Harms of exercise training in patients with cancer undergoing systemic treatment: a systematic review and meta-analysis of published and unpublished controlled trials

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eClinicalMedicine 2023;59: 101937
Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.101937

Summary

Background Exercise is recommended for people with cancer. The aim of this study was to evaluate the harms of exercise in patients with cancer undergoing systemic treatment.

Methods This systematic review and meta-analysis included published and unpublished controlled trials comparing exercise interventions versus controls in adults with cancer scheduled to undergo systemic treatment. The primary outcomes were adverse events, health-care utilization, and treatment tolerability and response. Eleven electronic databases and trial registries were systematically searched with no date or language restrictions. The latest searches were performed on April 26, 2022. The risk of bias was judged using RoB2 and ROBINS-I, and the certainty of evidence for primary outcomes was assessed using GRADE. Data were statistically synthesised using pre-specified random-effect meta-analyses. The protocol for this study was registered in the PROESPERO database (ID: CRD42021266882).

Findings 129 controlled trials including 12,044 participants were eligible. Primary meta-analyses revealed evidence of a higher risk of some harms, including serious adverse events (risk ratio [95% CI]: 1.87 [1.47–2.39], I^2 = 0%, n = 1722, k = 10), thromboses (risk ratio [95% CI]: 1.67 [1.11–2.51], I^2 = 0%, n = 934, k = 6), and fractures (risk ratio [95% CI]: 3.07 [3.03–3.11], I^2 = 0%, n = 203, k = 2) in intervention versus control. In contrast, we found evidence of a lower risk of fever (risk ratio [95% CI]: 0.69 [0.55–0.87], I^2 = 0% n = 1109, k = 7) and a higher relative dose intensity of systemic treatment (difference in means [95% CI]: 1.50% [0.14–2.85], I^2 = 0% n = 1110, k = 13) in intervention versus control. For all outcomes, we downgraded the certainty of evidence due to imprecision, risk of bias, and indirectness, resulting in very low certainty of evidence.

Interpretation The harms of exercise in patients with cancer undergoing systemic treatment are uncertain, and there is currently insufficient data on harms to make evidence-based risk-benefits assessments of the application of structured exercise in this population.

Funding There was no funding for this study.

Abbreviations: RDI, Relative dose intensity; RR, Risk ratio; CI, Confidence interval; MD, Difference in means; IQR, Interquartile range; RCT, Randomised controlled trial; non-RCT, Non-randomised controlled trial; SD, Standard deviation

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Keywords: Exercise; Harms; Adverse events; Oncology; Cancer; Chemotherapy

Research in context

Evidence before this study

Recent guidelines recommend exercise for patients with cancer. These guidelines are widely endorsed by national and international health authorities and have led to broad interest in implementation of exercise into standard care of cancer. The current guidelines are based on several previous systematic reviews demonstrating beneficial effects of exercise and suggesting that exercise is safe for cancer patients during systemic treatment; however, none of the systematic reviews on harms assessed the risk of bias or the certainty of evidence. Further, none of the previous reviews on harms included unpublished data, which is known to affect the magnitude, precision, and even direction of risk estimates of harms. Considering the well-documented inadequacy of harms assessment and reporting in oncology and exercise trials, these reviews may be misleading.

Added value of this study

Including data from 129 published and unpublished trials and more than 12,000 participants, we demonstrate that the harms of exercise, prescribed alone or as part of multimodal interventions, is uncertain in patients with cancer undergoing systemic treatments due to high risk of bias, poor reporting, and lack of trials. Specifically, we present early evidence of a higher risk of some harms, including serious adverse events and thromboses, in exercise versus control; we show that adverse events reporting is poor in exercise oncology trials; we demonstrate that inclusion of unpublished data nearly doubles the amount of eligible data and changes direction of pooled risk estimates of some types of adverse events; and we present evidence of selective non-reporting of harms outcomes. Notably, these findings differ markedly from similar systematic reviews that have been used to inform current cancer-specific exercise guidelines.

Implications of all the available evidence

Our study demonstrates that there is insufficient data on harms to perform accurate evidence-based risk-benefit analyses of structured exercise prescriptions in patients with cancer receiving systemic treatments. These findings may be considered in future revisions of current cancer-specific exercise guidelines.

Introduction

Exercise training is emerging as an adjunct treatment in the oncology setting.[1,2] During the last three decades, hundreds of trials have been performed in patients with cancer, with numerous studies reporting beneficial effects on physiological, biological, functional, and patient-reported outcomes.[1] These trials now underpin cancer-specific exercise and physical activity guidelines[3–8] and have led to broad interest in the implementation of structured exercise into standard care for cancer.[9–12] However, concerns regarding the harms of exercise during systemic cancer treatment have emerged. A recently published exercise trial in patients receiving chemotherapy for testicular cancer was prematurely terminated due to unexpected adverse events in the exercise group,[13] and the harms of exercise have been reported to be uncertain in some cancer populations, including patients with cachexia,[14] gastrointestinal cancers,[15] and haematological cancers.[16]

Accurate risk estimates of harms are critical to inform the evidence-based application of exercise in the oncology setting, and several recent systematic reviews have accordingly evaluated adverse events of exercise in patients undergoing systemic cancer treatments.[17–20] These reviews, however, did not consider the quality of the eligible evidence in the interpretation of their findings. Given the documented inadequacy of harms assessment in the oncology literature,[21,22] this is problematic and may have led to biased conclusions. In addition, the previous reviews were restricted to published data sources.[17–20] Inclusion of unpublished data, such as clinical trial registrations and conference abstracts, can influence the precision, magnitude, and even direction of pooled risk estimates of harms.[23,24] Collectively, these limitations are critical, and the previous systematic reviews may have misinformed cancer-specific exercise guidelines that currently underpin the clinical use of exercise as an adjunct treatment during systemic cancer treatment.

Therefore, we conducted this systematic review and meta-analysis of published and unpublished controlled trials to evaluate the harms of exercise in patients with cancer undergoing systemic treatment. Our primary objective was to compare adverse events, health-care utilization, and systemic treatment tolerability and response in exercise intervention versus control. Our secondary objectives were to evaluate the quality of adverse events reporting and to compare adverse events leading to trial withdrawal, discontinuation, or withdrawal in exercise intervention versus control.

Methods

This study is reported in accordance with the PRISMA statement[25] and its extensions for reporting harms[26] and

searching[27] (Supplementary Files S1–S4). Our review protocol[28] was prospectively registered at the Open Science Framework (osf.io/u8fn2/; Supplementary File S5) and PROESPERO (CRD42021266882) on October 20, 2021. Post-registration protocol changes are disclosed and justified in Supplementary File S6.

Eligibility criteria

Participants

We included trials that evaluated adult (age ≥18 years) participants diagnosed with cancer scheduled to undergo chemotherapy, immunotherapy, targeted therapy, or chemoradiation during the trial period. Trials were excluded if less than 50% of the participants received systemic cancer treatment and if more than 10% of the participants were non-cancer patients, unless subgroup data were available.

Trial designs

We included randomised controlled trials (RCTs), quasi-RCTs, and non-randomised controlled trials (non-RCTs). Quasi-randomization was defined as allocation that is not truly random but intend to produce balanced groups (e.g., allocation by date of birth or alternation).

Interventions and comparators

We included trials that compared standard care plus exercise with standard care alone or standard care plus attention control. No restrictions were made regarding co-interventions (e.g., nutrition), but we performed subgroup analyses of trials in which isolation of the exercise intervention was possible (e.g., exercise plus nutritional intervention versus nutritional intervention alone). Exercise was defined as planned, structured, and repetitive physical activity, and exercise was limited to aerobic and anaerobic exercises (e.g., walking, cycling), resistance training (i.e., exercise performed against body weight or external resistance), and sports activities (e.g., football). We excluded trials that evaluated alternative types of exercise (e.g., yoga, tai chi), targeted physiotherapy interventions (e.g., breathing exercises), physical activity behaviour interventions, and acute bouts of exercise only. We also excluded trials in which the comparators did not receive contemporary standard care.

Outcomes

The primary outcomes were:

- Adverse events, defined as "*any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure*".[29]
- Tolerability of systemic cancer treatment (dose delays, dose reductions, early discontinuations, and relative dose intensity (RDI)).
- Response to systemic cancer treatment (e.g., tumour response).
- Health-care utilization (e.g., hospitalisations, outpatient care).

The secondary outcomes were:

- Loss to follow-up, discontinuations, or withdrawals of participants due to adverse events.
- Quality of adverse events reporting, assessed as adherence to the CONSORT statement extension for reporting of harms.[30] Adherence was assessed using a 16-item scoring system adapted from previous studies[21,22,31] (Supplementary File S7). An item was given a score of '1' if it was reported and a score of '0' if it was unclearly reported or not reported. The quality of adverse events reporting was the summed score of all items, with each item being weighted equally. Assessments were performed independently by two authors (SNT, CS).

Search methods for identification of trials

We included data from published (i.e., peer-reviewed journal articles) and unpublished data sources (i.e., personal communication; conference abstracts; dissertations and theses; and trial registrations). Systematic searches for eligible trials were performed using the following electronic databases and trial registries:

- MEDLINE via PubMed (1946–October 25, 2021)
- EMBASE via Ovid (1974–October 25, 2021)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- CINAHL via EBSCO (1981–October 25, 2021)
- SPORTDiscus via EBSCO (1975–October 25, 2021)
- Dissertations & Theses: Global via ProQuest (1861–October 25, 2021)
- OpenGrey
- Clinicaltrials.gov
- The International Standard Randomized Controlled Trial Number Registry.
- The Australian New Zealand Clinical Trial Registry.
- The German Clinical Trial registry.

We performed backward and forward citation searches of eligible trials, using Citationchaser (Estech.shinyapps.io/citationchaser/). We contacted corresponding authors via standardised e-mails (two attempts separated by two weeks):

- If further information was required to assess eligibility, judge risk of bias, and/or extract data,
- to request data on pre-registered but non-reported eligible outcomes, or
- to request data on adverse events that were reported as reason for trial withdrawal, discontinuation, or loss to follow-up but were not otherwise reported in

the report (i.e., we asked whether there were more observed cases of the same type of adverse event that did not lead to withdrawal, discontinuation, or loss to follow-up). Data obtained in this manner were not included in primary analyses but in explorative meta-analyses only (see Additional Analyses).

An information scientist (AL) developed a search string consisting of four blocks of controlled vocabularies and free text words related to cancer, systemic cancer treatment, exercise, and trial design. No language or publication date restrictions were imposed (Supplementary File S8). The database searches were performed on October 25, 2021, the trial registry searches were performed on January 5, 2022, and forward/backward citation searches were performed on April 26, 2022.

Study selection and data collection

After deduplication, titles and abstracts were screened independently by two of three authors (SNT, MKF, CS), and clearly ineligible records were excluded. Screening of titles and abstracts was based on population, intervention, and design only. The full texts of the remaining records were screened independently by two of three authors (SNT, LMT, CS). Study selection disagreements were resolved by discussion involving the third screener.

Two authors (SNT, LMT) extracted data independently (see Supplementary File S5 for full list of extracted data items). Raw data are available in Supplementary File S9.

Risk of bias in individual trials

Risk of bias was assessed independently by two authors (SNT, CS) using the RoB 2[32] for RCTs/quasi-RCTs and the ROBIN-I[33] for non-RCTs (target randomised trial and confounders are specified in Supplementary File S10). Disagreements were resolved by involving one other author (IML). Our principal effect of interest was the effect of group allocation. Judgements were not performed for abstracts and trial registrations.

Data synthesis

Meta-analyses of a given outcome were performed if reported in two or more eligible trials. Risk ratios (RR) with 95% confidence intervals were used as summary measure for dichotomous outcomes, and difference in means (MD) with 95% confidence intervals were used as summary measure for continuous outcomes. Meta-analyses were performed in R via RStudio (v1.4.1717), using the 'meta' package[34] (see Supplementary File S11 for statistical code). Our principal effect of interest was the effect of group allocation, and meta-analyses of adverse events were performed separately per seriousness, type, and severity per type. All harms outcomes were included in the analyses independent of their reported relatedness to the exercise intervention or the systemic cancer treatment.

Dichotomous outcomes were synthesised using Mantel-Haenszel random-effects models without continuity correction, with the Paule-Mandel estimator of τ^2,[35] and with Hartung-Knapp adjustments.[36] Trials with zero events in both arms were excluded in primary analyses,[37] but we performed sensitivity analyses including these (see Additional Analyses). Continuous outcomes were synthesised using random-effects models with the restricted maximum likelihood estimator of τ^2 [35] and with Hartung-Knapp adjustments.[36]

Prediction intervals were calculated in meta-analyses with ≥10 comparisons and no clear funnel plot asymmetry.[37] I^2 was provided as a measure of heterogeneity and was interpreted as follows[38]: 0–40% might not be important, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity, 75–100% may represent considerable heterogeneity. In trials that evaluated multiple exercise interventions, the intervention groups were analysed separately.[39] Outcomes reported in one trial only were reported as raw data.

The strength of the relationship between year of publication and quality of adverse events reporting score was explored using Spearman's rank order correlation.

Publication bias and selective outcome (Non)-reporting bias

Contour-enhanced funnel plots were used to assess publication bias if ≥10 comparisons were made in meta-anlyses.[40,41] Funnel plot asymmetry was assessed by visual inspection and the Egger and the Harbord test for continuous and dichotomousness outcomes, respectively.[41]

Selective outcome non-reporting bias was assessed as the number of instances of undeclared non-reporting of preregistered eligible outcomes. Selective outcome reporting was assessed as the number of instances of undeclared reporting of non-preregistered eligible outcomes. A trial was defined as pre-registered if it was registered before trial initiation.

Certainty of evidence

Two authors (SNT, CS) independently assessed the certainty of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.[42] Summary of finding tables were made using GRADEpro GDT (www.gradepro.org) for primary outcomes included in meta-analyses.

Additional Analyses

We performed prespecified subgroup meta-analyses of trials by the following factors: Cancer site, exercise modality, type of systemic cancer treatment, exercise delivery, publication status, isolation of exercise intervention where possible.

We performed prespecified sensitivity analyses excluding small trials (<100 participants per arm[43]), excluding non-RCTs, excluding non-RCTs and RCTs with a high overall risk of bias, excluding trials for which we estimated means or standard deviations, and including trials with zero events in both arms in meta-analyses of dichotomous outcomes, using the treatment arm continuity correction method.[44]

We performed explorative meta-analyses including adverse events that were reported as reason for trial withdrawal but not otherwise reported in the report. However, these were performed only if we were able to obtain the full data set on the specific type of adverse events by contacting the trial authors (see Search methods for identification of trials section above).

Ethics statement

No ethic approvals were required for this study.

Role of funding source

The Centre for Physical Activity Research (CFAS) is supported by TrygFonden (grants ID 101390, ID 20045, and ID 125132). The funders had no role in the data collection, management, data analysis and interpretation, writing of the report, or the decision to submit the report for publication.

Results

Search results

The initial systematic search yielded 12,656 records. After deduplication and title/abstract screening, 909 records were selected for full-text screening and 129 reports from 117 trials were eligible. We then performed forward/backward citation searches, which yielded 10,018 records. Of these records, 188 were selected for full-text screening, and 12 reports from 12 trials were eligible. Thus, we included a total of 141 reports[13,45–184] from 129 trials (Fig. 1; see Supplementary File S12 for reasons for exclusion of records selected for full-text screening).

Description of eligible trials

Characteristics of the eligible trials are summarised in Table 1 and presented in full detail in Supplementary File S13. The eligible trials included a total of 12,044 allocated participants, with a median (IQR) sample size of 59 (68). Most (n = 108; 84%) trials were described as RCTs,[13,45–151] two (2%) were quasi-RCTs,[152,153] 18 (14%) were non-RCTs,[154–171] and one trial did not report the allocation method.[172] The most commonly studied tumour sites were breast (n = 46; 36%)[48,51,53,54,56,57,59–61,63,65,68,69,74,76,81,95,96,99–101,103,106,107,109,110,113,117,118,121,124,127,130,137,139–141,146,149,150,156,161,164,165,168,169] and mixed sites (n = 35; 27%).[47,55,66,67,70–73,80,85,87,88,91,94,102,104,111,115,116,120,123,125,126,134,135,138,142,144,145,147,148,152,157,171] Trial participants had a mean (SD) age of 55 (8) years. Three (2%) trials had harms[154,171] or treatment tolerability[156] as primary outcomes.

Description of the exercise interventions

The median (IQR) exercise intervention length was 12 (8) weeks, and 67 (52%) trials evaluated combined aerobic/anaerobic and resistance exercise.[50,55,59–61,63,64,66,67,70–74,77,78,80,86–88,90,92–95,98,99,101,105,106,109,110,113,115,116,123,125–132,135,136,138–140,143,145,147,149,153–156,158,162,163,167,168,170,175,178] Just over a quarter (n = 33; 26%) of the trials evaluated exercise in combination with other interventions[18,50,52,55,58,60,63,64,67,70,78,84,89,90,98,101,105,111,120,129,135–137,143,144,147,148,155,160,170,172,182]; isolation of exercise was possible in four (3%) of these.[120,135,148,170] Four (3%) trials[50,128,160,163] reported that the exercise intervention was modified according to pre-existing comorbidities, 11 (9%) trials[56,59,60,89,92,109,133,139,141,156,169] reported that the exercise dose was modified according to treatment-related adverse events or symptoms during the intervention period, and 4 (3%)[55,66,106,156,171,173] and 15 (12%)[48,53,66,69,74,80,105,133,142,147,150–152,158,171,173,174] trials reported specific exercise dose regression and progression rules, respectively (see Supplementary File S13). Six (5%) trials[76,112,125] paused the exercise program for a specific time period following administration of systemic treatment (on days of administration,[76,112,125] 24 h after administration[98,163], and 72 h after administration[113]), and one (<1%) trial[3,99] paused the exercise intervention following administration of systemic treatment until neutrophil counts were normalised (500 cells/mm). A total of 27 exercise contraindications were reported in 19 (15%) trials. These contraindications included fever (n = 9[70,77,82,83,104,116,128,129,160]); thrombocytopenia (n = 9[70,77,83,90,92,104,116,128,132]); anaemia (n = 7[64,83,116,128,129,132,160]); infection (n = 4[104,116,128,132]); acute bleeding (n = 4[70,77,83,128]); dizziness (n = 4[65,128,132,157]); nausea (n = 4[65,91,128,132]); chest tightness or pain (n = 3[65,85,157]); pain (n = 3[85,128,132]); hypotension (n = 2[70,77]); hypertension (n = 2[70,77]); leukocytopenia (n = 2[70,77]); petechiae (n = 2[70,83]); tachycardia (n = 2[70,77]); respiration frequency >20 breaths/minute (n = 2[70,77]); infections requiring treatment (n = 2[70,77]); dyspnoea (n = 2[85,91]); feeling of tachycardia (n = 1[91]); heart rate >180 beats/min–age during exercise (n = 1[161]); high grade cardiac arrhythmias (n = 1[116]); life-threatening clinical complications (n = 1[116]); psychological instability (n = 1[129]); vomiting (n = 1[128]); cardiac or nephrotoxic medication during chemotherapy (n = 1[128]); severe pain (n = 1[132]); swelling (n = 1[146]); hypertension during exercise (n = 1[161]); and bruises (n = 1[70]).

Risk of bias

Risk of bias in RCTs and quasi-RCTs are summarised Fig. 2 and presented in full detail in Supplementary File S14). Overall risk of bias was judged to be of some concerns in 37 (39%) judgements and to be high in 57 (61%) judgements. Thus, none of the results were

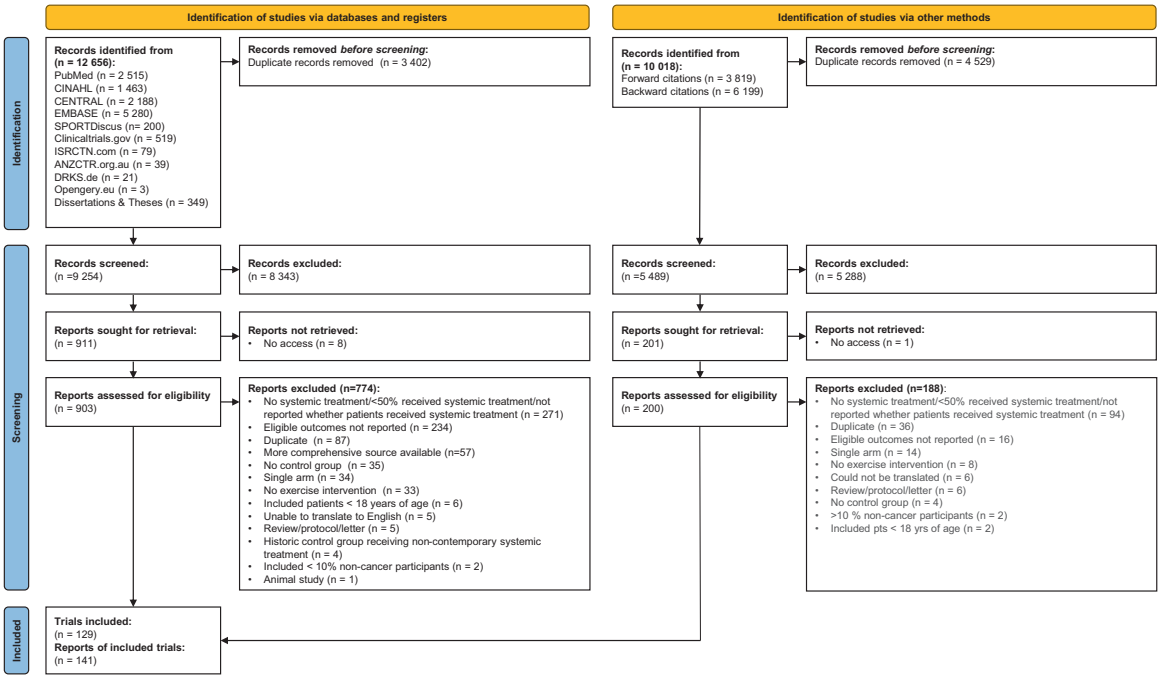

Fig. 1: PRISMA 2020 flow chart.

judged to be of low overall risk of bias. The most common source of high risk of bias was missing outcome data (n = 47; 50%).

Overall risk of bias of the non-RCTS was judged to be serious in six (75%) judgements and to be moderate in two (25%) judgements (Supplementary File S15). The most common source of serious bias was confounding (i.e., prognostic variables that predict the intervention received, n = 6; 75%).

Selective outcome reporting and non-reporting

We identified 26 preregistered trials[13,45,50,59,61,66,67,71,76,78,80–82,94,103,105,108,114,115,122,131,133,137,143,147,154] and 40 retrospectively registered trials.[6,52,55,60,63,64,68,70,72,74,75,77,84–87,89,90,92,93,98–100,106,112,117,122,130,134,138,139,141,142,146,149,151,159,162,171] Among the preregistered trials, we identified 25 preregistered eligible outcomes (i.e., outcomes eligible for the current review); of these outcomes, 13 (52%) were reported in the associated published reports, whereas 12 (48%) were omitted. One trial[13] disclosed and justified the non-reporting of a preregistered outcome (peak oxygen consumption). Among the 13 reported preregistered outcomes, two outcomes (sick leave and health-care utilization) from one trial[66] were switched from primary to secondary endpoints without providing justification. In the 26 preregistered trials, we identified 68 non-registered eligible outcomes from 16 published reports.[13,59,67,78,81,82,94,103,105,114,115,122,131,143,147,154] One trial[66] disclosed or justified the introduction of non-registered outcomes (myocardial infarction and pulmonary embolism; Supplementary File S16).

Comparison of intervention versus control

We performed meta-analyses of 45 outcomes (see Supplementary File S17 for all analyses). Results were similar in trials in which exercise could be isolated versus trials in which exercise could not be isolated. 255 comparisons were not included in meta-analyses due to poor reporting or too few eligible trials (Supplementary File S18).

Primary outcomes

Adverse events per seriousness. Meta-analysis of serious adverse events showed evidence of a higher risk in intervention versus control (Fig. 3A). This was also found in sensitivity analyses including trials with double zero events and excluding non-RCTs. The types serious adverse events are presented in Supplementary File S17. Subgroup analysis showed that the increased risk of serious adverse events in intervention was higher in unpublished versus published sources (unpublished: RR [95% CI]: 2.78 [1.97–3.92]; published: RR [95% CI]: 1.68 [1.10–2.57]; P = 0.0079). The summed weight of two comparisons from one trial[93] was 63%, but a similar risk estimate was found in a post-hoc sensitivity analysis excluding this trial (RR [95% CI]: 2.61 [2.03–3.35], I^2 = 0%, n = 1602, k = 8).

Report type	
Published report, n (%)	117 (90.7)
Conference abstract, n (%)	2 (1.6)
Trial registration, n (%)	5 (3.9)
Thesis or dissertation, n (%)	5 (3.9)
Trial design	
Sample size, median (IQR)	59 (68)
Non-small trials[a], n (%)	11 (8.5)
Allocation method	
Randomization, n (%)	108 (83.7)
Quasi-randomization, n (%)	2 (1.6)
Non-randomization, n (%)	18 (14.0)
Not reported, n (%)	1 (0.8)
Participants	
Age in years at baseline, mean (SD)	55 (7.6)
Tumour site[b], n (%)	
Breast (2C60-2C6Z)	46 (35.7)
Digestive organs (2B70-2C1Z)	15 (11.6)
Haematopoietic or lymphoid tissues (2A20-2B33)	15 (11.6)
Respiratory or intrathoracic (2C20-2C2Z)	9 (7.0)
Male genital organs (2C80-2C8Z)	2 (1.6)
Brain and central nervous system (2A00-2B3Z)	2 (1.6)
Skin (2C30-2C3Z)	1 (0.8)
Urinary tract (2C90-2C9Z)	1 (0.8)
Female genital organs (2C70-2C7Z)	2 (1.6)
Lip, oral cavity, or pharynx (2B60-2B6Z)	1 (0.8)
Mixed tumour sites	35 (27.1)
Planned systemic therapy, n (%)	
Chemotherapy	88 (68.1)
Targeted therapy	4 (3.1)
Immunotherapy	1 (0.8)
Chemoradiation	6 (4.7)
Any combination	30 (23.3)
Exercise intervention characteristics	
Modality, n (%)	
Aerobic/anaerobic	47 (34.3)
Resistance	23 (16.8)
Combined aerobic/anaerobic and resistance	67 (48.9)
Delivery, n (%)	
Supervised	68 (49.3)
Unsupervised	37 (26.8)
Combined supervised and unsupervised	26 (18.8)
Not reported	7 (5.1)
Exercise intervention length (weeks), median (IQR)	12 (8)
Concurrent non-exercise interventions, n (%)	
Exercise only	96 (74.0)
Exercise combined with other interventions	33 (26.0)

[a]Defined as >100 participants per trial arm.[43] [b]Codes in brackets refer to cancer sites according to the International Classification of Diseases, 11th revision.

Table 1: **Characteristics of the eligible trials.**

Adverse events per type. In meta-analysis of thromboses, we found evidence of a higher risk in intervention versus control (RR [95% CI]: 1.67 [1.11–2.51], n = 934, k = 6). Similar result was found in explorative meta-analysis including one additional trial[166] (RR [95% CI]: 1.70 [1.19–2.44], n = 954, k = 7). The summed weight of two comparisons from one trial[93] was 80%, but a similar risk estimate was found in a post-hoc sensitivity analysis excluding this trial (RR [95% CI]: 2.99 [2.89–3.09], I^2 = 0%, n = 814, k = 4). Most sensitivity analyses of thromboses could not be performed due to insufficient number of trials. Subgroup analysis showed that the increased risk of thromboses in intervention was higher in unpublished versus published sources (unpublished: RR [95% CI]: 2.94 [1.11–2.96]; published: RR [95% CI]: 1.57 [0.88–2.81]; P = 0.0006).

Meta-analyses revealed evidence of an increased risk of depression (RR: [95% CI]: 2.97 [2.66–3.31], n = 798, k = 2), neuropathy (RR [95% CI]: 1.87 [1.35–2.60], n = 129, k = 2), fractures (RR [95% CI]: 3.07 [3.03–3.11], n = 213, k = 2), and myocardial infarct (RR [95% CI]: 2.98 [2.03–4.37], n = 137, k = 2) in intervention versus control. Each of these analyses, however, included two trials only, and sensitivity analyses could not be performed.

We found no evidence of a difference in the risk of pulmonary embolisms (RR [95% CI]: 2.32 [0.83–6.51], n = 157, k = 4). However, in explorative meta-analysis including unpublished data from one trial,[55] we found an increased risk of pulmonary embolism in intervention groups (RR [95% CI]: 2.35 [1.14–4.86], n = 180, k = 5).

Compared to control groups, we found evidence of a lower risk of fever in intervention groups (RR: [95% CI]: 0.69 [0.55–0.87], n = 1109, k = 7). However, this difference was not evident in sensitivity analyses excluding small trials, non-RCTs, and non-RCTs and trials with high overall risk of bias.

Primary meta-analyses of 33 other types of adverse events showed no evidence of a difference in intervention versus control (Supplementary File S17).

Five (4%)[13,67,112,147,163] trials reported the relatedness of eligible harms outcome to the exercise intervention. Of these, two trials[112,147] reported that no adverse events were related to the intervention; one trial[67] reported that no serious adverse events were related to the intervention; one trial[13] reported that the relatedness to the intervention was uncertain; and one trial[163] reported that two serious adverse events (lumbar fractures) were possibly related to the exercise intervention. None of the eligible trials, however, described how the relatedness of the adverse event to the intervention (i.e., attribution method) was assessed (see Quality of Adverse Events Reporting).

Tolerability of systemic cancer treatment. Meta-analyses of tolerability of systemic cancer treatment are presented in Fig. 3B–E. We found evidence of a higher RDI of chemotherapy in intervention compared to control,

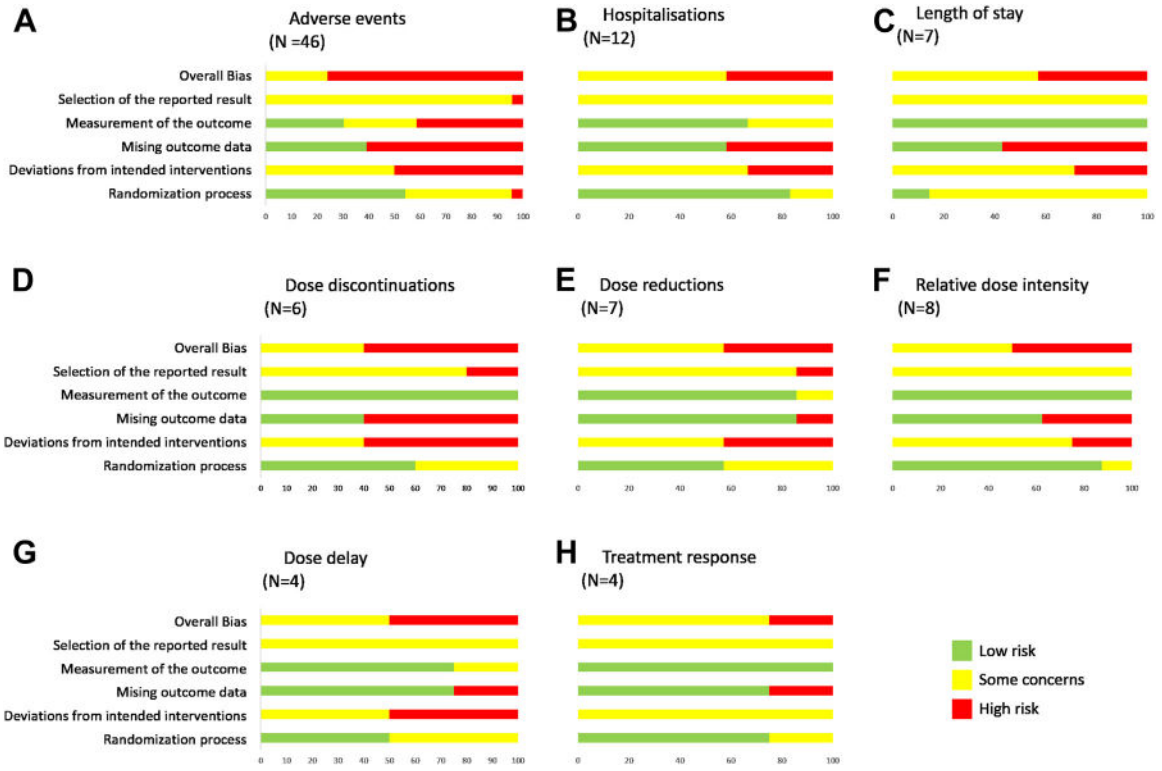

Fig. 2: Summary of risk of bias judgements of randomised and quasi-randomised trials for A) adverse events, B) hospitalisations, C) length of stay, D) discontinuations of systemic cancer treatment, E) dose reductions of systemic cancer treatment, F) relative dose intensity of systemic cancer treatment, G) dose delays of systemic cancer treatment, and H) response to systemic cancer treatment.

but this difference was not found in sensitivity analyses excluding non-RCTs, non-RCTs and RCTs with high overall risk of bias, and trials for which we estimated means and/or standard deviations.

Response to systemic cancer treatment. Six eligible trials reported tumour response to systemic cancer treatment, but meta-analyses were considered inappropriate due to highly heterogenous assessment methods and reporting (Supplementary File S18).

Health-care utilization. Meta-analysis of unscheduled hospitalisation and length of hospital stay revealed no evidence of a difference between intervention versus control (Fig. 3F and G). Similar results were found in sensitivity and explorative analyses.

Secondary outcomes

Trial discontinuations, withdrawals, and loss to follow-up due to adverse events. We found no evidence of a higher risk of trial withdrawals, discontinuations, and loss to follow-up due to adverse events in intervention compared to controls (RR [95% CI]: 1.13 (0.99–1.30), n = 7484, k = 83). In contrast, we found evidence of an increased risk of trial withdrawals, discontinuations, and loss to follow-up in intervention versus control in subgroup analyses of participatns with breast cancer (RR [95% CI]: 1.56 [1.10–2.23], k = 23) and supervised exercise (RR [95% CI]: 1.24 [1.02–1.52], k = 42).

Quality of adverse events reporting. Quality of adverse events reporting were assessed in 48 trials.[52,57,62,67,68,74,75,77,82,84,86–88,92–94,96,98,99,101,103–105,111,112,114,115,122,126,128,130,131,140–142,146,147,150–156,161,163,165,173] The median (IQR) reporting score was 5.0 (4.0) items, the highest score was 11 items (n = 1), and the lowest score was 0 items (n = 3). Item 6a was the most commonly reported item (n = 34; 72%), and item 4c and item 8d were the least commonly reported items (n = 0) (Table 2 and Supplementary File S19). In an explorative analysis, we found no evidence of a relationship between adverse events reporting quality score and year of publication (r = –0.058, P = 0.69, Supplementary File S17).

Certainty of evidence

The certainty of the evidence for our primary outcomes is presented in Table 3. For all outcomes, we downgraded the certainty of evidence due to imprecision, risk of bias, and indirectness, resulting in very low certainty of evidence.

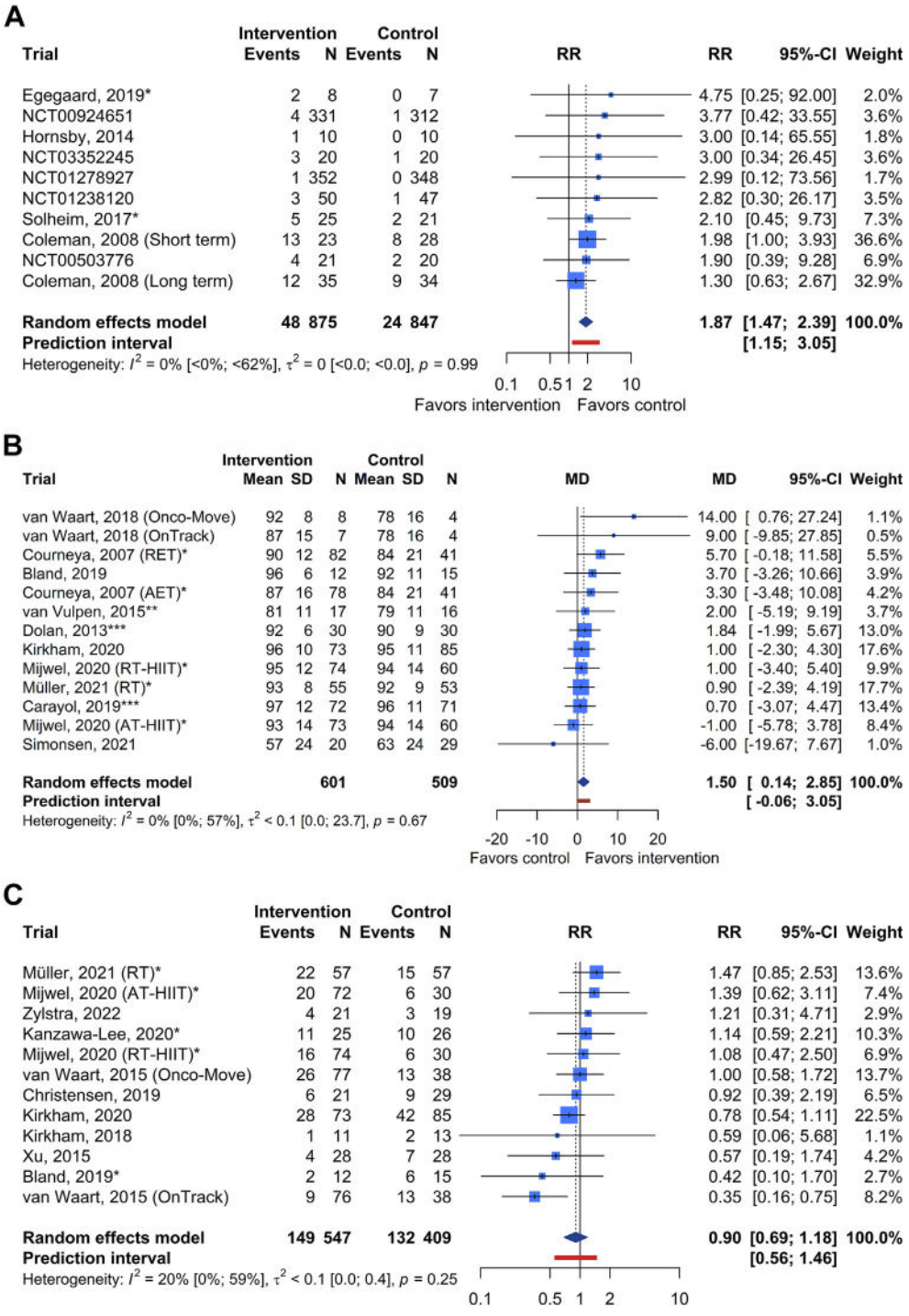

Fig. 3: Meta analyses of A) serious adverse events, B) relative dose intensity of systemic cancer treatment (%), C) dose reductions of systemic cancer treatment, D) dose delays of systemic cancer treatment, E) discontinuations of systemic cancer treatment, F) hospitalisations, and G) length of hospital stay (days). *some data are obtained from personal correspondence with trial authors; **means and standard deviations are estimated from medians and ranges or interquartile ranges; *** missing standard deviations are imputed.

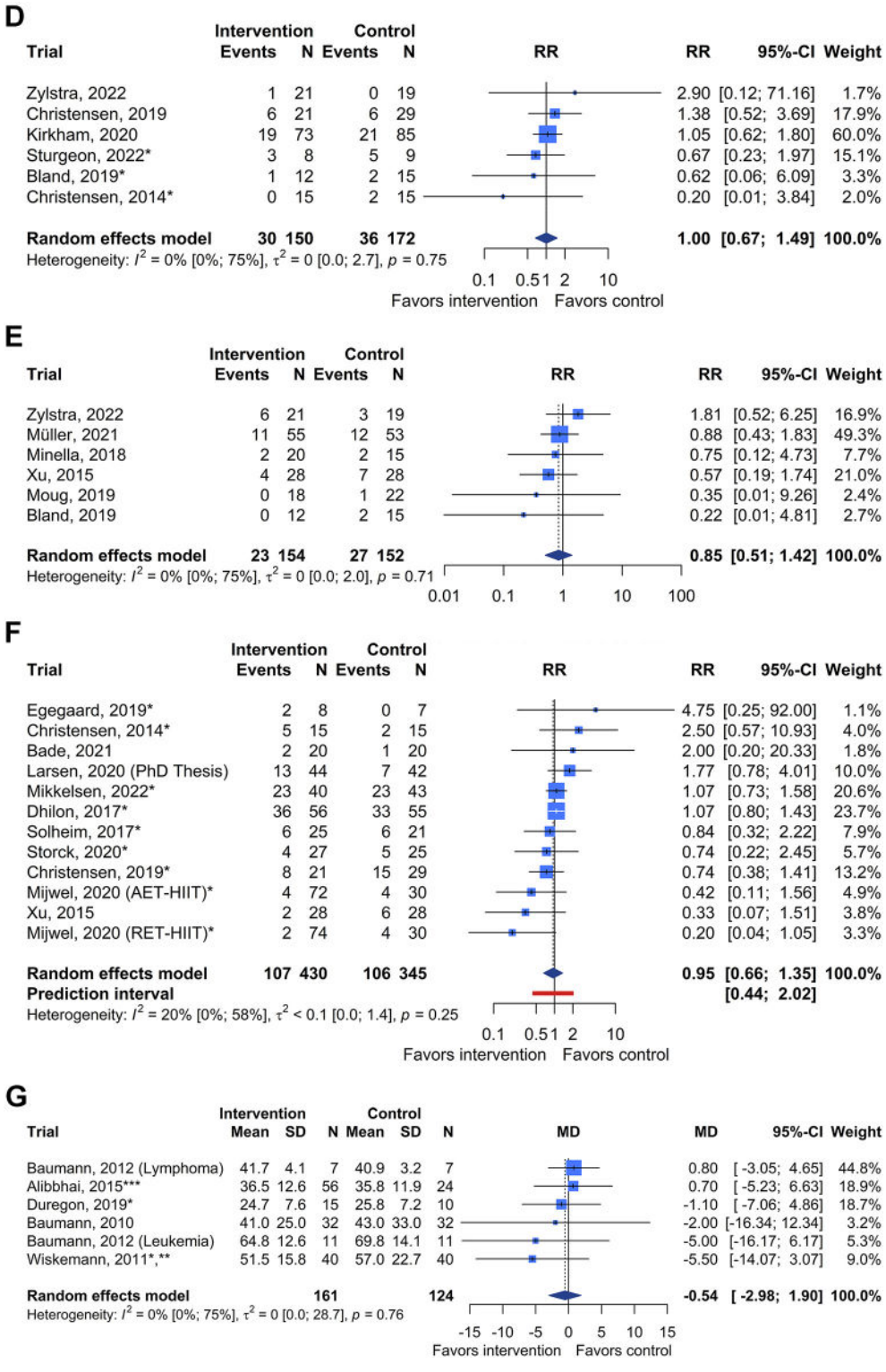

Fig. 3: Conitnued.

Items	Item reported, n (%)
Introduction	
1. In the title or abstract, trial states that safety or adverse events were assessed?	26 (54)
2. In the introduction, trial states that safety or adverse events were assessed?	23 (48)
Methods	
3a. Trial lists and defines all adverse events that were assessed.	12 (25)
3b. Trial specifies instruments that were used to assess adverse events.	19 (40)
4a. Trial describes how adverse events were collected.	18 (38)
4b. Trial describes when adverse events were collected.	20 (42)
4c. Trial describes attribution method.	0 (0)
5. Trial describes how adverse events were analysed.	21 (44)
Results	
6a. Trial reports number of participants discontinuing/withdrawing due to adverse events per arm.	34 (72)
6b. Trial describes adverse events leading to patient discontinuation or withdrawal.	6 (13)
7. Trial provides denominators used for each analysis of adverse events.	15 (31)
8a. Trial reports adverse events per severity per arm.	4 (8)
8b. Trial reports adverse events type per arm.	20 (42)
8c. Trial reports adverse events seriousness per arm.	2 (4)
8d. Trial reports how recurrent events were handled.	0 (0)
Discussion	
10. Trial provide a balanced discussion of benefits and harms.	18 (38)

Table 2: **Quality of adverse events reporting.**

Discussion

The primary finding of our systematic review and meta-analysis is that the evidence on harms of exercise, prescribed alone or as part of multimodal interventions, is uncertain in patients receiving systemic cancer treatment. We included data from more than 12,000 participants and 129 controlled trials; yet, data on harms were sparse, and nearly half of the eligible data on adverse events were identified in unpublished sources. In addition, we found evidence of poor adverse events reporting, the risk of bias was generally high, and many types of cancers and systemic treatments remain largely underrepresented in the eligible trials. These limitations collectively resulted in very low certainty of evidence, and our risk estimates are likely to differ substantially from the true risks. Thus, our study demonstrates that there is insufficient data on harms to perform evidence-based risk-benefit analyses of structured exercise prescriptions in patients with cancer receiving systemic treatments. Considering the broad interest in implementation of exercise in the general oncology setting,[9–11] well-designed confirmatory RCTs are needed to

Outcomes	Anticipated absolute effects[a]		Relative effects	No. participants (comparisons)	Certainty of evidence
	Risk with control	Risk with intervention (95% CI)			
Serious adverse events	30 per 1000	60 per 1000 (47–76)	RR: 1.84 (1.47–2.39)	1722 (10)	Very low[b]
Systemic cancer treatment tolerability					
Dose reductions	323 per 1000	290 per 1000 (223–281)	RR: 0.90 (0.69–1.18)	956 (12)	Very low[b]
Dose delays	209 per 1000	209 per 1000	RR: 1.00 (0.67–1.49)	322 (6)	Very low[b]
Dose discontinuations	149 per 1000	127 per 1000	RR: 0.85 (0.51–1.42)	154 (6)	Very low[b]
Relative dose intensity	Mean ranged from 57 to 96%	MD 1.5% higher (0.14 higher to 2.85 higher)	–	1110 (13)	Very low[b]
Health-care utilisation					
Hospitalisations	299 per 1000	278 per 1000	RR: 0.93 (0.86–1.32)	807 (13)	Very low[b]
Length of stay	Mean ranged from 25 to 70 days	MD 0.54 days lower (2.98 lower to 1.90 higher)	–	306 (6)	Very low[b]

CI: Confidence interval, MD: Difference in means, RR: Relative ratio. [a]The risk in intervention (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [b]We downgraded the certainty of evidence by one due to imprecision, by one due to risk of bias, and by one due to indirectness.

Table 3: **Summary of findings table for primary outcomes.**

establish harms of exercise in patients with cancer receiving systemic therapies.

We found evidence of an increased risk of some adverse events, including thromboses and serious adverse events, in intervention versus control. While these findings may raise concerns, it should be noted that our risk estimates are inaccurate, and the incidence of harms generally was low, with only few types of adverse events exceeding an incidence of 10%. In comparison, in studies assessing harms of systemic cancer treatments, the most common adverse events typically occur in more than 20% of the patients.[185–187] It should also be acknowledged that medical interventions come with risk of adverse events, and future trial are required to evaluate whether potential harms of exercise are acceptable considering the potential beneficial effects. Although our risk estimates are inaccurate, it is notable that our findings differ markedly from recent similar systematic reviews reporting that exercise is safe during systemic cancer therapy.[17–20,188] We contend, however, that these reviews are methodologically limited and potentially misleading due to lack of certainty of evidence and risk of bias assessments. These assessments are core methods of systematic reviews,[189] and their absence in previous reviews is critical considering the well-documented inadequacy of harms assessment and reporting in oncology[21] and exercise[31] trials. In addition, none of the previous reviews included unpublished data. Underreporting of harms is common in the published medical literature and may threaten the validity of data syntheses of adverse events.[190] In line with this, we found that the increased risk of serious adverse events and thromboses in the intervention groups was higher in the unpublished data, and inclusion of unpublished sources changed the direction of the risk estimates for some outcomes, including pulmonary embolisms and thromboses.

The quality of adverse events reporting was generally poor, and we found that several critical aspects of data collection and analyses were lacking. Notably, none of the eligible trials reported attribution methods and less than half reported adverse events per type and severity or described how adverse events were collected. This lack of transparent reporting limits the reproducibility, replicability, and credibility of the eligible trials. In addition, we found evidence of selective outcome reporting and non-reporting. Perhaps most concerning is our finding that nearly half of all preregistered harms outcomes were silently omitted from the published reports. This threatens the validity of the eligible trials and may result in biased risk estimates. Another concern is that only 20% of the trials were prospectively registered, and the majority of the eligible literature was thus noncompliant with international standards for conducting medical clinical research.[191]

Compared to controls, the intervention groups had a higher risk of trial withdrawals due to adverse events in subgroup analyses of participants with breast cancer and participants receiving supervised exercise. Withdrawals due to adverse events was included as a surrogate measure of harms, as we expected the eligible data to be sparse. We acknowledge that this outcome may not reflect the true risk, but instead could be attributed to a higher degree of active surveillance in the intervention groups. Yet, harms leading to withdrawal may provide information, as they ultimately reflect the willingness of patients and clinicians to continue exercise despite the presence of harms.

Limitations of this study should be considered. We made post-registration changes in the protocol, most notably including specification of methods of heterogeneity estimation and handling of trials with double zero events. These, however, were made before data collection was completed, and none of our analyses were sensitive to these changes. In addition, we combined trials that investigated different types of cancers, treatments, and exercise modalities. While this approach may limit the generalisability of our findings, it closely reflects current exercise guidelines and clinical practice, where exercise is recommended and applied with little distinction between different cancers and treatments. The low completeness of the evidence should also be considered in the interpretation of our findings. Although we identified 129 eligible trials, most trials evaluated participants with breast cancer or mixed cancers, whereas other cancers remain largely underrepresented. Moreover, most eligible trials evaluated participants undergoing chemotherapy, and the harms of exercise in patients receiving immunotherapy, targeted therapies, and chemoradiation remains largely unknown.

Compared to similar systematic reviews,[17–20,188] the strengths of this study include a preregistered protocol, including a pre-planned statistical data synthesis; transparent disclosure and justification of protocol deviations; and a more comprehensive search strategy, using 11 databases and trial registries as well as forward/backward citation searches of eligible trials.

This study may inform the design of future research. To be of clinical relevance, assessment of adverse events of particular relevance for specific cancers and their treatments should be a prerequisite in future clinical exercise oncology trials. Furthermore, to prevent the methodological issues identified in this study, including poor outcome assessment and reporting, future trials should adhere to harms reporting guidelines,[30] apply standardised assessment tools,[29] and adopt open-science practices, including preregistration and transparent outcome reporting. Less than 15% of the eligible trials described how comorbidities, risk factors, or treatment-related adverse events were considered in the exercise prescription. Along with more conventional exercise dose prescription components,[192,193] these factors may be important in the design of exercise interventions for

patients receiving systemic cancer treatment. We suggest, therefore, that future trials describe the use of any relative or absolute exercise contraindications and how the dose is adjusted accordingly; report how the exercise intervention is modified according to pre-existing comorbidities and treatment-related adverse events; and report when the individual exercise sessions are prescribed relative to the administration of cancer treatment.

In conclusion, evidence for the harms of exercise, prescribed alone or as part of multimodal interventions, is uncertain in patients with cancer undergoing systemic treatments due to high risk of bias, poor reporting, and lack of trials. There is currently insufficient data on harms to make evidence-based risk-benefits assessments of the application of structured exercise in patients receiving systemic cancer treatments. Given the increasing interest in implementation of exercise into standard care of cancer, our findings are concerning, and well-designed confirmatory RCTs should be initiated to establish the harms of exercise in patients with cancer receiving systemic treatments.

Contributors

SNT and CS initiated and conceived the study; SNT and CS wrote the first draft of the protocol and the manuscript; all authors contributed to the design of the study; SNT, AL, and CS developed the systematic searches; SNT, IML, and CS developed the statistical analysis plan; SNT, MKF, and CS screened titles and abstracts of identified records; SNT, LMT, and CS screened reports selected for full-text screening; SNT, LMT, and CS extracted data; SNT and CS judged the risk of bias; SNT and CS assessed the certainty of evidence; SNT performed the statistical analyses; MMS contributed with knowledge of systemic treatment of cancer; SNT, IML, MKF, KAB, CF, JFC, and CS contributed with knowledge of exercise oncology; all authors edited and critically revised the protocol and the manuscript; all authors approved final version of the protocol and the manuscript. SNT and CS had directly access to all data and have verified the underlying data reported in the manuscript.

Data sharing statement

Raw data are available in Supplementary File S9.

Declaration of interests

All authors declare no conflicts of interest.

Acknowledgments

We thank CFAS associates Dr Tim Schauer, Dr Paula Sanchis Tortosa, and Beckey Trinh for screening, translation, and data extraction of non-English records, and CFAS associate Dr Cody Durrer for assistance with writing the statistical code in R.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101937.

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