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Review

Exercise-based interventions for cancer cachexia: A systematic review of randomised and non-randomised controlled trials

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ABSTRACT

Objective: Cachexia is a multifactorial syndrome characterised by involuntary weight loss and functional limitation. There is a strong theoretical rationale for the use of exercise in the management of cachexia, and evidence of benefit from exercise in general cancer patients. However, clinical studies of exercise interventions in cancer cachexia are limited. We aimed to synthesise current evidence on the delivery, acceptability, safety and outcomes of exercise interventions for adults with cancer cachexia.

Methods: We conducted a systematic review. Four databases were searched up to February 2023 for randomised (RCTs) and non-randomised (NRCTs) controlled studies. Eligibility and quality were independently assessed by two authors. Data on intervention components and structure, participant flow and adherence were tabulated. Clinical outcome data on body stature and composition, muscle strength, functional performance, and health-related quality of life were synthesised using effect direction plots.

Results: Twelve studies (9 RCTs, 3 NRCTs) involving a total of 898 patients (study range 20–374) as part of a multicomponent approach. Median programme completion was 75% (range 43%–100%) and adherence was generally high. Five adverse events were considered possibly related to an intervention, including muscle or joint pain, breathlessness on exertion. Overall, 12/16 (75%) outcomes demonstrated a positive direction of effect on body stature and composition, 8/10 (80%) on muscle strength, 14/22 (64%) on functional performance, and 3/8 (38%) on health-related quality of life. Multicomponent interventions showed more consistent effects on body stature, and resistance training interventions on muscle strength.

Conclusions: Exercise interventions appear to be safe and acceptable to people with cancer cachexia. Positive effects from exercise are more consistently observed for body stature or composition and muscle strength outcomes, than in functional capacity and health-related quality of life. The synergistic effects of exercise with other cachexia interventions, including drugs, should be examined in future robust studies.

Introduction

Cachexia is a complex metabolic syndrome that effects up to 80% of people with advanced cancer[1,2] and reduces quality of life, cancer treatment response and survival.[3,4] Cachexia can occur at any stage of cancer, and may be the first sign of cancer, but is more common in metastatic disease[5,6] and solid tumours of the lung, pancreas and upper-gastrointestinal tract.[7,8] Cancer cachexia can be measured across a spectrum, from pre-cachexia, which comprises anorexia and metabolic changes but limited weight loss, to refractory cachexia, where cancer is not responsive to treatment, weight loss is substantial, and life expectancy is less than three months.[6,9]

The functional impacts of cancer cachexia are extensive. Patients with cachexia often experience physical symptoms such as fatigue, weakness, and loss of appetite, which can have a negative impact on their quality of life.[10,11] This can be compounded by severe psychological symptoms such as depression, anxiety, and social isolation.[12] Caregivers of those living with cancer cachexia also experience social isolation and additional psychosocial burden, including stress, anxiety, and depression,[13] due to caregiving requirements. Economically, patients with cancer cachexia require more frequent hospitalisations, longer hospital stays, and increased health care resource utilisation, including diagnostic tests, medicine prescription, and nutritional support.[14,15] In addition to these direct health care costs, cancer cachexia can result in indirect costs,

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including lost productivity, ability to work and added caregiver burden.[16] These impacts highlight the pressing need for effective management of this condition.

There is no gold standard treatment for cachexia, although best cachexia management will include early identification and a multi-faceted approach that combines exercise, nutritional support, and pharmacological agents[17] with active symptom management.[18] Exercise in various forms has been demonstrated to provide numerous benefits to people with cancer. Aerobic training (e.g., walking, cycling or swimming) and resistance training (e.g., free or fixed weights or resistance bands) help to improve physical and psychosocial function in people with cancer, leading to improved quality of life.[19] Recent research suggests regular exercise may even alter disease progression and treatment response,[11,20] aiding immune function by increasing the number of immune cells in the body,[21] or reducing treatment side effects including fatigue, pain, nausea and vomiting.[22] Population-specific evidence for exercise and cancer cachexia is limited. In part this follows from most studies looking at people with early stage/curative disease. It is also a result of studies not assessing cachexia parameters, so even when exercise studies are on people with lung cancer, for example, the identification of cachexia is missing in reports.

We therefore aimed to synthesise available evidence around exercise interventions for adults with cancer cachexia. Our objectives were to describe content and delivery of programmes; understand acceptability and adherence; and determine the direction of effect on clinical outcomes.

Methods

This systematic review was not registered but otherwise reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Inclusion and exclusion criteria

Participants

Study participants including adults (aged 18 years or older), with a diagnosis of cancer, and meeting criteria to be diagnosed with cancer cachexia at any stage (pre-cachexia, cachexia or refractory cachexia). If the authors did not assess or diagnose participants with any stage of cachexia, baseline participant characteristics, e.g., weight loss history and body mass index (BMI), were used to judge the relevance of the study to the review objectives.

Interventions and comparators

Any studies that involved the use of exercise training as an individual intervention or integrated alongside other interventions were eligible. Both aerobic and endurance exercise training modalities were sought. Exercise programmes can include a variety of aspects such as type of training (aerobic, resistance, balance, flexibility, etc.), length of training (minutes), frequency (number of sessions/week), intensity (low, moderate, high) and duration of programme (weeks). We excluded programmes only offering general advice to be more physically active. All comparators were considered including alternative interventions, usual/standard care or no treatment arms.

Outcomes

Process outcomes included acceptability defined as uptake and completion of interventions, adherence and safety of the exercise interventions. Clinical outcomes included body composition and lean body mass, muscle strength, exercise or task performance, and health-related quality of life.

Study designs

We considered both randomised (RCTs) and non-randomised controlled trials (NRCTs) in adults with a clinical diagnosis of cancer and cachexia.

Search strategy

We developed a comprehensive electronic search strategy using a mixture of terms based on the target population, intervention, comparator and outcomes. See Appendix 1 for the detailed search strategy keywords. We searched the following electronic databases: Embase 1974 to 2023 February 27; Ovid MEDLINE 1946 to February 27, 2023; Global Health 1973 to 2023 Week 08; and APA PsycInfo 1806 to February Week 3 2023 and CENTRAL (the Cochrane Library) 2023, Issue 2.

Study retrieval

We utilised reference management software to compile results from different electronic databases and remove duplicate studies. Two review authors (CC, MM or AJG) independently assessed titles and abstracts of articles for relevance. We obtained full-text reports of potentially relevant studies for assessment against the inclusion criteria. Two review authors (CC, MM) discussed any disagreement amongst the selection of studies and resolved it by consensus discussion. No language restrictions were applied in the selection of studies.

Data extraction and management

Two review authors (CC, MM or EB) independently extracted data from the studies that were included after full text review and discussed the data extraction process. A data spreadsheet was used to store data relating to the eligibility, methods, study design, participants (age, gender, diagnosis), intervention (exercise type and intensity, session length and frequency, overall programme duration), patient flow, adherence to the exercise programme (either self-reported or objective), and the occurrence of any adverse events.

Data collection and analysis

One review author (CC) independently collected data from the results of the studies. Two review authors (CC, MM) were involved in reviewing and discussing the data analysis. The primary outcome was to study clinical outcomes in patients with cancer cachexia who used exercise as an intervention. Outcome data on the following domains was collected.

- Acceptability, assessed by uptake and completion rates (including reasons).
- Adherence, assessed by frequency of session attendance or self-report diaries.
- Safety, evaluated by any adverse, or serious adverse events, and relatedness to the intervention.
- Body stature and composition, weight, BMI, lean or fat mass generally assessed using anthropometry or bioelectrical impedance analysis.
- Muscle strength, usually as a measure of force, assessed using dynamometry.
- Functional performance, including measures of distance walked or time needed to walk a distance, timed sit-to-stand and other physical tasks, physical activity and global function.
- Health-related quality of life, evaluated through self-assessed disease-specific or generic questionnaires.

Methodological appraisal

Two review authors (CC, AJG) independently assessed risk of bias for each study using the Cochrane Collaboration's risk of bias tool, version 2.0 (RoB2). Six parameters were used to assess included studies: (1) Bias arising from the randomisation process; (2) bias due to deviations from intended intervention; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result;

and (6) overall risk of bias of included studies. Based on signalling questions and guidance withing the RoB2 tool, each parameter and the overall risk of bias for each study was classified into low risk of bias; some concerns; and high risk of bias.[23] A graphical risk of bias summary was produced using Microsoft Excel.

Data analysis

Study characteristics and findings were tabulated by outcome domain. No meta-analysis of data was possible due to substantial clinical, statistical, and methodological heterogeneity between the studies. An effect direction plot was produced using vote counting of studies based on the categorisation of effects from different interventions (resistance vs. combined training, exercise alone vs. combined) on clinical outcome domains.[24] Vote counts were based on the direction of effect, taken from the point estimate for between group differences (RCTs) or change pre-to-post intervention (NRCTs). This was favoured over counts based on statistical significance to acknowledge any underpowered studies that did not rule out clinically important effects.[25]

Results

Our search identified 3240 individual references after the removal of duplicates. We excluded 3119 studies after title and abstract screening. The remaining 121 references were listed as potentially relevant and full-text reports were retrieved. After full-text screening, 105 of these studies were removed. Four additional studies were not included in the report: two were classified as ongoing recruitment, one was classified as in process, and one did not have published results. The results from twelve total studies were included in the review (Fig. 1).

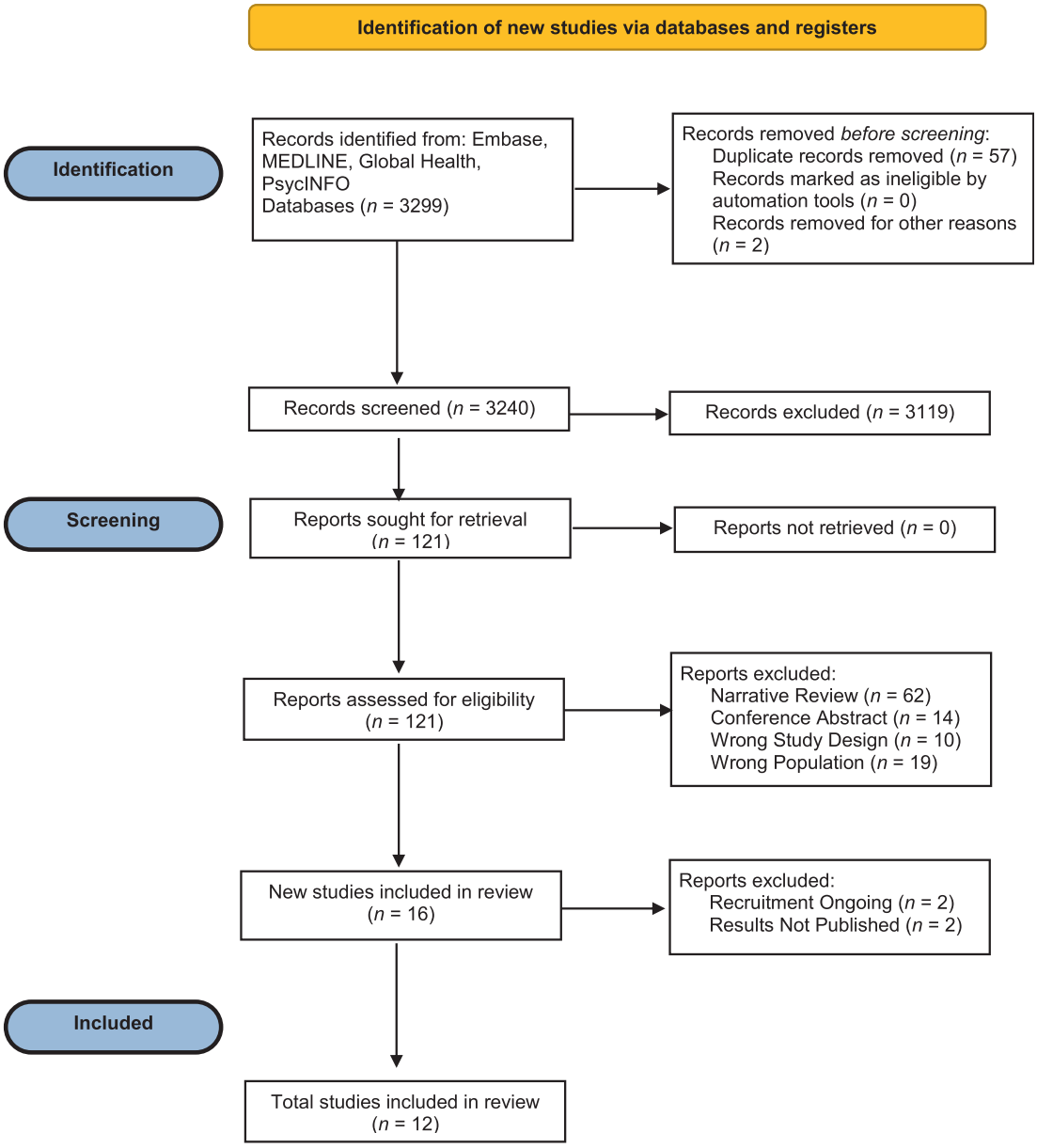

Fig. 1. Schematic of the PRISMA search strategy and screening procedure. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1
Description of included studies and interventions.

Study	Population and cancer treatment	Exercise intervention	Exercise programme description	Additional intervention(s)
Capozzi 2016[26] Canada, RCT	• 60 patients • Head and neck cancer • 49 male, 11 female • Age: 56.1 ± 9.2 • BMI: 27.3 ± 4.7 • Radiation Therapy alone or in conjunction with surgery and/or chemotherapy	• 12 or 24 weeks depending on group • 2 individualised sessions at home per week • 2 group-based sessions per week	• Progressive resistance training • Short, moderate intensity warmup followed by 2 sets of 8 repetitions at 8 to 10 repetitions maximum • 10 exercises targeting major muscle groups • Progression applied at weeks 4, 6 and 9 as appropriate	• Health education • Behaviour change support
Forget 2014[27] Belgium, RCT	• 54 patients • Various cancers • BMI: 25.0 (control), 23.9 (intervention) • Chemotherapy	• 12-week intervention • Daily physical exercise alone • 1 session a week with physiotherapist	not reported (abstract)	• Mirtazapine 30 mg/d • Weekly dietitian advice • Psychological support
Glare 2011[28] Australia, NRCT	• 54 patients • Lung or gastrointestinal cancer • 37 male, 17 female • Median age: 64 • 67% on chemotherapy	• 8-week intervention • Supervised exercise sessions at hospital • Training sessions at home	• Combined aerobic and strengthening exercises • Individually prescribed according to baseline physical assessments	• Individualised nutritional interventions • Symptom management
Grote 2018[29] Germany, RCT	• 20 patients • Head and neck cancer • 15 male, 5 female • Age: 60.9 ± 11.3 • Radiation Therapy, 65% in conjunction with chemotherapy	• 8-week intervention • Exercise sessions 3 times per week • 30 min per session • Undertaken in the hospital's department of physical and rehabilitation medicine, observed by a physiotherapist	• Dynamic resistance training • 5-min warmup on bicycle ergometer or an upper body cycle • 3 exercises for major muscle groups with 8–12 repetitions maximum for 3 sets each • Exercises included leg press, latissimus pull down and chest press	N/A
Hall 2021[30] United Kingdom, RCT	• 45 patients • Various cancers • 26 male, 19 female • Age: > 65: 30, 55–65: 7, < 55: 8	• 8-week intervention • Home-based programme	• Combined aerobic and resistance training, individualised for each patient • 60 min of exercise per week, usually walking at a moderate intensity (modified Borg scale 3–4 rating) • Resistance exercises focused on major muscle groups in upper and lower body, predominantly using body weight, included standing press-ups, half squats and shoulder thrusts, with sets advised 3 times per week	• Nutritional intervention
Kamel 2020[31] Egypt, RCT	• 40 patients • Pancreatic cancer • 26 male, 14 female • Age: 52.25 ± 4.91 (control), 51.6 ± 5.18 (intervention) • BMI: 21.06 ± 0.81 (control), 21.15 ± 1.45 (intervention) • Chemotherapy	• 12-week intervention • Groups of 1–4 patients at a time, supervised by specialised physical therapists • 2 sessions a week	• Resistance training using fixed machines • One set at low intensity, then 1–2 sets at medium intensity, 20 repetitions per set • Exercise weight and frequency progressive depending on performance • Exercises included leg press, leg extension, leg curl, seated row, latissimus pull down, back extension, butterfly reverse and crunch • General flexibility exercises also administered	N/A
Naito 2019[32] Japan, NRCT	• 30 patients • Lung and pancreatic cancer • 20 male, 10 female • Median age: 75 • BMI: 21.7 ± 3.2 • Chemotherapy	• 8-week intervention • Daily home-based exercise	• Resistance training and counselling to increase step count • Individualised exercise programme consisted of 3–5: sit-to-stand, calf raise, knee extension, knee raise, side leg raise • 3 sets and 10 repetitions for each exercise • Exercise frequency progressive depending on performance • Low exercise intensity reported using modified Borg scale	• Three nutritional sessions • Standard nutritional counselling • Supplements rich in brand amino acids
Parmar 2017[33] Canada, NRCT	• 374 patients • Various cancers • 208 male, 166 female • Age: 65.2 ± 13.3 • 63% had received chemotherapy	• 12-week intervention • Patients are encouraged to perform their programme at the hospital up to twice a week, supervised by physiotherapists • Patients are offered an individualised home exercise programme to perform alone or in addition to supervised programme	• Combined aerobic and resistance exercises • Individualised exercise intervention plan	• Individualised nutritional counselling and support

(*continued on next page*)

Table 1 (*continued*)

Study	Population and cancer treatment	Exercise intervention	Exercise programme description	Additional intervention(s)
Solheim 2017[34] Norway/UK, RCT	• 46 patients • Lung and pancreatic cancer • 26 male, 20 female • Median age: 59 (control), 63 (intervention) • BMI: 24.0 (21.9-25.3) (control), 24.2 (21.4–27.0) (intervention) • Chemotherapy	• 6-week intervention • Two 30-min sessions a week for aerobic training • Three 20-min sessions a week for resistance training	• Combined home-based aerobic and resistance training • Aerobic component led by patient choice • Resistance component consisted of 6 individualised exercises, including push-ups against the wall, overhead press, bicep curls, weighted squats, lunges and calf raises	• Celecoxib 300 mg/d • Two 220 mL cartons of oral nutritional supplements, each containing 1 g eicosapentaenoic acid • Nutritional counselling
Storck 2020[35] Switzerland, RCT	• 52 patients • Various cancers • 29 male, 23 female • Age: 63.1 ± 10.3 • BMI: 25.4 ± 4.7 • Chemotherapy	• 12-week intervention • 3 training sessions per week, 2 in hospital's physical therapy department and 1 home-based	• Combined aerobic, resistance and coordination training • Strength training individualised • Moderate intensity (modified Borg scale 4–6 rating) • Exercises varied by day, including use of strength bands, walking, cycling and strength exercise circuits	• Leucine rich supplement • Nutritional programme
Uster 2017[36] Switzerland, RCT	• 58 patients • Lung or gastrointestinal cancer • 40 male, 18 female • Age: 63.0 ± 10.12 • BMI: 25.8 ± 5.2	• 12-week intervention • 60-min exercise programme twice a week	• Resistance training • Six fixed-weight machines covering major muscle groups • Exercises included leg press, leg flexion, pull down, abdominal trainer and bench press with 10 kg barbell • Performed at 60%–80% of one repetition maximum in 2 sets of 10 repetitions • Weight and frequency progressive depending on performance	• A minimum of 3 standardised individual nutritional counselling sessions
Wiskemann 2019[37] Germany, RCT	• 65 patients • Pancreatic cancer • 24 male, 19 female • Age: 61.6 ± 8.0 • BMI: 23.9 ± 3.5 (control), 22.7 ± 2.8 (intervention) • Chemotherapy	• 24-week intervention • One group at home and one supervised group • Training 2 times per week • Each session usually lasted 60 min	• Heavily individualised resistance training • Machine-based resistance exercises included leg press, leg extension, leg curl, seated row, latissimus pull down, back extension, butterfly reverse, and crunch • First 5 exercises performed for 1 to 2 sets with 20 repetitions at a low to moderate intensity (50%–60% one repetition maximum during first 4 weeks • 3 sets with 8–12 repetitions at moderate to vigorous intensity (60%–80% one repetition maximum) after week 5 • Weight and frequency progressive depending on performance	N/A

RCT, randomised controlled trial; NRCT, non-randomised controlled trial; BMI, body mass index; N/A, not available.

Characteristics of included studies

In our search, we identified twelve studies (Table 1). Included studies were published in the period 2011–2020 and related to studies conducted in the UK ($n = 2$), Germany ($n = 2$), Switzerland ($n = 2$), Canada ($n = 2$) and Belgium, Australia, Egypt, Japan, and Norway (1 each). Nine of the studies were RCTs all with individual patient allocation and 3 of the studies were prospective cohort trials/NRCTs. A total of 898 patients were included in the studies (range 20–374), with various cancer diagnoses including head, neck, lung, gastrointestinal and pancreatic cancer. Five of the studies[26,30,35–37] did not specify the cachexia status of participants but baseline data were consistent with the consensus definition of cachexia identified by Fearon et al.[6]

Nine of the studies investigated a multimodal approach whilst three used exercise as the sole intervention. Eight prescribed a combined training intervention, with aerobic and resistance exercise; the remaining five prescribed resistance training. Details on session frequency, duration and individual exercises/target muscles groups was generally reported, though detail on how intensity was monitored, and any progression criteria was lacking.

Methodological quality

From the overall risk of bias assessment five studies showed low risk of bias, five studies some concerns and two studies high risk of bias (Fig. 2). Over half of the included studies presented at least one category of concern, most commonly deviation from the intended intervention and either missing or selected reporting of outcomes. The nutritional supplements and/or drugs were donated from pharmaceutical companies for use in two studies.

Process and safety outcomes

A total of 2487 patients were approached about participating in a study, and 898 accepted and were enrolled. The median rate of uptake was 21% (11%–93%). In total, 525 participants completed their studies, giving a median completion rate of 75% (43%–100%). For those taking part in a clinical trial and randomised into the intervention arm (181 participants), the median completion rate was 84% (51%–100%). The main reasons given for withdrawal from the studies were death and deterioration of the participant's clinical condition.

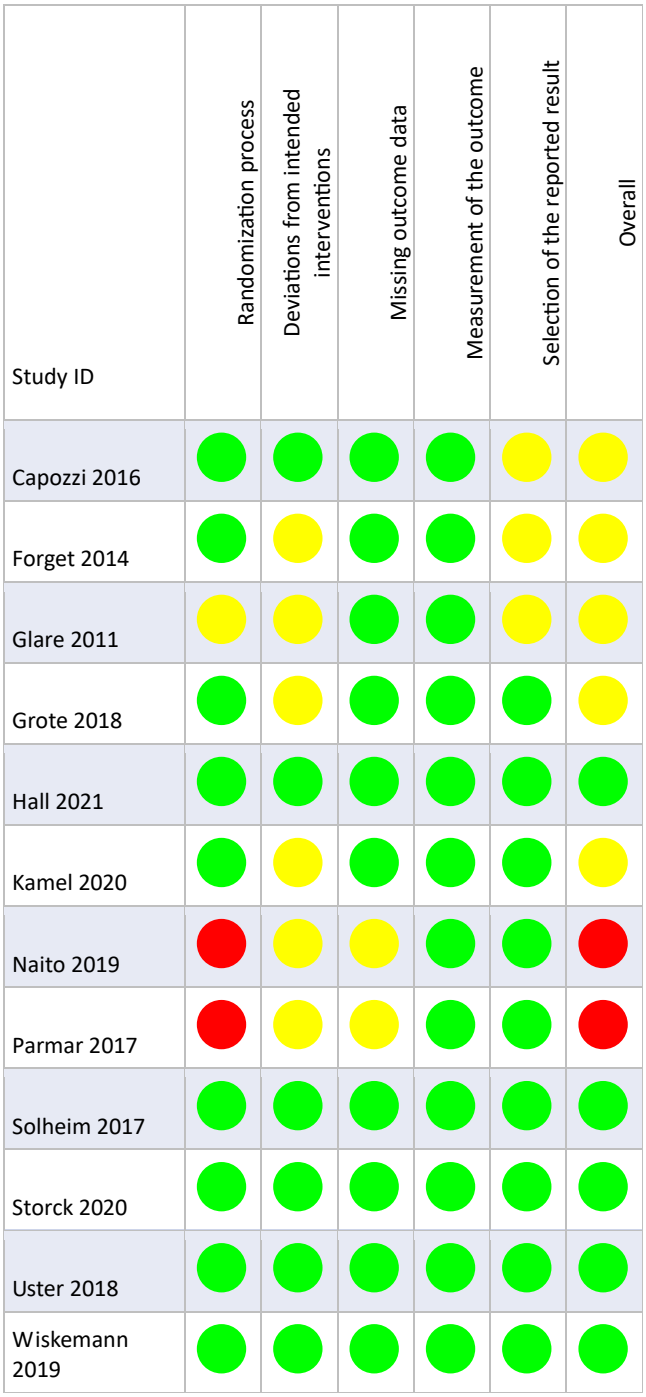

Fig. 2. Risk of bias summary. Key: green = low risk, yellow = some concerns, red = high risk.

Overall, the studies showed positive results for adherence, although this was measured differently across the studies, making it difficult to compare. Furthermore, studies with a multimodal approach reported adherence to each component separately. Adherence ranged from 41% for some intervention components, up to 107% for others, as some participants received more than the planned number of intervention sessions. Where both were reported, there was a tendency for adherence to be higher in home-based compared to centre-based exercise interventions.

Six of the studies reported on adverse events and serious adverse events. There were 25 serious adverse events across the studies, though none were found to relate to the intervention. Of 320 reported adverse events, five were possibly related to the study intervention. These included muscle pain, joint pain, and shortness of breath on exertion (see Table 2).

Clinical outcomes

Body stature and composition

Twelve studies (9 RCTs, 3 NRCTs) reported on 16 separate outcomes of weight, BMI, lean mass (whole body or appendicular), and skeletal muscle mass or indices. Overall, 12/16 (75%) outcomes demonstrated a positive direction of effect compared to 4/16 (25%) showing a lack of effect. In 11 instances there was a gain in weight, BMI or lean body mass following intervention including as compared to control. In the remaining 5 cases there was a relative preservation of weight, BMI or lean body mass on a background of weight or lean body mass loss (Table 3).

There was a suggestion of more consistent evidence of benefit from combined aerobic and resistance training, compared to resistance training, but more NRCT for the former (Fig. 3). Multicomponent interventions tended to show more consistent positive effect (10/13 cases) especially on weight and BMI (Fig. 3).

Muscle strength

Nine studies (7 RCTs, 2 NRCTs) reported on 10 separate outcomes of muscle strength including hand grip strength, peak force, or one-repetition maximum for major muscle groups. Overall, 8/10 (80%) outcomes indicated a positive direction of effect, compared to 2/10 (20%) showing a lack of effect. Both cases showing a lack of effect concerned hand grip strength; all outcomes of peak force in trained muscle groups were positive (Table 3, Fig. 3). There was more consistent evidence of benefit on muscle strength outcomes where resistance training was offered compared to combined aerobic and resistance training (Fig. 3).

Functional performance

Ten studies (7 RCTs, 3 NRCTs) reported on 22 separate outcomes; 9 relating to walking performance assessed using the 6- or 2-min or 400 m walk test, and 13 relating to other tasks including sit to stand, timed up and go, gait speed, and free-living activity via step counts, life-space questionnaire or Karnofsky Performance Scale. Overall, 14/22 (64%) studies indicated a positive direction of effect on this outcome, compared to 8/22 (36%) studies reporting a lack of effect (Table 3). There was no discernible pattern when comparing walking to non-walking tests. Positive effects were more consistent in NRCTs and for multicomponent interventions compared to exercise alone (Fig. 3).

Health-related quality of life

Seven studies (5 RCTs, 2 NRCTs) reported on 8 separate outcomes of health-related quality of life, assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and C15-PAL, FACT-G and FACT-An TOI, or the FHNSI-22 measures. Overall, 3/8 (38%) outcomes indicated a positive direction of effect, compared to 5/8 (62%) outcomes demonstrating a lack of effect. In many instances there was a decline in health-related quality of life and wide variation in the direction and degree of change (Table 3). There was no discernible pattern when comparing resistance to combined training interventions, and only one study where exercise was offered alone (Fig. 3).

Differences according to gender

In a post hoc explorative analysis, we searched included studies for clinical outcome data stratified by gender. Three studies (2 RCTs, 1 NRCT) provided some information. Parmar et al.[33] reported that at baseline males had better quality of life than females (trial outcome index: male 56.7 (17.1) vs. female 53.0 (17.9), $P = 0.04$), though there was no difference in change in this outcome by gender ($P = 0.18$). Storck et al.[35] reported in females had significantly less improvement in fatigue scores compared to males ($P < 0.05$). Finally, Wiskemann et al.[37] reported no meaningful changes in weight, peak force and functional performance outcomes when models were adjusted for covariates including gender.

Table 2
Acceptability, adherence and safety findings.

Study	Uptake	Completion	Main reasons for withdrawal	Adherence	Safety
Capozzi 2016[26]	13%	60%	Too ill or too busy ($n = 24$)	Immediate lifestyle intervention group: 45% ± 39% (median 42%) 12-week delayed lifestyle intervention group: 62% ± 43% (median 83%)	Not reported
Forget 2014[27]	Not reported	43%	Loss of follow up ($n = 20$) Withdrawal of consent ($n = 2$) Death ($n = 9$)	Weekly dietary advice: 100% Mirtazapine: 67% Increased physical activity: 41%	Not reported
Glare 2011[28]	93%	46%	Death, hospitalisation, lost interest, patient too busy or unwell to participate	Not reported	Not reported
Grote 2018[29]	20%	100%	N/A	Intervention group: 90% ± 37%	AEs: 0 SAEs: 0
Hall 2021[30]	37%	64%	Holiday ($n = 1$) Deterioration ($n = 12$) Travel ($n = 2$)	Intervention group: excellent (≥ 80%): 57%; good (50%–79%): 38%; poor (< 50%): 5%	AEs: 39 total (intervention arm ($n = 23$): 20; control arm ($n = 22$): 19) SAEs: 0
Kamel 2020[31]	53%	83%	Death ($n = 2$) Withdrawal from trial ($n = 3$) Disease progression ($n = 2$)	Intervention group: 85% Control group: 80%	Not reported
Naito 2019[32]	54%	97%	Deterioration ($n = 1$)	Intervention group: 97%	AEs: 55 total (50 unrelated to study; 5 related to study) SAEs: 4 (unrelated to study)
Parmar 2017[33]	N/A	43%	N/A	N/A	Not reported
Solheim 2017[34]	12%	89%	Death ($n = 2$) Deterioration ($n = 2$) Treatment side effects ($n = 1$)	Celecoxib: 76% Exercise components: 60% ONS: 48%	AEs: 214 total (intervention arm [$n = 25$]: 113; control arm [$n = 21$]: 101) SAEs: 21 total (unrelated to study) (intervention arm: 13; control arm: 8)
Storck 2020[35]	11%	79%	Death ($n = 1$) Withdrawal from trial ($n = 10$)	Hospital-based training sessions: 71% Home-based training sessions: 95% Nutritional counselling sessions: 107% ONS: 71%	AEs: 12 total (intervention arm [$n = 27$]: 6; control group [$n = 25$]: 6) SAEs: 0
Uster 2016[36]	13%	76%	Death (n =10) Withdrawal from trial (n=4)	Physical exercise training sessions: 67% ONS: 93% Nutritional counselling sessions: 90%	AEs: 0
Wiskemann 2019[37]	21%	74%	Death ($n = 3$) Withdrawal from trial ($n = 11$) Deterioration ($n = 8$)	Supervised training sessions: 64% Home-based training sessions: 78%	Not reported

N/A, not available; SAE, serious adverse event; ONS, oral nutritional supplements.

Discussion

Main findings

We aimed to determine the acceptability, safety and effects of exercise on clinical outcomes of cachexia in adults living with cancer. We included almost 900 patients with head, neck, lung, gastrointestinal or pancreatic cancer, across twelve studies (9 RCTs). Although rates of uptake were low, once patients were enrolled adherence and completion rates were high and favourable given the context of advanced cancer. There were no serious adverse events and only five adverse events considered as possibly related to the exercise intervention, typically joint or muscle pain, or exertional breathlessness. Overall, positive directions of effect were most common for outcomes of body stature (weight and BMI) and composition (75%) and muscle strength (80%), and less often observed for functional performance (64%) and health-related quality of life (38%). NRCTs tended to report positive direction of effects more than RCTs, although in some cases an intervention led to the preservation of weight on a background of deterioration. Multicomponent interventions showed more consistent positive effects on body weight and BMI, and resistance training interventions more often led to improvements in muscle strength.

Comparison to existing literature

There is growing interest and evidence around the use of exercise for people with cancer cachexia. In 2021, an updated Cochrane review was published that including four RCTs.[38] The objective of this current review was to present the current state of the science by including all randomised and non-randomised controlled trials, resulting in a total of 12 studies that were included and described in detail, thus gathering a broader evidence base. The current synthesis of these studies shows an increasing rate of exercise studies specific to cancer cachexia. It serves as a 'stock-take' and can help inform and shape future research in this area. In undertaking our current search, we identified four ongoing studies. Two were awaiting publication of findings, and two were actively recruiting participants. Three of the studies aim to investigate exercise in addition to nutritional support and supplements such as omega-3-fatty acids as an intervention. The last focuses on exercise with psychoeducational support. The target sample size for each study is 30, 20, 112, and 130 patients respectively,[39–42] hence these offer strong potential to progress this field with more robust evidence.

Implications for practice and research

Numerous studies have explored the impact of exercise on cancer cachexia, ranging from preclinical models to clinical trials.[43,44] These studies demonstrate promising findings, substantiated by this review, indicating that exercise can attenuate muscle wasting, improve physical function, and enhance overall well-being in cancer patients.[45] Although the literature in this field is growing, the limited evidence base is acknowledged by international guidelines.[46]

Further studies are required to assess clinical outcomes with more precision. Larger and more definitive trials are likely required to influence clinical guidelines, practice and commissioning. More widespread use of exercise interventions will also require higher rates of uptake in the target population, and currently the inconvenience of the lifestyle changes and demand of interventions can limit reach of exercise. This is particularly relevant for multicomponent interventions, where patients are asked to perform exercise several times a week in addition to attending nutritional counselling sessions, taking supplements and other interventional requirements. These may result in difficulty ensuring treatment fidelity; nevertheless, several components are likely needed to address the complexity of cancer cachexia.[46]

Table 3
Clinical outcomes data, baseline to post-intervention, presented as mean ± SD or median (inter-quartile range).

Study	Body stature and composition	Muscle strength	Functional performance	Health-related quality of life
Capozzi 2016[26]	**BMI (kg/m^2)** Immediate Intervention (II): 26.6 to 23.4 Delayed Intervention (DI): 28.0 to 24.8 **Lean body mass (kg)** II: 56.9 to 52.4 DI: 58.4 to 54.0	**Total hand grip (kg)** II: 82.0 to 82.2 DI: 83.4 to 82.1	**6-min walk test (m)** II: 615.2 to 658.7 DI: 655.4 to 673.2 **30 s sit to stand (*n*)** II: 15.6 to 17.3 DI: 15.9 to 18.4 **Sit and reach flexibility (cm)** II: 22.1 to 24.7 DI: 22.7 to 25.9	**FACT-An TOI** II: 109.4 to 108.4 DI: 109.3 to 106.3 **FHNSI-22** II: 68.6 to 66.0 DI: 68.1 to 66.0
Forget 2014[27]	**BMI (kg/m^2)** Intervention: 23.9 to 23.2 Control: 25.0 to 24.4 **Lean body mass (kg)** Intervention: 23.7 to 22.9 Control: 24.7 to 23.3	**Handgrip (kg)** Intervention: 28.6 to 24.8 Control: 27.0 to 24.0	N/A	**EORTC QLQ-C30** Intervention: 60.2 to 59.5 Control: 58.8 to 56.5
Glare 2011[28]	**Weight (kg)** Intervention: 62.7 to 63.4	N/A	**6-min walk test (m)** Intervention: 441.5 (186–675) to 570 **Karnofsky Performance Scale** Intervention: 70 (50–90) to 80	N/A
Grote 2018[29]	**Lean body mass (kg)** Intervention: 58.6 ± 4.9 to 59.1 ± 7.1 Control: 54.4 ± 12.5 to 52.7 ± 12.1	**Mean weighted load (%)** Intervention: leg press +19%, chest press +29.8%, latissimus pull-down +22.8%	N/A	**FACT-G** Intervention: 80.1 ± 11.2 to 64.4 ± 18.4 Control: 75.7 ± 18.8 to 59.5 ± 26.5
Hall 2021[30]	**Weight (kg)** Intervention: 71 (60–79) to 80 (62–88) Control: 70.8 (62–86) to 67 (57–87)	N/A	**2-min walk test (m)** Intervention: 114 (76–144) to 116 (75–138) Control: 104 (66–122) to 106 (68–122) **Timed up and go (secs)** Intervention: 13 (11–17) to 14 (12–21.8) Control: 16 (11–24) to 15 (12–23) **Daily step count** Intervention: 2954 (2168–4143) to 2898 (1055–5005) Control: 2294 (591–3821) to 2478 (727–3645) **Life space assessment** Intervention: 53 (32–81) to 50 (35–64) Control: 37 (31–52) to 48 (34–58)	**EORTC QLQ-C15-PAL** Intervention: 66.7 (50–83.3) to 66.7 (50–83.3) Control: 50 (45.8–70.8) to 66.7 (50–66.7)
Kamel 2020[31]	**Appendicular lean mass (kg)** Intervention: 22.6 ± 2.4 to 23.1 ± 2.3 Control: 22.7 ± 2.3 to 22.5 ± 2.2	**Peak force** Intervention: significant increase in of knee extensors, elbow flexors and elbow extensors	**400 m walk (secs)** Intervention: 270.3 ± 32.2 to 256.9 ± 34.2 Control: 266.4 ± 21.3 to 264.2 ± 22.4 **Chair rise time (secs)** Intervention: 13.8 to 12.5 Control: 13.8 to 13.5	N/A
Naito 2019[32]	**BMI (kg/m^2)** Intervention: 21.7 ± 3.2, change 0.4 ± 0.2 **Skeletal muscle index (cm^2/m^2)** Intervention: 40.7 ± 1.0, change 1.1 ± 0.5	**Handgrip (kg)** Intervention: 25.6 ± 1.2, change 0.2 ± 0.5	**6-min walk test (m)** Intervention: 422.4 ± 12.8, change 12.3 ± 10.9 **Five-time sit to stand test (secs)** Intervention: 10.8 ± 0.4, change −0.5 ± 1.0 **5 m gait speed (m/s)** Intervention: 1.2 ± 0.04, change 0.02 ± 0.4	N/A
Parmar 2017[33]	**Weight (kg)** Intervention: overall increase*	N/A	**6-min walk test (m)** Intervention: overall increase*	**FAACT** Intervention: 91.1 ± 21.9 to 100.8 ± 22.3
Solheim 2017[34]	**Weight (kg)** Intervention: 70.2 ± 13.0 to 70.8 ± 14.1 Control: 66.6 ± 10.5 to 64.9 ± 9.9 **Lumbar muscle mass (cm^3)** Intervention: 133.8 ± 25.2, change −2.8 ± 9.4 Control: 129.9 ± 29.6, change −5.0 ± 7.8	**Handgrip (kg)** Intervention: 35.7 ± 11.5 to 35.3 ± 9.9 Control: 32.3 ± 12.5 to 31.5 ± 12.4	**6-min walk test (m)** Intervention: 474.3 ± 79.1 to 474.4 ± 103.3 Control: 470.2 ± 87.2 to 490.5 ± 101.1	N/A
Storck 2020[35]	**BMI (kg/m^2)** Intervention: 24.0 ± 4.6, change 0.41 Control: 25.8 ± 4.9, change 0.04	**Handgrip (kg)** Intervention: 35.8 ± 9.8, change 2.0 Control: 35.7 ± 8.8, change −2.0	**60 s sit to stand (*n*)** Intervention: 24.8 ± 6.9, change 2.54 Control: 26.0 ± 9.6, change 2.2 **Timed up and go (s)** Intervention: 5.9 ± 1.9, change −0.2 Control: 6.3 ± 2.4, change 0.4 **Short physical performance battery** Intervention: 10.9 ± 1.4, change 0.4 Control: 10.3 ± 2.0, change	**EORTC QLQ-C30 dyspnoea** Intervention: 27.2 ± 26.2 to 26.7 ± 28.9 Control: 33.3 ± 28.9 to 18.2 ± 24.6

(*continued on next page*)

Table 3 (*continued*)

Study	Body stature and composition	Muscle strength	Functional performance	Health-related quality of life
Uster 2016**[36]	**Weight (kg)** Intervention: change 1.9 ± 0.8 Control: change 1.0 ± 0.9	**Handgrip (kg)** Intervention: change 1.7 ± 0.8 Control: change 1.2 ± 0.9 **1 repetition max leg press (kg)** Intervention: change −7 ± 12 Control: change −10 ± 11	**6-min walk test (m)** Intervention: change −17 ± 17 Control: change 19 ± 19 **30 s Sit to Stand (*n*)** Intervention: change 0.7 ± 0.6 Control: change 1.3 ± 0.7	**EORTC QLQ-C30** Intervention: 57.3 ± 4.2, change 2.7 Control: 65.2 ± 3.1, change 4.5
Wiskemann 2019[37]	**Weight (kg)** Intervention 1 (IG1): 71.1 to 73.5 Intervention 2 (IG2): 68.0 to 67.9 Control: 71.6 to 72.1	**Voluntary isometric and isokinetic peak force** Improved elbow, knee and hip strength Greater change in supervised to home based and upper to lower limb	**6-min walk test (m)** IG1: 563.4 ± 85.9 to 608.1 ± 68.0 IG2: 573.1 ± 79.6 to 597.5 ± 94.9 Control: 580.5 ± 71.5 to 610.3 ± 57.7	N/A

BMI, body mass index; DI, delayed intervention; FACT-An TOI, functional assessment of cancer therapy – anaemia trial outcome index; FHNSI, functional assessment of cancer therapy head & neck cancer symptom index; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-G, functional assessment of cancer therapy – General; EORTC QLQ-C15-PAL, European Organisation for Research and Treatment of Cancer Quality of Life in Palliative Cancer Care Patients; FAACT, functional assessment of anorexia/cachexia treatment; N/A, not available; II = immediate ontervention; * data was provided in a scatter plot but showed obvious improvement, ** data estimated from figures.

Future studies should ideally include detailed reports of exercise frequency, intensity and duration to help readers interpret and understand the differential effects of exercise training parameters on individuals with cancer cachexia. Alongside this, better clinical phenotyping in studies will improve understanding around how exercise programmes can be attuned to different contexts of cancer, cachexia stage and if there difference by gender and cancer treatment status. In the longer term, future studies may cross-over to address cachexia in other diseases including congestive heart failure and chronic respiratory disease, to share learning and accelerate improved clinical practice.

Strengths and limitations

Our review employed a comprehensive search strategy, utilising multiple databases and key search word terms alongside an in-depth screening process. We deliberately avoided limiting the inclusion criteria based on study design, which allowed us to gather a broad range of literature on the chosen topic. This approach was particularly valuable as we were interested in both randomised and non-randomised studies. In areas where obtaining conclusive evidence through randomised studies is unlikely, it is crucial to be inclusive and incorporate various

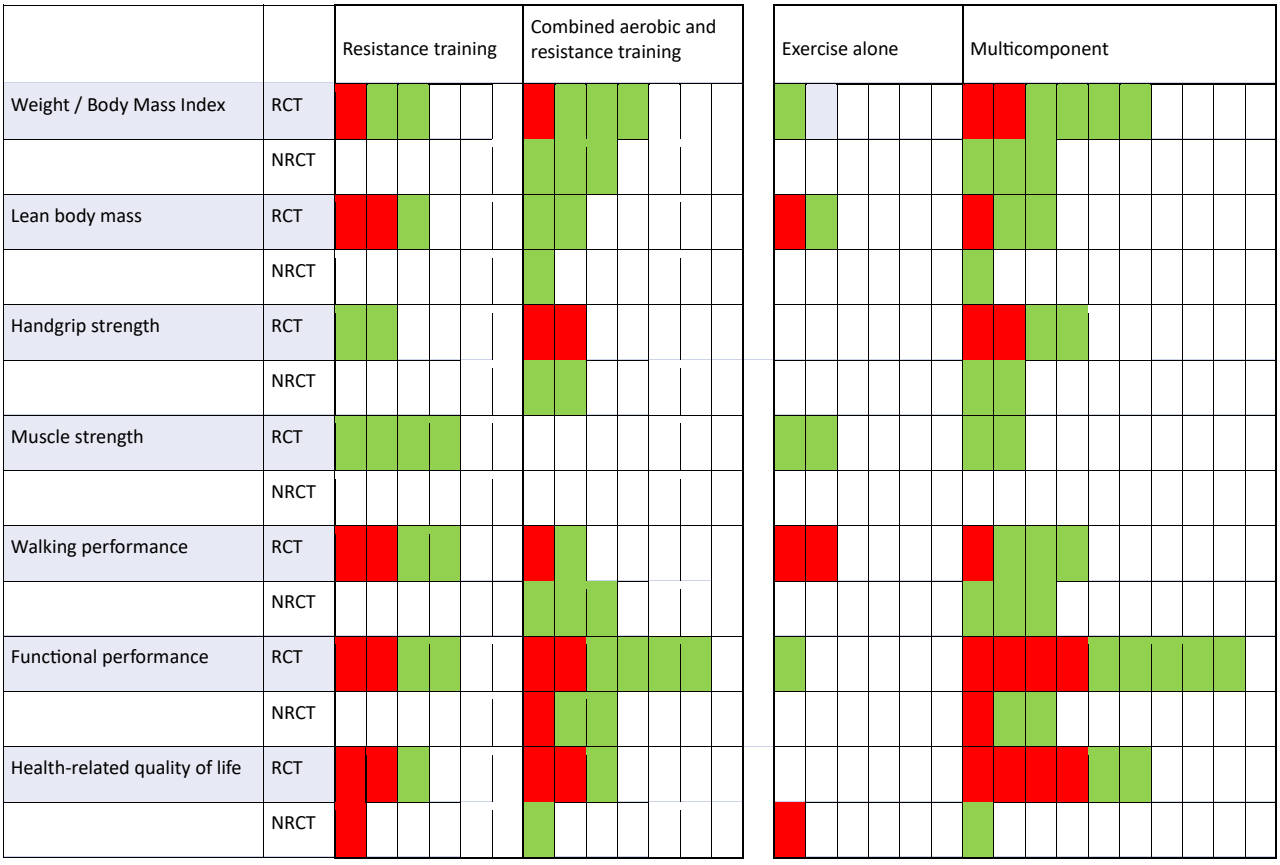

Fig. 3. Effect direction plot showing clinical outcomes according to intervention type. RCT, randomised controlled trial; NRCT, non-randomised controlled trial. Green cells indicate positive effect compared to control in case of RCT or pre-intervention in case of NRCT. Red cells indicate lack of effect.

study designs. Additionally, apart from examining clinical outcomes, we also explored interventions, delivery methods, and patient flow. This comprehensive analysis provided insights into patient acceptability and experience regarding exercise interventions.

We took a largely descriptive approach to the synthesis of data, but meta-analysis was not appropriate in this systematic review for several reasons. Firstly, there were an insufficient number of studies with comparable data on the outcomes of interest. Secondly, some of the included studies lacked proper control groups or randomisation, which is essential for conducting a reliable meta-analysis. Furthermore, there were variations in study design and interventions and this clinical heterogeneity made it difficult to pool results in a meaningful way. We conducted an overall assessment of the risk of bias and characterised common methodological limitations within the research field, but we did not directly incorporate the methodological appraisal in our interpretation of clinical outcomes. Finally, it is possible that we excluded studies that involved patients with cachexia, but who were not well characterised. We used baseline data to help overcome this, but strongly recommend future studies measure cachexia parameters directly.

Conclusions

This systematic review identified modest evidence to support the use and continued study of exercise training for the management of cancer cachexia. Exercise interventions appear to be safe in this population and, once enrolled, programmes are acceptable to the majority of patients based on adherence and programme completion. More consistent positive effects were observed for clinical outcomes of body stature and composition and muscle strength, as compared to exercise capacity and health-related quality of life. Exercise is most frequently studied alongside other interventions, and the synergistic effects should be examined in future robust studies.

CRediT author statement

CC: Conceptualization, Methodology, Data Extraction, Data Synthesis and Analysis, Writing, and Original and Revised Draft Preparation. EB: Data Extraction, Data Synthesis and Analysis, Writing, and Original and Revised Draft Preparation. AJG: Methodology, Data Synthesis and Analysis, and Revised Draft Preparation. MM: Conceptualization, Methodology, Data Synthesis and Analysis, Writing, and Original and Revised Draft Preparation. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethics statement

Not required.

Data availability statement

The data that support the findings of this study are available from the corresponding author, MM, upon reasonable request.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

Appendix A. Search strategy

- Database Field Guide Embase 1974 to 2023 February 27;
- Database Field Guide Ovid MEDLINE(R) ALL 1946 to February 27, 2023;
- Database Field Guide Global Health 1973 to 2023 Week 08;
- Database Field Guide APA PsycInfo 1806 to February Week 3 2023.

Keywords used in search:

The Cochrane Library (CENTRAL, DARE and HTA)

#1 MeSH descriptor: [Neoplasms] explode all trees.
#2 (cancer* or tumor* or tumour* or neoplasm* or malignant* or carcinoma* or adenocarcinoma* or choricarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*):ti,ab,kw (Word variations have been searched)
#3 #1 and #2.
#4 MeSH descriptor: [Weight Loss] explode all trees.
#5 (cachexia or cachexic):ti,ab,kw (Word variations have been searched)
#6 MeSH descriptor: [Malnutrition] explode all trees.
#7 (weight or underweight or malnutrition or wasting):ti,ab,kw (Word variations have been searched)
#8 #4 or #5 or #6 or #7.
#9 MeSH descriptor: [Exercise] explode all trees.
#10 MeSH descriptor: [Exercise Movement Techniques] explode all trees.
#11 MeSH descriptor: [Exercise Therapy] explode all trees.
#12 MeSH descriptor: [Physical Fitness] this term only.
#13 (exercise* or aerobic* or resistance* or strength* or walk* or endurance*):ti,ab,kw (Word variations have been searched)
#14 (physical* near/5 (fit* or active* or movement*)):ti,ab,kw (Word variations have been searched)
#15 #9 or #10 or #11 or #12 or #13 or #14.
#16 #3 and #8 and #15.

Embase (Ovid)

1. exp Neoplasms/
2. (cancer* or tumor* or tumour* or neoplasm* or malignant* or carcinoma* or adenocarcinoma* or choricarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original

title, device manufacturer, drug manufacturer, device trade name, keyword]
3. 1 or 2.
4. exp Weight Loss/
5. (cachexia or cachexic).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. exp Malnutrition/
7. (weight or underweight or malnutrition or wasting).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 4 or 5 or 6 or 7.
9. exp Exercise/
10. exp Exercise Movement Techniques/
11. exp Exercise Therapy/
12. Physical Fitness/
13. (exercise* or aerobic* or resistance* or strength* or walk* or endurance*).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. (physical* adj5 (fit* or active* or movement*)).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15. or/9–14.
16. 3 and 8 and 15.
17. random$.tw.
18. factorial$.tw.
19. crossover$.tw.
20. cross over$.tw.
21. cross-over$.tw.
22. placebo$.tw.
23. (doubel$ adj blind$).tw.
24. (single$ adj blind$).tw.
25. assign$.tw.
26. allocat$.tw.
27. volunteer$.tw.
28. Crossover Procedure/
29. double-blind procedure.tw.
30. Randomized Controlled Trial/
31. Single Blind Procedure/
32. or/17–31.
33. (animal/or nonhuman/) not human/
34. 32 not 33.
35. 16 and 34.

MEDLINE (Ovid)

1. exp Neoplasms/
2. (cancer* or tumor* or tumour* or neoplasm* or malignant* or carcinoma* or adenocarcinoma* or choricarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*).mp.
3. 1 or 2.
4. exp Weight Loss/
5. (cachexia or cachexic).mp.
6. exp Malnutrition/
7. (weight or underweight or malnutrition or wasting).mp.
8. 4 or 5 or 6 or 7.
9. exp Exercise/
10. exp Exercise Movement Techniques/
11. exp Exercise Therapy/
12. Physical Fitness/
13. (exercise* or aerobic* or resistance* or strength* or walk* or endurance*).mp.
14. (physical* adj5 (fit* or active* or movement*)).mp.
15. 9 or 10 or 11 or 12 or 13 or 14.
16. 3 and 8 and 15.
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. clinical trials as topic.sh.
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23.
25. 16 and 24

key:

mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt = publication type
ab = abstract
sh = subject heading
ti = title.

PSYCINFO

KEY("exercise") OR KEY("physical activity") AND KEY("cachexia")

Guide Global Health

#15 #14 AND #8.
#14 #13 AND #12.
#13 Topic=(human*)
#12 #11 OR #10 OR #9.
#11 Topic=(((single* OR double* OR trebl* OR tripl*) SAME (blind* OR mask*)))
#10 Topic=((controlled clinical trial OR controlled trial OR clinical trial OR placebo))
#9 Topic=((randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial))
#8 #7 AND #4 AND #1.
#7 #6 OR #5.
#6 Topic=((physical* near/5 (fit* or active* or movement*)))
#5 Topic=((exercise* or aerobic* or resistance* or strength* or walk* or endurance*))
#4 #3 OR #2.
#3 Topic=((weight or underweight or malnutrition or wasting))
#2 Topic=((cachexia or cachexic))
Databases = SCI-EXPANDED, CPCI-S Timespan = All years.
#1 Topic = ((cancer* or tumor* or tumour* or neoplasm* or malignant* or carcinoma* or adenocarcinoma* or choricarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*))

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