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

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Abstract

Exercise during 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 behavior change support (BCS) on CRF in patients undergoing (neo-)adjuvant cancer treatment. This was a multicenter, 2x2 factorial design randomized controlled trial (Clinical Trials NCT02473003) in Sweden. Participants recently diagnosed with breast (n = 457), prostate (n = 97) or colorectal (n = 23) cancer undergoing (neo-)adjuvant treatment were randomized to high intensity (n = 144), low-to-moderate intensity (n = 144), high intensity with BCS (n = 144) or low-to-moderate intensity with BCS (n = 145). The 6-month exercise intervention included supervised resistance training and

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home-based endurance training. CRF was assessed by Multidimensional Fatigue Inventory (MFI, five subscales score range 4-20), and 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. Overall, 577 participants (mean age 58.7 years) were randomized. Participants randomized 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 (ie <2). We found no differences in other CRF dimensions and no effect of additional BCS. There were few minor adverse events. 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.

KEYWORDS
behavior change, cancer-related fatigue, endurance training, oncology, resistance training

1 | INTRODUCTION

Cancer survival rates have improved due to earlier detection and advances in treatment.[1] However, cancer survivors report long-term challenges, such as cancer-related fatigue (CRF), physical deconditioning, and decreased health-related quality of life (HRQoL).[2] 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.[3] Prevalence of moderate-to-severe CRF during treatment is 30%-60%,[3] and clinically important CRF has been reported in one-third of patients up to 6 years after treatment.[4] Symptom clusters of co-occurring CRF, pain and psychological distress may be persistent[5] and are associated with lower HRQoL.[6] The etiology of CRF is multifactorial, and treatment-induced activation of pro-inflammatory cytokines may be one trigger.[3]

Exercise during and after treatment is effective in counteracting CRF,[7] possibly by lowering the inflammatory activity and/or by increasing physical fitness.[8] Exercise also improves HRQoL,[9] may increase chemotherapy completion rates,[10,11] and reduce the risk of cancer mortality.[12] International guidelines[13] recommend 3 sessions of at least moderate-intensity endurance training and/or 2 sessions of at least moderate-intensity 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.[13] While low-to-moderate intensity may be preferred by most patients,[14] one study found that moderate-to-high-intensity exercise during cancer treatment was beneficial for physical fatigue compared to low-intensity exercise.[10] 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.[13]

Many patients find it difficult to perform physical activity during oncological treatment, and they are on average less physically active than the general population.[15] In exercise interventions, adherence rates have been reported between 23%[16] and 84%, [17] depending on the characteristics of the sample, the intervention and the method used to calculate adherence. Interview studies indicate a need for individualized support to overcome barriers such as side effects and external demands.[18] Behavior change support (BCS) can be used to overcome such barriers. Systematic reviews and meta-analysis have identified behavior change strategies associated with high adherence and larger effect sizes in interventions designed to increase physical activity among cancer survivors. Examples of such techniques are self-monitoring,[19] goal-setting,[20] graded tasks,[20,21] social support[22] and supervision.[20,22] However, if BCS can influence health outcomes through increased intervention, adherence is unclear due to limitations in study methodology and reporting.[20,23]

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.

2 | METHODS

2.1 | Design

The Physical training and Cancer (Phys-Can) study was a Swedish three-center, 2 × 2 factorial design randomized controlled trial (Figure 1), previously described in depth.[24] Briefly, participants were randomized 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 participants 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.

2.2 | 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. The chemotherapy treatment period was typically 4 months for breast cancer and 6 months for colorectal cancer. Radiotherapy treatment was typically 2 months for prostate cancer and 3 weeks for breast cancer. Endocrine therapy was scheduled for 2.5-10 years and antibody treatment for 6-12 months.

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 (eg, severe heart failure, severe chronic obstructive pulmonary disease, or orthopedic conditions), treatment for an additional ongoing malignant disease, BMI < 18.5 kg/m^2 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.

2.3 | Interventions

The 6-month intervention was initiated at start of the (neo-) adjuvant cancer treatment as described in Table 2. The supervised, group-based resistance training at public gyms was performed twice/week (Figure S1). 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. Patients with breast cancer, scheduled for neo-adjuvant chemotherapy, exercised during the four months pre-surgery only. Standardized delivery of both exercise and additional BCS was assessed and enhanced as described in Table 2.

The intervention was developed by researchers with expertise in exercise physiology, BCS, and physiotherapy in collaboration with clinicians (oncologists and physiotherapists) and patient representatives.

2.4 | Outcomes and data management

Follow-up data collection was completed in November 2018. CRF was assessed with the Multidimensional Fatigue Inventory (MFI),[25] measuring General, Physical and Mental Fatigue, Reduced Motivation and Reduced Activity, each subscale range 4-20. Based on previous research,[10] the Physical Fatigue subscale was used for power calculation.

CRF was also assessed with Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scale,[26] a frequently used single-scale questionnaire with range 0-52.

All outcomes were assessed with well-established and validated methods completed at home, at baseline (before randomization) and immediately post-intervention. HRQoL was assessed with European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30,[27] anxiety and depression with Hospital Anxiety and Depression Scale (HADS)[28] and functioning in daily life with World Health Organization Disability Assessment Schedule (WHODAS) 2.0 Work and Social Participation subscales.[29] Muscle strength was assessed with 1 repetition maximum (RM) test of upper and lower extremities. Chemotherapy completion rate was reported as relative dose intensity based on data from medical records.[30] For details about assessment methods,

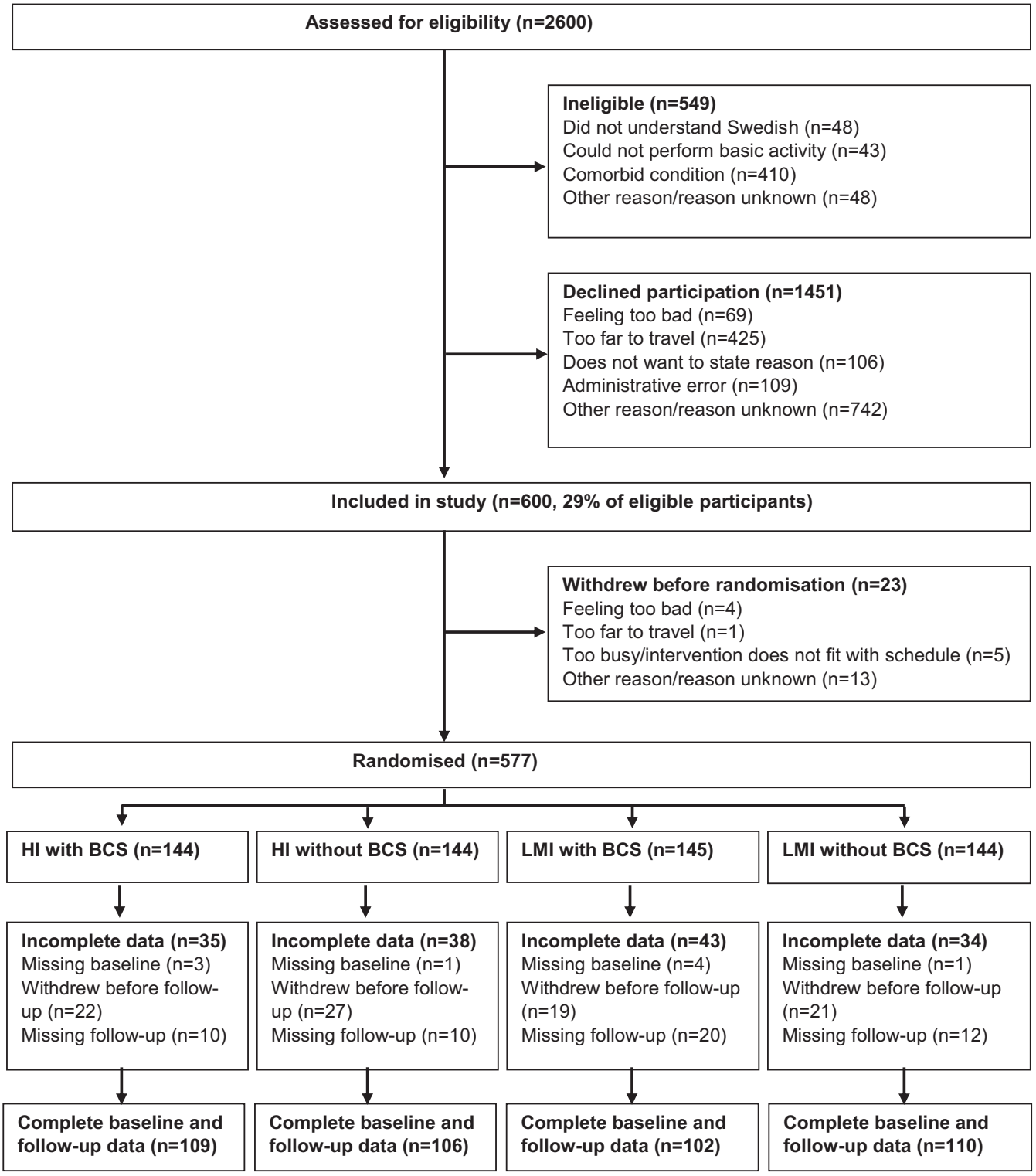

FIGURE 1 CONSORT diagram of flow of participants through the Phys-Can study. Numbers with (in)complete baseline and follow-up data are based on cancer-related fatigue (MFI physical fatigue subscale), exact numbers for other outcomes vary (Table 1). Follow-up refers to data collected at the post-intervention.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

Table S1. Composite scores for questionnaires 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 Table S1. A minimum of 80% wear time for four out of seven days was required for data to be included. Mean sedentary time per 24 hours was considered to be time spent at 0-1.5

METs according to SenseWear algorithms and mean time in moderate-to-vigorous intensity physical activity (MPVA) per 24 hours was considered to be that of at least 3 METs according to SenseWear algorithms.[31]

Cardiorespiratory fitness was independently assessed in dedicated exercise laboratories using maximal oxygen uptake (VO_2max) tests with gas exchange measurement, walking/running to exhaustion using a modified Balke protocol.[32] Tests were accepted if two out of three criteria were fulfilled: (a) tester judged the test as maximal, (b) Borg RPE[33] rating ≥ 17 and (c) respiratory exchange ratio (RER) ≥1.1.[34]

Exercise adherence was recorded as absolute numbers of performed sessions and calculated as % volume. Exercise volume (frequency, intensity, and time) was calculated as performed exercise divided by prescribed (maximum possible) exercise, in accordance with previous research.[35] This calculation resulted in one proportion (0%-100%) for resistance training and one proportion (0%-100%) for endurance training for each participant. These proportions were pooled to mean adherence per exercise component and intervention group. For details, Table 2 under the heading "Calculation of adherence."

2.5 | Sample size

An a-priori power calculation showed that 600 participants (150 per trial arm) were required to detect main factorial effects of exercise intensity and BCS on the MFI Physical Fatigue subscale,[36] 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.[24]

2.6 | Randomization

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 centers and 3 diagnoses) randomization was carried out following a permuted block design with 8 participants per block. Once baseline data collection was finalized, each participant was automatically assigned to an intervention group using a web-portal.

2.7 | 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.

2.8 | Statistical methods

Differences in baseline characteristics between those included in analysis and those who withdrew were examined using *t* tests for continuous variables and chi-squared tests for categorical variables.

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 × 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 center 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, center, 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 were deemed not to add additional precision for these outcomes.[37,38]

Differences between intervention groups in adherence to resistance and endurance training volume were examined using one-way ANOVA. Among participants in the low-to-moderate-intensity groups minutes of exercise above the prescribed intensity (ie, >60% of heart rate reserve) were compared between those who did and did not receive additional BCS using a *t* test.

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

Analyses were carried out in Stata version 15.0.

2.9 | 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 organization.

3 | RESULTS

3.1 | Recruitment

Six hundred (29%) of 2051 eligible patients agreed to participate (Figure 1). Participation rate per diagnosis was 30%

TABLE 1 Descriptive data for primary and secondary outcome measures at baseline and post-intervention (ie, 6-mo follow-up) for patients with data available

	HI with BCS				HI without BCS				LMI with BCS				LMI without BCS			
	Baseline		Follow-up		Baseline		Follow-up		Baseline		Follow-up		Baseline		Follow-up	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Primary outcome CRF																
MFI General Fatigue	134	11.1 (4.3)	107	10.2 (4.5)	135	11.3 (4.6)	105	10.2 (4.0)	139	11.6 (4.6)	110	10.4 (4.3)	136	11.4 (4.5)	117	10.8 (4.5)
MFI Physical Fatigue	136	11.3 (4.2)	112	8.8 (4.4)	134	11.0 (4.5)	107	8.3 (3.9)	139	11.1 (4.3)	106	9.5 (4.2)	138	11.3 (4.2)	111	10.2 (4.3)
MFI Reduced Activity	134	10.4 (3.9)	110	9.4 (4.4)	134	10.5 (4.2)	106	9.6 (3.9)	140	11.0 (4.1)	108	9.6 (3.8)	137	10.7 (4.1)	116	9.7 (4.1)
MFI Reduced Motivation	139	8.3 (3.5)	110	7.9 (3.4)	134	8.9 (3.4)	106	8.0 (3.2)	139	8.7 (3.6)	109	7.7 (3.2)	135	8.9 (3.3)	116	8.3 (3.6)
MFI Mental Fatigue	138	8.8 (4.1)	111	8.5 (4.2)	136	9.3 (4.0)	105	8.8 (3.8)	138	9.6 (4.2)	107	9.0 (3.9)	133	9.6 (3.9)	116	9.4 (4.2)
FACIT Fatigue subscale	140	41.9 (8.6)	112	41.8 (9.7)	137	40.8 (8.6)	108	42.5 (8.0)	139	39.9 (9.3)	112	42.2 (8.7)	141	39.6 (9.9)	116	41.9 (9.0)
Secondary outcomes																
EORTC QLQ-C30 Summary Score	135	85.2 (11.7)	111	84.4 (13.8)	136	81.8 (12.5)	106	86.6 (9.6)	133	82.5 (12.9)	111	86.6 (11.1)	134	82.4 (12.8)	112	84.9 (10.7)
HADS Depression	140	3.2 (3.2)	112	2.7 (3.2)	137	3.3 (3.2)	108	2.9 (3.2)	142	3.4 (3.2)	110	2.6 (2.8)	142	3.6 (3.2)	118	3.0 (2.9)
HADS Anxiety	140	4.9 (4.3)	112	3.9 (4.1)	137	5.9 (4.5)	108	4.0 (3.8)	142	5.6 (4.4)	110	3.9 (3.7)	142	5.8 (4.4)	118	4.0 (4.0)
WHODAS Work subscale	84	5.6 (5.1)	44	4.5 (4.7)	82	7.0 (5.8)	50	3.7 (3.4)	82	6.6 (5.4)	52	4.1 (3.7)	82	5.3 (5.1)	57	3.2 (3.9)
WHODAS Social Participation subscale	136	7.5 (5.6)	109	6.6 (5.6)	134	9.0 (5.5)	106	6.6 (4.9)	139	8.1 (5.7)	110	6.1 (5.3)	137	8.3 (5.1)	112	6.2 (4.8)
Average 1RM left and right leg, kg	118	59.7 (20.1)	93	66.7 (21.5)	119	56.2 (21.1)	97	65.5 (21.3)	122	58.8 (21.1)	99	63.0 (20.8)	119	54.9 (19.9)	109	60.3 (19.7)
1RM chest press, kg	119	32.7 (12.2)	94	36.6 (12.7)	118	32.4 (11.6)	101	36.8 (12.9)	119	34.1 (14.3)	98	37.6 (15.2)	116	31.5 (13.2)	106	34.9 (14.1)
VO_2max, mL/kg/min	107	30.5 (7.2)	92	30.0 (7.3)	121	30.9 (7.0)	97	30.8 (6.6)	115	31.2 (7.1)	99	30.3 (7.2)	121	29.1 (7.1)	95	28.4 (6.8)
Sleep, h/d	118	7.3 (1.0)	105	7.1 (0.9)	116	7.3 (0.9)	95	7.3 (1.1)	121	7.4 (1.1)	105	7.1 (1.1)	127	7.2 (1.2)	97	7.1 (1.3)
Sedentary time, h/d	118	18.3 (2.2)	105	18.0 (2.2)	116	18.1 (1.9)	95	17.9 (1.9)	121	18.2 (1.8)	105	18.0 (1.7)	127	18.7 (1.7)	97	18.4 (2.0)
MVPA, h/d	118	1.1 (0.8)	105	1.2 (0.8)	116	1.3 (1.0)	95	1.5 (1.1)	121	1.3 (0.8)	105	1.5 (0.8)	127	1.1 (0.7)	97	1.2 (0.9)
Relative Dose Intensity %[a]			75	90.2 (18.0)			72	92.6 (13.0)			75	93.6 (11.0)			76	92.9 (12.2)

Note: Abbreviations: 1RM, 1 repetition maximum; BCS, Additional behavior change support; CRF, Cancer-related fatigue; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, Hospital Anxiety and Depression scale; HI, High-intensity exercise; LMI, Low-to-moderate-intensity exercise; MFI, Multidimensional Fatigue Inventory; MVPA, moderate-to-vigorous intensity physical activity; SD, standard deviation; VO_2max, maximal volume of oxygen uptake; WHODAS, World Health Organization Disability Assessment Schedule.

[a]Relative dose intensity calculated only for patients treated with chemotherapy.

TABLE 2 Description of resistance training, endurance training and additional behavior change support (BCS) components of the intervention, according to 2017 CONSORT checklist for reporting randomized trials assessing non-pharmacological treatment

	Resistance training	Endurance training	Additional BCS
Content	*High intensity:* 3 × 6 RM (2 min rest between sets) once a week. Last set until failure. 3 × 10 RM (1 min rest between sets) once a week. Last set until failure. *Low-to-moderate intensity:* 3 × 12 repetitions at 50% of 6 RM (2 min between sets) once a week. 3 × 20 repetitions at 50% of 10 RM (1 min rest between sets) once a week. Two sessions per week.	*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 min, respectively. *Low-to-moderate intensity:* 150 weekly minutes of endurance activity (walking, cycling) in bouts of minimum 10 min at 40%-50% of HRR. HRR was determined for each participant based on a VO_2max test performed before the intervention.	Coaches guided participants in using strategies to facilitate adherence to the exercise, focusing mainly on the home-based endurance training: *Goal-setting* *Short-term action planning* *Self-monitoring* *Review of goal-setting* *Behavioral analysis* *Long-term coping planning*
Setting	Supervised at public gyms in groups of typically 5-10 participants. Separate groups for each of the four conditions.	Home-based.	Face-to-face concurrent with resistance training at the gym. Only *self-monitoring* was home-based and performed by the participants after endurance training. *Long-term coping planning* was performed at the end of the exercise period.
Tailoring	Individually adapted weights based on repeated testing of 6 and 10 RM in all exercises. Weights were lowered temporarily for participants struggling with severe side effects, and then successively increased. Exercises that caused pain were substituted with other exercises activating the same muscle groups.	Individually adapted intensity based on VO_2max tests and heart rate monitors. Type of activity according to individual preferences, eg walking, bicycling, running.	Adapted to the participants' 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 participant. *Analysis* by identifying determinants of training, based on logbooks and discussions. *Long-term coping planning* according to participants' preferences about maintained physical activity/exercise.
Standardization	Familiarization period of 6 wk. Six exercises; 3 for the upper extremities and three for the lower extremities. Four additional exercises for the trunk and pelvic floor were advised but not controlled (Figure S1). Progression based on testing of 6 and 10 RM every 4-6 wk.	Familiarization period of three weeks. All participants wore heart rate monitors and recorded their exertion according to the Borg RPE [27] in exercise logbooks.	Weekly reviews during the first month and then typically every 4-6 wk, 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 participants' *self-monitoring*.

(Continues)

TABLE 2 (Continued)

	Resistance training	Endurance training	Additional BCS
Provider adherence: assessment and enhancement	Three-day course for coaches on supervising participants' 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 participant, 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 participant 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 participants 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 participants. All participants completed standardized 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 participants 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 wk. *Long-term coping plans* were written; one copy for the participant 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 × performed number of repetitions, summed across all exercises and training sessions. Maximum possible training was weight × 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 × 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 × interval duration (2 min) × 2 × 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 × 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).

Abbreviations: HRR, Heart rate reserve; RM, Repetition maximum; RPE, Rating of perceived exertion; VO_2max, Maximum oxygen respiratory uptake.

for breast cancer, 22% for prostate cancer, and 20% for colorectal cancer. Participants, compared to those who declined participation, were younger (mean age 58.7 vs 63.6 years, *P*-value < .001) and less likely to have prostate or colorectal cancer than breast cancer (OR [95%CI]; colorectal cancer, 0.58 [0.36-0.92]; prostate cancer, 0.65 [0.51-0.83]). Twenty-three participants withdrew from the study before randomization. In total, 577 participants were randomized.

3.2 | Baseline characteristics of randomized participants

Breast cancer was the most common diagnosis (n = 457), followed by prostate cancer (n = 97) and colorectal cancer (n = 23). Most participants with breast (84.5%) or prostate (66.7%) cancer received combinations of (neo-)adjuvant treatments. Among these participants, the most common combinations were chemotherapy with radiotherapy and endocrine treatment for breast cancer (30.4%) and combined neo-adjuvant and adjuvant endocrine treatment for prostate cancer (51.5%). All participants with prostate cancer also received curative radiotherapy. All participants with colorectal cancer received adjuvant chemotherapy (Table 3). Time between diagnosis and randomization was median 61 (interquartile range 44-86) days, and there was a median of 7 (interquartile range 5-11) days between randomization and starting the intervention. Sociodemographic, disease, and treatment characteristics, as well as physical fitness and physical activity levels, were similar across all four intervention groups (Tables 3 and S2).

3.3 | Missing data

Overall, 89 randomized participants withdrew from the study before the follow-up assessment. The reasons for withdrawal were too far to travel/lack of time (n = 36), illness/side effects of treatment (n = 25) and lack of motivation/disliked training (n = 10), with similar distribution between intervention groups. Eighteen participants did not provide a reason. Missing baseline data on outcomes ranged from n = 20 (FACIT-F) to n = 113 (VO_2max) (Table S3). Missing data were not associated with intervention group, age, living situation, education, weight status, and general, physical or mental fatigue. However, individuals who were not included in the analysis of the main outcome had slightly lower cardiorespiratory fitness (VO2max mean [SD]: 29.2 [7.5] vs 30.8 [7.0] mL/kg/min *P*-value = .043) and HRQoL (EORTC QLQ-C30 summary score mean [SD]: 80.6 [13.7] vs 83.7 [12.0] *P*-value = .013) at baseline compared to those included.

3.4 | Primary outcome

Participants randomized 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]) (Table 4), while there were no differences for the other MFI subscales or for FACIT-F. Moreover, there were no main effects for additional BCS and no exercise intensity-BCS interactions for any CRF measures.

3.5 | 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 compared to low-to-moderate intensity, while in the groups not receiving BCS high-intensity exercise was associated with higher HRQoL compared to low-to-moderate intensity (Table 4 and Table S4).

Participants randomized to exercise at high- vs low-to-moderate intensity had better cardiorespiratory fitness (adjusted mean difference 1.61 [95% CI 0.19-3.04] mL/kg/min) and greater leg strength (adjusted mean difference 3.98 [95% CI 0.58-7.38] kg) (Table 4). There were no main or interaction effects of additional BCS for these outcomes. An exercise intensity-BCS interaction was observed for MVPA (Table 4).

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

For chemotherapy completion rates, 118 participants (39.6%) out of 298 had dose reduction or treatment discontinuation. Mean relative dose intensity was 90.2% in high intensity with BCS, 92.6% in high intensity without BCS, 93.6% in low-to-moderate intensity with BCS, and 92.9% in low-to-moderate intensity without BCS (Table S5). There were no adjustments of radiotherapy dose for any participant.

3.6 | Supplementary analyses

The results from the complete case analysis were similar to the main results, that is, the MFI Physical Fatigue scale differed significantly, in favor of the high-intensity exercise groups (Table S3). However, in contrast to the intention-to-treat analysis, VO_2max did not differ between groups in the complete cases analysis. Diagnosis-specific analyses

TABLE 3 Sociodemographic, disease and planned treatment data at baseline by intervention group for randomized participants. Data are mean (SD) or number (%). N vary due to missing data, % is of those with data available

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

(Continues)

TABLE 3 (Continued)

	HI with BCS (n = 144)	HI without BCS (n = 144)	LMI with BCS (n = 145)	LMI without BCS (n = 144)
Colorectal cancer[g]	5	6	6	6
T2-T4	5 (100.0)	6 (100.0)	6 (100.0)	5 (100.0)
N1-N2	5 (100.0)	4 (66.7)	4 (66.7)	5 (100.0)
Chemotherapy[h]	5 (100.0)	6 (100.0)	6 (100.0)	5 (100.0)

Abbreviations: BCS, Additional behavior change support; BMI, body mass index; HI, High-intensity exercise; LMI, Low-to-moderate-intensity exercise; T, tumor size. N, lymph node status.

[a]Exercise Stage Assessment Instrument categories 1-5 with 1 = Pre-contemplation stage and 5 = Maintenance stage, physically active longer than 6 mo.

[b]Visual analogue scale 0-100 mm anchored at "Not at all important" and "Very important".

[c]One participant in HI without BCS had stage T4d treated with curative intent. Two participants in LMI without BCS had N2 and one in LMI with BCS had N3.

[d]Chemotherapy was Epirubicine-based and/or Taxane-based.

[e]Breast and/or axilla.

[f]Brachy and/or external.

[g]One participant in HI with BCS had radically removed liver metastasis. One participant in HI with BCS and two in HI without BCS had pre-operative radiotherapy.

[h]Capecitabine-Oxaliplatin or Capecitabine only.

reflected the main results for all diagnostic groups (Tables S6 and Tables S7) but were underpowered for participants with colorectal cancer and weaker for those with prostate cancer.

3.7 | Intervention adherence

Participants completed on average 50.4% of the prescribed resistance training volume, with no differences between intervention groups (P =.438) (Figure 2). For attendance specifically, the absolute mean (SD) number of performed sessions during the intervention period was 25 (10). Reported per group, mean (SD) number of performed sessions was 23 (10) for high intensity with BCS, 24 (9) for high intensity without BCS, 26 (10) for low-to-moderate intensity with BCS, and 26 (8) for low-to-moderate intensity without BCS.

Adherence to home-based endurance training volume differed between groups (mean [SD] % was 38.8 (33.1) for high intensity with BCS, 41.6 (33.6) for high intensity without BCS, 57.7 (38.3) for low-to-moderate intensity with BCS, and 51.4 (38.7) for low-to-moderate intensity without BCS, P <.001) and pair-wise comparisons are presented in Figure 2. The absolute mean (SD) number of performed interval sessions during the intervention period was 23 (17) for high intensity with BCS and 23 (16) for high intensity without BCS. The mean (SD) number of continuous training sessions (minimum 10-minute bouts) was 73 (66) for low-to-moderate intensity with BCS and 70 (61) for low-to-moderate intensity without BCS. Among participants in the low-to-moderate-intensity groups those who received additional BCS performed more minutes of exercise above the prescribed intensity (ie, >60% of heart rate reserve) than those who did not receive additional BCS (506 vs 326 minutes, P-value = .026).

3.8 | Adverse events due to intervention

Thirty-two minor adverse events in 30 participants (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 events included muscle strains, joint pain, and dizziness. In addition, three participants needed to attend hospital as a result of exercise; one injured a finger, and two fainted.

4 | DISCUSSION

This was a large, second-generation RCT designed to examine the effects of exercise intensity per se on CRF and other health outcomes during cancer treatment. 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.[36] 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,

TABLE 4 Main effects of exercise intensity, additional behavior 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)

	Exercise intensity AMD (95%CI)	BCS AMD (95%CI)	Interaction AMD (95%CI)	*P*-value for interaction effect
Primary outcome CRF				
MFI General Fatigue	−0.36 (−1.04 to 0.33)	−0.20 (−0.91 to 0.51)	0.19 (−0.53 to 0.91)	.608
MFI Physical Fatigue	**−1.05 (−1.85 to −0.25)**	−0.43 (−1.21 to 0.34)	0.26 (−0.55 to 1.08)	.524
MFI Reduced Activity	0.22 (−0.49 to 0.92)	−0.35 (−1.04 to 0.35)	−0.05 (−0.76 to 0.67)	.899
MFI Reduced Motivation	0.05 (−0.53 to 0.64)	−0.27 (−0.83 to 0.30)	0.31 (−0.25 to 0.87)	.276
MFI Mental Fatigue	−0.26 (−0.94 to 0.42)	−0.20 (−0.88 to 0.48)	0.36 (−0.32 to 1.04)	.304
FACIT Fatigue subscale	−0.43 (−1.87 to 1.01)	−0.11 (−1.59 to 1.36)	−0.63 (−2.09 to 0.84)	.401
Secondary outcomes				
EORTC QLQ-C30 Summary Score	−0.64 (−2.42 to 1.15)	−0.77 (−2.51 to 0.97)	**−2.83 (−4.61 to −1.05)**	**.002**
HADS Depression	0.03 (−0.45 to 0.50)	−0.24 (−0.74 to 0.27)	0.17 (−0.32 to 0.66)	.495
HADS Anxiety	0.16 (−0.39 to 0.71)	0.23 (−0.35 to 0.81)	0.51 (−0.06 to 1.08)	.079
WHODAS Work subscale[a]	0.31 (−1.01 to 1.63)	0.42 (−0.86 to 1.71)	0.73 (−0.59 to 2.06)	.277
WHODAS Social Participation subscale	0.12 (−0.68 to 0.91)	0.36 (−0.45 to 1.18)	0.51 (−0.28 to 1.30)	.206
Average 1RM left & right leg, kg[b]	**3.98 (0.58 to 7.38)**	2.85 (−0.59 to 6.29)	−0.66 (−3.86 to 2.55)	.687
1RM chest press, kg[b]	0.41 (−1.62 to 2.44)	1.47 (−0.52 to 3.47)	−1.40 (−3.41 to 0.61)	.171
VO_2max, mL/kg/min[b]	**1.61 (0.19 to 3.04)**	0.76 (−0.68 to 2.20)	−1.25 (−2.67 to 0.16)	.082
Sleep, h/d[b]	0.10 (−0.15 to 0.34)	−0.03 (−0.27 to 0.22)	−0.10 (−0.33 to 0.14)	.422
Sedentary time, h/d[b]	−0.26 (−0.68 to 0.16)	−0.13 (−0.54 to 0.28)	0.26 (−0.14 to 0.66)	.204
MVPA, h/d[b]	0.06 (−0.14 to 0.26)	0.07 (−0.13 to 0.26)	**−0.26 (−0.45 to −0.07)**	**.008**
Relative Dose Intensity, %[c]	−1.54 (−4.46 to 1.39)	−0.99 (−3.94 to 1.96)	−1.99 (−4.93 to 0.95)	.184

Abbreviations: 1RM, 1 repetition maximum; 95%CI, 95% confidence intervals; AMD, Adjusted mean difference; BCS, Additional behavior change support; CRF, Cancer-related fatigue; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer, Quality of life Questionnaire C30; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, Hospital Anxiety and Depression scale; MFI, Multidimensional Fatigue Inventory; MVPA, moderate-to-vigorous intensity physical activity; VO_2max, maximal volume of oxygen uptake; WHODAS, World Health Organization Disability Assessment Schedule.

[a]For participants who reported working.

[b]Baseline values not included in analysis due to missing data > 10%.

[c]For participants treated with chemotherapy. Linear regression analyses adjusted for hospital, cancer site, and baseline measure of outcome. Bold indicates *P*-value < .05.

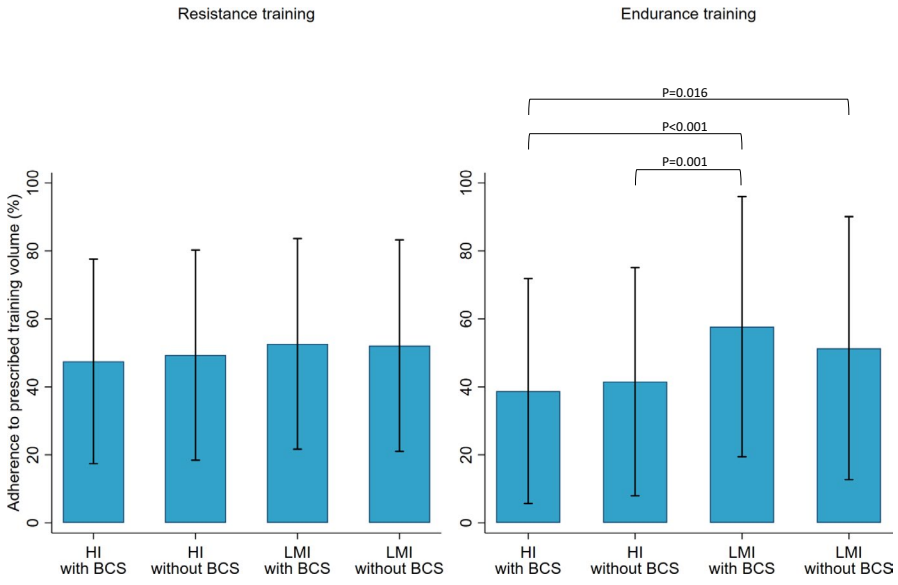

FIGURE 2 Adherence to prescribed strength and endurance training volume, by training group. Bars represent mean adherence, error bars indicate 1 standard deviation from the mean. Participants who dropped out of the study were recorded as 0 adherence to any remaining training sessions. P-values reflect pair-wise comparisons across the four intervention groups using Tukey post hoc tests. All other pair-wise comparisons resulted in *P*-values > .05. HI, high-intensity exercise, LMI, low-to-moderate-intensity exercise, BCS, additional behavior change support

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.

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,[10] but did not find a minimum clinically important difference between groups.[36] 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.[39] An RCT comparing high- and low-to-moderate-intensity endurance training within a multimodal rehabilitation program after treatment also reported no differences in CRF.[40] 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 supervised training, social support, graded tasks, and feedback. These methods have previously been associated with higher exercise adherence in cancer populations.[19,20] 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.

Adherence to the resistance training was within range of other exercise interventions including patients undergoing curative cancer treatment,[41,42] and exercise volume did not differ between groups. However, the adherence to the high-intensity endurance training was lower than previously reported in studies with similar populations[17,43] and lower than adherence in the low-to-moderate-intensity groups. One reason for the lower levels in the present study could be that the endurance training was home-based. This decision made as we, after conducting a feasibility study and receiving input from oncology clinicians and patient representatives, deemed it would be too demanding for our participants to exercise at the gym four times per week. To facilitate adherence to the endurance training, all participants had a familiarization period of four weeks and the average number of performed resistance and endurance sessions reached levels that could be expected to make a difference, particularly for participants with low fitness levels from start.

Another explanation for the lower adherence to high-intensity endurance training compared to other studies could be that we used a stringent method for calculating adherence, including drop-outs from the intervention and taking both intensity and time into account, rather than reporting attendance only. Detailed analysis of adherence according to FITT principles in the present study has been reported in a separate publication within the research group,[44] demonstrating that once the participants had made it to the gym, they adhered to the prescribed resistance training program to a large extent.

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.[45] Although significant, the small between-group difference in cardiorespiratory fitness is consistent with the idea that not only intensity, but also frequency, duration and volume are important exercise variables for cardiorespiratory fitness during cancer treatment.[46]

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,[47] 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.

Although only 29% of the approached patients consented to participate, the aim of this study was to compare high- vs low-to-moderate-intensity exercise for CRF. As such, internal validity was prioritized over external validity (generalizability). Our sample consisted of relatively healthy and motivated individuals; mainly well-educated women treated for breast cancer. Moreover, individuals included in the main analysis had a slightly higher cardiorespiratory fitness and health-related quality of life than those who dropped out after randomization. However, baseline levels of these factors did not differ between randomization groups for those included in the analysis. Participants varied in age, current exercise levels, and perceived importance of exercise, and it is unlikely that biological mechanisms related to exercise intensity differ in our sample compared with the broader population. However, we cannot claim that the results can be generalized to the total population of patients with curatively intended treatment for breast, prostate, or colorectal cancer, due to the different characteristics in the sample and the small proportions of patients with prostate and colorectal cancer.

4.1 | Strengths and limitations

A clear protocol and competent, trained coaches helped ensure that the intervention was delivered consistently across the different centers and the participants 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 missing data were not differential. However, difference between the intention-to-treat and the complete case analysis for VO_2max suggests that missing data for this analysis may be differential.

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-analyzed with other studies to inform research on diagnosis-specific effects. Blinding coaches and participants to the intervention were 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. Furthermore, adherence to the endurance training differed between groups indicating that we did not have full control of exercise volume for this intervention component.

5 | CONCLUSIONS

For CRF, we found no clinically important difference between participants randomized 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.

6 | PERSPECTIVE

It is well established that exercise during and after cancer treatment improves CRF[7] and international guidelines recommend cancer survivors to stay active and perform endurance and/or resistance training 2-3 times per week.[13] However, the importance of exercise intensity for CRF is unclear. The present study found that participants undergoing (neo-)adjuvant cancer treatment exercising at high intensity for 6 months demonstrated lower physical fatigue at post-intervention, compared to participants exercising at low-to-moderate intensity. However, the difference between groups was below the threshold for clinical importance. There was no effect of behavior change support (goal-setting, planning and self-monitoring of exercise) on fatigue. The 6-month intervention, including resistance and endurance training, caused few minor adverse events, indicating that exercise is safe even at high intensity and can be recommended to these patient groups. 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. Behavior change support in terms of 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.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

AUTHOR CONTRIBUTION

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. Demmelmaier, Henriksson, Mazzoni, Igelström, Ax, Sjövall, Hellbom, Pingel, Lindman, S Johansson, Velikova, Raastad, Buffart, Åsenlöf, Aaronson, Glimelius, Nygren, B Johansson, Börjeson, Berntsen, and Nordin involved in study conception and design. Demmelmaier, Henriksson, Mazzoni, Helgesen Björke, Igelström, Ax, Sjövall, Lindman, S Johansson, B Johansson, Börjeson, Berntsen, and Nordin involved in acquisition of data. Demmelmaier, Brooke, Henriksson, Mazzoni, Helgesen Björke, Pingel, Velikova, Raastad, Buffart, Åsenlöf, Aaronson, Glimelius, Nygren, B Johansson, Börjeson,

Berntsen, and Nordin involved in analysis and interpretation of data.

ETHICAL APPROVAL

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

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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