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LAVÍN-PÉREZ, Ana Myriam <http://orcid.org/0000-0001-9357-9987>, COLLADO-MATEO, Daniel, MAYO, Xian, HUMPHREYS, Liam, LIGUORI, Gary, COPELAND, Robert <http://orcid.org/0000-0002-4147-5876>, DEL VILLAR ÁLVAREZ, Fernando and JIMENEZ GUTIERREZ, Alfonso

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REVIEW ARTICLE

WILEY

High-intensity exercise to improve cardiorespiratory fitness in cancer patients and survivors: A systematic review and meta-analysis

Ana Myriam Lavín-Pérez[1,2,3] | **Daniel Collado-Mateo**[2] | **Xián Mayo**[2] | **Liam Humphreys**[4] | **Gary Liguori**[5] | **Robert James Copeland**[4] | **Fernando Del Villar Álvarez**[2] | **Alfonso Jiménez**[2,3,4]

[1]Program of Epidemiology and Public Health (Interuniversity), PhD International School of the Rey Juan Carlos University, Madrid, Spain
[2]Centre for Sport Studies, Rey Juan Carlos University, Madrid, Spain
[3]GO fitLAB, Ingesport, Madrid, Spain
[4]Advanced Wellbeing Research Centre, College of Health, Wellbeing and Life Sciences, Sheffield Hallam University, Sheffield, UK
[5]University of Rhode Island, Kingston, RI, USA

Correspondence
Daniel Collado-Mateo, Centre for Sport Studies Fuenlabrada, Rey Juan Carlos University, Madrid, Spain
Email: daniel.collado@urjc.es

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Improving cardiorespiratory fitness (CRFit) in cancer patients is crucial to increase survivorship, promote health, and improve quality of life. High-intensity training (HIT) has the potential to increase CRFit, perhaps better than other exercise modalities, but the extant evidence has yet to be fully explored. This systematic review and meta-analysis aimed to evaluate the effects of HIT on CRFit in cancer patients and survivors and to identify the optimal characteristics of the interventions (eg, cancer type, intervention timing, exercise modality, intervention's duration, and the number of minutes of high-intensity exercise in each session). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. A total of 31 articles (2515 participants) were included in the systematic review and 25 in the meta-analyses. CRFit significantly improved with HIT in comparison with a control group ($P < .00001$, SMD = 0.44 and a 95% confidence interval from 0.25 to 0.64). The results obtained in the sub-analysis were statistically significant except the comparison with the active group CRFit ($P = .13$). The results showed that higher effects could be achieved in: patients starting to exercise before treatment, interventions longer than eight weeks, programs including exclusively cardiovascular training and with a high-intensity part of session duration of at least 20 minutes.

KEYWORDS
cardiorespiratory fitness, exercise oncology, high-intensity training

1 | INTRODUCTION

Cancer remains a global public health problem despite considerable advances in prevention, treatment, and aftercare strategies. Cancer is the second leading cause of death in the United States, with ~1.7 million new cases diagnosed in 2019, more than 4800 each day.[1] Cancer patients often have to pass through different treatments (surgery, chemotherapy, radiotherapy, hormone therapy, etc) which affects their health, activities of daily living,[2] and cardiorespiratory fitness (CRFit). CRFit measures are clinically important due to being inversely associated with cancer-related death,[3] cancer risk and case fatality,[4] overall morbidity,[5] and increased health-related quality of life[6]; up to the point of being considered an independent risk factor for cardiovascular disease.[7] Moreover, several investigations have demonstrated a significant decrease in CRFit, measured by peak volume of oxygen consumption (VO_{2peak}), during cancer treatment, which is influenced by patients' clinical health, drug's cardiac side effects, and physical inactivity during the whole period.[8]

Chemotherapy and drug therapies have high toxicity and can damage organs such as liver or heart.[9] Depending on treatment course, this may leave to irreversible tissue damage. While cancer survivorship is growing,[10] so is cardiotoxicity. Cardiotoxicity is the toxic effect of anti-cancer drugs causing "dawning of hypotension or hypertension, arrhythmias, myocardial infarction and/or thromboembolism and myocarditis".[11] Cardiotoxicity side effects could be manifested in a short or long term,[12] increasing the risk of heart failure while decreasing CRFit.[13] Thus, the benefits of exercise in survivors must also be studied to evaluate the potential effects of rehabilitation therapies on the variables that can be affected by these side effects. In this regard, physical exercise before surgery,[14] during treatment,[15-17] and as a survivor [18] may mitigate cardiotoxicity [19] and the impact of cancer on CRFit,[20] quality of life,[21] chronic fatigue,[22] and anxiety or depression.[23,24] Exercise is safe, feasible,[25] and cost-effective [26]; however, the optimal intensity, duration, and mode at each stage of the cancer pathway remain unclear.[27] The consensus of exercise to cancer patients suggests; moderate-to-high intensity aerobic exercise, resistance exercise or a combination of both conduct on a frequency of 2-3 sessions per week for between 8 and 12 weeks.[27] While most cancer-related exercise interventions have been limited to low-intensity[28] and/or moderate-intensity exercise,[29] evidence is emerging from randomized controlled trials (RTC) to suggest that health outcomes are as good if not better from higher intensity exercise protocols in adult cancer survivors.[30,31]

High-intensity training (HIT) can induce greater improvements in CRFit than moderate continuous aerobic exercise in patients with heart failure[32] or stroke.[33] In cancer patients, different RTC of HIT have demonstrated improved CRFit in comparison with controls[34,35] or moderate-intensity exercise.[36] The optimal characteristics of high-intensity exercise are still unknown, and some examples of non-successful (in terms of CRFit) interventions can be read.[37,38] Therefore, an in-depth evaluation of the evidence for HIT and CRFit in cancer patients is needed. Beyond CRFit, exercise produces changes in the tumor microenvironment and lactate concentration. Thus with higher intensities, these changes could be greater and affect different health outcomes.[39] To our knowledge, two previous systematic reviews have explored the effect of high-intensity exercise on CRFit in patients with cancer. Firstly, Toohey et al[40] conducted a systematic review without meta-analysis of nine articles showing evidence of larger CRFit improvements after high-intensity exercise and suggesting that a multi-modal (combined cardiovascular and resistance exercises) program performed three times a week increases VO_{2max} (+21.35%). Secondly, Mugele et al conducted a review and meta-analysis[41] exploring the effects of high-intensity interval training (HIIT) on the CRFit of cancer patients and survivors, without considering resistance components and high-intensity continuous exercise. The study concluded that aerobic HIIT leads to positive outcomes compared to controls (including five studies) while the differences compared to moderate intensity are unclear (including four articles). The authors of the two reviews[40,41] concluded that the optimal characteristics of a high-intensity intervention (including duration, volume, exercise type, type of cancer, and timing) were unclear and therefore required further research.

With this in mind, the present systematic review and meta-analysis aimed to evaluate the effects of any type of HIT on CRFit in cancer patients and survivors. Furthermore, we also aimed to identify the optimal characteristics of HIT interventions by analyzing effects according to; cancer type, intervention timing (pre-treatment during treatment, and post-treatment), exercise modality (with or without resistance training), the length of the intervention (number of weeks) and the duration of the high-intensity exercise in each session (number of minutes).

2 | METHODS

The systematic review followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[42] It was registered in the International prospective register of systematic reviews (PROSPERO) with the identification number CRD42020167203. A change from the registered protocol is that the results reported here are only based on CRFit. Given the large number of analyses and figures included in the current manuscript, it was not possible to also include the analysis of overall quality of life and its dimensions.

2.1 | Data sources and searches

Searches were conducted using scientific databases: PubMed (MEDLINE) and Web of Sciences (including KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index). The search terms used were "cancer", "neoplasm", HIIT, "high intensity", "VO2", "aerobic capacity", "oxygen consumption", "oxygen uptake", "cardiorespiratory fitness", "physical fitness", "aerobic fitness" separated by the operators AND and OR. The following restrictions were added (a) articles published in English or Spanish, (b) published in the last 10 years and (c) not having the word "ultrasound" in the title (due to the misunderstanding with high-intensity focused ultrasound therapy). The search started in November 2019 and ended in February 2020.

The articles were incorporated if they fulfilled the following inclusion criteria: (a) participants had any kind of cancer, (b) the intervention included a HIT component, (c) the article reported effects on VO_{2peak}, and (d) the design included one or more comparison group/s. RCT and non-RCT were included. The following exclusion criteria were set: (a) The article was not written in English or Spanish, (b) the article was a consensus, guideline, letter to editor, conference abstract, case report, and/or a study protocol or design, and (c) the article was focused on childhood cancer. The term high intensity is defined herein to be any exercise program whose authors have described to have any "high-intensity" component including aerobic and anaerobic high-intensity components as well as resistance. Cardiovascular training is defined as any aerobic, anaerobic exercise (or a combination of both) focused on the improvement of the cardiovascular function such as cycling or exercise on a treadmill. The article selection was undertaken by the lead author (AMLP) and revised by the second researcher (DCM). There was no disagreement in the selection process.

2.2 | Risk of bias assessment

PEDro scale was used to evaluate the risk of bias. PEDro is specific in physical therapies, commonly adopted in sport sciences[43] and is considered a valid and reliable tool to assess eligibility, allocation to groups, blinding of allocation, and comparison between groups at baseline and its outcomes.[44]

2.3 | Data extraction

Following PRISMA methodology, participants, intervention, comparisons, results, and study design (PICOS) were obtained. Regarding participants, some baseline parameters were extracted, such as sample size, mean age, body mass index, physical activity level, cancer type, stage, type of treatment, and timing. Intervention characteristics included FITT principle (frequency, intensity, time, and type) together with the exercise description, intensity, progression of the exercise program, and adherence to the intervention (% attendance to the prescribed number of sessions). The activity of the comparison group(s) was also extracted. Furthermore, the outcome of the current systematic review and meta-analysis was CRFit. In this regard, VO_{2peak} values measured during the maximal or submaximal tests could be expressed in different units: mL/min or mL/min/kg. Regardless of the units shown, articles were included in the meta-analysis whenever it was possible. Detailed information of those articles which did not report sufficient data to be included in the meta-analyses is reported in the Supplementary data (Tables S2 and S3).

Finally, the study design was also reported since RCT and non-RCT were included. Data extraction was performed by the lead author (AMLP) and then checked by another author (DCM).

2.4 | Statistical analysis

Post-intervention means and standard deviations were extracted from the manuscript or supplemental data or calculated using reported data from high-intensity exercise group (HIEG) and the comparison group, which could be an inactive control group (CG) or a low-to-moderate intensity exercise group (LMEG).

All analyses were performed using the Review Manager Software (RevMan, 5.3).[45] The analysis method used was the inverse variance and random effects due to the heterogeneity of articles.[46] The standardized mean difference (SMD) was employed when there were different units of VO_{2peak} (mL/min/kg or mL/min) whereas mean difference (MD) was used for the same VO_{2peak} values (mL/min/kg). SMD was interpreted according to the Cochrane Handbook of Systematic Reviews.[47] The results obtained were represented with a confidence interval (CI) of 95%. The I2 statistic model calculated heterogeneity, and Z test was used for the overall effect.

To analyze the effectiveness of the interventions on CRF, the following group comparisons were performed: (1) according to the comparison group, HIEG compared to CG and HIEG compared to LMEG; (2) according to the type of cancer, HIEG vs an inactive CG in breast cancer patients and high-intensity interventions vs an inactive CG in lung patients (types of cancer with five or more articles were included); (3) according to the timing of the intervention, high-intensity interventions compare to an inactive CG before chemotherapy, high-intensity interventions compared to an inactive CG during chemotherapy and high-intensity interventions compare to an inactive CG after chemotherapy; (4) according to the type of exercise intervention, different subgroups were compared, relating in all of them the CRF outcome of the HIEG compared to an inactive CG including: (a) interventions of 8 or less weeks of duration and programs longer than 8 weeks; (b) interventions including a resistance component and cardiovascular only; (c) interventions involving sessions with a high-intensity duration of <20 minutes and independently with a duration of 20 minutes or more.

3 | RESULTS

3.1 | Study selection

A total of 214 total studies were identified in PubMed (98 studies) and Web of Science (116), and another three

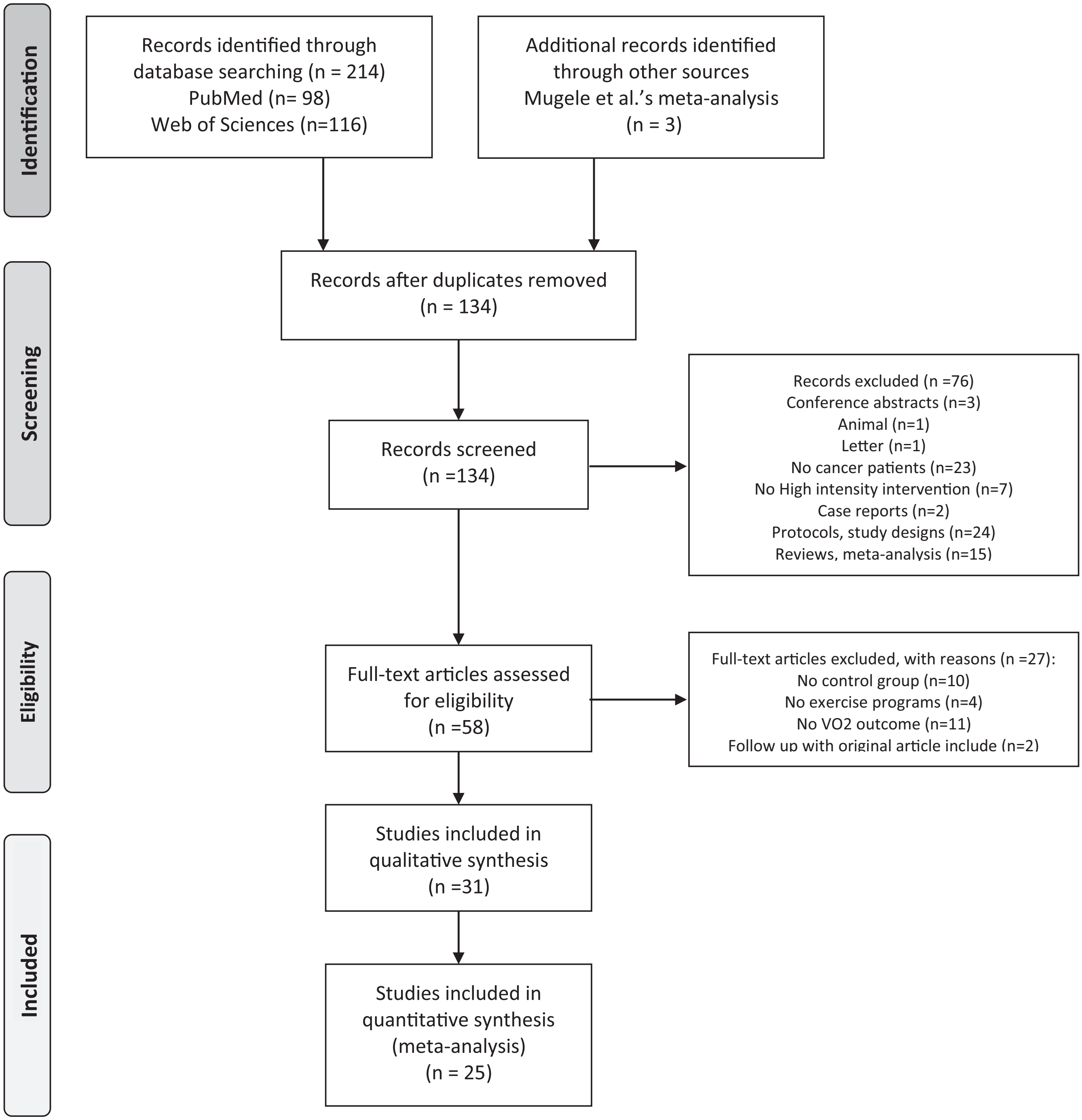


FIGURE 1 Study flow diagram

articles were recovered from a previous HIIT meta-analysis.[41] The flow diagram, in Figure 1, describes the process by which studies were included or excluded. Seventy-six studies were then excluded in the first screening and 27 in the full-text analysis. In total, 31 studies were included in the systematic review, 25 of which were incorporated in the meta-analysis.

3.2 | Risk of bias

Table 1 shows the internal and external validity of the articles included in the systematic review measured by the PEDro scale. The mean score of all the studies was 6.27 (range 3-8) on a scale from 0 to 10, with 10 being the highest score. The items related to blinding criteria were not commonly met. This

TABLE 1 Risk of bias using PEDro scale

Validity	Internal item	External items								Statistic items		Total score
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Wood et al (2020)	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Lee et al (2019)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Bhatia et al (2019)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	6
Alizadeh et al (2019)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	8
Northey, et al (2018)	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Mijwel et al (2018)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Devin et al (2018)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Christensen et al (2018)	Y	Y	N	Y	N	N	N	Y	Y	Y	N	5
Karenovics et al (2017)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Wall et al (2017)	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Schulz et al (2017)	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Persoon et al (2017)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Banerjee et a.l (2017)	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Adams et al (2017)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Toohey et al (2016)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Schmitt et al (2016)	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Licker et al (2016)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Dunne (2016)	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	8
Martin et al (2015)	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	7
Moller (2015)	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Kampshoff et al (2015)	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Devin et al (2015)	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Edvardsen et al (2015)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
West (2015)	Y	N	N	N	N	N	N	Y	Y	Y	Y	4
Dolan (2015)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Stefanelli (2013)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Midtgaard (2013)	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Andersen et al (2013)	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Hwang, et al (2012)	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Ademsen (2009)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7

is common in sport sciences since participants know at what intensity they have to exercise. Furthermore, therapists require exhaustive information of each participants need and undertake exercise training according to strict the intervention protocols.

3.3 | Participants characteristics

Participants' baseline characteristics of the studies included in the meta-analysis are shown in Table 2 and Table S1. Information on the remaining articles can be found in the Supplementary data (Table S2). The total sample size of all included studies was 2515 participants, 1115 from the CG, 1104 in the HIEG, and 296 belonging LMEG. The mean age of the participants was 51.8 years (24-72), 51.0 in the CG, 51.6 in the HIEG, and 55.7 in the other active group. There were 22 different cancer types included in the sample.

Articles involved breast cancer (n = 10), lung cancer (n = 6), colorectal cancer (n = 4), prostate cancer (n = 2), and testicular cancer (n = 1). Eight studies reported sample

TABLE 2 Baseline characteristics of the participants included in the meta-analysis

Study	Design	Group	Sample size (% of females)	Age mean (SD)	Cancer type (%)	Treatment (%)	Timing	BMI mean (SD)
Lee et al (2019)	RCT (pilot)	CG	n = 15 (100%)	44.7 (11.2)	Breast Cancer	Chemotherapy	During	30.1 (7.7)
		HIEG	n = 15 (100%)	49.1 (7.9)		Chemotherapy	During	33.1 (7.6)
Egegaard et al (2019)	RCT	CG	n = 7 (71.4%)	65 (4.7)	Non-small cell lung Cancer (NSCLC)	Chemoradiotherapy	During	24.2 (1.9)
		HIEG	n = 8 (62.5%)	64 (5.8)		Chemoradiotherapy	During	24.1 (4.4)
Northey et al (2018)	RCT (pilot)	CG	n = 6 (100%)	61.5 (7.8)	Breast cancer	Surgery + chemotherapy (16.67%) Surgery + radiation (33.3%) Surgery + chemotherapy +radiation (50%)	After	NR
		HIEG	n = 6 (100%)	60.3 (8.1)		Surgery + radiation (50%) Surgery + chemotherapy +radiation (50%)		NR
		MIEG	n = 5 (100%)	67.8 (7.0)		Surgery (20%) Surgery + radiation (80%)		NR
Mijwel et al (2018)	RCT	CG	n = 60 (100%)	52.6 (10.2)	Breast cancer	Chemotherapy	During	NR
		HIEG-R	n = 74 (100%)	52.7 (10.3)				NR
		HIEG-A	n = 72 (100%)	54.4 (10.3)				NR
Devin et al (2018)	RCT	HIEG	n = 18 (27.8%)	60.7 (11.7)	Colorectal cancer	Surgery (38.9%) Surgery + chemotherapy (50%) Surgery,+ Chemotherapy + Radiation (11.1%)	After	29.8 (3.6)
		HIEG-T	n = 20 (50%)	61.5 (10.2)		Surgery (30.0%) Surgery + chemotherapy (55.0%) Surgery + radiation (10.0%) Radiation + Chemotherapy (5.0%)	After	24.7 (4.5)
		MIEG	n = 19 (52.6%)	59.8 (11.4)		Surgery (36.8%) Surgery + chemotherapy (47.4%) Surgery + Chemotherapy +Radiation (15.8%)	After	26.5 (3.9)
Karenovics et al (2017)	RCT	CG	n = 77 (35%)	24.4 (4.1)	Lung cancer	Surgery (100%) Chemotherapy (12%)	After	24.4 (4.1)
		HIEG	n = 74 (45%)	25 (4.5)		Surgery (100%) Chemotherapy (8%)	After	25 (4.5)
Wall et al (2017)	RCT	CG	n = 47 (0%)	69.1 (8.4)	Prostate cancer	Radiotehrapy (85%)	During	NR
		HIEG	n = 50 (0%)	69.1 (9.4)		Radiotherapy (92%)	During	NR

(Continues)

TABLE 2 (Continued)

Study	Design	Group	Sample size (% of females)	Age mean (SD)	Cancer type (%)	Treatment (%)	Timing	BMI mean (SD)
Schulz et al (2017)	Pilot study (non-randomized)	CG	n = 11 (100%)	56.9 (7.0)	Breast cancer	Surgery (45.45%) Chemotherapy (63.63%) Radiotherapy (100%) Hormonal therapy (90.91%)	During	NR
		HIEG	n = 15(100%)	51.9 (9.8)		Surgery (60%) Chemotherapy (80%) Radiotherapy (40%) Hormonal therapy (66.7%)	During	NR
Persoon et al (2017)	RCT	CG	n = 55 (33%)	56	Multiple myeloma (53%) (Non-)Hodgkin lymphoma (47%)	NR	Afer transplation	NR
		HIEG	n = 54 (46%)	53.5	Multiple myeloma (54%) (Non-)Hodgkin lymphoma (46%)	NR	Afer transplation	NR
Banerjee et al (2017)	Feasability RCT	CG	n = 30 (10%)	72.5 (8.40)	Bladder cancer	Surgery (99%) Chemotherapy (17%)	Before	26.91 (11.60)
		HIEG	n = 30 (13%)	71.6 (6.8)		Surgery (100%) Chemotherapy (33%)	Before	27.09 (13.38)
Adams et al (2017)	RCT	CG	n = 28 (0%)	43.3 (9.9)	Testicular cancer	Surgery (96.4%) Chemotherapy (28.6%) Radiation (17.9%)	After	NR
		HIEG	n = 35 (0%)	40.0 (11.6)		Surgery (88.6%) Chemotherapy (42.9%) Radiation (17.1%)	After	NR
Toohey et al (2016)	RCT (pilot)	HIEG	n = 8 (100%)	47.25 (13.49)	Colon (6.25%)Cervical (6.25%) Melanoma (6.25%) Ovarian (12.5%) Breast (56.25%) Breast and uterine (6.25%) Breast and liver (6.25%)	Surgery (18.75%) Surgery + chemotherapy (12.5%) Surgery + radiation (6.25%) Surgery + Chemotherapy+Endocrine (12.5%) Surgery + Chemotherapy+Radiation + Endocrine (50%)	After	NR
		MIEG	n = 8 (100%)	55.88 (11.81)			After	NR
Schmitt et al (2016)	RCT	HIEG	n = 13 (100%)	53 (8)	Breast (85%) Ovarian (8%) Non-invasive urotelial (8%) Metastases (15%)	Surgery (100%) Chemotherapy (54%) Radiation (69%) Antihormonal (69%)	After	27.0 (5.3)
		LMIEG	n = 13 (100%)	54 (9)	Breast (77%) colon (8%) vaginal (8%) Non-Hodgkins lymphoma (8%) Metastases (8%)	Surgery (100%) Chemotherapy (69%) Radiation (69%) Antihormonal (54%)	After	26.2 (4.3)

(Continues)

TABLE 2 (Continued)

Study	Design	Group	Sample size (% of females)	Age mean (SD)	Cancer type (%)	Treatment (%)	Timing	BMI mean (SD)
Dunne et al (2016)	RCT	CG	n = 17 (23.5%)	62	Colorectal liver metastasis	Chemotherapy (60%)	Before	29.7 (4.2)
		HIEG	n = 20 (35%)	61		Chemotherapy (58.82%)	Before	29.7 (4.2)
Martin, et al (2015) c)	RCT	CG	n = 35 (0%)	66.9 (6.6)	Prostate cancer	Surgery (77.14%) Radiation (28.57%) Brachytherapy (11.43%) ADT (20%)	After	28 (3.7)
		HIEG	n = 27 (0%)	65.3 (7)		Surgery (81.48%) Radiation (18.52%) Brachytherapy (11.11%) ADT (11.11%)	After	27.6 (4.1)
		LIEG	n = 25 (0%)	65 (6.3)		Surgery (92%) Radiation (8%) ADT (12%)	After	26.4 (2.8)
Martin, et al (2015) a)	RCT	CG	n = 40(100%)	57.2 (9.8)	Breast cancer	Surgery (100%) Chemotherapy (67%) Radiation (71%) Hormone (98%)	After	26.3 (5.2)
		HIEG	n = 13 (100%)	53.5 (9)		Surgery (100%) Chemotherapy (77%) Radiation (54%) Hormone (85%)	After	27.9 (5.3)
		LIEG	n = 19(100%)	58.2 (9.6)		Surgery (100%) Chemotherapy (63%) Radiation (90%) Hormone (82%)	After	26.6 (4.8)
Møller et al (2015)	Feasibility RCT	CG	n = 16 (12.5%)	46.95 (9.19)	Colon and breast cancer	Chemotherapy	During	25.54 (4.90)
		HIEG	n = 15 (7.14%)	57.17 (10.51)		Chemotherapy	During	24.39 (5.27)
		LIEG	n = 77(100%)	48.49 (8.41)		Chemotherapy	During	23.8 (2.59)
Kampshoff et al (2015)	RCT	CG	n = 92 (78%)	54 (10.9)	Breast (63%) Colon (17%) Ovarian (6%) Lymphoma (9%) Cervix (2%) Testicles (4%)	Surgery (88%) Radiation (53%) Surgery + radiation (51%) Immunotherapy (20%) Homonal therapy (47%)	After	NR
		HIEG	n = 91 (80%)	54 (11.0)	Breast (68%) Colon (17%) Ovarian (4%) Lymphoma (10%) Testicles (1%)	Surgery (91%) Radiation (51%) Surgery + radiation (45%) Immunotherapy (18%) Homonal therapy (50%)	After	NR
		LMIEG	n = 95 (82%)	53 (11.3)	Breast (65%) Colon (20%) Ovarian (3%) Lymphoma (9%) Cervix (2%)	Surgery (92%) Radiation (43%) Surgery + radiation (41%) Immunotherapy (26%) Homonal therapy (42%)	After	NR

(Continues)

TABLE 2 (Continued)

Study	Design	Group	Sample size (% of females)	Age mean (SD)	Cancer type (%)	Treatment (%)	Timing	BMI mean (SD)
Devin et al (2015)	RCT	HIEG	n = 30 (40%)	61 (11.1)	Colonrectar cancer	Surgery (30.0%) Surgery + chemotherapy (50.0%) Surgery + radiation (3.3%) Surgery + chemotherapy +radiation (13.3%) Radiatión + chemotherapy (3.3%)	After	27.1 (4.8)
		MIEG	n = 17 (52.9)	61.5 (10.8)		Surgery (41.2%) Surgery + chemotherapy (41.2%) Surgery + chemotherapy +radiation (17.6%)	After	26.4 (3.4)
Edvardsen et al (2015)	RCT	CG	n = 31 (52%)	65.9 (8.5)	Lung cancer	Surgery (100%) Chemotherapy (29%) Radiation (13%)	After surgey	25.1 (5.2)
		HIEG	n = 30 (57%)	64.4 (9.3)		Surgery (100%) Chemotherpy (30%) Radiation (10%)	After surgey	25.4 (5.1)
West (2015)	Pilot study (non-randomized)	CG	n = 13 (31%)	72	Rectal cancer	Chemoradiation (100%)	Before surgery	24.9 (3.9)
		HIEG	n = 22 (36%)	64		Chemoradiation (100%)	Before surgery	27.4 (5.1)
Dolan at al. (2015)	RCT	CG	n = 10	59.4 (9)	Breast cancer	Surgery (100%) Chemotherapy (60%) Radiation (70%) Hormonetherapy (70%)	After	24.8 (4.4)
		HIEG	n = 12	56.2 (9)		Surgery (100%) Chemotherapy (75%) Radiation (58.3%) Hormonetherapy (66.67%)	After	25.8 (5.8)
		MIEG	n = 11	56.3 (9)		Surgery (100%) Chemotherapy (63.63%) Radiation (63.63%) Hormonetherapy (54.54%)	After	23.9 (3.1)
Stefanelli et al (2013)	RCT	CG	n = 40 (42.5%)	64.8 (7.3)	NSCLC	NR	Under lobectomy	27.6 (3.5)
		HIEG		65.5 (7.4)		NR	Under lobectomy	25.6 (4.5)

(Continues)

TABLE 2 (Continued)

Study	Design	Group	Sample size (% of females)	Age mean (SD)	Cancer type (%)	Treatment (%)	Timing	BMI mean (SD)
Andersen et al (2013)	RCT	CG	n = 107 (72%)	47.8 (10.4)	Breast (47.66%) Bowel (14.02%) Ovaries (8.41%) Testicles (6.54%) Oesopagus (0.93%) Brain (1.87%) Cervix (1.87%) Pharynx (0.93%) Pancreas (1.87%) Stomach (0.93%) Other diagnosis (5.61%) Hematological (9.43%)	NR	During	NR
		HIEG	n = 106 (79.2%)	47.1 (10.8)	Breast (49.05%) Bowel (13.21%) Ovaries (10.38%) Testicles(6.6%) Oesopagus (0.94%) Brain (0.94%) Cervix (1.88%) Pharynx (1.88%) Pancreas (0.94%) Stomach (0.94%) Other (2.83%) Hematological (10.38%)	NR	During	NR
Hwang et al (2012)	RCT	CG	n = 11 (36.4%)	58.5 (8.2)	Lung cancer	Surgery (36.4%) Chemotherapy (45.6%) Radiotherapy (45.5%)	During	23.1 (2.6)
		HIEG	n = 13 (61.5%)	61.0 (6.3)		Surgery (69.3%) Chemotherapy (76.9%) Radiotherapy (61.5%)	During	22.6 (2.4)

(Continues)

TABLE 2 (Continued)

Study	Design	Group	Sample size (% of females)	Age mean (SD)	Cancer type (%)	Treatment (%)	Timing	BMI mean (SD)
Adamsen et al (2009)	RCT	CG	n = 134 (70.9%)	47.2 (10.6)	Breast (44.03%) Bowel (12.68%) Ovaries (8.2%) Testicles (6.7%) Esophagus (2.23%) Brain (2.98%) Cervix (1.5%) Pharynx (0.74%) Pancreas (1.5%) Stomach (1.5%) Other (6.7%) Hematological malignancies (11.2%)	Chemotherapy	During	NR
		HIEG	n = 135 (74.8%)	47.2 (10.7)	Breast (44.44%) Bowel (13.33%) Ovaries (11.85%) Testicular (5.18%) Esophagus (1.48%) Brain (0.74%) Cervix (2.96%) Pharynx (1.48%) Pancreas (0.74%) Stomach (0.74%) Other (7.4%) Hematological malignancies (9.63%)	Chemotherapy	During	NR

Abbreviations: BMI, Body Mass Index; CG, control group; HIEG, high-intensity exercise group; HIEG-A, high-intensity exercise group with aerobic component; HIEG-R, high-intensity exercise group with resistance component; HIEG-T, high-intensity exercise group with tapered frequency; MIEG, moderate-intensity exercise group; NR, no reported; NR, not reported; RCT, randomized control trial; SD, standard desviation.

TABLE 3 Description of the high-intensity exercise interventions included in the meta-analysis

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Lee et al (2019)	CG	8 wk		Current level of Physical activity		
	HIEG	8 wk	30 min/ 3 times per week	Cycle exercise HIIT: 5 min warm-up, 20 min HIIT (7 × 1 min) and 5 min cooldown	Intervals at 90% (W Peak Power) 2 min at 10% (W Peak Power) Additional control: HR	Sessions: 82.3% Simple size:100%
Egegaard et al (2019)	CG	7 wk		Daily life	Activity tracker (Garmin®vívosmart®)	
	HIEG	7 wk	20 min/ 5 times per week	Ergometer cycle exercise: 5 min warm-up 1st and 3rd Intervals: 5x 30 s with 30 s rest 2nd interval: continuous cycling	Moderate-to-high intensity Warm-up: 50%-60% (W Peak Power) 1st, 3rd interval 80%-95% (W Peak Power) 2nd interval: 80% (W Power Peak) Additional control: HR	Sessions: 90.0% and adherence Simple size: 100%
Northey et al (2018)	CG	12 wk				
	HIEG	12 wk	20-30 min/ 3 times per week	5 min warm-up and cooldown 4-7× 30 s cycling intervals with 2 min active recovery	Warm-up and cooldown 50% PP Intervals of 95 and 115 rpm 90% of their maximum by the fourth interval 1 more interval per week Additional control: HR and RPE	Sessions: 79.4 ± 12.0% Simple size: 100%
	MIEG	12 wk	20-30 min/ 3 times per week	5 min warm-up and cooldown 20 min aerobic	Warm-up and cooldown 50% PP Aerobic 55%-65% PP Additional control: HR and RPE	Sessions: 78.7 ± 13.2%

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Mijwel et al (2018)	CG			Written American College of Sports Medicine exercise recommendations		
	HIEG-R	16 wk	60 min/ 2 times per week	5 min aerobic warm-up Resistance: 8-12 high-load repetitions of the major muscle groups Cycle exercise HIIT: 3 × 3 min intervals with 1 min recovery	Warm-up: 10-12 RPE Resistance: 70%-80% (RM) Aerobic: moderate 13-15 RPE HIIT: intervals at 16-18 RPE	Sessions: 68% Simple size: 88%
	HIEG-A	16 wk	60 min/ 2 times per week	5 min aerobic warm-up Cycle exercise HIIT: 3 × 3 min intervals with 1 min recovery Aerobic: 20 min of cycle ergometer, elliptical ergometer, or treadmill moderate continuous exercise	Warm-up: 10-12 RPE HIIT: intervals at 16-18 RPE Aerobic: 13-15 RPE	Sessions: 63%
Devin et al (2018)	HIEG	8 wk	38 min/ 3 times per week	Cycling exercise 10 min warm-up 4 × 4 min cycling bouts intervals with 3 min active recovery	Warm-up: 50%-70% HRpeak Intervals: 85%-95%HRpeak Recovery: 50%-70% HRpeak Additional control: RPE	Sessions: 100% Simple size: 99.3 ± 2.2%
	HIEG-T	8 wk	38 min/ Firt 4 wk : 3 times per week, Second 4 wk: 1 time per week			Simple size: 99.9 ± 0.5%
	MIEG	8 wk	50 min/ 3 times per week	Cycling continuous exercise	50%-70% HRpeak Additional control: RPE	Simple size: 100.0 ± 0.0%
Karenovics et al (2017)	CG					
	HIEG	Median of 25 days	34 min/ · times per week	5 min warm-up 2 × 10 min with 15 s cycling intervals with 15 s pauses and 4 min rest between series 5 min cooldown	Warm-up: 50% (WRpeak) Intervals: all-out effort Cooldown: 30% (WRpeak)	Session: 87 ± 18% Simple size: 100%

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Wall et al (2017)	CG	6 months		Normal physical activity and dietary routine.		
	HIEG	6 months	Clinic 60 min/ 2 times per week Home-based: 150 min/week	Clinic: 5 min warm-up (Aerobic and static stretching) Resistance: major upper and lower body muscle groups Weeks 1-4:2 sets, 12 repetitions. Weeks 5-8:3 sets, 10 repetitions. Weeks 9-12:3 sets, 8 repetitions. Weeks 13-16:4 sets, 6 repetitions Aerobic: 20-30 min in various machines 5 min cooldown Home-based: 150 min aerobic	Warm-up: 11-12 RPE Resistance: 6RM-12 RM Aerobic: 70%-90% HR in VO2max Home-based: 70%-90% HR in VO2max	Sessions: 69% Simple size:86%
Schulz et al (2017)	CG	6 wk				
	HIEG	6 wk	69 min/ 2 times per week	Aerobic: 15 min warm-up and 3 min cooldown, 10 × 1 min cycling intervals with 1 min active recovery Resistance:4 training blocks of 2 series of 8-12 repetitions 2 series, with interserial pause (3 min, motion sequence: concentric 2 s, isometric 1 s, excentric 4 s)	Warm-up 50% VO2max Intervals: 85%-100% VO2max 3.5-6.8 MET Strength 4.5MET (12-14 RPE)	Sessions: 97.22% Simple size: 100%
Persoon et al (2017)	CG	18 wk				
	HIEG	18 wk	60 min/ First 12 wk: 2 times per week. Until end: 1 time per week	Resistance: 6 standardized exercise muscles Week 1-12:2 series of 10 repetitions Aerobic: 2 × 8 min cycling Week 1-8 30 s blocks with 60 s blocks	Resistance: 65%-80% RM Aerobic: 30 s blocks at 65% (maximal short exercise capacity) 60 s blocks at 30% (maximal short exercise capacity) Load adjustment every 4 wk	Sessions: 86% Simple size: 92.6%

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Banerjee et al (2017)	CG					
	HIEG	8 sessions 3-6 wk	45-50 + cooldown/ 2 times per week	Cycle ergometer 5-10 min warm-up 6 × 5 min cycling intervals with 2.5 min active recovery	Warm-up: 50 W Intervals: 13-15 RPE 70%-85% HRmax (220-age) cadence 50-60 rev.min-1 Recovery 50 W Additional control: HR	Simple size: 90%
Adams, et al (2017)	CG	12 wk				
	HIEG	12 wk	35 min/ 3 times per week	5 min warm-up and cooldown 4 × 4 min walking/running intervals with 3 min active recovery	Warm-up: at ± 5% of the ventilatory threshold Intervals: 75% - 95% VO2máx Recovery: 5%-10% of the ventilatory threshold Additional control: HR	Sessions: 99% Simple size: 100%
Toohey et al (2016)	HIEG	12 wk	20-30 min/ 3 times per week	5 min warm-up 3 to 7 × 30 s cycling or treadmill intervals with 1 min rest 5 min cooldown	Intervals ≥ 85% (HRmax) Additional control: RPE and blood pressure	Sessions: 93.75% Simple size: 100%
	MIEG	12 wk	30 min/ 3 times per week	5 min warm-up 20 min cycle continuous Aerobic 5 min cooldown	≤ 55% predicted HRmax Additional control: RPE and blood pressure	
Schmitt et al (2016)	HIEG	3 wk 8 sessions	25 min/ 3 times per week	5 min warm-up 8 × 1 min intervals walking 2 min active recovery	Warm-up: 70% (HRpeak) Intervals: >95% (HRpeak)	93% partipants all sessions
	LMIEG	3 wk	75 min/6 sessions	60 min walking 15 min indoor cycling	Cycling: 60% (HRpeak)	
Dunne et al (2016)	CG	4 wk				
	HIEG	4 wk	30 min + warm-up + cooldown/12 sessions	Cycle ergometer exercise Warm-up Intervals of high and moderate intensity	High intensity > 90% (VO2 peak) Moderate intensity > 60% (VO2peak)	Sessions: 99% Simple size: 95%

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
West et al (2015)	CG	6 wk				
	HIEG	6 wk	30 min First 2 sessions. 40 min rest of sessions/ 3 times per week	5 min warm-up 3 min braked cycle ergometer intervals with 2 min intervals 5 min cooldown	3 min Intervals: 80% of oxygen uptake at lactate threshold 2 min intervals: 50% of the difference in work rates between peak oxygen uptake and oxygen uptake at lactate threshold	Sessions: 96% Simple size:100%
Martin et al (2015) c)	CG	8 wk				
	HIEG	8 wk	60 min/ 3 times per week	25 min Aerobic (walking/jogging) 25 min resistance 10 min static stretching	Aerobic: 75%-80% (VO2 max) Increase + 5% VO2 middle of the program Resistance: 65%-80% RM Additional control: HR	Sessions: 90% Simple size: 96%
	LIEG	8 wk	60 min/ 3 times per week	25 min Aerobic (walking/jogging) 25 min resistance 10 min static stretching	Aerobic: 60%-65% (VO2 max) Increase + 5% VO2 middle of the program Resistance: 50%-65% RM Additional control: HR	

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Martin et al (2015) a)	CG	8 wk				
	HIEG	8 wk	60 min/ 3 times per week	25 min Aerobic (walking/jogging) 25 min resistance 10 min static stretching	Aerobic: Week 1- 4 75% (VO2 max)/ Week 5-8 80% (VO2max) Increase + 5% VO2 middle of the program Resistance: 65%-80% RM Additional control: HR	Sessions: 90% Simple size: 96%
	LIEG	8 wk	60 min/ 3 times per week	25 min Aerobic (walking/jogging) 25 min resistance 10 min static stretching	Aerobic: Week 1- 4 60% (VO2 max)/ Week 5-8 65% (VO2max) Increase + 5% VO2 middle of the program Resistance: 50%-65% RM Additional control: HR	
Møller et al (2015) a) and b)	CG	12 wk				
	HIEG	12 wk	90 min (hiit sessions)/9 h per week	High-intensity sessions: 30 min warm-up 45 min resistance: 3series of 5-8 repetitions 15 min cycling aerobic interval training: cooldown (stretching and coordination training) Low- intensity sessions: 30-90 min of body awareness, relaxation or massage	Resistance:70%-100% RM- 5.5 METSs Aerobic: 70-250 W, 85%-95% (HRmax) 15 METs	a) Sessions: 74% Simple size: 82% b) Sessions: 50% Simple size 75%
	LIEG-H	12 wk	30 min per day/ 5 times per week	Low/moderate recreational physical activity level of 30 min/day and 10 000 steps/day	Pedometer data	

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Kampshoff et al (2015)	CG	12 wk				
	HIEG	12 wk	Depending on de week/ 2 times per week	Resistance: six exercise large groups 2 series of 10 rep Aerobic: 1st- 4th week: 2 × 8 min cycling intervals 30 s + 60 s blocks 4th- end:2 × 8 min cycling intervals 30 s + 30 s blocks 5th week-end additional Aerobic session: 8 min of cycling intervals 30 s + 30 s blocks and 8 min 3 × 5 min continuous ergometer with 1 min rest	Resistance: 70%-85% (RM) Aerobic: 30 s Interval 65% maximum short exercise capacity (MSEC) 60 s Interval: 30% (MSEC) Continuous ergometer: 80% (HRR) Load adjustment every 4 wk	Sessions: 74% and more than 80% of the sessions Simple size: 92%
	LMIEG	12 wk	Depending on de week/ 2 times per week	Resistance: six exercise large groups 2 series of 10 rep Aerobic: 1st- 4th week: 2 × 8 min cycling intervals 30 s + 60 s blocks 4th- end:2 × 8 min cycling intervals 30 s + 30 s blocks 5th week-end additional Aerobic session: 8 min of cycling intervals 30 s + 30 s blocks and 8 min 3 × 5 min continuous ergometer with 1 min rest	Resistance: 40-55% (RM) Aerobic: 30 s Interval 65% maximum short exercise capacity (MSEC) 60 s Interval: 30% (MSEC) Continuous ergometer: 40%-50% (HRR) Load adjustment every 4 wk	Sessions: 70%
Devin et al (2015)	HIEG	4 wk	38 min/ 3 times per week	10 min warm-up 4 × 4 min cycling intervals with 3 min active recovery	Warm-up: 50%-70% (HRpeak), W and cadence Intervals: 85%- 95% (HRpeak) Recovery: 50%- 70% (HRpeak) Additional control: RPE	Sessions: 100% Simple size: 97.0%
	MIEG	4 wk	50 min/ 3 times per week	Continuos cycling	50%-70% (HRpeak) Additional control: RPE, W and cadence	Sessions: 100% Simple size: 97.1%

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Edvardsen et al (2015)	CG	20 wk				
	HIEG	20 wk	60 min/ 3 times per week	Warm-up Interval uphill treadmill walking Resistance 3 series of leg press, leg extension, back extension, seat row, bicep curls, and chest-and-shoulder press	Intervals 80%-95% (HRpeak) Resistance: 6-12 RM Additional control: RPE	Sessions: 88 ± 29% Simple size: 83%
Dolan at al. (2015)	CG	6 wk				
	HIEG	6 wk	3 times per week	Walking exercise Intervals: Starting in 3.22 km and progressing to 4.02 km by week 5	Intervals from 50%-60% VO2 to 60%-90% VO2 Additional control: Distance and HR	Sessions: 99% Simple size: 100%
	MIEG	6 wk	3 times per week	Walking exercise	From 55 VO2 to 70% VO2 Additional control: Distance and HR	
Stefanelli et al (2013)	CG	3 wk				
	HIEG	3 wk	180 min/ 15 sessions	Respiratory exercise Aerobic: Rowing, cycle ergometer, and treadmill	Aerobic 70% CPET +10 W when the patient was able to tolerate the set load for 30 min	
Hwang et al (2012)	CG	8 wk		General exercise instructions and Theraband® Elastic Band		
	HIEG	8 wk	30-40 min/ 3 times per week	Treadmill o cycling ergometer sessions 10 min warm-up 2-5 min intervals with an active recovery 5 min cooldown	Intervals: 80% (VO2peak) 15-17 RPE Recovery: 60% (VO2peak) 11-13 RPE Load adjustment every 1-2 wk Additional control: HR, blood pressure and oxygen saturation	Sessions: 71.2% Simple size: 85%

(Continues)

TABLE 3 (Continued)

Study	Group	Duration	Sessions duration/ frequency	Exercise description	Intensity progression and control	Attendance
Adamsen et al (2009)	CG					
	HIEG	6 wk	90 min (hiit sessions)/ 9 h per week	High-intensity cycling sessions: 30 min warm-up 45 min resistance: 3 series of 5-8 repetitions 15 min aerobic interval training: cooldown (stretching and coordination training) Low- intensity sessions: 30-90 min of body awareness, relaxation or massage	Resistance:70%-100% RM- 5.5 METs Aerobic: 70-250 W, 85%-95% (HRmax) 15 METs	Sessions: 70.8% Simple size: 87,4%

Abbreviations: CG, control group; CPET, cardiopulmonary exercise test; HIEG, high-intensity exercise group; HIEG-A, high-intensity exercise group with aerobic component; HIEG-R, high-intensity exercise group with resistance component; HIEG-T, high-intensity exercise group with tapered frequency; HR, heart rate; METs, Metabolic equivalent; MIEG, moderate-intensity exercise group; PP, power peak; RM, repetition maximum; RPE, rate of perceived exertion; W, watios.

size comprised of different types of cancer patients. Eight interventions took place before surgery, eleven were during chemotherapy, and eight occurred after treatment. Patients' mean Body Mass Index ranged from 22.6 to 33.1 kg/m^2, and none were physically active prior to the study.

3.4 | Interventions characteristics

The exercise protocols included in the meta-analysis are described in Table 3. The characteristics of those not included can be seen in the Supplementary data (S3). High-intensity programs were supervised in clinics,[35,38,48-50] laboratories,[25,51-53] exercise centers,[34,54] outdoors,[30,55] or hospitals,[56-59] for instance. One study was carried out in the participant's home.[60] The interventions differed in duration: from two to five weeks,[36,48,61-65] six weeks,[55-58,66] from seven to eight weeks,[36-38,52] twelve-week,[31,51,67,68] or more than twelve weeks.[34,35,54,59,69,70] There were also interventions with different lengths depending on chemotherapy duration.[60,63,64] Also, only the results of the first six weeks of Moller et al[58] were included in the meta-analysis because beyond that time the intervention involved only sport practice.

Regarding the FITT principle, the studies' interventions are based on the following details:

The most usual frequency was three times per week[34,38,49-52,56-58,61,63,68-70] although there were programs of two times per week,[25,48,54,59,66,67] four times per week,[35] and five times per week.[37,65] Mean whole session duration was 56.73 minutes with some of 20 minutes,[31,37] from 20 to 30 minutes,[51] 30 minutes,[49,60,61,65,71] from 30 to 40 minutes,[50] 35 minutes,[63,64,70] 40 minutes,[57,68] 50 minutes,[48] 60 minutes,[34,38,54,59] 70 minutes,[25,66] 90 minutes,[56,58] and 180 minutes.[65] As for the type of exercise, most of the studies included the interval training as the high-intensity component,[25,34,36,48-52,54,56-64,66,68-70] except three using a more continuous form of high-intensity exercise.[35,38,65] The cardiovascular exercise was made in cyclo-ergometers,[25,36,37,48-52,56-58,61-64,66,69,72] walking or running,[30,34,38,55,60,68,70] or using different ergometer machines[31,50,59,65] with bouts of 15 seconds,[61,63,64] 30 seconds,[31,37,51,54,67,69] 1 minute,[30,52,66] 2 minutes,[57,60] 3 minutes, 4 minutes,[25,36,62,68,70] and 5 minutes.[48,50] Some of the programs started their progression in 70% or less of the maximum intensity target in the prior evaluation,[35,37,48,55,65,67] between 75% and 80%[38,57,59,60,64,70] and 85% or more intensity.[31,36,56,58,61,62,66,68,69] Moreover, some programs also included resistance training,[25,34,35,38,54,56,58,59,66,67,69] aerobic continuous exercise added to HIIT with reported intensities from 13 to 15 of Borg's rate of perceived exertion[37] and 80% of W_{peak},[59] or low-intensity components (stretching, breathing exercise or relaxing).[38,56,58]

The mean adherence rates (ie, Attendance at sessions) were 79.43% to the high-intensity interventions; aerobic only

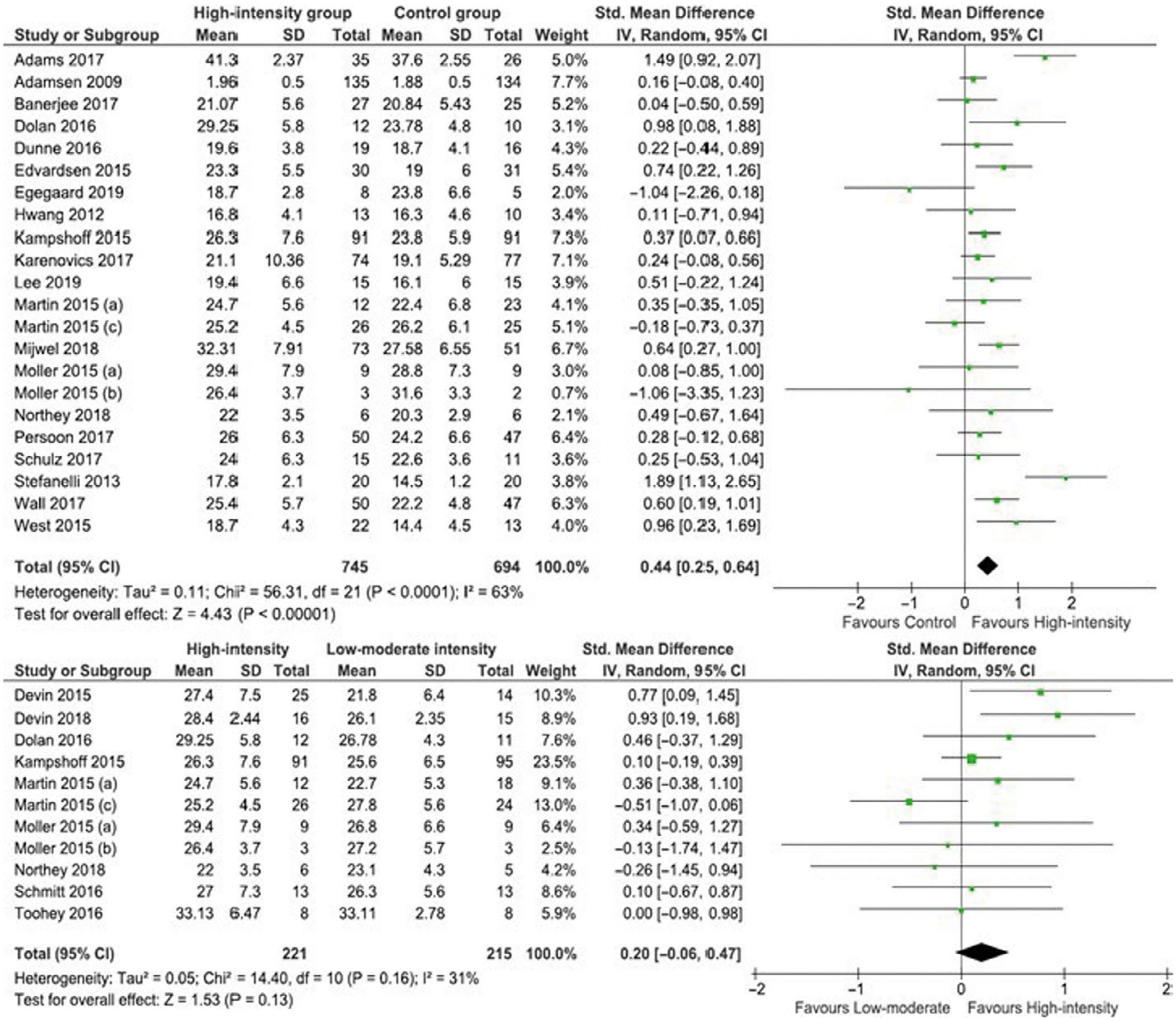


FIGURE 2 Effects in cardiorespiratory fitness of the comparisons between high-intensity group and control group, and high-intensity group and moderate-intensity group

87.87% and resistance training only was 73.33%. Interventions that focused on low and low to moderate-intensity exercise achieved an adherence rate of 88.75% regardless of exercise modality.

3.5 | Cardiorespiratory fitness measures

The assessment of CRFit was mostly conducted using maximal or submaximal incremental test with a gas analysis to assess VO_{2peak} (in mL/kg/min or mL/min). The CRFit test was carried out on a stationary bike or a treadmill. Cycle ergometer evaluations increased 5-15 W/min,[37,52] 10-20 W/min,[48] 20 W/min,[25,51,56,69] 25 W each 3 minutes,[66] 20-30 W/min,[36,62,66] 10-25 W/min,[49,57] or 30 W/min.[38] Treadmill assessments increment the incline 2% every 2 minutes,[70] or increased velocity and incline at the same time.[30] Some interventions used field test to estimate CRFit such as the 6MWT (Six-Minute-Walking-Test)[31] and Rockport Walk Test.[68]

3.6 | Cardiorespiratory fitness effects

3.6.1 | Overall results

Meta-analysis outcomes reported the effects of the studies reporting enough information to conduct the calculations. However, the results of those interventions that do not report enough data were reported in the Supplementary data (Table S3). The results in Figure 2 show that, in contrast to inactive CG (ie, usual care or waitlist group), the enhancement

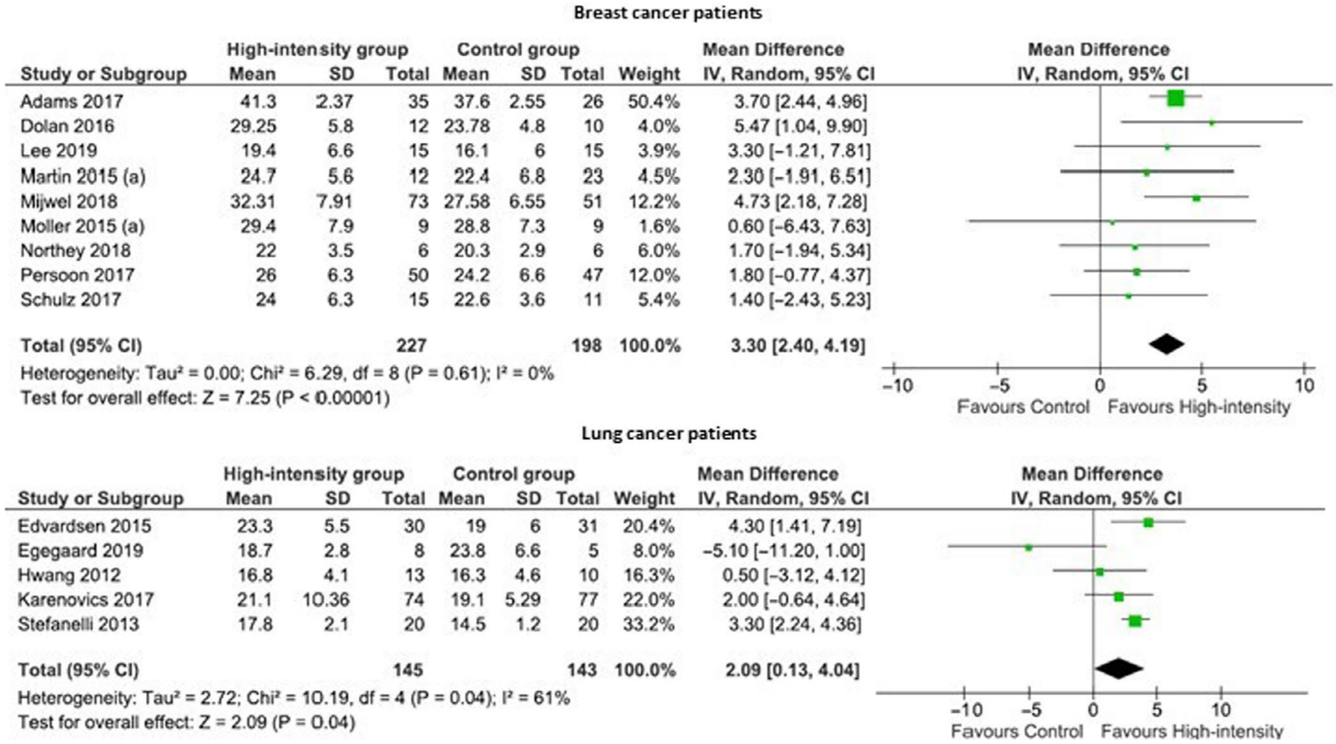


FIGURE 3 Effects of high-intensity exercise in cardiorespiratory fitness according to the type of cancer

of the VO_{2peak} in the HIEG was higher (P < .00001, with a SMD of 0.44 and a 95% CI from 0.25 to 0.64), which is considered a "moderate" effect.[47] In comparison with an active group (low to moderate or moderate-intensity exercise), however, the results were not different (P = .13; SMD = 0.20 with 95% CI from −0.06 to 0.47).

3.6.2 | High-intensity exercise for cancer types

As Figure 3 reports, the effects of HIT with respect to cancer type were evaluated by separately analyzing the results in those two cancer types with 5 or more studies, breast and lung. In breast cancer, patients and survivors achieved a significant improvement (P < .00001; MD = 3.30 mL/min/kg and a 95% CI from 2.40 to 4.19 mL/min/kg) compared with the inactive CG. Furthermore, patients with lung cancer showed a significant improvement (P = .04; MD = 2.09 mL/min/kg and a 95% CI from 0.13 to 4.04 mL/min/kg) compared to the inactive CG.

3.6.3 | Timing of the intervention

We also compared three different time periods (Figure 4; before, during, and after the treatments) according to the medical therapy (chemotherapy, radiotherapy, hormonotherapy, immunotherapy, and/or surgery). There was a statistically significant improvement in each of the three phases. The largest effects were observed for interventions that occurred before treatment (P = .01; SMD = 0.76 with 95% CI from 0.15 to 1.38). The P-value for during and after treatment was .005 and .03, respectively, with a SMD slightly lower during the chemotherapy (SMD = 0.35, 95% CI from 0.11 to 0.60) compared to after chemotherapy (SMD = 0.45 and 95% CI from 0.03 to 0.87).

3.6.4 | Exercise prescription

High-intensity protocols with or without resistance training component showed a significant improvement in VO_{2peak} (Figure 5). Based on the SMD, the only cardiovascular training interventions had more of an effect on CRFit (P = .001; SMD = 0.63 with 95% CI from 0.25 to 1.69) than combined cardiovascular-resistance programs (P < .0001; SMD = 0.32 with 95% CI from 0.17 to 0.48). In this regard, the only cardiovascular training programs achieved a moderate effect according to the SMD, while those programs including resistance training showed a small effect.

Moreover, regarding the duration of the exercise programs (Figure 6), interventions of 8 weeks or less had a significantly smaller effect on VO_{2peak} (P = .02; SMD = 0.32 with 95% CI from 0.06 to 0.58), compared to the moderate effect reported for programs lasting longer than 8 weeks (P < .00001;

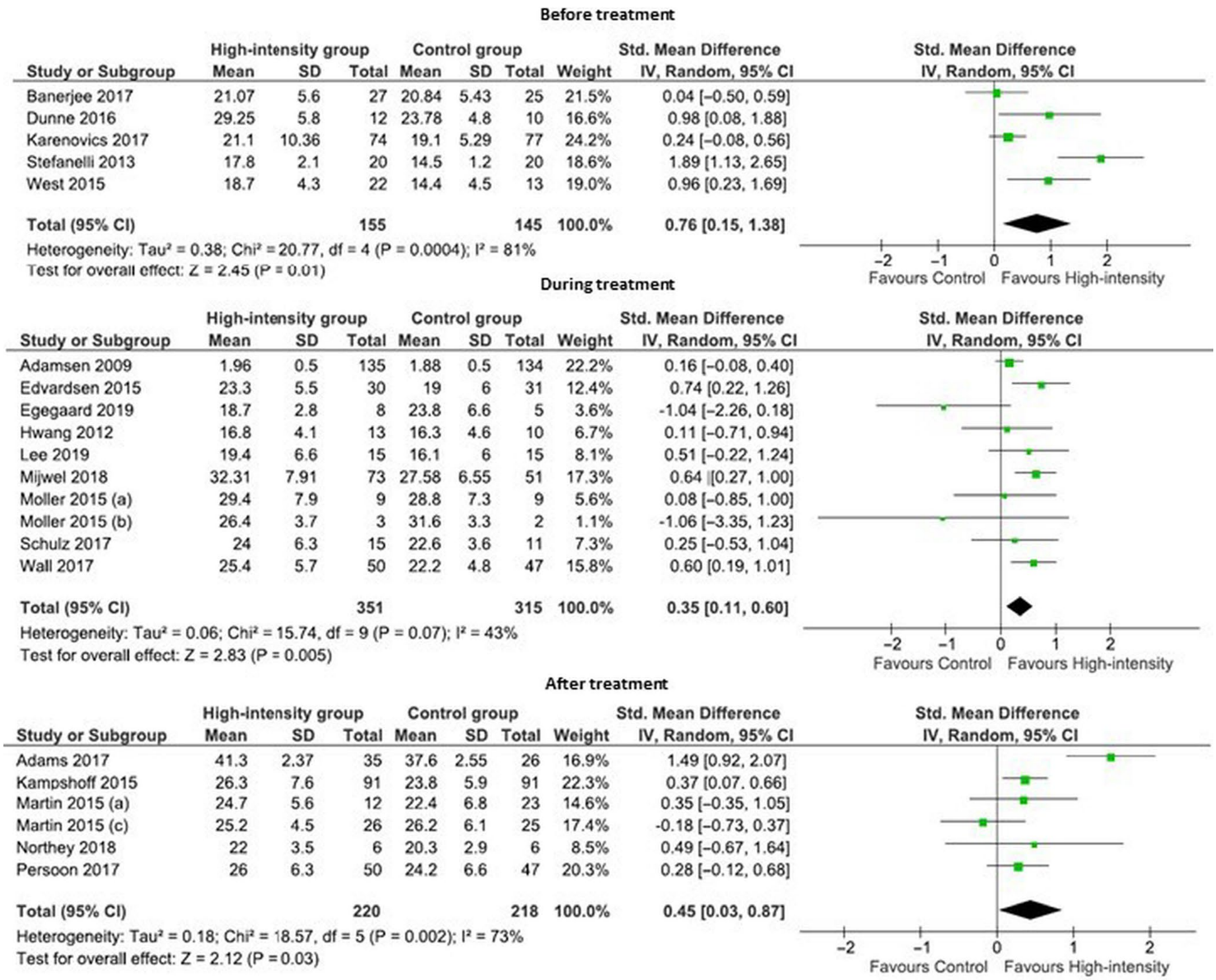


FIGURE 4 Effects of high-intensity exercise in cardiorespiratory fitness according to the treatment timing

SMD = 0.62 with 95% CI from 0.36 to 0.89). Looking for the optimal number of minutes of high intensity, Figure 7 shows HIT (principal part of the session) of less than 20 minutes shows small effect size (P = .003; SMD = 0.32 with 95% CI from 0.11 to 0.54) in contrast to the low-moderate effect achieved by interventions with a high-intensity part of 20 or more minutes (P = .02; SMD = 0.40 with 95% CI from 0.06 to 0.74).

4 | DISCUSSION

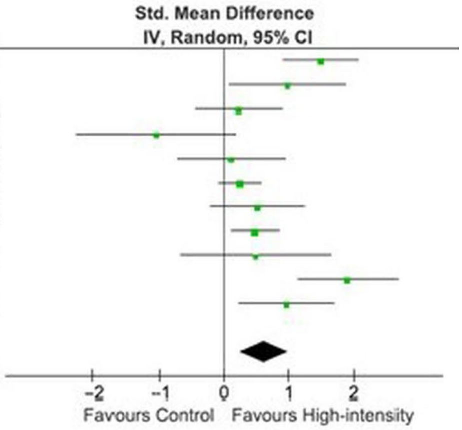
This systematic review and meta-analysis aimed to evaluate the effects of HIT on the CRFit of cancer patients and survivors. In addition, the study also aimed to identify the most effective high-intensity dose to achieve the greatest improvement in CRFit outcomes. Data showed that HIT significantly improves VO_{2peak} compared to an inactive control group, but there was difference in effect compared to moderate-intensity exercise. Regarding the most effective characteristics of exercise programs (Figure 8), HIT showed significant improvements in all phases of cancer treatment. The largest effect was seen in those interventions conducted before cancer treatment. A small effect was observed in interventions delivered during treatment, and a moderate effect in interventions after treatment. HIT interventions that were longer in duration than eight weeks were of at least 20 minutes, and included cardiovascular training component, were most effective in promoting improvements in CRFit. The largest VO_{2peak} improvement was reported in studies that focused on cardiovascular exercise modes, including cycling or running.

The assessment of CRFit is valuable in almost all health areas given the evidence based between low levels of VO_{2peak} and high risk of cardiovascular disease or mortality,[73] in addition to the association with mortality rates attributable to cancer.[74] Specifically, the American Heart Association showed that low CRFit level (<5 METs) in adults is linked

High-intensity aerobic training

Study or Subgroup	High-intensity group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adams 2017	41.3	2.37	35	37.6	2.55	26	10.5%	1.49 [0.92, 2.07]
Dolan 2016	29.25	5.8	12	23.78	4.8	10	7.7%	0.98 [0.08, 1.88]
Dunne 2016	19.6	3.8	19	18.7	4.1	16	9.7%	0.22 [−0.44, 0.89]
Egegaard 2019	18.7	2.8	8	23.8	6.6	5	5.7%	−1.04 [−2.26, 0.18]
Hwang 2012	16.8	4.1	13	16.3	4.6	10	8.3%	0.11 [−0.71, 0.94]
Karenovics 2017	21.1	10.36	74	19.1	5.29	77	12.7%	0.24 [−0.08, 0.56]
Lee 2019	19.4	6.6	15	16.1	6	15	9.1%	0.51 [−0.22, 1.24]
Mijwel 2018	30.63	6.29	70	27.58	6.58	51	12.3%	0.47 [0.11, 0.84]
Northey 2018	22	3.5	6	20.3	2.9	6	6.0%	0.49 [−0.67, 1.64]
Stefanelli 2013	17.8	2.1	20	14.5	1.2	20	8.9%	1.89 [1.13, 2.65]
West 2015	18.7	4.3	22	14.4	4.5	13	9.2%	0.96 [0.23, 1.69]
Total (95% CI)			**294**			**249**	**100.0%**	**0.63 [0.25, 1.00]**

Heterogeneity: Tau² = 0.26; Chi² = 36.67, df = 10 (P < 0.0001); I² = 73%
Test for overall effect: Z = 3.27 (P = 0.001)



High-intensity + resistance training

Study or Subgroup	High-intensity group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adamsen 2009	1.96	0.5	135	1.88	0.5	134	19.2%	0.16 [−0.08, 0.40]
Banerjee 2017	21.07	5.6	27	20.84	5.43	25	6.8%	0.04 [−0.50, 0.59]
Edvardsen 2015	23.3	5.5	30	19	6	31	7.3%	0.74 [0.22, 1.26]
Kampshoff 2015	26.3	7.6	91	23.8	5.9	91	15.7%	0.37 [0.07, 0.66]
Martin 2015 (a)	24.7	5.6	12	22.4	6.8	23	4.4%	0.35 [−0.35, 1.05]
Martin 2015 (c)	25.2	4.5	26	26.2	6.1	25	6.6%	−0.18 [−0.73, 0.37]
Mijwel 2018	32.31	7.91	73	27.58	6.55	51	12.0%	0.64 [0.27, 1.00]
Moller 2015 (a)	29.4	7.9	9	28.8	7.3	9	2.7%	0.08 [−0.85, 1.00]
Moller 2015 (b)	26.4	3.7	3	31.6	3.3	2	0.5%	−1.06 [−3.35, 1.23]
Persoon 2017	26	6.3	50	24.2	6.6	47	10.7%	0.28 [−0.12, 0.68]
Schulz 2017	24	6.3	15	22.6	3.6	11	3.6%	0.25 [−0.53, 1.04]
Wall 2017	25.4	5.7	50	22.2	4.8	47	10.4%	0.60 [0.19, 1.01]
Total (95% CI)			**521**			**496**	**100.0%**	**0.32 [0.17, 0.48]**

Heterogeneity: Tau² = 0.02; Chi² = 14.96, df = 11 (P = 0.18); I² = 26%
Test for overall effect: Z = 4.01 (P < 0.0001)

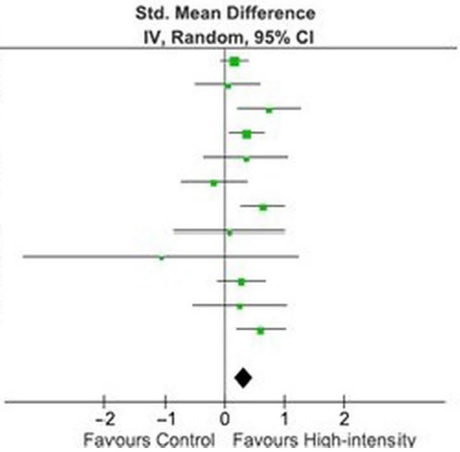


FIGURE 5 Effects of the type of exercise in cardiorespiratory fitness

to high risk for mortality, while higher CRFit levels (>8 to 10 METs) considerably reduce the risks.[75] Three of the included articles involved patients with baseline VO_{2peak} < 5 METs,[49,50,65] which suggests a high risk of mortality. In this regard, the highest SMD among all studies was observed in one of these three studies.[65] Therefore, the current meta-analysis demonstrates that high-intensity exercise can improve CRFit in cancer patients particularly when patients have low baseline levels which thereby produces the greatest public health benefit. This affirmation is highly relevant regarding that the association between physical activity and mortality is even larger among people with lower CRFit levels than those in the higher values as it proved a study with 498 135 biobank participants.[76]

A previous review by Mugele et al[41] found that HIT did not achieve higher benefits in CRFit than moderate-intensity training, which is confirmed here with a larger sample. However, exercising at high intensities provides a higher glycolytic metabolism,[77] inducing a decrease of intratumoral lactate concentration.[78] This physiological process is highly important due to exercise lactate reverts intratumoral lactate gradient inhibiting the production after exercise and decreasing its tumoral concentration according to the Warburg effect.[79] Consequently, inside the microenvironment, blood flow and 0_2 increases, as well as the blood perfusion, leading to a reduction in the hypoxia.[79] Moreover, HIT moderate the overexpression of reactive oxygen species limiting the tumor growth and inflammation.[80]

This meta-analysis showed that breast and lung cancer patients could benefit from HIT. This finding was also observed in previous literature reviews, including all types of intensity interventions in breast[20,81] and lung cancers.[82] Our results show, however, that the timing of the HIT according to the different phases of cancer treatments may be an important variable to consider. To our knowledge, this has not been investigated by previous reviews, with these results showing that the largest effects on CRFit are produced before the initiation of cancer treatment. This enhancement in prehabilitation is crucial as it could potentially improve the response to chemotherapy and prognosis[83] positively influence future cancer complication by infertility the tumoral microenvironment,[84] and reduce inflammation by decreasing potential overweight or obesity.[85] During treatment, improvements in CRFit have a smaller effect, which may be in part due to the negative effects of the treatment itself[8,86] (eg, the cardiotoxicity and heart damage) caused by cancer-treating drugs.[13]

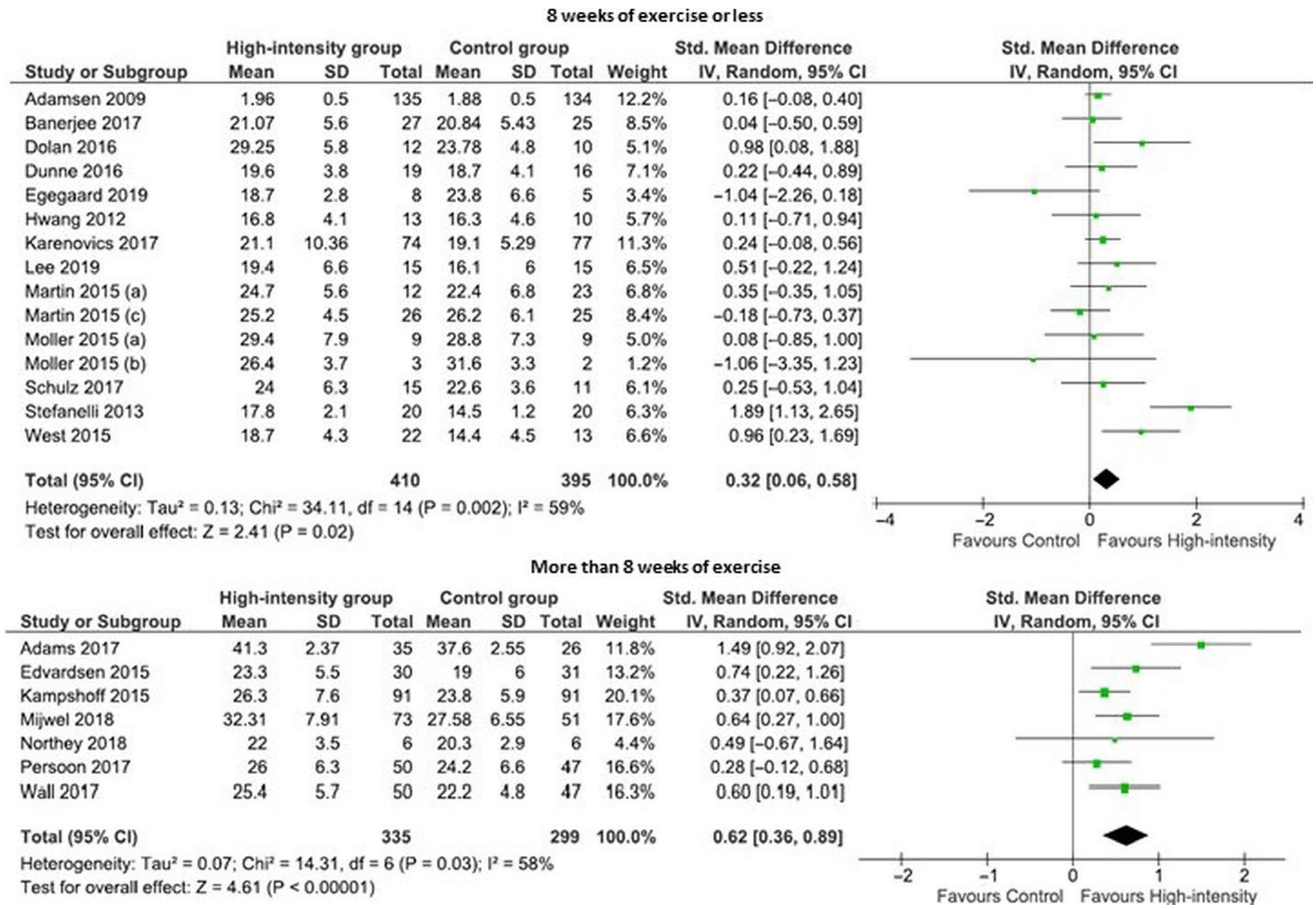


FIGURE 6 Effects of the intervention duration in cardiorespiratory fitness

After therapy, the aim is to increase CRFit, where possible beyond baseline and to avoid its decline even several years after[87] and to avoid the development of cardiovascular risk factors.[88] However, not all cancer treatments are so likely to decline CRFit, but exercise may still play an important role due to it stimulates the upregulation of immune cells pathways (specially natural killers) associated with a reduction in tumor growth and better cancer prognosis and response to immunotherapy.[89]

To our knowledge, this is the first meta-analysis to evaluate the effects of HIT on CRFit that includes resistance training. Our results showed that HIT including resistance training achieved smaller improvements in CRFit. It is important to note that resistance training based interventions as they enhance muscle function and send signs to positively modify the mentioned cancer microenvironment.[84] Furthermore, other benefits of resistance training include the avoidance of sarcopenia,[90,91] preventing the loss of muscle mass and muscle functionality caused by chemotherapy[92,93]; the reduction of myomatosis and chronic inflammation[94]; the decrease in free oxidative radicals and oxidative stress[95]; or the reduction of cardiovascular disease mortality[96] and all-cause of deaths.[97] However, the difference could be explained because of cardiovascular training interventions having higher adherence rates than interventions with resistance components. Future research may need to focus on strategies to enhance adherence in interventions with resistance components which might result in more substantial benefits.

High-intensity training interventions lasting more than eight weeks had a stronger effect in comparison with shorter programs that achieved small effects. In this regard, Toohey et al suggested that high-intensity programs must last at least four weeks in cancer survivors.[40] The number of studies included in this meta-analysis that involved programs of four or fewer weeks was not enough to reach the same conclusion. Regarding HIT components, the concrete high-intensity session duration (including movement and rest) was studied, and results revealed that sessions with a high-intensity part of 20 minutes or more could lead to slightly better results than shorter ones.

The current systematic review and meta-analysis has limitations. Firstly, the included articles had to be written in English or Spanish and indexed in PubMed or Web of Sciences (which includes all journals indexed in the Journal of Citation Reports), so eligible studies may have been omitted. Secondly, the information reported in some of the

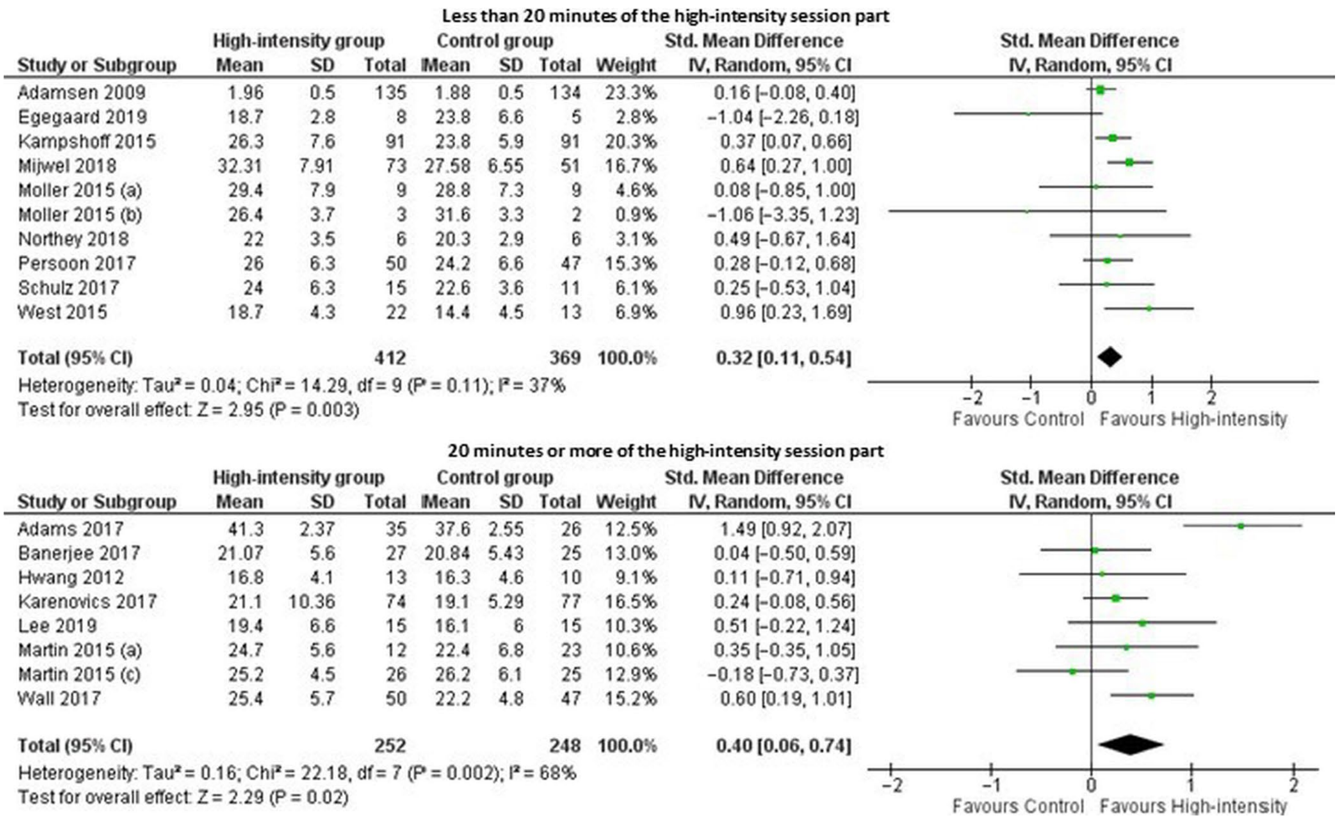


FIGURE 7 Effects of the high-intensity part of session duration in cardiorespiratory fitness

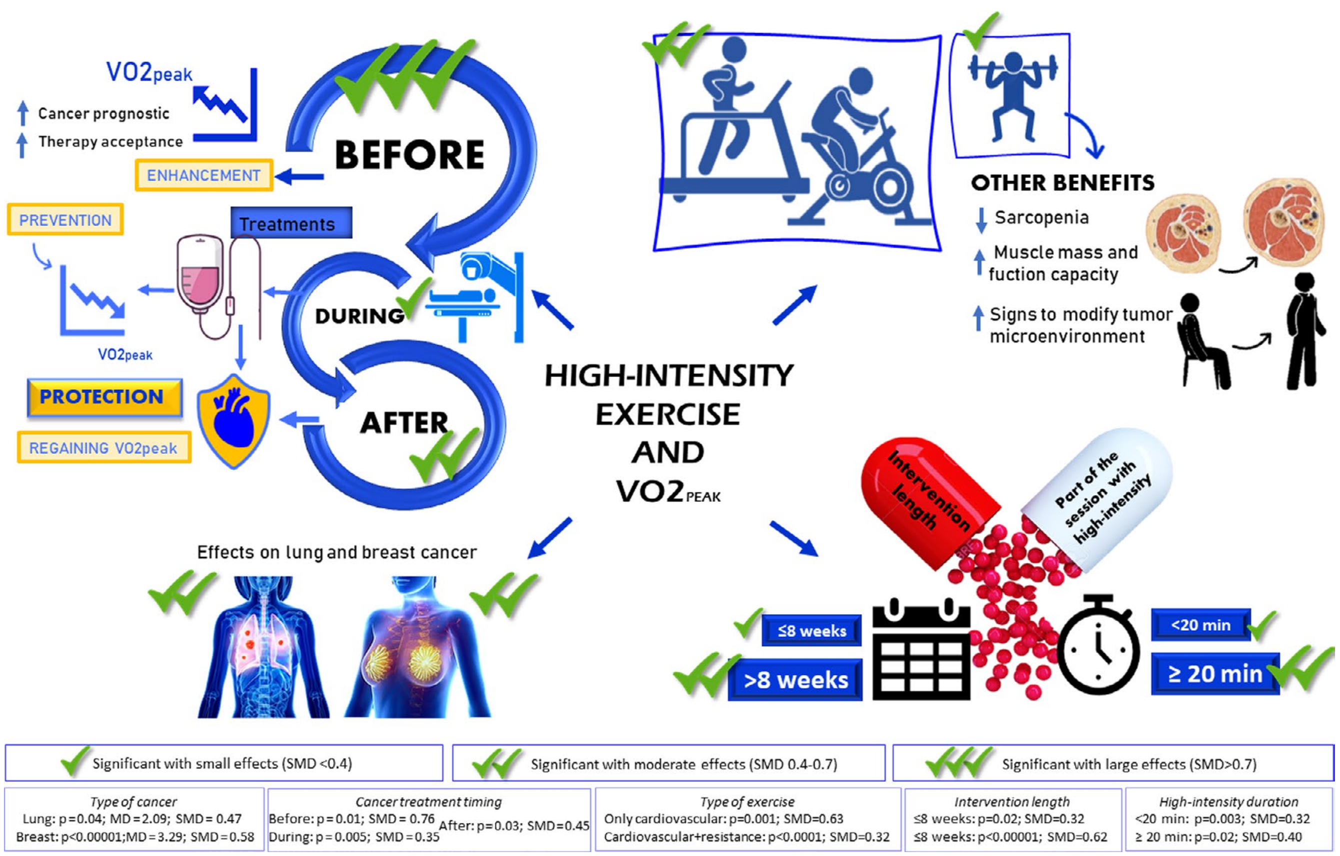


FIGURE 8 Summary of high-intensity exercise effects in cancer patients' cardiorespiratory fitness

articles was not enough to be included in the meta-analysis or the subgroup analyses. Thirdly, the number of studies did not allow to compute a meta-analysis in other cancer types and to make subgroups for each cancer type. Finally, it must be noted that the HIT optimal program characteristics were obtained including both cancer patients and survivors mixed in the meta-analyses, which could influence the results.

4.1 | Perspective

Given that CRFit is associated with cancer patients' survivorship, health, and quality of life, the identification of the most beneficial physical exercise intervention is of great interest. This meta-analysis, in contrast to the previous reviews,[40,41] went further by offering details about the specific characteristics of exercise programs to achieve the larger CRFit improvements. The present recommendations (ie, training before cancer treatment with programs of more than 8 weeks and with a HIT part of at least 20 minutes), based on the existing scientific evidence, can also help healthcare and physical exercise professionals to prescribe adequate high-intensity exercises for cancer patients. Future studies may focus on the evaluation of the exercise dose-response depending on the type of cancer and the treatment received, as well as to better explore the differences between HIT and moderate-intensity exercise.

5 | CONCLUSIONS

High-intensity training leads to positive effects on CRFit in cancer patients and survivors. The Research showed that high-intensity exercise had greater effects in patients initiating exercise before treatment. Although high-intensity exercise had positive but smaller effects during and after treatment, HIT exercise programs should last more than 8 weeks and include at least 20 minutes of high-intensity activity. Although the results showed that the CRFit effects of adding resistance training to HIT might be limited, it is still recommended for the many other health benefits. Further research is needed to provide additional conclusions about the optimal characteristics of high-intensity exercise programs in each specific cancer type.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Ana Myriam Lavín-Pérez https://orcid.org/0000-0001-9357-9987

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SUPPORTING INFORMATION

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

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