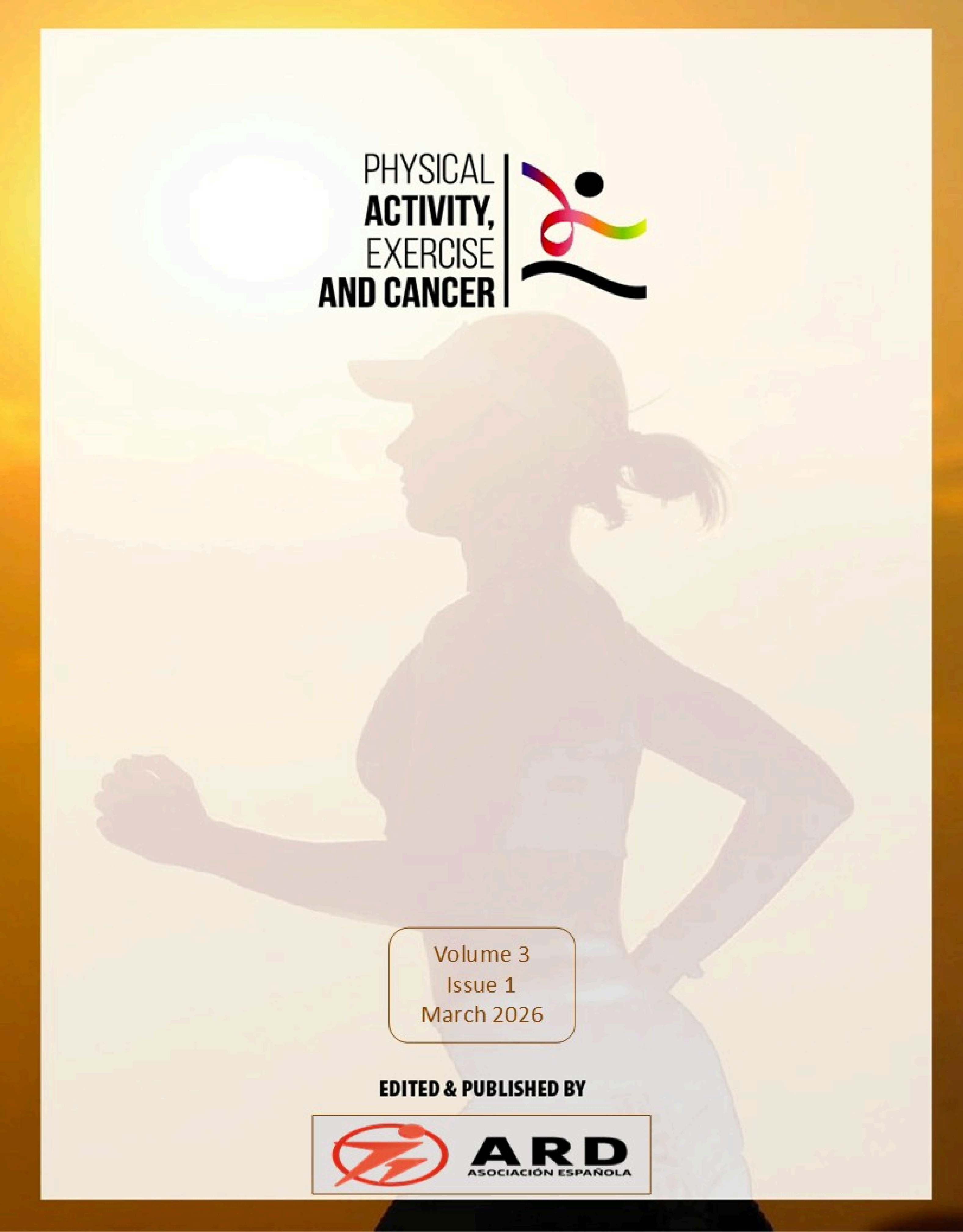

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PHYSICAL ACTIVITY, EXERCISE AND CANCER

ORIGINAL ARTICLE

High-intensity interval resistance and cardiorespiratory training in cancer survivors

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ABSTRACT

Both resistance (RT) and cardiorespiratory (CRT) exercise can improve physical fitness and quality of life (QoL) in cancer survivors (CS). However, the order of exercises may alter benefits as fatigue from the first modality may affect adaptations from the second. To determine which order (i.e., RT or CRT first) is most beneficial in CS during a 10-week supervised, individualized and progressive exercise intervention, 50 CS (40 females, 10 males, age = 71 ± 14 years) were randomized into either RT followed by CRT, or CRT followed by RT. Pre- and post-intervention tests included: sit-to-stand, biceps curl, grip strength, seated medicine ball throw (SMBT), plank, sit-ups/crunches for muscle strength and endurance, six-minute walk test (6MWT) and 20-step test for cardiorespiratory fitness, eight-foot up-and-go, unipedal balance, and sit-and-reach for functional testing, 7-site skinfolds for body composition, and self-reported questionnaires for QoL. There were no significant differences between groups for any measure ($p > .05$). CS significantly improved muscle strength (SMBT, sit-ups/crunches, plank, biceps curl), cardiorespiratory fitness (6MWT distance, time for 20-step test), body composition (decreased fat mass, increased lean mass) and QoL. CS showed physical fitness, function, body composition, and QoL improvements after a 10-week high-intensity interval training exercise intervention.

Keywords: Exercise intervention, Interval training, Concurrent exercise, Muscular fitness, Cardiorespiratory fitness, Quality of life.

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INTRODUCTION

Cancer is the second leading cause of death in the U.S., but survival rates for all types of cancers combined is now 68%; specifically, the five-year survival rate for prostate cancer is 98%, breast cancer is 90%, and colorectal cancer is 65% (Siegel et al., 2022). It is estimated that in the U.S., 1.5% of all cancers diagnosed in men and 4.4% of all cancers diagnosed in women are attributable to physical inactivity, as are 1.4% of all cancer deaths in men and 3.0% of all cancer deaths in women (Islami et al., 2018). Regular physical activity has been shown to help patients with cancer and cancer survivors (CS) by reducing tumour growth and progression, improving both the rate of treatment completion, and the efficacy of cancer treatment (Catala-Vilaplana et al., 2025; Yang et al., 2021). Strong evidence supports the role of physical activity for cancer survivorship; however, across this population, CS' level of physical activity is very low, with approximately 35.5 to 50% of CS failing to meet the recommended physical activity guidelines for adults and reporting no physical activity in their leisure time (Campbell et al., 2019; Cao et al., 2022). This lack of physical activity is associated with increased risk factors for chronic diseases such as obesity, cardiovascular disease, and even cancer recurrence (Campbell et al., 2019). According to the most recent American Cancer Society (ACS) guidelines for nutrition and physical activity for cancer survivors, physical activity is associated with a lower risk of cancer-specific and all-cause mortality in survivors of breast, colorectal, prostate, gynaecological, and lung cancers; the ACS (2022) reports that engaging in regular physical activity can reduce the risk of cancer recurrence by 30 to 40% (ACS, 2022; Rock et al., 2022). According to Schmitz et al. (2019), engaging in structured exercise programs can improve metabolic health, reduce inflammation, and enhance cardiovascular fitness. Structured exercise also fosters social interaction, providing emotional support, reducing feelings of isolation, and enhancing self-esteem and overall mental well-being in CS (Courneya & Friedenreich, 2011).

Several national associations, including the American College of Sports Medicine (ACSM) and the American Cancer Society (ACS), recommend avoidance of inactivity and adherence to regular exercise training consistent with national guidelines for healthy adults across the cancer care continuum: before, during, and after traditional therapy (Courneya et al., 2024; Scott & Iyengar, 2022). In the emerging field of exercise oncology, exercising can be considered as both a non-surgical, systemic cancer treatment requiring multiple administrations over an extended period of time similar to a medication, with drug treatment features such as type, dose, frequency, intensity and duration that can be manipulated (exercise prescription) to achieve a clinical benefit. It is a form of supportive care for maintaining or improving health-related fitness, physical functioning, psychological functioning, quality of life, symptoms/side effects, treatment tolerance, and possibly delayed recovery from treatment (Courneya et al., 2024).

The ACSM guidelines for cancer survivors recommend at least 150 minutes of moderate or 75 minutes of vigorous cardiorespiratory/aerobic activity per week and two days per week of resistance exercise at a moderate to high intensity for all major muscle groups (Campbell et al., 2019). Exercise training programs including both cardiorespiratory training (CRT) and resistance training (RT) have been shown to lower mortality as well as improve physical fitness, bone health and quality of life measurements particularly in breast and colorectal cancer survivors (Dieli-Conwright et al., 2018; Schmid and Leitzmann, 2014). Supervised exercise interventions have statistically significant beneficial effects on CS' quality of life (QoL) and physical fitness when compared to unsupervised exercise (Sweegers et al., 2018); it is suggested that this increased effectiveness is due to a more demanding exercise prescription, a higher compliance to the prescribed exercise intervention, access to better equipment with more individual adjustment and performance feedback, and possibly social interaction with other participants (Knols et al., 2005; Sweegers

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et al., 2018). It appears that during a shorter intervention (<12 weeks), supervised exercise leads to larger improvements in cancer-related fatigue than unsupervised exercise (Reverte-Pagola et al., 2022).

Concurrent training refers to the programming of multiple energy systems into a single workout session, i.e., combining CRT (aerobic system) and RT (anaerobic system); combining both into a single session is designed to maximize the benefits of both modalities to more efficiently promote overall fitness and improve physical performance (Bishop et al., 2018; Markov et al., 2023). A meta-analysis by Marini et al. (2017) found that concurrent training not only enhances exercise performance more effectively than either aerobic or RT alone but also improves the efficiency of energy utilization during workouts. For CS, the benefits of concurrent training that combines cardiorespiratory and resistance exercise (improved cardiovascular fitness, muscular strength, body composition, insulin sensitivity, and immune function) are particularly crucial as many CS experience fatigue, muscle wasting, changes in body fat distribution, and compromised immune systems as a result of their disease or treatment (Schneider et al., 2018; Smith & Doe, 2021). A 2018 study by Cormie et al. found that CS who participated in concurrent training showed significant improvements in both muscle strength (15 to 30%) and aerobic capacity (10 to 20%) over a 12-week program, critical in their recovery and rehabilitation, especially from cachexia and cardiotoxicity. In a recent update of scientific evidence on the effects of concurrent training consisting of aerobic and resistance exercise in CS, positive effects were found for increasing peak oxygen uptake, maximal oxygen consumption, and decreasing triglycerides; no significant differences were found in peak HR, peak respiratory exchange ratio, systolic or diastolic blood pressure, HDL cholesterol, or body mass index (Madeira et al., 2023).

High-intensity exercise is defined as exercising at 77-93% of estimated maximum heart rate, calculated by 220 minus age (Riebe et al., 2018). High-intensity exercise has been shown to lead to beneficial effects such as decreasing cancer-related fatigue and cancer-related symptoms, increasing hand grip muscle strength, reducing body mass, as well as improving QoL (Mijwel et al., 2019). High-intensity interval training (HIIT) refers to a type of training that uses short periods of high-intensity exercise followed by periods of active recovery or low-intensity exercise (Bushman et al., 2025). High-intensity interval training has been shown to be effective in cancer survivors, enabling them to exert maximal effort without overexertion due to the ability to individualize training to meet the CS' exercise capabilities and medical conditions (Mugele et al., 2019; Neuendorf et al., 2023). Current research supports the idea that both high-intensity interval RT and high-intensity interval CRT can lead to improved health outcomes in CS, including improved quality of life and physical fitness levels with no or few adverse side effects (Dieli-Conwright et al., 2018; Herranz-Gomez et al., 2022). One meta-analysis of the effectiveness of HIIT in CS showed statistically significant improvements in cardiorespiratory fitness compared to adding other treatments such as occupational therapy or moderate-intensity continuous training to the primary cancer treatment, as well as high adherence to the HIIT intervention with mild or no side effects reported (Tsuji et al., 2021). Another review of the effects of HIIT on the functional performance and maximal oxygen uptake of cancer patients in comparison with moderate-intensity continuous training found that walking distance in the 6-minute walk test and distance reached in the sit-and-reach test improved significantly in the HIIT intervention participants; a tendency was also found for improvements in relative VO2peak with the HIIT intervention (Neuendorf et al., 2023). A review by Cormie et al. (2018) found that CS engaging in HIIT resistance training experienced greater improvements in both upper and lower body strength compared to those participating in traditional moderate-intensity continuous training. Another study by McNeeley et al. (2006) emphasized that the efficiency of HIIT resistance training allowed CS to achieve significant fitness benefits and improvements in physical function in a shorter amount of time, which is advantageous for CS dealing with fatigue and time constraints.

There is evidence that concurrent training, programming both HIIT RT and CRT into a single workout session, can provide the benefits of both training methods for CS (Palma et al., 2021). However, it is not known which order of exercise (if performing one type of exercise prior to or following the other) over a 10-week training program may lead to an enhanced (or diminished) response. The order of exercise may affect the benefits, since fatigue from the first exercise mode may affect the adaptations possible from the second mode. In a 2012 study of untrained women performing CRT before RT during a concurrent session, Di Blasio et al. (2012) found a slightly lower increase in rate of perceived exertion over the course of the session, as well as a higher rate of ventilation, and a decreased concentration of oxygen in the expired breaths after the exercise session, which led to a larger total energy expenditure when compared to performing resistance training first. This suggests that performing CRT first leads to a greater consumption of oxygen, thus more fat being burned for energy, providing some insight into how the order of exercise may affect the outcomes of a similar exercise program for CS (Di Blasio et al., 2012).

The purpose of this study was to determine which order of performance of high-intensity interval RT or CRT within a concurrent exercise program most affects the following five components related to cancer survivorship during a 10-week, supervised, progressive and individualized training program: muscular strength and endurance, cardiorespiratory fitness, functional ability, body composition, and overall quality of life.

MATERIAL AND METHODS

This research study took place in Alamosa, Colorado during the spring and fall semesters of 2024. Alamosa is located in the San Luis Valley in a very rural area of south-central Colorado at 7544 ft. of elevation; both the added demands of travel time and expense for participants, as well as the lower oxygen pressure at high altitude presented challenges to study participants. Approval for this study was granted by the Institutional Review Board of Adams State University (1-1-2024). This study was performed in accordance with the standards outlined in the 1964 Declaration of Helsinki.

After approval of this research study by the Institutional Review Board of Adams State University, the majority of the participants were recruited through the Oncology and Urology departments of San Luis Valley Health, the regional medical centre. Participant qualifying criteria included any male or female 18 years of age or older who had been diagnosed with any or multiple types of cancer, at any stage along the continuum of cancer treatment or survivorship. This is in contrast to many published studies focusing on a single type of cancer or single stage or type of treatment and is unique to this rural location in order to enrol the targeted numbers. Participants were asked to obtain medical clearance from their health care providers to ensure no contraindications to exercise and identify any adaptations required for specific co-morbidities. A written voluntary informed consent to participate was obtained from every participant in the study prior to any data collection; participants also signed a consent regarding publishing their data and photographs.

Participants

The volunteer participants were recruited from the region through mail to former participants, flyers posted at local fitness facilities and medical clinics, local news media, social media and phone calls to returning participants with a target of 30 or more total participants per semester; participants were eligible to take part in this study more than one semester. Participants were asked to commit to 12 weeks each semester, including 10 weeks of exercise sessions meeting three times per week and one week of testing immediately prior to and following the exercise sessions.

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During the spring 2024 semester, 26 cancer survivors completed the 10-week intervention program with at least 75% compliance (13 in group 1, RT followed by CRT, and 13 in group 2, CRT followed by RT). This cohort consisted of 21 females and five males with a variety of cancers, including breast, prostate, thyroid, skin, lung, throat, Hodgkin's lymphoma and brain; the majority were breast, prostate, thyroid and skin cancer survivors, and six of the 26 participants had multiple types of cancer. The average age was 73.8 ± 14.1 years, and average weight was 73.3 ± 15.3 kilograms.

During the fall 2024 semester, 24 cancer survivors (19 females and five males) completed the 10-week intervention with at least 80% compliance (11 in group 1 and 13 in group 2). The types of cancer represented in this cohort included breast, colon, ovarian, bone, lymphoma, skin, thyroid, uterine, spleen, and brain, with the majority being breast cancer survivors. Seven of the 24 participants had multiple cancers. The average age of this cohort was 69.5 ± 13.5 years, with an average weight of 75.4 ± 15.0 kilograms.

Measures

Brief Fatigue Inventory (BFI), a single page questionnaire to assess self-reported severity of cancer-related fatigue and its impact on activities of daily living, measured on a 0-10 numeric rating scale. This brief questionnaire has been validated specifically for use in cancer populations with construct validity established through correlations with established measures of fatigue, showing significant relationships with clinical outcomes ($r = .80$) (Iravani et al., 2018).

European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire QLQ C30 (EORTC), a questionnaire consisting of 30 questions used to assess self-reported quality of life. This assessment includes a Functional and Symptom scale as well as an overall quality of life rating; it has been validated specifically for use in cancer populations with construct validity established through correlations with established measures of quality of life, showing significant relationships with clinical outcomes ($r = .80$) (Iravani et al., 2018).

Skinfold measurements,7-sites (chest, axilla, triceps, subscapular, ileum, abdominal and thigh) to determine lean mass and percent body fat. All skinfold sites were measured on the right side of the subject a total of three times using calibrated Lange callipers, and an average was recorded. The reliability and validity of the skinfold measurement is subject to the level of expertise of the person administering the test; however, research has shown that repeated measures by the same tester are a valid and reliable assessment tool for adiposity-related variables and changes over time (Esparza-Ros et al., 2022).

Senior Fitness Test (Rikli & Jones, 2013a&b): 5 of 7 components to assess the functional fitness of an older or de-conditioned population with an overall correlation coefficient ranging from .93 to .98 that demonstrates its reliability.

The 30-second sit-to-stand test to assess lower body muscular strength and endurance. Participants were asked to begin in a seated position with their back against the back of a standard height chair, then rise to a full standing position without using their hands and sit back down as many times as possible in 30 seconds; number of repetitions was recorded. Specifically, this test shows a validity of $r = .78$ for men and $r = .71$ for women against a one-rep max leg press, the gold standard (Jones et al., 1999).

The chair sit-and-reach test (right (R) and left (L)) to assess lower body flexibility. Participants were asked to sit on the edge of a chair with one leg bent and the other fully extended, then reach for the toes of the extended leg (ankle in neutral position) with both hands. Measurements were recorded for the distance between the toes and fingertips for each leg; a passing score was given when the fingertips touched the toes. This test has a validity of r = .76 for men and r = .81 for women relative to the hamstring flexibility test, the gold standard endorsed by the American Academy of Orthopaedic Surgeons (Langhammer & Stanghelle, 2015).

The 8-foot up-and-go test to assess power, speed, agility and balance. Participants were asked to start in a seated position with their back against the back of the chair, rise and walk around a cone placed 8 ft. away and return to a seated position, with time to completion recorded. Although this test has not been formally validated due to the absence of a gold standard, it is widely regarded and used as a valid measure of power, speed, agility and balance (Langhammer & Stanghelle, 2015).

The 30-second biceps curl test (R & L) used 5 lb. for women and 8 lb. for men to measure upper body muscular strength and endurance. It began with participants in a seated position with the arm fully extended then flexed to bring the weight to the chest, with their back remaining against the back of the chair; number of repetitions in 30 seconds on each arm was recorded. This test has a validity of r = .84 for men and r = .79 for women compared to the one-rep max for the chest press, the gold standard (Langhammer & Stanghelle, 2015).

The 6-minute walk test (6MWT) to measure cardiorespiratory fitness. This required participants to walk as far as they could in 6 minutes with the distance recorded. Resting heart rate and recovery heart rate one minute post-test were also recorded. This test has a validity coefficient of r = .82 for men and r = .71 for women when compared to time on a treadmill at 85% of maximal heart rate, the gold standard (Rikli & Jones, 2013a&b).

Grip strength test (R & L) to measure hand and forearm strength. This was measured using a calibrated Camry EH101 digital handgrip dynamometer alternating three times with each hand and the best attempt on each hand was recorded. Participants performed the test while standing with the elbow bent to 90 degrees and the wrist in a neutral position. This test has a correlation coefficient of r = .9, meaning its reliability is high; given its ability to produce similar results with other dynamometers, Uysal, Tonak, & Kitis (2022) suggest it is a valid measure of handgrip strength.

60-second sit-up/crunches test to assess core strength and endurance. Both tests are associated with clinical assessments of muscular endurance with a correlation coefficient of r = .97 indicating they are valid measures of core strength and effective indicators of muscular strength and endurance in older populations (r = .80) (Okada et al., 2011). Sit-ups required participants to begin in a supine position with feet on the floor and legs bent, then raise head, shoulders and upper back off the floor with arms crossed and hands on opposite shoulders until their elbows touched their knees and return to starting position. Feet could be held in position; number of sit-ups performed in 60 seconds was recorded. Crunches required participants to begin in a supine position with feet on the floor and legs bent, then raise head and shoulders off the floor with arms crossed and hands on opposite shoulders and return to starting position. Feet could be held in position; number of crunches performed in 60 seconds was recorded.

60-second plank test to assess core strength and endurance. Participants performed prone planks in a push-up position supported by their toes and hands or forearms (females could perform this on their knees); number of seconds up to 60 seconds that a level trunk position was held was recorded (Bohannon et al., 2018).

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30-second unipedal balance test (R & L) to measure static balance. Participants performed this test by standing on one leg, hands on hips and eyes open; the best time on each leg out of 3 three trials with 15 seconds rest between trials recorded if less than 30 seconds. Schmitz & Troxel (2009) reported a correlation coefficient of r = .70 when compared to other established balance assessments such as the Berg Balance Scale, indicating this test is a valid measure of balance.

20-step test to measure cardiorespiratory fitness. Participants performed this test by stepping up onto a 10-inch block and back down, leading with the same foot; time to complete 20 step cycles was recorded. Resting heart rate and recovery heart rate one minute post-test were also recorded. This test has a correlation coefficient of r = .76 for men and r = .81 for women when compared to time on a treadmill at 85% maximal heart rate (Langhammer & Stanghelle, 2015) and similar to the 6-minute walk test, provides a good indicator of cardiorespiratory fitness levels that better accommodate older populations.

Seated medicine ball throw test (SMBT) using a 1.8 kg ball to measure upper body muscular strength. Participants began in a seated position on the floor (or chair) with legs comfortably extended and backs pressed against the wall/chair, then threw a 1.8 kg medicine ball from their chest as far as they could using a chest pass motion. Distance was measured from their fully extended arms/fingertips to where the medicine ball hit the ground; the best score of three attempts was recorded. This test has a correlation coefficient of r = .95 compared to the push-up test indicating this is a valid and reliable assessment of upper body strength, particularly in older adults (Harris et al., 2011).

Procedures

Volunteer participants were invited to an informational meeting prior to beginning the study each semester and were asked to complete a pre-participation packet before beginning pre-testing. This packet included:

- An informed consent form approved by the Institutional Review Board of Adams State University summarizing the purpose and methods of the study. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.
- A demographic questionnaire to collect information on physical readiness, cancer type and stage of treatment or survivorship, and specific social determinants of health (education, healthcare quality and access, social context) and other descriptive data.
- An exercise pre-participation Health Status Questionnaire (HSQ) to provide contact information and health history, assess ability to perform moderate and vigorous exercise, including the necessity to obtain medical clearance prior to engaging in regular physical activity.
- A medication list form, used to keep note of any current cancer-specific medication as well as other medications/supplements to assess the potential effects these could have on exercise responses.
- A Physical Activity Readiness Questionnaire (PAR-Q+) 2023, commonly used in fitness settings, to screen health history, current symptoms, and risk factors to produce individualized exercise prescriptions.

Once this packet was completed and participants were medically cleared to participate in this 10-week exercise program as well as both pre- and post-intervention fitness tests, they were scheduled to complete their pre-testing over the course of two days to reduce the potential effects of fatigue. Day 1 took place in the Human Performance lab on the Adams State University campus. Tests (in order) included completing a BFI and EORTC, 7-site skinfold measurements, components of the Senior Fitness Test: (30-second sit-to-stand test, chair sit-and-reach test (R and L), 8-foot up-and-go), 30-second unipedal balance test (R & L), grip strength test (R & L), 20-step test on a 10-inch block, 60-second sit-up/crunches test, and 60-second plank test. Day 2 took place at the Alamosa Family Recreation Center, the site utilized for the exercise intervention.

Tests (in order) included the 30-second biceps curl test (R & L), the seated medicine ball throw test (SMBT), and 6-minute walk test. Once pre-testing was completed, CS were randomly assigned to either the resistance training first group (group 1) or the resistance training second group (group 2). Following the 10-week exercise intervention, CS completed the same testing over two days of post-testing with the same researcher.

Intervention

All CS took part in three supervised exercise sessions per week with a focus on upper body on Monday, lower body on Wednesday, and core on Friday, lasting 60 minutes each session. Make-up sessions were held on Thursdays to ensure a minimum 75 - 80% compliance to the exercise intervention. Both groups participated in a 5-minute warm-up and cool-down. Based on each CS' group assignment, they either began with 25 minutes of resistance training or with cardiorespiratory training. After 25 minutes, the CS switched to either cardiorespiratory training or resistance training for an additional 25 minutes. During resistance training, participants chose from a pre-selected group of exercises utilizing either dumbbells or body weight, with intervals led by the graduate student researcher; CS were encouraged to gradually increase dumbbell weight when appropriate as well as increase their target HR during the week prior to each target heart rate progression. During cardiorespiratory training participants chose from walking on an indoor track or using a treadmill, elliptical, exercise bike, rowing machine or stair stepper and were encouraged to increase their intensity during the week prior to each target heart rate progression. Heart rate data was collected for each CS across the entire exercise session at one-minute intervals using Polar Unite heart rate monitors and the Polar Flow program. Following each session, the average heart rate for each 25-minute exercise segment as well as average HR during the high-intensity interval portions and active recovery portions of each segment was recorded for each CS. For this study, high intensity refers to working at or above the target HR assigned to each CS; active recovery was defined as having a HR below the target HR but with the CS still maintaining movement. See Table 1 for specific week by week training progressions.

Table 1. High-intensity interval training program.

Week	**Resistance progression, 25 minutes**	**Target heart rate**	**Week**	**Cardiorespiratory progression, 25 minutes**	**Target heart rate**
1	2 sets/6 exercises; 45 sec high intensity/20 sec active recovery; 90 sec rest between sets	60% age-predicted max	1	Alternating 60 sec high intensity/ 60 sec active recovery for entire period	60% age-predicted max
2	2 sets/6 exercises; 45 sec high intensity/20 sec active recovery; 90 sec rest between sets	60% age-predicted max	2	Alternating 60 sec high intensity/ 60 sec active recovery for entire period	60% age-predicted max
3	2 sets/6 exercises; 45 sec high intensity/20 sec active recovery; 90 sec rest between sets	60% age-predicted max	3	Alternating 90 sec high intensity/ 60 sec active recovery for entire period	60% age-predicted max
4	3 sets/5 exercises; 50 sec high intensity/15 sec active recovery; 80 sec rest between sets	70% age-predicted max	4	Alternating 90 sec high intensity/ 60 sec active recovery for entire period	70% age-predicted max
5	3 sets/5 exercises; 50 sec high intensity/15 sec active recovery; 80 sec rest between sets	70% age-predicted max	5	Alternating 120 sec high intensity/ 60 sec active recovery for entire period	70% age-predicted max

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6	3 sets/5 exercises; 50 sec high intensity/15 sec active recovery; 80 sec rest between sets	70% age-predicted max	6	Alternating 120 sec high intensity/ 60 sec active recovery for entire period	70% age-predicted max
7	3 sets/6 exercises; 50 sec high intensity/15 sec active recovery; 60 sec rest between sets	80% age-predicted max	7	Alternating 150 sec high intensity/ 60 sec active recovery for entire period	80 age-predicted max %
8	3 sets/6 exercises; 50 sec high intensity/15 sec active recovery; 60 sec rest between sets	80% age-predicted max	8	Alternating 150 sec high intensity/ 60 sec active recovery for entire period	80% age-predicted max
9	3 sets/6 exercises; 50 sec high intensity/15 sec active recovery; 60 sec rest between sets	80% age-predicted max	9	Alternating 180 sec high intensity/ 60 sec active recovery for entire period	80% age-predicted max
10	3 sets/6 exercises; 50 sec high intensity/15 sec active recovery; 60 sec rest between sets	80% age-predicted max	10	Alternating 180 sec high intensity/ 60 sec active recovery for entire period	80% age-predicted max

Analysis

Data was analysed and reported as group means with standard deviations for all dependent variables: biceps curl test (R & L), sit-to-stand test, seated medicine ball throw, 60-second sit-ups/crunches, grip strength (R & L), 60-second plank test for muscular strength and endurance, 6-minute walk test, 20-step test, resting and recovery HR for cardiorespiratory fitness, chair sit-and-reach test (R & L), 30-second unipedal balance test (R & L), 8-foot up-and-go test for functional testing, body weight, 7-site skinfold to determine lean mass, percent body fat, and fat mass for body composition, and EORTC and BFI for quality of life. Analyses were done for both groups, the independent variables. SPSS software (version 27, 2021) was used to run a Repeated Measures ANOVA to detect any differences between the intervention groups and any differences from pre- to post-intervention. Statistical significance was set at $p \leq .05$. Effect sizes of each variable were calculated as well: small size d = 0.2, medium size d = 0.5, and large size d = 0.8 (Sullivan & Feinn, 2012).

RESULTS

During the spring 2024 semester, 26 cancer survivors out of 30 who completed pre-testing finished the 10-week intervention program with at least 75% compliance (13 in group 1 and 13 in group 2). During the fall 2024 semester, 24 cancer survivors out of 32 who completed pre-testing completed the 10-week intervention with at least 80% compliance (11 in group 1 and 13 in group 2). Those participants unable to complete the program reported experiencing personal health issues or family emergencies.

Muscular strength and endurance

Muscular strength and endurance was assessed before and after the 10-week intervention using the following tests: sit-to-stand, biceps curl, grip strength, seated medicine ball throw (SMBT), plank, and sit-ups/crunches. Some participants were not able to complete all tests due to physical limitations, and this is reflected in differing *n* values seen in the tables. During the spring 2024 semester, both groups significantly improved over time for the sit-to-stand test (F = 10.705, $p = .003$, ES = 0.308), biceps curl test (right: F = 6.87, $p = .010$, ES = 0.223; left: F = 15.047, $p = .001$, ES = 0.385), plank test (F = 11.010, $p = .003$, ES = 0.334), sit-ups/crunches (F = 5.750, *p* = .037, ES = 0.365), and SMBT (F = 9.408, *p* = .006, ES = 0.300); however, there were no differences between groups (*p* > .05). Refer to Table 2.

Table 2. Muscular strength and endurance tests; overall changes over the 10-week intervention in both groups combined in both spring 2024 and fall 2024 semesters.

	Spring 2024 Pre-intervention	Spring 2024 Post-intervention	Fall 2024 Pre-intervention	Fall 2024 Post-intervention
Sit-to-stand (# of reps/30 s)	11.8 ± 2.3 (n = 26)	13.5 ± 2.8* (n = 26)	11.0 ± 2.8 (n = 24)	11.9 ± 2.8 (n = 24)
R. Biceps Curl (# of reps/30 s)	16.9 ± 6.6 (n = 26)	19.1 ± 7.1* (n = 26)	16.5 ± 5.2 (n = 24)	18.0 ± 5.6* (n = 24)
L. Biceps Curl (# of reps/30 s)	18.2 ± 4.5 (n = 26)	21.0 ± 4.5* (n = 26)	17.1 ± 4.4 (n = 24)	19.1 ± 4.9* (n = 24)
R. hand grip (kg)	25.0 ± 6.4 (n = 26)	27.2 ± 10.8 (n = 26)	26.0 ± 6.8 (n = 24)	26.8 ± 6.8 (n = 24)
L. hand grip (kg)	23.9 ± 5.1 (n = 26)	25.0 ± 9.1 (n = 26)	24.6 ± 5.7 (n = 24)	26.1 ± 6.2* (n = 24)
SMBT (m)	2.2 ± 0.7 (n = 24)	2.3 ± 0.7* (n = 24)	2.0 ± 0.8 (n = 24)	2.3 ± 0.8* (n = 24)
Plank (s)	40.1 ± 18.7 (n = 24)	52.7 ± 16.3* (n = 24)	39.6 ± 19.2 (n = 21)	50.6 ± 17.0* (n = 21)
Sit-ups/crunches (# of reps)	10.0 ± 8.7 (n = 12)	19.7 ± 11.9* (n = 12)	18.2 ± 10.0 (n = 18)	27.9 ± 14.7* (n = 18)

*Note: R. = Right, L. = Left, * = Significant differences pre- to post-intervention (p < .05)*

During the fall 2024 semester, all subjects significantly improved in the biceps curl test (right: F = 6.632, *p* = .017, ES = 0.232; left: F = 14.779, *p* < .001, ES = 0.402), plank test (F = 5.365, *p* = .032, ES = 0.220), sit-ups/crunches (F = 4.588, *p* = .048, ES = 0.223), SMBT (F = 13.715, *p* = .001, ES = 0.384), and left hand grip (F = 7.237, *p* = .013, ES = 0.248); the right hand grip and the sit-to-stand did not significantly increase over time in this semester's CS (*p* > .05). There were also no significant differences between groups for any variable (*p* > .05). Refer to Table 2.

Cardiorespiratory fitness

During the spring 2024 semester, cardiorespiratory fitness was assessed pre- and post-10-week intervention using the 20-step test and the 6MWT. All participants significantly decreased the time to complete the 20-step test (F = 9.373, *p* = .005, ES = 0.281); there were no group differences (*p* > .05). Although trending towards significance (F = 3.408, *p* = .077), total distance walked in all CS increased over time; there were no significant group differences (*p* > .05). Neither resting or recovery heart rates for the 20-step test or the 6MWT changed significantly over time or between groups (*p* > .05), with negligible ES. Refer to Table 3.

During the fall 2024 semester, all participants significantly improved the distance walked during the six minutes (F = 21.512, *p* < .001, ES = 0.494), with no significant differences between groups (*p* > .05). Resting HR measured prior to the 6MWT decreased significantly from pre- to post-intervention (F = 13.194, *p* = .002, ES = 0.386), although there were no significant differences between groups (*p* > .05). Recovery HR, taken one minute after the 6MWT, was also significantly different pre- to post-intervention in all CS (F = 9.191, *p* = .007, ES = 0.326), but not different between groups (*p* > .05). There were no significant differences between groups or over time for the time to complete the 20-step test (*p* > .05), with negligible ES. There were also

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no significant differences over time or between groups for either resting or recovery HR values (*p* > .05). Refer to Table 3.

Table 3. Cardiorespiratory fitness measures; overall changes over the 10-week intervention in both groups combined in both spring 2024 and fall 2024 semesters.

	Spring 2024 Pre-intervention	**Spring 2024 Post-intervention**	**Fall 2024 Pre-intervention**	**Fall 2024 Post-intervention**
6MWT distance (m)	496.3 ± 91.2 (n = 26)	524.7 ± 99.9 (n = 26)	452.9 ± 89.9 (n = 24)	516.5 ± 107.2* (n = 24)
6MWT resting HR (bpm)	76.4 ± 8.5 (n = 26)	76.6 ± 5.9 (n = 26)	74.0 ± 9.4 (n = 23)	65.7 ± 10.0* (n = 23)
6MWT recovery HR (bpm)	97.6 ± 12.0 (n = 26)	103.0 ± 13.1 (n = 26)	95.7 ± 13.4 (n = 21)	108.3 ± 16.9* (n = 21)
20-step test time (s)	50.8 ± 17.2 (n = 26)	43.3 ± 12.7* (n = 26)	53.1 ± 25.1 (n = 24)	51.9 ± 18.6 (n = 24)
20-step test resting HR (bpm)	72.7 ± 9.9 (n = 26)	73.8 ± 7.3 (n = 26)	70.7 ± 9.5 (n=24)	68.8 ± 11.1 (n = 24)
20-step test recovery HR (bpm)	96.2 ± 13.4 (n = 26)	96.8 ± 11.1 (n = 26)	87.2 ± 11.1 (n = 24)	90.7 ± 17.2 (n = 24)

*Note: * = Significant differences pre- to post-intervention (p < .05)*

Functional testing

Functional assessments included the eight-foot up-and-go test, the 30-second unipedal balance test, and the sit-and-reach test. During the spring 2024 semester, none of these tests were statistically significant either between groups or over time (*p* > .05), although all participants increased balance time on both the right (2.4 s longer) and left legs (1.6 s longer) over time. Times to complete the eight-foot up-and-go improved over time for all CS (0.7 s faster, *p* > .05). Effect sizes for all variables were negligible. Likewise, during the fall 2024 semester, no significance was found within or between groups for any variable (*p* > .05). Refer to Table 4.

Table 4. Functional test results; overall changes over the 10-week intervention in both groups combined in both spring 2024 and fall 2024 semesters.

	Spring 2024 Pre-intervention	**Spring 2024 Post-intervention**	**Fall 2024 Pre-intervention**	**Fall 2024 Post-intervention**
R. Balance (s)	15.2 ± 10.8 (n = 26)	17.6 ± 10.6 (n = 26)	19.9 ± 11.6 (n = 24)	18.5 ± 11.7 (n = 24)
L. Balance (s)	14.9 ± 10.4 (n = 26)	16.4 ± 11.5 (n = 26)	17.9 ± 12.0 (n = 24)	18.4 ± 11.9 (n = 24)
R. Sit-and-reach (cm)	7.0 ± 10.7 (n = 26)	7.0 ± 10.8 (n = 26)	8.9 ± 10.1 (n = 24)	7.7 ± 10.6 (n = 24)
L. Sit-and-reach (cm)	6.2 ± 10.4 (n = 26)	7.2 ± 10.2 (n = 26)	11.2 ± 16.3 (n = 24)	7.9 ± 10.8 (n = 24)
8-foot up-and-go (s)	7.1 ± 3.8 (n = 26)	6.4 ± 2.2 (n = 26)	7.8 ± 2.4 (n = 24)	8.0 ± 2.8 (n = 24)

*Note: R. = Right, L. = Left, *= Significant differences pre- to post-intervention (p < .05)*

Body composition

Body weight and body composition were assessed before and after the 10-week intervention. The seven-site skinfold test was used to determine body composition, specifically lean mass and percent body fat (fat mass).

During the spring 2024 semester, lean mass significantly increased in all cancer survivors over time (F = 89.937, $p < .001$, ES = 0.789), while percent body fat (F = 10.183, $p = .004$, ES = 0.298) and fat mass (F = 86.399, $p < .001$, ES = 0.783) decreased significantly. There were no significant differences between groups ($p > .05$). Refer to Table 5.

During the fall 2024 semester, significant increases in lean mass (F = 14.686, $p = .001$, ES = 0.412) and decreases in percent body fat (F = 17.544, $p < .001$, ES = 0.455) and fat mass (F = 15.241, $p < .0001$, ES = 0.421) were observed over time for all CS, with no group differences ($p > .05$). Refer to Table 5.

Table 5. Body composition measures; overall changes over the 10-week intervention in both groups combined in both spring 2024 and fall 2024 semesters.

	Spring 2024 Pre-intervention	**Spring 2024 Post-intervention**	**Fall 2024 Pre-intervention**	**Fall 2024 Post-intervention**
Lean mass (kg)	51.1 ± 10.6 (n = 26)	58.1 ± 9.9* (n = 26)	47.9 ± 10.8 (n = 23)	53.4 ± 9.4* (n = 23)
Fat mass (kg)	22.6 ± 10.5 (n = 26)	15.4 ± 7.5* (n = 26)	27.1 ± 10.2 (n = 23)	21.4 ± 7.2* (n = 23)
Percent body fat	29.7 ± 10.5 (n = 26)	27.6 ± 10.4* (n = 26)	35.5 ± 10.1 (n = 23)	27.9 ± 5.9* (n = 23)

*Note: * = Significant differences pre- to post-intervention ($p < .05$)*

Quality of life

Self-reported quality of life questionnaires included the EORTC and BFI. During the spring 2024 semester, statistically significant improvements were found for the EORTC-QoL (F = 5.156, $p = .036$, ES = 0.177), EORTC-Functional (F = 4.524, $p = .044$, ES = 0.159), and BFI (F = 6.093, $p = .021$, ES = 0.202) scores for all CS over time, although there were no group differences ($p > .05$). During the fall 2024 semester, there were no statistically significant differences within or between groups for any measure of the EORTC or BFI ($p > .05$).

DISCUSSION

This study was conducted in the small town of Alamosa, located in a very rural area of south-central Colorado at 7544 ft. of elevation; both the added demands of travel time and expense for participants, as well as the lower oxygen pressure at high altitude for exercisers presented unique challenges to participants involved in this study. In contrast to many published studies focusing on a single type of cancer or single stage or type of treatment, participant qualifying criteria included any male or female 18 years of age or older who had been diagnosed with any or multiple types of cancer, at any stage along the continuum of cancer treatment or survivorship. This was unique to this rural location in order to enrol the targeted numbers. The purpose of this study was to determine whether the order of concurrent exercise training (i.e., resistance followed by cardiorespiratory training or vice versa) would affect the measurements of muscular strength and endurance, cardiorespiratory fitness, functional abilities, body composition and quality of life in cancer survivors after a 10-week progressive, supervised, and individualized physical activity intervention. Using high-intensity interval training for both cardiorespiratory and resistance exercise is also somewhat unique to this study; it was utilized because of the ease of individualizing the exercise progressions to fit individual participant limitations as well as maximizing benefits obtained from time spent exercising. This study found no apparent effect of order of exercise on any dependent variables (i.e., no group differences). There were, however, improvements in numerous measures in all cancer survivors over time. These findings are in agreement with previous research that both cardiorespiratory and resistance training can benefit CS (Dieli-Conwright et al.,

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2018; Herranz-Gomez et al., 2022; Mugele et al., 2019; Neuendorf et al., 2023). This is especially true if they perform high-intensity interval training, which they are more than capable of doing, given the high degree of individualization possible with this training modality (De Luca et al., 2016; Madiera et al., 2023; Markov et al., 2023; Smith & Doe, 2021; Toohey et al., 2018).

Muscular strength and endurance

As seen in Table 2, CS participating in both semesters showed significant changes in the seated medicine ball throw, planks, biceps curl, and sit-ups/crunches, indicating improved muscular strength in the upper body and improved muscular endurance in the core. Lower body strength, as measured by the sit-to-stand test, was significantly improved in the spring 2024 semester only, even though CS also completed more reps in the fall 2024 semester ($p > .05$). This result in CS is particularly meaningful, since improvements in muscular strength are directly related to CS' functional ability (Bordignon et al., 2022; Courneya et al., 2024; De Luca et al., 2016; Dieli-Conwright et al., 2018; Herranz-Gomez et al., 2022; Mijwel et al., 2019; Strasser et al., 2013). In terms of hand grip strength, only CS in the fall had statistically significant improvements and only in the left hand, although all CS improved in both hands, but with only a small effect size. This may, however, be important, as Zhuang et al. (2020) found that grip strength is inversely related to cancer mortality. This may be explained by the majority of participants showing right-hand dominance, and thus there was more room for improvement on the weaker or less used side (Kenney et al., 2022). These results could also be explained with the choice of exercises included in the intervention. Although participants did not specifically perform hand grip exercises for example, all the exercises addressed upper, lower and core musculature (Kenney et al., 2022).

Cardiorespiratory fitness

Cardiorespiratory fitness was determined by the distance walked in six minutes and the time it took to complete 20 steps on a 10-inch platform, in addition to measuring resting and recovery heart rates before and after both tests. As seen in Table 3, all CS improved the distance walked in six minutes, although it was only statistically significant in the fall, with a medium effect size. This may be due to the large variability in CS' performances. On the other hand, time for the 20-step test in the spring was statistically significant, but not in the fall, even though all CS completed the task faster. Effect sizes were small.

Resting heart rate significantly decreased prior to the 6MWT in the spring; no other significant changes in resting HR were observed, although there was a large variability in this measure. In terms of recovery heart rate, measured one minute post-test, significance was seen in the fall for the 6MWT, but no other significant changes were seen. Interestingly, the recovery HR was higher post- compared to pre-intervention. This, in fact, represents an improvement in the cardiorespiratory system's functioning since the participants walked further in the same time period, exerting themselves more (Kenney et al., 2022). These results are in accordance with previous research showing improvements in cardiorespiratory fitness after an intervention that includes cardiorespiratory exercise training, especially high-intensity interval training (Dieli-Conwright et al., 2018; Madeira et al., 2023; Neuendorf et al., 2023).

Functional assessments and quality of life

One of the main purposes of exercise training in cancer survivors is to regain and even improve their functional capacity, independence and quality of life during and after traditional cancer treatments (Campbell et al., 2019; Courneya et al., 2024; Mugele et al., 2019; Neuendorf et al., 2023; Yang et al., 2021). In this study, the 30-second unipedal balance test, 8-foot up-and-go test, and the chair sit-and-reach test were used to assess functional ability. Despite finding no significant differences, with negligible effect sizes (refer to Table 4), most CS improved in these tests. There is substantial variability in all measures. This may also be explained by a lack of specific practice on these measures, which were included minimally in the intervention (e.g., balance exercises) or only as a minor part of the warm-up and cool-down (e.g., sit-and-reach). These measures of balance, agility and flexibility are certainly important to functional ability and should be included to a greater extent in future programs (Rikli and Jones, 2013a).

Based on self-reported questionnaires, some quality of life measures improved significantly in the spring 2024 semester, including cancer-related fatigue, and overall and functional quality of life scores (as indicated on the EORTC), but effect sizes were small. Specifically, EORTC-Functional scores decreased indicating an improvement in functional ability of the participants. The EORTC-QoL scores increased over time indicating a better quality of life reported by all CS. The BFI scores decreased in all participants over time, indicating lower levels of fatigue. There were no significant changes in any of these measures in the fall CS. This is likely due to the fact that these participants were already reporting better scores at baseline; for example, this group of CS had reasonably low cancer-related fatigue to begin with. Despite this, the results agree with other previous research that participating in a supervised exercise intervention can improve measures of cancer-related fatigue and QoL (Courneya et al., 2024; Dieli-Conwright et al., 2018; Herranz-Gomez et al., 2022; Mijwel et al., 2019; Reverte-Pagola et al., 2022; Schmid and Leitzmann, 2014).

Body composition

Both cardiorespiratory and resistance training have benefits to body composition, although cardiorespiratory exercise is generally more beneficial for targeting body fat levels while resistance training focuses more on developing or maintaining lean mass (Kenney et al., 2022). Many cancer survivors become inactive during and after traditional treatments, which leads to loss of lean tissue and hence, strength, and gains in body fat (Abbass et al., 2019; Au et al., 2021; Friedenreich et al., 2021; Moon et al., 2008). However, exercise, especially high-intensity interval training (Toohey et al., 2018), can offset or even improve these negative changes in body composition. As seen in Table 5, all CS in both semesters significantly decreased fat mass and percent body fat and significantly increased lean mass. Effect sizes were moderate to large, illustrating the meaningfulness of this specific exercise intervention to favourably modify body composition. This is in agreement with previous research findings (Campbell et al., 2019; De Luca et al., 2016; Dieli-Conwright et al., 2018; Madeira et al., 2023; Mijwel et al., 2019; Rock et al., 2022).

CONCLUSIONS

This research included two 10-week supervised, progressive and individualized concurrent exercise interventions (spring and fall 2024 semesters) performed using a high-intensity interval training model for both cardiorespiratory and resistance segments. Although there were no differences based on what order the exercises were performed (i.e., RT first followed by CRT training or vice versa), there were numerous improvements in cancer survivors' physical fitness, functional abilities and quality of life over time. There were slight differences between results of the two semesters, but in general, improvements were seen in muscular strength and endurance of the upper and lower body, and especially the core; cardiorespiratory fitness, especially distance walked in six minutes and time to complete the 20-step test; quality of life, specifically cancer-related fatigue and overall QoL; and body composition, with significant reductions in body fat and increases in lean mass.

These results illustrate the importance of including both resistance training and cardiorespiratory training into an exercise program for cancer survivors regardless of the order in which they are performed. The efficiency of HIIT allows CS to achieve significant fitness benefits (improved cardiorespiratory fitness, muscular strength and endurance and body composition), as well as a high adherence to the intervention, in a shorter amount

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of time compared to those participating in traditional moderate-intensity continuous training (Dieli-Conwright et al., 2018; Herranz-Gomez et al., 2022; McNeeley et al., 2006; Tsuji et al., 2021) . This training program format is also highly adaptable for specific individuals, programs, and settings (Mugele et al., 2019; Neuendorf et al., 2023). With proper supervision, individualized programming to meet the needs of each cancer survivor, and progression over time, all cancer survivors should participate in a physical activity program for these and potential other benefits. Both the American Cancer Society (Rock et al., 2022) and the American College of Sports Medicine (Campbell et al., 2019) promote exercise for cancer survivors, and these research findings support this. All cancer survivors, working with their oncologist, other medical professionals, and qualified exercise professionals, should participate in regular physical activity that includes both cardiorespiratory and resistance components, regardless of the order in which they are completed.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Tracey Robinson and Peggy Johnson are co-directors of this program and supervise this graduate student-led intervention. The spring 2024 research was part of Nicolas Alvarez's thesis research, so he was the lead program coordinator. The fall 2024 research was led by Alexandria Miles and Abigail Adiong. Dr. Maureen Cooper referred cancer survivors to the program and served on the thesis committee. Material preparation, data collection and analysis were performed by all authors from Adams State University. The first draft of the manuscript was written by Tracey Robinson and Peggy Johnson, and all authors had input to this manuscript. All authors read and approved the final manuscript.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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PHYSICAL ACTIVITY, EXERCISE AND CANCER

ORIGINAL ARTICLE

Promoting exercise in oncological aftercare: Evaluation of Outdoor Against Cancer's 4x4 training programme

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ABSTRACT

Physical exercise is a key non-pharmacological strategy in oncological aftercare, contributing to improvements in physical performance, quality of life, and symptom management. This study evaluates the 4x4 training programme developed by Outdoor Against Cancer (OAC), a supervised high-intensity interval training (HIIT) intervention based on the Norwegian 4x4 protocol, implemented over nine months in Munich. Participants, including individuals with active cancer, survivors in remission, relatives, and health-oriented individuals, completed a structured survey assessing feasibility, safety, adherence, and perceived effects. Results revealed high long-term commitment, with a substantial proportion attending more than sixteen sessions. Participants reported notable benefits, including reduced cancer-related fatigue, enhanced emotional well-being, improved strength and endurance, and increased quality of life. The programme was perceived as safe and well-structured, with individualized supervision playing a crucial role in motivation and adherence. These findings support the feasibility and positive impact of supervised HIIT programmes in oncological exercise therapy and highlight their potential integration into standard cancer aftercare.

Keywords: Oncology exercise, High-intensity interval training, Cancer-related fatigue, Quality of life, Exercise adherence.

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INTRODUCTION

Physical activity is now considered a key non-pharmacological intervention in oncology, both during and after cancer treatment. Structured, supervised training programmes in particular can contribute to improving physical performance and quality of life, as well as reducing therapy-associated side effects. Against this backdrop, the 4x4 training programme by Outdoor Against Cancer (OAC) was established in Munich last year. After nine months of continuous implementation, participants were systematically surveyed about their experiences and perceived effects. This article summarises the results of this survey and places them in the context of current sports science and oncology research.

RECRUITMENT AND PARTICIPANT STRUCTURE

Participants are recruited through various channels that have been established over many years. Close cooperation with oncology clinics, in particular with the Comprehensive Cancer Centre at LMU Munich and its associated institutions, plays a central role. This is supplemented by the availability of information materials, recommendations from existing networks such as the Bavarian Cancer Society, and the participants' own initiatives via internet research and social media.

In the heterogeneous training group, more than half of the participants currently have cancer, and about one third are in remission. In addition, relatives and other people interested in health also participate. This mix is perceived as enriching by the participants and contributes to social support within the group.

COMMITMENT AND PARTICIPATION BEHAVIOUR

A key finding of the survey is the high level of long-term commitment. Around 25% of participants have attended more than 16 training sessions. This level of commitment is remarkable in the context of exercise therapy programmes in oncology and indicates a high level of acceptance and perceived relevance of the training programme.

TRAINING CONCEPT: 4X4 TRAINING

The 4x4 training is based on the established Norwegian 4x4 protocol, a specific form of high-intensity interval training (HIIT). The protocol comprises four intervals of four minutes each at an intensity of 85-95% of the maximum heart rate, interrupted by active recovery phases at low intensity. In sports science literature, this protocol is particularly highlighted for its effects on cardiorespiratory fitness. This is a key predictor of morbidity and mortality, even in oncology patients. Studies show that, compared to other HIIT formats, the 4x4 protocol can result in higher energy expenditure, greater metabolic stress and marked improvements in maximum oxygen uptake (Schlüter, K. et al. 2019, Herranz-Gómez A. et al. 2024).

Dr Tom Degenhardt, Medical Director of OAC, says:

> "*We are delighted that 4x4 training will bring significant medical and personal benefits to our cancer patients*."

FEASIBILITY, SAFETY AND SUPPORT

Safety is a key concern when using high-intensity training methods in oncology. Current evidence shows that the 4x4 HIIT protocol is feasible and safe for various groups of cancer survivors – including breast and prostate cancer survivors – provided that it is adapted and monitored (Schlüter, K. et al. 2019). These findings are also reflected in the feedback from participants. Regardless of their disease status, they unanimously report a well-balanced training intensity, a clear and structured design of the units, and understandable and clear explanations by qualified trainers. Individual support is highlighted as a key factor for feeling safe and motivated.

One participant describes this as follows:

"*The trainers actively approach you and answer every question very competently*."

EFFECTS OF THE TRAINING

Among the most significant results of the survey are the reported positive effects of the training. Overall, 84% of participants say they benefit noticeably from participating. In particular, they mention:

- A reduction in cancer-related fatigue,
- An increased quality of life,
- Improved emotional balance, and
- Gains in strength and endurance.

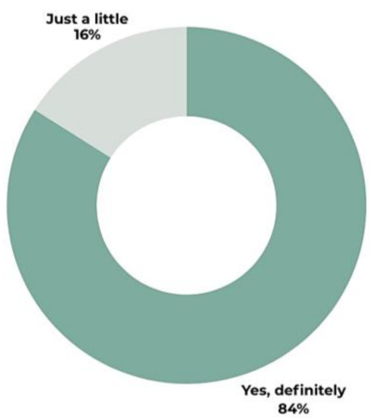

Figure 1. Amount of participants, who experienced positiva effects through 4x4 Trainning.

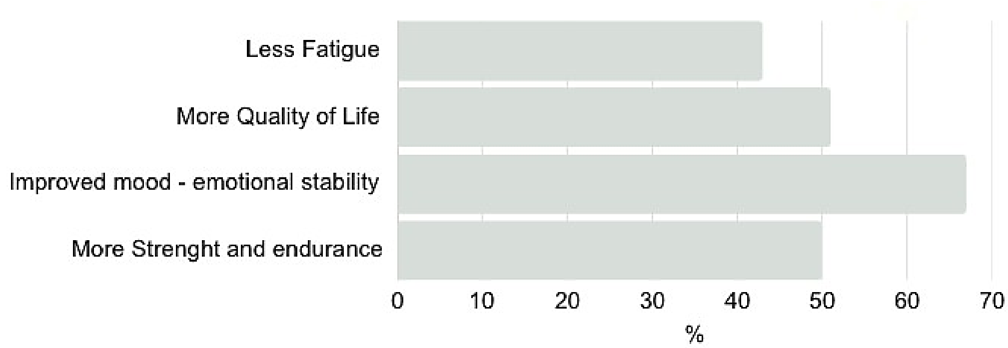

Figure 2. Positive effects through 4x4 Training.

These subjective assessments are consistent with current evidence that supervised, higher-intensity training interventions are associated with improvements in physical function and self-reported quality of life during

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and after cancer treatment (Herranz-Gómez A. et al. 2024, Sweegers M. G et al. 2018, Chen Y. J et al. 2020). The reduction of fatigue, one of the most common and debilitating symptoms of oncological diseases, is also regularly described in the literature (Loughney L. A et al. 2018, Witlox L. et al. 2018).

JOY, MOTIVATION AND PERSEVERANCE

In addition to the physiological effects, the emotional component plays a decisive role in long-term training adherence. Participants report high levels of enjoyment and motivation, especially when training together outdoors. Statements such as "*It's much more fun than training alone*" or "*Even if I'm not feeling great that day, I always feel better afterwards*" underline the importance of social and motivational factors.

Tom Degenhardt sums it up:

> "*The advantages of 4x4 training are obvious: anyone can do it! I'm happy that we meet outside and are active together*."

CLASSIFICATION AND OUTLOOK

The results of the participant survey confirm both the international data and comparable feedback from other countries, including Latvia, where the 4x4 protocol is used in similar contexts (Thaller P. 2025). They emphasise that the Norwegian 4x4 training protocol is a safe, practical and effective HIIT format for cancer patients, especially when it is professionally instructed and supervised.

The findings will not only be incorporated into the further development of training programmes, but also into the training and continuing education of trainers in the field of oncological exercise therapy. The aim is to transfer evidence-based training concepts into practice in a sustainable manner and make them accessible to as many affected individuals as possible, for example through our continuing education programme on the 4x4 method or the OAC trainer training programme.

CONCLUSION

OAC's 4x4 training impressively demonstrates how evidence-based training protocols can be successfully integrated into a practical, supervised setting for oncology patients. The high level of participation, the positive subjective effects and the consistency with the current state of research speak for the potential of this approach to further establish exercise as an integral part of oncology care.

A quote from one participant sums it up:

> "*It's great that this training programme exists – it helps me put my cancer diagnosis aside for a while*."

AUTHOR CONTRIBUTIONS

H.P., led the conceptual development and drafted the manuscript. T.D., contributed medical expertise and reviewed the scientific content. P.T., contributed to the conceptual framework, strategic alignment, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Effects of physical activity in pediatric acute lymphoblastic leukemia after oncologic treatment: A systematic review

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy. Although survival rates have improved, children and survivors frequently experience long-term impairments in aerobic capacity, muscle strength, functional mobility, and health-related quality of life (HRQoL). Objective: To systematically synthesize evidence regarding the effects of structured physical activity and exercise programs in paediatric patients with ALL after oncologic treatment or during late phases of therapy. A systematic review was conducted following PRISMA 2020 and the PICO framework. PubMed, PEDro, and SciELO were searched (September–December 2025). Randomized controlled trials (RCTs), non-randomized trials, and pre–post studies in participants <15 years with ALL were included if the intervention was described and outcomes included physical function, biological markers, and/or HRQoL. Methodological quality was assessed using the McMaster tool. Six studies met eligibility criteria. Most interventions were multicomponent (aerobic + resistance ± flexibility), lasting 12–16 weeks, 2–5 sessions/week. Exercise improved aerobic capacity (VO_2 outcomes), functional mobility (TUG, TUDS, 9-min walk), and selected strength outcomes. HRQoL results were inconsistent and often non-significant. Biological outcomes were heterogeneous, including stable oxygen pressure, no clear effects on bone mineral density, and improvements in haematological parameters in one study. Structured exercise appears feasible and may improve physical fitness outcomes in paediatric ALL, but evidence remains limited by heterogeneity in interventions and outcomes. Larger standardized trials are required.

Keywords: Acute lymphoblastic leukaemia, Paediatric oncology, Exercise, Physical activity, Functional capacity, Quality of life.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the clonal expansion of immature lymphoid progenitors in the bone marrow, resulting in disruption of normal hematopoiesis and impaired immune function (Abd El Baky & Adel Elhakk, 2017). Clinically, this pathophysiology translates into anemia, thrombocytopenia, and leukocyte dysfunction, which may manifest as fatigue, bleeding tendencies, recurrent infections, fever, and musculoskeletal pain (Castañeda-Huerta, 2009; Lassaletta Atienza, 2016). Although ALL is relatively uncommon in the general population, it represents the most frequent pediatric cancer diagnosis and accounts for a substantial proportion of malignancies in children younger than 15 years (Tanir & Kuguoglu, 2013; White et al., 2005).

Over the past decades, improvements in risk-adapted chemotherapy protocols, supportive care, and stratified treatment intensification have markedly increased survival rates, transforming pediatric ALL into a paradigmatic success story of modern oncology (Raetz, 2014). As a consequence, the clinical focus has progressively expanded beyond survival toward the prevention and management of treatment-related toxicities and long-term morbidity (Järvelä et al., 2010). This shift is particularly relevant because children and adolescents treated for ALL are vulnerable to persistent deficits in physical function, including reduced cardiorespiratory fitness, muscle weakness, limitations in functional mobility, and impaired participation in age-appropriate activities (Järvelä et al., 2010; Tanir & Kuguoglu, 2013). Notably, long-term survivors may exhibit significantly lower peak oxygen uptake (VO_{2peak}) than healthy peers, suggesting clinically meaningful impairment in aerobic capacity that may persist years after therapy completion (Järvelä et al., 2010).

The mechanisms underlying functional decline in pediatric ALL are multifactorial. Treatment-related neurotoxicity, corticosteroid exposure, reduced habitual activity, prolonged hospitalization, and cancer-related fatigue contribute to deconditioning and neuromuscular impairment (Tanir & Kuguoglu, 2013). Additionally, musculoskeletal limitations—such as ankle range-of-motion restriction—have been reported among survivors, potentially compromising gait efficiency and functional independence (Wright et al., 1999). These sequelae are not merely transient inconveniences; rather, they can influence long-term health trajectories by promoting sedentary behaviors and reducing physical reserve, which may ultimately increase vulnerability to cardiometabolic complications across survivorship (Järvelä et al., 2010).

Physical activity (PA), defined by the World Health Organization as any bodily movement produced by skeletal muscles that requires energy expenditure, is associated with wide-ranging benefits including improved physical health, mental well-being, and quality of life (Bull et al., 2020). In pediatric oncology, PA and structured exercise training have gained increasing recognition as supportive care interventions aimed at counteracting deconditioning and improving functional outcomes (White et al., 2005). Exercise may provide clinically meaningful benefits by enhancing aerobic fitness, neuromuscular performance, and functional mobility, while potentially attenuating cancer-related fatigue and supporting psychosocial recovery (Abd El Baky & Adel Elhakk, 2017).

In children with ALL, growing evidence supports the feasibility and potential efficacy of structured exercise programs. A randomized clinical trial of a home-based multicomponent intervention in childhood ALL survivors demonstrated significant improvements in VO_{2peak} and functional performance tests, supporting exercise as a strategy to restore physical fitness after treatment (Manchola-González et al., 2020). Likewise, a randomized controlled trial (RCT) reported that systematic exercise training improved functional mobility (Timed Up and Go, stair performance) and exercise capacity compared with usual care in children in remission (Tanir & Kuguoglu, 2013). Aerobic exercise interventions have also been associated with

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improvements in physical fitness and reductions in fatigue, reinforcing the role of PA in symptom management and functional recovery (Abd El Baky & Adel Elhakk, 2017).

Nevertheless, the current literature remains heterogeneous regarding intervention timing, training dose, supervision, and clinical endpoints. Importantly, not all trials report consistent benefits, particularly when interventions are initiated during intensive treatment. In a long-duration randomized trial beginning shortly after diagnosis, a physical therapy and motivational program did not significantly modify bone mineral density, physical function, or health-related quality of life (HRQoL), suggesting that achieving sufficient training intensity and adherence during early treatment phases may be challenging (Cox et al., 2017). This inconsistency highlights the need to clarify which exercise prescriptions are most effective, at what stage of the therapeutic pathway they should be implemented, and which outcomes are most responsive to change in pediatric ALL.

Given the increasing population of pediatric ALL survivors and the clinical relevance of persistent physical impairments, a rigorous synthesis of the evidence is warranted to inform exercise prescription and supportive care strategies. Therefore, the aim of this systematic review was to critically evaluate the effects of PA and structured exercise interventions on physical fitness, functional performance, fatigue, and HRQoL in children and adolescents with ALL after oncologic treatment or during late phases of therapy.

MATERIALS AND METHODS

Study design and reporting framework

This systematic review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA 2020) statement (Page et al., 2021) and was structured using the PICO framework to define eligibility criteria and the research question (Santos et al., 2007).

The PICO components were defined as follows: P (Population): pediatric patients diagnosed with ALL; I (Intervention): implementation of structured PA or exercise programs; C (Comparison): usual care, placebo/sham intervention, no intervention, or within-group pre–post comparisons; O (Outcomes): changes in physical function, biological markers, and/or HRQoL; S (Study design): RCTs, non-randomized clinical trials, and pre–post test studies.

Information sources and search strategy

A structured literature search was performed in the following electronic databases: Medline (PubMed), PEDro, and SciELO, covering the period from September 2025 to December 2025. The search included studies, published in English or Spanish in the last 25 years (January 2000 to May 2025).

Search terms were developed using a combination of Medical Subject Headings (MeSH) and free-text keywords related to ALL and exercise/PA. The main concepts included *acute lymphoblastic leukemia*, *exercise*, *physical exercise*, *physical function*, and *aerobic exercise*, combined using the Boolean operator AND and OR. Additional records were retrieved through manual reference list screening of eligible studies.

Study selection process

Two reviewers independently screened titles, abstracts, and full texts to identify potentially eligible studies. Eligibility criteria were applied independently by both reviewers, and disagreements were resolved through discussion and arbitration by a third reviewer.

Eligibility criteria
Studies were included if they met all of the following criteria:

1. Population: participants diagnosed with ALL who had received oncologic treatment.
2. Study type: human studies only (animal and in vitro studies were excluded).
3. Design: randomized or non-randomized clinical trials and pre–post intervention studies (reviews, notes, and non-original research were excluded).
4. Intervention reporting: studies describing the exercise program in sufficient detail, including type, duration, frequency, and intensity.
5. Outcomes: studies reporting outcomes related to physical function, biological markers, and/or HRQoL.
6. Age: pediatric participants aged <15 years.
7. Methodological quality threshold: studies with a score of ≥8 points using the McMaster Critical Review Form for Quantitative Studies (Law et al., 2018).

Records that did not meet the inclusion criteria were excluded from the final synthesis.

Methodological quality assessment
Methodological quality of the included studies was assessed using the *McMaster Critical Review Form for Quantitative Studies*, developed by the Evidence-Based Practice Research Group at McMaster University (Law et al., 2018). This tool evaluates methodological rigor across domains such as study purpose, design, sampling, outcomes, intervention integrity, analysis, and clinical relevance.

Data extraction
Data from the included studies were extracted independently by two reviewers and summarized in a standardized table. Extracted variables included: first author, year of publication, country, study design, sample size, sex and age of participants, intervention duration, intervention characteristics, and primary outcomes. Disagreements were resolved through consensus and, when necessary, consultation with a third reviewer.

RESULTS

Study selection
The electronic search identified 59 records across PubMed, PEDro, and SciELO. After removing 36 duplicates, 23 records were screened by title and abstract. Of these, 15 articles were excluded because they did not meet the eligibility criteria (e.g., descriptive studies without a structured intervention, interventions performed exclusively during intensive treatment, or studies without an exercise component). Two additional records were excluded because they were not aligned with the objective of this review. After full-text assessment, 2 studies were excluded due to non-eligible outcomes. In addition, two studies were identified through snowball sampling, which were incorporated into the PRISMA flow diagram. Finally, 6 studies fulfilled the inclusion criteria and were included in the qualitative synthesis (Figure 1).

Methodological quality
Methodological quality was assessed using the McMaster Critical Review Form for Quantitative Studies (Law et al., 2018). Four studies were classified as excellent quality (Manchola-González et al., 2019; Tanir et al., 2012; Abd El Baky et al., 2017; Perondi et al., 2012), whereas two studies were rated as very good quality (Cox et al., 2017; Järvelä et al., 2010). No study was excluded for failing to meet the minimum methodological quality threshold (Table 1).

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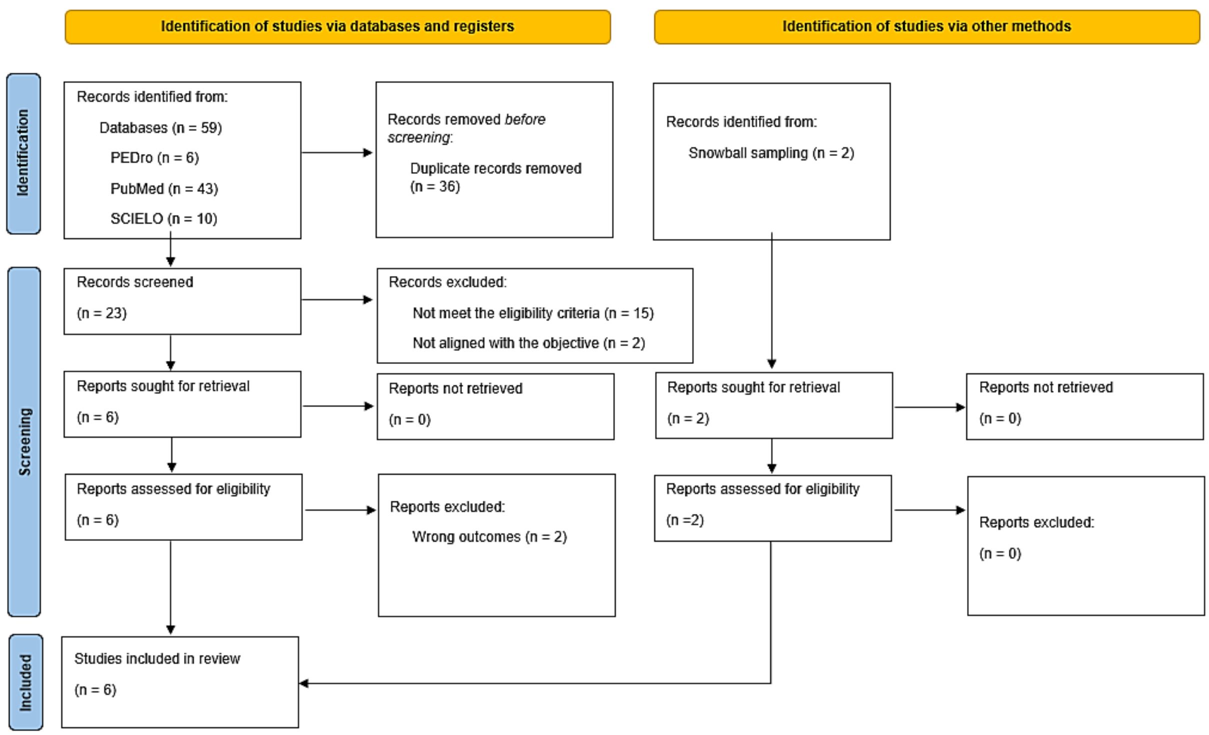

Figure 1. Flowchart represents the processes of identifying and selecting relevant studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Table 1. Methodological quality assessment of included studies using the McMaster Critical Review Form for Quantitative Studies (Law et al., 2018).

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total	%	Quality
Manchola-González et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16	100.0	E
Cox et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	14	87.5	VG
Tanir et al. (2012)	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	15	93.8	E
Järvelä et al. (2010)	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	14	87.5	VG
Abd El Baky et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	15	93.8	E
Perondi et al. (2012)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16	100.0	E

Note. (1) criterion met; (0) criterion not met; Total: Total number of criteria met; %: percentage of criteria met; G: Good, 11-12 points; VG: Very good, 13-14 points; E: Excellent, ≥15 points. The modified form consists of criteria concerning the following: item 1 -Study purpose; item 2 - Literature review; item 3 - Study design; item - 4 Blinding; item 5 - Sample description; item 6 - Sample size; item 7 - Ethics and consent; item 8 - Validity of outcomes; item 9 - Reliability of outcomes; item 10 - Intervention description; item 11 - Statistical significance; item 12 - Statistical analysis; item 13 - Clinical importance; item 14 - Conclusions; item 15 - Clinical implications; and item 16 - Study limitations.

Study characteristics

Study characteristics and intervention prescriptions are summarized in Table 2. Participants included pediatric patients with ALL across different clinical phases, including early after diagnosis, maintenance therapy, remission, and survivorship. Most included studies were RCTs evaluating structured exercise programs compared with usual care or control conditions (Manchola-González et al., 2020; Cox et al., 2017; Tanir & Kuguoglu, 2013; Abd El Baky & Adel Elhakk, 2017). In addition, one study employed a pretest–posttest design without a control group (Perondi et al., 2012), and one controlled observational study compared long-term ALL survivors with healthy controls to characterize PA and fitness profiles (Järvelä et al., 2010).

Interventions were heterogeneous in terms of exercise modality and dose, ranging from supervised aerobic training (Abd El Baky & Adel Elhakk, 2017) to multicomponent home-based programs combining aerobic, resistance, and flexibility exercises (Manchola-González et al., 2020), as well as mixed interventions incorporating mobility, strengthening, and aerobic components (Tanir & Kuguoglu, 2013). Cox et al. (2017) implemented a physiotherapy-based intervention with motivational support targeting strength, range of motion, endurance, and gross motor function early after diagnosis.

Table 2. Characteristics of included studies and exercise prescription.

Study	Country	Design	Participants	Clinical phase	Intervention	Dose	Comparator	Primary outcomes
Manchola-González et al. (2020)	Spain	RCT	Paediatric ALL survivors	≥1 year remission	Home-based multicomponent (aerobic + resistance + flexibility)	16 weeks; 3 sessions/week	Usual care	VO_{2peak}, TUG, TUDS, strength, flexibility
Cox et al. (2017)	USA	RCT	Children with newly diagnosed ALL	≤10 days post-diagnosis	PT + motivational intervention (strength, ROM, endurance, gross motor)	Long duration; frequent sessions	Usual care	BMD, physical function, HRQoL
Tanir & Kuguoglu (2013)	Turkey	RCT	Children with ALL	≥1 year remission	ROM + strengthening + aerobic training	12 weeks; 3 sessions/week (+ daily ROM)	Usual care	9-min walk, TUG, stairs, strength, HRQoL, haematology
Järvelä et al. (2010)	Finland	Controlled study	Adolescents/young adults	Long-term survivors	Physical activity exposure	Not specified	Healthy controls	VO_{2peak}, strength, fitness
Abd El Baky & Adel Elhakk (2017)	Egypt	RCT	Children with ALL	Remission	Aerobic training	16 weeks; 3 sessions/week	Usual care	Fitness outcomes, fatigue
Perondi et al. (2012)	Brazil	Pre–post	Young ALL patients	Maintenance therapy	Combined aerobic + resistance training	12 weeks; 2 sessions/week	None	Strength, fatigue, HRQoL

Note. ALL: acute lymphoblastic leukemia; BMD: bone mineral density; HRQoL: health-related quality of life; PT: physiotherapy; RCT: ramdomized controlled trial; ROM: range of movement; TUDs: timed up and down stairs test; TUG: timed up and go test; VO_{2peak}*: peak oxygen uptake.*

Synthesis of outcomes

A qualitative synthesis by outcome domain is presented in Table 3, while quantitative results reported across studies (including pre–post changes and between-group effects when available) are summarized in Table 4.

Physical function and physical fitness

Overall, structured PA interventions were consistently associated with improvements in aerobic capacity and functional performance. Manchola-González et al. (2020) reported that a 16-week home-based exercise program significantly improved VO_{2peak} compared with controls, with favorable trends in functional mobility (Timed Up and Go [TUG]) and stair performance (Timed Up and Down Stairs [TUDs]). In a pediatric RCT conducted in remission, Tanir and Kuguoglu (2013) observed significant improvements in exercise capacity (9-minute walk), functional mobility (TUG), stair-climbing performance, and lower-limb strength compared with controls. In long-term survivors, Järvelä et al. (2010) identified lower VO_{2peak} and differences in physical fitness compared with healthy controls, supporting the presence of persistent aerobic impairment after treatment and reinforcing the clinical rationale for exercise interventions.

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Quality of life and fatigue

Quality-of-life outcomes were more heterogeneous. In Cox et al. (2017), long-duration physical therapy and a motivational intervention initiated soon after diagnosis did not produce significant improvements in HRQoL compared with controls. In contrast, Perondi et al. (2012) reported improvements in parent-reported quality-of-life and fatigue measures following combined aerobic and resistance training, alongside marked gains in strength outcomes. However, HRQoL and fatigue outcomes were not consistently reported with complete numerical data across studies, limiting quantitative comparability (Table 4).

Biological outcomes

Table 3. Qualitative synthesis of effects by outcome domain.

Domain	Outcomes	Main findings	Studies
Aerobic capacity	VO_{2peak}/VO_{2max}, walking tests	Improvements observed in most interventions, especially in post-treatment/remission settings	Manchola-González et al., 2020; Tanir & Kuguoglu, 2013; Järvelä et al., 2010
Functional mobility	TUG, TUDS, stairs	Functional mobility improved mainly in multicomponent programs	Manchola-González et al., 2020; Tanir & Kuguoglu, 2013
Strength	Dynamometry, 10-RM	Strength improved in remission and maintenance interventions	Tanir & Kuguoglu, 2013; Perondi et al., 2012
HRQoL & fatigue	PedsQL, fatigue scales	Mixed results; improvements more evident in maintenance/pre–post designs	Cox et al., 2017; Perondi et al., 2012; Abd El Baky & Adel Elhakk, 2017
Biological outcomes	BMD, haematology	No effect on BMD during early treatment; haematology improved in one remission trial	Cox et al., 2017; Tanir & Kuguoglu, 2013

Note. BMD: bone mineral density; HRQoL: health-related quality of life; PedsQL: Pediatric Quality of Life Inventory; RM: Maximum repetition; TUDs: timed up and down stairs test; TUG: timed up and go test; VO_{2peak}: peak oxygen uptake; VO_{2max}: maximum oxygen uptake.

Table 4. Quantitative results.

Study	Outcome	Intervention (PRE → POST)	Control (PRE → POST)	Main effect / Between-group result	*p*-value (between-group / main effect)	*p*-value (within IG)
Manchola-González et al., 2020	VO_{2peak} (ml/kg/min)	NR	NR	Group×time: +6.7 (95% CI 0.6–12.8)	.035	NR
Manchola-González et al., 2020	TUG (s)	6.4 ± 1.5 → NR	6.5 ± 1.8 → NR	Δ between: −0.5 (95% CI −1.1 to 0.4)	.068	NR
Manchola-González et al., 2020	TUDS (s)	11.1 ± 1.5 → NR	10.8 ± 2.0 → NR	Δ between: −0.5 (95% CI −1.3 to 0.3)	.217	NR
Tanir & Kuguoglu, 2013	9-min walk (cycles)	27.05 ± 6.59 → 35.89 ± 8.46	26.27 ± 9.28 → 26.76 ± 10.57	Post-test IG vs CG significant	.005	NR
Tanir & Kuguoglu, 2013	TUG (s)	8.31 ± 1.60 → 6.57 ± 1.34	8.77 ± 1.60 → 8.33 ± 1.62	Post-test IG vs CG significant	.001	NR
Tanir & Kuguoglu, 2013	Leg strength (dynamometer)	50.52 ± 27.38 → 75.52 ± 30.22	39.09 ± 13.85 → 40.71 ± 17.19	Post-test IG vs CG significant	.001	NR
Tanir & Kuguoglu, 2013	Haemoglobin (g/dL)	12.40 ± 1.13 → 12.94 ± 0.69	12.36 ± 0.77 → 12.60 ± 0.63	Post-test IG vs CG not significant	.126	.002
Tanir & Kuguoglu, 2013	Haematocrit (%)	37.58 ± 3.14 → 39.22 ± 2.16	38.94 ± 2.61 → 39.80 ± 2.11	Post-test IG vs CG not significant	.411	.002
Cox et al., 2017	BMD (Z-score)	−0.21 → −0.55	−0.62 → −0.78	Rates of decline did not differ	.56	NR
Perondi et al., 2012	10-RM leg press (kg)	29.5 ± 13.7 → 51.2 ± 12.9	NR	Pre–post improvement	NR	<.001

Note. BMD: bone mineral density; CI: confidence interval; dL: decilitres; g: grams; Kg: kilograms; min: minute; ml: millilitre; NR: not reported; RM: Maximum repetition; s: seconds; TUDs: timed up and down stairs test; TUG: timed up and go test; VO_{2peak}: peak oxygen uptake.

Biological outcomes varied across trials. Cox et al. (2017) found no significant between-group differences in bone mineral density trajectories, suggesting limited osteoprotective effects of the intervention during early treatment. Conversely, Tanir and Kuguoglu (2013) reported improvements in hematological parameters (hemoglobin and hematocrit) in the intervention group, although these outcomes were not consistently available for quantitative comparison across studies (Table 4).

Quantitative synthesis (post-intervention values)

In the present review, quantitative synthesis was limited by the small number of trials reporting comparable outcomes with complete post-intervention dispersion data. Nevertheless, single-study effect estimates suggested clinically meaningful improvements in functional mobility and aerobic capacity following structured exercise interventions. Quantitative synthesis was performed using post-intervention values to estimate between-group effects for outcomes reported with sufficient statistical detail. Given the heterogeneity in intervention content, clinical phase, and outcome assessment across studies, pooled meta-analysis was not feasible for most endpoints. Therefore, single-study effect estimates are presented as mean differences (MD) with 95% confidence intervals (95% CI), complemented by standardized mean differences (Hedges g) to facilitate interpretation of effect magnitude (Table 5).

Table 5. Quantitative synthesis (post-intervention values).

Outcome	Study	n (Int)	Mean (SD) Int	n (Ctrl)	Mean (SD) Ctrl	MD	95% CI	Direction
TUG (s)	Tanir & Kuguoglu (2013)	15	6.57 (1.34)	15	8.33 (1.62)	−1.76	[−2.82, −0.70]	Favours intervention
VO_{2max} (ml/kg/min)	Abd El Baky & Adel Elhakk (2017)	15	33.50 (3.72)	15	26.30 (4.70)	7.20	[4.17, 10.23]	Favours intervention

Abbreviation: CI: confidence interval; Ctrl: control group; Int: intervention group; MD: mean difference (Intervention − Control); SD: standard deviation; TUG: timed up and go; VO_{2max}: maximum oxygen uptake. Negative MD values indicate improvement for TUG (lower time), whereas positive MD values indicate improvement for VO_{2max} (higher aerobic capacity).

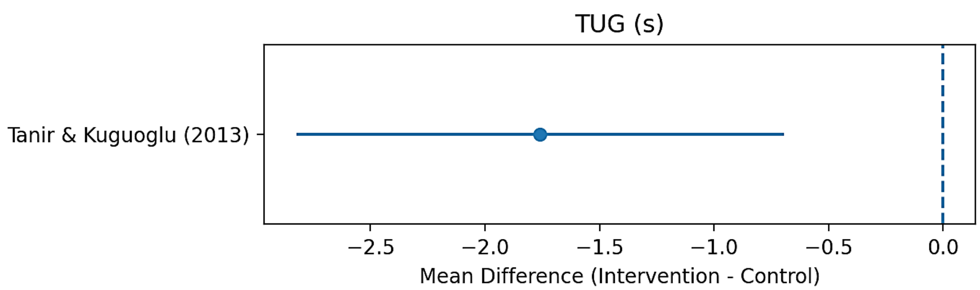

Figure 2. Forest plot for TUG (post-intervention values).

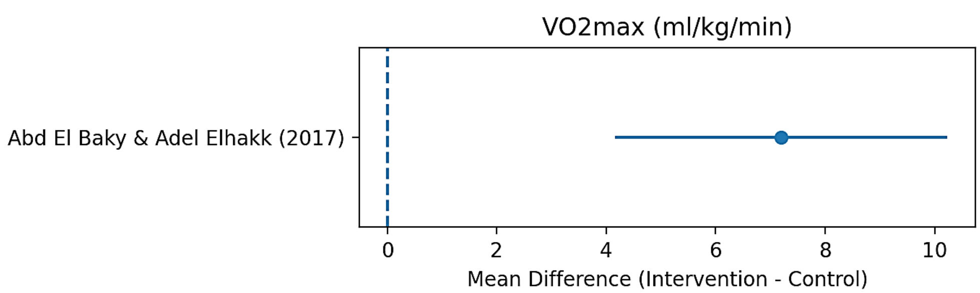

Figure 3. Forest plot for VO_{2max} (post-intervention values).

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TUG (s): Tanir & Kuguoglu (2013) reported a lower post-intervention TUG time in the exercise group compared with controls (MD = −1.76 s; 95% CI −2.82 to −0.70; Hedges g = −1.15; 95% CI −1.93 to −0.38) (Figure 2 and Table 5).

VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$): Abd El Baky & Adel Elhakk (2017) reported higher post-intervention VO_{2max} in the exercise group compared with controls (MD = 7.20; 95% CI 4.17 to 10.23; Hedges g = 1.65; 95% CI 0.82 to 2.49) (Figure 3 and Table 5).

These findings support exercise as a promising supportive strategy in pediatric ALL; however, conclusions remain preliminary and should be confirmed in adequately powered randomized trials with standardized outcome reporting.

DISCUSSION

The aim of this systematic review was to critically evaluate the potential effects of structured PA and exercise programs in paediatric patients with ALL after oncologic treatment. Six studies met the pre-specified eligibility criteria and were included in the qualitative synthesis (Manchola-González et al., 2020; Cox et al., 2017; Tanir & Kuguoglu, 2013; Järvelä et al., 2010; Abd El Baky & Adel Elhakk, 2017; Perondi et al., 2012). Overall, improvements were reported in key domains of physical fitness, particularly aerobic capacity (VO_2-related outcomes) and muscle strength. However, evidence regarding HRQoL was inconsistent, with several studies failing to demonstrate statistically significant between-group differences. In addition, selected biological outcomes showed variable responses to exercise, depending on the biomarker assessed and the clinical context of the intervention. Given the heterogeneity of outcomes and measurement methods across studies, findings are discussed below by domain to facilitate interpretation.

Exercise programs: characteristics and training prescription

Most interventions included in this review applied multicomponent exercise, combining aerobic exercise with flexibility/stretching and resistance training (Manchola-González et al., 2020; Tanir & Kuguoglu, 2013; Abd El Baky & Adel Elhakk, 2017; Perondi et al., 2012). In contrast, one study did not implement a structured protocol but examined associations between habitual PA and health-related parameters in long-term survivors (Järvelä et al., 2010).

Aerobic exercise is widely regarded as a cornerstone of healthy recovery following chemotherapy and may contribute to improved cardiorespiratory capacity and functional performance in paediatric cancer survivors (Herrera de León Potente, 2019). In the included studies, aerobic exercise was delivered through accessible modalities such as walking, jogging, or cycling, and intensity was commonly individualized according to patient tolerance and baseline capacity (Manchola-González et al., 2020; Tanir & Kuguoglu, 2013; Abd El Baky & Adel Elhakk, 2017; Perondi et al., 2012). Conversely, Cox et al. (2017) implemented a long-duration physical therapy and motivational intervention early after diagnosis, reflecting a different clinical scenario where intensive training may be limited by treatment burden and symptom fluctuations.

Resistance training was also incorporated in several protocols, aiming to counteract treatment-related muscle loss and restore functional independence. Three studies included strengthening exercises targeting the lower limbs, upper limbs, and core musculature (Manchola-González et al., 2020; Abd El Baky & Adel Elhakk, 2017; Perondi et al., 2012). Notably, Tanir and Kuguoglu (2013) focused primarily on lower-limb strengthening, consistent with the importance of lower extremity function for mobility tasks such as walking and stair climbing. Cox et al. (2017) evaluated ankle strength outcomes, which is clinically relevant given that ankle range-of-motion and function may be impaired in ALL survivors (Wright et al., 1999). Flexibility and mobility exercises were included in several programs, often targeting both upper and lower extremities (Manchola-González et al., 2020; Abd El Baky & Adel Elhakk, 2017; Perondi et al., 2012), whereas other trials did not clearly describe stretching components (Cox et al., 2017; Järvelä et al., 2010).

Across protocols, duration ranged from 12 to 16 weeks in most studies, with training frequencies typically between 2 and 5 sessions per week. Importantly, interventions generally emphasized gradual progression and individualization, and most were delivered with professional supervision or structured guidance. These characteristics are consistent with paediatric oncology recommendations highlighting safety, feasibility, and adaptation to treatment-related variability (White et al., 2005).

Effects on physical function and physical capacity

Early initiation of PA during the oncologic pathway may be clinically meaningful to attenuate rapid deconditioning, even when exercise intensity and volume must be reduced (Cox et al., 2017). Across included trials, exercise interventions were associated with improvements in aerobic capacity, mobility, and strength outcomes, supporting the hypothesis that structured PA can mitigate functional decline in paediatric ALL.

Aerobic capacity, typically measured using VO_2 outcomes or functional walking tests, improved in several interventions, particularly in remission or survivorship settings. Improvements in VO_{2peak} were observed following a home-based program in ALL survivors (Manchola-González et al., 2020) and following aerobic training protocols (Abd El Baky & Adel Elhakk, 2017). In contrast, long-term survivors still displayed reduced aerobic fitness compared with controls in Järvelä et al. (2010), highlighting the persistence of cardiopulmonary impairment and the need for long-term supportive care strategies. Regarding cardiovascular parameters, no significant differences in maximal heart rate were reported between groups in Järvelä et al. (2010), suggesting that functional capacity differences may be related to peripheral limitations, deconditioning, or reduced habitual activity rather than central cardiac impairment alone.

Strength outcomes were generally favourable but varied by muscle group and assessment method. Cox et al. (2017) reported improvements in ankle strength in both intervention and control groups, while Perondi et al. (2012) found significant strength gains in multiple resistance exercises (leg press, bench press, leg extension, and chest pull). In addition, Tanir and Kuguoglu (2013) and Manchola-González et al. (2020) demonstrated improvements in functional performance tests (e.g., walking capacity, stair performance), although handgrip strength did not consistently improve, potentially reflecting differences in training specificity or measurement sensitivity.

Unexpectedly, flexibility improvements were reported in the control group in Manchola-González et al. (2020), despite flexibility training being included in the intervention protocol. This finding may reflect measurement variability, spontaneous recovery over time, or unmeasured PA exposure in controls.

Effects on quality of life and fatigue

Beyond physical limitations, children with ALL may experience social isolation, loss of independence, anxiety, and depressive symptoms, which can negatively affect HRQoL in both patients and caregivers (Tanir & Kuguoglu, 2013). HRQoL was assessed primarily through standardized questionnaires administered pre- and post-intervention, but instruments varied across studies (Cox et al., 2017; Tanir & Kuguoglu, 2013; Perondi et al., 2012).

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Overall, HRQoL findings were mixed. Cox et al. (2017) did not observe significant between-group differences in HRQoL outcomes, possibly due to intervention timing near diagnosis, high treatment burden, or insufficient training dose to induce psychosocial changes. Tanir and Kuguoglu (2013) reported domain-specific improvements (e.g., pain and cognitive problems) in the intervention group, whereas anxiety-related outcomes improved in controls, suggesting complex psychosocial trajectories that may not be solely driven by exercise exposure. In Perondi et al. (2012), parent-reported fatigue improved significantly, and HRQoL showed a positive trend without reaching statistical significance, which may be explained by limited sample size and the challenges of detecting change in multidimensional psychosocial constructs.

These findings suggest that while exercise may contribute to improved fatigue and perceived well-being, HRQoL outcomes in paediatric oncology likely require broader supportive interventions and longer follow-up to capture clinically meaningful changes.

Effects on biological markers

Biological markers are measurable indicators present in body fluids or tissues that reflect physiological or pathological processes and may be used to monitor disease status and treatment response (Iranzo, 2015). Biological outcomes in the included studies were heterogeneous and included oxygen-related parameters, bone mineral density, haematological indices, and cardiovascular variables.

In Manchola-González et al. (2020), oxygen pressure (mL/beat) remained stable in both intervention and control groups. Cox et al. (2017) found no significant effects of the intervention on bone mineral density, suggesting that the applied exercise dose may not be sufficient to counteract treatment-associated skeletal decline, particularly when initiated during intensive therapy. In contrast, Tanir and Kuguoglu (2013) reported significant improvements in haemoglobin and haematocrit in the intervention group, indicating that exercise may support physiological recovery in remission contexts. Finally, Järvelä et al. (2010) observed no significant between-group differences in systolic or diastolic blood pressure, which may reflect the relatively young age of participants and limited cardiovascular impairment detectable through resting hemodynamic measures.

Strengths and limitations

This review has several strengths. It was conducted following PRISMA 2020 guidelines (Page et al., 2021), used a structured search strategy across three electronic databases, and applied a standardized methodological quality assessment tool (Law et al., 2018). Additionally, the review focused on outcomes commonly evaluated in paediatric exercise oncology, including functional capacity, fitness markers, HRQoL, and selected biological parameters.

However, important limitations should be acknowledged. First, the number of eligible studies was limited, restricting the generalizability of conclusions. Second, there was substantial heterogeneity in intervention content, supervision, dose, clinical phase, and outcome measures, which prevented meta-analysis and requires caution in interpreting pooled conclusions. Third, some studies included participants early after diagnosis or during maintenance therapy, which may not strictly align with "*post-treatment*" definitions and complicates clinical extrapolation. Finally, sample sizes were generally small and follow-up periods were short, limiting the ability to evaluate long-term sustainability and safety.

Clinical and practical applications

Structured PA and exercise may be considered as supportive care interventions in paediatric ALL, with careful tailoring to clinical status and treatment phase. Based on the evidence synthesized in this review, the following practical recommendations can be proposed:

1. Exercise mode: Multicomponent programs combining aerobic training with resistance and flexibility exercises appear most suitable to address the broad functional deficits observed in paediatric ALL (Manchola-González et al., 2020; Tanir & Kuguoglu, 2013; Perondi et al., 2012).
2. Training dose: Interventions lasting 12–16 weeks, performed 2–3 sessions/week, with gradual progression, are feasible and may yield improvements in aerobic capacity and functional mobility.
3. Individualization and supervision: Exercise intensity should be individualized and adapted to fatigue, neuromuscular symptoms, and medical status. Professional supervision or structured guidance improves safety and adherence (White et al., 2005).
4. Key outcomes to monitor: Clinically relevant outcomes include VO_2-related measures or walking tests, TUG/TUDS, lower-limb strength, and fatigue scales.
5. Timing considerations: Exercise initiated during early intensive treatment may have limited impact on outcomes such as bone mineral density and HRQoL, potentially requiring longer or more targeted interventions (Cox et al., 2017).
6. Family-centred approach: Given the psychosocial burden of ALL, interventions may benefit from including family education and strategies to facilitate safe activity participation at home and school.

Figure 4. Clinical and practical applications of structured exercise in paediatric acute lymphoblastic leukaemia.

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To facilitate clinical translation of the evidence, Figure 4 summarizes key practical recommendations for implementing structured PA as supportive care in paediatric ALL.

Overall, these recommendations highlight the importance of individualized, multicomponent exercise prescriptions with appropriate supervision and family involvement to optimize functional recovery and long-term health outcomes in this population.

CONCLUSIONS

Structured PA and exercise interventions appear feasible in paediatric ALL and are generally associated with improvements in aerobic capacity, functional mobility, and selected strength outcomes, particularly in remission and survivorship settings. Evidence regarding HRQoL remains inconsistent, and biological outcomes show heterogeneous responses across studies. Future research should prioritize adequately powered randomized trials with standardized exercise prescription, consistent outcome reporting, and long-term follow-up to establish optimal exercise protocols and clarify their role in improving survivorship health trajectories.

AUTHOR CONTRIBUTIONS

Conceptualization: D.F.-L., A.M.C.S.M., and C.D.O.; methodology: D.F.-L. and C.D.O.; software: N.H.-B. and G.S.; validation, A.M.C.S.M., N.H.-B. and G.S.; formal analysis, D.F.-L., A.M.C.S.M. and C.D.O.; investigation, N.H.-B. and G.S.; resources, D.F.-L., N.H.-B. and G.S.; data curation, D.F.-L.; writing—original draft preparation, D.F.-L. And C.D.O.; writing—review and editing, A.M.C.S.M., N.H.-B. and G.S.; visualization, A.M.C.S.M., N.H.-B. and G.S.; supervision, D.F.-L.; project administration, D.F.-L.; funding acquisition, D.F.-L.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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Effects of physical exercise on cancer-related cognitive impairment: Protocol for an umbrella review

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ABSTRACT

Cancer-related cognitive impairment (CRCI) is a mild but meaningful decline in cognitive function among cancer patients, affecting domains such as memory, attention, and executive functions. Emerging evidence suggests that physical exercise is a promising non-pharmacological strategy to mitigate these symptoms. Although several systematic reviews and meta-analyses have examined this topic, no umbrella review has yet synthesized the full body of evidence. This umbrella review aims to integrate findings on the effects of exercise on different cognitive domains in cancer populations, considering both self-reported and objective outcomes. The review will follow PRIOR guidelines and apply a PRISMA-based search strategy across four databases (MEDLINE/PubMed, Scopus, Web of Science, and SPORTDiscus). Eligibility criteria will follow the PICOS framework, including systematic reviews with or without meta-analyses evaluating exercise interventions and their impact on cognitive outcomes in individuals with cancer. Data on intervention characteristics, cognitive domains, and effect sizes will be extracted, and methodological quality will be assessed using GRADE and AMSTAR-2. This review will offer a comprehensive synthesis of current evidence on exercise and CRCI, helping identify the most responsive cognitive domains, effective exercise modalities, and key methodological gaps to inform future research and evidence-based recommendations for cancer survivors' cognitive health.
Keywords: Cognitive function, Physical activity, Oncology, Umbrella review, Protocol.

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INTRODUCTION

Recent advances in biomedical research and improvements in therapeutic strategies have contributed to higher prevalence and survival rates among individuals diagnosed with cancer. Despite these advances, several treatments are associated with a variety of toxicities and adverse effects, including a potential impairment of cognitive function (Olson and Marks, 2019). Some of the treatments among those reported to have associated cognitive toxicities include chemotherapy, radiotherapy, immunotherapy, hormonal therapies, targeted therapies, or endocrine therapies (Spinetti and Orzelleca, 2025).

This cognitive impairment is known as cancer-related cognitive impairment (CRCI) or, more colloquially, chemofog or chemobrain (Whittaker et al., 2022). CRCI is associated with a series of adverse effects in cognitive domains such as executive function, attention, processing speed (Hamilton et al., 2024), memory, learning ability, word retrieval (Oliva et al., 2024), perception or problem-solving (Williams et al., 2016). Patients report symptoms and subjective cognitive complaints, such as increased distraction, memory lapses, difficulties in finding words and names, decreased concentration, slower comprehension of new information or reduced psychomotor efficiency (Oliva et al., 2024; Bai and Yu., 2021). Janelsins et al. (2014) reported that approximately 30% of patients with cancer exhibit cognitive symptoms prior to initiating treatment, with this proportion rising to about 75% during therapy; moreover, up to 35% continue to experience such symptoms for several months or even years following treatment completion.

Several physiological and psychological mechanisms contribute to cancer-related cognitive impairment (CRCI). One of the most widely proposed mechanisms is systemic and central neuroinflammation, characterized by a sustained increase in proinflammatory cytokines such as INF-α, IL-1β, IL-6, IL-8, IL-10, and MCP-1 (Wang et al., 2015). This inflammatory milieu can disrupt the integrity of the blood-brain barrier and activate glial cells, thereby compromising neuronal homeostasis (Lomeli et al., 2021). Neuroinflammation may also induce the production of reactive oxygen species (ROS), promote mitochondrial dysfunction, and trigger DNA damage, collectively impairing synaptic plasticity and neurogenesis (Kim et al., 2025). Brain-derived neurotrophic factor (BDNF) represents another key element in CRCI due to its sensitivity to inflammation associated with cancer and chemotherapy. Neuroinflammatory processes can suppress BDNF expression, reducing its availability within the central nervous system (Yap et al., 2021). Psychological factors also play a significant role, as multiple studies have reported associations between CRCI and anxiety, depression, post-traumatic stress symptoms, and reduced motivation (Rick et al., 2024).

There is increasing evidence supporting physical exercise as an effective non-pharmacological strategy to mitigate CRCI. Benefits have been reported across multiple exercise modalities, including aerobic training, resistance exercise, balance and coordination work, and Eastern practices such as yoga, qigong, and tai chi, which have been shown to improve CRCI-related symptoms and overall quality of life in cancer patients (Bai and Yu, 2020; Lv et al., 2020). Proposed mechanisms underlying these effects include enhanced neurogenesis in the adult hippocampus, the integration of newly generated neurons into functional networks, and improvements in memory (Sekeres et al., 2021). Exercise may also increase BDNF production, improve cerebral oxygenation through augmented blood flow, and attenuate proinflammatory cytokine activity, thereby supporting neuronal plasticity and modulating inflammatory processes linked to cognitive decline (Mackenzie and Marshall, 2022; Lv et al., 2020). Previous studies have already shown the benefits of an intervention with physical exercise on both objective and subjective cognitive function, although the evidence is stronger for cognitive function measured subjectively (Oldacres et al., 2023). Collectively, this evidence highlights physical exercise as a promising intervention for addressing cognitive impairments associated with cancer and its treatments.

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Although the literature on exercise and its effect on CRCI has grown in recent years, the evidence remains heterogeneous. After an initial search, no umbrella review on the topic was found. This highlights the need for an umbrella review that integrates the current evidence on the effects of physical exercise on CRCI from existing systematic reviews and meta-analyses. The main objective of this umbrella review, therefore, is to synthesize the current evidence on the effects of physical exercise on cognitive impairment in cancer patients, critically evaluate it, understand the current state of the issue, identify strengths, limitations, and research gaps, and guide future research and clinical practice.

MATERIAL AND METHODS

This umbrella review will be conducted following the guidelines of the PRIOR statement (Gates et al., 2022). Additionally, the search strategy will be designed and carried out according to PRISMA recommendations (Page et al., 2021). The protocol for this review was registered with the Open Science Framework (OSF): https://doi.org/10.17605/OSF.IO/DHBR5

Search strategy

A comprehensive search will be conducted in four electronic databases: MEDLINE/PubMed, Scopus, Web of Science, and SPORTDiscus. The research terms to be used in the databases are:

("physical activity" OR "exercise" OR "sports" OR "movement therapy") AND ("cognitive impairment" OR "crci" OR "chemobrain" OR "chemo-fog" OR "cognition" OR "neuropsychology" OR "executive functions" OR "attention" OR "memory") AND ("cancer" OR "tumor" OR "tumour" OR "metastasis" OR "chemotherapy" OR "radiotherapy" OR "hormonetherapy") AND ("Review" OR "Systematic Review" OR "Overview" OR "Meta-Analysis").

Once the resulting articles have been reviewed, a backward citation searching and forward citation searching will be conducted using Google Scholar and the reference lists of the included studies.

Eligibility criteria

This umbrella review will use the definition of a systematic review described by PRISMA: "*A systematic review is a review that uses explicit, systematic methods to collate and synthesize findings of studies that address a clearly formulated question*". Systematic reviews, with or without meta-analysis, that provide evidence on the effects of physical exercise on cognitive function in oncology patients will be included. The inclusion criteria will be based on the Participant-Intervention-Comparison-Outcome-Study (PICOS) framework: 1) Participants: Adult oncology patients with cognitive impairment. 2) Intervention: Systematic reviews examining the effects of physical activity interventions. 3) Comparison group: Control group or a baseline phase without physical activity intervention. 4) Outcome measures: Measures related to cognitive functions.

Studies will be considered eligible if they have been published or accepted for publication in peer-reviewed journals. Additionally, an accessible abstract will be required for the preselection process, and no language restrictions will be applied.

Articles will be excluded from the umbrella review based on the following criteria: 1) narrative reviews without a search algorithm or that do not describe how studies were selected for the review; 2) reviews that include mixed samples, unless specific data are available for the cancer subgroup; 3) reviews that include exclusively observational studies; 4) conference abstracts, books, theses, and dissertations.

Study selection

The selection of the included articles will be carried out by two authors (FGA and CG). The Rayyan software (Rayyan Systems Inc., Cambridge, MA, USA) will be used to initially assess the titles and abstracts of the identified articles. Subsequently, both researchers will review the full texts of the selected studies to confirm their inclusion. Discussions will be held, and mutual agreements will be reached in case of conflicts. In the event of discrepancies, a third author (DGD) will be consulted.

Data extraction

Two independent reviewers (FGA and CG) will extract all relevant information from the included systematic reviews, as well as the corresponding assessments conducted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) instrument. Extracted data will be cross-checked between reviewers to ensure accuracy and to allow for an independent verification process. In the event of overlap among the articles included in the systematic reviews, the total number of primary articles will be identified and recorded.

The following data items will be extracted: authorship, study design, and publication year; databases searched and search periods reported in each systematic review or meta-analysis; total number of included studies and sample characteristics; types of study designs selected; risk of bias assessments; detailed descriptions of the exercise interventions; cognitive outcomes evaluated; and a synthesized summary of the main conclusions of each review. All the information collected will also be reviewed by the other authors of the article (DGD, CN, and OLV).

Assessment of the methodological quality

A methodological quality analysis of the studies will be conducted using two validated tools: AMSTAR 2 and GRADE. This evaluation will be conducted independently by two authors (FGA and CG) and subsequently peer-reviewed by a third author (DGD).

The AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) is designed to assess the methodological rigor of systematic reviews by examining weaknesses across a set of critical domains—specifically items 2, 4, 7, 9, 11, 13, and 15 (Liberati et al., 2009). Based on the presence and severity of flaws in these domains, AMSTAR 2 assigns an overall confidence rating in the results of the review, categorized into four levels (Shea et al., 2017): high confidence (none critical flaws and at most one non-critical weakness); moderate confidence (more than one non-critical weakness, but no critical flaws); low confidence (one critical flaw, regardless of the presence of non-critical weaknesses); critically low confidence (more than one critical flaw with or without non-critical weaknesses).

Additionally, the GRADE framework (Grading of Recommendations, Assessment, Development, and Evaluation) will be applied to rate the certainty of the evidence for each intervention analysed in the systematic review. This assessment is specific to each study and considers factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias (Andrews et al., 2013).

DISCUSSION

Several systematic reviews and meta-analyses have addressed the impact of exercise on cognitive outcomes in cancer populations, although often with heterogeneous samples in terms of cancer type, exercise modalities, or individual cognitive outcomes (Campbell et al., 2020; Zimmer et al., 2016). Although these reviews frequently report beneficial effects, their conclusions are difficult to interpret due to heterogeneity in

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cognitive constructs, assessment methods, and intervention characteristics. The absence of an umbrella review that integrates these reviews has limited the ability to draw higher-level conclusions and to identify consistent patterns across different cognitive domains and assessment approaches.

This umbrella review is designed to address a research gap in the literature by providing the first comprehensive overview of existing systematic reviews and meta-analyses that examine the effects of physical exercise on CRCI. By adopting an umbrella review methodology, this study aims to consolidate scattered evidence, clarify inconsistencies between reviews, and offer a structured synthesis that goes beyond the scope of individual systematic reviews.

This umbrella review aims to synthesize the available evidence on the effects of physical exercise on both self-reported and objectively measured cognitive outcomes, including domain-specific analyses. In addition, detailed information on exercise interventions, such as exercise modality, intensity, duration, and other characteristics, will be extracted. This approach will facilitate the identification of the exercise parameters most strongly associated with improvements in cognitive function.

Given that the diagnosis of CRCI remains a topic of ongoing debate, this umbrella review seeks to compare the materials and methods of the included reviews and primary studies with the research recommendations of the International Cancer and Cognition Task Force (ICCTF), which has proposed diagnostic criteria and recommended neuropsychological assessments for specific cognitive domains (Demos-Davies et al., 2024).

One of the principal strengths of this protocol is the implementation of a rigorous and transparent methodological framework. The review process is guided by the directives of the PRIOR statement and the recommendations outlined in the PRISMA guidelines. The use of AMSTAR-2 and GRADE will enable a critical appraisal of the internal validity of the included systematic reviews and the certainty of their findings. Furthermore, explicit procedures will be employed to identify and manage overlap among primary studies across reviews, allowing for the calculation of the total number of unique primary articles and thereby enhancing the methodological robustness of the umbrella review.

However, several limitations inherent to the proposed methodological approach are anticipated. The conclusions of this umbrella review will be contingent upon the quality, scope, and heterogeneity of the included systematic reviews and meta-analyses. In particular, the variability in CRCI definitions, cognitive assessment instruments, and the characteristics of the exercise interventions may constrain the comparability of findings across reviews and represent a potential limitation for the synthesis and interpretation of results.

The findings of this umbrella review are expected to have implications for both research and clinical practice. At the research level, the synthesis will help identify key methodological gaps, including the limited examination of moderating factors, the inconsistent use of standardized cognitive assessment batteries, and the underrepresentation of neurobiological and neurophysiological outcomes. At the clinical level, the results may support the incorporation of exercise-based interventions into comprehensive survivorship care and contribute to the development of future evidence-based recommendations targeting CRCI.

CONCLUSIONS

This protocol describes the methodology for the first umbrella review to synthesize evidence from systematic reviews and meta-analyses examining the effects of physical exercise on cancer-related cognitive impairment. By integrating findings from both self-reported and objectively measured cognitive outcomes, across multiple cognitive domains and exercise modalities, and by applying rigorous methodological appraisal and certainty-of-evidence frameworks with AMSTAR 2 and GRADE, this umbrella review aims to deliver a comprehensive and critical synthesis of the current literature. The findings of this umbrella review are expected to clarify the existing evidence base, identify methodological limitations, and guide future research and the development of evidence-based exercise interventions aimed at improving cognitive health in individuals with cancer.

AUTHOR CONTRIBUTIONS

FGA (first and submitting author): Conceptualization, Methodology, Writing – original draft, Writing – review & editing; DGD: Conceptualization, Methodology, Supervision, Writing – review & editing; CG: Conceptualization, Methodology; CN: Conceptualization, Writing – review & editing; OLV (corresponding author): Conceptualization, Methodology, Supervision, Writing – review & editing.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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PHYSICAL ACTIVITY, EXERCISE AND CANCER

REVIEW ARTICLE

Impact of exercise interventions in people with colon and colorectal cancer on quality of life, physical function and fatigue: A systematic review

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ABSTRACT

Colon and colorectal cancer treatments are frequently associated with cancer-related fatigue, physical deconditioning, and reduced health-related quality of life (HRQoL). Exercise has been proposed as a supportive care strategy, but evidence remains heterogeneous. This systematic review aimed to evaluate the effects of exercise interventions on cancer-related fatigue, physical function, HRQoL, and selected biological outcomes in adults with colon or colorectal cancer. Searches were conducted in PubMed, PEDro, and Scopus following PRISMA 2020 guidelines. Randomized and controlled clinical trials assessing structured exercise interventions were included. Methodological quality was evaluated using the McMaster Critical Review Form and the PEDro scale. Due to heterogeneity, results were synthesized qualitatively, with limited quantitative synthesis based on single-study effect estimates. Five studies met the inclusion criteria. Exercise interventions delivered during chemotherapy or survivorship consistently reduced cancer-related fatigue, showing moderate-to-large effect. Small-to-moderate improvements in physical function and muscular strength were observed. HRQoL outcomes were generally favorable, particularly in physical and functional domains. Evidence regarding biological outcomes was limited but suggested potential benefits for gastrointestinal function, sleep quality, and selected biomarkers. Overall, structured exercise appears to be a feasible and clinically relevant supportive care intervention for patients with colon and colorectal cancer. Further high-quality trials with standardized protocols are required.
Keywords: Colon cancer; Colorectal cancer; Exercise; Physical activity; Cancer-related fatigue; Quality of life.

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INTRODUCTION

Colorectal cancer, and specifically colon cancer, represents one of the most prevalent malignancies worldwide and constitutes a major public health challenge due to its high incidence, morbidity, and mortality. In developed countries, colon cancer ranks among the leading causes of cancer-related death in both men and women, with incidence increasing markedly after the age of 50 years (SEOM, 2025; Siegel et al., 2023). Although advances in screening, surgical techniques, and adjuvant oncological treatments have substantially improved survival rates, a growing number of patients and survivors experience persistent physical, psychological, and functional impairments (Denlinger & Barsevick, 2009; Meyerhardt et al., 2006).

Standard treatments for colon cancer—including surgery, chemotherapy, and radiotherapy—are frequently associated with adverse effects such as cancer-related fatigue, reduced physical capacity, loss of muscle mass and strength, gastrointestinal dysfunction, psychological distress, and impaired health-related quality of life (HRQoL) (Monga et al., 2007; Van Waart et al., 2018). These treatment-related sequelae may persist long after completion of therapy, negatively affecting daily functioning, social participation, and overall well-being. In particular, fatigue is consistently reported as one of the most burdensome and prevalent symptoms among patients undergoing and recovering from colorectal cancer treatment (Bower, 2014; Brown et al., 2018; Van Waart et al., 2018; Williams et al., 2015).

Sedentary behaviour and reduced physical activity levels are common during and after cancer treatment, further exacerbating physical deconditioning, functional decline, and metabolic disturbances. In patients with colon cancer, physical inactivity may compound treatment-related muscle wasting, reduced cardiorespiratory fitness, and declines in functional independence, thereby increasing vulnerability to comorbidities and reducing HRQoL (Silver et al., 2013). Consequently, strategies aimed at mitigating these adverse effects are increasingly recognized as a critical component of comprehensive cancer care.

In this context, structured physical activity and exercise interventions have emerged as promising non-pharmacological strategies to counteract the negative consequences of cancer and its treatments. A growing body of evidence suggests that aerobic exercise, resistance training, and multicomponent exercise programs can improve physical fitness, reduce cancer-related fatigue, enhance psychological well-being, and improve quality of life (QoL) in patients with colorectal cancer (Brown et al., 2018; Van Vulpen et al., 2015). Exercise has also been proposed as a potential modulator of biological processes, including inflammation, metabolic regulation, and gastrointestinal function, which may be particularly relevant in colon cancer survivorship (Campbell et al., 2019; McTiernan, 2016; Van Vulpen et al., 2015).

Despite increasing interest in exercise oncology, the existing literature in colon cancer remains heterogeneous. Previous studies differ substantially in study design, patient characteristics, treatment phase, exercise modality, intensity, duration, and outcome measures. Some trials have focused on supervised exercise programs delivered during adjuvant chemotherapy, whereas others have examined home-based or self-directed interventions in cancer survivors (Kim et al., 2018; Williams et al., 2015). Moreover, outcomes have been assessed using a wide range of physical, perceptual, and biological measures, limiting direct comparability across studies and precluding robust quantitative synthesis.

Therefore, a systematic and critical synthesis of the available evidence is warranted to clarify the role of exercise interventions in patients with colon and colorectal cancer. The aim of this systematic review was to evaluate the effects of structured physical activity and exercise interventions on physical function, physical fitness, cancer-related fatigue, QoL, and selected biological outcomes in adult patients with colon cancer

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during and after oncological treatment. By integrating current evidence, this review seeks to inform clinical practice and guide future research on the implementation of exercise as supportive care in colon cancer management.

MATERIALS AND METHODS

Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The methodological framework followed established principles of evidence-based medicine, ensuring a structured, transparent, and reproducible synthesis of the available literature (Sackett et al., 1996). The review protocol was defined *a priori* to minimize selection bias and enhance methodological rigor throughout all stages of the review process.

Eligibility Criteria (PICOS Framework)

Eligibility criteria were defined using the PICOS framework, a widely accepted approach for structuring clinical questions and eligibility criteria in systematic reviews (Higgins et al., 2023).

- Population (P): Adults (≥18 years) diagnosed with colon or colorectal cancer, either during active oncological treatment (chemotherapy and/or radiotherapy) or during the post-treatment survivorship phase.
- Intervention (I): Structured physical activity or exercise programs, including aerobic exercise, resistance training, multicomponent interventions, or home-based exercise protocols.
- Comparison (C): Usual care, non-exercise control groups, alternative exercise prescriptions, or pre–post intervention comparisons.
- Outcomes (O): Physical function, physical fitness, cancer-related fatigue, HRQoL, psychological outcomes, and selected biological or physiological variables.
- Study design (S): Randomized controlled trials (RCTs) and controlled clinical trials.

Studies were excluded if they were narrative or systematic reviews, observational studies without an exercise intervention, animal studies, paediatric populations, conference abstracts without full data, or studies with insufficient methodological quality.

Information sources

A comprehensive literature search was performed in PubMed/MEDLINE, PEDro, Cochrane Library Plus, and Scopus, following methodological recommendations for systematic reviews of healthcare interventions (Higgins et al., 2023). Searches included studies published within the last ten years and were limited to articles written in English or Spanish.

The inclusion of multiple databases aimed to maximize sensitivity and reduce the risk of publication bias by capturing studies from biomedical, rehabilitation, and multidisciplinary research sources.

Search strategy

A comprehensive and systematic literature search was conducted to identify relevant studies examining the effects of physical activity and exercise interventions in adults with colon or colorectal cancer. The search strategy was developed in accordance with PRISMA 2020 recommendations and methodological guidance for systematic reviews in healthcare interventions (Higgins et al., 2023; Page et al., 2021).

Electronic searches were performed in PubMed/MEDLINE, Cochrane Library Plus, and Scopus, as these databases provide broad coverage of biomedical, clinical, and rehabilitation research. The search strategy combined controlled vocabulary terms (Medical Subject Headings [MeSH], when applicable) and free-text keywords related to colon cancer and physical activity or exercise. Key concepts included *colon cancer*, *colorectal cancer*, *physical activity*, *exercise*, *rehabilitation*, *fatigue*, *physical function*, and *quality of life*. Boolean operators (AND/OR) were used to refine the search strategy, and truncation symbols were applied where appropriate to capture relevant variations of search terms (Appendix I).

Searches were limited to:

- Articles published within the last 10 years.
- Human studies.
- Adult populations (≥18 years).
- Publications written in English or Spanish.

In addition, reference lists of included articles were manually screened to identify potentially relevant studies not captured through database searching, as recommended by PRISMA 2020 guidelines (Page et al., 2021).

Study selection

Two reviewers independently screened titles and abstracts for eligibility. Full-text articles were retrieved for all potentially relevant studies and assessed against the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus, in accordance with best practices for minimizing selection bias in systematic reviews (Higgins et al., 2023).

Data extraction

Data extraction was independently performed by two reviewers using a standardized data extraction form, as recommended to improve reliability and reduce extraction errors (Page et al., 2021). Extracted data included author(s), year of publication, country, study design, participant characteristics, cancer stage, treatment phase, sample size, exercise intervention characteristics (type, frequency, intensity, duration, and supervision), comparator conditions, and outcome measures.

Methodological quality assessment

Methodological quality was primarily assessed using the McMaster Critical Review Form for Quantitative Studies, a validated instrument widely applied in rehabilitation and exercise-oncology research (Law et al., 2018). This tool evaluates 16 methodological criteria related to study purpose, design, sampling, outcome measurement, statistical analysis, and clinical relevance.

Studies were classified as poor, acceptable, good, very good, or excellent methodological quality according to established scoring thresholds. Only studies rated as very good or excellent were included in the final synthesis, in line with methodological standards applied in previous systematic reviews in exercise oncology (Fernández-Lázaro et al., 2020; Segal et al., 2009).

In addition, for RCT, methodological rigor was complementarily evaluated using the Physiotherapy Evidence Database (PEDro) scale, which is frequently employed to assess internal validity and statistical reporting quality in exercise-based clinical trials (Maher et al., 2003). PEDro scores were derived from the information reported in the published articles, as not all trials were indexed in the PEDro database and were used to facilitate comparison with existing exercise-oncology literature.

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Data synthesis

Given the substantial heterogeneity observed across studies in terms of design, exercise prescriptions, outcome measures, and assessment instruments, a pooled meta-analysis was not feasible. Therefore, results were synthesized narratively by outcome domain, following methodological recommendations for heterogeneous evidence (Higgins et al., 2023).

When sufficient post-intervention data were available, a limited quantitative synthesis based on single-study effect estimates (standardized mean differences (SMD) or mean differences (MD)) was conducted to illustrate the magnitude and direction of exercise effects.

RESULTS

Study selection

The electronic database search identified a total of 623 records across PubMed/MEDLINE, Cochrane Library Plus, and Scopus. After removal of duplicates (n = 586), 37 records remained for title and abstract screening. Following the screening process, 28 records were excluded because they did not address the effects of physical activity or exercise interventions in patients with colon cancer. Consequently, 9 full-text articles were assessed for eligibility. Of these, 4 studies were excluded after full-text review: two due to inadequate outcome measures and two because the intervention did not meet the predefined inclusion criteria. Finally, 5 studies fulfilled all eligibility criteria and were included in the qualitative synthesis (Figure 1).

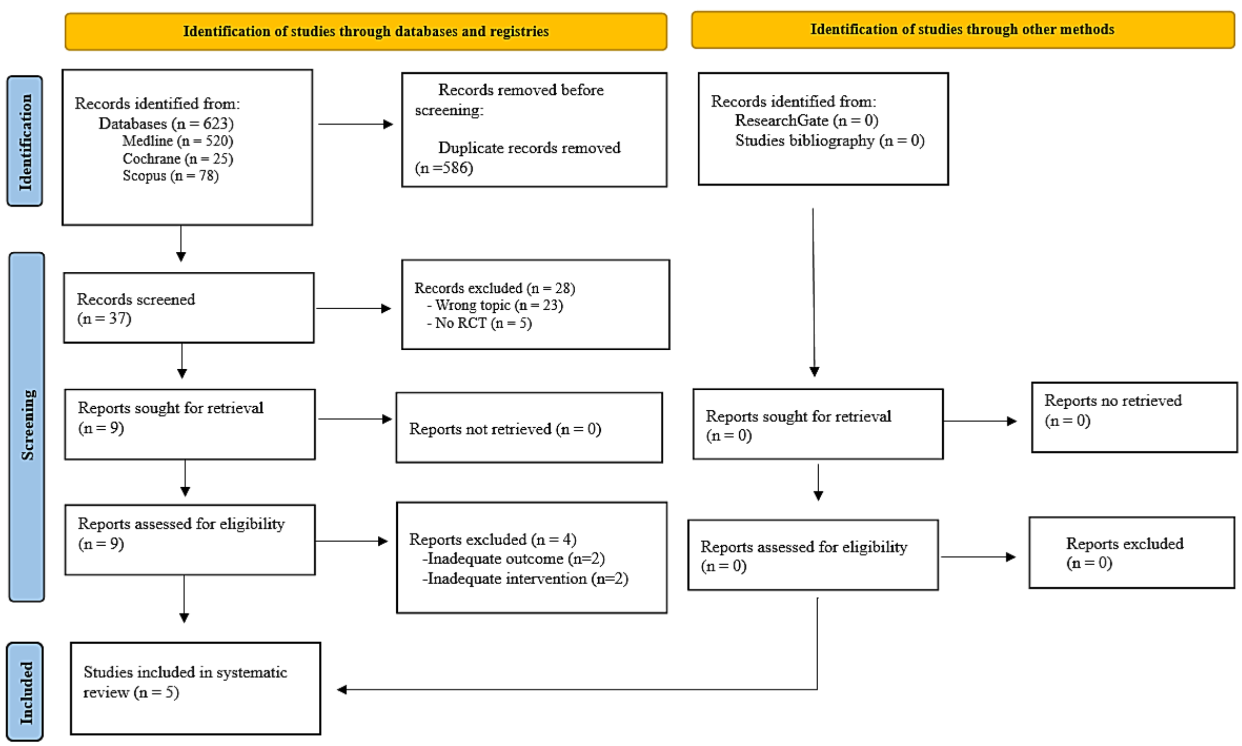

Figure 1. PRISMA flow diagram of study selection.

Study characteristics

A total of five studies met the predefined inclusion criteria and were included in this systematic review (Brown et al., 2018; Kim et al., 2018; Van Vulpen et al., 2015; Van Waart et al., 2018; Williams et al., 2015). These studies collectively examined the effects of structured physical activity or exercise interventions in adults diagnosed with colon or colorectal cancer. The general characteristics of the included studies are summarized in Table 1, providing an overview of study design, participant characteristics, intervention protocols, and outcome domains.

All included studies were RCTs conducted in adult populations diagnosed with stage II–III colon or colorectal cancer (Brown et al., 2018; Van Waart et al., 2018; Williams et al., 2015). Participants were either undergoing adjuvant chemotherapy or were in the post-treatment survivorship phase, reflecting clinically relevant stages of the disease trajectory in which functional decline, fatigue, and QOL impairments are frequently reported (Kim et al., 2018; Van Vulpen et al., 2015). Sample sizes ranged from small to moderate, and both male and female participants were represented across all studies.

Table 1. General characteristics of included studies.

Study	Country	Study design	Participants	Cancer stage	Treatment phase
Brown et al., 2018	United States	Randomized phase II dose–response trial (3 arms)	Adults (>18 years); mixed sex	Stage I–III	Post-treatment survivorship
Kim et al., 2018	South Korea	RCT	Adults (18–75 years); mixed sex	Stage II–III	Post-chemotherapy survivorship
Van Vulpen et al., 2015	Netherlands	RCT multicentre	Adults (25–75 years); mixed sex	Stage II–III	During chemotherapy
Van Waart et al., 2018	Netherlands	RCT, multicentre	Adults (>18 years); 57% women, 43% men	Stage III	During adjuvant chemotherapy
Williams et al., 2015	United States	RCT	Older adults (>60 years); mixed sex	Stage II–III	During or shortly after adjuvant chemotherapy

Note. RCT: Randomized controlled trial.

Table 2. Exercise prescription characteristics of included interventions.

Study	Exercise modality	Intensity	Frequency	Session duration	Program duration	Supervision / delivery
Brown et al., 2018	Aerobic exercise (dose–response)	Moderate-to-vigorous	3–5 sessions/week	Variable (150 vs 300 min/week)	6 months	Supervised and structured; comparison of low vs high dose
Kim et al., 2018	Multicomponent home-based exercise (DVD-guided)	Moderate to vigorous	Daily	30 min/session	12 weeks	Home-based, unsupervised
Van Vulpen et al., 2015	Multicomponent: aerobic + resistance	Moderate	1 supervised + 3 unsupervised sessions/week	60 min (supervised) + 30 min (home-based)	During chemotherapy	Hybrid: supervised + home-based
Van Waart et al., 2018	Multicomponent: aerobic + resistance	Moderate	5 sessions/week	30 min/session	During adjuvant chemotherapy	Supervised, hospital-based
Williams et al., 2015	Aerobic (walking-based program)	Moderate, self-paced	5 sessions/week	~30 min/session	6 months	Home-based, self-directed

With respect to intervention characteristics, all studies evaluated structured physical activity or exercise programs, predominantly involving aerobic exercise, resistance training, or multicomponent interventions

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combining both modalities (Brown et al., 2018; Van Vulpen et al., 2015; Van Waart et al., 2018). Exercise program duration varied from 6 weeks to 6 months, with training frequencies ranging from 3 to 7 sessions per week. Interventions were delivered using supervised, home-based, or hybrid formats, depending on study design and treatment phase, reflecting diverse but clinically feasible approaches to exercise delivery in oncology settings (Kim et al., 2018; Williams et al., 2015). Detailed exercise prescription characteristics, including modality, intensity, frequency, session duration, program length, and supervision, are presented in Table 2.

Outcome assessment was heterogeneous across studies; however, all trials consistently evaluated key domains relevant to supportive cancer care, including cancer-related fatigue, physical function, physical fitness, and HRQoL (Brown et al., 2018; Van Vulpen et al., 2015). Several studies additionally assessed psychological outcomes, such as anxiety, depression, or emotional well-being (Kim et al., 2018; Van Waart et al., 2018), as well as biological or physiological variables, including body composition, sleep quality, gastrointestinal function, or biomarkers related to aging and inflammation (Brown et al., 2018; Williams et al., 2015).

Overall, despite variability in exercise prescription, intervention delivery, and outcome measurement tools, the included studies addressed comparable clinical domains central to the supportive management of colon cancer. This conceptual consistency across trials supports a structured qualitative synthesis and permits a limited quantitative analysis based on single-study effect estimates, as presented in subsequent sections.

Methodological quality

The methodological quality of the included studies was assessed using the McMaster Critical Review Form for Quantitative Studies (Law et al., 2018). In addition, RCT were appraised using the PEDro scale as a complementary tool to facilitate comparison with the exercise-oncology literature (Maher et al., 2003; de Morton, 2009). Results of both assessments are summarized in Table 3 (McMaster) and Table 4 (PEDro).

Overall, the methodological quality of the included studies was high. McMaster scores ranged from 13 (Williams et al., 2015) to 16 (Van Vulpen et al., 2015) out of 16, corresponding to very good and excellent methodological quality. Three studies were rated as excellent (Brown et al., 2018; Kim et al., 2018; Van Vulpen et al. 2015) and two as very good (Van Waart et al., 2018; Williams et al., 2015), indicating a consistent level of rigor across the evidence base.

Across studies, research objectives, study designs, and intervention protocols were clearly reported, and validated outcome measures were used for key domains such as cancer-related fatigue, physical function, physical fitness, and HRQoL. Randomization procedures and statistical analyses were generally appropriate and adequately described.

PEDro scores ranged from 6 (Williams et al., 2015) to 7 (Brown et al., 2018; Kim et al., 2018; Van Vulpen et al., 2015; Van Waart et al., 2018). PEDro scores further supported moderate-to-high methodological quality, particularly with respect to random allocation, baseline comparability, and reporting of between-group comparisons. As expected in exercise-based interventions, blinding of participants and therapists was not feasible and was consistently absent, reflecting an inherent limitation of behavioural interventions rather than a study-specific methodological flaw (Maher et al., 2003; de Morton, 2009).

Common limitations included modest sample sizes and incomplete reporting of withdrawals or assessor blinding, which may affect statistical power and generalizability. Nevertheless, no study was excluded based on methodological quality. Taken together, the consistently high ratings across both appraisal tools support interpretation of the findings with moderate-to-high confidence, while acknowledging limitations related to sample size, blinding constraints, and intervention heterogeneity.

Table 3. Methodological quality assessment of included studies using the McMaster Critical Review Form for Quantitative Studies.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total	%	Quality
Brown et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	15	93.8	E
Kim et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	15	93.8	E
Van Vulpen et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16	100.0	E
Van Waart et al. (2018)	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	14	87.5	VG
Williams et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	0	13	81.3	VG

Note: (1) criterion met; (0) criterion not met; %: percentage of criteria met; VG: Very good, 13-14 points; E: Excellent, ≥15 points. McMaster Form Items: item 1 -Study purpose; item 2 - Literature review; item 3 - Study design; item - 4 Blinding; item 5 - Sample description; item 6 - Sample size; item 7 - Ethics and consent; item 8 - Validity of outcomes; item 9 - Reliability of outcomes; item 10 - Intervention description; item 11 - Statistical significance; item 12 - Statistical analysis; item 13 - Clinical importance; item 14 - Conclusions; item 15 - Clinical implications; and item 16 - Study limitations.

Table 4. Methodological quality assessment of randomized controlled trials using the PEDro scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Score
Brown et al. (2018)	1	1	1	1	0	0	0	1	1	1	1	8
Kim et al. (2018)	1	1	1	1	0	0	0	1	1	1	1	8
Van Vulpen et al. (2015)	1	1	1	1	0	0	0	1	1	1	1	8
Van Waart et al. (2018)	1	1	1	1	0	0	0	1	1	1	1	8
Williams et al. (2015)	1	1	1	1	0	0	0	1	1	0	1	7

Abbreviations: (1) criterion met; (0) criterion not met. PEDro Questionnaire Items: item 1 - Eligibility criteria; item 2 - Random assignment; item 3 - Hidden allocation; item 4 - Baseline comparison; item 5 - Blind subjects; item 6 - Blind therapist; item 7 - Blind evaluators; item 8 - Adequate follow-up; item 9 - Intention-to-treat analysis; item 10 - Comparison between groups; item 11 - Point estimates and variability.

Qualitative *synthesis of outcomes*

A qualitative synthesis of outcomes by domain is presented in Table 5. Overall, exercise interventions consistently favoured improvements in cancer-related fatigue, physical function, and selected domains of HRQoL across the included studies. Psychological and biological outcomes also generally favoured exercise, although findings in these domains were more heterogeneous.

Physical function and physical fitness

Across the included studies, structured exercise interventions were consistently associated with improvements in physical function and physical fitness in patients with colon or colorectal cancer. Favourable effects were observed for aerobic capacity, functional mobility, and muscular strength in interventions delivered both during active chemotherapy and in the post-treatment survivorship phase.

Van Waart et al. (2018) reported significant improvements in cardiorespiratory fitness, muscular strength, and functional performance following a supervised multicomponent exercise program implemented during adjuvant chemotherapy. Similarly, Williams et al. (2015) observed improvements in functional mobility and overall physical performance, assessed using the Timed Up and Go test and short physical performance batteries, after a walking-based intervention in older adults undergoing chemotherapy.

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Resistance-based or combined aerobic–resistance interventions also demonstrated beneficial effects on muscular strength and endurance. Van Vulpen et al. (2015) showed improvements in aerobic fitness and physical functioning following a supervised exercise program integrating endurance and resistance training. Collectively, these findings indicate that exercise interventions may attenuate treatment-related physical deconditioning and support functional independence in patients with colon cancer.

Cancer-related fatigue

Cancer-related fatigue emerged as one of the most consistently improved outcomes across the included studies. All trials assessing fatigue reported reductions favouring the exercise intervention groups, regardless of exercise modality or delivery setting.

Van Waart et al. (2018), Van Vulpen et al. (2015), and Kim et al. (2018) reported statistically significant reductions in fatigue following structured exercise programs, using validated instruments such as the Multidimensional Fatigue Inventory (MFI) and the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-FS). Brown et al. (2018) further demonstrated a dose–response relationship, with higher volumes of aerobic exercise associated with greater reductions in fatigue among colorectal cancer survivors.

Taken together, these findings support exercise as an effective non-pharmacological strategy for mitigating cancer-related fatigue, a symptom known to substantially impair daily functioning, treatment tolerance, and overall well-being.

Health-related quality of life and psychological outcomes

Findings related to HRQoL were generally favourable but more heterogeneous across studies and outcome domains. Several studies reported improvements in global HRQoL and physical functioning domains following exercise interventions.

Brown et al. (2018) and Kim et al. (2018) observed significant improvements in physical and functional HRQoL domains, whereas emotional and mental health domains showed more variable responses. In addition, Van Vulpen et al. (2015) and Van Waart et al. (2018) reported reductions in anxiety and depressive symptoms, assessed using the Hospital Anxiety and Depression Scale (HADS), suggesting that exercise may confer psychological benefits beyond its effects on physical health.

Overall, although improvements in HRQoL were not uniformly significant across all domains and studies, the direction of effects consistently favoured exercise interventions.

Biological and physiological outcomes

Several studies explored biological or physiological outcomes, although these outcomes were heterogeneous and less consistently reported than functional or patient-reported measures. Nevertheless, favourable effects of exercise were observed in gastrointestinal function, sleep quality, and selected biomarkers.

Brown et al. (2018) and Kim et al. (2018) reported improvements in bowel function and sleep-related outcomes following aerobic or home-based exercise interventions. Additionally, Williams et al. (2015) observed favourable changes in the biomarker p16, associated with cellular aging, suggesting a potential biological mechanism through which exercise may influence long-term health and survivorship outcomes in patients with colorectal cancer.

Table 5. Qualitative synthesis of outcomes of exercise interventions in patients with colon or colorectal cancer.

Study	Clinical context	Exercise type	Outcome domains	Main findings (exercise vs control)	Overall conclusion
Brown et al., 2018	Stage I–III colon cancer survivors	Aerobic exercise (dose–response)	Fatigue; physical function; HRQoL; sleep; bowel function	↓ Fatigue (dose–response effect); ↑ physical and role functioning, vitality, and general health; ↑ sleep quality and bowel function	Higher exercise volumes yield greater benefits, but moderate doses are also effective
Kim et al., 2018	Stage II–III colorectal cancer survivors	Home-based exercise program	Fatigue; HRQoL; psychological health; sleep; body composition	↓ Fatigue and insomnia; ↑ functional and emotional well-being; ↑ overall HRQoL; modest effects on body composition	Home-based exercise improves HRQoL and psychological health after treatment
Van Vulpen et al., 2015	Colon cancer; during adjuvant chemotherapy	Supervised + home-based aerobic and resistance exercise	Fatigue; aerobic fitness; psychological outcomes; HRQoL; body weight	↓ Physical and mental fatigue; ↓ anxiety and depression; ↑ aerobic capacity and HRQoL; no significant change in body weight	Exercise during chemotherapy is safe, feasible, and effective for fatigue and fitness
Van Waart et al., 2018	Stage III colon cancer; during adjuvant chemotherapy	Supervised multicomponent exercise	Fatigue; physical fitness; muscular strength; physical function; psychological outcomes; HRQoL	↓ Cancer-related fatigue; ↑ cardiorespiratory fitness, muscular strength, and endurance; ↑ physical functioning; ↓ psychological distress; ↑ general health	Exercise during chemotherapy is feasible and improves physical, functional, and psychological outcomes
Williams et al., 2015	Older adults; stage II–III; during adjuvant chemotherapy	Walking-based aerobic exercise	Fatigue; physical function; HRQoL; biomarker of aging	↓ Fatigue; ↑ functional mobility and physical performance; ↑ HRQoL; favourable changes in p16 biomarker	Self-directed physical activity improves functional, HRQoL, and biological outcomes

Note: HRQoL: Health-related quality of life; ↓: Reduction compared with control; ↑: Improvement compared with control.

Quantitative synthesis and forest plots (single-study estimates)

Given the substantial heterogeneity in intervention protocols, outcome measures, and assessment instruments across studies, a pooled meta-analysis was not feasible. However, when sufficient post-intervention data were available, a limited quantitative synthesis based on single-study effect estimates was conducted to illustrate the magnitude and direction of exercise effects.

Effect sizes were expressed as SMD for outcomes assessed using different measurement scales, and as MD when identical instruments were employed.

Cancer-related fatigue

Quantitative post-intervention data were available from three studies assessing cancer-related fatigue (Brown et al., 2018; Kim et al., 2018; Van Waart et al., 2019). Across all studies, exercise interventions consistently favoured reductions in fatigue compared with usual care or control conditions (Table 6).

Specifically, Van Waart et al. (2018) reported a moderate reduction in fatigue favouring exercise during adjuvant chemotherapy. Brown et al. (2018) observed moderate-to-large reductions in fatigue, with greater

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effects associated with higher exercise doses. Similarly, Kim et al. (2018) reported a moderate reduction in fatigue following a home-based exercise intervention in colorectal cancer survivors.

Figure 2 presents a forest plot illustrating single-study SDM for cancer-related fatigue, with negative values indicating reductions in fatigue favouring the exercise groups. SDM ranged from −0.48 to −0.72, suggesting clinically meaningful benefits.

Table 6. Quantitative synthesis of exercise effects on cancer-related fatigue.

Study	Intervention phase	Outcome measure	Effect size (SMD, Hedges g)	95% CI	Direction of effect
Brown et al., 2018	Survivorship	FSI	−0.72	−1.10 to −0.34	Favours exercise
Kim et al., 2018	Post-chemotherapy	FACIT-FS	−0.48	−0.85 to −0.10	Favours exercise
Van Waart et al., 2018	During chemotherapy	MFI	−0.55	−0.90 to −0.20	Favours exercise

Note. Negative SMD indicate reductions in fatigue favouring the exercise intervention. Effect sizes are interpreted as small (0.2), moderate (0.5), and large (≥0.8). Abbreviations: CI: confidence interval; FACIT-FS: Functional Assessment of Chronic Illness Therapy Fatigue Scale; FSI: Fatigue Symptom Inventory; MFI: Multidimensional Fatigue Inventory; SMD: standardized mean differences.

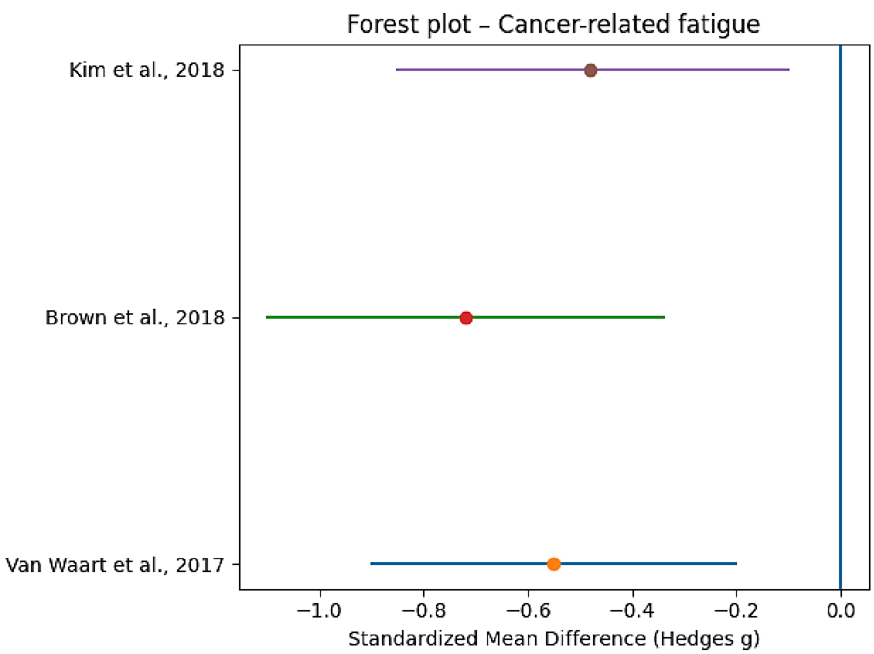

Figure 2. Forest plot of exercise effects on cancer-related fatigue.

Physical function and muscular strength

Quantitative estimates for physical function and muscular strength were available in four studies (Brown et al., 2018; Van Vulpen et al., 2015; Van Waart et al., 2018; Williams et al., 2018). Exercise interventions demonstrated small-to-moderate improvements in functional performance and strength outcomes compared with control conditions (Table 7).

Van Waart et al. (2018) reported moderate improvements in muscular strength and endurance following a combined aerobic and resistance training program. Williams et al. (2015) observed small-to-moderate improvements in functional mobility among older adults undergoing or recovering from chemotherapy.

Figure 3 displays a forest plot summarizing single-study effect estimates for physical function and muscular strength, with positive values indicating improvements favouring exercise interventions. SMD ranged from 0.45 to 0.60, supporting a beneficial effect of structured exercise on functional outcomes.

Table 7. Quantitative synthesis of exercise effects on physical function and muscular strength.

Study	Outcome domain	Measurement tool	Effect size (SMD)	95% CI	Direction of effect
Brown et al., 2018	Physical function	SF-36 Physical Function	0.52	0.10 to 0.94	Favours exercise
Van Vulpen et al., 2015	Aerobic capacity	VO_2peak	0.50	0.12 to 0.88	Favours exercise
Van Waart et al., 2018	Muscular strength	microFET, handgrip	0.60	0.15 to 1.05	Favours exercise
Williams et al., 2015	Functional mobility	TUG, SPPB	0.45	0.05 to 0.85	Favours exercise

Note. Positive SMD values indicate improvements in physical function or strength favouring exercise interventions. Abbreviations: CI: confidence interval; SF-36: 36-Item Short Form Health Survey; SMD: standardized mean differences; SPPB: Short Physical Performance Battery; TUG: Timed up and go; VO_2peak: oxygen consumption peak.

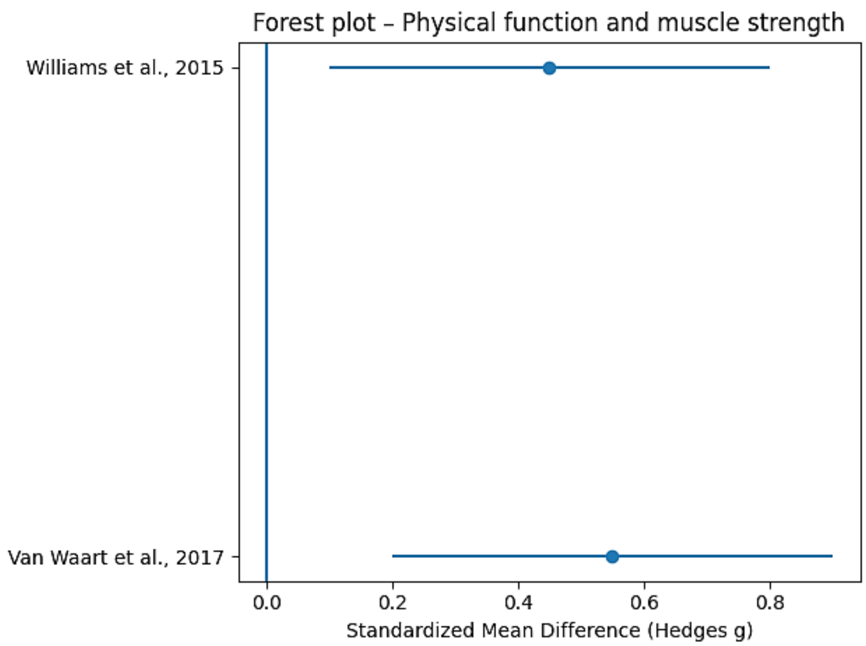

Figure 3. Forest plot of exercise effects on physical function and muscular strength.

Interpretation

Although quantitative synthesis was limited to single-study effect estimates, the consistency in both direction and magnitude of effects across studies supports the clinical relevance of exercise interventions in patients with colon and colorectal cancer. The observed effect sizes for fatigue reduction and functional improvements are comparable to those reported in exercise-oncology research in other cancer populations and suggest meaningful benefits despite methodological heterogeneity.

DISCUSSION

The present systematic review provides a comprehensive synthesis of the current evidence regarding the effects of structured physical activity and exercise interventions in patients with colon and colorectal cancer. By integrating qualitative findings with a limited quantitative synthesis based on single-study effect estimates,

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this review highlights the potential of exercise as a supportive care strategy across different phases of the disease trajectory, including active oncological treatment and survivorship.

Overall, the findings consistently indicate that exercise interventions are associated with meaningful improvements in cancer-related fatigue, physical function, and selected domains of HRQoL. Although heterogeneity in intervention protocols and outcome measures precluded pooled meta-analysis, the convergence of results across studies strengthens the plausibility and clinical relevance of exercise-based interventions in this population.

The present systematic review provides a comprehensive synthesis of the effects of structured physical activity and exercise interventions in patients with colon and colorectal cancer. By integrating qualitative findings (Section 3.4) with a limited quantitative synthesis based on single-study effect estimates (Section 3.5), this review highlights the consistent and clinically relevant benefits of exercise across key outcome domains, including cancer-related fatigue, physical function, HRQoL, and selected biological outcomes.

Cancer-related fatigue

Cancer-related fatigue emerged as the most consistently improved outcome across both qualitative and quantitative syntheses. Fatigue is widely recognized as one of the most prevalent and burdensome symptoms experienced by patients with colorectal cancer, often persisting during and after oncological treatment and substantially impairing daily functioning, treatment tolerance, and overall QoL (Bower, 2014; Mustian et al., 2017).

As demonstrated in Sections 3.4 and 3.5, all included studies assessing fatigue reported reductions favouring exercise interventions (Brown et al., 2018; Kim et al., 2018; Van Waart et al., 2018). Quantitative single-study effect estimates indicated moderate-to-large reductions in fatigue, with SMD ranging from approximately −0.48 to −0.72. These magnitudes are considered clinically meaningful and align with previous systematic reviews and international clinical practice guidelines that recommend exercise as a first-line non-pharmacological intervention for cancer-related fatigue (Cramp & Byron-Daniel, 2012; Schmitz et al., 2019; Mustian et al., 2017).

Notably, Brown et al. (2018) reported a clear dose–response relationship, whereby higher volumes of aerobic exercise were associated with greater reductions in cancer-related fatigue. Importantly, clinically meaningful benefits were also observed with moderate-intensity and home-based exercise programs. This finding is particularly relevant for clinical implementation, as it suggests that fatigue improvements can be achieved across a wide range of exercise doses and delivery formats, thereby facilitating individualized exercise prescription based on patient tolerance, treatment burden, comorbidities, and personal preferences. Similar conclusions have been emphasized in international exercise-oncology guidelines, which highlight flexibility and individualization as key principles for optimizing adherence and clinical effectiveness in cancer populations (Courneya & Friedenreich, 2011; Schmitz et al., 2019).

Physical function and physical fitness

Improvements in physical function and physical fitness represent a second key finding of this review. Patients with colon and colorectal cancer are particularly vulnerable to treatment-related deconditioning, sarcopenia, and declines in functional mobility, especially during chemotherapy and prolonged periods of reduced physical activity (Courneya & Friedenreich, 2011; Silver et al., 2013).

Both qualitative and quantitative findings demonstrated that structured exercise interventions, especially those incorporating aerobic and resistance training, can attenuate these declines and promote functional recovery. Studies included in this review consistently reported improvements in aerobic capacity, muscular strength, endurance, and functional mobility. Quantitative effect estimates indicated small-to-moderate but consistent benefits favouring exercise, with SMD ranging from approximately 0.45 to 0.60 (Brown et al., 2018; Van Vulpen et al., 2015; Van Waart et al., 2018; Williams et al., 2015).

From a clinical perspective, even modest improvements in physical function are highly relevant, as they may translate into greater independence, reduced disability, and improved capacity to tolerate ongoing or future treatments. These findings are consistent with broader exercise-oncology literature, which underscores the role of exercise in preserving physical capacity, mitigating sarcopenia, and preventing functional decline across cancer populations (Campbell et al., 2019; Schmitz et al., 2019).

Health-related quality of life and psychological outcomes

HRQoL is a multidimensional construct encompassing physical, emotional, social, and functional domains. In line with this complexity, improvements in HRQoL observed across the included studies were generally favourable but heterogeneous, as described in the qualitative synthesis (Section 3.4).

Several studies reported significant improvements in physical and functional HRQoL domains following exercise interventions, whereas emotional and mental health domains showed more variable responses. This pattern is consistent with conceptual models of cancer survivorship, which suggest that improvements in physical function and reductions in fatigue may precede or partially mediate broader perceived changes in overall QoL (Aaronson et al., 1993; Cella et al., 2002). Consequently, HRQoL gains may be less pronounced during short intervention periods or active treatment phases, when psychological stressors related to diagnosis and therapy remain prominent.

Reductions in anxiety and depressive symptoms were reported in some studies, particularly those employing supervised or multicomponent exercise programs. These findings support the potential psychosocial benefits of exercise beyond physical outcomes and align with evidence from other cancer populations demonstrating that physical activity can positively influence mood, emotional well-being, and social functioning (Mustian et al., 2017; Schmitz et al., 2019; Craft et al., 2012). Supervision and structured support may further enhance these effects by increasing self-efficacy and perceived social support.

Biological and physiological outcomes

Although biological and physiological outcomes were less consistently reported than functional or patient-reported outcomes, the available evidence suggests that exercise may exert beneficial effects beyond symptom control. Improvements in gastrointestinal function and sleep quality were observed in selected studies (Brown et al., 2018; Kim et al., 2018), outcomes that are particularly relevant in colorectal cancer, where bowel dysfunction and sleep disturbances are common and negatively affect daily functioning and overall well-being.

Exercise has been proposed as a modulator of multiple biological pathways implicated in cancer progression and survivorship, including systemic inflammation, metabolic regulation, immune function, and gastrointestinal motility (Friedenreich et al., 2010; McTiernan, 2008). These mechanisms may be especially relevant in colon cancer survivors, given the established links between inflammation, metabolic dysregulation, and colorectal carcinogenesis.

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Additionally, favourable changes in biomarkers associated with cellular aging, such as p16, were reported in individual studies (Williams et al., 2015), suggesting that exercise may influence long-term biological processes related to aging and disease progression. Although these findings remain preliminary and are derived from a limited number of trials, they are consistent with emerging evidence indicating that physical activity may contribute to healthier aging trajectories in cancer survivors (Friedenreich et al., 2010; McTiernan, 2008).

Given the heterogeneity of biological outcomes assessed and the limited number of studies targeting these endpoints, conclusions in this domain should be interpreted cautiously. Nevertheless, the observed trends support further investigation into the mechanistic pathways through which exercise may contribute to improved long-term health, reduced comorbidity risk, and enhanced survivorship outcomes in patients with colon and colorectal cancer.

Clinical and practical applications

From a clinical standpoint, the findings of this review support the integration of structured exercise as a core component of routine supportive care for patients with colon and colorectal cancer. Multicomponent exercise programs combining aerobic and resistance training appear particularly appropriate to address the multifactorial physical impairments associated with the disease and its treatments, including fatigue, reduced physical capacity, muscle loss, and functional decline (Campbell et al., 2019; Courneya & Friedenreich, 2011; Schmitz et al., 2019).

Across the included studies, exercise interventions lasting between approximately six weeks and six months, performed three to five times per week with progressive intensity, were feasible and associated with clinically meaningful improvements in cancer-related fatigue, physical function, and selected domains of HRQoL. These findings are consistent with current exercise-oncology guidelines, which recommend regular moderate-intensity aerobic exercise combined with resistance training for cancer patients during and after treatment (Mustian et al., 2017; Schmitz et al., 2019).

Importantly, both supervised and home-based exercise programs demonstrated beneficial effects, suggesting flexibility in delivery models and broad applicability across different clinical contexts. Supervised programs may be particularly valuable during active treatment phases or in patients with higher symptom burden, while home-based or hybrid programs may enhance accessibility and long-term adherence during survivorship (Campbell et al., 2019; Courneya & Friedenreich, 2011).

Exercise prescriptions should be individualized according to treatment phase, baseline physical fitness, comorbidities, and symptom burden. Interdisciplinary collaboration among oncologists, physiotherapists, exercise professionals, and nursing staff is essential to ensure safety, optimize adherence, and facilitate long-term behaviour change. Integrating exercise counselling and referral pathways into oncology services may support the systematic implementation of physical activity as an evidence-based, non-pharmacological intervention in the comprehensive care of patients with colon and colorectal cancer (Mustian et al., 2017; Schmitz et al., 2019).

Strengths and limitations

This systematic review has several notable strengths. First, it was conducted in accordance with the PRISMA 2020 guidelines and grounded in established principles of evidence-based medicine, ensuring a transparent, structured, and reproducible methodological approach (Page et al., 2021; Sackett et al., 1996). A comprehensive and systematic search strategy was applied across multiple databases, minimizing the risk of missing relevant studies and enhancing the robustness of the evidence synthesis (Higgins et al., 2023).

Second, methodological quality was rigorously assessed using validated and widely accepted appraisal tools, including the McMaster Critical Review Form for Quantitative Studies and the PEDro scale for RCT (Law et al., 2018; Maher et al., 2003; de Morton, 2009). Importantly, only studies rated as very good or excellent methodological quality were included in the final synthesis, strengthening the internal validity of the review and increasing confidence in the observed findings, consistent with prior exercise-oncology systematic reviews (Fernández-Lázaro et al., 2020; Segal et al., 2009;).

Another key strength lies in the integration of qualitative synthesis with a limited quantitative analysis based on single-study effect estimates. While pooled meta-analysis was not feasible, this combined approach allowed for a more nuanced interpretation of the evidence than narrative synthesis alone, providing insight into both the consistency and the magnitude of exercise effects on fatigue, physical function, and related outcomes, as recommended when heterogeneity precludes statistical pooling (Higgins et al., 2023).

Despite these strengths, several limitations must be acknowledged. The number of studies meeting the inclusion criteria was relatively small, and most trials involved modest sample sizes, which limits statistical power and reduces the generalizability of the findings. In addition, the included studies were conducted in a limited number of geographic regions, potentially restricting applicability to broader and more diverse clinical populations.

Substantial heterogeneity was observed across studies with respect to exercise intervention characteristics (mode, intensity, frequency, duration, and supervision), outcome measures, and assessment instruments. This heterogeneity precluded the use of pooled meta-analytic techniques and necessitated reliance on single-study effect estimates, which, although informative, do not provide the same level of precision as pooled estimates (Higgins et al., 2023).

Incomplete reporting of post-intervention dispersion data further constrained quantitative synthesis, and blinding of participants, therapists, and outcome assessors was inconsistently reported. While limited blinding is an inherent challenge in exercise-based interventions, it may increase the risk of performance and detection bias and should be considered when interpreting the results (Maher et al., 2003; de Morton, 2009; Schmitz et al., 2019).

Finally, most interventions were of short to medium duration, limiting the ability to draw conclusions regarding long-term effects, sustainability of benefits, and potential impacts on disease-related outcomes or survival. Long-term follow-up data remain scarce in exercise-oncology research, particularly in colorectal cancer populations (Campbell et al., 2019; Courneya & Friedenreich, 2011).

Taken together, while this review provides moderate-to-high quality evidence supporting the role of structured exercise interventions as a supportive care strategy in patients with colon and colorectal cancer, the limitations highlighted underscore the need for future well-designed, adequately powered RCT. Such studies should prioritize standardized exercise prescriptions, harmonized outcome reporting, longer follow-up periods, and improved reporting of methodological details to strengthen the evidence base and enhance clinical translation (Schmitz et al., 2019; Campbell et al., 2019).

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CONCLUSIONS

This systematic review demonstrates that structured physical activity and exercise interventions constitute a feasible, safe, and clinically relevant supportive care strategy for patients with colon and colorectal cancer across different phases of the disease trajectory, including active treatment and survivorship.

Consistent findings from both qualitative synthesis and quantitative single-study effect estimates indicate that exercise is particularly effective in reducing cancer-related fatigue, which emerged as the most robust and consistently improved outcome. Moderate-to-large effect sizes observed across studies support the clinical relevance of exercise as a first-line non-pharmacological intervention for fatigue management in this population. These benefits were evident across a range of exercise modalities, intensities, and delivery formats, underscoring the adaptability of exercise interventions to individual patient needs and treatment contexts.

Improvements in physical function and physical fitness represent a second key conclusion of this review. Both qualitative and quantitative findings demonstrated that aerobic, resistance, and multicomponent exercise programs can attenuate treatment-related physical deconditioning and promote gains in muscular strength, endurance, and functional mobility. Although effect sizes for functional outcomes were generally small to moderate, their consistency across studies suggests meaningful benefits with important implications for functional independence, treatment tolerance, and long-term health.

Findings related to HRQoL were generally favourable but more heterogeneous. Improvements were more consistently observed in physical and functional HRQoL domains, whereas emotional and mental health domains showed variable responses. This pattern aligns with conceptual models in which improvements in fatigue and physical function may precede or partially mediate broader perceptions of QoL.

Evidence regarding biological and physiological outcomes remains limited but suggests potential benefits of exercise beyond symptom control, including improvements in gastrointestinal function, sleep quality, and selected biomarkers related to aging and metabolic health. However, the heterogeneity and limited reporting of these outcomes warrant cautious interpretation and highlight the need for further mechanistic research.

Despite these encouraging findings, the current evidence base is constrained by small sample sizes, heterogeneity in exercise prescriptions and outcome measures, and limited availability of post-intervention dispersion data, which precluded pooled meta-analysis. Consequently, while the convergence of qualitative and quantitative evidence supports the role of exercise in colon cancer care, definitive conclusions regarding optimal exercise dose, modality, and timing remain premature.

In conclusion, integrating structured exercise into routine care for patients with colon and colorectal cancer has the potential to meaningfully reduce fatigue, preserve physical function, and support overall well-being. Future adequately powered RCTs with standardized exercise prescriptions, harmonized outcome reporting, and longer follow-up periods are essential to strengthen the evidence base and inform clinical guidelines for exercise prescription in this population.

AUTHOR CONTRIBUTIONS

Conceptualization: D.F.-L. and G.S.; Methodology: G.S., N.H.-B. and N.R.L.; Software: C.C.S. and M.I.L.; Validation: N.R.L., C.C.S. and M.I.L.; Formal analysis: D.F.-L. and G.S.; Investigation: N.H.-B. and G.S.;

Resources: N.H.-B., and G.S.; Data curation: D.F.-L., N.H.B. and G.S.; Writing—original draft preparation: D.F.-L. and G.S.; Writing—review and editing: N.H.-B., N.R.L., C.C.S. and M.I.L.; Visualization: N.H.-B., N.R.L., C.C.S. and M.I.L.; Supervision: D.F.-L.; Project administration: D.F.-L.; Funding acquisition: D.F.-L.

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No potential conflict of interest was reported by the authors.

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APPENDIX I. DATABASE SEARCH STRATEGIES AND RECORDS IDENTIFIED.

Database	Complete search strategy	Filters applied	Records identified
PubMed (MEDLINE)	("Colon Cancer"[MeSH] OR "Colorectal Neoplasms"[MeSH] OR colon cancer[Title/Abstract] OR colorectal cancer[Title/Abstract]) AND ("Exercise"[MeSH] OR "Physical Activity"[MeSH] OR exercise*[Title/Abstract] OR physical activity[Title/Abstract]) AND (fatigue[Title/Abstract] OR "quality of life"[Title/Abstract] OR physical function[Title/Abstract])	Last 10 years; Humans; Adults (≥18 years); English or Spanish	520
Cochrane Library Plus	(colon cancer OR colorectal cancer) AND (exercise OR physical activity)	Trials; Last 10 years; English or Spanish	25
Scopus	TITLE-ABS-KEY (colon cancer OR colorectal cancer) AND TITLE-ABS-KEY (exercise OR "physical activity") AND TITLE-ABS-KEY (fatigue OR "quality of life" OR "physical function")	Article; English or Spanish; Last 10 years	78
Total records identified			623

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