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REVIEW ARTICLE

Effectiveness of exercise training on cancer-related fatigue in colorectal cancer survivors: a systematic review and meta-analysis of randomized controlled trials

Pedro Machado[1,2,4] · Miguel Morgado[4] · João Raposo[4] · Marco Mendes[4] · Cândida G. Silva[1,4,5] · Nuno Morais[1,3,4,6]

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Abstract

fPurpose To investigate the effects of exercise training on cancer-related fatigue (CRF) in colorectal cancer survivors.

Methods Randomized controlled trials published between 1 January 2010 and 19 October 2020, selected through online search conducted in PubMed, Scopus, Web of Science, SPORTDiscus and PEDro databases, were included. Eligible trials compared the effect of exercise training interventions, versus non-exercise controls on CRF, in colorectal cancer survivors, during or after treatment. The methodological quality of individual studies was analysed using the Physiotherapy Evidence Database (PEDro) scale. Standardized mean differences (SMD) that were pooled using random-effects models were included as the effect size. In addition, 95% prediction intervals (PI) were calculated.

Results Six trials involving 330 colorectal cancer patients met the inclusion criteria and presented reasonable to good methodological quality. An overall small-to-moderate effect of exercise training on CRF was found ($SMD = -0.29$: 95% CI: [−0.53; −0.06]; $p = 0.01$; PI: [−0.63; 0.04]; low-quality evidence). Subgroup analysis revealed moderate effects of exercise interventions performed during chemotherapy ($SMD = -0.63$; 95% CI: [−1.06; −0.21]; $p = 0.003$) and small, non-significant effects, when exercise training was performed after cancer treatment ($SMD = -0.14$; 95% CI: [−0.43; 0.14]; $p = 0.32$). Steady improvements were achieved when a combination of aerobic plus resistance exercise was used, in interventions lasting 12 to 24 weeks.

Conclusion Exercise training could be regarded as a supportive therapy for the clinical management of CRF in colorectal cancer patients undergoing chemotherapy, but further studies are necessary to clarify the effects of exercise interventions on CRF after cancer treatment.

Keywords Colorectal cancer · Fatigue · Oncology · Physical activity · Rehabilitation · Exercise training

✉ Pedro Machado
pedro.machado@ipleiria.pt

[1] Center for Innovative Care and Health Technology (ciTechCare), Polytechnic of Leiria, Leiria, Portugal

[2] University of Coimbra, Research Unit for Sport and Physical Activity (CIDAF, UID/PTD/04213/2019), Faculty of Sport Sciences and Physical Education, Coimbra, Portugal

[3] Saúde Positiva, Clínica de Saúde Física e Mental, Aveiro, Portugal

[4] School of Health Sciences (ESSLei), Polytechnic of Leiria, Leiria, Portugal

[5] Coimbra Chemistry Centre, Institute of Molecular Sciences (CQC-IMS), Department of Chemistry, University of Coimbra, Coimbra, Portugal

[6] Centre for Rapid and Sustainable Product Development (CDRSP), Polytechnic of Leiria, Marinha Grande, Portugal

Introduction

The epidemiologic relevance of cancer is growing worldwide. Over 19 million new cases were estimated in 2020 and previsions are showing that these numbers will continue to increase, up to 28.4 million of new cancer cases in 2040 [1].

Colorectal cancer (CRC) is the second leading cause of cancer death and the third most commonly diagnosed form of cancer globally, comprising 10% of all cancer diagnoses [1]. With improvements in survival being consistently demonstrated [2–4], the burden of CRC is expected to increase in the future, which has led oncology research and health systems increasingly concerned about symptoms that interfere with the quality of life of these patients [5–9].

One of the most prevalent and distressing symptoms affecting the quality of life of CRC patients is cancer-related fatigue (CRF) [8, 10]. CRF has been described as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with functioning" [6]. Patients with cancer frequently report CRF as the symptom that mostly disturbs their daily life, even more than pain or nausea, which can generally be managed by medication [11]. CRF, on the other hand, is often undiagnosed, left untreated or poorly managed [6].

In CRC survivors, fatigue is present in approximately half of patients with localized tumours, and in 2/3 of those with metastatic/recurrent disease [10]. This debilitating symptom usually peaks immediately after adjuvant chemotherapy, being experienced by 70% of patients, but remains a significant problem until 10-year post-diagnosis, persisting in 39% of long-term CRC survivors [10, 12]. In this view, efforts to better manage this symptom throughout the trajectory of the disease are now considered a high priority in clinical practice [6, 8].

Current clinical guidelines for supportive care in oncology [6, 13] recommend exercise training, as an effective intervention in preventing or improving CRF, during active and post-treatment phases. The claims of beneficial effects of exercise training on this symptom, however, have been mainly demonstrated in patients with breast cancer, advising caution in extrapolating this recommendation to other types of cancer [14–17]. In fact, the value of Clinical Practice Guidelines [6] is disputed in this regard because a systematic review published in 2014 found no valuable short- or long-term effects of exercise training in CRC [18]. However, the results from that review have been pooled from a limited and small number of eligible trials [18], and, more recently, two systematic reviews integrating new studies about this topic found that exercise training leads to improvements in fatigue symptoms among CRC survivors [19, 20].

The strength of these findings was however limited by the inclusion of clinical trials combining exercise training with health education and dietary interventions [19, 20], which could have influenced the effect estimates given that these interventions may also improve CRF [21–23]. In addition, none of these reviews performed a subgroup analysis exploring whether exercise training effect differs between patients during and following CRC treatment. This could be clinically relevant because CRF is more severe during chemotherapy [10], and the effect of exercise training is predictively larger in cancer patients with higher fatigue levels [24]. Lastly, despite the recommendations to routinely report prediction interval in meta-analysis, representing the most sensible way to summarize the results of heterogeneous studies and allowing more robust conclusions [25–27], previous systematic reviews only reported summary effect size combined with a confidence interval [19, 20], which is considered insufficient for clinical decision making since it only summarizes the average treatment effect [27].

Taken together, these limitations justify an updated systematic review and meta-analysis, reporting the prediction interval in addition to the summary estimate that will illustrate which range of true effects can be expected in future clinical trials and including a subgroup analysis aiming to investigate if the exercise training effect on CRF varies between patients during and after CRC treatment.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. (PRISMA) [28].

Protocol and registration

The protocol for this systematic review and meta-analysis was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO) (record no. CRD42020206435).

Eligibility criteria

The eligibility criteria were developed using the participants, intervention, comparator, outcome and type of study (PICOS) approach [29].

Participants

Adult (≥ 18 years of age) colorectal cancer survivors were defined by the Nacional Cancer Institute: an individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life [30].

Intervention

Exercise training was defined as a type of physical activity that consists of a well-defined and structured plan that aims to increase or maintain the person's physical conditioning [15]. Studies in which the experimental group combined exercise training with another type of intervention (e.g. cognitive-behavioural therapy or nutrition) were excluded.

Comparison

Participants receiving usual care, with no exercise training (e.g. chemotherapy/radiotherapy or instructions for the continuation of usual activities).

Outcome

The selected studies should have collected, as a primary or secondary outcome, the intensity of fatigue by means of a self-reported measure for cancer patients [6, 31].

Type of studies

Only randomized controlled trials (RCTs), published in English, between January 1, 2010 (year of publication of the first physical activity guidelines for cancer survivors by the American College of Sports Medicine) [32], and October 19, 2020, were considered. Feasibility trials were excluded. It was also defined the possibility of including studies that, in addition to patients with CRC, integrated participants with other types of cancer, if these studies performed a subgroup analysis that assessed the intensity of CRF specifically for patients with CRC.

Search strategy

Relevant studies were searched using a combination of the following free-text words: exercise OR "physical activity" OR "aerobic training" OR "resistance training" OR "strength training" AND "cancer-related fatigue" OR "cancer related fatigue" OR fatigue AND colorectal OR colon OR rectal, in the electronic databases the Physiotherapy Evidence Database (PEDro), PubMed, Scopus, Web of Science and SPORTDiscus. Searches were limited to articles published in English language. The first and second authors (PM and MM) conducted the search on the platforms within the same week, to ensure that the articles were obtained in the same time period. Detailed information about the search strategy is provided in Online Resource 1.

Identification and selection of studies

Records retrieved by the searches were imported into the software EndNote X8 (Thompson Reuters, San Francisco, CA, USA) and duplicates were removed. Studies' selection procedure was performed in two phases by two independent reviewers (PM and MM). First, the titles and abstracts were screened using a hierarchical approach for exclusions: study design (RCT), intervention (exercise training), population (CRC patients) and outcome (CRF assessment tool). If one reviewer recognized that a potential article met the inclusion criteria or if there was insufficient information to decide on the inclusion or exclusion, the article was retained to the second screening phase. Subsequently, a full text reading procedure was followed in this screening phase. Studies that had been identified by mutual consent were included in the review. In case of disagreement between the reviewers, an independent third reviewer (JR) appraised the article, and the final decision was a combination of the three evaluations. The Cohen's kappa coefficient was calculated to evaluate interrater reliability in the initial and full text screenings [33]. Kappa values ≤ 0 suggest no agreement between reviewers, 0.01–0.20 none to slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81–1.00 as almost perfect agreement [33].

Data extraction

Data were extracted using a standardized form for each article. The extracted data included the following topics: (1) studies characteristics, (2) participant's demographics and clinical characteristics, (3) exercise training dose, (4) CRF severity and measurement tool. Data extraction was independently performed by two reviewers (JR and MM) with any discrepancies being resolved through discussion with a third reviewer (PM). When information regarding any of the above topics was unclear, the authors of the original reports were contacted to provide details. Data were recorded in a spreadsheet and results were summarized for comparison between studies.

Assessment of the methodological quality of included studies

Two reviewers (PM and MM) independently appraised the methodological quality of the studies included using PEDro scale [34]. Any disagreement on eligibility was resolved through discussion with another reviewer (CS). PEDro scale comprises 11 items rated with 0 or 1: Eligibility criteria, randomized allocation, hidden allocation, baseline comparison between groups, participants, physiotherapists and blind assessors, adequate follow-up, intention to treat the analysis, comparison between groups and point estimate and variability.

Based on these items, a score of 0 to 10 is attributed to the RCTs (eligibility criteria not accountable). According to the PEDro scale, studies with a score of 0 to 3 have a "poor" methodological quality, between 4 to 5 "reasonable", 6 to 8 "good" and 9 to 10 "excellent" [34].

Data analysis and synthesis of results

To summarize and compare studies, mean and standard deviation (SD) values of CRF scores were directly pooled and analysed with standardized mean differences (SMDs) and 95% confidence intervals (CIs) [35]. Additionally, prediction intervals (PI) were calculated for the purpose of estimating the treatment effect in future clinical trials [25–27].

In cases where higher scores represented lower fatigue levels, the mean value was subtracted from the maximum possible value of the scale to ensure that all the scales varied in the same direction throughout the analysis. For interpretation, an SMD of 0.2 represents a "small" effect, an SMD of 0.5 represents a "medium" effect and an SMD of 0.8 represents a "large" effect.

Study-specific estimates were pooled with random-effect models. The statistical heterogeneity among studies was assessed using the I^2 index [36]. This index represents the percentage of variation in the global estimate that is attributable to heterogeneity ($I^2 = 25\%$: low; $I^2 = 50\%$: moderate; $I^2 = 75\%$: high heterogeneity).

Forest plots were created to visually illustrate the effects in the meta-analysis of the different studies and the global estimation. Considering that CRF is expected to peak during chemotherapy treatment [10, 37], and that the effect of exercise training is predictively larger in cancer patients with worse baseline fatigue levels [24], a subgroup analysis was performed to differentiate the effectiveness of exercise training in in patients receiving chemotherapy treatment and in the post-treatment phase. R [38] and RStudio [39] were used to perform all analyses. R package meta was used to conduct standard meta-analysis [40]. Statistical significance was defined as a p-value < 0.05.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of evidence [41]. Evidence was downgraded if there were

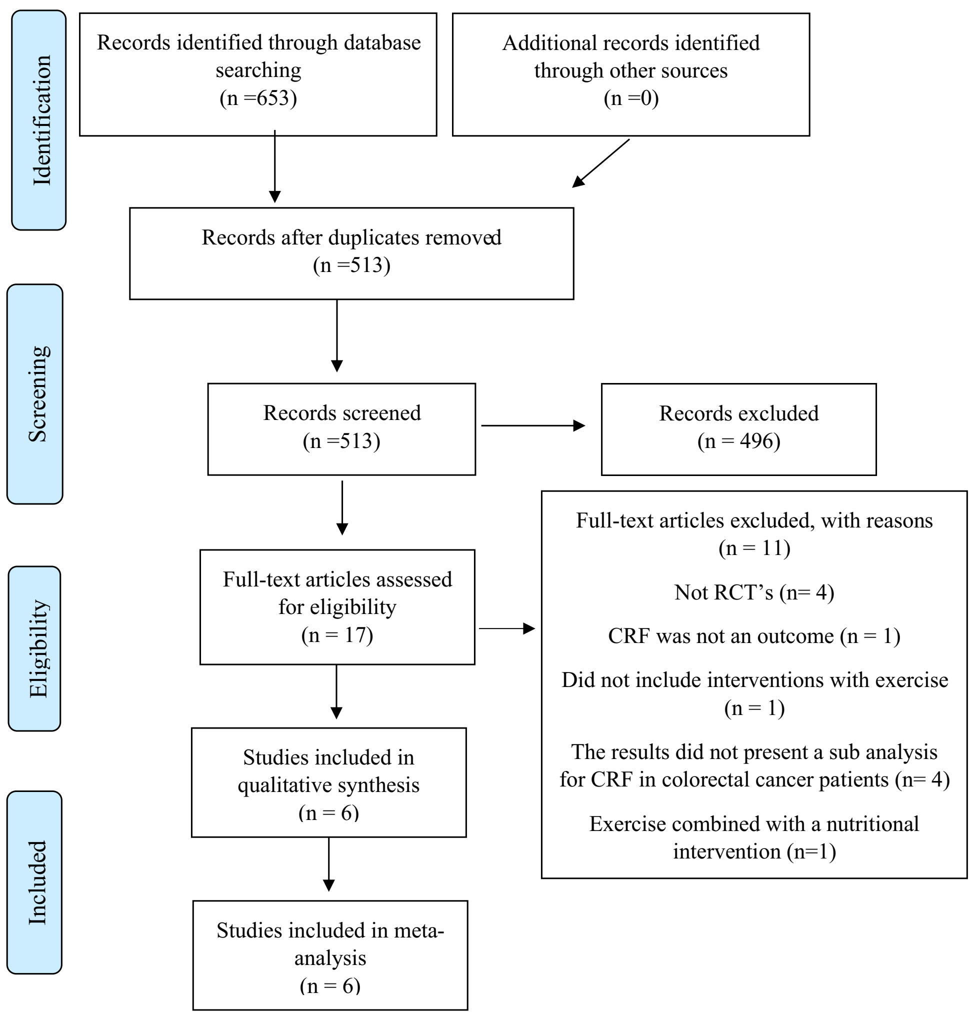

Fig. 1 PRISMA flowchart of process of identification of eligible studies. Abbreviations: CRF, cancer-related fatigue; RCT, randomized controlled trial

Table 1 Characteristics of the included studies

Leading author, year	Sample size (n)/ sex (male (M); female(F))	Tumour stage/treatment status	Intervention group (I.G.)	Control group (C.G.)	Instrument to assess CRF	Outcome comparison with control group (without exercise)
Lu, 2019 [50]	I.G. ($n=43$) $M=26$; $F=17$ C.G. ($n=44$) $M=30$; $F=14$	Stage I, II, III During cancer treatment: adjuvant chemotherapy with CAPOX (22%), FOLFOX (52%) and FOLFIRI (26%)	Baduanjin qigong exercise	Usual care for CRF control (NCCN Guidelines. Version 2. 2018)	Brief Fatigue Inventory (BFI)	Significant improvement in CRF at 24 weeks with no significant difference between the two groups at 12 weeks
Kim, 2019 [49]	I.G. ($n=37$) $M=18$; $F=19$ C.G. ($n=34$) $M=17$; $F=17$	Stage II, III After cancer treatment: previous treatment with surgery and adjuvant chemotherapy	Home-based exercise programme (aerobic and resistance exercise)	Instruction for the continuation of the usual activities	Functional Assessment of Cancer Therapy: Fatigue (FACT-F)	Significant improvement in CRF
Brown, 2018 [47]	I.G.1 ($n=14$) $M=7$; $F=7$ I.G.2 ($n=12$) $M=4$; $F=8$ C.G. ($n=13$) $M=4$; $F=9$	Stage I, III After cancer treatment: 72% of patients previously treated with adjuvant chemotherapy	Home-based exercise programme I.G.1: low-dose aerobic exercise — 150 min/week I.G.2: high-dose aerobic exercise — 300 min/week	Usual care (maintain physical activity levels or follow the physician recommendations)	Fatigue Symptom Inventory (FSI)	Significant improvement in CRF only in the group that performed the highest aerobic exercise dose (300 min)
Van Vulpen, 2016 [52]	I.G. ($n=17$) C.G. ($n=16$) $M=21$; $F=12$	Stage I-III During cancer treatment: adjuvant chemotherapy with capecitabine (12%) and CAPOX (88%)	Aerobic and resistance exercise supervised by a physiotherapist	Usual care (chemotherapy and radiotherapy) Instruction for the continuation of the usual activities	Dutch version (Multidimensional Fatigue Inventory (MFI) e Fatigue Quality List (FQL)	Significant improvement in physical fatigue at 18 weeks and general fatigue at 36 weeks in the intervention group
Cramer, 2016 [48]	I.G ($n=27$) C.G ($n=27$) $M=33$; $F=21$	Stage I-III 96.3% of patients after cancer treatment: previous treatment with surgery, chemotherapy (46%) and radiotherapy (22%)	Hatha yoga	Instruction for the continuation of the usual activities	FACT-F	No significant improvement in CRF between the two groups
Pinto, 2013 [51]	I.G. ($n=20$) C.G. ($n=26$) $M=20$; $F=26$	Stage I-III After cancer treatment: previous treatment with surgery, chemotherapy (73%) and radiotherapy (35%)	Home-based exercise programme (aerobic exercise)	Weekly telephone contact for symptom monitoring and distribution of information leaflets	FACT-F	No significant improvement in CRF between the two groups at 12 weeks, 24 weeks and 48 weeks

issues with risk of bias across studies, inconsistency of results, publication bias, imprecision and indirectness, according to the recommendations of the GRADE Working Group [42–46].

Results

Study selection

The flowchart of the search, screening and selection of study process is presented in Fig. 1. A total of 663 records were obtained from the electronic databases. After removing duplicates, 513 records remained. Screening based on the title and abstract resulted in the selection of 17 articles. Of these 17 records, 11 articles were excluded following the evaluation of the full text because eligibility criteria were not verified. Six studies met the eligibility criteria and were included in the qualitative and quantitative syntheses [47–52]. Agreement between reviewers on title/abstracts (kappa = 0.87) and full text (kappa = 0.72) screenings was strong and moderate, respectively.

Study characteristics

Table 1 describes the characteristics of the included studies. A total of 330 CRC survivors participated in these studies: 170 individuals were allocated to the intervention group (exercise training), and 160 were in the control group. All patients were diagnosed with histologically confirmed non-metastatic CRC (tumour stage I–III).

In three studies ($n = 156$), exercise training was delivered after CRC treatment [47, 49, 51]. In one study ($n = 54$), 3.7% of the participants were undergoing adjuvant chemotherapy and the remaining were not receiving any type of treatment [48]. In the other two studies ($n = 120$), all participants were undergoing adjuvant chemotherapy treatment during the intervention [50, 52]. Control groups received usual care that, in addition to standard CRC treatment, consisted in, advising patients to continuing their usual activities [48, 49, 52] or maintaining their physical activity levels [47], delivering education sessions about CRF [50], distributing information leaflets and calling participants for symptom monitoring [51].

Methodological quality of the studies

The six studies included were evaluated following the 11 items of the PEDro scale (Table 2). Three of the included studies [48, 51, 52] presented a good methodological quality (score of 6 and 7) and the remaining three [47, 50] had a reasonable methodological quality (score of 5). Only two study performed a hidden allocation [48, 52].

Table 2 Results of the assessment of methodological quality of individual studies

Author, year	Eligibility criteria	Randomized allocation	Hidden allocation	Baseline comparison between groups	Blind participants	Blind Physical Therapists	Blind assessors	Proper follow-up	Intention to treat analysis	Comparison between groups	Point estimate and variability	Total score
Lu, 2019 [50]	✓	✓	×	✓	×	×	×	✓	×	✓	✓	5/10
Kim, 2019 [49]	×	✓	×	✓	×	×	×	×	✓	✓	✓	5/10
Brown, 2018 [47]	✓	✓	×	✓	×	×	×	✓	×	✓	✓	5/10
Van Vulpen, 2016 [52]	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	7/10
Cramer, 2016 [48]	✓	✓	✓	✓	×	×	×	×	✓	✓	✓	6/10
Pinto, 2013 [51]	✓	✓	×	✓	×	×	✓	✓	✓	✓	✓	7/10

Table 3 Characteristics of the exercise training intervention

Author, year	Type of supervision	Type of exercise	Frequency (sessions per week)	Intensity (%VO2máx; METs/hour; %HRmax)	Session time	Programme duration (in weeks)
Lu, 2019 [50]	In person	Baduanjin qigong	5	Not reported	20–40 min	24
Kim, 2019 [49]	Telephone and in person	Aerobic Resistance	7	18 METs/h/week until 6th week 27 METs/h/week from 6th until 12th week (10,000 daily steps, including 3000 steps at an intensity above 65% of max HR + DVD w/ muscle strengthening exercises, 3 sets of 5–7 exercises, 12 repetitions)	30 min (DVD w/ muscle strengthening exercises) + time to complete 10,000 daily steps	12
Brown, 2018 [47]	Telephone	Aerobic	Not reported	50−70% of maximum HR estimated for age	150 min/week (low-dose) 300 min/week (high-dose)	24
Van Vulpen, 2016 [52]	In person	Aerobic Resistance	2	Aerobic: Interval training alternating intensity between HR at the level of the ventilatory threshold (measured by CPET) (3 sets × 2 min increasing to 2 sets × 7 min) and periods with HR below ventilatory. Threshold (3 sets × 4 min increasing until 1 set × 7 min) Resistance exercise: (2 sets × 10 repetitions at 65% of 1-RM) with gradual increase until (1 set × 10 reps at 75% 1-RM) and (1 set × 20 reps at 45% 1-RM)	60 min	18
Cramer, 2016 [48]	In person	Hatha yoga	1	Not reported	90 min	10
Pinto, 2013 [51]	Telephone	Aerobic	5	64–6% of max HR	150 min/week	12

Abbreviations: CPET: Cardiopulmonary Exercise Testing; DVD (Digital Versatile Disc); HR (Heart Rate); Max HR (Maximum Heart Rate); MET (Metabolic Equivalent of task); min (minutes); RM (Repetition Maximum);

Intervention characteristics

A detailed description of the exercise training dose prescribed is presented in Table 3. The total duration of the exercise training interventions varied from 18 to 24 weeks in the two studies conducted in CRC patients undergoing chemotherapy [50, 52] and from 10 to 24 weeks in the studies conducted in patients following completion of CRC treatment [47–49, 51]. The type of exercise most commonly prescribed was aerobic exercise (10,000 steps per day or 150–300 min per week at an intensity of 50–75% of the estimated maximum heart rate), which was performed in four of the included studies ($n=100$) [47, 49, 51, 52]. The modes of aerobic exercise were walking, biking and unspecified home-based aerobic exercises [47, 49, 51]. In two studies ($n=54$), a combination of aerobic and resistance exercise was used (2 to 3 sets of 10–20 repetitions, 45–75% 1-maximum repetition [1-RM]), and in both, a significant reduction in CRF was achieved [49, 52]. One study ($n=39$) compared the effect of two different doses of aerobic exercise training on CRF and found that only the group ($n=12$) that performed a high exercise dose (300 min per week with an intensity between 50 and 75% of the estimated maximum heart rate) reached significant reduction in CRF [47]. In the remaining two studies, the type of exercise prescribed was Baduanjin qigong ($n=43$)[50] and Hatha yoga ($n=27$) [48], both characterized by sequences of different body positions in combination with breathing control exercises, being classified as low-intensity exercise training [50]. Of these two types of exercise, only Baduanjin qigong, performed by patients undergoing chemotherapy, achieved significant reductions in CRF, measured at 24 weeks, with no differences between groups at 12 weeks of intervention [50]. The length of the Hatha yoga intervention was 10 weeks and had a low adherence by patients [48].

The progression was identified in three studies [49, 51, 52] and consisted in increasing exercise volume, from 10 min on at least 2 days/week to 30 min on at least 5 days/week [51] or intensity, increasing the time at the ventilatory threshold or progressing from 65 to 75% of 1-RM [52].

Supervision in the intervention programmes varied between weekly telephone-based [51] and presential meetings [48, 50, 52]. In two studies, supervision was carried out by telephone and in-person, during clinical/exercise encounters [47, 49].

The majority of the studies delivered educational sessions and used digital platforms or DVDs to instruct the participants about the exercises to be performed [50–52]. A weekly supervision/encounter between the exercise training specialist and the participants was scheduled to monitor the fulfilment of goals, provide positive reinforcement and implement strategies to overcome barriers that occurred during the programmes [47, 51].

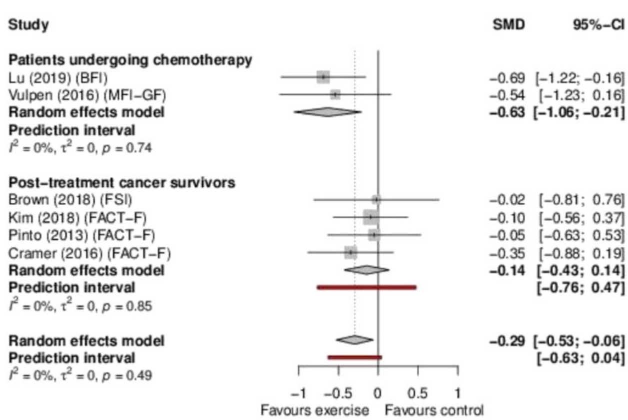

Fig. 2 Forest plot of effect of exercise training on cancer-related fatigue. Abbreviations: BFI, brief fatigue inventory; CI, confidence interval; FACT-F, Functional Assessment of Cancer Therapy — Fatigue; FSI, Fatigue Symptom Inventory; MFI-GF, Multidimensional Fatigue Inventory — General Fatigue; SMD, standardized mean difference

Characteristics of outcome measures

Three of the six studies included applied the Functional Assessment of Cancer Therapy: Fatigue (FACT-F) to evaluate CRF [48, 49, 51]. The others applied three different measurement tools, namely the Brief Fatigue Inventory (BFI) [50], the Fatigue Symptom Inventory (FSI) [47] and the (Multidimensional Fatigue Inventory) MFI [52].

Meta-analysis

Low heterogeneity between studies ($I^2=0\%$) was found both in the global and subgroup analyses (Fig. 2). Globally, a small-to-moderate positive effect of exercise training in patients' fatigue was observed (*SMD* = −0.29: 95% *CI*: [−0.53; −0.06]; $p=0.01$). The prediction interval for SMD ranged from −0.63 to 0.04. Subgroup analysis revealed a moderate-to-large effect of exercise training in

Table 4 GRADE evidence profile

Certainty assessment						No. of patients		Effect	Certainty
No. of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Exercise training	Control group	SMD (95% CI)	
Six (RCT)	Serious[a]	Serious[b]	Not serious	Not serious	Undetected	170	160	−0.29 (95% *CI*: −0.53; −0.03)	⨁⨁◯◯ low

Abbreviations: *CI*, confidence interval); *SMD*, standardized mean difference; *RCT*, randomized controlled trial. [a]Hidden allocation not performed in four studies, outcome assessors not blinded in five studies, not analysed using intention to treat in two studies. [b]Wide prediction interval across studies patients undergoing chemotherapy ($SMD = -0.63$; 95% *CI*: [−1.06; −0.21]; $p = 0.003$; $n = 120$) [50, 52]. In the subgroup of post-treatment CRC survivors, there was uncertainty about the effect of exercise training on CRF ($SMD = -0.14$; 95% *CI*: [−0.43; 0.14]; $p = 0.32$; $n = 180$) [47–49, 51]. The prediction interval in the latter ranged from −0.76 to 0.47.

GRADE assessment

The evidence about the effect of exercise training on CRF was rated as low-quality because most of the included studies presented serious risk of bias due to the lack of hidden allocation [47, 49–51] and unblinded assessors [47–50, 52]. In addition, inconsistency was downgraded because a wide prediction interval was found (−0.63 to 0.04) (Table 4).

Considering the insufficient number of studies to meet rigorous criteria for creating a funnel plot [53], the evaluation of publication bias would be speculative and we decided not rating down the evidence, despite all studies presented small sample sizes [54].

Discussion

The aim of this systematic review and meta-analysis was to investigate the effect of exercise training in CRF among CRC survivors. Our findings suggest that exercise is, globally, an effective intervention to reduce fatigue symptoms in these patients (small-to-moderate effect), however, the robustness of results is challenged by the overall low-quality of the evidence.

Our results are partially in accordance with previous systematic reviews that also found a therapeutic benefit of exercise training on fatigue among CRC survivors [19, 20]. However, by complementing summary effect size with prediction intervals, we provide initial evidence of a large variability in the exercise training effects on CRF in future clinical trials, highlighting the need to identify the subgroup of patients that could benefit most from exercise interventions.

The results of our subgroup-analysis in fact suggest that exercise training may be the most beneficial for patients receiving adjuvant chemotherapy. This is probably related with higher levels of CRF of these patients at baseline [50, 52], as consequence of chemotherapy [10] and in accordance with previous research underlining that the effects of exercise interventions are expectably larger in cancer patients with worse baseline levels of fatigue [24]. Clinically, exercise training could be regarded as a powerful supportive therapy for the management of such prevalent problem in CRC patients undergoing chemotherapy, adding also benefits in other adverse events, such as nausea and gastric reflux [55].

With respect to patients following CRC treatment, the effect of exercise training on CRF was marginal and with wide prediction intervals (−0.76 to 0.47). Hence, the effect of future exercise interventions is unclear at the time. One potential explanation for these unclear results is the fact that the studies included in this subgroup analysis were not designed to target CRC survivors with higher baseline fatigue levels, the subgroup of patients that may obtain stronger benefits from exercise interventions [24]. Additionally, it is likely that higher exercise doses may be required to manage this problem in survivors following CRC treatment. This rationale is supported by one study that compared the effects of two exercise training doses and found that 150 min of weekly aerobic exercise was insufficient to reduce CRF, but a higher exercise volume (300 min per week) significantly improved CRF and quality of life [47]. In another study, 150 min of aerobic exercise per week at 50–70% of peak heart rate was insufficient to improve cardiorespiratory fitness and body composition in CRC survivors, in comparison to a high-intensity exercise training, highlighting the importance of prescribing higher exercise doses in this population to maximise effects [56]. These distinctive effects of exercise training between patients undergoing and after CRC treatment are in agreement with a previous meta-analysis [57]. Grounded mostly in studies conducted in breast and prostate cancer survivors, in that meta-analysis, it was also found beneficial effects of exercise interventions in CRF among patients undergoing active cancer treatment but non-significant differences in patients after anticancer treatment [57]. Therefore, further studies in survivors after CRC treatment are necessary to definitively clarify the effects of exercise training on this symptom. Of great importance, these studies should recruit patients with higher baseline fatigue values [24, 58] and assess the effects of exercise doses superior to 150 min of moderate intensity aerobic exercise to manage this problem.

Based on the results of this review, the dose of exercise training that demonstrated more consistent improvements on CRF was a combination of resistance exercise (2 to 3 sets of 10–20 repetitions, 45–75% 1-maximum repetition [1-RM], for the main muscle groups) with aerobic exercise (10,000 steps per day or 150 min per week at an intensity of 50–75% of the estimated maximum heart rate), in programmes lasting 12 to 24 weeks [49, 52]. This exercise dose is within the standards of the ACSM for the clinical management of CRF [15]. The integration of resistance training on the exercise programmes could be particularly important to mitigate fatigue symptoms in CRC patients because skeletal muscle dysfunction caused by oxaliplatin treatment is possibly involved in the pathogenesis of CRF [59], and resistance training is an effective intervention to improve muscle function among these patients [55].

Other types of exercise training used in two studies integrated in this systematic review [48, 50], such as Hatha yoga and Baduanjin qigong, consisting in performing different postures in combination with breathing control exercises, and categorised as low-intensity exercise, showed contradictory results (Tables 1 and 3). Several factors may have contributed to these findings. Firstly, the exercise programme with Baduanjin qigong, which significantly reduced CRF, was implemented in patients with CRC undergoing chemotherapy, where CRF levels are more severe [10]. It is known that even low-intensity exercise can bring benefits in these patients, as seen in other types of cancer, particularly in women with breast cancer [60]. In the exercise programme of Hatha yoga [48], the low adherence of the participants and the short period of intervention (10 weeks) might have limited the efficacy of this exercise modality. Therefore, at the moment there is an amount of uncertainty that prevents the recommendation of these modalities for the clinical management of CRF in CRC survivors and consequently, additional high-quality research is required to assess the effect of these types of exercise on fatigue symptoms. Finally, it should be emphasized that CRF has many causative elements and is rarely an isolated symptom, occurring most commonly in a symptom cluster [13]. Particularly in CRC patients, the presence of cognitive symptoms, anxiety, depression, increased number of comorbidities and lower haemoglobin was associated with greater fatigue [10]. Therefore, as recommended by clinical guidelines, assess fatigue contributing factors and integrate exercise training in an interdisciplinary approach tailored to the needs of each individual might be clinically relevant to optimally manage this symptom [13].

Strengths and limitations

The strengths of this systematic review rely on the rigorous effort to strictly follow PRISMA guidelines and the clinical relevance in investigating the effect of exercise training on CRF specifically in CRC patients. The selection of studies was performed by two independent reviewers with a strong and moderate agreement on the title/abstract and full text screening, respectively. To eliminate potential confounding factors, studies where exercise was combined with other interventions, like psychological therapy, that also shows beneficial effects on this symptom [61], were excluded. Finally, in addition to traditional effect size statistics, the prediction interval was calculated, which could inform what true effects of exercise training on CRF can be expected in future exercise studies in CRC patients.

Nonetheless, the main findings of this systematic review need to be considered in the context of some key limitations, including the small number of eligible RCTs with small sample sizes which could influence the external validity and increase the possibility of type II error. Although all the included studies were RCTs, only two studies carried out a hidden allocation [48, 52], which could lead to an overestimation of the exercise training effects [62, 63]. Additionally, the heterogeneity of the exercise interventions between the included studies limits more robust recommendations about the exercise training dose that should be prescribed to manage fatigue among CRC survivors.

Clinical implications

Our meta-analysis provided evidence that exercise training is an effective supportive therapy to the clinical management of CRF, especially in patients undergoing chemotherapy. Despite the heterogeneity in the exercise dose prescribed prevents us to recommend a specific amount of exercise to manage CRF, steady improvements were achieved when a combination of aerobic plus resistance exercise was used, in interventions lasting 12 to 24 weeks.

For decision-makers involved in health policies, it should be underlined that exercise training is significantly more effective than the available pharmaceutical options to manage CRF [61] and in addition to its beneficial impact on this problem, the implementation of exercise programs during adjuvant treatment for patients with colon cancer, resulted in a cost saving of 4321 euros, demonstrating to be an effective and cheaper intervention [64].

Conclusion

In CRC survivors, exercise training is an effective intervention to reduce CRF and could be prescribed as a rehabilitation option to the clinical management of this highly prevalent problem, particularly in patients undergoing chemotherapy. Further studies are necessary to clarify the effects of exercise training on CRF after CRC treatment.

This conclusion is based on low-quality evidence; hence, there is a need for more well-designed randomized controlled trials that investigate the effectiveness of exercise training to prevent or reduce CRF in these patients.

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Author contribution All the authors contributed to conceived and the designed the study. PM, MM, JR and MM conducted the screening of studies and data extraction. CS and NM provided statistical expertise and contributed to the analysis, discussion and preparation of manuscript. All authors participated in the revision and final approval of the manuscript.

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Declarations

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