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The effect of exercise interventions on hospital length of stay and admissions during cancer treatment: a systematic review and meta-analysis

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Keywords: Cancer, exercise, physical activity, hospitalization, admission, chemotherapy, radiation therapy, stem cell transplant, length of stay

Abstract (240 words)

Objective: To assess the effect of participating in an exercise intervention compared with no exercise during cancer treatment on the duration and frequency of hospital admissions.

Design: Systematic review and meta-analysis.

Data sources: Medline, EMBASE, PEDro and Cochrane Central Registry of Randomized Controlled Trials.

Eligibility criteria for selecting studies: Randomised studies published until August 2023 evaluating exercise interventions during chemotherapy, radiotherapy or stem cell transplant regimens, compared with usual care, and which assessed hospital admissions (length of stay and/or frequency of admissions).

Study appraisal and synthesis: Study quality was assessed using the Cochrane Risk-of-Bias tool and GRADE assessment. Meta-analyses were conducted by pooling the data using random-effects models.

Results: Of 3918 screened abstracts, 20 studies met inclusion criteria, including 2635 participants (1383 intervention, 1252 control). Twelve studies were conducted during hematopoietic stem cell transplantation regimens. There was a small effect size in a pooled analysis that found exercise during treatment reduced hospital length of stay by 1.40 days (95% CI: -2.26 to -0.54 days; low-quality evidence) and lowered the rate of hospital admission by 8% (difference in proportions = -0.08, 95% CI: -0.13 to -0.03, low-quality evidence) compared with usual care.

Conclusion: Exercise during cancer treatment can decrease hospital length of stay and admissions, although a small effect size and high heterogeneity limits the certainty. While exercise is factored into some multidisciplinary care plans, it could be included as standard practice for patients as cancer care pathways evolve.

Introduction

In 2020, there were approximately 19.3 million new cancer diagnoses worldwide [1]. Cancer treatment typically involves prolonged regimens that can result in extended hospitalization due to adverse treatment-effects and reduced physical function [2]. The number of cancer patients requiring systemic therapies is projected to increase by 53% from 9.8 million in 2020 to 15 million in 2040 [3], so interventions that reduce complications from treatment are warranted.

Different cancer treatments have varying levels of supportive care needs which can impact the risk of repeated and prolonged hospital stays. For example, hematopoietic stem cell transplantation (HSCT) is a common treatment for haematological malignancies in adults and children [4]. HSCT typically requires staying in a single-bed isolation room for 4-6 weeks due to the risk of bleeding complications and infection caused by immunodeficiency and neutropenia [5]. Treatments including surgery, chemotherapy, radiotherapy, and immune or targeted therapies also carry a risk of hospital admission to manage common side-effects such as dyspnoea, pain, cachexia and fatigue [6]. Repeated and prolonged hospitalization remains a significant physical, psychosocial, logistical and economic burden for patients, caregivers, and healthcare systems. Lengthy periods of hospitalization can disrupt the rest-activity cycle with associated physical deconditioning and sleep deprivation, while also increasing the risk of falling, infections [7], impeding quality of life (QoL) [8], alongside reducing satisfaction with care [9]. The physical deconditioning from extended sedentary periods, which can cause fatigue, muscle wasting and reduced physical function can further worsen quality of life [10].

Hospital length of stay for cancer patients varies by age, cancer type, insurance, treatment, co-morbidity and country [11]. In a high-income country such as Australia in 2019-20, there were 1.3 million cancer-related hospitalizations, accounting for one in nine of all hospitalizations, with the age-standardized admission rate increasing by 20% in the past 20 years [12, 13]. In the United States in 2017, the average duration for adults who were admitted to hospital principally for their cancer was for 6.5 days [14]. A population-wide analysis in a middle-income country such as Brazil found that patients with breast, prostate, colorectal, cervix, lung and stomach cancer in 2010-14 spent a median of six days in hospital during their first year after diagnosis [15]. For patients treated for advanced cancers or haematological malignancies, the hospital length of stay is typically prolonged to 29 and 26 days, respectively [16, 17]. Extended and repeated hospital stays can be costly for healthcare systems and individual payers, with the average cost of \$3,400 USD per day [14]. A recent systematic review found no hospital-initiated intervention (e.g. clinical pathways, multidisciplinary care, case management, hospitalist services) exhibited significantly reduced hospital length of stay across high-risk

populations [18]. However, this systematic review did not include any studies incorporating exercise as an intervention. Therefore, appraising the evidence around the effectiveness of exercise-based interventions in reducing hospital length of stay and admissions is critical among patients undergoing cancer treatment who may experience reduced physical function, and numerous side-effects and co-morbidities [6].

In the past two decades, physical activity (i.e. any movement resulting in energy expenditure, such as leisure-time activities) and exercise (i.e. planned and structured physical activity with the aim to improve fitness) have become increasingly recognized as an important intervention for cancer patients to engage in during and following treatment [19]. Leading oncology organizations now recommend incorporating regular aerobic and resistance exercise into standard practice during and after treatment, however the optimum dose and intensity recommended during treatment is still unknown [20, 21]. For patients with more complex medical attention, such as those with advanced cancer, exercise has been evidenced to be feasible, safe and beneficial [22]. Exercise in patients with cancer has been shown to improve QoL, functional capacity, cardiorespiratory fitness, reduce symptom burden (e.g. fatigue), and modulate systemic inflammation [23, 24]. Furthermore, epidemiological analyses show that cancer patients with higher doses of moderate to vigorous physical activity have a reduced risk of cancer recurrence and mortality [25]. Patients with reduced cardiorespiratory fitness before treatment have been shown to have lower chemotherapy completion rates, thus improving this modifiable risk factor in de-conditioned patients by exercising during treatment may improve clinical outcomes [26]. Although there is a growing body of evidence supporting the role of exercise in cancer care, it remains unclear whether exercising during prolonged cancer treatment regimens can reduce hospital length of stay. This study proposed to fill the gap in the literature regarding the effect of exercise during frequently prescribed cancer treatments on hospital outcomes, and by specific exercise parameters (type, frequency, and level of supervision), in adults and children with cancer. The primary aim of this study examined the effect of exercise interventions on the hospital length of stay and admissions rate for cancer patients undergoing HSCT, chemotherapy and/or radiotherapy treatment regimens, with secondary aims examining specific exercise parameters and by age group.

Methods

Search strategy and selection criteria

This systematic review was conducted in accordance with the Cochrane Collaboration methods for systematic reviews [27], and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (Supplementary Table 1) [28]. The review protocol was registered with PROSPERO (2022 CRD42022309639). Electronic database searches using combinations of keywords for “cancer”, “treatment”, “exercise” and “hospitalization” were undertaken in Medline via Pubmed, EMBASE, Cochrane Central Register of Controlled Trials and PEDro (full search details are shown in Supplementary Table 2). The initial search included studies published in peer-reviewed journals from inception to 23rd March 2022. All databases were searched again on 9th August 2023 to ensure the articles included in this manuscript were current prior to publication. No additional eligible studies identified between March 2022 and August

2023. Reference lists of relevant reviews were manually searched for any additional articles which were not identified in the database searches.

Eligibility criteria

The Participant, Intervention, Comparator, and Outcome (PICO) framework [29] was used to organize the inclusion criteria. The inclusion criteria included studies encompassing: 1) adult or childhood cancer patients of any age, cancer type and disease stage, 2) undergoing cancer treatment regimens including chemotherapy, radiotherapy, or stem cell/bone marrow transplant as individual therapy modality or combined regimens, 3) randomized controlled trials (RCT) which implemented an exercise intervention (i.e. repeated bouts of exercise) during the period of the cancer treatment regimen (e.g. chemotherapy protocol), be it aerobic-based, resistance-based or mixed, which could be delivered as a supervised in-hospital intervention by an exercise professional or other member of the medical team, or an unsupervised intervention where a program is created for the participant to complete by themselves in hospital or at home, or a combination, compared to a usual care control group, and 4) studies assessing the hospital length of stay and/or number of hospital admissions. Studies were included when interventions other than exercise were also applied as part of the study (e.g. education, meditation, nutritional interventions), and studies published in any language were permitted. Single-arm and non-randomized studies, systematic reviews, case studies and conference abstracts were excluded.

Study selection and data extraction

Studies identified during the electronic database search were imported in the data management software for systematic reviews, Covidence (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Duplicate titles were removed. Abstract and title screening were screened initially, followed by full text review and then data extraction, with each step dual-screened between three independent authors (100% by DM, and 50% each by HW and YR). Authors (DM, AM, MD, CS, DS, TL) have prior experience with conducting systematic reviews and meta-analyses. To ensure consistency, reviewing co-authors (DM, HW, YR) received guidance from a university librarian with expertise in systematic reviews, and underwent weekly meetings over 12 weeks to discuss progress and challenges. Conflicts were resolved by discussion among these three authors, with an external reviewer consulted if consensus could not be achieved (CS). Study details extracted included country, recruitment dates, age, sex, type of cancer diagnosis and treatment type (i.e. chemotherapy, radiotherapy, HSCT) of participants. Data extraction for exercise intervention characteristics included type (e.g. aerobic, resistance), dose (e.g. sessions, repetitions, intensity), frequency (e.g. times per week), setting (e.g. supervised in-hospital, home-based), duration (e.g. minutes, weeks), compliance (i.e. number of sessions completed compared with prescribed) and what the control group was instructed to do. Hospital length of stay data was reported as days spent in hospital and proportion of the study group admitted to hospital. Authors from studies with incomplete data on hospital length of stay outcomes were contacted on up to two occasions.

Quality assessment

The Cochrane Risk of Bias 2 tool (RoB 2) was used to assess the risk of bias of the randomized controlled trials [30]. The RoB 2 evaluates sources of bias from random sequence generation, allocation concealment, blinding of personnel, patients and outcome assessors, incomplete outcome data, selective outcome reporting and other sources. Each bias category was ranked as “low”, “high” or “some concerns”. All studies were dual-assessed for bias between independent researchers (100% by JL, and 50% each by TL and CS), with disagreements resolved by discussion with the lead author (DM).

The quality of evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [31], categorizing the level of evidence as ‘high’, ‘moderate’, ‘low’ or ‘very low,’ using the criteria: risk of bias, inconsistency (i.e. unexplained heterogeneity), indirectness (i.e. population, intervention and/or outcome differences), imprecision (i.e. wide CIs leading to uncertainty) and other considerations (e.g. publication bias).

Outcomes

The primary outcome of interest was the potential effect of participating in an exercise intervention during cancer treatment on hospital length of stay, frequency of hospital admissions, or proportion of study group admitted to hospital, compared with a usual-care control group. Adverse events of the exercise interventions were reported as a secondary outcome.

Data synthesis and analysis

Descriptive statistics were used to summarize study characteristics. Tables and figures were also used to present the data. Inter-rater reliability for all dual-screened processes was assessed by calculating the proportional agreement between assessors. Hospital length of stay was reported as a continuous outcome (days), while rate of hospital admission was reported as a dichotomous outcome. In the initial stage of the meta-analysis, means and standard deviations were extracted from the included studies where the outcome was continuous. If not reported, we derived means and standard deviations from sample size, median, interquartile range, minimum and maximum values [32]. When the outcome was dichotomous, the number of events and total number of participants were extracted. Effect sizes in the form of mean difference or differences in proportions with their 95% confidence intervals (CIs) were then calculated for each study, which were presented by treatment type. To handle heterogeneity from study effects were pooled using restricted maximum likelihood random effects estimation. Furthermore, statistical heterogeneity was assessed by means of an I^2 test and was categorised as low (<50%), moderate (51%-75%), or high according to predefined criteria [33]. This was calculated to estimate how much the total variability in the effect size estimates was due to heterogeneity among the true effects [34]. To further assess heterogeneity, subgroup analyses were performed by the cancer treatment (i.e. chemotherapy only, chemotherapy and radiation, HSCT), with sensitivity analyses conducted by exercise type, number of sessions, and level of supervision. Additionally, we tested the association between the mean difference effect

and each sub-group using meta-regression. The possible presence of publication bias was assessed using Egger's test [35]. All analyses were conducted using Stata Version 18 (StataCorp LLC, College Station, Texas).

Protocol deviations

Our final manuscript deviated from the original PROSPERO registration by focusing only on RCTs, adding adverse events as a secondary outcome, conducting sensitivity analyses investigating the effect of different exercise doses on hospitalisation outcomes, and searching four rather than six electronic databases (details listed in Supplementary Table 3).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting of this research, however the authorship team will disseminate the findings through their established consumer networks (i.e. oncology community and non-government organisations).

Equity, diversity, and inclusion statement

The author group is gender-balanced and consists of junior, mid-career and senior researchers from different disciplines (including exercise physiology, implementation science, medical oncology, epidemiology, and biostatistics). Although the research was conducted in Australia, some of the researcher team are from different countries and a range of ethnicities. All the studies reported in this manuscript were conducted in high-income countries, with the small number of studies reporting ethnicity having a high Caucasian representation, and thus we acknowledge the findings may not be generalizable to low- and middle-income countries and other ethnicities, warranting addressing in future studies.

Results

Literature search

A total number of 4349 studies were retrieved through the initial search strategy. After removing 430 duplicates, 3919 abstracts were initially screened. After screening the titles and abstracts, 118 full-text articles were read. Following the full-text review of these publications, 98 studies were excluded based on the inclusion and exclusion criteria. Finally, 20 articles were included in the systematic review [36-55], and 19 articles in the meta-analyses (Figure 1) [36-42, 44-55]. One study was not included in the meta-analysis because it did not include data about hospital length of stay despite conducting a between-group comparison [43]. There was good inter-rater agreement in the initial abstract screening (96% proportional agreement) and 72% agreement at the assessment for full text inclusion.

Study characteristics

Study characteristics are reported in Table 1. The systematic review included data from 2635 participants recruited (1383 in exercise interventions, 1252 in control groups), with a median sample size across studies of 70 (range: 29-711). Sixty-two percent of participants were female. Eighteen studies were conducted in adults (mean age = 52.2±10.9 years) [37-40, 42-55] and two studies in children (mean age = 11.0±3.5 years) [36, 41]. Studies were conducted in Germany (n=7) [38, 41, 42, 49, 52-54], the United States (n=5) [36, 43, 44, 51, 55], Canada (n=2) [37, 40], Sweden (n=1) [50], Denmark (n=1) [39], France (n=1) [47], Scotland (n=1) [45], Switzerland (n=1) [48], and Netherlands (n=1) [46]. Studies were conducted in patients with haematological cancers (n=14) [36-41, 43, 44, 49, 51-55], breast cancer (n=2) [45, 50], and mixed solid tumours (n=4) [42, 46-48]. Studies were conducted during HSCT (n=12) [36, 38-41, 43, 44, 51-55], chemotherapy (n=3) [37, 49, 50], chemoradiation (n=4) [45-48], and across both chemotherapy and HSCT (n=1) [42]. The median recruitment rate was 71% (range 18-99%). There is clear evidence of clinical heterogeneity in the included studies as shown by the diversity in the study populations, both in age and sex.

Table 1: Clinical characteristics of included studies.

	Country	Date of recruitment	Age range, years (mean±SD)	Total number of participants (% of eligible, consented, and randomized)	Female	Diagnosis, stage (if known)
Potiaumpai (2021)	United States	NR	Hematopoietic stem cell transplantation 40-80 (58.8±7.6)	35 (61%)	16 (46%)	AML, ALL, CLL, MDS, MM, other lymphomas
Pahl (2020)	Germany	Jun 2016 – Oct 2017	32-63 Exercise: 50-63 (55), Control: 32-63 (56)	44 (NR)*	14 (32%)	AML, ALL, CLL, CMML, MDS, MM, myelofibrosis, SG, severe aplastic anemia
Santa Mina (2020)	Canada	Oct 2014 – Oct 2018	>17 Exercise: 50.4 ±18.1, Control: 48.4 ±13.0	30 (15%)	15 (50%)	Leukemia, lymphoma, MDS, MNGIE
Senn-Malashonak (2019)	Germany	Jan 2011 – Dec 2014	Median (range). Exercise: 5-17 (11), Control: 6-18 (12)	70 (42%)	48 (69%)	Leukemia, MDS, lymphoma, neuroblastoma, nephroblastoma, nasopharynx carcinoma, soft tissue sarcoma
Wallek (2018)	United States	Jan 2011 – Dec 2014	5-17 (10.9 ± 3.5)	53 (32%)	18 (34%)	Leukemia, MDS, solid tumor, lymphoma
Hacker (2017)	United States	May 2013 – Aug 2015	19-73 (53.3±12.2)	67 (37%)	26 (39%)	Hematological cancer
Jacobsen (2014)	United States	Jan 2011 – Jun 2012	18-76 Median: Exercise: 58 (20±76) Exercise+Stress management: 57 (20±75) Stress management: 57 (18±75) CON: 55 (19±76)	711 (NR)	306 (43%)	AML, ALL, CML, CLL, MDS, MPS, MM, PCD, lymphoma

Wiskemann (2011)	Germany	May 2007 – Oct 2007	18-71 (48.8)	105 (94%)	34 (32%)	AML, ALL, CML, CLL, MDS, secondary AML, MPS, MM, other lymphomas, aplastic anemia
Baumann (2011)	Germany	2002 – 2005	Exercise: 41.41 ± 11.78 Control: 42.81 ± 14.04	47 (NR)	17 (52%)**	AML, ALL, CML, CLL, MPS, MDS, CMML, MM, PID
Baumann (2010)	Germany	Mar 2002 – Jul 2004	Exercise: 44.9 ± 12.4 Control: 44.1 ± 14.2	64 (NR)†	29 (45%)	AML, ALL, CML, multiple myeloma, NHL/CLL, MDS/MPS, solid tumor
Jarden (2009)	Denmark	Apr 2005 – Nov 2007	18-65 (39.1 ± 12.2)	42 (51%)	16 (38%)	AML, ALL, CML, AA, MDS, WM, PNH, myelofibrosis
DeFor (2007)	United States	Jul 2003 – Aug 2005	18-68 (47)	100 (82%)	39 (39%)	Hematological cancer
Chemotherapy alone						
Mijwel (2020)	Sweden	Mar 2013 – Jul 2016	18-70 Aerobic: NR (54.4 ± 10.3)‡ Resistance: NR (52.7 ± 10.3) Control: NR (52.6 ± 10.2)	240 (28%)	240 (100%)	Breast cancer Stage I-IIIa
Wehrle (2019)	Germany	Jun 2010 – Feb 2013	Aerobic: 47.7 (21.9 ± 63.4)	29 (74%)	9 (41%)***	Acute leukemia
Alibhai (2015)	Canada	Jun 2011 – Feb 2013	23-80 (57 ± 14.7)	81 (71%)	37 (46%)	AML Mixed Cytogenetic risk group
HSCT + chemotherapy						
Dimeo (1997)	Germany	NR	18-60 EX: NR (39 ± 10) CON: NR (40 ± 11)	70 (88%)	51 (73%)	Solid tumors
Chemo- and radiotherapy						
Arrieta (2019)	France	Oct 2011 – May 2016	76.7 ± 5.0	301 (67%)	180 (60%)	Breast cancer Colon cancer Hepatocellular carcinoma, Adenocarcinoma, Lymphoma
May (2017)	Netherlands	2010 – 2013	25-75 Breast (Exercise: 50 ± 7.9, Control: 49.4 ± 7.6), Colorectal (Exercise: 57.4 ± 11.2, Control: 59.1 ± 8.9)	194 (82%)	176 (91%)	Breast cancer Colon cancer Stage I-III
Mutrie (2007)	Scotland	Jan 2004 – Jan 2005	29-76 (51.9 ± 9.5)	201 (65%)	201 (100%)	Breast cancer Stage 0-III
Uster (2018)	Switzerland	Mar 2012 – Oct 2014	32-81 (63.0)	58 (48%)	18 (31%)	Gastrointestinal cancer Lung cancer

Stage IV

Data presented as range (mean) or number (%). NR denotes not reported. * Per-protocol analysis. ** 14 patients deceased during hospitalization, leaving behind 33 survivors. *** Reasons for prematurely terminating study participation were mental overload (n=3), change in diagnosis (n=2), persistent thrombocytopenia <10/nl (n=1), or death (n = 1), none of which were associated with exercise – leaving behind 22 participants. † 15 (8 of the treatment arm and 7 of the control arm) deceased during hospitalization for HSCT. ‡ AT-HIIT = moderate-intensity aerobic and high-intensity interval training; RT-HIIT = resistance and high-intensity interval training. AA: aplastic anemia; ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; CLL: chronic lymphocytic leukemia; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPS: myeloproliferative syndrome; MNGIE: mitochondrial neurogastrointestinal encephalopathy syndrome; NHL: non-Hodgkin lymphoma; PCD: primary ciliary dyskinesia; PID: primary immune deficiency; PNH: paroxysmal nocturnal hemoglobinuria; SG: septic granulomatosis; SAA: severe aplastic anemia; WM: Waldenstrom macroglobulinaemia.

Exercise interventions

Type of exercise interventions

Data regarding the exercise interventions are presented in Table 2. Exercise interventions were combined aerobic, resistance and stretching (n=6) [36-41], aerobic only (n=4) [42-44, 55], aerobic and resistance (n=2)

[45, 46], aerobic, resistance and balance (n=2) [47, 48], aerobic versus resistance (n=2) [49, 50], resistance only (n=1) [51], aerobic, stretching and activities of daily living (n=1) [52], aerobic, resistance, stretching and activities of daily living (n=1) [53], and whole body vibration (n=1) [54]. In summary, aerobic exercise (n=17/20) and resistance exercise (n=14/20) were the most commonly used interventions in the included trials.

Table 2. Exercise intervention characteristics of the included studies.

Author	Days/week, Duration	Intensity	Exercise	Control	Co-interventions	Duration	Compliance/adherence
Hematopoietic stem cell transplantation							
Potiaumpai et al	4 days/week (3× supervised, 1×unsupervised) (Duration increased gradually from 5 to 30 min)	5-6/10 RPE (moderate) for multidirectional drills and 7-8/10 RPE (high) for walking	Multidirectional walking drills: <ul style="list-style-type: none"> • a weighted eight-rung agility ladder • forward, backward, sideways, and diagonal walking 	Physical activity counselling Given encouragement to be physically active Self-monitor their daily steps using a pedometer	No	1 month	Walk: 79%
Pahl et al	Daily, one-on-one training (20 mins/each)	Low	Whole-body vibration training of the legs standing on the side-alternating vibration plate	Conducted mobilization of the spine and stretching of the whole body	No	5.5 weeks	NR
Santa Mina et al	3 days/week: 1× supervised facility-based and 2× unsupervised home-based sessions (90-150 min per week)	Aerobic: 60% HR reserve	Resistance bands and exercise diary were given 3-5 min aerobic warm-up 30-45 min resistance training involved the use of free weights and/or resistance bands 10-15 min aerobic exercise: stationary bike, treadmill, or elliptical trainer Aerobic exercise in the home setting involved brisk walking Sessions concluded with yoga-based stretching and relaxation breathing	Stationary bikes and exercise placards (in-door exercise recommendations) were provided	No	3 months	Inpatient phase Aerobic: 50% Resistance: 99% Control: NR
Senn-Malashonak et al	5 days/week (30-60 mins/each)	Aerobic: Moderate (12-14/20 RPE) Resistance: 1-3× 7-15 reps of 3-5 exercises	Resistance, endurance, and flexibility training	Mental and relaxation training	No	3 months	Exercise: 94% Control: 68%
Wallek et al	5 days/week (40-60 min/each)	Aerobic: 60-80% HRmax, 12-14/20 RPE. Resistance: 1-3× 8-15 reps for 3-6 exercises	Use of barbells, balls, rubber bands, steps, and bicycle ergometer. Training intensity was controlled via self-reported rating of perceived exertion	Mental and relaxation training	No	2 months	Exercise: 94% (3.1 ± 0.6 sessions per week)
Hacker et al	3 days/week (1× supervised and 2x unsupervised) 18 strength training sessions	Moderate, 13/20 RPE	Progressive resistance and strength training using: <ul style="list-style-type: none"> • elastic resistance bands • body weight (be it sit-ups or wall push-ups) 	During hospitalization, two visits per week during which hospital experience was discussed. After discharge, 1-on-1 health education sessions (1/week, 6 weeks).	Education included health protection, working with doctors, finances, recommendations after HSCT	2.5 weeks	83% for exercise sessions 97% for education sessions
Jacobsen et al	3-5 days/week (20-30 min/each)	Moderate: 50-75% HR reserve	One of four interventions: self-directed exercise, self-administered stress management, combinatorial exercise and stress management training, or usual care A pamphlet, a digital video disc (DVD) and a diary were given. Stress management training involved targeted-paced abdominal breathing, muscle relaxation, and coping strategies	A DVD, alongside brief discussion with an interventionist, were provided. Only general advice regarding exercise and stress management was offered (such that physical activity patterns and participants' own stress management techniques were maintained).	Pedometer and a relaxation CD were provided. Patients were re-contacted at 30 and 60 days post HSCT to review goals, barriers, and offer encouragement.	Duration of inpatient stay	67%: self-guided relaxation. 34%: deep breathing 12%: relaxation audiotapes 4%: videos
Wiskemann et al	In-patient intervention: 3-5x endurance sessions during hospitalization 2x resistance sessions per week (20-40 min/each)	Moderate-high Aerobic: 12-14/20 RPE for 20-40 mins Resistance: 14-16/20 RPE for 2-3x 8-20 repetitions	Endurance training: 20-40 minute walking in the outpatient setting. Cycling and treadmill walking during hospitalization Strength training involved the use of stretch bands and focuses upon the upper or lower extremities, the whole body, or bed exercises (inpatient settings)	Step counters were given to record daily physical activity. Controls were visited at the same frequency by research staff. Controls had access to treadmills and stationary cycles to complete themselves (but not prescribed)	No	6 weeks	Before admission: 88% During hospitalization: 83% After discharge (for 6-8 weeks): 87%
Baumann et al (2011)	Twice a day Endurance training (10-20 min/day) Activities of daily living training (ADL-training) (20 min/day)	Exercise: 'slightly strenuous' or 'strenuous' (Borg scale) Control: low intensity, 'not strenuous' (Borg scale)	Endurance training was conducted on a cycle ergometer; if unable to complete this for 10-20 minutes without disruption, then interval training was conducted. ADL-training was performed during chemotherapy and post-engraftment and involved strength, coordination, stretching, walking, and stair climbing exercises.	Standard physiotherapy Individual active and passive mobilization treatment – 10 min gymnastic, 5 min stretching, and massages – performed by a physiotherapist (5 days a week, 20 min each)	No	7.5 weeks	NR
Baumann et al (2010)	Activities of daily living training (ADL-training): 5 days/week (20 min/each)	'Slight strenuous' to 'strenuous' (Borg Rate)	Aerobic endurance training on a bicycle ergometer combined with activities of daily ADL-training	10-minute gymnastics, low-intensity coordination training, and massages Controls underwent low-intensity active and passive mobilization,	No	3.5 weeks	NR

	Aerobic endurance training: 5-7 days/week (10-20 min each)	of Perceived Exertion scale)		which consists of gymnastics, massages, extensions, and coordination training.			
Jarden et al	Dynamic exercise: 5 days/week (60±10 min/each) Resistance training: 3 days/week	Stationary cycling: low to moderate intensity, 10-13/20 RPE Resistance training: low to moderate intensity, 10-13/20 RPE Relaxation: low intensity, 6-9/20 RPE	A multimodal intervention encompassing exercise, relaxation, and psychoeducation regarding capacity, functional performance. Dynamic exercises consisted of neck movements, shoulder rotations, hip flexion and extension, calf raise, ankle dorsiflexion and plantar-flexion, in addition to abdominal and back muscle exercises. After cycling, stretching was conducted. Resistance training was comprised of “free hand and ankle weights, bicep curl, shoulder press, triceps extension, chest press, flyer, squat, hip flexion, knee extension, and leg curl and extension”	5 days/week (20 min/each) ‘Modified logbook’ was given to document the mode, frequency, and duration of exercise during hospitalization. Physiotherapy was given after HSCT for up to 1.5 hours weekly. There was no stationary cycling ergometer given unless otherwise requested. All outcome measures needed to be completed within the same time frame as the exercise group.	Psychoeducation was based on behavioral and cognitive therapy techniques to facilitate adjustment to diagnosis and treatment. The aim was to foster personal control and increase motivation and self-efficacy.	4 to 6 weeks	81% completed all requirements. Questionnaires at 3 months: Exercise: 81% Control: 62% Questionnaires at 6 months: Exercise: 76% Control: 62%
DeFor et al	Twice a day (15 min/each)	NR	During hospitalization: 15-minute walk on a treadmill twice a day and cycling for <20 mins/day every other day. After discharge, participants would walk at a comfortable speed for >30 min/day	Controls were not told to do any exercise and not given a treadmill unless otherwise requested.	No	5 months	Adherence to physical activity for at least 5 times/week: Exercise: 62% Control: 38%
Chemotherapy alone							
Mijwel et al	2 days/week (60 min/each)	Aerobic: 20 mins moderate intensity 13-15/20 RPE + 3x3 mins (high-intensity), RPE=16-18/20 on cycle Resistance: 70-80% 1RM, 2-3x 8-12 reps + 3x3 mins (high-intensity) RPE=16-18/20 on cycle.	Interval training, combined with endurance or resistance training	Exercise recommendations were given (American College of Sports Medicine guidelines)	No	16 weeks	Adherence to the exercise intervention: RT-HIIT: 68% AT-HIIT: 63% Adherence to intensity: RT-HIIT: 83% AT-HIIT: 75%
Wehrle et al	3 days/week (30-45 min/each)	Aerobic: 60-70% HRmax, RPE=12-14/20. Resistance: 4-6x Body weight, bands/dumbbell machines. RPE=12-14/20.	Endurance group: training on an upright stationary bicycle Resistance group: bodyweight exercises	low-intensity mobilization and stretching was given to avoid psychosocial bias	Nutritional counselling was offered by dietitians and physiotherapists to all participants	2 months	Endurance group: 69% Resistance group: 76% Control: 60%
Alibhai et al	4-5 days/week (30-60 min/each)	Light-moderate, RPE=3-6/10	Aerobic, resistance, and flexibility training exercises Exercise was documented using weekly tracking sheets	Walking on a regular basis Any exercise was documented using weekly tracking sheets	No	5 months	54%
Hematopoietic stem cell transplantation and chemotherapy							
Dimeo et al	Daily (30 min/each)	50% cardiac reserve 15x1min (mean workload=32±5 Watts)	Aerobic exercise (cycling ergometer in the supine position)	Usual care without changing daily physical activity level	No	4 weeks	82% (±10%)
Chemotherapy and radiation therapy							
Arrieta et al	2 days/week	Low to high and focused on avoiding pain and exhaustion	Balance and proprioception exercises, aerobic training, and stretching exercises	French National Nutrition Health Program (PNNS) booklet was given, which recommends 30 minutes of exercise per day	No	NR 1-year follow up 2-year follow up	Planned phone calls: 81% Exercise: 70%
May et al	5 days/week (2x supervised, 3x unsupervised) (supervised: 60 min/each, home-based: 30 mins each)	Aerobic: either ‘3x 2 min increasing to 2x 7 min’ or below ‘3x 4 min decreasing to 1x 7 min’ ventilatory threshold. Resistance: 45-75% 1RM Home exercise at moderate intensity	5-min warming up, 50-min strength training, and 5-min cooling down	Usual care Habitual physical activity pattern	No	18 weeks	Breast cancer: 83% Colon cancer: 89%
Mutrie et al	3 days/week (2x supervised, 1x unsupervised) 14 exercise classes (45 min each)	Moderate intensity, 50-75% HRmax	45 min supervised group exercise: 5-10 min warm up 20 min walking cycling, low-level aerobics, or muscle strengthening exercises. Relaxation exercises	Usual care Exercise guideline leaflet entitled “exercise after cancer diagnosis”	No	12 weeks	Breast cancer: 83% Colon cancer: 89%
Uster et al	2 days/week (60 min each)	Aerobic: 10 mins warm up.	Warm-up, strength, and balance training	Usual care without changing their daily physical activity level	Protein-rich snacks and oral nutritional	12 weeks	Mean: 67% Median: 75%

	24 sessions in total	Resistance: 60-80% 1RM			supplements post-session		
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Data are range (mean) or number (%). *Adherence is defined as the percentage of hospital days of exercise completed under supervision. AT-HIIT: moderate-intensity aerobic and high-intensity interval training, RT-HIIT: resistance and high-intensity interval training, RPE: rating of perceived exertion, 1RM: 1-repetition maximum (i.e., maximal weight that a participant can lift for a single repetition).

Exercise Program Details

The median exercise intervention length was 5.5 weeks (range 2-52). Most interventions included moderate intensity exercise (n=18) [36-53], with one study being low intensity [54] and one not reporting intensity [55]. The mean length of sessions was 38 minutes (SD: 14, range: 10-70) and 4.4 sessions/week (SD: 1.7, range: 2-7). Interventions were fully supervised (n=11) [36, 37, 39, 41, 42, 48-50, 52-54] or partially supervised with a home-based component (n=7) [38, 40, 44-46, 51, 55], and unsupervised (n=2) [43, 47]. Of supervised programs, n=15 were delivered one-on-one [36-42, 44, 49-55], and n=3 were group-based sessions [45, 46, 48]. Median compliance with exercise interventions, which was reported in 15 studies, was 70.7% (SD: 22.3%, range: 54-94.4%). The average withdrawal rate was 28% and 24% in exercise and control groups, respectively.

Additional interventions delivered

In addition to delivering the exercise intervention, some intervention groups also received relaxation (n=3) [39, 40, 43], dietary guidance (n=2) [48, 49], and motivational interviewing (n=1) [45].

Control groups

Whilst three control groups received usual care only [42, 46, 48], other control groups received other interventions including resources (n=5) [40, 43, 45, 47, 50], physiotherapy (n=4) [39, 49, 53, 54], exercise education (n=2) [39, 51], mental relaxation (n=2) [36, 41], bike access (n=2) [40, 55], a pedometer (n=2) [38, 44], and stretching and gymnastics sessions (n=1) [52]. Additionally, two control groups were offered the study exercise intervention after the control period [40, 45].

Hospital length of stay and rate of admissions

All 20 included studies described the length of stay (n=17) or rate of admission (n=5) in the exercise intervention and control groups (Table 3). Of the 17 studies reporting on length of stay (days), only one study presented statistically significant reductions in hospital length of hospital stay, with Dimeo et al that identifying that participants who cycled for 30 minutes/day for 4 weeks, averaged 13.6 (2.2) days in hospital versus 15.2 (3.6) days in the control group (p=0.03) [42]. In the five studies reporting the proportion of patients admitted to hospital in the study period [37, 45, 47, 50, 51], two reported statistically lower rates of hospital admission among the exercise groups. Mijwel et al found that 2/74 (3%) and 4/72 (6%) of participants, who received two 60 minute/week resistance, or aerobic exercise, respectively, plus high-intensity interval exercise for 16 weeks, were hospitalized throughout their treatment compared to 8/60 (13%) of the control group (p=0.02) [37]. Mutrie

et al found that participants who undertook 3 sessions/week of moderate multi-modal exercise for 12 weeks were hospitalized at half the rate throughout treatment compared with the control group (10/99 [10%] vs 20/102 [20%], p=0.04) [36].

Table 3. Hospital length of stay and admission rate among patients in exercise and control groups of included studies.

Hospital length of stay (days)			
Mean (SD)			
	Exercise group	Control group	p-value
Hematopoietic stem cell transplantation			
Potiaumpai et al	12.9 (4.3)	11.7 (4.0)	.41
Pahl et al	38.0 (range: 35–43.5)	41 (range: 37–44)	NR
Santa Mina et al	27.4 (3.8)	28.6 (3.5)	.81
Senn-Malashonak et al	39.0 (range: 22-74)	42.0 (range: 26-93)	NR
Wallek et al	Intervention group (fit): 36 (range: 22-74) Intervention group (unfit): 40.5 (range: 26-57)	Control group (fit): 39 (range: 27-53) Control group (unfit): 43.5 (range: 26-93)	>.05
Hacker et al	16.7 (4.2)	18.1 (5.5)	NR
Jacobsen et al	NR	NR	.42
Wiskemann et al	45.0 (range: 24-92)	43.0 (range: 22-120)	.64
Baumann et al (2011)	56.1 (20.7)	51.4 (16.4)	NR
Baumann et al (2010)	41 (25)	43 (33)	NR
Jarden et al	34.7 (5.6)	35.0 (6.1)	.88
DeFor et al	32 (IQR: 15-42)	35.5 (IQR: 24.5-38.5)	.37
Dimeo et al	13.6 (2.2)	15.2 (3.6)	.03
Chemotherapy			
Wehrle et al	Aerobic: 33 (IQR: 31-41) Resistance: 35 (IQR: 33-52)	37 (IQR: 34-43)	.50
Alibhai et al	36.5 ⁺	35.8 ⁺	.76
Chemotherapy and radiotherapy			
May et al	Breast cancer: 1.9 (3.1) Colon cancer: 2.6 (4.6)	Breast cancer: 1.6 (2.8) Colon cancer: 8.8 (11.8)	NR
Uster et al	5.9 (10.3)	8.3 (10.3)	.18
Rate of hospital admission (%)			
Hacker et al	3/33 (9%) re-admitted post- intervention	8/34 (23%) re-admitted post-intervention	NR
Mijwel et al	RT+HIIT: 2/74 (3%) of the group AT+HIIT: 4/72 (6%) of the group	8/60 (13%) of the group	RT vs control: .02 AT vs control: >.05
Alibhai et al	3/57 (5.6%) of group	3/24 (12.5%) of the group	.26
Arrieta et al	22/121 (18%) at 1-year follow-up 21/86 (25%) at 2-year follow-up	20/128 (16%) at 1-year follow-up 29/100 (29%) at 2-year follow-up	1-year: >.05 2-year: >.05
Mutrie et al	10/99 (10%)	20/102 (20%)	.04

NR: not reported, IQR: inter-quartile range, HIIT: High-intensity interval training, RT: Resistance training, AT: Aerobic training. Hospital length of stay data listed as mean (standard deviation) days, unless otherwise indicated as median with range or interquartile range. ⁺: Standard deviation not reported.

Meta-analysis

Sixteen studies reporting hospital length of stay were included in the meta-analysis (522 in exercise interventions, 473 in control groups) [36-46, 48, 49, 51-55]. For hospital length of stay, there was a small effect size for all pooled studies favouring the exercise groups spending 1.40 days less (95% CI: -2.26 to -0.54, p<0.01) in hospital compared to the control groups (Figure 2). Sub-analyses found a small effect that the exercise groups spent 1.55 days less (95% CI: -2.61 to -0.50) for HSCT compared to usual care. In other treatment protocols, the exercise groups spent 0.67 days less (95% CI: -4.24 to 2.91) for chemotherapy) and 0.86 days less (95% CI: -2.09 to 0.36) for combined chemotherapy and radiation compared to usual care,

however these sub-analyses were not statistically significant. Egger's test suggested no evidence of publication bias ($p=0.68$). The amount of statistical heterogeneity was low with overall $I^2 = 22.86\%$ and subgroup I^2 not exceeding 24.82%.

Five studies reporting the rate of hospital admission were included in the meta-analysis (446 in exercise interventions, 360 in control groups) [37, 45, 47, 50, 51]. There was a small effect size in the pooled analysis favouring exercise (Figure 3). There was an 8% reduced risk of hospital admission in the exercise group (Difference in proportions: -0.08, 95% CI: -0.13 to -0.03, $p<0.01$). As only five studies were pooled, Egger's test was not conducted for this meta-analysis. There was no evidence of statistical heterogeneity, as $I^2=0$.

In sensitivity-analyses, meta-regression on main outcomes mean difference and exercise type, number of sessions, and level of supervision, removing studies with a control groups which were offered exercise equipment but no prescribed intervention, and separating by adult and child studies, did not explain the variation in either hospital length of stay or admission outcomes (Supplementary Material).

Adverse events from exercise interventions

Ten studies reported investigating adverse events. Of these, eight reported no adverse events from the exercise interventions [37, 39-41, 45, 48, 49, 53]. One study reported no serious adverse events, however documented two exercise sessions that ceased early due to two minor adverse events, including knee pain and discomfort [54]. One study, which reported no adverse events from the exercise intervention, had one participant fall during the baseline 6-minute walk test, and subsequently withdrew from the study [40]. Finally, one study reported that participants kept a daily log which included self-reporting of adverse events, however these findings were not presented in the article [38].

Quality Assessment

Over two-thirds of included studies had at least one risk of bias domain that was judged to be high risk (Supplementary Figures 1 and 2). These trials were at high or unclear risk for selection bias relating to the randomization, deviations from the intended interventions, missing outcome data, measurement of the outcome, or selective reporting. Based on the GRADE rating system, the evidence for the effect of exercise on hospital length of stay was low quality, and low quality for rate of admissions (Supplementary Table 4). The quality of evidence was downgraded because of risk of bias due to methodological limitations identified using the RoB 2, and imprecision, due to the confidence intervals being close to the no difference line. Due to the variability of bias assessments, which ranged from low to high across the five domains, especially for the second domain (i.e., Bias due to deviations from intended interventions), the presence of methodological heterogeneity is highly likely.

Discussion

Our study reviewed and synthesized data from 20 RCTs examining the impact of participating in exercise interventions during chemotherapy, radiotherapy or stem cell transplant cancer treatment regimens on hospital length of stay and rate of admissions. It found that patients who participated in exercise interventions during treatment spent 1.40 days less in hospital and had an 8% lower risk of hospital admission than non-exercising controls. However, findings should be evaluated with caution due to the low quality of evidence using the GRADE rating system. This systematic review and meta-analysis are important as it evaluates a potential low-cost intervention to mitigate a major concern among cancer patients, this being lengthy and repeated hospital stays.

Prolonged hospital stays are associated with increased risk of re-admission and mortality [56]. Our findings of reduced time spent in hospital and reduced risk for admissions may have important implications for the healthcare system, as there can be a high financial burden imposed on individuals and institutions bearing the costs of repeated and prolonged hospitalization [57]. In-patient hospital costs have been shown to account for 68% of all cancer-related costs in the first year after diagnosis [58] and are steadily increasing. Embedding exercise into treatment plans could deliver significant health system savings through earlier discharge as well as improving individual patient outcomes. Recent calls have been made to make hospital care more efficient and less costly [59], so our findings to potentially prevent admissions and reduce the burden on hospital bed pressure and the healthcare system are timely. Our study adds to the literature a potential intervention to combat hospital length of stay, with a recent systematic review, which did not investigate exercise interventions, unable to identify any interventions to reduce hospital length of stay [18]. Although our study was not a health economic analysis, future studies should investigate whether the cost of delivering exercise programs offsets the money saved from preventing patient admissions and reduced hospital length of stay. Given a converging international consensus on incorporating exercise into standard cancer care [20, 21], exercise during treatment may allow patients to optimize their health and reduce their likelihood of hospital admission. Organizational limitations have been identified as the key barrier to implementing exercise into routine cancer care, using the expertise of a multi-disciplinary team in implementing and/or prescribing exercise, and preparing broader community-based exercise groups and settings will likely assist [60, 61].

Given the known psychological, physical and financial burden of repeated admissions and prolonged hospital stays, supportive care interventions are urgently required to reduce the likelihood or duration of hospitalization. Exercise before cancer treatment, termed 'prehabilitation', has been shown to improve clinical outcomes including reduced hospital length of stay. Prehabilitation studies, commonly conducted prior to cancer surgery, have been shown to reduce hospital length of stay by up to four days following gastrointestinal cancer surgery [62] and 4-8 days before lung cancer surgery [63, 64]. Additionally, there is moderate-quality evidence that preoperative exercise halved the amount of postoperative complications in lung cancer patients, and improved postoperative QoL in oral and prostate cancer patients [65]. Although our study identified a smaller effect size regarding length of hospital stay compared with exercise interventions delivered prior to cancer surgery, the

difference identified in our study applied on a population-level may still provide a cost-effective intervention to assist with reducing pressure on the healthcare system, while concurrently applying numerous health benefits. Further, reducing unplanned hospital admissions has been shown to reduce healthcare costs [66], which can add to the importance of our study findings. Several issues are needed to be resolved to adapt current models of cancer care to implement exercise, including developing a trained workforce, overcome barriers such as payments and ensuring exercise is recommended by the patient's medical oncologist [67]. One example is by adapting oncology models of care from other chronic diseases such as the World Health Organization's 'Package of interventions for rehabilitation' for cardiopulmonary conditions, which recommends incorporating exercise, healthy lifestyle education and stress management to improve function and clinical outcomes [68], a model demonstrating reduced risk and duration of hospital re-admissions and mortality [69].

There are likely multiple mechanisms regarding the effect of different exercise types during cancer treatment on risk of admission and hospital length of stay. Exercise can improve physical function by adaptations in cardiovascular (particularly aerobic exercise) and skeletal muscle systems (particularly resistance exercise) [23]. Greater physical function has been shown to decrease hospital length of stay, while patients with reduced physical function can be referred for risk-reduction interventions such as exercise to improve their tolerance of treatment and side-effects [70]. Physical therapy programs focused on mobility have also displayed evidence to reduce hospital length of stay and risk of readmissions [71], with potential reduction in falls risk a contributing factor. Exercise has also been shown to reduce depressive and anxious symptoms [23], which may be important clinically given poor psychological health associates with longer hospital length of stay and higher likelihood of readmissions [72]. People with cancer have displayed a 15-30% increased risk of being admitted to hospital for a falls-related injury due to their symptoms and de-conditioning [73]. Balance and muscle strengthening exercises have numerous clinical benefits, particularly in older patients, to reduce their falls and fracture risk [74], which forms one common mechanism of reducing the risk of being admitted to hospital as identified in our study. When discussing the potential effect of different exercise types, most studies in our review included an aerobic exercise component, so comparisons between exercise types were not possible. Additionally, sensitivity analyses conducted as part of this study did not identify that there was an optimal exercise type, dose or level of supervision to reduce time or risk of being admitted to hospital. Given the current exercise-oncology guidelines recommend a combination of aerobic and resistance exercise [20, 21], we recommend a combined exercise program in-line with the guidelines is likely to be beneficial.

Exercise during cancer treatment has been shown to be safe. For instance, in children with cancer, an evaluation of 35,110 exercise sessions found severe adverse events occurred at a rate of 0.02% [75]. Half the studies in our review reported upon safety, in which most reported no adverse events from exercise. As 10% (2/20) of our included studies offered no exercise supervision, a small risk of both adverse events, and under-reporting of adverse events remains. Supervision should be encouraged during treatment to minimize such possibilities, particularly in the early stages of habituating participants to a consistent exercise program. Future studies should systematically report exercise-related adverse events to improve the evidence of harms assessment, and could

incorporate measurable methods to better understand patient, caregiver and staff experiences and challenges [76].

This is the first systematic review and meta-analysis to investigate the effect of exercise during chemotherapy, radiotherapy and stem cell transplant cancer treatments on hospital length of stay and admission rates. Our methods have multiple strengths including protocol registration in PROSPERO, a comprehensive database search strategy, dual-screening of the abstract and full-text selection, data extraction, risk of bias assessments and pooling of data using meta-analysis of RCTs, representing the gold standard of evidence generation. However, our findings should be interpreted with caution. Whilst statistical heterogeneity was assessed to be low, clinical and methodological heterogeneity was not, due to variability in the age and sex of study populations and quality of study evidence. Our study was not able to account for any possible missing data from the included studies, which may have affected the statistical calculations and produced biased estimates [77]. Many studies had high risk of bias, mostly due to high drop-out, low adherence to the exercise interventions, and lack of blinding, highlighting the challenges in conducting allied health interventions [78], and presenting potential difficulties for patients to commit to interventions requiring additional visits during the treatment period where they are susceptible to various adverse events. Only one study in our review had a primary outcome assessing the effect of exercise on hospitalization admissions [50], thus future studies that are adequately powered to measure hospital length of stay are required to confirm our findings. There may be confounders our study could not include in the analysis that may have affected the relationship between exercise during treatment and hospital length of stay, including pre-diagnosis physical activity levels, baseline fitness, demographic characteristics or insurance status. Future research which includes analyses by age, sex, cancer type and other details on potential confounders or effect modifiers, as well as including other therapies such as immunotherapy and hormone therapies, will be beneficial. Further data on implementation, cost-effectiveness, and cost-utility of different exercise programs will also be useful.

Conclusion

Our systematic review and meta-analysis of RCTs found that exercising during treatment led to a significant reduction in days spent in hospital and rate of hospital admission. While the effect size of this difference was small, there may be important clinical relevance to patients wanting to stay out of hospital, which also may have economic benefits to healthcare systems. The heterogeneity of exercise interventions, patient characteristics, and quality assessment of the included studies suggested that these findings should be interpreted cautiously. While exercise is factored into some multidisciplinary care plans, its inclusion as standard practice for most patients who would benefit should be considered as cancer care pathways evolve.

What is already known?

- Exercise in patients diagnosed with cancer has been shown to improve quality of life, functional capacity, cardiorespiratory fitness, reduce symptom burden and lower the risk of recurrence and mortality.
- Numerous oncology organisations internationally now endorse exercise during and after cancer treatment.
- It is unknown whether participating in a structured exercise intervention during chemotherapy, radiotherapy or stem cell transplant regimens reduces the duration and frequency of hospital admissions.

What are the new findings?

- This systematic review and meta-analysis evaluates the evidence regarding the association between participating in exercise interventions during cancer treatment and reductions in the duration and frequency of hospital admissions.
- There was a small but significant effect size in a pooled analysis that structured exercise during treatment reduced hospital length of stay by 1.40 days compared to usual care.
- Structured exercise during cancer treatment was demonstrated to be safe, and contributed to an 8% lower rate of hospital admission.

STATEMENTS AND DECLARATIONS

Competing interests: The authors have no competing interests to declare that are relevant to the content of this article.

Contributorship: DM was responsible for the conceptualization and design of the study. DM, HW and YR were responsible for the selection of articles and data extraction. JL, TL and CS were responsible for further data extraction and risk of bias assessment with justification. DM, JL, CS, and AM were responsible for assessing study methodologies. DM and JL were responsible for preparing the tables. MD was responsible for the meta-analysis. All authors were responsible for writing and editing of the manuscript. All authors approved the final manuscript.

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Figure legends

Figure 1. Flow chart of included studies.

Figure 2. Meta-analysis of the difference in days spent in hospital between those cancer patients participating in an exercise intervention versus control. Negative values favour exercise.

Figure 3. Meta-analysis of the difference in the proportion of participants with cancer admitted to hospital in exercise and control groups. Negative values favour exercise.

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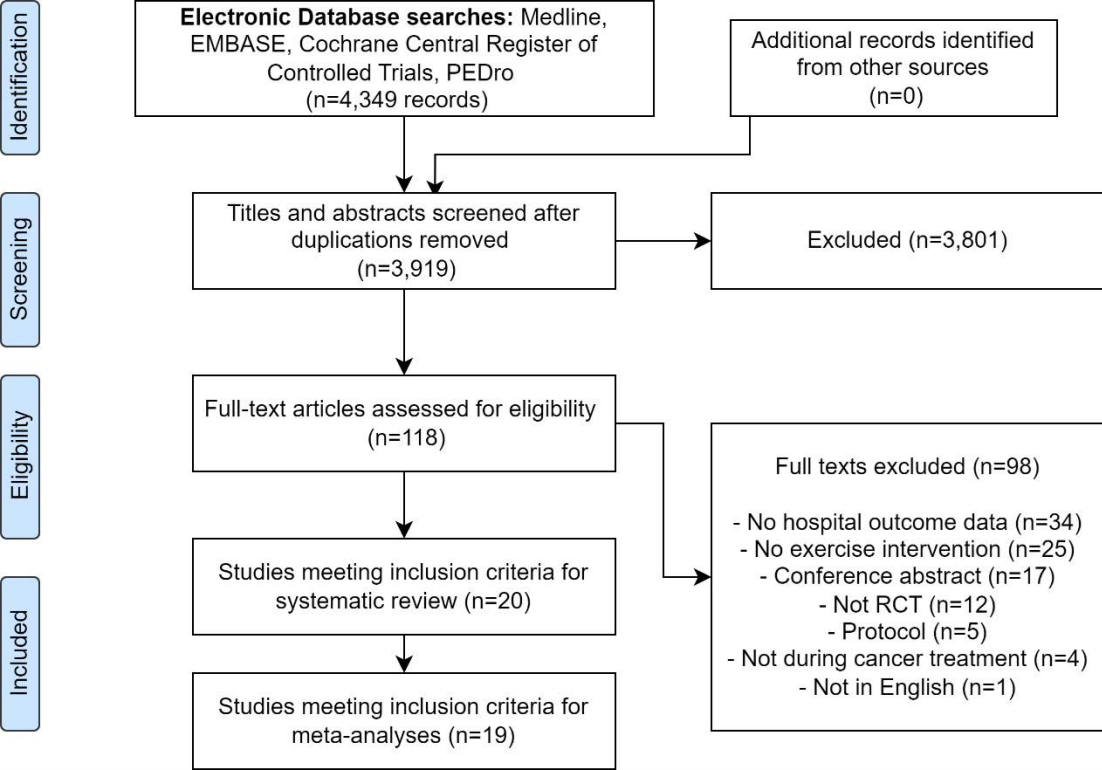
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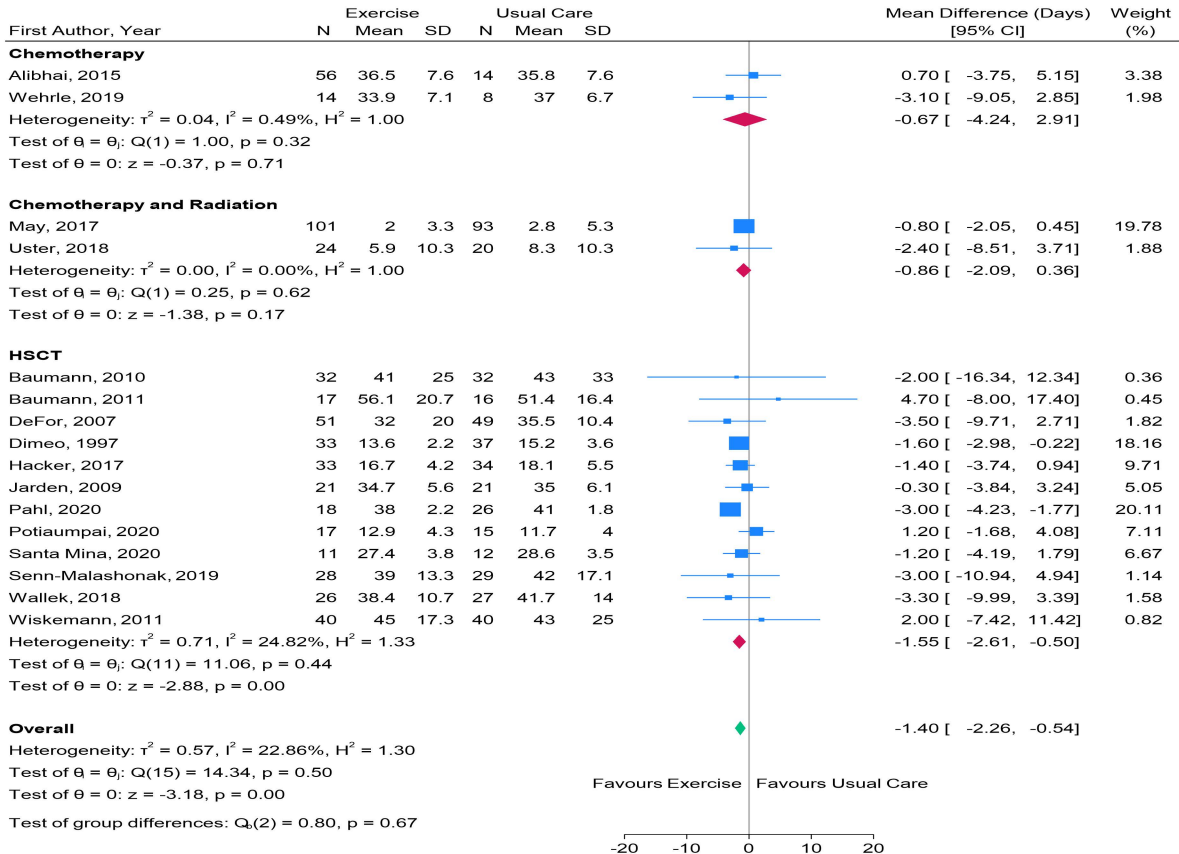
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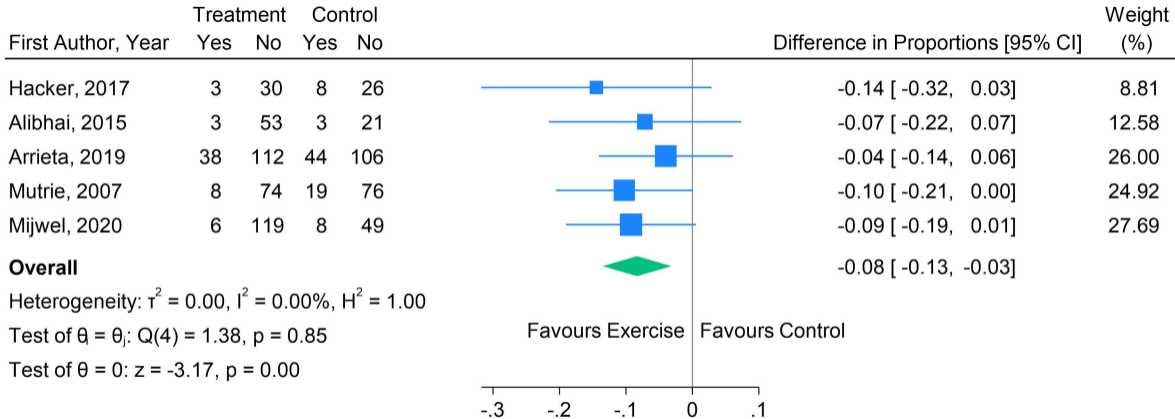
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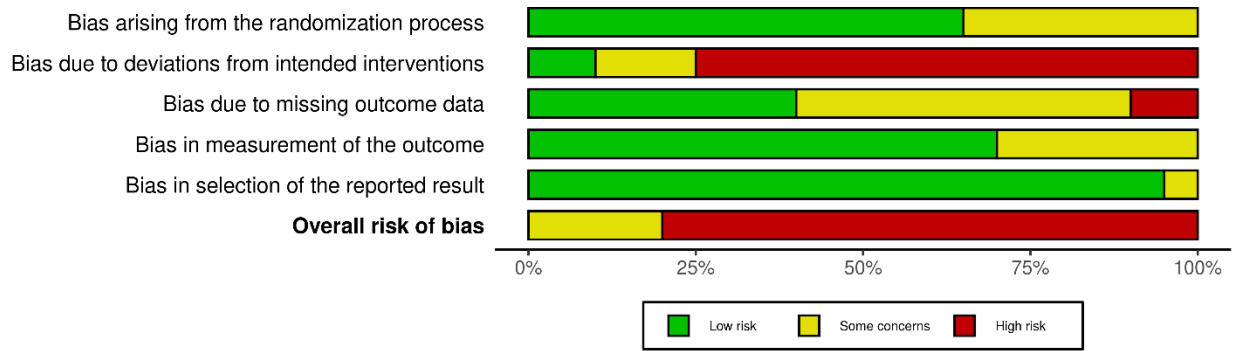


Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Alibhai 2015	+	X	+	+	+	X
Arrieta 2019	+	X	-	+	+	X
Baumann 2010	-	+	+	-	+	-
Baumann 2011	-	X	+	-	+	X
DeFor 2007	+	X	+	+	+	X
Dimeo 1997	-	X	+	+	+	X
Hacker 2017	+	X	-	-	-	X
Jacobsen 2014	-	X	+	+	+	X
Jarden 2009	+	-	-	+	+	-
May 2017	+	X	+	+	+	X
Mijwel 2020	+	X	-	+	+	X
Mutrie 2007	+	-	+	+	+	-
Pahl 2020	+	X	-	+	+	X
Potiaumpai 2021	+	X	-	-	+	X
SantaMina 2020	+	X	-	+	+	X
Senn-Malashonak 2019	-	-	-	-	+	X
Uster 2018	+	X	X	+	+	X
Wallek 2018	-	X	X	-	+	X
Wehrle 2019	+	X	-	+	+	X
Wiskemann 2011	-	+	-	+	+	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low

Supplementary Figure 1. Risk of bias assessment of randomized controlled trials using the traffic light plot from the Cochrane Risk of Bias 2 tool (RoB 2).



Supplementary Figure 2. Weighted summary plot of the overall types of bias encountered in included randomized controlled trials from the Cochrane Risk of Bias 2 tool (RoB 2).



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4, 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4, 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4-6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5-6



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7
Study characteristics	17	Cite each included study and present its characteristics.	Page 7-10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 15-16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 10-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 15-16
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 14-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 14-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 14-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 14-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 14-15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16
	23b	Discuss any limitations of the evidence included in the review.	Page 17/18
	23c	Discuss any limitations of the review processes used.	Page 18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16-18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 19
Competing interests	26	Declare any competing interests of review authors.	Page 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 19

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Supplementary Table 2: Database search details and results.

Database: Medline via Pubmed			
Date of initial Search: 23.2.22			
Search #	Concept/Explanation	Search Terms	# of Results
# 1	Cancer	cancer OR oncolog* OR neoplasm OR tumor OR tumour OR malignan*	5461712
# 2	Treatment	chemother* OR "radiation therapy" OR radiotherapy OR chemoradiation OR "Stem Cell Transplant*" OR "Bone Marrow Transplant*" OR hsct	1110890
# 3	Exercise	"physical activit*" OR exercis* OR exercising OR "resistance training" OR "resistance exercise" OR "aerobic training" OR "aerobic exercise" OR cycling OR "endurance training" OR "endurance exercise" OR yoga OR "tai chi" OR "weight training"	1395770
# 4	Hospitalization	hospitali* OR admitted OR inpatient OR "length of stay" OR "patient readmission"	862441
# 5	1 and 2 and 3 and 4		2709
Database: EMBASE			
Date of initial Search: 23.2.22			
Search #	Concept/Explanation	Search Terms	# of Results
# 1	Cancer	cancer OR oncolog* OR neoplasm OR tumor OR tumour OR malignan*	6062590
# 2	Treatment	chemother* OR "radiation therapy" OR radiotherapy OR chemoradiation OR "Stem Cell Transplant*" OR "Bone Marrow Transplant*" OR hsct	1663983
# 3	Exercise	"physical activit*" OR exercis* OR exercising OR "resistance training" OR "resistance exercise" OR "aerobic training" OR "aerobic exercise" OR cycling OR "endurance training" OR "endurance exercise" OR yoga OR "tai chi" OR "weight training"	881572
# 4	Hospitalization	hospitali* OR admitted OR inpatient OR "length of stay" OR "patient readmission"	1341618
# 5	1 and 2 and 3 and 4		543
Database: Cochrane Central Register of Controlled Trials			
Date of initial Search: 23.2.22			
Search #	Concept/Explanation	Search Terms	# of Results
# 1	Cancer	cancer OR oncolog* OR neoplasm OR tumor OR tumour OR malignan*	241812

# 2	Treatment	chemother* OR "radiation therapy" OR radiotherapy OR chemoradiation OR "Stem Cell Transplant*" OR "Bone Marrow Transplant*" OR hsct	122106
# 3	Exercise	"physical activit*" OR exercis* OR exercising OR "resistance training" OR "resistance exercise" OR "aerobic training" OR "aerobic exercise" OR cycling OR "endurance training" OR "endurance exercise" OR yoga OR "tai chi" OR "weight training"	149952
# 4	Hospitalization	hospitali* OR admitted OR inpatient OR "length of stay" OR "patient readmission"	108685
# 5	1 and 2 and 3 and 4		166

Supplementary Table 3. GRADE summary of quality of evidence

Quality assessment							Mean Difference /Difference in Proportions (95% CI)	Quality of evidence
No. of studies (No. of participants in meta-analysis)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Outcome: Mean difference of days spent in hospital between cancer patients participating in an exercise intervention versus control								
16 studies (995 participants)	RCTs	Serious ¹	Not serious	Not serious	Serious ²	Not serious	Mean Difference: 1.40 days (95% CI: -2.26 to -0.54 favouring exercise)	Low
Outcome: Difference in the proportion of participants with cancer admitted to hospital in exercise intervention and control groups								
5 studies (806 participants)	RCTs	Serious ¹	Not serious	Not serious	Serious ²	Not serious ³	Difference in proportions: -0.08 (-0.13 to -0.03) favouring exercise	Low

¹ Some studies had high risk of bias due to their methodology (RoB 2)

² Confidence intervals are close to the no difference line

³ The possibility of publication bias cannot be excluded as it was not measured due to the small number of studies (n=5), but it was/was not considered sufficient to downgrade the quality of evidence