyMedia Inc., Pittsburgh, PA, USA). The participants were instructed to wear the monitor for seven consecutive days at baseline and the monitor was delivered at the day the \( \dot{V}O_2 \)\(_{\text{max}} \) test was performed. The cut-points defining moderate-to-vigorous intensity PA was above 3 metabolic equivalents (METs)[212]. The accepted limits were at least four days with registration and at least 80% wearing time each day.

The two samples were comparable in respect to baseline characteristics, where mean age were 59 years and both samples included approximately 80% women
with breast cancer, 15% men with prostate cancer and 4-5% patients with colorectal cancer (Table 7).

Table 7. Baseline characteristics of the participants performing baseline $\dot{V}O_2$max testing in the Phys-Can Intervention study and the Phys-Can Cohort study.

<table>
<thead>
<tr>
<th></th>
<th>Phys-Can Intervention</th>
<th>Phys-Can Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>535</td>
<td>80</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>59 (12)</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>430 (80)</td>
<td>67 (84)</td>
</tr>
<tr>
<td>Living with a partner, n (%)</td>
<td>402 (75)</td>
<td>58 (73)</td>
</tr>
<tr>
<td>Completed University, n (%)</td>
<td>309 (58)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>Sick-leave, n (%)</td>
<td>180 (34)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>100% sick leave, n (%)</td>
<td>150 (28)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30), n (%)</td>
<td>84 (16)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>19 (3.5)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>421 (79)</td>
<td>66 (83)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>93 (17)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>21 (3.9)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>EORTC QLQ C30, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status/QoL</td>
<td>66.3 (20.2)</td>
<td>70.7 (17.7)</td>
</tr>
<tr>
<td>Physical Function</td>
<td>88.5 (13.5)</td>
<td>90.0 (11.5)</td>
</tr>
<tr>
<td>Physical fatigue, MFI, mean (SD)</td>
<td>11.2 (4.3)</td>
<td>11.7 (3.6)</td>
</tr>
<tr>
<td>MVPA, hours/day, mean (SD)</td>
<td>1.23 (0.8)</td>
<td>1.12 (0.6)</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SD) or n (%). *Abbreviations: BMI=Body Mass Index; Mod-to-vig intensity PA=Moderate-to-vigorous intensity PA; QoL=Quality of life. Notes: Financial situation: worst=1, best=10. MFI, Physical fatigue: 4=low fatigue, 20=high fatigue. Global health status/QoL: 0=low quality of life, 100=high quality of life. Physical Function: 0=low/unhealthy level of functioning, 100=high/healthy level of functioning. Moderate-to-vigorous intensity=PA at or above 3 metabolic equivalents (METs). The accepted limits were at least four days with registration and at least 80% wearing time each day.

5.2.5 Exercise interventions

The six-month intervention was initiated at start of the cancer treatment. Patients scheduled for neoadjuvant treatment of breast cancer exercised for four months only. The intervention consisted of supervised, group-based resistance training.
two times per week at local public gyms and home-based endurance training, with or without additional BCS.

**Resistance training**

Resistance training sessions consisted of three sets of six exercises (seated leg press, chest press, leg extension, seated row and seated leg curl on weight machines, and seated overhead press using dumbbells), see appendix. Participants randomised to high intensity exercise trained with 6 repetitions per set and 2 min rest between sets (first weekly session) or 10 repetitions per set and 1 min rest between sets (second weekly session, with a 6 and 10 repetition maximum (RM) load in first and second session respectively) and continued to failure in the last set of each exercise. Participants randomised to low-to-moderate intensity exercise trained at 50% of 6 RM with 12 repetitions per set and 2 min rest between sets (first weekly session) or 50% of 10 RM and 20 repetitions per set and 1 min rest between sets (second weekly session). Thus, the resistance training volume (weight x repetitions) was the same in both intensity groups. Participants were also asked to regularly perform sit-ups, the plank, bird-dog and pelvic floor exercises. Participants attended the gym at the same time as other individuals randomised to the same intervention group and were supervised in these sessions by a coach. Additional members of gym staff helped the coaches to supervise the resistance training sessions and conducted strength testing.

**Endurance training**

The endurance training was home-based and followed up by a coach at the gym on a weekly basis. Participants wore heart rate monitors and recorded perceived exertion according to the Rating of Perceived Exertion (RPE) Borg scale [214] in an exercise logbook. Participants in the high intensity (HI) group were instructed to perform interval training twice per week. The HI training was composed of five intervals of two minutes of exercise (e.g. running, cycling or walking uphill) at 80-90% of heart rate reserve (HRR) followed by two minutes’ rest. An additional interval was added every fourth week until 10 intervals were reached. Participants randomised to low-to-moderate intensity (LMI) exercise were instructed to perform 150 minutes of endurance-based activity such as cycling and walking. The PA should be accumulated in bouts of at least 10 minutes at an intensity of 40-50% of HRR.

The first six weeks of the intervention were considered a familiarisation period where participants learned to use equipment and individual workloads were
established. The resistance training was adjusted over the intervention period to maintain relative exercise intensity using 6 and 10 RM tests every fourth to every sixth week. Progression in the HI group was secured by adding intervals, while there was no progression in the endurance training in the LMI group.

**Behaviour change support**

Self-regulatory behaviour change support (BCS) were provided for half of the participants in each of the two intensity groups. These were strategies to facilitate adherence to the HI and LMI exercise programs, respectively. These support strategies were directed to support adherence to the exercise intervention, but with a primarily focus on the endurance training as it was home-based. In addition, an objective of including BCS was to facilitate maintenance of exercise according to individual preferences after the completion of the interventions. The BCTs included a) behavioural goal-setting, b) short-term action planning, c) self-monitoring, d) review of behaviour goals, e) problem solving and functional behaviour analysis to identify individualised determinants of exercise behaviour, and f) long-term coping planning to maintain physical exercise by own choice after the intervention was completed.

**5.2.6 Adherence to exercise**

In all groups, coaches contacted participants by telephone if they missed one or more resistance training session and encouraged them to attend the next session. To monitor adherence to the exercise protocol, all participants completed standardised logbooks for both resistance and endurance training. These logbooks were checked by coaches to ensure exercise was completed at the appropriate intensity. Feedback was provided when needed. Participants’ adherence to the training protocols was calculated as performed exercise divided by prescribed exercise.

For *resistance training*, data for each session was recorded in individual logbooks and was used to calculate performed exercise as performed weight*performed number of repetitions, summed across all exercises and training sessions. Prescribed exercise was prescribed weight*prescribed number of repetitions summed across all exercises and prescribed training sessions. The prescribed weight and number of repetitions was defined by the resistance training protocol and repeated individual maximal testing through the exercise period. For attendance to the resistance training, this was calculated as number
attended resistance training sessions / number prescribed resistance training sessions.

For *endurance training*, adherence was calculated in the high intensity exercise groups as performed number of intervals*interval duration summed across all training sessions with an average or reported intensity of at least 72%HRR (corresponding to 90% of the 80% that was the lower HRR limit). This adjustment was made to account for biking sessions where heart rate is normally lower than during running, despite similar exertion level [217]. We used a combination of data recorded in individual logbooks and HR data from interval training sessions, which was processed using a custom written program to detect interval number and mean interval duration. Prescribed exercise in the high intensity training groups was prescribed number of intervals * prescribed interval duration (2 minutes) * 2 * prescribed number of weeks of training. In the low-to-moderate intensity training groups, performed exercise was calculated as performed or reported minutes of activity at an intensity of 40-60% of HRR, accounting for the general heart rate increase which is commonly observed during chemotherapy treatment [24]. The calculation was based on a combination of data recorded in individual logbooks and heart rate data from training sessions. Prescribed exercise in the low-to-moderate intensity training groups was 150*prescribed number of weeks of training. For participants in the low-to-moderate intensity training groups, we also calculated minutes of activity at ≥60%, which enabled adjustment for high intensity exercise in this group.

Adherence to the exercise interventions are presented in Table 8. We found that the adherence to endurance training was higher in the low-to-moderate intensity exercise group, but no difference was found between intensity groups regarding resistance training. The median adherence for all the 331 participants with accepted pre-and post-intervention VO₂max tests was 57.4% (n=165).
Table 8. Adherence to the exercise interventions for patients with complete pre- and post-intervention assessment of $\dot{V}O_2$max (n=331).

<table>
<thead>
<tr>
<th></th>
<th>HI n=162</th>
<th>LMI n=169</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence endurance training (%)</td>
<td>51 (31)</td>
<td>62 (33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time&gt;60%HRR in LMI groups (mins)</td>
<td></td>
<td>630 (1092)</td>
<td></td>
</tr>
<tr>
<td>Adherence resistance training (%)</td>
<td>63 (20)</td>
<td>66 (18)</td>
<td>0.149</td>
</tr>
<tr>
<td>Attendance resistance training (%)</td>
<td>64 (23)</td>
<td>66 (22)</td>
<td>0.511</td>
</tr>
</tbody>
</table>

Data are mean (SD) for patients with complete pre- and post-intervention assessment of $\dot{V}O_2$max. HI: High intensity exercise; LMI: Low-to-moderate intensity exercise; HRR: heart rate reserve. *difference between group means tested using independent samples t-test.

5.2.7 Data management in Paper II and III

For the present thesis, all data from the questionnaires and physical tests were uploaded and saved in a web-portal custom-made for managing the result variables investigated in the Phys-Can study. From the web-portal, we as researchers in the project could download the specific data needed for our research, and I had responsibility to assure that the $\dot{V}O_2$max results were under control (i.e. that test-summaries were correctly calculated and written). From the portal, we downloaded the data into excel files, cleaned the datasets and transferred them to statistical programs for analysis. In addition to data that could be retrieved through this portal, some data were processed through other custom-made programs (HR datafiles and detection of a $\dot{V}O_2$ plateau), which are described below.

Heart rate data management (Paper III)

To be able to report adherence to the exercise intensity, HR monitors were used during the home-based endurance training. These HR-files, which included a large amount of data, were uploaded and dealt with in two different data-programs. The two programs were developed together with experts within data-programming. These programs enabled us to systematise and categorise the HR-registrations according to achievement or not of the prescribed exercise intensity, session duration and total duration. One program was custom-made for low-to-moderate intensity, and the other program for the high intensity exercise prescriptions. The rationale for two different programs was that the exercise prescriptions did not only differ in relation to intensity, but also other exercise characteristics. In the low-to-moderate intensity groups, the HR registrations
were, according to the exercise prescriptions, of a continuous exercise character, which is more straight-forward when the intention is to investigate the time spent above (and under) an intensity HR zone. Since the high intensity groups performed interval training, the program needed to be able to detect number of intervals in each exercise session, intensity at these intervals and the total duration of each session. Thus, the latter program had some more advanced settings to be able to retrieve this information, to calculate adherence.

\[ \dot{V}O_2 \] plateau-detection (Paper II)

Regarding the criterion \( \dot{V}O_2 \) plateau, a computer program was developed to detect whether a \( \dot{V}O_2 \) plateau or levelling off occurred during the test-time. Using this program, each of the excel files with the test-results were processed by an algorithm based on the definition of \( \dot{V}O_2 \) plateau by Taylor et al [218], where a change in \( \dot{V}O_2 \) should be less than 150 ml from one minute to the next minute (\( \Delta \dot{V}O_2 \leq 150 \text{ ml/min} \)). Additionally, \( \dot{V}O_2 \) plateaus within the cut-offs of \( \leq 80 \text{ ml/min} \) and \( \leq 50 \text{ ml/min} \) were studied with similar definitions using the program. The highest average in \( \dot{V}O_2 \) over a minute was compared with the minute before or the minute after and whether \( \dot{V}O_2 \) for these time points differed \( \leq 150 \text{ ml} \), \( \leq 80 \text{ mL} \) and \( \leq 50 \text{ ml} \).

5.3 Statistical analyses

5.3.1 Paper I

To adjust for differences in \( \dot{V}O_2 \text{max} \) at baseline, we used independent group differences to calculate effect sizes. There were three different formats used when calculating effect sizes, depending on the information available in the papers. By one procedure post intervention means, confidence intervals (CI’s) and sample sizes of both intervention and control group were used to calculate effect sizes. Second, if differences between groups were reported, the mean difference, sample size of both intervention and control group, independent groups p-value and number of tails were used to calculate effect sizes. Last, if only the raw differences between pre- and post-intervention scores were reported, the mean difference with the upper and lower limit, sample size of both intervention and control group and CI were used to calculate effect sizes. Hedges’g was calculated to adjust for small sample sizes [219]. A study was considered an outlier and excluded from further analyses if the 95% CI of the calculated effect size did not overlap with the 95% CI of the overall effect size. Cohen’s convention was used to interpret the effect sizes: an effect size of 0.2
was considered small, 0.5 was considered moderate, and 0.8 was considered large [220]. Because the samples and interventions were expected to be heterogeneous, the effect sizes were pooled with a random-effects model, taking differences in the effects between the studies into consideration. The $I^2$ statistic was reported as an indicator of heterogeneity, with an $I^2$ of 25% representing low heterogeneity, 50% representing moderate heterogeneity, and 75% representing high heterogeneity [221].

Subgroup analyses were conducted to study the differences in effects between studies with several exercise- and intervention-related characteristics: 1; frequency of training sessions per week categorised into 2-3 times/week, 3 times/week and ≥4 times/week, 2; intensity categorised using MET values, 3; delivery mode dichotomised into supervised when a supervised exercise component was included and unsupervised when there were no instructor present. Additionally, we performed a meta-regression analysis to study the association of $\dot{V}O_2$max with the 4; session duration, 5; weekly exercise duration, 6; weekly exercise volume, 7; intervention duration referring to the duration of the intervention period in weeks, and 8; intervention volume calculated as the total exercise volume × intervention duration. When analysing and reporting session durations from combination trials (AET+RET), the total duration of the exercise session was reported and used in the analyses. Due to the observed variety in exercise prescriptions regarding type of exercise (i.e. cycling, running, walking, football-activities and interval vs continuous exercise etc.), there were too few studies to investigate this particular FITT factor in the meta-analysis.

In the meta-regression, Z-values and p-values were presented to provide information about the regression coefficient and significance of the relationship between the variable and the effect size.

To study the possible interference of including resistance exercise, we also conducted sensitivity analyses in which combination trials (RET+AET) [201, 203-205] were excluded. All analyses were conducted using Comprehensive Meta-Analysis software, version 2.2.064 (National Institutes of Health, Bethesda, MD, USA).

Publication bias was investigated by inspecting the funnel plot, and Duval and Tweedie’s procedure [222]. By this procedure missing studies are imputed to achieve symmetry around the centre of the funnel plot. The effect was then recalculated based on this procedure. Publication bias was suggested by the
presence of significant dispersion between the true effect size and the calculated effect size as seen by Egger’s test.

5.3.2 Paper II

Demographic data and results from the \( \dot{V}O_2 \)peak tests were presented as mean values ± standard deviation (SD) and numbers with percentages. For descriptive purposes, the average \( \dot{V}O_2 \)peak within ‘fulfilment’ and ‘not fulfilment’ of a variety of criteria and cut-points used in the literature were presented in figure 5 using GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

To analyse associations between the criteria variables and the test leader’s evaluation, logistic regression analysis was performed using The Hosmer step-down procedure [223]. The predicting variables included in the initial bivariate analysis were achievement of a \( \dot{V}O_2 \) plateau, HRpeak, RERpeak, Borgs’ RPEpeak and \( f_R \)peak. In addition, \( \dot{V}O_2 \)peak, diagnosis, age, body mass and test time were included as adjusting variables. All variables significant at the 0.25 level were included in the multivariate analysis: in the final model. We calculated the Odds Ratio’s (OR’s) and Confidence Intervals (CI’s) for 0.10 units for RERpeak. To investigate collinearity and interaction, pairwise correlations were performed for all the five predicting variables (achievement of a \( \dot{V}O_2 \) plateau, HRpeak, RERpeak, Borgs’ RPEpeak and \( f_R \)peak) in addition to \( \dot{V}O_2 \)peak and test-time.

Further, a Receiver Operating Characteristic (ROC) analysis was performed to establish cut-points for variables found to be associated to the test leader’s evaluation. In other words, for the associated criteria, the cut-points where the sensitivity and specificity were highest in correctly categorise the test leaders’ evaluation (meaning as ‘to exhaustion’ or ‘not to exhaustion’) were established.

Last, a cross-validation of the cut-points found in the ROC-analysis s was performed on the Phys-Can Cohort study, using a cross-table. More detailed, the sensitivity and specificity in categorising the \( \dot{V}O_2 \)max tests correctly based on the test leaders’ evaluations were checked by adopting results from the intervention sample to the cohort sample.

The analyses were performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) and Statistical Analysis System (SAS version 9.1.3, SAS).
5.3.3 Paper III

In Paper III, which is Phys-Can’s main paper (where cancer related fatigue is the main outcome, and cardiorespiratory fitness and all the other outcomes are secondary) multiple linear regression was used to estimate the main effect for 1) exercise intensity, 2) BCS, and 3) the interaction, on each outcome. Results are presented as adjusted mean difference with 95% Confidence Intervals (95% CI). Analyses were conducted according to intention-to-treat (ITT), i.e. participants were analysed as randomised regardless of intervention adherence. Models included baseline measures of the outcome to increase precision and were adjusted for centre and cancer diagnosis to account for the stratified design. Missing data were accounted for using multiple imputations by chained equations. Auxiliary variables were age, education level, hospital, diagnosis, treatment with chemotherapy, baseline values of outcome measure and intervention group. Where missing data at baseline were >10%, baseline data for that outcome was not included as an auxiliary variable or as a variable in the main models, as baseline data was deemed not to add additional precision for these outcomes.

Supplementary analyses were based on complete cases only in order to compare the results with and without imputation of missing data. In additional analyses, each cancer diagnosis was examined separately; these models were adjusted for centre and baseline measures of the outcome variable.

In order to further examine the clinical significance of any statistically significant differences in the primary outcome (cancer related fatigue), responder analysis was used to present the proportion of patients whose change scores represented a minimum clinically important difference of 2 for the MFI subscales [224] and 3 for the FACIT-F scale [225].

All analyses in Paper III were carried out in Stata version 15.0.

5.3.4 Additional analyses included in the thesis

To account for adherence to the exercise prescriptions and \( \dot{V}O_2\text{max} \) at baseline, additional linear regression analysis was performed including the 331 participants with an accepted \( \dot{V}O_2\text{max} \) test from before and after the intervention. To display the differences in post-intervention \( \dot{V}O_2\text{max} \) values by using different covariates in the analyses, we presented both the crude, the adjusted (age, diagnosis, hospital, baseline \( \dot{V}O_2\text{max} \)) and the adjusted in addition to adherence variable in the linear regression analysis.
5.3.5 Level of statistical significance

An alpha level of $p \leq 0.05$ was set as the criterion for statistical significance across all the analyses performed in the three papers and in the thesis.

5.3.6 Power calculations

Regarding Paper I, a power calculation was not performed, but we stated that we needed at least 10 RCT’s with relevant information available in the articles, or by author correspondence, to be able to conduct the meta-analysis.

The power calculation in Paper II and III was based on $\dot{V}O_2$ as the dependent variable. To be able to detect a minimally clinically important mean difference of 10% (Standard deviation, 20%) in $\dot{V}O_2$ between the low-moderate vs. high intensity groups after 6 months, with a power of 80% and a 5% significance level, we needed at least 150 patients in each group of the two intensity-groups (300 in total), when taking into account possible missing values and drop-outs of.

With this high number of participants performing baseline $\dot{V}O_2$ measurements in the Phys-Can intervention study, this was evaluated as a solid basis to investigate the objectives elucidated in Paper II.

5.4 Ethical considerations

The Phys-Can intervention trial was registered in ClinicalTrials.gov (TRN = NCT02473003, Oct 2014) and ethical approval was obtained from the Regional Ethical Review Board in Uppsala (Dnr 2014/249). Patients received both orally and written information about the study. The information included what participation meant, that being part of the study was completely voluntary and that they could withdraw from participating at any time without any consequences for their treatment. Patients were given time to consider their participation and written informed consent was obtained from each participant before entering the study.
6 SUMMARY AND DISCUSSION OF FINDINGS

6.1 \( \dot{V}O_2 \)\textsubscript{max} criteria

The peak values from the \( \dot{V}O_2 \)\textsubscript{max} tests and test duration are presented in Table 9. We observed that participants in Phys-Can responded similarly to healthy age-matched individuals regarding peak values of \( \dot{V}O_2 \), RER, Borg’s RPE and HR [121, 122].

**Table 9.** Peak values and test-duration from the \( \dot{V}O_2 \)\textsubscript{max} tests performed at baseline in the Phys-Can Intervention study (n=535) and the Phys-Can Cohort study (n=80), presented in mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Phys-Can Intervention (n=535)</th>
<th>Phys-Can Cohort (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}O_2 )\textsuperscript{peak} (ml/kg/min)</td>
<td>29.8 (7.3)</td>
<td>29.2 (7.1)</td>
</tr>
<tr>
<td>HR\textsuperscript{peak} (beats/min)</td>
<td>166 (19)</td>
<td>168 (19)</td>
</tr>
<tr>
<td>RER\textsuperscript{peak} (( \dot{V}CO_2 )/( \dot{V}O_2 ))</td>
<td>1.16 (0.10)</td>
<td>1.19 (0.11)</td>
</tr>
<tr>
<td>VE\textsuperscript{peak} (volume in l/min)</td>
<td>79 (20)</td>
<td>79 (19)</td>
</tr>
<tr>
<td>( f_R )\textsuperscript{peak} (breaths/min)</td>
<td>40 (7.8)</td>
<td>41 (6.4)</td>
</tr>
<tr>
<td>Borg scale (RPE\textsubscript{6-20})</td>
<td>17.9 (1.6)</td>
<td>17.0 (1.3)</td>
</tr>
<tr>
<td>Test-duration (min)</td>
<td>9.9 (2.8)</td>
<td>9.4 (2.6)</td>
</tr>
</tbody>
</table>

*Abbreviations*: \( \dot{V}O_2 \) = oxygen uptake; HR = heart rate; RER = Respiratory Exchange Ratio; \( \dot{V}CO_2 \) = carbon dioxide production; VE = ventilation; \( f_R \) = respiratory frequency; RPE = ratings of perceived exertion.

For the intervention study, \( \dot{V}O_2 \)\textsuperscript{peak} was significantly (p<0.001) higher in the 465 (87%) tests evaluated ‘to exhaustion’ (30.3 CI: 29.6; 30.9) than ‘not to exhaustion’; n=70 (26.6 CI: 24.9; 28.3). In the cohort study, only 4 of 80 tests were rated ‘not to exhaustion’.

The percentage distribution and mean \( \dot{V}O_2 \)\textsuperscript{peak} in subjects fulfilling and not fulfilling different cut-points within the end-criteria of \( \dot{V}O_2 \)-plateau, RER, predicted HR (Tanaka) and Borg’s RPE are presented in Figure 3. Regarding all cut-points within the criteria of RER, predicted HR and Borg’s RPE, the mean \( \dot{V}O_2 \)\textsuperscript{peak} was significantly higher in the ‘fulfilled’ groups than in the ‘not fulfilled’ groups (p<0.001 – p=0.033). Within the \( \dot{V}O_2 \)-plateau criterion, there was no difference in \( \dot{V}O_2 \)\textsuperscript{peak} for the \( \Delta \dot{V}O_2 \leq 150 \text{ ml/min} \) cut-point (p=0.970). Interestingly, the mean \( \dot{V}O_2 \)\textsuperscript{peak} was higher in the ‘not fulfilled’ groups than in
the ‘fulfilled’ groups for the <80 ml/min (p<0.001) and the <50 ml/min (p=0.028) cut-points. The largest difference in \( \dot{V}O_2 \) peak was observed between individuals who fulfilled (n=514; 30.1 ml/kg/min) and those who did not fulfil (n=21; 22.2 ml/kg/min) the RER ≥ 1.0 criterion (p<0.001).

**Figure 3.** Mean \( \dot{V}O_2 \) peak stratified on fulfilling and not fulfilling end-criteria for \( \dot{V}O_2 \)max in patients diagnosed with breast, prostate or colorectal cancer (n=535).

*Abbreviations:* RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion on Borg scale 6-20; \( \dot{V}O_2 \) = oxygen uptake; \( \dot{V}CO_2 \) = carbon dioxide production. *Notes:* Tanaka, HR\(_{\text{max}}\) = 208 - (0.7\times\text{age}), Plateau, Δ\( \dot{V}O_2 \) = a change in \( \dot{V}O_2 \) of less than 150, 80 or 50 ml/min from one minute to the next minute.
6.1.1 A plateau in oxygen uptake

In this present study, nearly all patients (91%) fulfilled the most accessible cut-point ($\Delta\dot{V}O_2 \leq 150$ ml/min). Furthermore, 63% and 45% fulfilled the $\leq 80$ and $\leq 50$ ml/min cut-points, respectively. In a study including 23 patients with metabolic syndrome (~56 years old), the researchers found 94%, 59% and 24% fulfilling the same three cut-points, respectively [226]. Although their exercise protocol, consisting of a constant speed of 6 km/h with an increase in inclination of 2% each minute, was different from the protocol used in Phys-Can, the percentage of patients fulfilling each cut-point was similar to what we found [226]. Furthermore, in a study including 67 men and 68 women (~37 years old) who were obese or overweight, the participants performed a maximal exercise test, consisting of a constant fast-paced walking speed with a grade increase of 2.5% each minute [197]. Wood et al. (2010) found that 46% of the participants fulfilled their definition of a $\dot{V}O_2$ plateau: ‘increase in $\dot{V}O_2 < 50\%$ of that expected for the change in mechanical work’ (on page 472) [197]. In Phys-Can, this definition would, on average, have been $\Delta\dot{V}O_2 \leq 128$ ml/min; hence, slightly stricter than our $\Delta\dot{V}O_2 \leq 150$ ml/min cut-point. In another study, including 71 post-menopausal, overweight and obese sedentary women (~60 years old), the researchers evaluated the frequency of meeting the plateau criterion ($\Delta\dot{V}O_2 < 2.0$ ml/kg/min) during a $\dot{V}O_2$ max test [198]. First, when performing the test using the Bruce protocol, only 18% of participants fulfilled the criterion, and when the modified Balke protocol was used, 36% fulfilled the criterion [198]. When mean body mass (73 kg) is accounted for in this present study, the most accessible plateau definition is $\Delta\dot{V}O_2 < 2.05$ ml/kg/min. Hence, in this present study, the most accessible plateau cut-point was achieved by far more participants than those in the study by Misquita et al. (2001) [198].

There are different definitions concerning what a $\dot{V}O_2$ plateau is, and the original one from 1955 by Taylor et al. [218] was based on discontinuous ramp protocols performed over a few days. Although the modified Balke protocol is a continuous graded protocol, it is not steep. The inclination is gradually increased by only 2% each minute until 12%, and from that point only the speed is increased by 0.5 km/h each minute (representing approximately 1 MET increase each minute). Due to very small expected $\dot{V}O_2$ increments between each stage in our test protocol, the $\leq 150$ ml/min cut-point was believed to fit best and therefore included in the regression analysis. However, there are some concerns deserving a critical view related to our plateau-findings.
Considering the following: 1) mean \( \dot{V}O_2 \) peak was the same in the participants that fulfilled and not fulfilled the \( \leq 150 \) ml/min cut-point and 2) mean \( \dot{V}O_2 \) peak was higher in the participants not fulfilling the \( \leq 80 \) and \( \leq 50 \) ml/min cut points. Considering these two observations, in addition to the acknowledged complexity and challenges related to the practical use of the \( \dot{V}O_2 \) plateau in verifying \( \dot{V}O_2 \) max [194, 227], makes us question the validity of using \( \dot{V}O_2 \) plateau as a criterion verifying \( \dot{V}O_2 \) max, at least in the present population.

6.1.2 Respiratory exchange ratio

Considering that the participants in Phys-Can had a mean age of 59 years old, the mean RER peak of 1.16 (Table 9) is comparable to the mean RER of 1.17 in the 50 to 64-year-old age group in Edvardsen et al. (2014) [196]. As RER max was found to decline with age in Edvardsen et al. (2014), our observation of 56% fulfilling the RER \( \geq 1.15 \) agrees well with their findings of 65% fulfilling the \( \geq 1.15 \) cut-point [196]. Furthermore, our 77% fulfilling RER \( \geq 1.10 \) and 96% fulfilling RER \( \geq 1.00 \) are similar to Edvardsen et al. (2014) finding 80% and 95% for the same cut-points. Consequently, many participants in Phys-Can fulfilled the age-related recommended cut-point for healthy individuals: RER \( \geq 1.05 \) (91%) [196].

In the study including younger overweight and obese adults, the fulfilment of the RER \( \geq 1.15 \) criterion was higher (89%) [197] than in Phys-Can, but this result may be related to a steeper test protocol. Shorter and faster test protocols are found to result in higher RERpeak values compared with ramp tests of longer durations [178]. When performing a maximal test using the Bruce protocol, 51% of obese, menopausal women fulfilled the RER \( \geq 1.10 \) criterion, and when performing the second test, using a modified Balke protocol, 59% fulfilled the RER \( \geq 1.10 \) criterion [198].

In healthy and clinical populations, the rationale for choosing one cut-point instead of another seems to be lacking, and since more than six or seven different cut-points have been applied, ranging from \( \geq 1.00 \) to \( \geq 1.20 \) [228], the previously selected cut-points seem arbitrary [178]. Of the RCTs included in the systematic review and meta-analysis (Paper I), the RER \( \geq 1.1 \) cut-point was applied in four of the studies [203, 204, 207, 208]. In Uth et al. (2014) [90], the RER \( \geq 1.05 \) was selected, and in Al-Majid et al. (2015), they used other criteria. However, in eight of the RCTs included in the review, no criteria verifying \( \dot{V}O_2 \) max were reported [15, 22, 93, 201, 202, 205, 209, 210].
6.1.3 Age-predicted maximal heart rate

Many patients in Phys-Can (76%) fulfilled both the strictest cut-point of ≥95% predicted HRpeak, and almost all (93%) fulfilled the most accessible cut-point of ≥85% predicted HRpeak. Comparable observations were made for obese and overweight adults, with 83% reaching to at least within 11 beats of the age-predicted HRmax [197]. Misquita et al. (2001) found that the age-predicted HR criterion was achieved by fewer participants (64%) [198]; however, the criterion applied in their study was stricter than when certain percentages of age-predicted HRmax are used.

Due to 10 to 12 beat-per-minute variations in HRmax in healthy individuals, even when considering age [229, 230], predicting HRmax from age is not valid [231, 232], and is likely to under- or overestimate HRmax on an individual level. A potentially greater variation is applied to patients with cancer due to the documented effect certain cancer treatments may have on cardiac function [233], commonly observed as increased submaximal HR [234]. In patients with congestive heart failure using beta-blockers, higher HR at rest and lower HRmax have been observed [235]; hence, such medications could also disrupt the use of this criterion. Consequently, the age-predicted HRmax is presumably a problematic criterion to apply in both healthy individuals [108, 198] and in patients with cancer, before, during and after cancer treatment.

It is notable that, since HR normally increases linearly with \( \dot{V}O_2 \) during increasing work rate exercise [236], percentages of measured HRmax could potentially be used as a valid criterion for patients newly diagnosed with cancer. However, in many types of heart disease, the HR increase increases faster relative to the increase in \( \dot{V}O_2 \), due to, for example, a reduced left ventricular function [237]. Consequently, knowing that cancer treatments and their cytotoxic effects may lead to reduced cardiac function [69, 70] [66-68], there might be a difficulty using measured HRmax as well as age-predicted HRmax as criteria for patients who have undergone cancer treatment. Furthermore, to our knowledge, an HRmax-test is usually not performed on clinical populations before the \( \dot{V}O_2\text{max} \) test; consequently, age-predicted HRmax is applied instead (if this criterion is applied in verifying \( \dot{V}O_2\text{max} \)).

6.1.4 Borg ratings of perceived exertion

Congruent with our observations, 84% of participants in Edvardsen et al. (2014) achieved the most frequently used cut-point of RPE ≥17. There was a large discrepancy between the percentage of patients reaching RPE ≥17 (86%; 30.2
ml/kg/min) and ≥18 (65%; 30.4 ml/kg/min) in the Phys-Can study; consequently, selecting the strictest criterion would exclude many tests. At the same time, small differences in $\dot{V}O_2$ peak in fulfilling the two cut-points were evident. Despite close relations between the scores on the scale and the physiological measures of intensity, such as HR, BLa$\dagger$ [238], and work rate during exercise [239], the validity in using RPE as a criterion in $\dot{V}O_2$ max testing has been questioned [240]. The validity of the use of the criterion depends on the subject’s understanding of the scale and its associated verbal descriptors, as well as the ability to differentiate between discomfort and physiological fatigue and motivation [177]. It is proposed that physically inactive individuals unaccustomed to exercise until exhaustion are likely to report perceived maximal exertion before they actually reach their ‘true’ $\dot{V}O_2$ max [175].

In summary, we observed that newly diagnosed cancer patients responded similarly to healthy age-matched individuals in peak values of $\dot{V}O_2$, RER, Borg’s RPE and HR [121].

6.1.5 Breathing frequency

In addition to the criteria often used when verifying $\dot{V}O_2$ max, we chose to investigate how breathing frequency ($f_R$) could be a criterion and included it as part of the criteria variables in the regression and ROC analyses. The rationale behind investigating $f_R$ was mainly based on experiences from the lab, in which this variable is often used as a ‘help-criterion’ by experienced test leaders. When searching the literature to determine whether $f_R$ had been applied as a criterion, no studies were found. However, in 2014 [241], 2016 [242] and 2017 [199], Nicolo et al. discussed how $f_R$ could work as a reflection of physiological strain during high-intensity training, and they found that the time course of $f_R$ is related to scores on Borg’s scale [241]. Although Nicolo et al. focused on the applicability of using $f_R$ as a measure of exertion rates during exercise (as a supplement or substitute for, for example, Borg’s scale), this variable is interesting to elucidate as a possible additional criterion verifying $\dot{V}O_2$ max. Wasserman et al. found that, for 95% of all healthy men between 34 and 74 years old, $f_R$ is less than 55 breaths/min during maximal effort [109]. In a summary table in the review by Leclerc from 2017, < 30 breaths/min is set as a cut-point, suggesting that a submaximal effort has been made [243].
### 6.2 Criteria and cut-points associated with the test leader’s evaluation

The criteria of RERpeak, Borg’s RPE and $f_R$ peak were associated with the test leader’s evaluation of whether a test was defined as ‘to exhaustion’. Neither the HRmax criterion nor attaining a $\dot{V}O_2$ plateau at the end of the $\dot{V}O_2$max test was associated with the test leader’s evaluation (Table 10). When adjusting for age, diagnosis, $\dot{V}O_2$peak and test duration, the probability of being categorised as ‘to exhaustion’ more than doubled for each 0.1 increase in RER (OR: 2.07, 95%CI 1.39–3.08) and for each unit increase in Borg’s RPE (OR: 2.05, 95%CI 1.67–2.51) (Table 10). For every 10 breaths/min increase in $f_R$, the probability of being categorised as ‘to exhaustion’ increased by 60% (Table 10).

#### Table 10. Regression summaries for bivariate- and multivariate analysis with test-leaders’ subjective evaluation of the $\dot{V}O_2$max test as the dependent variable. The coefficients are given with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Effect variable</th>
<th>Bivariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_R$ peak, breaths/min</td>
<td>1.12 (1.07, 1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR$_{peak}$, beat/min</td>
<td>1.02 (1.00, 1.04)</td>
<td>0.017</td>
</tr>
<tr>
<td>RER$_{peak}$, $\dot{V}CO_2$/$\dot{V}O_2$</td>
<td>2.21 (1.59, 3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Borg scale, RPE $6-20$</td>
<td>2.04 (1.68, 2.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plateau, $\Delta \dot{V}O_2 \leq 150$ ml/min</td>
<td>2.22 (1.01, 4.87)</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>1.06 (1.01, 1.12)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>2.07 (1.39, 3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2.05 (1.67, 2.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Abbreviations**: CI = Confidence interval; OR’s = Odds Ratio’s; $f_R$ = respiratory frequency; HR = heart rate; RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion; $\dot{V}CO_2$ = carbon dioxide production; $\dot{V}O_2$= oxygen uptake. **Notes**: Adjusted for age, diagnosis, $\dot{V}O_2$peak and test-duration.

#### 6.2.1 Cut-points established through the ‘ROC’ curves

Within the variables associated with the test leader’s evaluation, the cut-points that were found to have the highest sensitivity and specificity in predicting the evaluation were RER $\geq$1.14, RPE $\geq$18 and $f_R$ $\geq$40.

The true positive rate (TPR) for $f_R$ $\geq$40 was 0.55 (95%CI 0.51 to 0.60), for RER $\geq$1.14; 0.66 (95% CI 0.62 to 0.70), and for Borg≥18; 0.71 (95% CI 0.67 to 0.75). The probabilities of correctly classifying the test leader’s evaluations were 77% for Borg’s RPE, 73% for RER and 70% for $f_R$. When combining the three criteria, the predicted probability was the best (86%) (Fig. 4).
Figure 4. Receiver operating characteristic curves for RER, Borg’s RPE and $f_R$, with the test-leader’s evaluation as the outcome variable (n=535). *Abbreviations:* RER = Respiratory Exchange Ratio; ROC = receiver operating characteristic; RPE = ratings of perceived exertion; $f_R$ = respiratory frequency.

The RER $\geq 1.14$ cut-point found through the ROC analysis is located in the upper part of the range and close to $\geq 1.15$, which was applied in a study including healthy, fit individuals [193], in a study including overweight and obese adults [197], and originates from the work by Issekutz et al. from the 1960s [244, 245]. An important factor to consider when choosing the most suitable RER cut-point is which test protocol is planned for the $\dot{V}O_2_{\text{max}}$ testing. Since a more rapid incremental work rate increases the anaerobic energy contribution, the rate of HCO$_3^-$ buffering of lactic acid-derived H$^+$ ions is increased (i.e. the rate of CO$_2$ output will be greater because it follows the rate of H$^+$ buffering) [246]. Consequently, the RER cut-points should probably be made protocol specific by applying slightly stricter cut-point values when using rapid protocols. However, we have not investigated this issue in the present study, and more research regarding protocol-specific RER cut-points is necessary.

A scoring on the Borg scale of $\geq 18$ RPE has been applied in some studies [206, 207], in addition to $\geq 19$ [197] and $\geq 17$ [226]. An RPE of $\geq 18$ is practically very close to both $\geq 17$ and $\geq 19$, as they are all within the ‘red’ category between ‘very
hard’ and ‘extremely hard’ (before 20; ‘maximal effort’) on the Borg scale. In the present study, the discrepancy between the percentage of patients reaching RPE ≥17 (86%) and ≥18 (65%) was large. Since there was only a small difference in $\dot{V}O_2\text{peak}$ between participants fulfilling the two cut-points (30.2 ml/kg/min vs. 30.4 ml/kg/min), we suggest that an RPE of ≥17 is sufficiently strict. Moreover, by applying an RPE of ≥17, we prevent excluding patients who could easily have subjectively evaluated their RPE as ≥18 as ≥17.

The cut-point of $f_R$≥40 breath/min was found to have the combined highest sensitivity and specificity to the test leader’s evaluation of whether a test was defined as ‘to exhaustion’. This cut-point was reached by 52%, and these patients had significantly (p<0.001) higher $\dot{V}O_2\text{peak}$ than patients not achieving this cut-point (32 vs. 27 ml/kg/min). Since $f_R$ has not been investigated systematically with the purpose of acting as a criterion in $\dot{V}O_2\text{max}$ testing previously, more research must confirm our findings.

In Table 11, the numbers of participants fulfilling one, two or three of the criteria in addition to the mean $\dot{V}O_2\text{peak}$ are presented.

### Table 11. Numbers of participants and mean peak oxygen uptake fulfilling one criterion or combinations of criteria. N=535.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Participants, n (%)</th>
<th>$\dot{V}O_2\text{peak}$, ml/kg/min (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPE of ≥18</td>
<td>345 (64)</td>
<td>30.4 (7.2)</td>
</tr>
<tr>
<td>RER ≥1.14</td>
<td>325 (61)</td>
<td>31.5 (6.9)</td>
</tr>
<tr>
<td>$f_R$ ≥ 40</td>
<td>274 (51)</td>
<td>32.4 (7.4)</td>
</tr>
<tr>
<td>RER ≥1.14 + RPE of ≥18</td>
<td>220 (41)</td>
<td>31.8 (6.7)</td>
</tr>
<tr>
<td>RPE of ≥18 + $f_R$ ≥ 40</td>
<td>196 (37)</td>
<td>32.5 (7.4)</td>
</tr>
<tr>
<td>RER ≥1.14 + $f_R$ ≥ 40</td>
<td>199 (37)</td>
<td>33.4 (6.6)</td>
</tr>
<tr>
<td>RER ≥1.14 + $f_R$ ≥ 40 + RPE of ≥18</td>
<td>140 (26)</td>
<td>33.3 (6.5)</td>
</tr>
</tbody>
</table>

**Abbreviations:** RER = Respiratory Exchange Ratio; ROC = receiver operating characteristic; RPE = ratings of perceived exertion; SD = standard deviation; $\dot{V}O_2\text{peak}$ = peak oxygen uptake; $f_R$ = respiratory frequency.

When applying one of these criteria, as many as 190 (RPE), 210 (RER) or 261($f_R$) participants are excluded, and by applying additionally one or two criteria, many tests are consequently excluded. When applying all three criteria, 395 out of 535 tests are ‘not accepted’ and would probably be too strict. Of the 140 participants who fulfilled all three cut-points, the mean $\dot{V}O_2\text{peak}$ was 33.3 (SD: 6.5) ml/kg/min, which is a similar mean as when fulfilling only the RER.
≥1.14 and \( f_R \geq 40 \) cut-points. Hence, adding the RPE of \( \geq 18 \) cut-point to these two, and thereby excluding 59 more participants, does not seem to be related to higher \( \dot{V}O_2 \) peak and may possibly not increase the validity of the included tests.

A more liberal approach would be to define that one or two out of the three criteria should be fulfilled, in addition to the test leader’s evaluation that the test was performed ‘to exhaustion’. In our sample of newly diagnosed cancer patients, 321 (60%) participants, with a mean \( \dot{V}O_2 \) peak of 33 (SD: 7.3) ml/kg/min, fulfilled the test leader’s evaluation (‘to exhaustion’) in addition to two of three cut-points (within RER, RPE and \( f_R \)) found in the ROC analysis. When focusing on the typically used criteria of RER and RPE, we found that when applying the two-out-of-three-criteria approach (having the test leader’s evaluation as one criterion), the number of accepted tests increased to 423 (79%), with a mean \( \dot{V}O_2 \) peak of 30.7 (SD: 7.2) ml/kg/min.

Whether the \( f_R \) could serve as an additional criterion for verifying \( \dot{V}O_2 \) max should be further investigated since, to our knowledge, it has not been applied in that setting previously. However, a \( f_R \) peak of \( \geq 40 \) breath/min could already be suggested to act as a cut-point that could help the test leader to evaluate the degree of exhaustion.

In summary, we suggest applying a ‘two-out-of-three approach’, including 1) the test leader’s evaluation (‘to exhaustion’); 2) RER ≥1.1 – 1.15; and 3) an RPE of \( \geq 17 \) or \( \geq 18 \) when verifying \( \dot{V}O_2 \) max in newly diagnosed cancer patients. Since cut-points within criteria may need to be adjusted for patients during or after cancer treatment, there is a need to elucidate how criteria and cut-points should be applied within these groups of patients.

### 6.3 Exercise-induced effect on \( \dot{V}O_2 \) max during cancer treatment

The results from the systematic review and meta-analysis of 13 studies demonstrate that exercise interventions with an aerobic component during (neo-)adjuvant cancer treatment positively impacted \( \dot{V}O_2 \) max compared with controls that did not receive any exercise intervention (Fig. 5).
The effect of exercise during cancer treatment on cardiorespiratory fitness is defined as moderate (ES: 0.46, 95%CI, 0.23 to 0.69) based on the included RCTs in the present thesis’ review and meta-analysis (Fig. 5). The finding of a beneficial effect on $\dot{V}O_2$max in cancer patients exercising during cancer treatment, compared with patients not exercising, is supported by findings reported in the meta-analysis including six RCTs by Jones et al. (2011), who found an increase in $\dot{V}O_2$max of 2.90 ml/kg/min (95% CI, 1.16 to 4.64) in patients who had been exercising during (two studies) or after cancer treatment (four studies) [152]. Furthermore, similar findings were reported in a meta-analysis from 2018, in which the included RCTs studied patients exercising before surgery (n=5), during (n=16) or after (n=27) cancer treatment. The exercise interventions were found to increase $\dot{V}O_2$max by 2.13 ml/kg/min (95% CI, 1.58 to 2.67) compared with control groups [153]. It should be noted that these meta-analyses from 2011 and 2018 include studies that investigated patients exercising during and before or after cancer treatment, which may be why they found large increases in cardiorespiratory fitness in exercising groups. In addition, the researchers included both maximal and submaximal cardiorespiratory fitness tests, compared with the present review, which only includes maximal tests.
Cardiorespiratory fitness is the most important predictor of all-cause mortality in healthy individuals and patients with CVD [7, 8]. Knowing that low cardiorespiratory fitness is associated with increased cardiovascular mortality in patients with breast cancer [5, 145] means that all beneficial changes in $\dot{V}O_2$max are clinically relevant. Cardiorespiratory fitness reflects the integrated ability to transport oxygen from the atmosphere to the mitochondria to perform physical work [107]. Consequently, this ability is directly related to numerous bodily systems and is, thus, considered a valid reflection of total body health [107].

Patients with cancer have been found to have impaired cardiorespiratory fitness, both before, during and after cancer treatment [5, 6, 95, 117, 119, 126, 247]. We know also that cancer treatments may negatively affect the cardiovascular and muscular system [70] and may cause side effects such as fatigue [77, 82], which can lead to physical inactivity. Therefore, patients with cancer should be encouraged to exercise in order to slow the decline, maintain or increase their cardiorespiratory fitness during (neo-)adjuvant cancer treatment.

### 6.4 FITT – factors

It is challenging to investigate each exercise characteristic within the FITT factors separately and isolated from the others. Exercise frequency, intensity and duration affect each other, and one characteristic may compensate for another to achieve the same effect on an outcome, such as $\dot{V}O_2$max (e.g. if there is a lack of time, intensity may be increased). Another challenge is that there are very few studies in which differences in the various FITT factors have been directly compared with each other.

Through the meta-analysis, we found no differences between studies with different exercise frequencies ($p=0.140$) and intensities ($p=0.090$) regarding significant effect on $\dot{V}O_2$max (Table 12). Furthermore, improvements in $\dot{V}O_2$max were significantly larger for studies with longer session durations ($z$-value, 2.30; $p=0.020$), longer weekly exercise durations ($z$-value, 2.53; $p=0.010$), and larger weekly exercise volumes ($z$-value, 3.57; $p < 0.001$) (Table 12). However, studies with shorter intervention durations displayed significantly larger improvements in $\dot{V}O_2$max than studies with longer intervention durations ($z$-value, −2.80; $p=0.005$) (Table 12).
Table 12. Overall and subgroup analysis of effect sizes (Hedge’s g) and heterogeneity (n=14 comparisons).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Effect size, g (95% CI)</th>
<th>I²</th>
<th>Between-group difference (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>14</td>
<td>0.53 (0.27;0.78)</td>
<td>69.65*</td>
<td></td>
</tr>
<tr>
<td>Overall without outlier</td>
<td>13</td>
<td>0.46 (0.23;0.69)</td>
<td>64.42*</td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention duration</strong> (regression)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supervision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsupervised</td>
<td>2</td>
<td>0.42 (-0.75;1.59)</td>
<td>57.37*</td>
<td></td>
</tr>
<tr>
<td>Supervised</td>
<td>11</td>
<td>0.49 (0.26;0.72)</td>
<td>81.60*</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>4</td>
<td>0.21 (-0.19;0.61)</td>
<td>41.53</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0.65 (0.42;0.87)</td>
<td>30.19</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>3</td>
<td>0.32 (-0.24;0.89)</td>
<td>69.01*</td>
<td></td>
</tr>
<tr>
<td>Intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-moderate</td>
<td>2</td>
<td>0.42 (-0.75;1.59)</td>
<td>81.60*</td>
<td></td>
</tr>
<tr>
<td>Moderate-high</td>
<td>3</td>
<td>0.50 (0.15;0.85)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>0.48 (0.19;0.77)</td>
<td>67.87*</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AET</td>
<td>8</td>
<td>0.48 (0.19;0.76)</td>
<td>53.50*</td>
<td></td>
</tr>
<tr>
<td>AET+RET</td>
<td>5</td>
<td>0.42 (-0.03;0.86)</td>
<td>78.24*</td>
<td></td>
</tr>
<tr>
<td><strong>Duration (regression)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session duration</td>
<td>13</td>
<td>2.24</td>
<td>0.03*</td>
<td></td>
</tr>
<tr>
<td>Weekly duration</td>
<td>13</td>
<td>2.48</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>Volume (MET’s/week)</td>
<td>13</td>
<td>3.17</td>
<td>0.002*</td>
<td></td>
</tr>
<tr>
<td>Volume (MET’s total duration)</td>
<td>13</td>
<td>-0.51</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

Note: Outlier Al Majid et al. (2015) is removed from analyses. Abbreviations: AET, aerobic exercise training; CI, Confidence Interval; g, the Hedges’g statistics; I², heterogeneity; MET’s, Metabolic equivalents and RET, resistance training. *significant (<0.05).
6.4.1 Frequency

Exercise frequency is not associated with improvements in $\dot{V}O_2_{\text{max}}$ in the present systematic review and meta-analysis. The exercise characteristic frequency has not been investigated in relation to training effects in many studies, when adjusting for exercise volume [154]. However, in the meta-analysis by Huang et al. (2016), they found a peak increase in $\dot{V}O_2_{\text{max}}$ when exercising 3.5 days/week, and that more and fewer days produced smaller effect sizes. However, it is unclear from their study whether they adjusted or accounted for total exercise volume in their analyses. In addition, they conclude that more clinical controlled studies are needed to confirm their results [156].

Both the ACSM’s PA recommendations for healthy individuals [103] and the latest exercise guidelines for cancer survivors [102] point towards that exercise frequency largely depends on duration and intensity. For example, a patient recently diagnosed with breast cancer may prefer (or is recommended) to exercise at high intensity (e.g. interval sessions on 85-95% of HR reserve, with two-minute intervals and two-minutes rest * 6-8 intervals) to induce time-efficient improvements in $\dot{V}O_2_{\text{max}}$ [248]. Another patient may not want (or is not recommended) to perform high-intensity exercise, but instead walk for 40 minutes at moderate intensity (40-60% HR reserve). Hence, exercise frequency needs to be adjusted according to duration and intensity and be prescribed appropriately for the outcome of interest [249].

6.4.2 Intensity

In our meta-analysis, we found no significant differences in the training-induced change in $\dot{V}O_2_{\text{max}}$ by exercising at different intensities within the categories ‘low-moderate’, ‘moderate-high’ and ‘high’. However, there was a trend that the effect on $\dot{V}O_2_{\text{max}}$ was larger in studies with higher exercise intensity ($p=0.09$) (Paper I).

**Phys-Can, intention-to-treat analysis**

In the analyses performed according to ITT (including multiple imputations), the mean post-intervention $\dot{V}O_2_{\text{max}}$ difference between intensity groups was 1.60 (95% CI; 0.12 to 3.07) ml/kg/min (Paper III), adjusted for age, education level, hospital, diagnosis and treatment with chemotherapy. Since missing $\dot{V}O_2_{\text{max}}$ results at baseline were more than 10%, $\dot{V}O_2_{\text{max}}$ at baseline was not included as a covariate in the ITT analysis.
Our main results indicate that exercising at HI produced significantly larger differences in \( \dot{V}O_2 \text{max} \) compared with LMI. This finding agrees with one previous study in which the aim was to investigate two different PA/exercise programs with different intensities in patients undergoing cancer treatment [157]. Importantly, in PACES, by van Waart et al., the exercise programs differed in intensity, type, supervision and weekly exercise volume. Rather than studying the effect of intensity per se on changes in cardiorespiratory fitness, two different physical activity/exercise interventions were investigated [157]. In Phys-Can, however, there was an effort to control exercise volume, and endurance training was performed at home for participants in both the HI and LMI groups, which is different from the PACES design. Furthermore, the PACES design used the maximal short exercise capacity on the steep ramp test to evaluate changes in cardiorespiratory fitness, and not a direct measure of \( \dot{V}O_2 \text{max} \) [157].

Among the studies performed in the post-treatment setting, a beneficial effect on cardiorespiratory fitness by performing HIIT compared with continuous LMI exercise was found [163, 164]. However, the two RCTs by Devin et al. from 2016 and 2018 were conducted several months (years) after finishing treatment for colorectal cancer [163, 164], making it difficult to compare their findings with results from this present study.

Other RCTs performed in a post-treatment setting reported no differences in \( \dot{V}O_2 \text{max} \) between intensity groups [158, 160-162]. One RCT was designed to be comparable to Phys-Can; the REACT study by Kampshoff and colleagues from 2015 [158]. The two exercise arms in the REACT study only differed regarding exercise intensity; whereas, the prescribed exercise type, duration and frequency was similar in the HI and LMI interval exercise groups [158]. Large improvements in \( \dot{V}O_2 \text{max} \) were observed in the HI exercise group, but the difference between intensity groups did not reach a statistically significant level [158]. One limitation regarding the REACT study was that Kampshoff et al. used predicted and not measured HRmax when prescribing intensity. Knowing that there is 10 to 12 beat-per-minute variations in HRmax in healthy individuals [229, 230] and estimating HRmax based on this formula is problematic [231, 232], with supposedly even larger variations in a diseased population due to beta-blocker use or other medications [233, 234, 250]. In the RCTs by Dolan et al. (2016) and Schmitt et al. (2016), no differences in \( \dot{V}O_2 \text{max} \) were found in women performing continuous LMI or HIIT after their cancer treatment [161, 162]. However, the studies lasted only six and three weeks, respectively; thus, these interventions may have been too short to produce differences in \( \dot{V}O_2 \text{max} \) between intensity groups. In Martin et al. (2015), the non-significant difference
between intensity groups ceased when additional assessments were performed four months post-intervention, finding HI to preserve \( \dot{V}O_2 \)max better than the low-intensity group [160].

It is notable that neither the PACES study nor the REACT study includes adherence rates; each only reports the numbers of attended exercise sessions [157, 158]. These two RCTs performed ITT analyses and did not adjust for the reported exercise attendance rate in their analysis.

When evaluating exercise interventions, there is a need for thoroughly control of the total exercise volume (i.e. combination of intensity and duration) and exercise adherence [154]. It is challenging to construct study designs that enable valid adherence reporting [251]. In Phys-Can, we focused on reporting adherence to the exercise prescriptions. The exercise adherence was significantly higher (p=0.001) in the LMI group (62%) than in the HI exercise group (51%) (Table 8). Furthermore, the participants in the LMI group exercised above 60% HRR for an average of 630 (SD: 1092) minutes across the six-month intervention. Therefore, each week, the participants in the LMI group performed, on average, ~26 minutes above the intensity they were prescribed (calculating for a 24-week intervention). We believe that the lower adherence to the HI exercise may have contributed to the relatively small difference in \( \dot{V}O_2 \)max between groups. Since the adherence was higher among participants exercising at LMI, longer exercise durations may have compensated for the lower exercise intensity, and/or the participants exercised at higher intensities than prescribed.

**Phys-Can, complete-case analysis**

Linear regression analysis for the 331 participants with an accepted \( \dot{V}O_2 \)max test at pre- and post-intervention (a complete-case analysis) was performed in this present thesis. Baseline \( \dot{V}O_2 \)max (p≤0.001) and adherence (p≤0.001) were significantly associated with the difference in post-intervention \( \dot{V}O_2 \)max between intensity groups. In Fig. 6, the crude, relative difference in \( \dot{V}O_2 \)max at post-intervention between LMI and HI groups (p=0.263), the difference when adjusting for age, diagnosis, hospital and baseline \( \dot{V}O_2 \)max (p=0.205), and the difference when adding adherence as an additional variable in the model (p=0.036) are presented.
Figure 6. Relative (%) difference in maximal oxygen uptake after six months of exercise and cancer treatment (mean with 95% Confidence Intervals), n=331. Differences are presented as crude, adjusted for covariates (age, diagnosis, hospital and \( \dot{V}O_2 \)max at baseline) and adjusted for covariates and adherence. 

Abbreviation; \( \dot{V}O_2 \)max, maximal oxygen uptake. * = difference between intensity groups (p≤0.05).

The post-intervention differences presented in Fig. 6 elucidate that, particularly when adding adherence in the analysis, a change in the results was evident, highlighting that adherence is important to consider (adjust for) when evaluating the effect of two different exercise interventions.

To elucidate further the importance of adherence, we conducted stratified analysis based on median adherence (57.4%). For participants at or above median adherence (n=165), a significant difference in post-intervention \( \dot{V}O_2 \)max (-3.13, 95% CI; -5.04 to -1.23 ml/kg/min) was found between intensity groups. Moreover, when adjusting for age, diagnosis, hospital and baseline \( \dot{V}O_2 \)max, the difference (-1.59, 95% CI; -2.73 to -0.45 ml/kg/min) between intensity groups remained significant. In contrast, for participants with less than 57.4% (n=166) exercise adherence, there was no difference in crude (-0.71, 95% CI; -1.50 to 2.91 ml/kg/min) or adjusted (0.01, 95% CI; -1.07 to 1.09 ml/kg/min) post-intervention \( \dot{V}O_2 \)max between intensity groups. These findings substantiate the notion that participants need to perform the training with a certain diversity in intensity in order to produce a difference in effect on \( \dot{V}O_2 \)max.
In addition to the possible explanation related to the group-differences in exercise adherence, the small between groups differences in Phys-Can may also partly be explained by the exercise intensity in the LMI group being within or above a possible intensity range in which healthy older adults have been found to achieve improvement in $\dot{V}O_{2}\text{max}$ [156]. In the meta-analysis by Huang et al. (2016), the intensity level at which $\dot{V}O_{2}\text{max}$ gains began to be effective was around 35 to 50% of HRR [156]. This response to low exercise intensities is confirmed in another meta-analysis by Høydal (2017), which includes a variety of exercise studies with healthy, overweight and obese individuals at different ages, in addition to various patient groups (e.g. heart failure, hypertension, metabolic syndrome and young with fatigue) [252]. Although Høydal found that the improvements in $\dot{V}O_{2}\text{max}$ were related to increasing exercise intensity, the lowest intensity-category (<45% of relative $\dot{V}O_{2}\text{max}$) also affected $\dot{V}O_{2}\text{max}$ [252]. According to Swain et al. (2002) [253], individuals with a baseline $\dot{V}O_{2}\text{max}$ below 40 ml/kg/min are supposed to expect improvements in $\dot{V}O_{2}\text{max}$ at a minimum ~38% of $\dot{V}O_{2}\text{max}$, supporting the findings in Huang et al. (2016) and Høydal (2017) [156, 252].

Based on the ITT- and complete-case analysis (when adjusting for adherence) from Phys-Can, a significant difference in $\dot{V}O_{2}\text{max}$ was observed between patients who had exercised at HI or LMI during cancer treatment. When investigating the crude difference in $\dot{V}O_{2}\text{max}$ among the 331 participants with complete cases at pre- and post-intervention, no significant difference was observed between intensity groups. However, when adding adherence in the regression model, the relative difference in $\dot{V}O_{2}\text{max}$ became significant, with an improvement in the HI group. Collectively, the results from the meta-analysis (Paper I), from Phys-Can (Paper III) and the additional analysis performed in this thesis, there is support that HI exercise is most beneficial for improving $\dot{V}O_{2}\text{max}$ in patients undergoing treatment for cancer, given that the patients can manage to complete the HI training.

6.4.3 Type

Due to there being few studies in the meta-analysis, we could neither investigate the effect on $\dot{V}O_{2}\text{max}$ between AET and RET nor between different types of endurance training.

In the studies by Devin et al. (2016 and 2018), HIIT on a cycle was more effective at improving $\dot{V}O_{2}\text{max}$ compared with LMI continuous training on a cycle for people previously treated for colorectal cancer [163, 164]. In contrast,
no difference in $\dot{V}O_2\text{max}$ was found between HIIT and continuous moderate-intensity walking or running [161]. However, as mentioned previously, to our knowledge, there are no studies in which different types of endurance training are compared in the exercise-oncology field without also differing in exercise duration, intensity (volume) or frequency. No studies in which different modalities (e.g. exercise vs cycle) are compared were found in the exercise-oncology literature.

However, some studies have compared the effect on different outcomes (e.g. fatigue, quality of life, physical functioning, fitness, body composition, adiponectin, leptin, insulin-like growth factors and chemotherapy completion rates) by performing AET or RET in cancer patients undergoing cancer treatment. In the RCT conducted by Segal et al. (2009), 121 prostate cancer patients initiating radiotherapy with or without ADT were randomly assigned to usual care, RET or AET for 24 weeks [93]. Their findings, that both RET and AET led to improvements in $\dot{V}O_2\text{max}$ compared with patients in the usual care group, were discussed as being partly explained by some participants in the RET group who additionally performed some AET on their own [93]. Another explanation for their finding may be that RET caused significantly improved muscle strength compared with AET [93]. In a meta-analysis of RCTs including adults with coronary heart disease (34 studies) performing RET, the researchers found RET to be as efficient as AET in improving cardiorespiratory fitness [254]. Findings supportive of the expected adaptations to RET and AET were observed in the study by Courneya et al. (2013), in which patients randomly assigned to the HIGH group (150 min AET) had a larger beneficial change in $\dot{V}O_2\text{max}$ than those performing AET at 75 min (STAN), and compared with the COMB group, which practised both RET and AET [170]. In a study in which patients who underwent ADT for prostate cancer were randomly assigned to either home-based AET or RET for 24 weeks, no significant difference in estimated $\dot{V}O_2\text{max}$ was found between the exercise groups [255]. The main outcomes of interest in that particular study concerned adipokines and insulin-like growth factors, rather than cardiorespiratory fitness. Santa Mina et al. (2013) found RET to be superior to AET in affecting adipokine levels and, in both exercise groups, favourable changes in body composition and aerobic fitness were correlated with favourable levels both mid-way and at the end of the six-month intervention [255].

6.4.4 Time (duration)

In our meta-analysis, we found a larger beneficial effect of increased session duration and weekly exercise duration on $\dot{V}O_2\text{max}$. However, regarding
intervention duration, we observed that the effect sizes decreased with longer durations (Table 12). There are findings in the literature supporting these results. Regarding session duration, Huang et al. (2016) found in their meta-analysis a dose-response relationship between an increasing session duration of AET and \( \dot{V}O_2 \) max in healthy elderly adults [156]. Interestingly, they found a ceiling effect (\( \dot{V}O_2 \) max did not increase further) in session durations of approximately 45 minutes [156]. In the aforementioned multicentre randomised trial including breast cancer patients, Courneya et al. (2013) found that weekly AET for 150 minutes (at 70%-75% of \( \dot{V}O_2 \) peak) produced more beneficial changes in \( \dot{V}O_2 \) max (-2.5, 95%CI, -3.2 to -1.8 ml/kg/min) than 75 minutes of AET at the same intensity (-3.4, 95%CI, -4.1 to -2.7 ml/kg/min), supporting our findings that increasing session and weekly duration is associated to beneficial changes in \( \dot{V}O_2 \) max [170]. It is notable that the adjusted between-group differences at post-intervention were small in the study by Courneya et al. (2013); +0.9 (95%CI, -0.1 to 1.9 ml/kg/min) [170]. Increasing exercise intensity may compensate for session duration, making the exercise more time-efficient [165, 248]. In respect to meta-analysis results related to the larger \( \dot{V}O_2 \) max improvements evident in shorter vs longer interventions, these may result from lower adherence in exercise interventions lasting longer [256], but due to a lack of information about adherence in the included RCTs, this observation could not be further investigated.

6.4.5 Summary of the four exercise characteristics

In summary, since all FITT factors may interchangeably influence \( \dot{V}O_2 \) max, it is challenging to disentangle whether it is one specific variable or a combination of variables that results in larger improvements (or less decline) in \( \dot{V}O_2 \) max. In the meta-analysis, neither frequency nor intensity was per se associated with beneficial changes in \( \dot{V}O_2 \) max. Instead, exercise duration and volume were associated with changes in \( \dot{V}O_2 \) max. However, since weekly exercise duration and volume are a function of frequency, intensity and session duration, the combination of these variables seems important. In Phys-Can, the difference in post-intervention \( \dot{V}O_2 \) max was not large between the HI and LMI exercise groups. There were no differences between intensity groups when analysing complete cases. However, when adjusting for adherence to the endurance training, there was a significant effect of exercising at HI vs. LMI in Phys-Can. Overall, the results support the notion that exercise intensity is important, but also that the combination of intensity and duration (exercise volume) is essential.
to consider when aiming to improve/maintain VO$_2$max in patients undergoing treatment for cancer.

### 6.5 Methodological considerations

There are some methodological-related aspects that should be discussed as they are potentially threats to the external and internal validity of this present study.

#### 6.5.1 External validity

**Recruitment and representative of the population**

In Phys-Can, 29% of the available patients consented to participate. The included participants in Phys-Can had a mean age of 59 years old (mean and median age of the 331 participants with pre-post VO$_2$max was 57 years old) and were mainly well-educated women being diagnosed with breast cancer stage I or II. The participants agreed to take part in a comprehensive six-month exercise intervention, indicating that they had high motivation and readiness to adopt (or maintain) exercise during demanding cancer treatment. However, the participants varied in age, current PA levels and perceived importance of exercise. The participants did not develop the idea of participating in the exercise intervention, nor did they contact the project themselves, but were recruited by oncology nurses and physicians at the oncology departments at Lund, Linköping and Uppsala.

When comparing Phys-Can participants with participants involved in other large exercise intervention studies, there are some similarities and some dissimilarities. In both the REACT and the PACES studies, the largest proportion of participants were women with breast cancer, although ovarian, lymphoma, cervix and testis cancer could also be included in the REACT study, and colon cancer could be included in the PACES study [157, 158]. Of the 577 randomised patients in Phys-Can, the distribution is 79%, 17% and 4% for respectively breast-, prostate- and colorectal cancer. This percentage distribution does not represent the distribution in the general cancer population, in which the incidence of breast and prostate cancer stands for approximately similar percentages within each gender (prostate: 28% and breast: 22%), and in both genders, colorectal cancer accounts for approximately 13% of the total cancer incidence [32].
In Norway, median age at diagnosis is 62 years old, 69 years old and 73 years old for breast-, prostate- and colon cancer, respectively [32]; thus, slightly older than the patients randomly assigned to exercise in Phys-Can. However, in the PACES and the REACT studies, the average age of the participants was slightly younger than in Phys-Can. In the study by Courneya et al. (2013), in which only women with breast cancer were included, the mean age was approximately 50 years old [170]. Regarding recruitment in these three studies, 37%, 44% and 41% of eligible patients participated in the REACT study, the PACES study and the study by Courneya et al. (2013), respectively [157, 158, 170]. The recruitment-process was not well reported in the PACES study, but in the REACT study and the study by Courneya et al., eligible participants were identified and referred to the study by their treating oncologist [157, 158, 170], a similar recruitment method as in Phys-Can. In summary, the participants in Phys-Can were slightly younger than the general, newly diagnosed cancer population in Norway, but at the same age or older than comparable exercise intervention studies. Furthermore, we clearly managed to recruit mostly women (with breast cancer), a common observation in exercise intervention studies in the exercise-oncology field [12]. That most studies published in the exercise-oncology field have included breast cancer patients [12] makes the generalisability to other cancer populations uncertain, since patients with breast cancer are often younger than, for example, colorectal and prostate cancer patients [30]. The treatments are different also, especially between prostate- and breast cancer patients.

The results are not representable for breast cancer patients with a higher disease-stage or with other types of cancer than breast and prostate. Since the inclusion of patients diagnosed with colorectal cancer was low, we cannot generalise our findings to this patient group.

6.5.2 Internal validity

Test-instruments

In Phys-Can, a treadmill instead of a cycle ergometer was chosen when performing the $\dot{V}O_2\text{max}$ test. The rationale for this choice was that most participants in the pilot study prior to Phys-Can stated that they would prefer walking or running as their aerobic exercise modality. Further, walking (or running) is a more familiar way of moving [177], and upright walking causes greater muscle mass use [177]. Generally, 12 to 20% higher $\dot{V}O_2\text{max}$ levels are reached when tests are performed on treadmills rather than on a cycle ergometer [124].
Due to the small increments in energy expenditure from one level to the next in the Balke protocol, this is often used and assumed to be a suitable protocol when performing maximal testing in clinical populations [257]. In Phys-Can, different alternatives were piloted before initiating the main study. A modified version of the Balke protocol was found to be suitable, in which the changes in inclination were set to 0.5% each minute (instead of the original increase of 1% each minute). Since the treadmills on the different sites could not increase the inclination to higher than 12%, this was the highest inclination used, and after this, only the speed increased each minute.

Ideally, to be more certain that a maximal effort was made on the $\dot{V}O_2$max test (both pre- and post-intervention), we would have re-tested all our participants in Phys-Can, making sure that we had the most valid results as the basis for prescribing exercise intensity and when comparing pre- and post-intervention values. However, this approach was not possible due to practical and financial considerations.

When testing cardiorespiratory fitness in clinical oncology research, a full cardiopulmonary exercise test (CPET) may, in some circumstances, be recommended, enabling assessment of clinical status in addition to $\dot{V}O_2$max [130, 258]. In Phys-Can, the rationale for performing $\dot{V}O_2$max testing of participants was, first, to enable individualised exercise intensity prescriptions based on HRmax achieved during the $\dot{V}O_2$max test; and second, to define cardiorespiratory fitness at baseline and post-treatment/intervention. A physician comprehensively examined all the patients prior to the $\dot{V}O_2$max test and participation in the exercise intervention.

The definition of a $\dot{V}O_2$ plateau, as included in Paper II, is perhaps not the most suitable method due to the protocol differences between the discontinuous test protocols applied on healthy young men in the 1950s by Taylor et al. [218] and the modified Balke protocol used in Phys-Can. In addition, we did not include relative body mass in the equation, which is a limitation. The rationale for using the definition suggested by Taylor et al. (1955) was that this was the original definition [177] and has been applied in many studies. One criticism related to applying the Taylor definition is that it is too liberal when using continuous graded protocols, especially for elderly patients and unfit individuals [196]. There is much debate and criticism related to aspects concerning the plateau criterion: the methodology for detecting it, its definition, its existence, its reliability, and the prevalence of fulfilling it within and between studies [189, 195, 259]. Therefore, we decided not to emphasise the criterion and the different
methodological approaches for detecting it. However, in Paper II, we investigated two stricter \( \dot{\text{V}}\text{O}_2 \) plateau cut-points in the linear regression model as well. Neither the \( \Delta \dot{\text{V}}\text{O}_2 \leq 80 \) nor the \( \leq 50 \text{ ml/min} \) cut-points were significantly associated with the test leader’s evaluation.

**Blinding of assessors**

The test leaders were blinded regarding which intensity group the patient they tested had been randomly assigned to. Optimally, this approach would have been applied for all \( \dot{\text{V}}\text{O}_2 \text{max} \) tests, but for practical reasons, this was not accomplished in all the post-intervention tests. This approach was mostly a challenge in Uppsala, since two of the instructors from the exercise groups assisted in a few \( \dot{\text{V}}\text{O}_2 \text{max} \) tests. Blinding exercise instructors and coaches regarding which exercise group their patients were randomly assigned to was not practically possible, as others also have reported [154]. The participants were not blinded regarding which exercise programme they were part of, mainly due to practical issues related to the fact that participants in the different exercise groups spoke about their exercise to one another at the gyms.

**The time course and ‘the Hawthorne effect’**

Simply being part of an exercise study may influence participants to change their behaviour and habits, potentially increasing their PA level above the exercise intensity prescribed [154]. The consequence for Phys-Can could be that the participants in the LMI groups increased their exercise intensity, making the two exercise groups more alike. This consequence may be even more pronounced or potent considering that the participants are part of a six-month study. During an intervention period, there is always a chance that participants randomly assigned to one exercise group are not convinced that the programme they are assigned to is the most health-inducing of the two. Consequently, they may choose to not exercise as prescribed. Furthermore, when participants do not adhere to their exercise programme, the findings related to the differences between the two intensity groups are invalid. In Phys-Can, the adherence to the endurance training was higher in the LMI group, supporting the conjecture that the two intensity groups may have developed to be more equal than intended. Consequently, we may question the validity of the findings from the ITT analysis, since adherence was not adjusted for.

When designing and performing exercise intervention studies in which two exercise programmes are compared, instead of only one exercise group and one
control group, extra focus is necessary to ensure adherence to the prescribed exercise frequency, type, duration and intensity [154]. Intensity, which was prescribed differently between the two exercise groups in Phys-Can, is one exercise characteristic that is challenging to control. However, comprehensive instructions and follow-ups were provided by the exercise instructors in Phys-Can. In addition, the participants registered their exercise in logbooks and wore HR monitors during the AET, ensuring as high adherence as possible in a six-month exercise intervention with a relatively large exercise volume. We still need to remember that exercise duration and volume are challenging to control, and not all PA was registered in the logbooks.

Considerations related to statistical analyses

In the meta-analysis in Paper I, we did not contact the authors of each study to ask for the raw data, which potentially could have enabled more precise estimates of the effect sizes presented. Instead, we used the reported information found in the published papers, although we did contact some authors regarding additional information not presented in the published paper (which made these studies eligible for the meta-analysis). The categorisation of the subgroups within exercise frequency (2-3, 3 and >4 times/week) and intensity (‘low-moderate’, ‘moderate-high’ and ‘high’) may be too overlapping to investigate properly how these factors affect changes in $\dot{V}O_2$max. Moreover, due to only being a few studies, we were unable to perform stratified analyses based on cancer treatment, which is important to consider when interpreting the findings.

In Paper II, a ROC analysis was performed to establish cut-points for the three criteria found to be associated with the outcome: the test leader’s evaluation (‘to exhaustion’ or not). These cut-points were further cross-validated on a cohort including a smaller sample of comparable patients, but since only four of the tests in this cohort were evaluated as ‘not to exhaustion’, the findings from the cross-validation are considered to be descriptive.

Both a complete-case analysis and an ITT analysis (including multiple imputations for missing values) were conducted to investigate the effect of intensity and BCS on the outcomes in Paper III. When performing a complete-case analysis to study the efficiency of an exercise intervention on an outcome, adherence is important to include in the regression models [154]. If we do not account for adherence to the prescribed exercise (to the frequency, intensity, type and time/duration), we only measure the effect of the randomisation, not the exercise that has been performed. Although ITT analysis is the recommended
and most conservative approach when analysing the effectiveness of an intervention in an RCT [260], there are some arguments in favour of performing per-protocol analysis as well. A per-protocol analysis would primarily (and to a larger degree) enable analyses of the direct association between the performed exercise and the outcome of interest. However, we did not know in advance exactly how the endurance training would be performed, since the participants were offered the possibility to choose their practical approach individually. An important argument for not choosing a per-protocol analysis was that there is no consensus in the literature regarding how patients undergoing treatment for cancer should exercise. Therefore, we decided that we would rather adjust for exercise adherence in the analyses performed in this thesis.

In the ITT analysis, baseline \( \dot{V}O_2 \text{max} \) was not included as a covariate due to >10% missing at baseline [261]. Adherence to the exercise was not included in the ITT analysis either. However, in the additional analyses in this present thesis, we included baseline \( \dot{V}O_2 \text{max} \) and adherence when investigating the differences in post-intervention \( \dot{V}O_2 \text{max} \). When the baseline value of a measure such as \( \dot{V}O_2 \text{max} \) is not included as a covariate in the regression model, we do not adjust for the by-chance differences at baseline, which may, consequently, affect the results [154, 262, 263]. In this present thesis, we focused on elucidating the differences observed by including certain adjusting variables (baseline \( \dot{V}O_2 \text{max} \) and adherence) in the regression models. Other covariates included in the regression models were age, diagnosis and hospital. Without going into depth regarding these covariates, age was chosen because we know that cardiorespiratory fitness decreases with age, and that it may be more challenging for older individuals to handle demanding exercise interventions. Since Phys-Can mainly had patients with breast- and prostate cancer, we selected diagnosis instead of gender, since this variable adds potential disease characteristics (and some of the differences related to the diagnose-specific treatments, e.g. chemotherapy vs. ADT). Hospital was also added as a covariate due to the possibility that different sites would perform the exercise and testing with variations, although there was a focus on preventing this.

In Paper II, we adjusted for age, diagnosis, \( \dot{V}O_2 \text{peak} \) and test duration in the logistic regression, since these variables may be associated with the test leader’s evaluation of whether the participants performing the \( \dot{V}O_2 \text{max} \) test were exercising ‘to exhaustion’.
**Ethical considerations**

When designing an exercise intervention study in which the objective is to investigate causal relationships, the gold standard is considered to be RCT. The main aim of Phys-Can was to determine the effects of LMI and HI exercise with or without BCTs on cancer related fatigue and health related quality of life in persons with cancer, both during treatment and in the long-term, post-treatment survivorship period. If the study design had enabled randomisation to either one of the two exercise intensities or to usual care (which received no extra attention), we could have additionally reported the effects of two different exercise arms compared with usual care. However, cancer patients are recommended to be as physically active as possible and to exercise regularly [13, 101, 102]. There are many previously published RCTs that have investigated one or two exercise intervention arms with a control group, finding a beneficial effect on $\dot{V}O_2$max from exercising compared with being in a control group [153]. Additionally, as the exclusive aim in Phys-Can was to compare LMI against HI, there was no need for a control group. Therefore, Phys-Can’s second-generation study design, in which two exercise intensities are compared, with no patients being randomly assigned to a control group, is a reasonable approach to answer the present study’s objectives.

Furthermore, given the aim of investigating interval training at HI in Phys-Can, which has not been widely studied in the exercise-oncology field, we did not want to include patients who were at high risk. Only breast-, prostate- and colorectal cancer patients were eligible. The rationale for choosing these three subgroups was that these patients may safely perform PA and exercise [206, 208, 264-267]. Moreover, only patients scheduled to begin (neo-)adjuvant treatment with a curative intent were eligible, which was chosen for the same reason, in addition to patients being prescribed a six-month exercise intervention with follow-up measurements. Additionally, we intend to follow the participants 10 years after the exercise intervention and to evaluate the cost-effectiveness related to their participation. By including cancer types with high incidence and prevalence, as well as excluding patients with the most severe disease stages, enables a high possibility for many patients being alive 10 years later.

Geographical proximity to the public gyms used to perform the exercise is important to be able to attend and adhere to the exercise interventions. Furthermore, gyms close to the participant’s homes facilitate a smooth transition from a study setting to maintained exercise on their own, post-intervention. Many
eligible patients living far from these gyms chose not to participate because of the distance.

Patient representatives were actively involved during the entire process and were part of the discussions from planning to implementation of the Phys-Can study.

**Validity of findings related to cut-points found in the receiver operating characteristic analysis**

The rationale for selecting different cut-points verifying \( \dot{V}O_2 \text{max} \) in Paper III, rather than exactly the cut-points resulting from the ROC analysis, was mainly that the findings in Paper II are somewhat premature and needs to be confirmed in future studies.

We should remember that the cut-points \( \text{RER} \geq 1.14 \), \( \text{RPE} \geq 18 \) and \( f_R \geq 40 \) were derived through the ROC analysis, in which the test leaders’ evaluations were the effect variable. As discussed previously, there are some uncertainties in relying completely on the test leaders’ evaluations, as well as on the precise cut-points that, consequently, were established through the ROC analysis. In other studies in which criteria have been investigated, two or three \( \dot{V}O_2 \text{max} \) tests have been compared, enabling findings related to criteria cut-points or the fulfilment of a \( \dot{V}O_2 \) plateau for the investigated populations: young fit men [259], obese, post-menopausal women [198], athletes [194] and overweight and obese adults [197]. To our knowledge, regression or ROC models including typical \( \dot{V}O_2 \text{max} \) criteria variables and one effect variable (e.g. the test leader’s evaluation [as in our study]) have not previously been performed on any population. Furthermore, one important reason for choosing slightly more liberal cut-points in Phys-Can’s main paper (Paper III) was that we only investigated these criteria (and cut-points) in newly diagnosed cancer patients, without yet having been affected by any cancer treatments. Whether patients who have undergone chemotherapy and other cancer treatments would have responded differently, especially related to the RER criterion, is speculative. Based on these arguments, we selected the test leader’s evaluation and two often-used criteria and cut-points from the literature (and not far from the ‘ROC-cut-points’) – \( \text{RER} \geq 1.1 \) and Borg’s \( \text{RPE} \geq 17 \) – when verifying \( \dot{V}O_2 \text{max} \) in Paper III. Applying these cut-points also enabled us to compare our results better with previous published studies (which mainly have applied the \( \text{RER} \geq 1.1 \) [172, 228]).
7 CONCLUSIONS

The overarching aim of this present thesis was to address whether exercise intensity can affect cardiorespiratory fitness from time of diagnosis until post-treatment. Secondarily, the aim was to increase the validity of cardiorespiratory fitness tests among patients diagnosed with cancer. The main conclusions are summarised as follows:

1. When describing peak values and the fulfilment of various \( \dot{V}O_2 \text{max} \) criteria in a population of newly diagnosed patients with breast-, prostate- and colorectal cancer, we observed that this group of patients responded similarly to healthy age-matched individuals in peak values of \( \dot{V}O_2 \), RER, Borg’s RPE and HR. Furthermore, the participants fulfilled criteria cut-points within a \( \dot{V}O_2 \) plateau, RER, Borg’s RPE and HR largely similarly to that reported in healthy individuals. More specifically, 91% fulfilled the most accessible \( \dot{V}O_2 \)-plateau criterion, 77% fulfilled the RER≥1.1 cut-point, and 65% fulfilled the ≥18 RPE cut-point.

2. The criteria of RERpeak, Borg’s RPE and \( f_R \) peak were associated with the test leader’s evaluation of whether a test was defined as being ‘to exhaustion’. Within these three variables, the cut-points found to have the highest sensitivity and specificity for predicting the test leader’s evaluation were RER ≥1.14, RPE ≥18 and \( f_R \) ≥40. In summary, we suggest applying a ‘two-out-of-three approach’, including 1) the test leader’s evaluation (‘to exhaustion’); 2) RER ≥1.1 – 1.15; and 3) an RPE of ≥17 or ≥18 when verifying \( \dot{V}O_2 \text{max} \) in newly diagnosed cancer patients.

3. From the systematic review and meta-analysis of 13 studies, exercise interventions with an aerobic component during (neo-)adjuvant cancer treatment positively impacted \( \dot{V}O_2 \text{max} \), compared with controls that did not receive any exercise intervention. The beneficial effect of aerobic exercise on \( \dot{V}O_2 \text{max} \) was defined as moderate (ES: 0.46, 95%CI, 0.23 to 0.69). Our results confirm findings previously reported in other meta-analyses.
4. From the meta-analysis, longer session- and weekly duration, in addition to exercise volume (combination of duration and intensity), were significantly associated to positive changes in VO₂max. Neither frequency nor intensity was significantly associated with changes in VO₂max per se. However, the results from the Phys-Can RCT reveal a positive effect on changes in VO₂max by exercising at high vs. low-to-moderate intensity. A thorough control of exercise volume and adherence to the exercise is important to observe such positive changes in patients undergoing treatment for cancer. Overall, exercise intensity seems important for improvements in VO₂max, together with total exercise volume. As weekly exercise volume are a function of frequency, intensity and session duration, the combination of these variables seems important for improvements in VO₂max.

7.1 Clinical implications

The work from Paper II represents a starting point towards having a more thoroughly prepared set of criteria verifying VO₂max in a population of newly diagnosed patients with cancer. Relating the findings to clinical practice, we do not suggest including predicted HRmax as a criterion. On the basis of our observations, in addition to the complexity of detecting a VO₂ plateau when using different methodologies (e.g. test protocols and data acquisition) [172], further research is needed regarding using VO₂ plateau as a criterion. We recommend RER (in the range between ≥1.1 and ≥1.15) and RPE (≥17 or ≥18), in addition to the test leader’s evaluation, as criteria. Whether ſpeak can be an additional criterion verifying VO₂max must be determined in future studies.

Cardiorespiratory fitness is an important clinical measure for predicting mortality in patients with cancer [11]. Therefore, the observed improvements or maintenance of VO₂max observed in patients exercising during treatment for cancer highlights the importance of informing, encouraging and facilitating PA and exercise for this group. To preserve or increase VO₂max during cancer treatment, sufficiently long exercise duration (session and weekly) and weekly volume (combination of intensity and duration) seem to be the most important factors to consider. Furthermore, it seems that exercise intensity is an important factor associated with improvements to and maintenance of VO₂max. However, this finding should be confirmed in well-planned studies controlling for exercise volume and monitoring adherence.
7.2 Perspectives for future research

Regarding improving the validity of $\dot{V}O_2$max testing, in general, and within newly diagnosed cancer patients specifically, a course for future investigations should be to determine whether the $f_R$ variable may be part of the criteria variables. In addition, it would be interesting to precede with comparable methodological approaches as in Schneider et al. (2019) [268], in which a supramaximal verification bout was performed following the $\dot{V}O_2$max test to validate the $\dot{V}O_2$max results [171]. Whether achievement of the same $\dot{V}O_2$max value in the verification bout is a valid criterion should be investigated together with the results from Paper II regarding associated criteria and cut-points in patients newly diagnosed with cancer who are undergoing treatment and post-treatment.

To achieve better insights into how exercise frequency, intensity, type and time should most efficiently affect cardiorespiratory fitness, more RCTs, in which one of the exercise factors is differently prescribed in two exercise groups (controlling for exercise volume), are needed. It would also be interesting to investigate moderators for changes in cardiorespiratory fitness (e.g. initial cardiorespiratory fitness level, exercise-history, sociodemographic- and economic status, type of diagnosis and disease-stage and comorbidities/medications). Exercise is likely to be beneficial for most patients who are undergoing or finished with treatment. However, there is need for more knowledge related to the characteristics of those who do not manage adhering to the exercise interventions, and how we may identify and approach these individuals in order to improve exercise adherence. More research is needed to be able to target the exercise/PA prescriptions to achieve the greatest effect on different outcomes that are clinically important, such as cardiorespiratory fitness, physical function, cancer related fatigue or muscle mass/body fat.

Generally, future exercise interventions need to report both the planned and the performed exercise according to frequency, intensity, type and time.
8 REFERENCES


25. Furmaniak, A.C., M. Menig, and M.H. Markes, Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database of Systematic Reviews, 2016(9).


Paper I
INTRODUCTION

Increasing numbers of people are living with the short- and long-term adverse effects of cancer and cancer treatment.1 The American College of Sports Medicine and the American Cancer Society recommend physical exercise as an intervention strategy to help patients with cancer to manage symptoms, improve physical capacity, and improve quality of life during and after treatment.2,3 Prospective observational studies have shown that physically active cancer survivors have a...
lower risk of cancer recurrence and improved survival than inactive cancer survivors.

Cardiorespiratory fitness, assessed by measurement of the maximal oxygen uptake \( \text{VO}_{2\text{max}} \), is the most important predictor of all-cause mortality in both healthy individuals and patients with cardiovascular disease.\(^4\)\(^5\) Additionally, a low \( \text{VO}_{2\text{max}} \) is associated with increased cardiovascular mortality in patients with breast cancer.\(^6\)\(^7\) Compared with healthy individuals, substantially lower \( \text{VO}_{2\text{max}} \) values have been observed in patients with various types of cancer\(^8\) as well as in patients with breast cancer\(^6\)\(^9\)\(^11\) and prostate cancer\(^12\) before, during, and after cancer treatment.

Sufficient \( \text{VO}_{2\text{max}} \) in patients is related to higher physical activity level\(^13\) and daily functioning and fewer toxic effects of radiotherapy, chemotherapy, and androgen deprivation therapy on the cardiovascular system, respiratory system, and skeletal muscles.\(^14\)\(^20\)

Frequency, intensity, and duration determine the total exercise volume. To improve \( \text{VO}_{2\text{max}} \), the training principle of overload must be present by increasing frequency, intensity, or exercise duration above the initial physical exercise levels.\(^21\) Regular aerobic exercise training (AET) following this principle of overload may improve \( \text{VO}_{2\text{max}} \) by peripheral adaptations within the muscles and increased cardiac output.\(^22\)

The number of exercise trials aiming to improve \( \text{VO}_{2\text{max}} \) in patients with cancer has increased during the last few decades. Two meta-analysis in 2011 and 2018 concluded that AET is associated with significant and clinically relevant beneficial changes in \( \text{VO}_{2\text{max}} \) among patients both when undergoing cancer treatment and when finished.\(^23\)\(^24\) However, these meta-analyses did not investigate the role of exercise frequency, intensity, type, and time (FITT factors) on the change in \( \text{VO}_{2\text{max}} \), nor did they exclusively include studies investigating the effect of exercise during cancer treatment.

Two recent randomized controlled trials (RCTs)\(^25\)\(^26\) investigated the effects of different exercise programs and weekly exercise volumes on \( \text{VO}_{2\text{max}} \) among patients with breast cancer undergoing cancer treatment. Van Waart et al\(^26\) found less decline in cardiorespiratory fitness during chemotherapy in patients randomized to a supervised moderate- to high-intensity combined resistance and aerobic exercise program compared with patients participating in a home-based low- to moderate-intensity, aerobic exercise program and patients randomized to a usual care control group. Courneya et al\(^25\) compared the effects of different exercise types and volumes on \( \text{VO}_{2\text{max}} \) in patients with breast cancer and found the effect of higher aerobic exercise volume to be superior.

In the healthy population, there is evidence that AET involving moderate- to high-intensity exercise for at least 40-60 minutes per session, three times per week is effective in improving \( \text{VO}_{2\text{max}} \).\(^27\) Time efficiency can be enhanced by increasing the exercise intensity and shortening the duration.\(^28\) No consensus has yet been reached regarding the optimal exercise prescriptions in terms of FITT factors of exercise to improve \( \text{VO}_{2\text{max}} \) in patients undergoing treatment for cancer.

The present systematic review and meta-analysis of RCTs was performed to determine the effect of AET on \( \text{VO}_{2\text{max}} \) and elucidate how the FITT factors may influence training-induced changes in \( \text{VO}_{2\text{max}} \) among patients with cancer receiving adjuvant or neoadjuvant treatment.

## METHODS

### Search strategies

An electronic database search of Medline and Embase was performed through OvidSP. To identify relevant papers, the search was based on predefined terms regarding population, intervention, comparison, and outcome (PICO) terms using both MeSH terms and free text: Population (P): patients with cancer who are undergoing (neo-)-adjuvant cancer treatment; Intervention (I): supervised and unsupervised physical exercise interventions involving an aerobic component; Comparison (C): patients receiving standard of care or who were on a waiting list or on attention control; and Outcome (O): cardiorespiratory fitness. The literature search was conducted in April 2016 and updated in January 2019. Reviews and references of relevant papers were searched for additional studies. The search string is presented as supplementary material (Appendix S1).

### Inclusion criteria

The present meta-analysis included RCTs of adult (>18-year old) patients with cancer that evaluated the effects of an exercise intervention with an AET component during treatment compared with a usual care control group. Studies in patients with all cancer types during (neo)-adjuvant treatments (radiotherapy, chemotherapy, radio-chemotherapy, or hormone therapy) with curative intent were included. Additionally, studies were included when the cardiorespiratory fitness test was conducted at baseline and at the end of the exercise intervention, directly through measurements of maximal oxygen uptake or indirectly by estimating \( \text{VO}_{2\text{max}} \) from a maximal exercise test. We excluded studies in which patients participated in an exercise intervention before or after surgery and did not receive any concurrent adjuvant cancer treatment, studies evaluating combined lifestyle interventions, for example, interventions focusing on exercise and diet or other medical/dietary supplements, studies investigating patients both during and after treatment, and studies that examined cardiorespiratory fitness with a submaximal exercise test.

If relevant information regarding FITT factors and \( \text{VO}_{2\text{max}} \) in both patients randomized to the exercise group
and the control group could not be derived from the published paper or via correspondence with the author, the study was included in the systematic review but not in the meta-analysis.

### 2.3 Study selection and data extraction

One reviewer (ACHB) removed duplicates and screened titles and abstracts for eligibility. Full-text assessments were done by two reviewers (ACHB and MGS).

After assessing eligible studies for the meta-analysis, two additional reviewers (LMB and SB) also reviewed and accepted the decisions involving inclusion of studies. Details regarding study inclusion are provided in the CONSORT statement (Figure 1).

Reviewers ACHB and MGS independently extracted information regarding the study population: country, cancer site, disease stage, medical treatment, number of patients at baseline and at follow-up, age, and sex. Both reviewers also independently extracted the characteristics of the exercise interventions, methods of VO₂max testing, and post-intervention VO₂max scores or changes from baseline (in L/min, mL/min, mL/min/kg, or metabolic equivalents of task [METs]). If not reported, the outcomes of patients randomized to the exercise and control groups were derived via correspondence with the author.

The classification of prescribed exercise intensity was based on the American College of Sports Medicine guidelines. The input for classification was intensity, moderate, moderate-high, and high intensity. Exercise intensity was indicated by the value of METs; we used a value of 1.5 METs to indicate low intensity, 3.0 METs to indicate low-moderate intensity, 4.5 METs to indicate moderate intensity, 6.0 METs to indicate moderate-high intensity, and 7.5 METs to indicate high intensity exercise.

### 2.4 Risk-of-bias assessment

Risk-of-bias assessment was performed by two independent reviewers (ACHB and MGS, LMB, or SB) using TESTEX, a validated 15-item scale specific for assessing risk of bias in exercise training studies. Each study was rated according to five items on study quality and 10 items on reporting, with a maximum score of 15 points. The quality assessments of the reviewers were compared, and disagreements were resolved by discussion among all four raters.

### 2.5 Statistical analysis

To adjust for differences in VO₂max at baseline, we used independent group differences to calculate effect sizes. There were three different formats used when calculating effect sizes, depending on the information available in the paper. By one procedure post-intervention means, confidence intervals (CIs) and sample sizes of both intervention and control group were used to calculate effect sizes. Second, if differences between groups were reported, the mean difference, sample size of both intervention and control group, and CI were used to calculate effect sizes. Last, if only raw differences were reported, the mean difference with the upper and lower limit, sample size of both intervention and control group, and CI were used to calculate effect sizes. Hedges’ g was calculated to adjust for small sample sizes. A study was considered an outlier and excluded from further analyses if the 95% CI of the calculated effect size did not overlap with the 95% CI of the overall effect size. Cohen's convention was used to interpret the effect sizes: an effect size of 0.2 was considered small, 0.5 was considered moderate, and 0.8 was considered large.

Because the samples and interventions were expected to be heterogeneous, the effect sizes were pooled with a random effects model, taking differences in the effects between the studies into consideration. The I² statistic was reported as an indicator of heterogeneity, with an I² of 25% representing low heterogeneity, 50% representing moderate heterogeneity, and 75% representing high heterogeneity.

Subgroup analyses were conducted to study the differences in effects between studies with several exercise- and intervention-related characteristics: 1; frequency of training sessions per week categorized into 2-3 times/wk, 3 times/wk and ≥ 4 times/wk, 2; intensity categorized using MET values, 3; delivery mode dichotomized into supervised when a supervised exercise component was included and unsupervised when there were no instructor present. Additionally, we performed a meta-regression analysis to study the association of VO₂max with the 4; session duration, 5; weekly exercise duration, 6; weekly exercise volume, 7; intervention duration referring to the duration of the intervention period in weeks, and 8; intervention volume calculated as the total exercise volume × intervention duration. When reporting and analyzing session durations from combination trials (AET + RET), the total exercise session duration was reported and used in the analyses. Due to the observed variety in exercise prescriptions regarding type of exercise (ie, cycling, running, walking, football-activities, and interval vs continuous exercise etc), there were too few studies to investigate this particular FITT factor. In the following text, FITT will refer to frequency, intensity, and time (duration).
In the meta-regression, $Z$-values and $P$-values were presented to provide information about the regression coefficient and significance of the relationship between the variable and the effect size.

To study the possible interference of including resistance exercise, we also conducted sensitivity analyses in which combination trials (RET + AET)\textsuperscript{35-38} were excluded. All analyses were conducted using Comprehensive Meta-Analysis software, version 2.2.064 (National Institutes of Health, Bethesda, MD, USA).

Publication bias was investigated by inspecting the funnel plot, and Duval and Tweedie’s procedure.\textsuperscript{39} This procedure imputed missing studies to achieve symmetry around the center of the funnel plot. The effect was then recalculated based on this procedure. Publication bias was suggested by the presence of significant dispersion between the true effect size and the calculated effect size as seen by Egger's test. An alpha level of $P \leq 0.05$ was set as the criterion for statistical significance.

3 | RESULTS

3.1 | Study characteristics

In total, 2038 unique records were identified from the database search, and 123 full texts were assessed for eligibility. In
accordance with our present criteria, 14 RCTs were included in the systematic review (Figure 1). Five studies did not present sufficient data to calculate effect sizes, but we obtained data from four studies through author correspondence. For one study, we were unable to obtain data to calculate effect sizes, resulting in a total of 13 studies included in the meta-analysis. One study presented results for female and male patients separately and was therefore included separately in the present study, resulting in a sample size of 14 comparisons in the meta-analysis.

3.2 Study population characteristics

The 14 studies in the systematic review encompassed 1332 patients (range, 14-269 patients per study), with 751 in the intervention group and 581 in the control group (Table 1). Various cancer types and (neo-)adjuvant treatments were represented in the studies: seven studies included patients with breast cancer receiving chemotherapy, radiotherapy, or both; three studies included patients with prostate cancer receiving radiotherapy or androgen deprivation therapy; three studies included patients receiving chemotherapy for colon cancer, acute myeloid leukemia, or mixed cancer types; and one study included a mixed cancer population receiving a variety of treatments (radiation and/or chemotherapy). The patients’ mean age varied from 45 to 69 years, and 70% of the participants were women.

3.3 Exercise intervention characteristics

Eleven of the included RCTs were two-armed studies comparing aerobic exercise or combined aerobic and resistance exercise with a control group (Table 2). Three RCTs were three-armed studies comparing aerobic exercise and resistance exercise separately with a control group. In two studies, exercise sessions were unsupervised, and in 12 studies exercise sessions were supervised by an exercise instructor. The median frequency of exercise was 3 d/wk (range: 2-5 d/wk); seven studies prescribed “high” intensity exercise, five “moderate–high”, and two “low–moderate” intensity exercise. The median duration of exercise sessions was 35 minutes (range, 27-90 minutes). One study did not present the time exercised during each session and the median duration of the interventions was 11.5 weeks (range, 5-24 weeks). The median weekly exercise duration was 120 minutes (range, 80-270 minutes), and the median weekly exercise volume was 720 MET min/wk (range: 390-2025 MET min/wk).

3.4 Methods of cardiorespiratory fitness testing

The VO2max was measured directly in 11 studies: while running or walking on a treadmill in seven studies and while bicycling on a cycle ergometer in four studies (Table 2). Two studies included a maximal treadmill test with
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Freq./wk</th>
<th>Intended int. range</th>
<th>Int. cat.</th>
<th>Int. monitoring</th>
<th>Duration range/session, in min</th>
<th>Mean, in min</th>
<th>Modality (cont./interval.)</th>
<th>Weekly min. and MET's</th>
<th>Fitness test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamsen et al. (2009)</td>
<td>6 wk AET+RET Superv.</td>
<td>3</td>
<td>85%-95% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>High</td>
<td>HR</td>
<td>90</td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CE (interval)</td>
<td>270 min 2025 MET's</td>
<td>CE</td>
</tr>
<tr>
<td>Alibhai et al. (2015)</td>
<td>5 wk AET+RET Superv.</td>
<td>4-5</td>
<td>50%-75% HRR</td>
<td>Mod-High</td>
<td>HR, BORG</td>
<td>30-60</td>
<td>45&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CE, TM, Walk. (cont.)</td>
<td>203 min 1215 MET's</td>
<td>TM</td>
</tr>
<tr>
<td>Al-Majid et al. (2015)</td>
<td>11 wk AET Superv.</td>
<td>2-3</td>
<td>50%-80% HRR</td>
<td>Mod-High</td>
<td>HR</td>
<td>30-40</td>
<td>33</td>
<td>TM (cont.)</td>
<td>82 min 494 MET's</td>
<td>TM</td>
</tr>
<tr>
<td>Courneya et al. (2007)</td>
<td>17 wk AET Superv.</td>
<td>3</td>
<td>60%-80% VO&lt;sub&gt;2&lt;/sub&gt;max</td>
<td>High</td>
<td>NA</td>
<td>15-45</td>
<td>27</td>
<td>CE, TM, ET (cont.)</td>
<td>80 min 603 MET's</td>
<td>TM</td>
</tr>
<tr>
<td>Drouin et al. (2005)</td>
<td>7 wk AET Unsup.</td>
<td>3-5</td>
<td>50%-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Low-Mod</td>
<td>HR</td>
<td>20-45</td>
<td>33</td>
<td>Walk. (cont.)</td>
<td>130 min 390 MET's</td>
<td>TM</td>
</tr>
<tr>
<td>Griffith et al. (2009)</td>
<td>13 wk AET Unsup.</td>
<td>5</td>
<td>50%-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Low-Mod</td>
<td>NA</td>
<td>25-35</td>
<td>30</td>
<td>Walk. (cont.)</td>
<td>150 min 450 MET’s</td>
<td>TM</td>
</tr>
<tr>
<td>Hornsby et al. (2014)</td>
<td>12 wk AET Superv.</td>
<td>3</td>
<td>60%-100% VO&lt;sub&gt;2&lt;/sub&gt;peak</td>
<td>High</td>
<td>HR</td>
<td>20-45</td>
<td>31</td>
<td>CE (cont. + interval)</td>
<td>92 min 686 MET’s</td>
<td>CE</td>
</tr>
<tr>
<td>Kim et al. (2006)</td>
<td>8 wk AET Superv.</td>
<td>3</td>
<td>60%-70% VO&lt;sub&gt;2&lt;/sub&gt;peak</td>
<td>High</td>
<td>HR</td>
<td>35</td>
<td>35</td>
<td>CE, TM, Walk. (cont.)</td>
<td>105 min 788 MET’s</td>
<td>TM</td>
</tr>
<tr>
<td>MacVicar et al. (1989)</td>
<td>10 wk AET Superv.</td>
<td>3</td>
<td>60%-85% HRR</td>
<td>High</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CE (interval)</td>
<td>NA NA</td>
<td>TM</td>
</tr>
<tr>
<td>Monga et al. (2007)</td>
<td>8 wk AET Superv.</td>
<td>3</td>
<td>65% HRR</td>
<td>High</td>
<td>HR</td>
<td>45-50</td>
<td>48</td>
<td>Walk. on TM (cont.)</td>
<td>143 min 1069 MET’s</td>
<td>TM</td>
</tr>
<tr>
<td>Segal et al. (2009)</td>
<td>24 wk AET Superv.</td>
<td>3</td>
<td>60%-75% VO&lt;sub&gt;2&lt;/sub&gt;peak</td>
<td>High</td>
<td>HR</td>
<td>20-45</td>
<td>33</td>
<td>CE, TM, ET (cont.)</td>
<td>98 min 731 MET’s</td>
<td>TM</td>
</tr>
</tbody>
</table>

(Continues)
the modified Bruce protocol to estimate VO$_2$max$^{36}$ or to calculate METs.$^37$ One study estimated VO$_2$max indirectly using a stepwise work capacity test on a stationary exercise cycle.$^{35}$ Of the studies included in the meta‐analysis, the type of exercise modality performed during the exercise sessions matched the modality of the cardiorespiratory fitness test (ie, cycling and running).$^{35,36,40,42-48}$ In one study, the participants conducted their cardiorespiratory fitness test on a cycle ergometer and performed football exercises during the exercise sessions.$^{49}$ In two other studies, a cycle ergometer was used in the test but the type of AET performed during exercise sessions was not reported.$^{37,38}$

### 3.5 Risk-of-bias assessment

The median TESTEX score was 11.5 (range, 3‐14; Table 3). Three studies$^{37,38,45}$ reported blinding of the outcome assessors. Six studies$^{36,40,43,44,46,48}$ monitored physical activity in the control group. Seven studies$^{35,37,38,43-45,48}$ used an intention‐to‐treat analysis. Four studies$^{42,43,45,48}$ provided a clear plan for progression of the prescribed exercise by increasing frequency, session duration, and intensity throughout the intervention period, aiming to adjust the relative total exercise volume for the participants. In one study, both frequency and session duration were adjusted during the intervention.$^{39}$ In one study,$^{36}$ exercise intensity was adjusted based on self‐reported perceived exertion. In two studies,$^{37,38}$ a combination of self‐reported perceived exertion and heart rate (HR) monitoring was used to identify training progression. In one of these studies, the maximum HR was reassessed by a sub‐maximal cardiopulmonary exercise test every 4 weeks,$^{37}$ and in the other study, the reassessment method was not reported.$^{38}$ Two studies reported adjustment of intensity based on HR measurements but lacked information on how these adjustments were made.$^{46,47}$ Four studies$^{35,40,41,44}$ did not report any form of intensity monitoring or adjustments of frequency, intensity, and/or session duration throughout the exercise intervention period.

### 3.6 Adherence

In three studies, intensity and duration were included in the assessment of adherence to the intervention.$^{36,45,46}$ In another three studies, adherence was mentioned but the authors did not include any descriptions on how they assessed adherence and to what part of the intervention they measured adherence.$^{40,43,48}$ Two other studies reported adherence to frequency and duration, but not to intensity.$^{37,34}$ While three studies only reported the attendance rate.$^{37,42,49}$ In one study, self‐reported adherence to all of the FITT factors was registered at the end of the intervention.$^{38}$ And in two studies the authors did not report any attendance or adherence to the prescribed exercise intervention.$^{41,47}$
3.7 | Meta-analysis and overall effects

After excluding one outlier, a significant moderate positive effect was found on \( \dot{V}O_{2\text{max}} \) (effect size = 0.46, 95% CI = 0.23-0.69; Table 4 and Figure 2). Heterogeneity was indicated to be high \( (I^2 = 64, P = 0.001) \).

3.8 | Analysis of FITT factors

We found no significant differences between studies with different exercise frequencies \( (P = 0.140) \) and intensities \( (P = 0.090) \) with respect to improvements in \( \dot{V}O_{2\text{max}} \) (Table 4).

Improvements in \( \dot{V}O_{2\text{max}} \) were significantly larger for studies with larger session durations (z-value, 2.30; \( P = 0.020 \)), longer weekly exercise durations (z-value, 2.53; \( P = 0.010 \)), and larger weekly exercise volumes (z-value, 3.57; \( P < 0.001 \)). The intervention volume was also significantly associated with the intervention effects on \( \dot{V}O_{2\text{max}} \) (z-value, 1.96; \( P = 0.049 \)). Studies with shorter intervention durations showed significantly larger improvements in \( \dot{V}O_{2\text{max}} \) than studies with longer intervention durations (z-value, −2.80; \( P = 0.005 \)). The results of the sensitivity analysis including studies evaluating AET only were in line with the primary analyses for exercise frequency (z-value, 2.14; \( P = 0.030 \)). In contrast to the main analyses, the sensitivity analyses showed no significant differences in effects on \( \dot{V}O_{2\text{max}} \) across session duration (z-value, 0.61; \( P = 0.540 \)), weekly exercise duration (z-value, 1.60; \( P = 0.110 \)), or intervention duration (z-value, −0.44; \( P = 0.660 \)).

3.9 | Assessment of publication bias

There was a symmetric distribution when investigating the funnel plot. The trim-and-fill procedure suggested that three studies were missing, resulting in an adjusted effect size of 0.38 (0.12-0.60). Egger’s test was not statistically significant \( (P = 0.197) \), suggesting no publication bias.

4 | DISCUSSION

This systematic review and meta-analysis of 13 studies showed that exercise interventions with an aerobic component during (neo-)adjuvant cancer treatment resulted in positive changes in \( \dot{V}O_{2\text{max}} \) compared with standard care control. We found a larger beneficial effect of increased session duration, weekly exercise duration, and weekly exercise volume on \( \dot{V}O_{2\text{max}} \).

The observed significant moderate beneficial effect on \( \dot{V}O_{2\text{max}} \) among patients with cancer who performed an exercise intervention during (neo-)adjuvant treatment compared with the control group corresponds to results reported in two previous meta-analyses. However, in contrast to these previous meta-analyses, we exclusively focused on studies that included patients undergoing (neo-)adjuvant treatment and completed maximal assessments of cardiorespiratory fitness. The choice of only including maximal exercise tests was based on the knowledge that the use of submaximal exercise tests to predict \( \dot{V}O_{2\text{max}} \) often over- or underestimate \( \dot{V}O_{2\text{max}} \). Overestimation of \( \dot{V}O_{2\text{max}} \) among patients with cancer undergoing treatment may result from chemotherapy-induced autonomic dysfunction causing higher HR_{rest} and at submaximal exercise levels. The observed moderate beneficial changes in \( \dot{V}O_{2\text{max}} \) are clinically relevant because \( \dot{V}O_{2\text{max}} \) is an important predictor of all-cause mortality. Our results, combined with previous findings of impaired \( \dot{V}O_{2\text{max}} \) among patients with cancer, emphasize the clinical importance of increasing or maintaining \( \dot{V}O_{2\text{max}} \) in this phase of the cancer trajectory.

In contrast to healthy populations in which AET aims to improve cardiorespiratory fitness, only small improvements, maintenance or a less steep decline of \( \dot{V}O_{2\text{max}} \) is expected in patients undergoing chemotherapy, and this has been confirmed in previous randomized controlled trials. Previous studies in patients with prostate cancer treated with androgen deprivation therapy (ADT) have also presented small improvements or maintenance in \( \dot{V}O_{2\text{max}} \).

To our knowledge, the present meta-analysis is the first to study the effect of frequency, intensity, session duration, weekly duration, and weekly volume on \( \dot{V}O_{2\text{max}} \) only in a population of patients with cancer undergoing (neo-)adjuvant treatment. Our finding that longer session durations are associated with improvements in \( \dot{V}O_{2\text{max}} \) is supported by a meta-analysis of Huang et al., who found a dose-response relationship between an increasing session duration and \( \dot{V}O_{2\text{max}} \) in healthy older adults (67.45 ± 5.25 years of age) performing AET. Prescribing exercise sessions of long enough duration may thus be important to have beneficial effects on \( \dot{V}O_{2\text{max}} \) in patients with cancer. Notably, Huang et al. found a ceiling effect; the \( \dot{V}O_{2\text{max}} \) gain did not increase further after approximately 45 minutes. Due to the relatively small number of studies and the large variation in intervention characteristics, it is difficult to derive whether a ceiling effect exists among patients with cancer. The most optimal session duration needs to be confirmed in future studies.

Our observation that longer weekly exercise durations and larger weekly exercise volumes were more beneficial than shorter durations corresponds to previous findings by Courneya et al., who investigated patients exercising during chemotherapy for breast cancer. The authors found that a weekly duration of 150 minutes AET at 70%-75% of \( \dot{V}O_{2\text{peak}} \)
resulted in more beneficial changes in \( \dot{V}O_2 \text{max} \) than AET with a weekly duration of 75 minutes at the same intensity. This was also observed in a meta-analysis of exercise trials in healthy young adults on the combined effect of session duration and intensity on \( \dot{V}O_2 \text{max} \).\textsuperscript{54} Although exercise duration and volume seem important to increase or maintain \( \dot{V}O_2 \text{max} \), we cannot determine the specific recommended exercise duration or volume from the present study.

The finding of less beneficial changes in \( \dot{V}O_2 \text{max} \) in interventions with longer durations may result from lower adherence in exercise interventions lasting longer.\textsuperscript{55} We cannot investigate the issue concerning adherence based on the information given in the included studies. As Nilsen et al\textsuperscript{56} advocates, more novel methods for reporting exercise volume and adherence throughout the entire exercise intervention are needed.

No differences in \( \dot{V}O_2 \text{max} \) were found between subgroups with respect to exercise frequency and intensity. This finding was unexpected and in contrast to previous studies of healthy populations in which strong associations between exercise frequency and intensity were reported. In addition to session duration, Huang et al\textsuperscript{53} found also a dose-response relationship between cardiorespiratory fitness and increasing exercise intensities in older adults. An intensity ceiling was though found around 70%-73% of HR reserve, where higher intensities did not induce further enhancements in \( \dot{V}O_2 \text{max} \).\textsuperscript{53}

Results from published exercise interventions investigating the effect of exercise intensity among patients undergoing treatment for cancer have shown that higher intensities tend to be more efficient for improving or maintaining \( \dot{V}O_2 \text{max} \). Van Waart et al\textsuperscript{26} found that moderate- to high-intensity exercise had larger effects on \( \dot{V}O_2 \text{max} \) than low- to moderate-intensity exercise. Importantly, whether these findings are caused by the prescribed intensity levels or by other differences related to the exercise programs (eg, exercise type or supervision) remain unclear. Larger improvements in \( \dot{V}O_2 \text{max} \) after high intensity compared to low-moderate intensity exercise were also found in the RCT by Kampshoff et al,\textsuperscript{57} who studied the effects of exercising after the completion of (neo-)adjuvant treatment. The findings in these particular exercise interventions are supported in the present study by the—although not statistically significant—larger effects on \( \dot{V}O_2 \text{max} \) in studies with higher intensity. More importantly, the findings of the present meta-analysis point

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Overall TESTEX score. #Higher scores indicate lower risk of bias. *Median. Criterion, study quality: 1, eligibility; 2, randomization; 3, allocation concealed; 4, groups similar at baseline and 5, blinding of assessors. Criterion, study reporting: 6a, outcome measures assessed >85% of participants; 6b, reporting of adverse events (AE’s); 6c, reporting of attendance; 7, intention-to-treat analysis; 8a, reporting of between-group statistical comparisons for the primary outcome; 8b, reporting of between-group statistical comparisons are reported for at least one secondary outcome; 9, reporting of point estimates and measures of variability; 10, activity monitoring in control group; 11, if exercise load in titrated to keep relative intensity constant; 12, if exercise volume and energy expenditure can be calculated. Definitions: Relative exercise intensity constant: 1 point is given if an increase in either intensity, session duration or frequency is reported, if Borg scale has been used as a measure of relative intensity or if there's been one or more measures of resting heart rate after a few weeks of adapting the exercise intervention. Reporting of AE’s are events occurring from baseline testing, through the intervention period and until post-testing. These events could be death, hospitalization, etc; events either making the participant drop out of study or miss exercise sessions. To get 1 point, AE's could be reported explicitly in text, or shown in flowcharts.
to the direction that total exercise volume seems to be more important than exercise intensity alone, although this must be confirmed in future studies.

The fact that all FITT factors will interchangeably influence the effect on $\dot{V}O_2^{max}$ makes it challenging to disentangle whether it is one specific variable or a combination of variables that results in larger improvements in $\dot{V}O_2^{max}$ within a limited number of studies. Consistent with findings in a previous review of patients with cancer,58 the studies included in the present meta-analysis used a variety of exercise programs, prescribing different frequencies, levels of intensity, session and intervention durations and types of exercise. Given the lack of consensus regarding optimal and specific exercise prescriptions for patients with cancer undergoing treatment59 and generally in the exercise oncology literature,21 this diversity in the content of exercise interventions is not surprising. This large heterogeneity in combinations of FITT factors makes it challenging to separately compare individual factors and may be a second explanation for why we did not find differences in effects on $\dot{V}O_2^{max}$ between different exercise frequencies and intensities. Also, small sample sizes may have affected the results in our meta-analysis; 6 of the studies included intervention groups comprising only 7-29 patients.38,40,42,45,47,49 Consequently, there were large CIs and overlaps in CIs within the different frequency and intensity groups.

In a healthy population, both moderate and high intensity exercise are effective to improve $\dot{V}O_2^{max}$.27,54 However, in a meta-analysis of exercise trials among healthy young adults, no enhanced effect of high intensity compared to moderate intensity was observed on $\dot{V}O_2^{max}$, but as in our study there was rather a dose-response relationship between exercise volume and $\dot{V}O_2^{max}$.54 However, in a meta-analysis on studies including healthy elderly people53 and in patients with

### Table 4: Pooled effects of exercise on $\dot{V}O_2^{max}$ in patients during cancer treatment, all studies

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<tr>
<th></th>
<th>N</th>
<th>Effect size, g (95% CI)</th>
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<th>Between-group difference (P-value)</th>
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<td>Overall without outlier</td>
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<td>0.46 (0.23; 0.69)</td>
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<td>Intervention duration</td>
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<td>Unsupervised</td>
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<td>Supervised</td>
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<tr>
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<tr>
<td>2-3</td>
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<td>0.21 (−0.19; 0.61)</td>
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<tr>
<td>3</td>
<td>6</td>
<td>0.65 (0.42; 0.87)</td>
<td>30.19</td>
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<tr>
<td>&gt;4</td>
<td>3</td>
<td>0.32 (−0.24; 0.89)</td>
<td>69.01*</td>
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<tr>
<td>Low-moderate</td>
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<tr>
<td>Moderate-high</td>
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<td>0.23 (−0.06; 0.52)</td>
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<td>High</td>
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<tr>
<td>Duration (regression)</td>
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<td>Weekly duration</td>
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<tr>
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<td>Volume (MET’s total duration)</td>
<td>13</td>
<td>1.96</td>
<td>0.049</td>
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Note: Outlier Al Majid et al. (2015) is removed from analyzes.

Abbreviations: AET, aerobic exercise training; CI, Confidence Interval; g, the Hedges’ g statistics; $I^2$, heterogeneity; MET’s, Metabolic equivalents; RET, resistance training.

*Significant (<0.05).
coronary heart disease, results suggested a beneficial effect of an increasing exercise intensity on $\dot{V}O_{2\text{max}}$.\textsuperscript{53}

It should, however, be noted that our findings on exercise intensity are based on the prescribed and not the actual performed exercise intensity. Additionally, prescribed intensities were often based on heart rate. Prescribing optimal exercise intensity for patients undergoing cancer treatment is challenging with heart rate-based intensity protocols, because chemotherapy and/or radiation may impact the cardiac, pulmonary and vascular system, hemoglobin concentration, and oxidative capacity,\textsuperscript{63} which further alters HRrest and reduces HR reserve.

4.1 | Strengths and limitations

The strengths of the present study are the systematic searches of two large databases, our specific focus on patients during (neo-)adjuvant cancer treatment only, the exclusive inclusion of interventions with aerobic components, and the systematic investigation into the role of FITT factors. In addition, we included only studies with direct and indirect assessments of $\dot{V}O_{2\text{max}}$, resulting in a high internal validity. Although we accepted different exercise modes when performing the $\dot{V}O_{2\text{max}}$ tests, most of the RCTs\textsuperscript{35,36,40,42-48} conducted the same exercise mode during the test and during the intervention, assuming that this aspect is not a limitation. Another strength of the present study is that we performed a quality assessment of the included RCTs and found that most of them reported their prescribed frequency, intensity, time, and type of exercise.\textsuperscript{35-38,40,42,43,45-49} However, some important limitations should be noted. First, the heterogeneity among studies was high, possibly due to the diversity of sample sizes, cancer types and treatments, characteristics of exercise programs, and methods and exercise modes included during the $\dot{V}O_{2\text{max}}$ test. Second, the number of studies included in the present meta-analysis to investigate differences in intervention characteristics, FITT factors, and associations with changes in $\dot{V}O_{2\text{max}}$ was rather small. Third, it was not possible to adjust for $\dot{V}O_{2\text{max}}$ scores at baseline in all studies. Studies without adjustment could have a risk of regression to the mean\textsuperscript{42,45}, thus, patients with lower baseline $\dot{V}O_{2\text{max}}$ values have a greater potential to enhance their $\dot{V}O_{2\text{max}}$ than patients with higher baseline values.\textsuperscript{64} Fourth, with respect to the FITT factor time, the time spent in both AET and RET was included when reporting and analyzing the session duration from the four combination trials\textsuperscript{35-38} (Table 2). Fifth, the impact of different types of exercise and modalities was not assessed in our study. Finally, 70% of the included participants are women, most of them with breast cancer, which hampers the generalization of the results to patients with other types of cancer. However, this gender distribution reflects the current body of research in the field of exercise oncology.\textsuperscript{65,66}

4.2 | Conclusion and perspectives

The present systematic review and meta-analysis supports earlier findings that exercise interventions with an aerobic component have beneficial effects on $\dot{V}O_{2\text{max}}$ in patients undergoing (neo-)adjuvant treatment for cancer compared to control.\textsuperscript{53,24} This finding highlights the importance of exercise during (neo-)adjuvant treatment to prevent reductions in $\dot{V}O_{2\text{max}}$ from the time of diagnosis and during (neo-)adjuvant treatment. By also studying the effect of frequency,
intensity, and duration on \( \dot{V}O_2\text{max} \) in a more detailed matter, the present study supplies the field with a more specific understanding of how different exercise prescriptions could have various impact on this important clinical outcome.

We observed larger beneficial changes in \( \dot{V}O_2\text{max} \) among exercise interventions with longer session durations, weekly exercise durations, and larger weekly exercise volumes. With respect to frequency and intensity, no differences between subgroups were found, but as weekly exercise duration and volume are a function of frequency, intensity, and session duration, the combination of these variables seems important. Due to the mentioned limitations with prescribed intensities and adherence, cautions need to be taken when interpreting our results regarding how different exercise prescriptions may influence \( \dot{V}O_2\text{max} \). We cannot omit intensity being an important exercise factor, and more studies are needed. Though, based on our findings, exercise duration and volume seem most important to maintain or increase \( \dot{V}O_2\text{max} \). Exercise frequency, intensity, and duration should therefore be considered carefully for sufficient exercise volume to induce beneficial changes in \( \dot{V}O_2\text{max} \) when prescribing exercise for patients with cancer. To better individualize exercise prescriptions, there is a need for well-designed structured exercise intervention trials investigating how aerobic exercise performed at different frequencies, intensities, and or durations affect \( \dot{V}O_2\text{max} \) in different groups of patients with cancer. Future studies should also report adherence to the different FITT factors as part of the planning of exercise interventions for cancer patients undergoing (neo-)adjuvant treatment.

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ORCID

Ann Christin Helgesen Bjørke | https://orcid.org/0000-0002-5238-9826

REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Paper II
Criteria for the determination of maximal oxygen uptake in patients newly diagnosed with cancer: *baseline data from the randomized controlled trial of physical training and cancer (Phys-Can)*

Ann Christin Helgesen Bjørke 1*, Truls Raastad 2,1 and Sveinung Berntsen 1.

1 Department of Sport Science and Physical Education, University of Agder, Kristiansand, Norway

2 Department of Physical Performance, Norwegian School of Sport Sciences, Oslo, Norway

**Abstract**

**Introduction.** Maximal oxygen uptake (\(\dot{V}O_2\text{max}\)) is a measure of cardiorespiratory fitness often used to monitor changes in fitness during and after treatment in cancer patients. There is, however, limited knowledge in how criteria verifying \(\dot{V}O_2\text{max}\) work for patients newly diagnosed with cancer. Therefore, the aim of this study was to describe the prevalence of fulfillment of typical criteria verifying \(\dot{V}O_2\text{max}\) and to investigate the associations between the criteria and the test leader’s evaluation whether a test was performed “to exhaustion”. An additional aim was to establish new cut-points within the associated criteria.

**Methods.** From the Phys-Can randomized controlled trial, 535 patients (59 ±12 years) newly diagnosed with breast (79%), prostate (17%) or colorectal cancer (4%) performed an incremental \(\dot{V}O_2\text{max}\) test on a treadmill. The test was performed before starting (neo-)adjuvant treatment and an exercise intervention. Fulfillment of different cut-points within typical criteria verifying \(\dot{V}O_2\text{max}\) was described. The dependent key variables included in the initial bivariate analysis were achievement of a \(\dot{V}O_2\) plateau, peak values for maximal heart rate, respiratory exchange ratio (RER), the patients’ rating of perceived exertion on Borg’s scale6–20 and peak breathing frequency (\(f_R\)). A receiver operating characteristic analysis was performed to establish cut-points for variables associated with the test leader’s evaluation. Last, a cross-validation of the cut-points found in the receiver operating characteristic analysis was performed on a comparable sample of cancer patients (n=80).
**Results.** The criteria RERpeak (<0.001), Borg’s RPE (<0.001) and $f_R$ peak (p=0.018) were associated with the test leader’s evaluation of whether a test was defined as “to exhaustion”. The cut-points that best predicted the test leader’s evaluation were RER $\geq 1.14$, RPE $\geq 18$ and $f_R \geq 40$. Maximal heart rate and $VO_2$ plateau was not associated with the test leader’s evaluation.

**Conclusion.** We recommend a focus on RER (in the range between $\geq 1.1$ and $\geq 1.15$) and RPE ($\geq 17$ or $\geq 18$) in addition to the test leader’s evaluation. Additionally, a $f_R$ peak of $\geq 40$ breaths/min may be a cut-point to help the test leader evaluate the degree of exhaustion. However, more research is needed to verify our findings, and to investigate how these criteria will work within a population that are undergoing or finished with cancer treatment.

**Introduction**

A continuously increasing number of people are living with or have survived cancer [1], with most new cases occurring in persons aged 50 years and older [2]. Importantly, although improved treatment strategies have increased survival from cancer [3], most cancer treatments are collectively accompanied with negative effects on healthy cells and tissues [4-6]. Low levels of physical activity in people diagnosed with cancer [7], in combination with side effects from treatments causing injuries to the cardiovascular and muscular system [6, 8-10], are potent reasons for the clinically relevant impairments in cardiorespiratory fitness often observed in cancer treated individuals [11-14].

Patients with cancer are recommended to be as physically active as their abilities and conditions allow before, during and after cancer treatment [15, 16]. However, current exercise recommendations are rather general [17] and do not differ much for patients with cancer compared with the healthy population [18]. Based on a lack of individually tailored physical activity and exercise guidelines (e.g. frequency, intensity, type and time), second-generation trials, where specific exercise prescriptions are being investigated, are needed [19]. To be able to prescribe tailored exercise programs involving endurance training and to evaluate the effect of exercise programs, valid measurements of cardiorespiratory fitness are fundamental. One important challenge with maximal exercise tests in various patient groups, and older adults in general, is whether tests are performed with maximal effort [20]. A consequence of using submaximal test results is prescribing an exercise intensity that is too low. In addition,
comparisons within (e.g. comparing different exercise intensities) and between studies is complicated if we rely on biased data [21].

When measuring cardiorespiratory fitness, direct assessment of maximal oxygen uptake (\(\dot{V}O_2\text{max}\)) is acknowledged as the gold standard [22]. To ensure high validity and reliability of a \(\dot{V}O_2\text{max}\) test (i.e. results can be reproduced), accurate instruments and experienced personnel are important [23]. Different patients and healthy individuals have various levels of experience with exercise and subjective evaluations of their effort. Furthermore, among patients with cancer, the heterogeneity may be even larger because they often are older [2], more unfit [11], and may have comorbidities and side effects like fatigue or pain [4, 24, 25]. Therefore, when assessing such a heterogenetic group of people, objective criteria to support the decision whether a patient with cancer has reached her/his maximal effort (verifying \(\dot{V}O_2\text{max}\)) is important [23].

The most widely used objective criteria, a plateau or levelling off in \(\dot{V}O_2\) with increasing workload, has been extensively debated the last 20–30 years [26-31]. Variations in the number of subjects attaining a \(\dot{V}O_2\) plateau are seen across studies [32], and secondary criteria are also included when verifying \(\dot{V}O_2\text{max}\). The term \(\dot{V}O_2\text{peak}\) (the highest value attained during exercise [33]) is often used when involving exercise-naive and/or clinical populations, as there is an assumption that these persons seldom reach their highest physiologically attainable value (\(\dot{V}O_2\text{max}\)) [33]. In the literature, estimated peak heart rate (HR), peak respiratory exchange ratio (RER), post exercise blood lactate (BLa’), and self-reported Rating of Perceived Exertion (RPE) on Borg’s scale6-20 (or other scales), with a variety of cut-points, are reported as secondary criteria to verify \(\dot{V}O_2\text{max}\) [34, 35]. How close these secondary criteria are associated with \(\dot{V}O_2\text{max}\) is not well validated. Because they all have pros and cons, the criteria and their cut-points have been discussed in the literature [23, 34-36]. Furthermore, there is no consensus on how to apply these criteria in various populations [23], but some suggestions have been made for healthy athletes [34], healthy adult subjects between 20 and 85 years [37], and for overweight or obese adults [38, 39]. It might be challenging to apply these criteria in patients newly diagnosed with cancer, and whether this population have the same physiological responses as other populations is questionable. Nevertheless, the use of well-defined objective criteria in testing newly diagnosed cancer patients is probably more important than in healthy populations because both the patient and
test leader might be afraid of pushing towards maximal effort. In addition to the often-used criteria, respiratory frequency ($f_R$) has been suggested as a valid variable for defining maximal effort [40], but to our knowledge, $f_R$ has not been used as a criterion in $\dot{V}O_2\text{max}$ testing. Personal experiences from test-laboratories, in which $f_R$ has been found to be useful as part of the effort-evaluation of people performing a $\dot{V}O_2\text{max}$ test, is another rationale for adding this variable as a possible secondary criteria to verify $\dot{V}O_2\text{max}$.

The test leader’s subjective evaluation whether a $\dot{V}O_2\text{max}$ test is performed to exhaustion is important when considering the validity of $\dot{V}O_2\text{max}$ tests. Although evaluations of exertion are based on predefined observations of body language and facial expressions, subjectivity is still part of the test leader’s evaluation. How test personnel give instructions and how they verbally encourage the person being tested are examples of possible biases that may affect the validity of the test results [41]. Submaximal results may occur if the test leader is inexperienced and is too “kind”; meaning that he/she does not motivate the person being tested enough, or even terminates the test before a maximal effort has been reached, of various reasons (e.g. the cancer diagnosis, comorbidities or age). Because of the aforementioned challenges of using the $\dot{V}O_2$ plateau in the evaluation of whether $\dot{V}O_2\text{max}$ is reached, we are dependent on experienced and highly skilled test leaders who are able to evaluate whether a test is performed to exhaustion. In the present study we chose this somewhat experimental approach, by giving the test leaders’ evaluation of each $\dot{V}O_2\text{max}$ test a focus in the statistical analyses.

To our knowledge, there are only one published study where criteria verifying $\dot{V}O_2\text{max}$ have been investigated within a population of patients diagnosed with cancer [42]. Schneider et al. (2019) investigated how a supramaximal verification bout could be applied in relation to feasibility and whether it could serve as a criterion when verifying $\dot{V}O_2\text{max}$ in survivors from breast and prostate cancer [42]. The present study will support researchers and test leaders in their decision concerning which secondary criteria to apply when evaluating future $\dot{V}O_2\text{max}$ tests in newly diagnosed patients with breast, prostate or colorectal cancer. Presumably, not all $\dot{V}O_2\text{max}$ tests in the future will be performed with an added verification bout. We present the fulfillment of a variety of criteria with different cut-points in our sample of patients. The primary objective was to determine which of the following variables: $\dot{V}O_2$ plateau, RERpeak, HRpeak, Borg’s RPE and $f_R$ peak, were associated with the test leader’s subjective evaluation
of whether the tests were defined as “to exhaustion”. In addition, cut-points within the associated criteria were established. A second objective was to cross-validate these cut-points in a comparable sample of patients with cancer.

**Methods**

**Design and participants**

The Phys-Can study was a multicenter randomized exercise trial with a descriptive observational study to be used for comparison [43]. For the intervention trial involving exercise, 600 adults (≥18 years) recently diagnosed with either curable breast, prostate or colorectal cancer scheduled to begin their (neo-)adjuvant therapy in Uppsala, Linköping and Malmö/Lund (Sweden) were included. Exclusion criteria were stage IIIb-IV breast cancer, inability to perform basic activities of daily living, cognitive disorders, severe psychiatric disease or other disabling conditions that might contraindicate high intensity exercise (e.g. severe heart failure, severe chronic obstructive pulmonary disease or orthopaedic conditions), treatment for an additional ongoing malignant disease, BMI<18.5 kg/m² or pregnancy. This main study was performed between March 2015 and November 2018. Full descriptions of the purpose, the design and enrollment of the study are presented elsewhere [43]. The observational study included 102 people following the same eligibility criteria and was performed between September 2014 and February 2015. All persons deemed as eligible by a physician/oncologist were contacted by a member of the research staff who provided verbal and written information about the study. Those who agreed to participate in the study gave their written informed consent before baseline data collection. For the purpose of the present study and analyses performed herein, 535 and 80 participants with \( \dot{V}O_2 \text{max} \) data at baseline (within the first week after diagnosis) were included from the intervention- and observational study, respectively. Three tests were excluded due to obvious technical issues (e.g. leakages from the face mask or technical errors), but otherwise, all available baseline \( \dot{V}O_2 \text{max} \) tests were included in the analyses.

The Phys-Can intervention study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2014/249) and registered in ClinicalTrials.gov (TRN = NCT02473003, October, 2014).
Cardiorespiratory fitness test

The participants were told not to eat, and drink anything other than water 2 hours before the test. In addition, they were told not to perform strenuous physical activity on the test day or the day before. At the test location, height and body mass were measured to the nearest 0.5 cm and 0.1 kg, respectively, while wearing light clothes and no shoes [43].

Participants performed a continuously graded exercise test on a motorized treadmill (In Uppsala; SportsArt Fitness Tr32, Washington, USA, in Lund; Rodby RL2500E, Vänge, Sweden and in Linköping; GE T2100, Helsinki, Finland (in 2015) and Rodby RL2000, Vänge, Sweden (the remaining study period)) using a modified Balke protocol. Following a 5-min warm-up with increasing workload, participants started at 4 km/h with an inclination of 2%. The inclination increased with 2% each minute until reaching 12%, from which only the speed increased 0.5 km/h per minute until exhaustion [43]. Gas exchange data were obtained breath-by-breath, using the following different gas-analyzers: Uppsala; Viasys Vmax Encore, Care Fusion, San Diego, USA (accepted measurement errors for O2 analyzer: ±0.06 – 1%), Lund; Jaeger Oxycon Pro, CareFusion, Hoechberg, Germany (accepted measurement errors for O2 analyzer: ±0.05%) and in Linköping; Jaeger Oxycon Pro, CareFusion, Germany, Hoechberg (until Dec 15) and Cosmed Quark CPET, Rome, Italy (accepted measurement errors for O2 analyzer: ±0.02%) in the remaining study period. The software used was: Uppsala; Vmax Encore and Cardiosoft ECG, Version 6.7, San Diago, USA, Lund; LabManager, Jlab, CareFusion, version 5.31.0, Hoechberg, Germany and in Linköping; LabManager, Jlab, CareFusion, version 5.31.0.83, Hoechberg, Germany (in 2015) and Cosmed Quark PFT Ergo, Rome, Italy for the remaining study period. To assess the rate of perceived exertion (RPE), Borg’s scale6–20 was applied during and at the end of the V̇O₂max test [44]. Instructions in how to use this scale were given before the test.

During the test, HR was measured using a Polar RS400 HR monitor in Uppsala, a Coded Polar receiver 4208 (connected to Oxycon Pro) in Lund and a heart rate receiver in the EKG equipment (GE Healthcare, CASE GE (connected to the Oxycon Pro) and a Cosmed SZ990 receiver (connected to the Cosmed Quark CPET) in Linköping. The peak average over 5 or 15 seconds was used when presenting HRpeak. Regarding V̇O₂, RER and fR, the highest 60 s mean of the 10-, 15- or 30 s sampling averages (acquisition time differed between the tests/labs) in the last part of the test was reported as the peak value. When describing
fulfillment of different percentages of predicted HR, the Tanaka equation, \(208 - (0.7 \times \text{age})\) was applied because this has been found to be more valid than the often-used \(220 - \text{age}\) HRmax equation [45].

**Detecting a plateau in oxygen uptake**

A computer program was developed to detect whether a \(\dot{V}O_2\) plateau or leveling off occurred during the test time. Using this program, each of the extracted excel files with the test results were processed using an algorithm based on the definition of \(\dot{V}O_2\) plateau by Taylor and colleagues [46], where a change in \(\dot{V}O_2\) should be less than 150 mL from one minute to the next (\(\Delta \dot{V}O_2 \leq 150 \text{ ml/min}\)). Additionally, the cut-points of \(\leq 80 \text{ ml/min}\) and \(\leq 50 \text{ ml/min}\) were studied with similar definitions using the program. The highest average in \(\dot{V}O_2\) over 1 minute was compared with the minute before or the minute after and whether \(\dot{V}O_2\) for these time points differed \(\leq 150 \text{ mL, } \leq 80 \text{ mL and } \leq 50 \text{ mL}\). Each of these three cut-points was investigated to descriptively present the prevalence of fulfilling each cut point. In the logistic regression analysis, the cut-point of \(\leq 150 \text{ ml/min}\) was chosen to be included because this is believed to fit best with our test-protocol which has very small expected \(\dot{V}O_2\) increments between each stage [46].

**Test leader evaluation**

After completing the tests, the test leaders were instructed to report factors related to challenges that could affect test outcomes. Additionally, each test leader reported the evaluation of every test with respect to whether the test was defined as “to exhaustion”. The evaluation was based on the observed body language, such as unsteady walking/running, bending the upper body (e.g. bending forward), facial expression showing exhaustion, hyperventilation and other signs reflecting that a maximal effort had been given. All test leaders were instructed, certified and followed up by the same person in the Phys-Can project group. A pilot-study was additionally conducted before the Phys-Can intervention study, where the predefined standards and test protocols were proven by the test leaders (and with some cancer patients).
Participant characteristics and questionnaires

Living situation, education, sick-leave, smoking status and diagnosis were retrieved through questionnaires and medical journals. The Multidimensional Fatigue Inventory (MFI) [47] and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer patients (EORTC QLQ C30) [48] were used to retrieve information about physical fatigue, global health status and physical function.

Physical activity monitoring

The number of hours in moderate to vigorous intensity physical activity per day was retrieved from the physical activity monitor SenseWear Armband Mini (BodyMedia Inc., Pittsburgh, PA, USA). The activity monitor was delivered on the day the VO\textsubscript{2}max test was performed. Patients were instructed to wear it for 7 consecutive days, accepting at least 4 days of registration with at least 80% wearing time each day. Physical activity registrations above 3 metabolic equivalents (METs) were defined as moderate to vigorous intensity physical activity [49].

Statistical analyses

Patient characteristics and results from the VO\textsubscript{2}peak tests were presented as mean values ± standard deviation (SD) and numbers with percentages. For descriptive purposes, the mean VO\textsubscript{2}peak within “fulfillment” and “not fulfillment” of a variety of criteria and cut-points used in the literature were presented in a figure using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California, USA, www.graphpad.com).

To determine associations between the criteria variables and the test leader’s evaluation, logistic regression analysis was performed using the Hosmer step-down procedure [50]. The key dependent variables included in the initial bivariate analysis were achievement of a VO\textsubscript{2} plateau, HRpeak, RERpeak, Borgs’ RPEpeak and \(f_k\)peak. In addition, VO\textsubscript{2}peak, diagnosis, age, body mass and test time were included as adjusting variables. All variables significant at the 0.25 level were included in the final multivariate model. The odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated for 0.10 units regarding RERpeak. To
investigate collinearity and interaction, pairwise correlations were performed for all the five key dependent variables in addition to $\dot{V}O_{2}\text{peak}$ and test time. Furthermore, a receiver operating characteristic (ROC) analysis was performed to establish cut-points for variables associated with the test leader’s evaluation. These cut-points represented the point where the sensitivity and specificity were highest in correctly categorizing the test leader’s evaluation (“to exhaustion” or not). Finally, a cross-validation of the cut-points found in the ROC analysis was performed on the participants in the Phys-Can Cohort study, using a cross-table.

The analyses were performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0, IBM Corp., Armonk, NY, USA) and Statistical Analysis System (SAS version 9.1.3, SAS, North Carolina, USA). The level of statistical significance was set to 0.05.

**Results**

Baseline characteristics of the participants in the intervention and in the cohort study are presented in Table 1. The two samples were comparable in respect to all characteristics, where mean age was 59 years and both samples included approximately 80% women with breast cancer, 15% men with prostate cancer and 4%–5% patients with colorectal cancer.
Table 1. Baseline characteristics of the participants in the Phys-Can Intervention study and the Phys-Can Cohort study, presented in mean (SD) or numbers (%).

<table>
<thead>
<tr>
<th></th>
<th>Phys-Can Intervention</th>
<th>Phys-Can Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects, n</td>
<td>535</td>
<td>80</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>59 (12)</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>430 (80)</td>
<td>67 (84)</td>
</tr>
<tr>
<td>Living with a partner, n (%)</td>
<td>402 (75)</td>
<td>58 (73)</td>
</tr>
<tr>
<td>Completed University, n (%)</td>
<td>309 (58)</td>
<td>39 (49)</td>
</tr>
<tr>
<td>Sick-leave, n (%)</td>
<td>180 (34)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>100% sick leave, n (%)</td>
<td>150 (28)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>Obesity (BMI≥30), n (%)</td>
<td>84 (16)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>19 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>421 (79)</td>
<td>66 (83)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>93 (17)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>21 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Physical fatigue, MFI, mean (SD)</td>
<td>11.2 (4)</td>
<td>11.7 (4)</td>
</tr>
<tr>
<td>EORTC QLQ C30, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status/QoL</td>
<td>66.3 (20.2)</td>
<td>70.7 (17.7)</td>
</tr>
<tr>
<td>Physical Function</td>
<td>88.5 (13.5)</td>
<td>90.0 (11.5)</td>
</tr>
<tr>
<td>MVPA, hours/day, mean (SD)</td>
<td>1.23 (0.8)</td>
<td>1.12 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=Body Mass Index; MVPA=Moderate-to-vigorous intensity physical activity; QoL=Quality of life.

Notes: Financial situation: worst=1, best=10. MFI, Physical fatigue: 4=low fatigue, 20=high fatigue. Global health status/QoL: 0=low quality of life, 100=high quality of life. Physical Function: 0=low/unhealthy level of functioning, 100=high/healthy level of functioning. Moderate-to-vigorous intensity=physical activity at or above 3 metabolic equivalents (METs).

Peak values and test duration from the cardiorespiratory fitness test are given in Table 2. The prevalence of fulfilment of the three VO₂ plateau criteria cut-points in the intervention and cohort study were: \( \Delta VO₂ ≤ 150 \text{ ml/min} \); 90% and 86%, \( \Delta VO₂ ≤ 80 \text{ ml/min} \); 63% and 65%, and \( \Delta VO₂ ≤ 50 \text{ ml/min} \); 45% and 53%.
Table 2. Peak values and test-duration from the \( \dot{V}O_2\text{max} \) -tests performed at baseline in the Phys-Can Intervention study and the Phys-Can Cohort study, presented in mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Phys-Can Intervention</th>
<th>Phys-Can Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}O_2\text{peak}, \text{ml/kg/min} )</td>
<td>29.8 (7.3)</td>
<td>29.2 (7.1)</td>
</tr>
<tr>
<td>HR\text{peak}, \text{beats/min}</td>
<td>166 (19)</td>
<td>168 (19)</td>
</tr>
<tr>
<td>Predicted HR\text{max}, %*</td>
<td>99 (9.2)</td>
<td>100 (9.6)</td>
</tr>
<tr>
<td>RER\text{peak}, ( \dot{V}CO_2/\dot{V}O_2 )</td>
<td>1.16 (0.10)</td>
<td>1.19 (0.11)</td>
</tr>
<tr>
<td>VE\text{peak}, l/min</td>
<td>79 (20)</td>
<td>79 (19)</td>
</tr>
<tr>
<td>( f_R\text{peak}, \text{breaths/min} )</td>
<td>40 (7.8)</td>
<td>41 (6.4)</td>
</tr>
<tr>
<td>Borg scale, RPE 6-20</td>
<td>17.9 (1.6)</td>
<td>17.0 (1.3)</td>
</tr>
<tr>
<td>Test-duration, min</td>
<td>9.9 (2.8)</td>
<td>9.4 (2.6)</td>
</tr>
</tbody>
</table>

Abbreviations: \( f_R \) = respiratory frequency; RER = Respiratory Exchange Ratio; \( \dot{V}CO_2 \) = carbon dioxide production; \( \dot{V}O_2 \) = oxygen uptake; VE = ventilation. *Percentage of predicted maximal heart rate, by the Tanaka formula.

In the intervention study there were 465 (87%) and 70 (13%) tests evaluated as “to exhaustion” and “not to exhaustion”, respectively. The corresponding numbers were 76 (95%) and 4 (5%) in the cohort study. For the intervention study, \( \dot{V}O_2\text{peak} \) was significantly (\( p<0.001 \)) higher in the tests evaluated as “to exhaustion” (30.3 ml/kg/min, CI: 29.6–30.9) than “not to exhaustion” (26.6 ml/kg/min, CI: 24.9–28.3).

The percentage distribution and mean \( \dot{V}O_2\text{peak} \) in subjects fulfilling and not fulfilling different cut-points within the criteria of \( \dot{V}O_2 \) plateau, RER, predicted HR (Tanaka) and Borgs’ RPE are presented in Fig 1. Regarding the \( \dot{V}O_2 \) plateau criterion, the most accessible cut-point (\( \Delta \dot{V}O_2 \leq 150 \text{ ml/min} \)) was fulfilled by nearly all patients (91%), but mean \( \dot{V}O_2\text{peak} \) was the same as in patients who had not fulfilled this cut-point. The prevalence of fulfillment of cut-points was reduced by being stricter (\( \leq 80 \) [63%] and \( \leq 50 \text{ ml/min} \) [45%]), but mean \( \dot{V}O_2\text{peak} \) was significantly higher (\( p<0.001 \) and \( p=0.028 \), respectively) in the patients who did not fulfill these two cut-points (Fig 1). The largest difference in \( \dot{V}O_2\text{peak} \) was observed between individuals who fulfilled (n=514; 30.1 ml/kg/min) and those who did not fulfill (n=21; 22.2 ml/kg/min) the RER\( \geq 1.0 \) criterion (\( p<0.001 \)). Many patients fulfilled the strictest cut-point of \( \geq 95\% \) predicted HR\text{peak} (76%). Regarding scoring on Borg’s scale, mean
VO₂peak in “fulfilled” vs “not fulfilled” did not differ across the three cut-points.

Fig 1. Mean (with SD) VO₂peak stratified on fulfilling and not fulfilling criteria for VO₂max in patients diagnosed with breast, prostate or colorectal cancer (n=535).

Abbreviations: RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion on Borg scale 6-20; VO₂ = oxygen uptake; VCO₂ = carbon dioxide production.

Notes: Tanaka, HRmax = 208 - (0.7 * age), Plateau, ΔVO₂ = a change in VO₂ of less than 150, 80 or 50 ml/min from one minute to the next minute.

As seen in the bivariate analysis presented in Table 3, fR peak, HRpeak, RERpeak, peak Borg’s RPE and plateau were significantly associated with the test leader’s evaluation (adjusted for age, diagnosis, VO₂peak and test duration). Of the four adjusting variables, test duration was the only variable that was significantly associated to the test leader’s evaluation (p=0.010). In the multivariate analysis, peak values for fR, RER and Borg’s RPE remained significantly associated with the test leader’s evaluation (Table 3). When adjusting for age,
diagnosis, VO₂peak and test duration, the probability of being categorized as “to exhaustion” was doubled both for each 0.1 increase in RER (OR: 2.07, 95%CI 1.39–3.08) and for each unit increase in Borg’s RPE (OR: 2.05, 95%CI 1.67–2.51). For each 10 breaths/min increase in f_R, the probability of being categorized as “to exhaustion” was increased by 60%.

Table 3. Odds ratios (OR’s) from bivariate- and multivariate analysis with test-leaders’ subjective evaluation of the VO₂max test as the outcome variable.

<table>
<thead>
<tr>
<th>Effect variable</th>
<th>Bivariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR’s (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Ṙ_O₂ peak, breaths/min</td>
<td>1.12 (1.07, 1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HṘ_peak, beat/min</td>
<td>1.02 (1.00, 1.04)</td>
<td>0.017</td>
</tr>
<tr>
<td>Ṙ_EṘ_peak, VĊ_O₂/VO₂</td>
<td>2.21 (1.59, 3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Borg scale, RPE 6–20</td>
<td>2.04 (1.68, 2.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plateau, ΔVO₂ ≤150 ml/min</td>
<td>2.22 (1.01, 4.87)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

The coefficients are given with 95% confidence intervals. Abbreviations: CI = Confidence interval; OR’s = Odds Ratio’s; f_R = respiratory frequency; HR = heart rate; RER = Respiratory Exchange Ratio; RPE = rates of perceived exertion; VĊ_O₂ = carbon dioxide production; VO₂ = oxygen uptake.

Notes: Adjusted for age, diagnosis, VO₂peak and test-duration.

The three cut-points for these associated criteria, calculated from the ROC curves (Fig 2), were $f_R \geq 40$ (true positive rate (TPR): 0.55, 95%CI 0.51–0.60), RER $\geq 1.14$ (TPR: 0.66, 95% CI 0.62–0.70) and Borg$\geq 18$ (TPR: 0.71, 95% CI 0.67–0.75). The probabilities of correctly classifying the test leader’s evaluations were 77% for Borg’s RPE, 73% for RER and 70% for $f_R$. When combining the three criteria, the predicted probability was the best (86%).
Fig 2. A: Receiver operating characteristic curves for RER, Borg’s RPE and $f_R$, with the test-leader’s evaluation as the outcome variable. B: Number and percentage of patients fulfilling one, two and three of the criteria cut-points in the Phys-Can intervention study (n=535).

Abbreviations: RER = Respiratory Exchange Ratio; ROC = receiver operating characteristic; RPE = ratings of perceived exertion; $f_R$ = respiratory frequency.

When performing the cross-validation analysis in the cohort study, three of the four (75%) tests classified as “not to exhaustion” were correctly classified. Regarding the tests classified as “to exhaustion” by the test leaders, 50 of the 76 tests (66%) were correctly classified. In total, 66% of the tests were correctly classified, and 34% were misclassified.
Discussion

The criteria RERpeak, Borg’s RPE and $f_R$ peak were associated with the test leader’s evaluation of whether a test was defined as “to exhaustion”. The cut-points that could best predict the test leader’s evaluation were $\text{RER} \geq 1.14$, $\text{RPE} \geq 18$ and $f_R \geq 40$. Neither the HRmax criterion, nor attaining a $\dot{V}_O_2$ plateau at the end of the $\dot{V}_O_2$max test was associated with the test leader’s evaluation.

Of note, we observed that newly diagnosed cancer patients (before beginning treatment) responded similarly to healthy age-matched individuals in peak values of $\dot{V}_O_2$, RER, Borg’s RPE and HR, although the present results are peak values (before applying any criteria verifying $\dot{V}_O_2$max) and the results from Edvardsen et al. were max values [51]. In addition, the cut-points of RER and RPE found through our ROC analysis did not differ from previously used cut-points in various populations [32, 52]. Therefore, we may assume that the cancer disease, per se, have not affected their ability to push themselves close to their maximal effort. Hence, the findings in the present study may be useful and transferable to other age-matched healthy individuals.

There is no “blueprint” regarding which outcome variable to apply when investigating criteria to verify $\dot{V}_O_2$max. Our experimental approach, in which the test leader’s evaluation is used for this purpose, has not been tried in this setting previously to our knowledge and is important to have in mind when interpreting our findings. Importantly, strong efforts were made in reducing the variation between test leaders through making the standards and protocols uniform for performing the tests, and all test leaders were certified by the same person who coordinated and ensured the quality of this part of the Phys-Can project.

Respiratory exchange ratio

The RER≥1.14 cut-point that was determined through the ROC analysis, is similar to ≥1.15, which is a strict cut-point used in some studies [32], and to our knowledge, originates from the work by Issekutz et al from the 1960s [53]. In the present study, a finding of 56% participants fulfilling the ≥1.15 criterion, was in agreement with Edvardsen and colleagues’ participants (aged 20–85 years), where 65% achieved this cut-point [37], especially when taking age into consideration. In a study of younger (mean age 37 years) overweight and
obese adults, the prevalence of achieving RER≥1.15 was higher (89%) [38]. In similar treadmill protocols, RERpeak was found to decrease with age [37], and considering that our participants had a mean age of 59 years, the mean RERpeak of 1.16 in the present study was comparable to the mean RERpeak of 1.17 seen in participants from 50 to 64 years old in Edvardsen and colleagues’ study [37]. Nearly all subjects (96%) in the present study fulfilled the RER≥1.0 criterion and 91% reached the age-related recommended cut-point of RER≥1.05 for healthy individuals [37]. Schneider et al. (2019) [42] found percentage of fulfillment of the RER≥1.1 cut-point (84%) to be similar as in the present study (77%), though slightly higher, possibly because of using a cycle ergometer.

In healthy and clinical populations, the rationale for choosing one cut-point instead of another seems to be lacking, and because several cut-points have been used previously, ranging from 1.00 to 1.20 [52], the selected cut-points may have been arbitrary [35]. Explanations for why people attain different levels of RERpeak at maximal tests are not fully understood, but age may affect RERmax [37]. Another factor is the test protocol used. Because a more rapid incremental work rate increases the anaerobic energy contribution, the rate of HCO$_3^-$ buffering of lactic acid-derived H$^+$ ions is increased (i.e. the rate of CO$_2$ output will be greater because it follows the rate of H$^+$ buffering) [54]. Consequently, shorter and faster test protocols result in higher RERpeak values compared with ramp tests that are of longer durations [35]. The RER cut-off values should therefore probably be made protocol specific.

Food intake and medication are also important factors that may affect RERpeak. It was suggested that habitual dietary patterns that influence the systemic acid load may account for 19% of the variability observed in RERpeak [55]. In women treated with chemotherapy and tamoxifen-like drugs, the accumulation of lactate was less compared with healthy women, especially at high exercise intensity (70% of ŖVO$_2$max) [56]. In combination with the observed lower carbohydrate oxidation and greater fat oxidation, the authors suggested that the cancer itself, and/or the medications received, may disrupt normal energy metabolism in patients with cancer during exercise [56]. This highlights the importance of validating these criteria in different patient groups, and in cancer patients the validation should also be made in tests completed during treatment.
Perceived exertion

A Borg’s RPE of ≥18, found in our ROC analysis, did not differ from cut-points often seen in the literature, with observed cut-points of ≥17, ≥18 or ≥19 [52]. Congruent with our observations, 84% of participants in Edvardsen et al. (2014) achieved the most frequently used cut-point of RPE≥17. Despite close relationships between scores on Borg’s scale and physiological measures of intensity, such as HR, BLa` [57], and work rate during exercise [58], the validity of Borg’s scale as a criterion in VO₂max testing has been questioned [59]. The validity in the use of this criterion depends on the subject’s understanding of the scale and associated verbal descriptors, the ability to differentiate between discomfort and physiological fatigue and motivation [60]. It has been proposed that physically inactive individuals not accustomed to exercise until exhaustion are likely to report perceived maximal exertion before they actually reach their true VO₂max [21]. The discrepancy between the percent of participants reaching RPE≥17 (86%; 30.2 ml/kg/min) and ≥18 (65%; 30.4 ml/kg/min) was large in our study, congruent with no differences in VO₂peak within fulfilling the two cut-points. Consequently, choosing an RPE≥17 cut-point would probably also work well for this patient group.

Respiratory frequency

Through the ROC analysis, ≥40 breaths/min was found to be the cut-point best associated with the test leader’s evaluation. This cut-point was reached by 52% of the participants, and these participants had a significantly (p<0.001) higher VO₂peak (32 ml/kg/min), than participants not achieving this cut-point (27 ml/kg/min). To our knowledge, ḟR has not been used as a criterion verifying VO₂max in previous studies, but there are implications that ḟR is a potentially valid measure that reflects physical effort. In two studies by Nicolo et al. [40, 61], the authors describe why ḟR is a better marker of physiological strain compared with the variables VO₂, HR and BLa`. The nonlinear increase of ḟR during incremental exercise follows the level of acidosis from lactate production and is not affected by muscle damage or glycogen depletion, suggesting that physical effort is more causally linked with ḟR than BLa`. In addition, ḟR is closely related to RPE in fit males (20±3 years) and does not seem to be affected by choice of test protocol [61]. Whether ḟR is a valid criterion to apply as part of verifying VO₂max needs to be investigated in future studies.
Age predicted maximal heart rate

The age predicted HRmax was not significantly associated to the test leader’s evaluation of whether the test was performed “to exhaustion”. In \( \dot{V}O_2 \text{max} \) tests performed in different populations, fulfillment of various cut-points representing percentages of age predicted HRmax are often seen [39, 62]. Because of 10- to 12-beats-per-minute variations in HRmax in healthy individuals, even when taking age into account [63, 64], predicting HRmax is problematic [65, 66], and is likely to underestimate or overestimate HRmax on an individual level. A potentially greater variation is added in patients with cancer owing to the documented impact certain cancer treatments have on cardiac function [67], which is commonly observed as increased HR [68]. In addition, on the basis of the possible positive effects of beta-blockers (which cause lower HR or a “ceiling” in HR) in relation to cancer prognosis [69], such medications also contribute to complicating the use of this criterion. Taking these factors together, the age predicted HRmax is presumably a problematic criterion to apply in both healthy individuals [22, 39] and in patients with cancer, before, during and after cancer treatment.

Plateau in oxygen uptake

Finding as many as 91% to achieve the \( \leq 150 \text{ ml/min} \) plateau cut-point may be interpreted as a positive finding. However, the mean \( \dot{V}O_2 \text{peak} \) was the same as in the patients that did not fulfill this cut-point. Whether or not \( \leq 150 \text{ ml/min} \) plateau cut-point fits the participants and protocol in the present study, could be discussed. The modified Balke protocol involves very small \( \dot{V}O_2 \)-increments from one stage to the next, and therefore seems the most suitable for the 150 ml/min cut-point, compared to the other two cut-points applied in the present study. A plateau in \( \dot{V}O_2 \) stands out as the most widely used criterion for verifying \( \dot{V}O_2 \text{max} \) [23], but some authors doubt that such a physiological plateau exists [30]. Others argue that a \( \dot{V}O_2 \) plateau exists, but the methodology used to identify it is central for detecting it [36]. The type of test protocol and sampling acquisition may affect the observation of a plateau [31, 32], in addition to age and fitness [23], although other studies do not agree on this [33]. Although researchers do not agree on the rationale, undoubtedly there are huge variations in the number of subjects fulfilling the plateau criterion in different studies [32]. Based on all considerations, questions are raised regarding the validity of using the plateau criterion verifying true
\( \text{VO}_2\text{max} [70] \) and other researchers have concluded that the \( \text{VO}_2 \) plateau is not a reliable physiological marker for maximal effort in all subjects [71].

**Strengths**

In a large sample of patients newly diagnosed with cancer, we have managed to elucidate criteria for validating \( \text{VO}_2\text{max} \) tests differently from what has been previously seen in the literature. Thorough and consistent instructions and follow-up of the test leaders enabled conditions to be as similar as practically possible for all participants, independent of when or where they performed their \( \text{VO}_2\text{max} \) tests. The test leaders were also generally experienced with exercise testing and/or with the clinical populations before the start of the Phys-Can. By including \( f_R \) in our analyses, we have started to explore another possible variable as a new criterion or normative to apply in validation of \( \text{VO}_2\text{max} \) tests.

**Limitations**

Few patients with colorectal cancer were included, so generalization to this or other non-included types of cancer are questionable. Furthermore, because there were only 4 of 80 (5%) \( \text{VO}_2\text{max} \) tests evaluated as “not to exhaustion” in the cohort study, our cross-validation was more of a descriptive approach. The \( O_2 \) analyzers were from different producers across the three sites, and this may be a source of bias between the tests performed in Lund, Linköping and Uppsala. For practical reasons, validity tests were, unfortunately, not performed between the various \( O_2 \) analyzers. Measurements of \( \text{BLa}^- \) were not taken after the \( \text{VO}_2\text{max} \) tests in the Phys-Can study. Although the RER value correlates highly with \( \text{BLa}^- \) [72], a measure of \( \text{BLa}^- \) would have expanded the number of objective criteria assessed. In addition, high inter-subject variability (from 5 to 17 mM) in post-exercise lactate has been reported [73] and is, accordingly, another criterion that is difficult to standardize [35]. The definition of a \( \text{VO}_2 \) plateau, as included in the present study, is perhaps not the most suitable method because of the protocol-differences between the discontinuous test protocols applied on healthy young men in the 1950s by Taylor et al. and the modified Balke protocol used in Phys-Can. In addition, we did not incorporate relative body mass into the equation. The validity of the results from the cross-validation, where a correct classification of “to exhaustion” were made in only 66% of cases from the cohort study, when applying the best three criteria can be questioned. However, the low number of tests classified as “not to
exhaustion” in the cohort study makes the data figures too small to conclude anything related to how well the criteria fits another comparable sample of individuals. Last, in the present study we did not include a verification bout directly after each of the \( \dot{V}O_2 \text{max} \) tests, which potentially could have been a better approach than the test-leaders evaluation as the effect variable when investigating the different criteria and their cut-points.

**Conclusions and future perspectives**

Relating the findings to clinical practice, we suggest avoiding the predicted HR\text{max} criterion. On the basis of the observations in the present study, in addition to the complexity of detecting a \( \dot{V}O_2 \) plateau when using different methodologies (e.g. test protocols and data acquisition) [23], we suggest not placing emphasis on this criterion either. We recommend a focus on RER (in the range between \( \geq 1.1 \) and \( \geq 1.15 \)) and RPE (\( \geq 17 \) or \( \geq 18 \)) in addition to the test leader’s evaluation. Also, a \( f_R \) peak of \( \geq 40 \) breaths/min may be an additional cut-point to help the test leader evaluate the degree of exhaustion, but more research is needed to determine whether this should be used as a criterion.

A course for future investigations may be to determine whether the \( f_R \) variable could be part of the criteria verifying \( \dot{V}O_2 \text{max} \). In addition, it would be interesting to precede with comparable methodologic approaches as in Schneider et al. (2019) [42], where a supramaximal verification bout was performed after the \( \dot{V}O_2 \text{max} \) test, in order to validate the initial \( \dot{V}O_2 \text{max} \) results, only apply the method using treadmill [20]. Also, a submaximal verification phase [36] which probably is more feasible for cancer patients, would be interesting to apply and investigate further. Whether achievement of the same \( \dot{V}O_2 \text{max} \) value in the verification bout is a valid criterion could be investigated together with the results from the present study, in patients in different phases of their cancer disease. In a recent study by Santa Mina et al. (2020), the authors describe their lab-experiences from testing 44 patients with cancer, in which only 14% achieved all of their \( \dot{V}O_2 \text{max} \) criteria, and none reached a \( \dot{V}O_2 \) plateau [74]. Hence, it is also important to investigate criteria for verifying \( \dot{V}O_2 \text{max} \) in patients that are undergoing or have finished cancer treatment, as these patients may have other responses and may have more difficulties in pushing themselves to maximal effort.
References


Paper III
Does exercise intensity matter for fatigue during (neo-)adjuvant cancer treatment? The Phys-Can RCT


*Ingrid Demmelmaier and Hannah L Brooke contributed equally to this work

Author institutions and affiliations

PhD Ingrid Demmelmaier, PhD Hannah L Brooke, PhD Anna Henriksson, MSc Anne-Sophie Mazzoni, Professor Karin Nordin, Uppsala University, Department of Public Health and Caring Sciences, Uppsala, Sweden

MSc Ann Christin Helgesen Bjørke, Professor Sveinung Berntsen, University of Agder, Department of Sport Science and Physical Education, Kristiansand, Norway

PhD Helena Igelström, Professor Pernilla Åsenlöf, Uppsala University, Department of Neuroscience, Uppsala, Sweden

MSc Anna-Karin Ax, Professor Sussanne Börjeson, Linköping University, Department of Oncology and Department of Medical and Health Sciences, Linköping, Sweden

PhD Katarina Sjövall, Lund University, Department of Oncology and Skåne University Hospital, Department of Oncology, Lund, Sweden

PhD Maria Hellbom, Stockholm Health Care Services, Centre for Cancer Rehabilitation, Stockholm, Sweden

PhD Ronnie Pingel, Uppsala University, Department of Statistics, Uppsala, Sweden

PhD Henrik Lindman, PhD Silvia Johansson, Professor Bengt Glimelius, Professor Peter Nygren, PhD Birgitta Johansson, Uppsala University, Department of Immunology, Genetics and Pathology, Uppsala, Sweden

Professor Galina Velikova, University of Leeds, Leeds Cancer Centre, Leeds Institute of Medical Research at St James's, Leeds, UK
Professor Truls Raastad, Norwegian School of Sport Sciences, Department of Physical Performance, Oslo and University of Agder, Department of Sport Science and Physical Education, Kristiansand, Norway
PhD Laurien M Buffart, Radboudumc, Department of Physiology, Nijmegen, The Netherlands
Professor Neil K Aaronson, The Netherlands Cancer Institute, Division of Psychosocial Research & Epidemiology, Amsterdam, The Netherlands

Corresponding author

PhD Ingrid Demmelmaier, Uppsala University, Department of Public Health and Caring Sciences, Husargatan 3, Post Box 564, 751 22 Uppsala, Sweden
ingrid.demmelmaier@pubcare.uu.se

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Conflict of interest

The authors declare they have no conflict of interest.

Word count

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List of abbreviations in text

CRF = Cancer-Related Fatigue
BCS = Behaviour Change Support
MFI = Multidimensional Fatigue Inventory
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue scale
HRQoL = Health-Related Quality-of-Life
BMI = Body Mass Index
VO_{2}\text{max} = Maximal Oxygen uptake
Borg RPE = Borg Rating of Perceived Exertion
RER = Respiratory Exchange Ratio
HADS = Hospital Anxiety and Depression Scale
EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30
ABSTRACT

Background
Exercise during and after cancer treatment improves cancer-related fatigue (CRF), but the importance of exercise intensity for CRF is unclear. We compared the effects of high vs. low-to-moderate intensity exercise with or without additional behaviour change support (BCS) on CRF in patients undergoing (neo-)adjuvant treatment.

Methods
This was a multicentre, 2x2 factorial design randomised controlled trial (Clinical Trials NCT02473003) in Sweden. Patients recently diagnosed with breast, prostate or colorectal cancer undergoing (neo-)adjuvant treatment were randomised to high or low-to-moderate intensity exercise, with or without additional BCS. The 6-month exercise intervention consisted of supervised resistance training and home-based endurance training. CRF was assessed by the Multidimensional Fatigue Inventory (MFI, subscales score range 4-20), and the Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F, score range 0-52). Multiple linear regression for main factorial effects was performed according to intention-to-treat, with post-intervention CRF as primary endpoint.

Results
Overall, 577 patients (mean age 58.7 years) were randomised. Patients randomised to high vs. low-to-moderate intensity exercise had lower physical fatigue (MFI Physical Fatigue subscale; mean difference -1.05 [95% CI:-1.85,-0.25]), but the difference was not clinically important (i.e.< 2). We found no differences in other CRF dimensions and no effect of additional BCS. There were few minor adverse events.

Conclusion
For CRF, patients undergoing (neo-)adjuvant treatment for breast, prostate or colorectal cancer can safely exercise at high or low-to-moderate intensity, according to their own preferences. Additional BCS does not provide extra benefit for CRF in supervised, well-controlled exercise interventions.
What are the findings?

- Patients undergoing (neo-)adjuvant cancer treatment exercising at high intensity for six months demonstrated lower physical fatigue at post-intervention, compared to patients exercising at low-to-moderate intensity. However, the difference between groups was below the threshold for clinical importance.
- There was no effect of behaviour change support (goal-setting, planning and self-monitoring of exercise) on fatigue.
- The six-month intervention, including resistance and endurance training, caused few minor adverse events in patients undergoing (neo-)adjuvant treatment.

How might it impact on clinical practice in the future?

- The important message to clinicians is that patients undergoing (neo-)adjuvant treatment for breast, prostate or colorectal cancer can be advised that it is safe to exercise at either high or low-to-moderate intensity, according to their own preferences.
- Behaviour change support (goal-setting, planning and self-monitoring of exercise) may be unnecessary if patients are relatively healthy, motivated for exercise and participate in supervised, well-controlled interventions.
- The occurrence of few minor adverse events indicates that exercise is safe, even at high intensity, and can be recommended to these patient groups.
BACKGROUND

Cancer survival rates have improved due to earlier detection and advances in treatment. However, cancer survivors report long-term challenges, such as cancer-related fatigue (CRF), physical deconditioning, and decreased health-related quality-of-life (HRQoL). CRF is defined as a distressing, persistent sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning. Prevalence of moderate-to-severe CRF during treatment is 30-60%, and clinically important CRF has been reported in one-third of patients up to 6 years after treatment. The aetiology of CRF is multifactorial and treatment-induced activation of pro-inflammatory cytokines may be one trigger.

Exercise during and after treatment is effective in counteracting CRF, possibly by lowering the inflammatory activity and/or by increasing physical fitness. Exercise also improves HRQoL, may increase chemotherapy completion rates, and reduce the risk of cancer mortality. International guidelines recommend 3 sessions of at least moderate intensity endurance training and/or 2 sessions of resistance training each week to counteract CRF. However, the evidence-base regarding the ideal 'exercise prescription' in terms of exercise frequency, intensity, duration, and type, for cancer survivors is insufficient. While low-to-moderate intensity may be preferred by most patients, one study found that moderate-to-high intensity exercise during cancer treatment was beneficial for physical fatigue compared to low intensity exercise. However, exercise volume was not controlled for, so the importance of intensity per se could not be determined. Second-generation studies comparing different exercise intensities in relation to side-effects, such as CRF, are therefore needed.

Many patients find it difficult to perform physical activity during oncological treatment and they are on average less physically active than the general population. Interview studies indicate a need for individualised support to overcome barriers such as side-effects and external demands. BCS, including self-monitoring and behavioural goal-setting, can be used to overcome such barriers. However, if BCS can influence health outcomes through increased intervention adherence is unclear due to limitations in study methodology and reporting.

The primary aim of this second-generation study was to determine the effects of high vs. low-to-moderate intensity exercise with or without additional BCS on CRF (primary
endpoint) in patients undergoing (neo-)adjuvant cancer treatment. Secondary aims were to determine the effects on HRQoL, anxiety/depression, function in daily life, cardiorespiratory fitness, muscle strength, level of physical activity, sedentary time, sleep and treatment completion rates.

METHODS

Design

The Physical training and Cancer (Phys-Can) study was a Swedish three-centre, 2x2 factorial design randomised controlled trial (Figure 1), previously described in depth.19 Briefly, patients were randomised to high or low-to-moderate intensity exercise, with or without additional BCS (ClinicalTrials.gov NCT02473003). The Swedish Ethical Review Authority approved the study (Dnr 2014/249).

Coaches (qualified and experienced physiotherapists, n=13 or personal trainers, n=2) were assigned to lead an intervention group based on logistics, scheduling and their additional competence in BCS. Each coach supervised patients in both exercise intensity groups. However, coaches who provided additional BCS supervised only those groups.

There were no major changes to the study after the trial commenced.

Participants

Participants were recruited from Uppsala, Lund and Linköping University hospitals from March 2015 to April 2018. Eligible participants, assessed by an oncologist, were >18 years, literate in Swedish and recently diagnosed with curable breast (women only), prostate or colorectal cancer, scheduled to begin (neo-)adjuvant chemotherapy, radiotherapy and/or endocrine therapy.

Exclusion criteria were stage IIIb-IV breast cancer, inability to perform basic activities of daily living, cognitive disorders, severe psychiatric disease or other disabling conditions that might contraindicate high intensity exercise (e.g. severe heart failure, severe chronic obstructive pulmonary disease or orthopaedic conditions), treatment for an additional ongoing malignant disease, BMI<18.5 kg/m² or pregnancy. A research nurse/assistant provided oral and written information to eligible participants prior to
start of treatment. Those willing to participate gave written informed consent before baseline data collection.

Interventions

The 6-month intervention was initiated at start of the (neo-)adjuvant cancer treatment as described in Table 1. The supervised, group-based resistance training at public gyms was performed twice/week (Suppl. Figure 1). The home-based endurance training at high intensity consisted of interval training, performed twice/week, while low-to-moderate intensity endurance training consisted of 150 weekly minutes of walking or biking. Additional BCS, such as goal-setting, planning and self-monitoring, was delivered face-to-face jointly with the resistance training sessions. Breast cancer patients scheduled for neo-adjuvant chemotherapy exercised during the four months pre-surgery only. Standardised delivery of the intervention was assessed and enhanced as described in Table 1.

Outcomes and data management

Follow-up data collection was completed in November 2018. The primary outcome, CRF, was assessed with the Multidimensional Fatigue Inventory (MFI), measuring General, Physical and Mental Fatigue, Reduced Motivation and Reduced Activity, each subscale range 4-20. Based on previous research, the Physical Fatigue subscale was used for power calculation.

CRF was also assessed with Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale, a single scale questionnaire with range 0-52.

All outcomes (Table 2) were assessed with well-established and validated methods, completed at home, at baseline (before randomisation) and immediately post-intervention. Composite scores were calculated according to published instructions.

Physical activity was measured using SenseWear Armband mini (BodyMedia Inc., Pittsburgh, PA, USA) at baseline and post-intervention, as described in supplementary table 2. A minimum of 80% wear time for four out of seven days was required for data to be included. Cardiorespiratory fitness was independently assessed in dedicated exercise labs using maximal oxygen uptake (VO$_{2\text{max}}$) tests, walking/running to exhaustion using a modified Balke protocol. Tests were accepted if two out of three
criteria were fulfilled: 1) tester judged the test as maximal, 2) Borg RPE\textsuperscript{27} rating ≥17 and 3) respiratory exchange ratio (RER) ≥1.1.

Exercise adherence was calculated as performed exercise/prescribed exercise, in accordance with previous research,\textsuperscript{28} as described in table 1.

**Sample size**

An *a-priori* power calculation showed that 600 patients (150 per trial arm) were required to detect main factorial effects of exercise intensity and BCS on the MFI Physical Fatigue subscale,\textsuperscript{29} with a minimum clinically important difference of 2 points (SD 5) post-intervention and 80% power at alpha level 0.05. This calculation allowed for missing data and drop-out from the study.\textsuperscript{19}

**Randomisation**

The random allocation sequence with a ratio of 1:1:1:1 was computer generated and thus concealed from all research staff. Within each stratum (3 centres and 3 diagnoses) randomisation was carried out following a permuted block design with 8 patients per block. Once baseline data collection was finalised, each patient was automatically assigned to an intervention group using a web-portal.

**Blinding**

Blinding of coaches and participants to the intervention group was not feasible. However, coaches and participants were informed that there was limited evidence for which intensity would be more beneficial for CRF.

**Statistical methods**

Multiple linear regression was used to simultaneously estimate the main effect for exercise intensity (high vs. low-to-moderate intensity) and BCS (with vs. without), and their interaction (intensity x BCS) on each outcome post-intervention. Results are presented as adjusted mean difference with 95% Confidence Intervals (95%CI). Analyses were conducted according to intention-to-treat. Models included baseline measures of the outcome to increase precision and were adjusted for centre and cancer diagnosis.

Missing data were accounted for using multiple imputations by chained equations. Auxiliary variables used to inform imputed values were age, education level, centre,
diagnosis, chemotherapy treatment, baseline values of outcome measure and intervention group. Where missing data at baseline were >10%, baseline data for that outcome were not included as an auxiliary variable or as a variable in the main models, as baseline data was deemed not to add additional precision for these outcomes.

A supplementary analysis based on complete cases was performed. In addition, each cancer diagnosis was examined separately; these models were adjusted for centre and baseline measures of the outcome variable.

Analyses were carried out in Stata version 15.0.

**Patient and public involvement**

Patient representatives, one from each diagnosis group, were included in the project group. They were involved in the design of the study, the content of the intervention, informational material, and provided feedback on the burden of the intervention. They will help disseminate the results within their respective patient organisation.

**RESULTS**

**Recruitment**

Six hundred (29%) of 2051 eligible patients agreed to participate (Figure 1). Participants, compared to those who declined participation, were younger (mean age 58.7 vs 63.6 years, \( p \)-value<0.001) and less likely to have prostate or colorectal cancer than breast cancer (OR [95%CI]; colorectal cancer, 0.58 [0.36-0.92], \( p \)-value=0.02; prostate cancer, 0.65 [0.51-0.83], \( p \)-value=0.001). Twenty-three participants withdrew from the study before randomisation. In total, 577 patients were randomised.

**Baseline characteristics of randomised participants**

Breast cancer was the most common diagnosis (n=457), followed by prostate cancer (n=97) and colorectal cancer (n=23). Time between diagnosis and randomisation was median 61 (interquartile range 44-86) days and there was a median of 7 (interquartile range 5-11) days between randomisation and starting the intervention. Sociodemographic, disease and treatment characteristics were similar across all four intervention groups (Table 3 and Suppl. Table 3).
Missing data

Overall, 89 randomised patients withdrew from the study before the follow-up assessment. Additionally, missing data on outcomes ranged from n=40 (FACIT-F, HADS Anxiety and Depression scales) to n=106 (VO₂max) (Suppl. Table 5). Missing data were not associated with intervention group, age, living situation, education, or BMI.

Primary outcome

Patients randomised to exercise at high compared with low-to-moderate intensity had lower MFI physical fatigue (adjusted mean difference -1.05 [95% CI, -1.85 to -0.25, p-value=0.011]) (Table 4). There were no statistically significant differences for the other MFI dimensions or for FACIT-F. Moreover, there were no main effects for additional BCS and no exercise intensity-BCS interactions for any CRF measures.

Secondary outcomes

There were no main effects of exercise intensity or additional BCS on HRQoL based on the EORTC QLQ C-30 Summary Score (Table 4). However, there was an interaction effect indicating that in the groups receiving additional BCS, high intensity exercise was associated with a lower HRQoL for some dimensions compared to low-to-moderate intensity, while in the groups not receiving BCS high intensity exercise was associated with higher HRQoL (Table 4).

Patients randomised to exercise at high vs. low-to-moderate intensity had better cardiorespiratory fitness (adjusted mean difference 1.61 [95% CI 0.19-3.04, p-value=0.027] ml/kg/min) and greater leg strength (adjusted mean difference 3.98 [95% CI 0.58-7.38, p-value=0.022] kg) (Table 4). There were no main or interaction effects of additional BCS on these outcomes. An exercise intensity-BCS interaction was observed for moderate-to-vigorous intensity physical activity.

There were no main or interaction effects of the intervention on anxiety, depression, functioning in daily life, sleep, sedentary behaviour, chemotherapy completion rates or relative dose intensity (Table 4).

For chemotherapy completion rates, 118 patients (39.6%) out of 298 had dose reduction or treatment discontinuation (Suppl. Table 3). There were no adjustments of radiotherapy dose for any patient.
**Supplementary analyses**

The results from the complete case analysis were similar to the main results, i.e. the MFI Physical Fatigue scale differed significantly, in favour of the high intensity exercise groups (Suppl. Table 5). However, in contrast to the intention-to-treat analysis, VO$_{2\text{max}}$ did not differ between groups in the complete cases analysis. Diagnosis-specific analyses reflected the main results for all diagnostic groups (Suppl. Tables 6 and 7) but were underpowered for patients with colorectal cancer and weaker for those with prostate cancer.

**Intervention adherence**

Participants completed on average 50.4% of the prescribed resistance training volume, with no differences between intervention groups (one-way ANOVA p=0.438) (Figure 2). Adherence to endurance training differed between groups (range, 38.8-57.7%; one-way ANOVA p<0.001) and pair-wise comparisons are presented in Figure 2. Among participants in the low-to-moderate intensity groups those who received additional BCS performed more minutes of exercise above the prescribed intensity (i.e. >60% of heart rate reserve) than those who did not receive additional BCS (506 vs 326 minutes, t-test p-value=0.026).

**Adverse events due to intervention**

Thirty-two minor adverse events in 30 patients (n=8 high intensity with BCS, n=12 high intensity without BCS, n=6 low-to-moderate with BCS, n=4 low-to-moderate without BCS) prevented them from completing the ongoing training session. These included muscle strains, joint pain, and dizziness. In addition, three patients needed to attend hospital as a result of exercise; one injured a finger, and two fainted.

**DISCUSSION**

This was a large, second-generation RCT with the major strength that exercise volume was the same in all intervention groups, which enabled us to examine exercise intensity *per se*. High intensity resistance and endurance exercise yielded significantly lower physical fatigue compared to low-to-moderate intensity exercise in patients undergoing (neo-)adjuvant treatment, but the magnitude of effect did not reach the minimal clinically important difference of two points. Further, there were no differences
between groups in other CRF dimensions. There were few minor adverse events, which indicates that exercise is safe, even at high intensity, for these patient groups. Although there were small benefits of high intensity exercise for muscle strength and cardiorespiratory fitness, overall, patients undergoing (neo-)adjuvant treatment for breast, prostate or colorectal cancer can be advised to exercise at either intensity, according to their own preferences. Finally, our results suggest that, in a motivated and relatively healthy sample, additional BCS does not influence CRF directly or through increased adherence.

In line with our results, van Waart et al demonstrated statistically lower physical fatigue after combined resistance and endurance exercise at moderate-to-vigorous intensity compared to low intensity walking during adjuvant chemotherapy, but did not find a minimum clinically important difference between groups. However, van Waart et al did not control for exercise volume, which limited the possibilities to draw conclusions about the effect of exercise intensity per se.

Kampshoff et al reported no between-group differences in CRF for high vs low-to-moderate intensity exercise after cancer treatment. An RCT comparing high and low-to-moderate intensity endurance training within a multimodal rehabilitation program after treatment also reported no differences in CRF. However, both of those studies evaluated shorter interventions after treatment, and are not directly comparable to our study.

Additional BCS did not improve CRF or other health outcomes. This may be because all groups were provided with some aspects of BCS, such as structured training, graded tasks and feedback. These methods have previously been associated with higher exercise adherence in cancer populations. This element of the study design was a balance between enhancing adherence to the intervention protocol and evaluating the contribution of additional BCS. One other plausible explanation for the lack of effect of additional BCS on CRF is that participants were relatively healthy and well-motivated. It is possible that a broader, more heterogeneous clinical population would benefit from such support. Further, long-term-effects of BCS on adherence and CRF need to be examined.

Post-intervention muscle strength was higher in the high intensity exercise group, which is in line with literature indicating that higher loads increase maximal strength.
more, even after controlling for exercise volume.\textsuperscript{32} Although significant, the small between-group difference in cardiorespiratory fitness is consistent with the idea that in addition to intensity, frequency, duration and volume are important exercise variables for cardiorespiratory fitness during cancer treatment.\textsuperscript{33}

Other secondary outcomes did not differ between groups. Thus, while it is well-known that exercise during cancer treatment is beneficial compared to usual care for a number of health outcomes,\textsuperscript{34} the results of our second-generation study indicate that patients can exercise at either high or low-to-moderate intensity without missing out on improvement of several prevalent side effects.

Our sample consisted of relatively healthy and motivated individuals, mainly well-educated women treated for breast cancer. Nonetheless, participants varied in age, current exercise levels and perceived importance of exercise. Although only 29\% of the approached patients consented to participate, the aim of this study was to compare the efficacy of high vs. low-to-moderate intensity exercise on CRF. As such, internal validity was prioritised over external validity. It is unlikely that biological mechanisms related to exercise intensity differ in our sample compared with the broader population. Therefore, our results represent a valid and clinically relevant estimate of the efficacy of high vs. low-to-moderate intensity exercise on CRF and other side effects.

**Strengths and limitations**

A clear protocol and competent, trained coaches helped ensure that the intervention was delivered consistently across the different centres and the patients were closely monitored and given frequent face-to-face feedback regarding intensity. Objective measures were used to assess physical activity as well as maximal testing of cardiorespiratory fitness and muscle strength. Supplementary complete cases analysis showed largely similar results as the main analysis, suggesting that bias was not introduced by imputation of missing data.

The study was not powered to draw conclusions about the effects of exercise intensity on CRF for specific diagnosis groups. However, diagnosis specific results for breast cancer and colorectal cancer were of the same magnitude and direction as the main results. These findings can be meta-analysed with other studies to inform research on
diagnosis-specific effects. Blinding coaches and participants to the intervention was not feasible. However, there was not strong *a priori* information about which intensity would be better for CRF, so this is unlikely to introduce serious bias. Since we did not have full control of the home-based endurance training, bias may have been introduced if there was differential reporting between groups. However, this was limited by providing participants with a heart rate monitor to objectively measure intensity and duration of home-based training, rather than relying on self-report.

**CONCLUSIONS**

For CRF, we found no clinically important difference between patients randomised to high vs low-to-moderate intensity exercise. Patients undergoing (neo-)adjuvant treatment for breast, prostate or colorectal cancer can therefore be advised to exercise at either intensity, according to their own preferences. There were few and minor adverse events during the intervention, indicating that exercise is safe, even at high intensity, for these patient groups. In a motivated and relatively healthy sample, additional BCS is not likely to influence CRF. Future studies are needed to evaluate such support in broader clinical populations.
Acknowledgements

The authors would like to acknowledge the study participants, the clinicians involved in recruitment, the staff at the public gyms where the resistance exercise was performed, and the patient representatives who contributed with their perspectives. We also acknowledge Dr Pernille Höjman, Centre for Physical Activity Research and Centre of Inflammation and Metabolism, Rigshospitalet Copenhagen, Denmark, who contributed substantially to the project but sadly passed away in April 2019.

Contributors

All authors were involved in drafting the article or revising it critically for important intellectual content and agreed to be accountable for all aspects of the work ensuring that questions related to the accuracy and integrity of the work were appropriately resolved. All authors approved of the final version to be submitted.

Study conception and design: Demmelmaier, Henriksson, Mazzoni, Igelström, Ax, Sjövall, Hellbom, Pingel, Lindman, S Johansson, Velikova, Raastad, Buffart, Åsenlöf, Aaronson, Glimelius, Nygren, B Johansson, Börjeson, Berntsen, Nordin.

Acquisition of data: Demmelmaier, Henriksson, Mazzoni, Helgesen Björke, Igelström, Ax, Sjövall, Lindman, S Johansson, B Johansson, Börjeson, Berntsen, Nordin.

Analysis and interpretation of data: Demmelmaier, Brooke, Henriksson, Mazzoni, Helgesen Björke, Pingel, Velikova, Raastad, Buffart, Åsenlöf, Aaronson, Glimelius, Nygren, B Johansson, Börjeson, Berntsen, Nordin.

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Conflict of interest

The authors declare they have no conflict of interest.

Patient consent for publication

Not required

Ethical approval

16
The Swedish Ethical Review Authority approved the study (Dnr 2014/249). All participants gave written informed consent.

Data sharing statement

Deidentified participant data (including data dictionaries) will be shared upon reasonable request for research purposes by contacting corresponding author.

ORCID iD

Ingrid Demmelmaier 0000-0002-2068-4708

REFERENCES


Figure legends

Figure 1. CONSORT diagram of flow of participants through the Phys-Can study. Numbers with (in)complete baseline and follow-up data are based on cancer related fatigue (MFI physical fatigue subscale), exact numbers for other outcomes vary (see Table 3). Follow-up refers to data collected at the post-intervention. HI: high intensity exercise, LMI: low-to-moderate intensity exercise, BCS: additional behaviour change support.

Figure 2. Adherence to prescribed strength and endurance training volume, by training group. Bars represent mean adherence, error bars indicate 1 standard deviation from the mean. Participants who dropped out of the study were recorded as 0 adherence to any remaining training sessions. P-values reflect pair-wise comparisons across the four intervention groups using Tukey post-hoc tests. All other pair-wise comparisons resulted in p-values >0.05. HI: high intensity exercise, LMI: low-to-moderate intensity exercise, BCS: additional behaviour change support.

Supplementary figure 1. Illustrations of resistance training exercises.
Table 1 Description of resistance training, endurance training and additional behaviour change support (BCS) components of the intervention, according to 2017 CONSORT checklist for reporting randomized trials assessing non-pharmacological treatment.

<table>
<thead>
<tr>
<th>Resistance training</th>
<th>Endurance training</th>
<th>Additional BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Content</strong></td>
<td>High intensity:</td>
<td>Coaches guided patients in using strategies to facilitate adherence to the exercise, focusing mainly on the home-based endurance training:</td>
</tr>
<tr>
<td></td>
<td>3 x 6 RM (2 minutes rest between sets) once a week. Last set until failure.</td>
<td>Goal-setting</td>
</tr>
<tr>
<td></td>
<td>3 x 10 RM (1 minute rest between sets) once a week. Last set until failure.</td>
<td>Short-term action planning</td>
</tr>
<tr>
<td></td>
<td>Low-to-moderate intensity: 3 x 12 repetitions at 50% of 6 RM (2 minutes between sets) once a week.</td>
<td>Self-monitoring</td>
</tr>
<tr>
<td></td>
<td>3 x 20 repetitions at 50% of 10 RM (1 minute rest between sets) once a week.</td>
<td>Review of goal-setting</td>
</tr>
<tr>
<td></td>
<td>Two sessions per week.</td>
<td>Behavioural analysis</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Supervised at public gyms in groups of typically 5-10 patients. Separate groups for each of the four conditions.</td>
<td>Long-term coping planning</td>
</tr>
<tr>
<td><strong>Tailoring</strong></td>
<td>Individually adapted weights based on repeated testing of 6 and 10 RM in all exercises. Weights were lowered temporarily for patients struggling with severe side-effects, and then successively increased. Exercises that caused pain were substituted with other exercises activating the same muscle groups.</td>
<td>Adapted to the patients’ needs; fewer/short reviews if goals were easily reached every week. Goal-setting and action planning specifying when, where and how to train. Based on interviews about previous exercise habits. Self-monitoring by extended logbooks with facilitators and barriers in specific situations. Review and adjustment of goal-setting to be important and realistic to the patient. Analysis by identifying determinants of training, based on logbooks and discussions. Long-term coping planning according to patients’ preferences about maintained physical activity/exercise.</td>
</tr>
<tr>
<td><strong>Standardisation</strong></td>
<td>Familiarisation period of six weeks. Six exercises; three for the upper extremities and three for the lower extremities. Four additional exercises for the trunk and pelvic floor were advised but not controlled (see Supplementary Figure 1). Progression based on testing of 6 and 10 RM every 4-6 weeks.</td>
<td>Weekly reviews during the first month and then typically every 4-6 weeks, included in week-to-week checklists. Printed sheets for coaches to align the procedures for goal-setting, action planning, review of goal-setting, analysis and long-term coping planning. Electronic or printed extended logbooks for patients’ self-monitoring.</td>
</tr>
</tbody>
</table>

**Endurance training**

| High intensity: Twice-weekly interval sessions. Two minutes of exercise (running, cycling, walking up-hill) at 80-90% HRR followed by two minutes of active rest. Progression from 5 intervals, adding intervals over time until max 10 intervals. Warm-up and cool-down for 5-10 minutes respectively. | HRR was determined for each participant based on a VO$_{2\text{max}}$ test performed before standardized performance. |

**Additional BCS**

| Low-to-moderate intensity: 150 weekly minutes of endurance activity (walking, cycling) in bouts of minimum 10 minutes at 40-50% of HRR. | Coaches guided patients in using strategies to facilitate adherence to the exercise, focusing mainly on the home-based endurance training: |
| Goal-setting | Goal-setting and action planning |
| Short-term action planning | Review of goal-setting |
| Self-monitoring | Behavioural analysis |
| Review of goal-setting | Long-term coping planning |
| Long-term coping planning | Adapted to the patients’ needs; fewer/short reviews if goals were easily reached every week. Goal-setting and action planning specifying when, where and how to train. Based on interviews about previous exercise habits. Self-monitoring by extended logbooks with facilitators and barriers in specific situations. Review and adjustment of goal-setting to be important and realistic to the patient. Analysis by identifying determinants of training, based on logbooks and discussions. Long-term coping planning according to patients’ preferences about maintained physical activity/exercise. |

HRR was determined for each participant based on a VO$_{2\text{max}}$ test performed before standardized performance.
| Provider adherence: assessment and enhancement | Three-day course for coaches on supervising patients’ exercise according to a detailed intervention protocol. Repeated on-site visits and project group meetings with research staff on five occasions. Twice-monthly teleconferences with coaches from each site to discuss and align the delivery of the intervention. Week-by-week checklist for each patient, corresponding to the intervention protocol, was used by coaches. | See left. | BCS coaches had three additional course days with theory and practice on BCS and a detailed protocol. Repeated on-site visits by research staff and project meetings on five occasions. Audio recordings of reviews were used twice to assess the coaches’ use of BCS and feedback was provided to them by research staff. Non-BCS coaches had a protocol specifying what they were not allowed to do. These restrictions and any problems with adhering to them were followed up repeatedly at on-site visits and project meetings. |
| Participant adherence: assessment and enhancement | Week-by-week checklist for each patient with attendance, 6 and 10 RM test results and notes about deviations from the protocol. Printed logbooks where target weights were recorded by the coaches. The coaches checked adherence to the protocol and gave feedback at each session. If patients did not attend a resistance training session, they were contacted by telephone and encouraged to attend the next session. | Files from heart rate monitors were reviewed by coaches together with the patients. All patients completed 23standardized logbooks for endurance training, either electronically or by paper. Pulse files and logbooks were checked for intensity and overall adherence and feedback was provided. | For self-monitoring, the extended logbooks were checked regularly by the coaches and the patients were encouraged to use them. Goal-setting reviews and analysis were performed weekly during the first month of the exercise period and then typically every 4-6 week. Long-term coping plans were written; one copy for the patient and one for the coach to follow up. Telephone follow-up by coach at 3 and 9 after end of the exercise period. |
| Calculation of adherence | Performed training divided by maximum possible training using logbook data. Performed training was performed weight x performed number of repetitions, summed across all exercises and training sessions. Maximum possible training was weight x number of repetitions according to the protocol summed across all exercises and maximum possible training sessions. | Performed training divided by maximum possible training using a combination of logbook and pulse file data. **High intensity:** Performed training was number of intervals x interval duration summed across all training sessions with an average intensity of minimum 90% of the 80% lower HRR limit. This adjustment was made to take into account biking sessions; lower HR despite similar exertion level as running. Maximum possible training was number of intervals x interval duration (2 minutes) x 2 x number of weeks of training according to the protocol. **Low-to-moderate intensity:** Performed training was minutes of activity of an intensity of 40-60% of HRR. Adjustment of upper limit was made as general heart rate increase is common during chemotherapy/cortisol treatment. Maximum possible training was 150 x number of weeks of training according to the protocol. In addition, calculation of minutes of activity at >60%, enabling adjustment for high intensity. | Performed number of sessions including reviews and action planning divided by the maximum possible number of sessions according to the protocol \( (n = 9) \). |
RM = Repetition maximum, HRR = Heart rate reserve, VO₂max = Maximum oxygen respiratory uptake, RPE = Rating of perceived exertion
### Table 2. Methods and interpretation of pre-specified primary and secondary outcome measures

<table>
<thead>
<tr>
<th>Instrument/method</th>
<th>Assessed by</th>
<th>Score Range</th>
<th>Interpretation of higher score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer-related fatigue</td>
<td>MFI subscales for General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity [20]</td>
<td>Self-reported questionnaire</td>
<td>4-20</td>
</tr>
<tr>
<td></td>
<td>FACIT-Fatigue Scale [21]</td>
<td>Self-reported questionnaire</td>
<td>0-52</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>EORTC QLQ-C30 summary score [22]</td>
<td>Self-reported questionnaire</td>
<td>0-100</td>
</tr>
<tr>
<td></td>
<td>EORTC QLQ-C30 Functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning)</td>
<td>Self-reported questionnaire</td>
<td>0-100</td>
</tr>
<tr>
<td></td>
<td>EORTC QLQ-C30 Symptom scales/items (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties)</td>
<td>Self-reported questionnaire</td>
<td>0-100</td>
</tr>
<tr>
<td>Anxiety and depression</td>
<td>HADS anxiety subscale and depression subscale [23]</td>
<td>Self-reported questionnaire</td>
<td>0-21</td>
</tr>
<tr>
<td>Functioning in daily life</td>
<td>WHODAS 2.0 Work subscale and Social Participation subscale [24]</td>
<td>Self-reported questionnaire</td>
<td>0-16 and 0-32</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>Maximal oxygen uptake during walking/running to exhaustion using a modified Balke protocol [25]</td>
<td>Independent assessor</td>
<td>13-59 (mL/kg/min)</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>1 repetition maximum of upper extremities (chest press) and lower extremities (seated leg press average of both legs)</td>
<td>Intervention coaches</td>
<td>10-70 kg and 10-150 kg</td>
</tr>
<tr>
<td>Sleep</td>
<td>SenseWear armband mini worn for 7 days with mean hours sleep per 24 hrs measured according to SenseWear algorithms</td>
<td>Objective measurement</td>
<td>0-13 hrs</td>
</tr>
<tr>
<td>Sedentary time</td>
<td>SenseWear armband mini worn for 7 days with mean sedentary time per 24 hrs considered to be time spent at 0-1.5 METs according to SenseWear algorithms</td>
<td>Objective measurement</td>
<td>0-24 hrs</td>
</tr>
<tr>
<td>Moderate-to-vigorous intensity physical activity</td>
<td>SenseWear armband mini worn for 7 days with mean time in moderate-to-vigorous intensity activity per 24 hrs considered to be that of at least 3 METs according to SenseWear algorithms</td>
<td>Objective measurement</td>
<td>0-6 hrs</td>
</tr>
<tr>
<td>Chemotherapy completion rates</td>
<td>Relative dose intensity, calculated as (planned or projected dose (mg/BSA)*weeks)/(received dose (mg/BSA)*weeks) extracted from medical records [26]</td>
<td>Research staff</td>
<td>0-100</td>
</tr>
</tbody>
</table>

MFI: Multidimensional Fatigue Inventory; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; HADS: Hospital Anxiety and Depression scale; WHODAS: World Health Organization Disability Assessment Schedule; MET: metabolic equivalent of task; BSA: body surface area.
Table 3. Sociodemographic, disease and planned treatment data at baseline by intervention group for randomised patients.

<table>
<thead>
<tr>
<th></th>
<th>HI with BCS (n=144)</th>
<th>HI without BCS (n=144)</th>
<th>LMI with BCS (n=145)</th>
<th>LMI without BCS (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>59.3 (13.0)</td>
<td>58.1 (11.4)</td>
<td>58.0 (11.6)</td>
<td>59.6 (11.8)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>115 (79.9)</td>
<td>116 (80.6)</td>
<td>118 (81.4)</td>
<td>116 (80.6)</td>
</tr>
<tr>
<td><strong>Living situation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with partner</td>
<td>112 (80.0)</td>
<td>114 (83.2)</td>
<td>117 (84.2)</td>
<td>109 (79.6)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>79 (56.0)</td>
<td>84 (60.9)</td>
<td>92 (65.7)</td>
<td>81 (58.3)</td>
</tr>
<tr>
<td><strong>Smoking or using snuff</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>72 (57.6)</td>
<td>70 (54.3)</td>
<td>76 (59.8)</td>
<td>70 (53.4)</td>
</tr>
<tr>
<td>Previous/less than daily</td>
<td>44 (35.2)</td>
<td>53 (41.1)</td>
<td>47 (37.0)</td>
<td>47 (35.9)</td>
</tr>
<tr>
<td>Daily</td>
<td>9 (7.2)</td>
<td>6 (4.7)</td>
<td>4 (3.1)</td>
<td>14 (10.7)</td>
</tr>
<tr>
<td><strong>Weight status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, BMI 18-24.9 kg/m²</td>
<td>60 (45.5)</td>
<td>72 (52.2)</td>
<td>66 (49.3)</td>
<td>69 (50.0)</td>
</tr>
<tr>
<td>Pre-obese, BMI 25-29.9 kg/m²</td>
<td>44 (33.3)</td>
<td>46 (33.3)</td>
<td>54 (40.3)</td>
<td>44 (31.9)</td>
</tr>
<tr>
<td>Obese, BMI&gt;29.9 kg/m²</td>
<td>28 (21.2)</td>
<td>20 (14.5)</td>
<td>14 (10.4)</td>
<td>25 (18.1)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (57.7)</td>
<td>78 (58.6)</td>
<td>77 (55.4)</td>
<td>93 (66.4)</td>
</tr>
<tr>
<td><strong>Current exercise habits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance training since &gt;6 months</td>
<td>41 (35)</td>
<td>49 (40)</td>
<td>51 (42)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>Resistance training since &gt;6 months</td>
<td>27 (23)</td>
<td>25 (21)</td>
<td>22 (19)</td>
<td>14 (12)</td>
</tr>
<tr>
<td><strong>Self-reported importance of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI endurance training</td>
<td>56 (32)</td>
<td>58 (34)</td>
<td>60 (31)</td>
<td>54 (34)</td>
</tr>
<tr>
<td>LMI endurance training</td>
<td>77 (28)</td>
<td>76 (27)</td>
<td>79 (26)</td>
<td>79 (22)</td>
</tr>
<tr>
<td>Resistance training</td>
<td>68 (29)</td>
<td>71 (30)</td>
<td>72 (29)</td>
<td>70 (29)</td>
</tr>
<tr>
<td><strong>Breast cancer†</strong></td>
<td>113</td>
<td>115</td>
<td>116</td>
<td>113</td>
</tr>
<tr>
<td>T in situ-T1</td>
<td>69 (69.7)</td>
<td>63 (63.6)</td>
<td>56 (55.4)</td>
<td>69 (69.7)</td>
</tr>
<tr>
<td>T2-T3</td>
<td>30 (30.3)</td>
<td>35 (35.4)</td>
<td>45 (44.6)</td>
<td>30 (30.3)</td>
</tr>
<tr>
<td>N1</td>
<td>15 (15.2)</td>
<td>16 (16.2)</td>
<td>15 (14.9)</td>
<td>17 (17.2)</td>
</tr>
<tr>
<td>Chemotherapy††</td>
<td>70 (67.3)</td>
<td>66 (61.1)</td>
<td>69 (64.5)</td>
<td>71 (67.0)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>60 (85.7)</td>
<td>52 (78.8)</td>
<td>58 (84.1)</td>
<td>61 (85.9)</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>10 (14.3)</td>
<td>14 (21.2)</td>
<td>11 (15.9)</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>Antibody treatment</td>
<td>20 (28.6)</td>
<td>19 (28.8)</td>
<td>17 (24.6)</td>
<td>23 (32.4)</td>
</tr>
<tr>
<td>Radiotherapy†††</td>
<td>84 (80.8)</td>
<td>88 (81.5)</td>
<td>85 (79.4)</td>
<td>92 (86.8)</td>
</tr>
<tr>
<td>Endocrine treatment</td>
<td>72 (69.2)</td>
<td>75 (69.4)</td>
<td>84 (78.5)</td>
<td>79 (74.5)</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td>26</td>
<td>23</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>T1-T2</td>
<td>20 (76.9)</td>
<td>19 (82.6)</td>
<td>17 (73.9)</td>
<td>18 (72.0)</td>
</tr>
<tr>
<td>T3-T4</td>
<td>2 (7.7)</td>
<td>3 (13.0)</td>
<td>1 (4.3)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>N1</td>
<td>1 (3.8)</td>
<td>0</td>
<td>3 (13.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Radiotherapy‡</td>
<td>25 (100.0)</td>
<td>20 (100.0)</td>
<td>22 (100.0)</td>
<td>25 (100.0)</td>
</tr>
<tr>
<td>Endocrine treatment</td>
<td>13 (50)</td>
<td>13 (56.5)</td>
<td>10 (43.5)</td>
<td>15 (60)</td>
</tr>
<tr>
<td><strong>Colorectal cancer†††</strong></td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>T2-T4</td>
<td>5 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>5 (100.0)</td>
</tr>
<tr>
<td>N1-N2</td>
<td>5 (100.0)</td>
<td>4 (66.7)</td>
<td>4 (66.7)</td>
<td>5 (100.0)</td>
</tr>
<tr>
<td>Chemotherapy†††</td>
<td>5 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>5 (100.0)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). N vary due to missing data, % is of those with data available.
HI: High intensity exercise; LMI: Low-to-moderate intensity exercise; BCS: Additional behaviour change support; BMI: body mass index.

*Exercise Stage Assessment Instrument categories 1-5 with 1=Pre-contemplation stage and 5=Maintenance stage, physically active longer than 6 months.**Visual analogue scale 0-100 mm anchored at 'Not at all important' and 'Very important'. T: tumour size. N: lymph node status. †One patient in HI without BCS had stage T4d treated with curative intent. Two patients in LMI without BCS had N2 and one in LMI with BCS had N3. ††Chemotherapy was Epirubicine-based and/or Taxane-based. †††Breast and/or axilla. †Brachy and/or external. ††††One patient in HI with BCS had radically removed liver metastasis. One patient in HI with BCS and two in HI without BCS had pre-operative radiotherapy. †††††Capecitabine-Oxaliplatin or Capecitabine only.
### Table 4. Main effects of exercise intensity, additional behaviour change support and interaction post-intervention after multiple imputation by chained equations to account for missing data, presented as adjusted mean difference and 95% confidence intervals (n=577).

<table>
<thead>
<tr>
<th></th>
<th>Exercise intensity AMD (95%CI)</th>
<th>p-value</th>
<th>BCS</th>
<th>p-value</th>
<th>Interaction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome CRF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFI General Fatigue</td>
<td>-0.36 (-1.04 to 0.33)</td>
<td>0.307</td>
<td>-0.20 (-0.91 to 0.51)</td>
<td>0.579</td>
<td>0.19 (-0.53 to 0.91)</td>
<td>0.608</td>
</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td><strong>-1.05 (-1.85 to -0.25)</strong></td>
<td><strong>0.011</strong></td>
<td>-0.43 (-1.21 to 0.34)</td>
<td>0.272</td>
<td>0.26 (-0.55 to 1.08)</td>
<td>0.524</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>0.22 (-0.49 to 0.92)</td>
<td>0.548</td>
<td>-0.35 (-1.04 to 0.35)</td>
<td>0.324</td>
<td>-0.05 (-0.76 to 0.67)</td>
<td>0.899</td>
</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>0.05 (-0.53 to 0.64)</td>
<td>0.853</td>
<td>-0.27 (-0.83 to 0.30)</td>
<td>0.357</td>
<td>0.31 (-0.25 to 0.87)</td>
<td>0.276</td>
</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>-0.26 (-0.94 to 0.42)</td>
<td>0.459</td>
<td>-0.20 (-0.88 to 0.48)</td>
<td>0.566</td>
<td>0.36 (-0.32 to 1.04)</td>
<td>0.304</td>
</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>-0.43 (-1.87 to 1.01)</td>
<td>0.555</td>
<td>-0.11 (-1.59 to 1.36)</td>
<td>0.881</td>
<td>-0.63 (-2.09 to 0.84)</td>
<td>0.401</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30 Summary Score</td>
<td>-0.64 (-2.42 to 1.15)</td>
<td>0.482</td>
<td>-0.77 (-2.51 to 0.97)</td>
<td>0.386</td>
<td><strong>-2.83 (-4.61 to -1.05)</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>HADS Depression</td>
<td>0.03 (-0.45 to 0.50)</td>
<td>0.916</td>
<td>-0.24 (-0.74 to 0.27)</td>
<td>0.355</td>
<td>0.17 (-0.32 to 0.66)</td>
<td>0.495</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>0.16 (-0.39 to 0.71)</td>
<td>0.569</td>
<td>0.23 (-0.35 to 0.81)</td>
<td>0.431</td>
<td>0.51 (-0.06 to 1.08)</td>
<td>0.079</td>
</tr>
<tr>
<td>WHODAS Work subscale*</td>
<td>0.31 (-1.01 to 1.63)</td>
<td>0.640</td>
<td>0.42 (-0.86 to 1.71)</td>
<td>0.517</td>
<td>0.73 (-0.59 to 2.06)</td>
<td>0.277</td>
</tr>
<tr>
<td>WHODAS Social Participation subscale</td>
<td>0.12 (-0.68 to 0.91)</td>
<td>0.774</td>
<td>0.36 (-0.45 to 1.18)</td>
<td>0.382</td>
<td>0.51 (-0.28 to 1.30)</td>
<td>0.206</td>
</tr>
<tr>
<td>Average 1RM left &amp; right leg, kg**</td>
<td><strong>3.98 (0.58 to 7.38)</strong></td>
<td><strong>0.022</strong></td>
<td>2.85 (-0.59 to 6.29)</td>
<td>0.104</td>
<td>-0.66 (-3.86 to 2.55)</td>
<td>0.687</td>
</tr>
<tr>
<td>1RM chest press, kg**</td>
<td>0.41 (-1.62 to 2.44)</td>
<td>0.689</td>
<td>1.47 (-0.52 to 3.47)</td>
<td>0.148</td>
<td>-1.40 (-3.41 to 0.61)</td>
<td>0.171</td>
</tr>
<tr>
<td>VO2max, ml/kg/min**</td>
<td><strong>1.61 (0.19 to 3.04)</strong></td>
<td><strong>0.027</strong></td>
<td>0.76 (-0.68 to 2.20)</td>
<td>0.300</td>
<td>-1.25 (-2.67 to 0.16)</td>
<td>0.082</td>
</tr>
<tr>
<td>Sleep, hrs/day**</td>
<td>0.10 (-0.15 to 0.34)</td>
<td>0.444</td>
<td>-0.03 (-0.27 to 0.22)</td>
<td>0.837</td>
<td>-0.10 (-0.33 to 0.14)</td>
<td>0.422</td>
</tr>
<tr>
<td>Sedentary time, hrs/day**</td>
<td>-0.26 (-0.68 to 0.16)</td>
<td>0.219</td>
<td>-0.13 (-0.54 to 0.28)</td>
<td>0.535</td>
<td>0.26 (-0.14 to 0.66)</td>
<td>0.204</td>
</tr>
<tr>
<td>MVPa, hrs/day**</td>
<td>0.06 (-0.14 to 0.26)</td>
<td>0.546</td>
<td>0.07 (-0.13 to 0.26)</td>
<td>0.502</td>
<td><strong>-0.26 (-0.45 to -0.07)</strong></td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Relative Dose Intensity, %***</td>
<td>-1.54 (-4.46 to 1.39)</td>
<td>0.302</td>
<td>-0.99 (-3.94 to 1.96)</td>
<td>0.509</td>
<td>-1.99 (-4.93 to 0.95)</td>
<td>0.184</td>
</tr>
</tbody>
</table>

* For patients who reported working. **Baseline values not included in analysis due to missing data >10%. ***For patients treated with chemotherapy. Linear regression analyses adjusted for hospital, cancer site, and baseline measure of outcome. Bold indicates p-value<0.05. AMD: Adjusted mean difference; 95%CI: 95% confidence intervals; BCS: Additional behaviour change support; CRF: Cancer-related fatigue; MFI: Multidimensional Fatigue Inventory; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30.
HADS: Hospital Anxiety and Depression scale; WHODAS: World Health Organization Disability Assessment Schedule; 1RM: 1 repetition maximum; VO$_{2\text{max}}$: maximal volume of oxygen uptake; MVPA: moderate-to-vigorous intensity physical activity.
### Supplementary Table 1. Surgical treatment by cancer diagnosis. % is of all randomised patients with available data.

<table>
<thead>
<tr>
<th></th>
<th>HI with BCS</th>
<th>HI without BCS</th>
<th>LMI with BCS</th>
<th>LMI without BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast conserving surgery</td>
<td>98 (100.0)</td>
<td>102 (100.0)</td>
<td>99 (100.0)</td>
<td>99 (100.0)</td>
</tr>
<tr>
<td>Axillary surgery</td>
<td>94 (95.9)</td>
<td>100 (98.0)</td>
<td>96 (97.0)</td>
<td>95 (96.0)</td>
</tr>
<tr>
<td>Axillary node dissection only</td>
<td>11 (11.7)</td>
<td>13 (13.0)</td>
<td>10 (10.4)</td>
<td>14 (14.7)</td>
</tr>
<tr>
<td>Sentinel node only</td>
<td>69 (73.4)</td>
<td>75 (75.0)</td>
<td>69 (71.1)</td>
<td>67 (69.1)</td>
</tr>
<tr>
<td>Both</td>
<td>14 (14.9)</td>
<td>12 (12.0)</td>
<td>17 (17.7)</td>
<td>14 (14.7)</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemicolecotomy</td>
<td>4 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>5 (100.0)</td>
</tr>
<tr>
<td>Left hemicolecotomy</td>
<td>0</td>
<td>3 (50.0)</td>
<td>4 (66.7)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>1 (20.0)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rectal excision</td>
<td>0</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Frontal resection of rectum</td>
<td>2 (40.0)</td>
<td>0</td>
<td>1 (16.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

HI: High intensity exercise; LMI: Low-to-moderate intensity exercise; BCS: Additional behaviour change support
**Supplementary Table 2.** Main effects of exercise intensity, additional BCS and interaction on each subscale of the EORTC QLQ-C30 at 6-month follow-up after multiple imputation by chained equations to account for missing data*, presented as adjusted mean difference and 95% confidence intervals (n=577).

<table>
<thead>
<tr>
<th></th>
<th>Exercise intensity AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>0.10 (-1.95 to 2.15)</td>
<td>0.924</td>
<td>0.82 (-1.29 to 2.93)</td>
<td>0.445</td>
<td>-1.81 (-3.90 to 0.28)</td>
<td>0.090</td>
</tr>
<tr>
<td>Role functioning</td>
<td>-2.79 (-6.77 to 1.18)</td>
<td>0.168</td>
<td>-1.86 (-5.96 to 2.24)</td>
<td>0.372</td>
<td>-2.85 (-6.91 to 1.21)</td>
<td>0.168</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>-1.47 (-4.61 to 1.68)</td>
<td>0.360</td>
<td>-2.28 (-5.49 to 0.93)</td>
<td>0.164</td>
<td>-2.91 (-6.06 to 0.24)</td>
<td>0.070</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>0.53 (-2.68 to 3.73)</td>
<td>0.747</td>
<td>-1.35 (-4.62 to 1.91)</td>
<td>0.416</td>
<td>-4.80 (-8.00 to -1.60)</td>
<td>0.003</td>
</tr>
<tr>
<td>Social functioning</td>
<td>-1.88 (-5.43 to 1.67)</td>
<td>0.299</td>
<td>0.77 (-2.83 to 4.37)</td>
<td>0.675</td>
<td>-2.38 (-5.90 to 1.14)</td>
<td>0.185</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.19 (-3.72 to 3.34)</td>
<td>0.915</td>
<td>1.35 (-2.03 to 4.73)</td>
<td>0.434</td>
<td>2.93 (-0.44 to 6.30)</td>
<td>0.089</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.44 (-1.15 to 2.03)</td>
<td>0.587</td>
<td>0.56 (-1.08 to 2.20)</td>
<td>0.502</td>
<td>1.84 (0.22 to 3.47)</td>
<td>0.026</td>
</tr>
<tr>
<td>Pain</td>
<td><strong>4.44 (0.47 to 8.41)</strong></td>
<td><strong>0.029</strong></td>
<td>2.01 (-1.94 to 5.96)</td>
<td>0.317</td>
<td>3.02 (-0.97 to 7.02)</td>
<td>0.138</td>
</tr>
<tr>
<td>Dyspnœa</td>
<td>-2.29 (-5.79 to 1.21)</td>
<td>0.198</td>
<td>0.14 (-3.42 to 3.71)</td>
<td>0.936</td>
<td>1.27 (-2.27 to 4.82)</td>
<td>0.480</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.48 (-3.60 to 6.56)</td>
<td>0.567</td>
<td>0.42 (-4.65 to 5.49)</td>
<td>0.871</td>
<td>9.22 (3.95 to 14.49)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Appetite loss</td>
<td>0.41 (-1.96 to 2.77)</td>
<td>0.735</td>
<td>-0.76 (-3.25 to 1.72)</td>
<td>0.546</td>
<td>0.46 (-1.92 to 2.83)</td>
<td>0.707</td>
</tr>
<tr>
<td>Constipation</td>
<td>-2.27 (-5.46 to 0.93)</td>
<td>0.164</td>
<td>-1.19 (-4.33 to 1.96)</td>
<td>0.458</td>
<td>0.54 (-2.64 to 3.71)</td>
<td>0.739</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-2.15 (-5.57 to 1.27)</td>
<td>0.218</td>
<td>0.55 (-2.95 to 4.05)</td>
<td>0.759</td>
<td>1.57 (-1.84 to 4.98)</td>
<td>0.366</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>0.65 (-2.61 to 3.91)</td>
<td>0.694</td>
<td>-1.34 (-4.66 to 1.98)</td>
<td>0.428</td>
<td>-0.14 (-3.41 to 3.14)</td>
<td>0.935</td>
</tr>
</tbody>
</table>

*Linear regression analyses adjusted for hospital, cancer site, and baseline measure of outcome. Bold indicates p-value<0.05. EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; AMD: Adjusted mean difference; 95%CI: 95% confidence intervals; BCS: Additional behaviour change support.
**Supplementary Table 3.** Chemotherapy completion rates for randomised patients and reason for chemotherapy dose reduction or treatment discontinuation*

<table>
<thead>
<tr>
<th>Reason for chemotherapy dose reduction/discontinuation (n [%])</th>
<th>HI with BCS</th>
<th>HI without BCS</th>
<th>LMI with BCS</th>
<th>LMI without BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Colorectal cancer</td>
<td>Breast cancer</td>
<td>Colorectal cancer</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Mean relative dose intensity (mean [SD])**</td>
<td>92.4 (13.7)</td>
<td>59.8 (39.3)</td>
<td>93.3 (12.9)</td>
<td>84.9 (12.8)</td>
</tr>
<tr>
<td>Relative dose intensity &lt;85% (n [%])***</td>
<td>13 (18.6)</td>
<td>3 (60.0)</td>
<td>8 (12.1)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Chemotherapy dose reduction/discontinuation (n [%])</td>
<td>28 (40.0)</td>
<td>4 (80.0)</td>
<td>23 (34.8)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td>Myelosuppression*****</td>
<td>14 (50.0)</td>
<td>0</td>
<td>8 (34.8)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (17.9)</td>
<td>1 (25.0)</td>
<td>3 (13.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (7.1)</td>
<td>0</td>
<td>0</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (17.9)</td>
<td>1 (4.3)</td>
<td>2 (14.3)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4 (14.3)</td>
<td>2 (50.0)</td>
<td>5 (21.7)</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>Constipation/diarrhoea</td>
<td>3 (10.7)</td>
<td>1 (25.0)</td>
<td>1 (4.3)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular signs/symptoms</td>
<td>3 (10.7)</td>
<td>0</td>
<td>0</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>4 (14.3)</td>
<td>1 (25.0)</td>
<td>2 (8.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>2 (7.1)</td>
<td>2 (8.7)</td>
<td>4 (14.3)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Other*****</td>
<td>4 (14.3)</td>
<td>2 (50.0)</td>
<td>3 (13.0)</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3.6)</td>
<td>5 (21.7)</td>
<td>3 (10.7)</td>
<td>1 (4.5)</td>
</tr>
</tbody>
</table>

*Chemotherapy completion rates are calculated for randomised patients treated with chemotherapy with available data. ** Relative dose intensity can be <100% due to delays in treatment, reduction of administered dose or discontinuation of treatment. ***Relative dose intensity <85% is considered to be of clinical relevance. ****Patients could have more than one reason for chemotherapy dose reduction. *****Including febrile neutropenia, low blood cell count. *****Including fatigue, allergic reactions such as Urticaria, and reduced general condition. HI: High intensity exercise; LMI: Low-to-moderate intensity exercise; BCS: Additional behaviour change support.
## Supplementary Table 4. Descriptive data for primary and secondary outcome measures at baseline and post-intervention (i.e. 6 month follow-up) for patients with advanced cancer

<table>
<thead>
<tr>
<th></th>
<th>HI with BCS</th>
<th>HI without BCS</th>
<th>LMI with BCS</th>
<th>LMI without BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>mean (SD)</td>
<td>n</td>
<td>mean (SD)</td>
</tr>
<tr>
<td><strong>Primary outcome CRF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFI General Fatigue</td>
<td>134 (4.3)</td>
<td>107 (4.5)</td>
<td>135 (4.6)</td>
<td>105 (4.0)</td>
</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td>136 (4.2)</td>
<td>112 (4.4)</td>
<td>134 (4.5)</td>
<td>107 (3.9)</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>134 (3.9)</td>
<td>110 (4.4)</td>
<td>134 (4.2)</td>
<td>106 (3.9)</td>
</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>139 (3.5)</td>
<td>110 (3.4)</td>
<td>134 (3.4)</td>
<td>106 (3.2)</td>
</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>138 (4.1)</td>
<td>111 (4.2)</td>
<td>136 (4.0)</td>
<td>105 (3.8)</td>
</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>140 (8.6)</td>
<td>112 (8.6)</td>
<td>137 (8.6)</td>
<td>108 (8.0)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30 Summary Score</td>
<td>135 (11.7)</td>
<td>111 (13.8)</td>
<td>136 (12.5)</td>
<td>106 (9.6)</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>140 (3.2)</td>
<td>112 (3.2)</td>
<td>137 (3.2)</td>
<td>108 (3.2)</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>140 (4.3)</td>
<td>112 (4.1)</td>
<td>137 (4.5)</td>
<td>108 (3.8)</td>
</tr>
<tr>
<td>WHODAS Work subscale</td>
<td>84 (5.1)</td>
<td>44 (4.7)</td>
<td>82 (5.8)</td>
<td>50 (3.4)</td>
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<tr>
<td>WHODAS Social Participation subscale</td>
<td>136 (5.6)</td>
<td>109 (6.6)</td>
<td>134 (5.5)</td>
<td>106 (4.9)</td>
</tr>
<tr>
<td>Average 1RM left and right leg, kg</td>
<td>118 (20.1)</td>
<td>93 (21.5)</td>
<td>119 (21.1)</td>
<td>97 (21.3)</td>
</tr>
<tr>
<td>1RM chest press, kg</td>
<td>119 (12.2)</td>
<td>94 (12.7)</td>
<td>118 (11.6)</td>
<td>101 (12.9)</td>
</tr>
<tr>
<td>VO2max, ml/kg/min</td>
<td>107 (7.2)</td>
<td>92 (7.3)</td>
<td>121 (7.0)</td>
<td>97 (6.6)</td>
</tr>
<tr>
<td>Sleep, hrs/day</td>
<td>118 (1.0)</td>
<td>105 (0.9)</td>
<td>116 (0.9)</td>
<td>95 (1.1)</td>
</tr>
<tr>
<td>Sedentary time, hrs/day</td>
<td>118 (2.2)</td>
<td>105 (2.2)</td>
<td>116 (1.9)</td>
<td>95 (1.9)</td>
</tr>
<tr>
<td>MVPA, hrs/day</td>
<td>118 (0.8)</td>
<td>105 (1.2)</td>
<td>116 (1.0)</td>
<td>95 (1.5)</td>
</tr>
<tr>
<td>Relative Dose Intensity %*</td>
<td>75 (18.0)</td>
<td>92.6 (13.0)</td>
<td>75 (11.0)</td>
<td>93.6 (12.2)</td>
</tr>
</tbody>
</table>

*Relative dose intensity calculated only for patients treated with chemotherapy. HI: High intensity exercise; LMI: Low-to-moderate intensity exercise; BCS: Additional behaviour change support; SD: standard deviation; CRF: Cancer-related fatigue; MFI: Multidimensional Fatigue Inventory; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; HADS: Hospital Anxiety and Depression scale; WHODAS: World Health Organization Disability Assessment Schedule; 1RM: 1 repetition maximum; VO2max: maximal volume of oxygen uptake; MVPA: moderate-to-vigorous intensity physical activity.
Supplementary Table 5. Main effects of exercise intensity, additional BCS and interaction post-intervention for complete cases of each outcome, presented as adjusted mean difference and 95% confidence intervals*

<table>
<thead>
<tr>
<th>Primary outcome CRF</th>
<th>n</th>
<th>Exercise intensity</th>
<th>AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFI General Fatigue</td>
<td>425</td>
<td>-0.26 (-0.96 to 0.44)</td>
<td>0.459</td>
<td>-0.19 (-0.89 to 0.51)</td>
<td>0.596</td>
<td>0.30 (-0.40 to 1.00)</td>
<td>0.394</td>
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</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td>427</td>
<td>-1.22 (-1.94 to -0.50)</td>
<td><strong>0.001</strong></td>
<td>-0.18 (-0.90 to 0.55)</td>
<td>0.634</td>
<td>0.47 (-0.26 to 1.19)</td>
<td>0.206</td>
<td></td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>424</td>
<td>0.22 (-0.46 to 0.90)</td>
<td>0.525</td>
<td>-0.22 (-0.90 to 0.46)</td>
<td>0.522</td>
<td>0.20 (-0.48 to 0.88)</td>
<td>0.565</td>
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</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>429</td>
<td>0.01 (-0.54 to 0.56)</td>
<td>0.974</td>
<td>-0.17 (-0.72 to 0.38)</td>
<td>0.542</td>
<td>0.33 (-0.22 to 0.88)</td>
<td>0.235</td>
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</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>424</td>
<td>-0.22 (-0.85 to 0.42)</td>
<td>0.501</td>
<td>-0.34 (-0.97 to 0.29)</td>
<td>0.294</td>
<td>0.31 (-0.32 to 0.95)</td>
<td>0.331</td>
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</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>442</td>
<td>-0.55 (-1.95 to 0.84)</td>
<td>0.437</td>
<td>-0.15 (-1.54 to 1.24)</td>
<td>0.828</td>
<td>-0.54 (-1.94 to 0.85)</td>
<td>0.443</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>n</th>
<th>Exercise intensity</th>
<th>AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30 Summary Score</td>
<td>417</td>
<td>-0.29 (-2.00 to 1.42)</td>
<td>0.739</td>
<td>-0.26 (-1.97 to 1.45)</td>
<td>0.767</td>
<td>**-2.79 (-4.50 to -1.07)</td>
<td><strong>0.002</strong></td>
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</tr>
<tr>
<td>HADS Depression</td>
<td>443</td>
<td>0.15 (-0.31 to 0.60)</td>
<td>0.528</td>
<td>-0.27 (-0.73 to 0.18)</td>
<td>0.233</td>
<td>0.13 (-0.32 to 0.59)</td>
<td>0.568</td>
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</tr>
<tr>
<td>HADS Anxiety</td>
<td>443</td>
<td>0.12 (-0.40 to 0.64)</td>
<td>0.645</td>
<td>0.16 (-0.36 to 0.67)</td>
<td>0.552</td>
<td>0.25 (-0.27 to 0.77)</td>
<td>0.339</td>
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</tr>
<tr>
<td>WHODAS Work subscale</td>
<td>172</td>
<td>0.30 (-0.81 to 1.40)</td>
<td>0.593</td>
<td>0.52 (-0.59 to 1.62)</td>
<td>0.356</td>
<td>0.32 (-0.80 to 1.44)</td>
<td>0.571</td>
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</tr>
<tr>
<td>WHODAS Social Participation subscale</td>
<td>420</td>
<td>0.22 (-0.55 to 0.99)</td>
<td>0.573</td>
<td>0.25 (-0.52 to 1.02)</td>
<td>0.524</td>
<td>0.51 (-0.26 to 1.28)</td>
<td>0.197</td>
<td></td>
</tr>
<tr>
<td>Average 1RM left and right leg (kg)</td>
<td>394</td>
<td><strong>3.89 (2.14 to 5.63)</strong></td>
<td>&lt;<strong>0.001</strong></td>
<td>-0.26 (-2.01 to 1.50)</td>
<td>0.772</td>
<td>-0.23 (-1.98 to 1.51)</td>
<td>0.792</td>
<td></td>
</tr>
<tr>
<td>1RM chest press (kg)</td>
<td>394</td>
<td><strong>0.98 (0.13 to 1.82)</strong></td>
<td><strong>0.024</strong></td>
<td>-0.16 (-1.01 to 0.69)</td>
<td>0.715</td>
<td>0.42 (-0.43 to 1.27)</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>VO_{max} (ml/kg/min)</td>
<td>331</td>
<td>0.41 (-0.35 to 1.17)</td>
<td>0.286</td>
<td>0.60 (-0.16 to 1.35)</td>
<td>0.121</td>
<td>-0.26 (-1.01 to 0.50)</td>
<td>0.502</td>
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<tr>
<td>Sleep (hrs/day)</td>
<td>356</td>
<td>0.07 (-0.10 to 0.23)</td>
<td>0.449</td>
<td>-0.13 (-0.30 to 0.04)</td>
<td>0.131</td>
<td>-0.01 (-0.18 to 0.16)</td>
<td>0.945</td>
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<tr>
<td>Sedentary time, hrs/day</td>
<td>356</td>
<td>0.00 (-0.28 to 0.28)</td>
<td>0.991</td>
<td>-0.02 (-0.30 to 0.26)</td>
<td>0.877</td>
<td>-0.03 (-0.31 to 0.25)</td>
<td>0.829</td>
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</tr>
<tr>
<td>MVPA, hrs/day</td>
<td>356</td>
<td>-0.05 (-0.19 to 0.08)</td>
<td>0.449</td>
<td>0.05 (-0.08 to 0.19)</td>
<td>0.451</td>
<td>-0.08 (-0.22 to 0.06)</td>
<td>0.250</td>
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</tr>
<tr>
<td>Relative Dose Intensity, %**</td>
<td>298</td>
<td>-1.82 (-4.70 to 1.06)</td>
<td>0.214</td>
<td>-0.90 (-3.78 to 1.98)</td>
<td>0.538</td>
<td>-1.94 (-4.82 to 0.94)</td>
<td>0.186</td>
<td></td>
</tr>
</tbody>
</table>

*Linear regression analyses adjusted for hospital, cancer site, and baseline measure of outcome. **For patients treated with chemotherapy. Bold indicates p-value<0.05. Relative dose intensity calculated at end of treatment, this analysis was therefore not adjusted for baseline measure. AMD: Adjusted mean difference; 95%CI: 95% confidence intervals; BCS: Additional behaviour change support; CRF: Cancer-related fatigue; MFI: Multidimensional Fatigue Inventory; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; HADS: Hospital Anxiety and Depression scale; WHODAS: World Health Organization Disability Assessment Schedule; 1RM: 1 repetition maximum; VO_{max}: maximal volume of oxygen uptake; MVPA: moderate-to-vigorous intensity physical activity
### Supplementary Table 6. Descriptive data for primary and secondary outcome measures at baseline and post-intervention for patients with data available

<table>
<thead>
<tr>
<th></th>
<th>HI with BCS</th>
<th>HI without BCS</th>
<th>LMI with BCS</th>
<th>LMI without BCS</th>
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<tr>
<td><strong>Breast cancer</strong></td>
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<tr>
<td><strong>Primary outcome CRF</strong></td>
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</tr>
<tr>
<td>MFI General Fatigue</td>
<td>106 (4.3)</td>
<td>108 (4.6)</td>
<td>112 (4.6)</td>
<td>109 (4.3)</td>
</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td>106 (4.2)</td>
<td>106 (4.5)</td>
<td>112 (4.3)</td>
<td>109 (4.0)</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>104 (3.8)</td>
<td>106 (4.3)</td>
<td>115 (4.1)</td>
<td>108 (4.0)</td>
</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>109 (3.5)</td>
<td>106 (3.5)</td>
<td>113 (3.7)</td>
<td>108 (3.4)</td>
</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>108 (4.2)</td>
<td>108 (4.7)</td>
<td>110 (4.1)</td>
<td>106 (4.0)</td>
</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>109 (8.7)</td>
<td>109 (8.8)</td>
<td>112 (9.5)</td>
<td>111 (10.1)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
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<tr>
<td>EORTC Summary Score</td>
<td>104 (11.9)</td>
<td>108 (12.5)</td>
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<tr>
<td>HADS Depression</td>
<td>109 (3.2)</td>
<td>109 (3.3)</td>
<td>115 (3.3)</td>
<td>112 (3.3)</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>109 (4.2)</td>
<td>109 (4.4)</td>
<td>115 (6.2)</td>
<td>112 (4.5)</td>
</tr>
<tr>
<td>WHODAS Work subscale</td>
<td>72 (4.9)</td>
<td>70 (5.0)</td>
<td>69 (5.3)</td>
<td>67 (5.3)</td>
</tr>
<tr>
<td>WHODAS Social Participation subscale</td>
<td>106 (5.4)</td>
<td>108 (5.3)</td>
<td>113 (5.8)</td>
<td>109 (5.0)</td>
</tr>
<tr>
<td>Average 1RM left and right leg (kg)</td>
<td>90 (17.3)</td>
<td>74 (19.9)</td>
<td>96 (18.4)</td>
<td>91 (17.6)</td>
</tr>
<tr>
<td>1RM chest press (kg)</td>
<td>90 (7.8)</td>
<td>91 (8.0)</td>
<td>93 (9.2)</td>
<td>89 (8.7)</td>
</tr>
<tr>
<td>VO2max (ml/kg/min)</td>
<td>83 (7.5)</td>
<td>98 (7.5)</td>
<td>76 (7.4)</td>
<td>98 (6.7)</td>
</tr>
<tr>
<td>Sleep (hrs/day)</td>
<td>91 (1.0)</td>
<td>91 (0.9)</td>
<td>95 (1.1)</td>
<td>101 (1.1)</td>
</tr>
<tr>
<td>Sedentary time, hrs/day</td>
<td>91 (2.3)</td>
<td>91 (1.8)</td>
<td>95 (1.8)</td>
<td>101 (1.7)</td>
</tr>
<tr>
<td>MVPA, hrs/day</td>
<td>91 (0.7)</td>
<td>91 (0.9)</td>
<td>95 (0.8)</td>
<td>101 (0.7)</td>
</tr>
<tr>
<td>Relative Dose Intensity, %</td>
<td>70 (13.7)</td>
<td>66 (12.9)</td>
<td>69 (7.0)</td>
<td>71 (9.8)</td>
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<td><strong>Prostate cancer</strong></td>
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<tr>
<td><strong>Primary outcome CRF</strong></td>
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<td></td>
</tr>
<tr>
<td>MFI General Fatigue</td>
<td>23 (3.9)</td>
<td>21 (4.1)</td>
<td>21 (3.9)</td>
<td>24 (4.9)</td>
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<tr>
<td>MFI Physical Fatigue</td>
<td>26 (3.6)</td>
<td>22 (4.2)</td>
<td>21 (4.3)</td>
<td>25 (4.6)</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>25 (3.6)</td>
<td>22 (3.2)</td>
<td>19 (3.2)</td>
<td>25 (4.3)</td>
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<tr>
<td>MFI Reduced Motivation</td>
<td>25 (3.0)</td>
<td>22 (2.4)</td>
<td>20 (3.2)</td>
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<tr>
<td>MFI Mental Fatigue</td>
<td>25 (3.3)</td>
<td>22 (2.6)</td>
<td>19 (3.6)</td>
<td>23 (2.6)</td>
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<tr>
<td>FACIT Fatigue subscale</td>
<td>26 (6.9)</td>
<td>22 (8.2)</td>
<td>21 (7.7)</td>
<td>25 (8.6)</td>
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<tr>
<td><strong>Secondary outcomes</strong></td>
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<tr>
<td>EORTC Summary Score</td>
<td>26 (7.3)</td>
<td>22 (10.6)</td>
<td>19 (8.9)</td>
<td>24 (13.1)</td>
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<tr>
<td>HADS Depression</td>
<td>26 (1.8)</td>
<td>22 (1.9)</td>
<td>21 (2.7)</td>
<td>25 (2.6)</td>
</tr>
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<td>HADS Anxiety</td>
<td>26 (2.8)</td>
<td>22 (2.2)</td>
<td>21 (2.7)</td>
<td>25 (3.0)</td>
</tr>
<tr>
<td>WHODAS Work subscale</td>
<td>10 (3.8)</td>
<td>10 (2.5)</td>
<td>11 (1.7)</td>
<td>14 (2.0)</td>
</tr>
</tbody>
</table>
### Supplementary Table 6. Cont.

*Relative dose intensity calculated at end of treatment for patients treated with chemotherapy. HI: High intensity exercise; LMI: Low-to-moderate intensity exercise; BCS: Additional behaviour change support; SD: standard deviation; CRF: Cancer-related fatigue; MFI: Multidimensional Fatigue Inventory; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; HADS: Hospital Anxiety and Depression scale; WHODAS: World Health Organization Disability Assessment Schedule; 1RM: 1 repetition maximum; VO_{2max}: maximal volume of oxygen uptake; MVPA: moderate-to-vigorous intensity physical activity.
### Supplementary Table 7. Main effects of exercise intensity, additional BCS and interaction post-intervention after multiple imputation by chained equations to account for missing data, for patients with breast cancer (n=457), prostate cancer (n=97) and colorectal cancer (n=23) separately, presented as adjusted mean difference (AMD) and 95% confidence intervals

<table>
<thead>
<tr>
<th></th>
<th>Exercise intensity AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast cancer</strong></td>
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<tr>
<td><strong>Primary outcome CRF</strong></td>
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</tr>
<tr>
<td>MFI General Fatigue</td>
<td>-0.34 (-1.14 to 0.46)</td>
<td>0.400</td>
<td>-0.31 (-1.13 to 0.51)</td>
<td>0.460</td>
<td>0.25 (-0.57 to 1.08)</td>
<td>0.544</td>
</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td>-1.08 (-1.99 to -0.17)</td>
<td><strong>0.020</strong></td>
<td>-0.57 (-1.47 to 0.32)</td>
<td>0.208</td>
<td>0.36 (-0.58 to 1.30)</td>
<td>0.448</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>0.26 (-0.56 to 1.09)</td>
<td>0.533</td>
<td>-0.41 (-1.22 to 0.39)</td>
<td>0.312</td>
<td>-0.19 (-1.03 to 0.65)</td>
<td>0.652</td>
</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>0.05 (-0.60 to 0.70)</td>
<td>0.882</td>
<td>-0.22 (-0.88 to 0.44)</td>
<td>0.508</td>
<td>0.35 (-0.29 to 0.99)</td>
<td>0.285</td>
</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>-0.29 (-1.07 to 0.49)</td>
<td>0.468</td>
<td>-0.19 (-0.99 to 0.62)</td>
<td>0.645</td>
<td>0.35 (-0.45 to 1.14)</td>
<td>0.390</td>
</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>-0.34 (-2.05 to 1.37)</td>
<td>0.697</td>
<td>-0.16 (-1.94 to 1.63)</td>
<td>0.864</td>
<td>-0.59 (-2.32 to 1.14)</td>
<td>0.503</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EORTC QLQ-C30 Summary Score</td>
<td>-1.00 (-3.10 to 1.11)</td>
<td>0.353</td>
<td>-1.34 (-3.40 to 0.71)</td>
<td>0.200</td>
<td><strong>-2.94 (-5.04 to -0.85)</strong></td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>HADS Depression</td>
<td>0.09 (-0.46 to 0.63)</td>
<td>0.760</td>
<td>-0.29 (-0.87 to 0.29)</td>
<td>0.330</td>
<td>0.14 (-0.44 to 0.71)</td>
<td>0.633</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>0.12 (-0.53 to 0.77)</td>
<td>0.723</td>
<td>0.30 (-0.38 to 0.98)</td>
<td>0.383</td>
<td>0.58 (-0.10 to 1.26)</td>
<td>0.095</td>
</tr>
<tr>
<td>WHODAS Work subscale*</td>
<td>0.23 (-1.23 to 1.69)</td>
<td>0.758</td>
<td>0.81 (-0.63 to 2.26)</td>
<td>0.266</td>
<td>1.26 (-0.19 to 2.71)</td>
<td>0.087</td>
</tr>
<tr>
<td>WHODAS Social Participation subscale</td>
<td>-0.03 (-0.96 to 0.91)</td>
<td>0.958</td>
<td>0.78 (-0.19 to 1.75)</td>
<td>0.116</td>
<td>0.78 (-0.15 to 1.72)</td>
<td>0.099</td>
</tr>
<tr>
<td>Average 1RM left and right leg, kg**</td>
<td><strong>4.70 (1.06 to 8.34)</strong></td>
<td><strong>0.012</strong></td>
<td>2.74 (-0.98 to 6.46)</td>
<td>0.148</td>
<td>0.52 (-2.93 to 3.98)</td>
<td>0.765</td>
</tr>
<tr>
<td>1RM chest press, kg**</td>
<td>1.00 (-1.13 to 3.14)</td>
<td>0.355</td>
<td>1.18 (-0.94 to 3.29)</td>
<td>0.274</td>
<td>-0.22 (-2.31 to 1.86)</td>
<td>0.834</td>
</tr>
<tr>
<td>VO_{2max}, ml/kg/min**</td>
<td><strong>1.71 (0.04 to 3.38)</strong></td>
<td><strong>0.045</strong></td>
<td>0.54 (-1.10 to 2.17)</td>
<td>0.521</td>
<td>-0.79 (-2.44 to 0.85)</td>
<td>0.342</td>
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<tr>
<td>Sleep, hrs/day**</td>
<td>0.12 (-0.16 to 0.39)</td>
<td>0.409</td>
<td>-0.08 (-0.35 to 0.19)</td>
<td>0.551</td>
<td>-0.08 (-0.34 to 0.18)</td>
<td>0.532</td>
</tr>
<tr>
<td>Sedentary time, hrs/day**</td>
<td>-0.22 (-0.69 to 0.25)</td>
<td>0.360</td>
<td>0.02 (-0.44 to 0.48)</td>
<td>0.926</td>
<td>0.14 (-0.31 to 0.59)</td>
<td>0.539</td>
</tr>
<tr>
<td>MVPA, hrs/day**</td>
<td>0.05 (-0.18 to 0.27)</td>
<td>0.672</td>
<td>0.02 (-0.20 to 0.24)</td>
<td>0.874</td>
<td>-0.16 (-0.37 to 0.05)</td>
<td>0.140</td>
</tr>
<tr>
<td>Relative Dose Intensity, %***</td>
<td>-1.93 (-4.67 to 0.80)</td>
<td>0.165</td>
<td>-0.40 (-3.16 to 2.36)</td>
<td>0.777</td>
<td>-0.93 (-3.69 to 1.82)</td>
<td>0.506</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome CRF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFI General Fatigue</td>
<td>-0.55 (-2.00 to 0.91)</td>
<td>0.456</td>
<td>0.70 (-0.83 to 2.23)</td>
<td>0.362</td>
<td>-0.15 (-1.64 to 1.34)</td>
<td>0.843</td>
</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td>-0.78 (-2.26 to 0.71)</td>
<td>0.299</td>
<td>0.52 (-0.99 to 2.03)</td>
<td>0.492</td>
<td>-0.14 (-1.65 to 1.37)</td>
<td>0.854</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>0.36 (-1.09 to 1.82)</td>
<td>0.620</td>
<td>0.35 (-1.11 to 1.82)</td>
<td>0.631</td>
<td>0.19 (-1.27 to 1.66)</td>
<td>0.795</td>
</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>-0.14 (-1.47 to 1.19)</td>
<td>0.839</td>
<td>-0.13 (-1.41 to 1.14)</td>
<td>0.837</td>
<td>-0.13 (-1.41 to 1.16)</td>
<td>0.845</td>
</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>-0.46 (-1.81 to 0.89)</td>
<td>0.500</td>
<td>-0.31 (-1.57 to 0.95)</td>
<td>0.629</td>
<td>0.41 (-0.86 to 1.68)</td>
<td>0.520</td>
</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>-0.68 (-3.33 to 1.97)</td>
<td>0.610</td>
<td>-0.17 (-2.82 to 2.49)</td>
<td>0.902</td>
<td>-0.07 (-2.80 to 2.67)</td>
<td>0.962</td>
</tr>
</tbody>
</table>
### Supplementary Table 7. Cont.

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Exercise intensity AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30 Summary Score</td>
<td>0.10 (-3.53 to 3.73)</td>
<td>0.956</td>
<td>1.44 (-2.00 to 4.89)</td>
<td>0.406</td>
<td>-1.94 (-5.32 to 1.44)</td>
<td>0.257</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>0.02 (-1.00 to 1.03)</td>
<td>0.975</td>
<td>0.16 (-0.84 to 1.16)</td>
<td>0.753</td>
<td>0.13 (-0.88 to 1.13)</td>
<td>0.804</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>0.09 (-0.78 to 0.95)</td>
<td>0.841</td>
<td>0.22 (-0.67 to 1.11)</td>
<td>0.622</td>
<td>0.03 (-0.83 to 0.90)</td>
<td>0.936</td>
</tr>
<tr>
<td>WHODAS Work subscale*</td>
<td>2.02 (-1.20 to 5.23)</td>
<td>0.200</td>
<td>-2.63 (-6.31 to 1.05)</td>
<td>0.146</td>
<td>-1.36 (-4.89 to 2.17)</td>
<td>0.418</td>
</tr>
<tr>
<td>WHODAS Social Participation subscale</td>
<td>0.69 (-0.70 to 2.09)</td>
<td>0.323</td>
<td>-0.15 (-1.56 to 1.26)</td>
<td>0.829</td>
<td>-0.54 (-1.99 to 0.92)</td>
<td>0.464</td>
</tr>
<tr>
<td>Average 1RM left and right leg, kg**</td>
<td>-0.06 (-8.96 to 8.83)</td>
<td>0.989</td>
<td>0.46 (-8.13 to 9.06)</td>
<td>0.914</td>
<td>-2.20 (-10.87 to 6.47)</td>
<td>0.614</td>
</tr>
<tr>
<td>1RM chest press, kg**</td>
<td>-3.00 (-8.29 to 2.30)</td>
<td>0.263</td>
<td>0.38 (-4.92 to 5.69)</td>
<td>0.886</td>
<td>-2.93 (-8.41 to 2.55)</td>
<td>0.291</td>
</tr>
<tr>
<td>VO2max, ml/kg/min**</td>
<td>1.01 (-1.91 to 3.94)</td>
<td>0.491</td>
<td>1.55 (-1.31 to 4.40)</td>
<td>0.283</td>
<td>-1.18 (-4.13 to 1.77)</td>
<td>0.428</td>
</tr>
<tr>
<td>Sleep, hrs/day**</td>
<td>0.01 (-0.61 to 0.63)</td>
<td>0.969</td>
<td>0.35 (-0.27 to 0.96)</td>
<td>0.267</td>
<td>-0.11 (-0.73 to 0.51)</td>
<td>0.729</td>
</tr>
<tr>
<td>Sedentary time, hrs/day**</td>
<td>-0.25 (-1.32 to 0.82)</td>
<td>0.641</td>
<td>-0.70 (-1.75 to 0.36)</td>
<td>0.194</td>
<td>0.59 (-0.48 to 1.66)</td>
<td>0.277</td>
</tr>
<tr>
<td>MVPA, hrs/day**</td>
<td>0.08 (-0.40 to 0.56)</td>
<td>0.748</td>
<td>0.26 (-0.22 to 0.74)</td>
<td>0.292</td>
<td>-0.55 (-1.03 to -0.07)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

### Colorectal cancer

#### Primary outcome CRF

<table>
<thead>
<tr>
<th>Exercise intensity AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFI General Fatigue</td>
<td>1.09 (-3.35 to 5.54)</td>
<td>0.601</td>
<td>-1.61 (-7.60 to 4.37)</td>
<td>0.564</td>
<td>0.80 (-3.76 to 5.36)</td>
</tr>
<tr>
<td>MFI Physical Fatigue</td>
<td>-1.38 (-6.50 to 3.75)</td>
<td>0.551</td>
<td>-2.48 (-8.83 to 3.86)</td>
<td>0.387</td>
<td>1.39 (-3.54 to 6.31)</td>
</tr>
<tr>
<td>MFI Reduced Activity</td>
<td>0.85 (-3.01 to 4.70)</td>
<td>0.634</td>
<td>-1.69 (-5.82 to 2.44)</td>
<td>0.385</td>
<td>2.80 (-1.11 to 6.72)</td>
</tr>
<tr>
<td>MFI Reduced Motivation</td>
<td>-0.15 (-3.31 to 3.00)</td>
<td>0.917</td>
<td>-1.15 (-4.24 to 1.95)</td>
<td>0.430</td>
<td>0.65 (-2.51 to 3.82)</td>
</tr>
<tr>
<td>MFI Mental Fatigue</td>
<td>1.16 (-2.46 to 4.79)</td>
<td>0.490</td>
<td>0.41 (-3.02 to 3.84)</td>
<td>0.797</td>
<td>0.33 (-3.45 to 4.10)</td>
</tr>
<tr>
<td>FACIT Fatigue subscale</td>
<td>-2.37 (-9.21 to 4.48)</td>
<td>0.453</td>
<td>0.59 (-6.91 to 8.10)</td>
<td>0.862</td>
<td>-3.75 (-10.98 to 3.47)</td>
</tr>
</tbody>
</table>

#### Secondary outcomes

<table>
<thead>
<tr>
<th>Exercise intensity AMD (95%CI)</th>
<th>p-value</th>
<th>BCS AMD (95%CI)</th>
<th>p-value</th>
<th>Interaction AMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30 Summary Score</td>
<td>1.30 (-9.67 to 12.26)</td>
<td>0.798</td>
<td>1.23 (-9.78 to 12.23)</td>
<td>0.809</td>
<td>-4.59 (-16.22 to 7.04)</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>-0.05 (-2.55 to 2.44)</td>
<td>0.962</td>
<td>-0.74 (-3.30 to 1.82)</td>
<td>0.524</td>
<td>0.81 (-1.63 to 3.25)</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>0.52 (-2.80 to 3.85)</td>
<td>0.724</td>
<td>-0.89 (-4.09 to 2.32)</td>
<td>0.541</td>
<td>-0.39 (-3.48 to 2.69)</td>
</tr>
<tr>
<td>WHODAS Work subscale*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHODAS Social Participation subscale</td>
<td>0.56 (-4.28 to 5.39)</td>
<td>0.804</td>
<td>-4.93 (-11.14 to 1.28)</td>
<td>0.107</td>
<td>-1.46 (-6.53 to 3.60)</td>
</tr>
<tr>
<td>Average 1RM left and right leg, kg**</td>
<td>8.34 (-14.90 to 31.59)</td>
<td>0.439</td>
<td>15.99 (-7.71 to 39.68)</td>
<td>0.161</td>
<td>-17.21 (-41.01 to 6.59)</td>
</tr>
<tr>
<td>1RM chest press, kg**</td>
<td>2.66 (-13.59 to 18.92)</td>
<td>0.727</td>
<td>12.02 (-4.26 to 28.29)</td>
<td>0.134</td>
<td>-15.78 (-32.83 to 1.27)</td>
</tr>
<tr>
<td>VO2max, ml/kg/min**</td>
<td>0.87 (-7.89 to 9.63)</td>
<td>0.824</td>
<td>1.61 (-7.59 to 10.80)</td>
<td>0.695</td>
<td>-11.05 (-20.34 to -1.76)</td>
</tr>
<tr>
<td>Sleep, hrs/day**</td>
<td>0.12 (-1.19 to 1.43)</td>
<td>0.845</td>
<td>-0.22 (-1.51 to 1.07)</td>
<td>0.711</td>
<td>-0.98 (-2.25 to 0.30)</td>
</tr>
<tr>
<td>Sedentary time, hrs/day**</td>
<td>-0.79 (-2.83 to 1.24)</td>
<td>0.399</td>
<td>-0.74 (-2.69 to 1.22)</td>
<td>0.417</td>
<td>1.34 (-0.58 to 3.26)</td>
</tr>
</tbody>
</table>
MVPA, hrs/day** 0.11 (-0.91 to 1.12) 0.817 0.29 (-0.70 to 1.28) 0.532 -1.15 (-2.14 to -0.15) 0.028
Relative dose intensity, %*** 2.56 (-21.64 to 26.76) 0.824 -8.56 (-32.78 to 15.66) 0.461 -15.05 (-41.21 to 11.12) 0.238

* Insufficient data to calculate estimates. **Baseline values not included in analysis due to missing data >10%. ***For patients treated with chemotherapy. Linear regression analyses adjusted for hospital, cancer site, and baseline measure of outcome. Bold indicates p-value<0.05. AMD: Adjusted mean difference; 95%CI: 95% confidence intervals; BCS: Additional behaviour change support; CRF: Cancer-related fatigue; MFI: Multidimensional Fatigue Inventory; FACIT: Functional Assessment of Chronic Illness Therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; HADS: Hospital Anxiety and Depression scale; WHODAS: World Health Organization Disability Assessment Schedule; 1RM: 1 repetition maximum; VO_2max: maximal volume of oxygen uptake; MVPA: moderate-to-vigorous intensity physical activity.
Assessed for eligibility (n=2600)

Ineligible (n=549)
- Did not understand Swedish (n=48)
- Could not perform basic activity (n=43)
- Comorbid condition (n=410)
- Other reason/unknown reason (n=48)

Declined participation (n=1451)
- Feeling too bad (n=69)
- Too far to travel (n=425)
- Does not want to state reason (n=106)
- Administrative error (n=109)
- Other reason/unknown reason (n=742)

Included in study (n=600, 29% of eligible participants)

Withdrew before randomisation (n=23)
- Feeling too bad (n=4)
- Too far to travel (n=1)
- Too busy/intervention does not fit with schedule (n=5)
- Other reason/unknown reason (n=13)

Randomised (n=577)

HI with BCS (n=144)
- Incomplete data (n=35)
  - Missing baseline (n=3)
  - Withdrew before follow-up (n=22)
  - Missing follow-up (n=10)
- Complete baseline and follow-up data (n=109)

HI without BCS (n=144)
- Incomplete data (n=38)
  - Missing baseline (n=1)
  - Withdrew before follow-up (n=27)
  - Missing follow-up (n=10)
- Complete baseline and follow-up data (n=106)

LMI with BCS (n=145)
- Incomplete data (n=43)
  - Missing baseline (n=4)
  - Withdrew before follow-up (n=19)
  - Missing follow-up (n=20)
- Complete baseline and follow-up data (n=102)

LMI without BCS (n=144)
- Incomplete data (n=34)
  - Missing baseline (n=1)
  - Withdrew before follow-up (n=21)
  - Missing follow-up (n=12)
- Complete baseline and follow-up data (n=110)

Figure 1. CONSORT diagram of flow of participants through the Phys-Can study. Numbers with (in)complete baseline and follow-up data are based on cancer related fatigue (MFI physical fatigue sub-scale), exact numbers for other outcomes vary (see Table 3). Follow-up refers to data collected at the end of the 6 month intervention. HI: High intensity exercise; LMI: Low-to-moderate intensity exercise, BCS; additional behaviour change support.
Figure 2. Adherence to prescribed strength and endurance training volume, by training group. Bars represent mean adherence, error bars indicate 1 standard deviation from the mean. Participants who dropped out of the study were recorded as 0 adherence to any remaining training sessions. P-values reflect pair-wise comparisons across the four intervention groups using Tukey post-hoc tests. All other pair-wise comparisons resulted in p-values >0.05. HI: high intensity exercise, LMI: low-to-moderate intensity exercise, BCS: additional behaviour change support.
Appendix
## Resistance training program

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Illustration</th>
<th>Target muscles</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Seated leg press</strong></td>
<td><img src="100x100" alt="Illustrations" /></td>
<td><img src="100x100" alt="Diagram" /></td>
<td>Place your feet on the footplate with shoulderwidth distance. Sit close to the footplate without losing contact with the backrest. Tighten your abdomen and press your lower back against the backrest. Press your feet to the footplate and stretch your knees until almost fully extended. Return to the starting position and repeat.</td>
</tr>
<tr>
<td><strong>2. Chest press</strong></td>
<td><img src="100x100" alt="Illustrations" /></td>
<td><img src="100x100" alt="Diagram" /></td>
<td>Sit with relaxed shoulders and a firm grip on the handles. Let your elbows be in level with the handles. Press the handles forward until your arms are completely straight and then retract them back towards your chest.</td>
</tr>
<tr>
<td><strong>3. Leg extension</strong></td>
<td><img src="100x100" alt="Illustrations" /></td>
<td><img src="100x100" alt="Diagram" /></td>
<td>Sit with your knees bent and with good support for your lower back. Extend your legs fully. Retract your legs controlled back to the starting position and repeat.</td>
</tr>
<tr>
<td><strong>4. Seated row</strong></td>
<td><img src="100x100" alt="Illustrations" /></td>
<td><img src="100x100" alt="Diagram" /></td>
<td>Sit with your back straight and press your chest against the pillow. Hold the handles. Keep your arms straight and release your shoulders forward. Pull the handles back as far as you can. Squeeze the shoulder blades together in the end position. Keep contact with the chest pad throughout the movement.</td>
</tr>
<tr>
<td><strong>5. Seated leg curl</strong></td>
<td><img src="100x100" alt="Illustrations" /></td>
<td><img src="100x100" alt="Diagram" /></td>
<td>Make sure you have good support for the lower back and fix the upper body with the help of the handles. Press the wrists against the cushion, bend your knees maximally and return slowly to the starting position.</td>
</tr>
<tr>
<td><strong>6. Seated overhead press</strong></td>
<td><img src="100x100" alt="Illustrations" /></td>
<td><img src="100x100" alt="Diagram" /></td>
<td>Stand or sit (on a bench or a chair). Hold the dumbbells in front of you close to your shoulders. Press the dumbbells over your head until your arms are straight. Lower your arms and go back to the starting position.</td>
</tr>
</tbody>
</table>

**Supplementary Figure 1. Illustrations of resistance exercises**

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BESLUT
2014-08-27

Dnr 2014 / 249

SÖKANDE FORSKNINGSHUVDMAN

Uppsala universitet
Box 256
751 05 UPPSALA

Övriga forskningshuvudmän:

Linköpings universitet
Lunds universitet

Forskare som genomför projektet:

Karin Nordin
Inst. för folkhälso- och vårdvetenskap
Uppsala universitet
Box 564
751 22 UPPSALA

UPPGIFTER OM FORSKNINGSPROJEKTET ENLIGT ANSÖKAN
INKOMMEN TILL NÄMNDEN 2014-05-30 SAMT INKOMMEN
KOMPLETERING 2014-08-04

Projektbeskrivning:

Phys-Can (PHYsical traning and CANcer, fysiskt träning och cancer) - effekter av fysisk träning och beteendemedicinska strategier för att förebygga och minimera cancerrelaterade fatigue, förbättra livskvaliteten och sjukdomsutfall hos cancerpatienter.

Regionala etikprövningsnämnden i Uppsala meddelar följande

BESLUT

Nämnden bifaller ansökanen och godkänner med stöd av 6 § lagen (2003:460) om etikprövning av forskning som avser människor den forskning som anges i ansökan med komplettering.
Erinran

Godkännandet upphör att gälla om forskningen inte har påbörjats inom två år efter slutgiltigt beslut.

På nämndens vägnar

Per-Erik Nistér
ordförande

Beslutande:
Per-Erik Nistér, f.d. rådman, ordförande

Ledamöter med vetenskaplig kompetens
Marieann Högman, respirationsfysiologi, Brita Karlström, geriatrik, Lars von Knorring, psykiatri, vetenskaplig sekreterare, Susan Pfeifer, pediatrik, Bengt Simonsson, hematologi, vetenskaplig sekreterare - föredragande, LarsWiklund, anestesiologi, Agneta Yngve, nutrition

Ledamöter som företrädger allmänna intressen
Bengt Jansson, Ola Ström, Christina Wahrolin, Margareta Åkerlind Skuteli

Exp. till:
Forskare: Karin Nordin
Forskningshuvudmannens företrädare: prefekt Johan Hallqvist, Inst. för folkhälsos- och vårdvetenskap, Uppsala universitet, Box 564, 751 22 Uppsala