Effects and moderators of exercise on muscle strength, muscle function and aerobic fitness in patients with cancer: a meta-analysis of individual patient data

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ABSTRACT

Objective To optimally target exercise interventions for patients with cancer, it is important to identify which patients benefit from which interventions.

Design We conducted an individual patient data meta-analysis to investigate demographic, clinical, intervention-related and exercise-related moderators of exercise intervention effects on physical fitness in patients with cancer.

Data sources We identified relevant studies via systematic searches in electronic databases (PubMed, Embase, PsycINFO and CINAHL).

Eligibility criteria We analysed data from 28 randomised controlled trials investigating the effects of exercise on upper body muscle strength (UBMS) and lower body muscle strength (LBMS), lower body muscle function (LBMF) and aerobic fitness in adult patients with cancer.

Results Exercise significantly improved UBMS (β=0.20, 95% Confidence Interval (CI) 0.14 to 0.26), LBMS (β=0.29, 95% CI 0.23 to 0.35), LBMF (β=0.16, 95% CI 0.08 to 0.24) and aerobic fitness (β=0.28, 95% CI 0.23 to 0.34), with larger effects for supervised interventions. Exercise effects on UBMS were larger during treatment, when supervised interventions included ≥3 sessions per week, when resistance exercises were included and when session duration was >60 min. Exercise effects on LBMS were larger for patients who were living alone, for supervised interventions including resistance exercise and when session duration was >60 min. Exercise effects on aerobic fitness were larger for younger patients and when supervised interventions included aerobic exercise.

Conclusion Exercise interventions during and following cancer treatment had small effects on UBMS, LBMS, LBMF and aerobic fitness. Demographic, intervention-related and exercise-related characteristics including age, marital status, intervention timing, delivery mode and frequency and type and time of exercise sessions moderated the exercise effect on UBMS, LBMS and aerobic fitness.

INTRODUCTION

Patients with cancer often experience physical problems as a result of cancer or cancer treatment.[1–3] Previous randomised controlled trials (RCTs) and meta-analyses have reported beneficial effects of exercise on physical fitness in patients with cancer.[4–7] Physical fitness is defined by the body's ability to carry out daily tasks without excessive fatigue and is important for functional independence and quality of life (QoL).[8 9] Physical fitness includes, among others, upper body muscle strength (UBMS), lower body muscle strength (LBMS), lower body muscle function (LBMF) and aerobic fitness.[10]

A reduction in skeletal muscle mass during (neo-)adjuvant chemotherapy has been shown to be related to higher treatment toxicity and poorer survival.[11–13] In the general population, poor LBMF is related to reduced functional independence and lower QoL[14 15] and is a significant predictor of mortality.[16] Aerobic fitness was reported to be 25% lower in patients with breast cancer after chemotherapy than in healthy sedentary women.[17] Functional independence is at risk when maximal aerobic fitness decreases below 15 mL/kg/min,[18] and aerobic fitness is a well-established predictor of QoL[19] and mortality[4 20] in patients with cancer. Consequently, maintaining and improving strength, muscle function and aerobic fitness may be important during and following cancer treatment for functional independence and to improve QoL and potentially survival.[8 9]

Previous RCTs and meta-analyses have reported beneficial effects of exercise during and following

treatment on muscle strength[5–8 21 22] and aerobic fitness[4 6–8 21 23 24] in patients with different types of cancer. To effectively target and refine exercise interventions, it is important to identify which patients benefit from which exercise programmes. In addition, characteristics of the interventions may influence their effects on UBMS, LBMS, LBMF or aerobic fitness.[25–27]

Previously, we used data collected in the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) study[28] to conduct an individual patient data (IPD) meta-analysis to study demographic, clinical, intervention-related and exercise-related moderators of exercise intervention effects on self-reported QoL and self-reported physical function.[29] Exercise effects on QoL and physical function were not significantly different between subgroups of patients with different demographic and clinical characteristics. However, moderators of the effect of exercise interventions may differ by outcome. Studies investigating moderators of the exercise intervention effects on physical fitness are scarce, and single RCTs are generally underpowered to investigate such moderator effects. The use of IPD from multiple RCTs allows testing of moderators with interaction tests in larger samples.[30] Therefore, we aimed to identify demographic, clinical, intervention-related and exercise-related moderators of the exercise intervention effect on UBMS, LBMS, LBMF and aerobic fitness using IPD available in the POLARIS database.[29]

METHODS
Study and patient selection
We identified and obtained data from relevant studies as part of the POLARIS study. A description of the methods of study identification and selection has been published previously, and detailed information on the study inclusion can be found elsewhere.[28 29] Principal investigators of RCTs eligible to be included in the POLARIS study received a letter of invitation to join the consortium. After expressing interest, they signed a data sharing agreement. Anonymised data from study participants were shared in various formats, which were recoded, and checked for completeness and consistency with published results. The study protocol was registered in PROSPERO in February 2013 (CRD42013003805).[28] In total, 34 RCTs evaluating the effects of exercise in patients with cancer were included in the POLARIS database. Of these studies, 28 reported UBMS, LBMS, LBMF and/or aerobic fitness and were included in the current IPD meta-analysis (figure 1). Due to a small sample of patients with metastatic disease, we excluded 50 patients with metastatic disease and another 15 patients for whom this information was missing .

DATA EXTRACTION
Study and patient characteristics (ie, country where the RCT was conducted, sample size, cancer type, mean age, sex and outcome measure), intervention characteristics (ie, timing, mode and duration of intervention delivery) and exercise characteristics (ie, frequency, intensity, type and time, often referred to as FITT-factors) were extracted by two independent researchers (MGS and LMB) and were based on documentation in published papers (online supplementary table 1).

Risk of bias assessment
We used the risk-of-bias assessment tool of the Cochrane Collaboration[31] to assess the risk of bias of the studies based on published papers. In our previous publication, we reported the risk of bias on random sequence generation, allocation concealment, incomplete outcome, incomplete reporting, adherence and
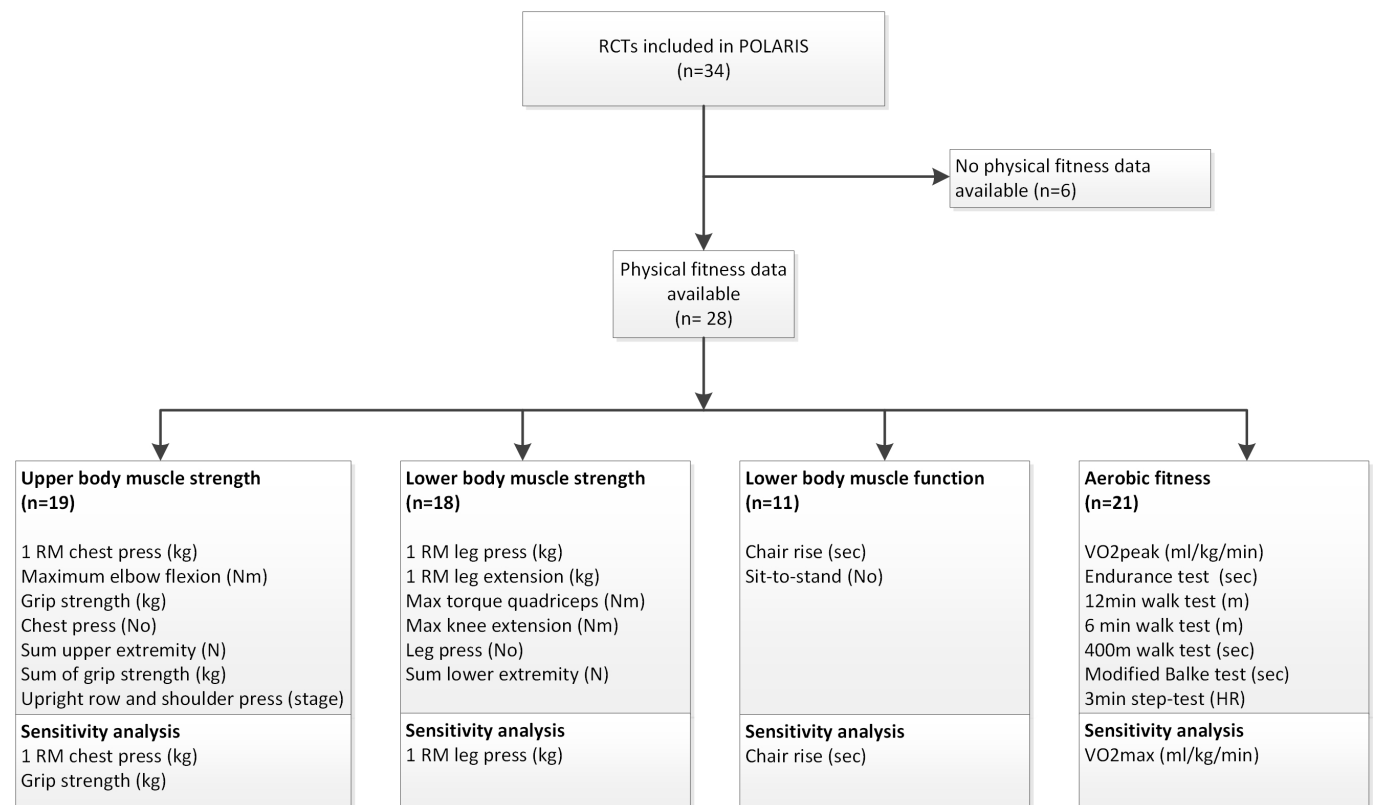

Figure 1 Flow of data inclusion. 1 RM, 1-repetition maximum; N, Newton; Nm, newton*meter; No, number of repetitions; RCT, randomised controlled trial; stage, based on number of repetitions and weight held; VO$_2$peak, peak oxygen consumption.

contamination.[29] For the present study, we additionally assessed the risk of detection bias by judging blinding of outcome assessor. Two authors (MGS and LMB) independently judged this item as high risk of bias if the outcome assessor was not blinded or low risk of bias if the outcome assessor was blinded. If no information on blinding of outcome assessor was reported, the principal investigator of the study was contacted.

Outcome measures

The current IPD meta-analysis focused on UBMS, LBMS, LBMF and aerobic fitness after completion of the exercise intervention (figure 1). Studies included in the current meta-analysis measured UBMS with a one-repetition maximum (1RM) chest press (kg),[8 9 32–40] maximum elbow flexion (Newton*metre (Nm)),[7 41] maximum grip strength (kg),[6 23 24 42 43] number of repetitions of chest press at 30%–35% of individual's body mass (No),[44] sum of upper extremity isometric muscle strength measured using a handheld dynamometer (Newton (N)),[45] sum of best right and left grip strength (kg)[46] or an upright row and shoulder press exercise (stage based on number of repetitions and weight held).[47] Four studies also reported grip strength in addition to the 1RM chest press or maximum elbow flexion and were included in the sensitivity analysis on grip strength.[7 38–41] LBMS was measured using a 1RM leg press (kg)[9 32–40] or leg extension (kg),[8] maximum isometric quadriceps torque (Nm),[6 23 43 48–51] maximum isometric knee extension (Nm),[7 41] number of repetitions of leg press at 100%–110% of individual's body mass (No)[44] or sum of lower body isometric muscle strength (hip abductors and flexors and knee flexors and extensors) measured using a handheld dynamometer (N).[45] LBMF was measured using the chair rise (time in seconds to rise from the chair five times)[32 33 35–40 44] or sit-to-stand test (number of times that participants raised to a full stand in 30s; No).[7 24 41 43] Aerobic fitness was measured using a direct (maximal) or indirect (submaximal) cardiopulmonary exercise test (peak oxygen uptake, VO_2peak, in mL/kg/min),[6 8 23 24 32 33 42–44 48 52–54] during an endurance test (s) at 75% of maximal workload measured during a maximal short exercise capacity,[7 41] as distance (m) walked in 12[55] or 6 min,[45 56] during a 400 m walk test (s),[32 35–37] a modified Balke test (time in seconds to reach 70% of age-predicted maximum heart rate (HR) during submaximal treadmill test)[46] or a 3 min step test (HR at test completion).[47]

To be able to pool the different measures per outcome, we recoded individual scores into z-scores by calculating the mean score at baseline from all individuals per outcome measure and subtracting the mean score from the individual score. The result was divided by the mean SD per outcome measure at baseline. We used the z-scores for further analyses. If studies used more than one measure to investigate one of the outcomes, we used the best established measure based on the order provided in figure 1 and table 1.

Moderators of exercise on physical fitness

Potential demographic moderators included baseline age, sex, marital status (dichotomized into unmarried or living alone vs married or living with partner) and education level (dichotomised

Table 1 Baseline upper body muscle strength (UBMS), lower body muscle strength (LBMS), lower body muscle function (LBMF) and aerobic fitness of patients in the exercise and control group

Baseline values	n	Exercise (n=1944) Mean (SD)	n	Control (n=1571) Mean (SD)
UBMS, mean (SD)				
Chest press (1RM)	658	35.2 (16.1)	512	32.4 (16.8)
Max elbow flexion (Nm)	150	30.5 (12.1)	72	28.7 (13.0)
Grip strength (kg)	378	35.3 (10.7)	290	36.4 (9.8)
Chest press (No)	8	0.0 (0.0)	7	0.3 (0.8)
Sum upper extremity (N)	40	152.7 (46.8)	39	155.4 (54.7)
Sum of best right and left grip strength (kg)	68	69.6 (23.1)	33	72.4 (21.4)
Row and shoulder press (stage)	134	7.0 (2.8)	60	6.3 (3.6)
LBMS, mean (SD)				
Leg press (1RM)	498	104.0 (42.9)	430	99.6 (44.3)
Leg extension (1RM)	160	54.1 (26.1)	82	56.4 (27.7)
Max quadriceps torque (Nm)	268	105.5 (35.0)	309	103.9 (36.4)
Max knee extension (Nm)	153	69.5 (19.7)	77	63.8 (17.6)
Leg press (No)	8	11.1 (7.6)	7	16.3 (6.2)
Sum lower extremity (N)	40	185.5 (54.8)	39	186.7 (63.2)
LBMF, mean (SD)				
Chair rise (s)	339	12.2 (3.2)	273	12.0 (3.1)
Sit to stand (No)	406	17.5 (5.2)	230	16.2 (4.2)
Aerobic fitness, mean (SD)				
VO_2peak (mL/kg/min)	824	23.1 (6.8)	677	23.7 (7.5)
Endurance test (s)	168	773.5 (536.2)	85	684.8 (515.8)
12 min walk test (m)	99	997.4 (211.0)	100	975.4 (234.6)
6 min walk test (m)	66	505.6 (107.5)	64	499.0 (118.5)
400 m walk test (sec)	190	273.7 (55.2)	128	271.3 (46.6)
Modified Balke test (sec)	69	375.1 (284.4)	33	351.1 (289.7)
Step test (HR)	117	122.5 (16.1)	46	115.2 (14.7)

1RM, one-repetition maximum; AE, aerobic exercise; N, Newton; Nm, newton*metre; No, number of repetitions; RE, resistance exercise; t, time; VO_2peak, peak oxygen consumption.

into low–medium, including elementary, primary or secondary school, lower or secondary vocational education vs high, including higher vocational, college or university education).[29]

Potential clinical moderators included body mass index (BMI), type of cancer (categorised into breast, male genitourinary, haematological, gastrointestinal, gynaecological, respiratory tract or other types) and type of treatment (surgery, chemotherapy, radiotherapy, hormone therapy or stem cell transplantation; all dichotomised into previous or current treatment vs no treatment). Since the majority of patients were women with breast cancer, we also investigated the moderator effect of type of cancer by dichotomising patients with breast cancer vs patients with other types of cancer.

Potential intervention-related moderators included timing of intervention delivery in relation to primary cancer treatment (categorised into during treatment and post-treatment, based on the Physical Activity and Cancer Control framework[57]), delivery mode of intervention (supervised when exercise sessions were conducted (partly) under supervision vs unsupervised when exercise sessions were performed at home) and intervention duration (categorised into ≤12 weeks, >12–24 weeks and >24 weeks).

Potential exercise-related moderators (ie, FITT-factors) included exercise frequency (dichotomised into <3 vs ≥3 sessions per week for supervised exercise and <5 vs ≥5 sessions per week for unsupervised exercise), exercise intensity (categorised into low, medium and high intensity based on the American College of Sports Medicine guidelines[58]), exercise type (categorised into aerobic exercise (AE); resistance exercise (RE); combined aerobic and resistance exercise (AE+RE); and combined resistance and impact loading exercise (RE+impact)) and session duration (categorised into ≤30 min, >30–60 min or >60 min per session). In addition, we calculated mean exercise volume (ie, frequency × session time) per week as a possible exercise-related moderator to investigate whether differences in effects as a result of exercise frequency are related to session duration. According to international physical activity guidelines,[58] weekly exercise volume was dichotomised into <150 min/week versus ≥150 min/week for both supervised and unsupervised exercise interventions.

Statistical analyses

We conducted one-step IPD meta-analyses without imputation of missing data to study the effects and moderators of exercise on UBMS, LBMS, LBMF and aerobic fitness.[59] First, using z-values, we evaluated exercise effects by regressing the postintervention value of the outcome on the intervention, adjusted for the baseline value, using linear mixed model analyses. We used a two-level structure (1: patient; 2: study) and accounted for clustering of patients within studies by adding a random intercept on study level. In addition, we checked whether it was necessary to adjust the overall effect for age, sex, marital status, education level, BMI and cancer type, but because unadjusted effect sizes were not different from adjusted effects, unadjusted effect sizes were reported. Exercise intervention effects (β) and 95% Confidence Intervals (CIs) were reported, and because z-values were used, the effects correspond to a Cohen's d effect size.[60] Second, we conducted sensitivity analyses using raw data (ie, in their own unit of measurement) of the most frequently used outcome measures of UBMS, LBMS, LBMF and aerobic fitness (ie, chest press, grip strength, leg press, chair rise and directly measured VO_2peak) (figure 1).

All potential moderators were analysed in separate models, and for each potential moderator of exercise intervention effects, we examined significance of interaction terms with the likelihood ratio test. We reported χ^2 values, df and p values. When a significant interaction was found, exercise intervention effects and 95% CI were reported per stratum. If a significant interaction of a continuous variable was found, exercise intervention effects were reported for subgroups to facilitate interpretation of the results. In case a three-armed RCT had two exercise study arms with different exercise characteristics, we tested the difference between exercise characteristics using dummy variables,[29] because interaction testing was not possible for that characteristic. In that case, we reported regression coefficients ($\beta_{difference\_in\_effect}$) and 95% CI of the between-group difference in z-scores. If there was a significant between group difference, exercise intervention effects were reported per stratum. Effects of 0.2 were considered small, 0.5 as moderate and at or above 0.8 as large.[60 61]

To reduce ecological bias (ie, bias that occurs when trials differ in other study level characteristics than the moderator of interest[62]), within-trial interaction was separated from between trial interaction and the individual values of the moderator were centred around the mean study value of that moderator. Due to the significant moderator effect of delivery mode on UBMS, LBMS and aerobic fitness, and because exercise characteristics differ between supervised and unsupervised exercise interventions, we investigated moderator effects of FITT-factors for supervised and unsupervised exercise interventions separately. Statistical analyses were performed using SPSS V.22.0 and R V.3.2.5.[63]

RESULTS
Study characteristics

The POLARIS database included 28 RCTs that evaluated the effect of exercise on UBMS, LBMS, LBMF and/or aerobic fitness (figure 2). In total, 3515 patients were included, of whom 1944 were randomised to the intervention group and 1571 to the control group. Nineteen RCTs evaluated the effect of exercise on UBMS, 18 on LBMS, 11 on LBMF and 21 on aerobic fitness (online supplementary table 1). The mean age of the participants was 54.9 (SD 11.7) years, 75% were female, 67% were diagnosed with breast cancer, 49% were highly educated and 76% were married or lived with a partner (table 2).

Regarding intervention characteristics, 10 RCTs investigated the effects of an exercise intervention during treatment, 14 following treatment, 3 during or following treatment and one pretreatment, during treatment or following treatment. Twenty-two RCTs investigated the effect of a supervised exercise intervention, five investigated an unsupervised exercise intervention and one investigated the effect of both an unsupervised and supervised exercise intervention arm. Eleven RCTs investigated an intervention duration of ≤12 weeks, seven a duration of >12–24 weeks, eight a duration of >24 weeks and two reported median intervention duration only (online supplementary table 1).

Seventeen RCTs evaluating supervised exercise investigated a frequency of <3 times per week, and six RCTs evaluated a frequency of ≥3 times per week. Three RCTs evaluating unsupervised exercise sessions investigated a frequency of <5 times per week, two RCTs ≥5 times per week and one RCT did not report exercise frequency. For both supervised and unsupervised, 2 RCTs investigated the effect of low–moderate intensity exercise, 9 investigated moderate intensity, 16 investigated moderate–high intensity and 1 investigated high intensity exercise. Eight study arms investigated the effect of AE, 5 the effect of RE, 14 the
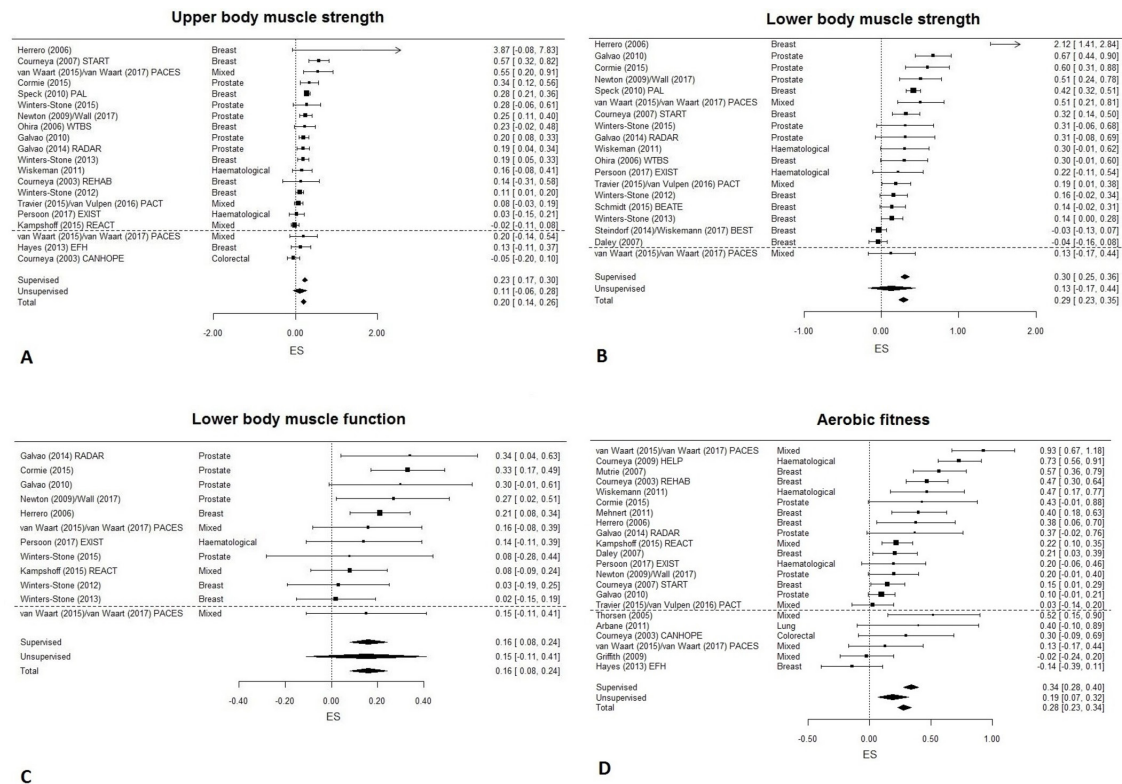
Figure 2 Forest plots of the effect sizes (ESs) of exercise intervention effects on upper body muscle strength (A), lower body muscle strength (B), lower body muscle function (C) and aerobic fitness (D). Data represent the regression coefficients (95% CIs) of the effects of exercise on physical fitness (in z-scores). Supervised interventions are presented above the dashed line and unsupervised interventions below. Pooled effects are presented at the bottom of the figures.

effect of AE+RE and 4 the effect of RE+impact training. Eight RCTs investigated the effect of ≤30 min per exercise session, 16 of >30–60 min, 3 of >60 min per session and 1 RCT did not report session duration (online supplementary table 1).

Risk of bias assessment

We previously reported the risk of bias of 26 of the 28 included RCTs.[29] The risk of bias assessment of two RCTs[36 43] could not be performed at that time because the papers were not yet published. Twenty-two RCTs were at low risk for selection bias,[6–9 23 24 32–34 37–39 42 45–50 52 54–56] allocation bias,[6–8 23 24 32–34 37–39 42 44 45 47–50 52–56] and attrition bias due to the amount or handling of incomplete data,[6–9 23 24 32 33 37–40 42 46–50 52–55 64] 21 RCTs were at low risk for bias due to selective outcome reporting,[6–9 23 24 32–34 37 38 40 42 45–50 52 55 56] 11 RCTs reported high adherence to the intervention[6 23 34 38 40 42 44 45 47 52–56] and 6 RCTs met the criteria of low risk of bias regarding limited contamination.[8 24 38–40 42] Risk for detection bias was low in 13 RCTs due to adequate blinding of outcome assessors[6 9 23 24 34 38–40 43 44 47 55 56 64] and high in 15 RCTs[7 8 32 33 36 37 42 45 46 48 50–54] (online supplementary table 1). Because the lack of blinding could contribute to an overestimation of the overall effects, we investigated whether risk for detection bias was a moderator of the exercise effect on UBMS, LBMS, LBMF and aerobic fitness. There was a moderator effect of the risk for detection bias on UBMS ($\chi^2=6.86$, df=1, p=0.01) and aerobic fitness ($\chi^2=14.04$, df=1, p<0.01) with larger effects for studies at high risk for detection bias.

Effects of exercise on physical fitness

Exercise interventions significantly improved UBMS (β=0.20, 95% CI 0.14 to 0.26), LBMS (β=0.29, 95% CI 0.23 to 0.35), LBMF (β=0.16, 95% CI 0.08 to 0.24) and aerobic fitness (β=0.28, 95% CI 0.23 to 0.34; table 3). Based on sensitivity analyses using a subset of the data with the original measurement unit, exercise significantly improved chest press (1RM) (β=4.86, 95% CI 3.65 to 6.07 kg), leg press (1RM) (β=16.56, 95% CI 13.15 to 19.97 kg), chair rise (β=−0.60, 95% CI −0.91 to −0.28 s) and VO_2peak (β=1.80, 95% CI 1.34 to 2.27 mL/kg/min) compared with the control group. There were no significant between group differences for grip strength (β=0.19, 95% CI −0.39 to 0.76 kg).

Demographic and clinical moderators

Intervention effects on LBMS were significantly larger ($\chi^2=5.12$, df=1, p=0.02) for patients who were unmarried or living alone (β=0.37, 95% CI 0.23 to 0.51) than for those who were married or lived with their partner (β=0.22, 95% CI 0.14 to 0.30). Intervention effects on aerobic fitness were significantly larger ($\chi^2=6.22$, df=1, p=0.01) for younger patients. Effect sizes were 0.41 (95% CI 0.31 to 0.52) for patients aged <50 years, 0.22 (95% CI 0.15 to 0.29) for patients aged 50–70 years and 0.23 (95% CI 0.07 to 0.40) for patients aged >70 years. No other demographic or clinical characteristic significantly moderated the effects on UBMS, LBMS, LBMF or aerobic fitness (table 3).

Intervention-related moderators

Timing of intervention delivery significantly moderated the effect on UBMS ($\chi^2=4.17$, df=1, p=0.04). There were larger

Table 2 Demographic, clinical, intervention-related and exercise-related characteristics of patients in the exercise and control group.

	Exercise (n=1944)	Control (n=1571)
Demographic		
Age, mean (SD) years	54.9 (11.9)	55.0 (11.6)
Age categories (years), n (%)		
< 50	648 (33.3)	501 (31.9)
50–70	1070 (55.0)	892 (56.8)
≥70	216 (11.1)	165 (10.5)
Unknown	10 (0.5)	13 (0.8)
Sex, n (%)		
Men	496 (25.5)	396 (25.2)
Women	1448 (74.5)	1175 (74.8)
Married/living with partner, n (%)		
Yes	1150 (59.2)	891 (56.7)
No	336 (17.3)	294 (18.7)
Unknown	458 (23.6)	386 (24.6)
Education level, n (%)		
Low/middle	864 (44.4)	657 (41.8)
High	816 (42.0)	632 (40.2)
Unknown	264 (13.6)	282 (18.0)
Clinical		
BMI, mean (SD) kg/m^2	27.08 (5.0)	27.42 (5.3)
BMI categories, n (%)		
Underweight (BMI <18.5 kg/m^2)	13 (0.7)	18 (1.2)
Normal weight (BMI 18.5–<25 kg/m^2)	697 (35.9)	513 (32.7)
Overweight (BMI 25–<30 kg/m^2)	676 (34.8)	549 (35.0)
Obese (BMI ≥30 kg/m^2)	447 (23.0)	390 (24.8)
Unknown	111 (5.7)	101 (6.4)
Cancer type, n (%)		
Breast	1297 (66.7)	1056 (67.2)
Male genitourinary	287 (14.8)	221 (14.1)
Haematological	190 (9.8)	183 (11.7)
Gastrointestinal	126 (6.5)	76 (4.8)
Gynaecological	16 (0.8)	17 (1.1)
Respiratory track	23 (1.2)	15 (1.0)
Other	5 (0.3)	3 (0.2)
Surgery, n (%)*		
No	265 (14.3)	219 (14.8)
Yes	1458 (78.8)	1144 (77.5)
Unknown	127 (6.9)	113 (7.7)
Chemotherapy, n (%)		
No	498 (25.6)	412 (26.2)
Prior to intervention	663 (34.1)	618 (39.3)
During intervention	715 (36.8)	479 (30.5)
Unknown	68 (3.5)	62 (4.0)
Radiotherapy, n (%)		
No	850 (43.7)	616 (39.2)
Prior to intervention	720 (37.0)	650 (41.4)
During intervention	297 (15.3)	253 (16.1)
Unknown	77 (4.0)	52 (3.3)
Hormone therapy		
Breast cancer survivors (n= 2353), n (%)		
No	672 (51.8)	545 (51.6)
Yes	365 (28.1)	261 (24.7)
Unknown	260 (20.1)	250 (23.7)
Prostate cancer survivors (n=508), n (%)		
No	0 (0.0)	0 (0.0)
		Continued

Table 2 Continued

	Exercise (n=1944)	Control (n=1571)
Prior to intervention	50 (17.4)	50 (22.6)
During intervention	190 (66.2)	125 (56.6)
Unknown	47 (16.4)	46 (20.8)
SCT, n (%)†		
Allogeneic	40 (42.6)	40 (42.1)
Autologous	54 (57.5)	55 (57. 9)
Intervention related‡		
Timing of intervention, n (%)		
Pre–during–following treatment	40 (2.1)	
During treatment	1113 (57.3)	
Following treatment	791 (40.7)	
Mode of intervention delivery, n (%)		
(Partly) Supervised	1527 (78.6)	
Unsupervised	417 (21.5)	
Duration of intervention (weeks), n (%)		
≤12	644 (33.1)	
>12-24	495 (25.5)	
>24	605 (31.1)	
Unknown§	200 (10.3)	
Exercise related		
Exercise frequency, n (%)		
2 times per week	1250 (64.3)	
3 times per week	286 (14.7)	
4 times per week	192 (9.9)	
≥5 times per week	193 (9.9)	
Unknown	23 (1.2)	
Exercise intensity, n (%)		
Low	0 (0.0)	
Low–moderate	167 (8.6)	
Moderate	510 (26.2)	
Moderate–vigorous	985 (50.7)	
Vigorous	91 (4.7)	
Unknown	191 (9.8)	
Exercise type, n (%)		
AE	437 (22.5)	
RE	385 (19.8)	
AE+RE	957 (49.2)	
RE+impact training	165 (8.5)	
Exercise session duration (min), n (%)		
≤30	544 (28.0)	
>30–60	1148 (59.1)	
>60	186 (9.6)	
Unknown	66 (3.4)	

*Proportion of survivors without SCT (n=3326).
†Proportion of survivors with SCT (n=189).
‡Proportion of survivors from intervention groups (n=1944).
§Intervention duration of individual patients unknown for three studies, but mean or median was reported.
AE, aerobic exercise; BMI, body mass index; n, number; RE, resistance exercise; SCT, stem cell transplantation.

effects when exercise interventions were delivered during treatment (β=0.26, 95% CI 0.17 to 0.36) than following treatment (β=0.13, 95% CI 0.06 to 0.21). In addition, the moderator effect of timing of the intervention delivery remained significant after adjusting for intervention delivery mode. The exercise intervention effects on UBMS, LBMS and aerobic fitness were significantly larger for supervised than for unsupervised

Table 3 Effects and moderators of the effects of exercise on upper body muscle strength, lower body muscle strength, lower body muscle function and aerobic fitness.

	UBMS χ² (df), p values	UBMS β (95% CI)	LBMS χ² (df), p values	LBMS β (95% CI)	LBMF χ² (df), p values	LBMF β (95% CI)	Aerobic fitness χ² (df), p values	Aerobic fitness β (95% CI)
Effect of exercise	17.11 (1), < to 0.01*	0.20 (0.14 to 0.26)*		0.29 (0.23 to 0.35)*		0.16 (0.08 to 0.24)*		0.28 (0.23 to 0.34)*
Demographic moderators								
Age continuous	0.10 (1), 0.76		0.57 (1), 0.45		0.70 (1), 0.40		6.22 (1), 0.01*	
Age <50								0.41 (0.31 to 0.52)*
Age 50–70								0.22 (0.15 to 0.29)*
Age >70								0.23 (0.07 to 0.40)*
Sex	0.97 (1), 0.32		0.59 (1), 0.44		2.17 (1), 0.14		0.00 (1), 0.98	
Marital status	1.90 (1), 0.17		5.12 (1), 0.02*		0.84 (1), 0.36		1.78 (1), 0.18	
Partner				0.22 (0.14 to 0.30)*				
Unmarried/living alone				0.37 (0.23 to 0.51)*				
Education level	0.02 (1), 0.88		2.71 (1), 0.10		2.03 (1), 0.16		0.97 (1), 0.33	
Clinical moderators								
BMI continuous	0.68 (1), 0.41		0.19 (1), 0.66		1.15 (1), 0.28		0.00 (1), 0.98	
Cancer type	0.77 (4), 0.94		0.26 (1), 0.61		2.06 (4), 0.73		7.69 (5), 0.17	
Breast cancer versus other cancer types	0.47 (1), 0.50		0.26 (1), 0.61		0.58 (1), 0.45		0.77 (1), 0.38	
Surgery	0.32 (1), 0.57		1.71 (1), 0.19		0.02 (1), 0.88		3.34 (1), 0.07	
Chemotherapy	0.06 (1), 0.81		0.00 (1), 0.95		2.42 (1), 0.12		0.34 (1), 0.56	
Radiotherapy	0.61 (1), 0.43		2.88 (1), 0.09		1.80 (1), 0.18		0.60 (1), 0.44	
Hormone therapy for breast cancer	0.84 (1), 0.36		0.00 (1), 0.96		0.58 (1), 0.45		1.83 (1), 0.18	
Intervention-related moderators								
Timing of intervention	4.17 (1), 0.04*		0.02 (1), 0.90		1.04 (1), 0.31		2.05 (1), 0.15	
During		0.26 (0.17 to 0.36)*						
Following		0.13 (0.06 to 0.21)*						
Delivery mode†– supervised versus unsupervised		0.19 (0.05 to 0.34)*†		0.30 (0.12 to 0.48)*†		0.02 (−0.16 to 0.19)†		0.23 (0.12 to 0.34)*†
Supervised		0.23 (0.17 to 0.30)*		0.30 (0.25 to 0.36)*				0.34 (0.28 to 0.40)*
Unsupervised		0.11 (−0.06 to 0.28)		0.13 (−0.17 to 0.44)				0.19 (0.07 to 0.32)*
Intervention duration (weeks)	1.69 (2), 0.43		2.57 (2), 0.28		1.10 (2), 0.58		8.47 (2), 0.01*‡	
≤12								0.38 (0.30 to 0.46)*
> to 12–24								0.27 (0.17 to 0.38)*
> to 24								0.14 (−0.02 to 0.30)
Exercise-related moderators for supervised exercise								
Frequency			0.01 (1), 0.92		0.05 (1), 0.83		0.29 (1), 0.59	
< to 3 times/week		0.16 (0.11 to 0.22)*						
≥3 times/week		0.49 (0.28 to 0.70)*						
Intensity†– Moderate–vigorous and vigorous versus low–moderate and moderate		0.11 (−0.04 to 0.27)†		−0.12 (−0.34 to 0.09)†		−0.04 (−0.17 to 0.10)†		0.04 (−0.09 to 0.17)†

Continued

Table 3 Continued

	UBMS		LBMS		LBMF		Aerobic fitness	
	χ² (df), p values	β (95% CI)	χ² (df), p values	β (95% CI)	χ² (df), p values	β (95% CI)	χ² (df), p values	β (95% CI)
Type†								
AE+RE versus AE		0.26 (0.07 to 0.44)*		0.42 (0.25 to 0.59)*		–		−0.08 (−0.22 to 0.06)
RE versus AE		0.54 (0.37 to 0.71)*		0.29 (0.14 to 0.44)*		–		−0.31 (−0.49 to −0.13)*
RE+impact training versus AE		0.27 (0.04 to 0.50)*		0.28 (0.07 to 0.48)*		–		−0.21 (−0.48 to 0.06)
RE versus AE+RE		0.28 (0.14 to 0.43)*		−0.13 (−0.26 to −0.01)*		–		−0.23 (−0.42 to −0.03)*
RE+impact training versus AE+RE		0.02 (−0.16 to 0.19)		−0.14 (−0.30 to 0.02)		−0.00 (−0.16 to 0.16)		−0.13 (−0.37 to 0.12)
RE+impact training versus RE		−0.27 (−0.47 to −0.07)*		−0.01 (−0.18 to 0.16)		–		0.10 (−0.20 to 0.40)
Time of exercise session (min)	14.01 (2), 0.01*		9.07 (2), 0.01*		0.05 (1), 0.83		1.48 (2), 0.48	
≥ 30		0.49 (0.28 to 0.70)*		0.31 (0.15 to 0.47)*				
> to 30–60		0.16 (0.09 to 0.23)*		0.26 (0.19 to 0.34)*				
> to 60		0.42 (0.24 to 0.60)*		0.51 (0.40 to 0.62)*				
Weekly exercise volume	3.48 (1), 0.06		1.46 (1), 0.23		0.05 (1), 0.83		0.10 (1), 0.75	
Exercise-related moderators for unsupervised exercise								
Frequency	0.56 (1), 0.46		–		–		1.47 (1), 0.22	
Intensity†− moderate–vigorous and vigorous versus low-moderate and moderate		–		–		–		0.14 (−0.17 to 0.45)†
Type†− AE+RE versus AE		0.12 (−0.23 to 0.47)		–		–		−0.16 (−0.39 to 0.06)
Time of exercise session (min)	0.03 (1), 0.86		–		–		8.86 (1), < to 0.01*	
≤ 30								0.28 (0.13 to 0.42)*
> to 30–60								−0.14 (−0.39 to 0.11)
Weekly exercise volume	–		–		–		1.47 (1), 0.23	

*Statistically significant.

†Interaction testing for a study-level moderator was not possible, and differences between subgroups were tested using dummy variables. Regression coefficients (β difference_in_effect) and 95% CIs are reported, which represent the between group difference in z-scores.

‡Log likelihood ratio not significant after correction for delivery mode ($\chi^2 = 4.35$, p=0.11).

AE, aerobic exercise; LBMS, lower body muscle strength; LBMF, lower body muscle function; RE, resistance exercise; UBMS, upper body muscle strength.

interventions (UBMS $\beta_{difference\_in\_effect}$=0.19, 95% CI 0.05 to 0.34, LBMS $\beta_{difference\_in\_effect}$=0.30, 95% CI 0.12 to 0.48 and aerobic fitness $\beta_{difference\_in\_effect}$=0.23, 95% CI 0.12 to 0.34). Effects of unsupervised exercise interventions on aerobic fitness remained significant but not for UBMS and LBMS. Intervention duration moderated the effect of exercise on aerobic fitness (χ^2=8.47, df=1, p=0.05). There were larger effects for an intervention duration of ≤12 weeks (β=0.38, 95% CI 0.30 to 0.46) than of >24 weeks (β=0.14, 95% CI −0.02 to 0.30). The moderator effect of intervention duration was no longer significant after adjustment for delivery mode (χ^2=4.36, df=1, p=0.11). No other intervention-related characteristics significantly moderated the effects on UBMS, LBMS, LBMF or aerobic fitness.

Exercise-related moderators for supervised exercise

Exercise frequency significantly moderated the effects of supervised exercise interventions on UBMS (χ^2=17.11, df=1, p<0.001). There were larger effects for an exercise frequency of ≥3 times/week (β=0.49, 95% CI 0.28 to 0.70) than <3 times/week (β=0.16, 95% CI 0.11 to 0.22; table 3). There were larger effects for supervised exercise interventions including RE on UBMS and LBMS than exercise without RE (table 3). There were larger effects for supervised exercise interventions including RE on UBMS than a combination of AE+RE ($\beta_{difference\_in\_effect}$=0.29, 95% CI 0.14 to 0.43), while the effect was significantly smaller for LBMS ($\beta_{difference\_in\_effect}$=−0.13, 95% CI −0.26 to −0.01). There were smaller effects for supervised exercise interventions including RE on aerobic fitness than exercise including an AE component (RE vs AE $\beta_{difference\_in\_effect}$=−0.31, 95% CI −0.49 to −0.13, RE vs AE+RE $\beta_{difference\_in\_effect}$=−0.23, 95% CI −0.42 to −0.03), except for RE+impact vs AE, for which the difference in effect was not statistically significant ($\beta_{difference\_in\_effect}$=−0.21, 95% CI −0.48 to 0.06). Exercise session duration moderated the effects on UBMS (χ^2=14.01, df=2, p<0.01) and LBMS (χ^2=9.07, df=2, p=0.01), with significantly larger effects for a session duration of >60 min (UBMS; β=0.42, 95% CI 0.24 to 0.60, and LBMS; β=0.51, 95% CI 0.40 to 0.62) than a session duration of >30–60 min (UBMS; β=0.16, 95% CI 0.09 to 0.23, and LBMS; β=0.26, 95% CI 0.19 to 0.34 for LBMS). Weekly exercise volume did not moderate the exercise effect for any outcome.

Exercise-related moderators for unsupervised exercise

The effects of unsupervised exercise on aerobic fitness were moderated by session duration (χ^2=8.86, df=1, p<0.01). There were larger effects for a session duration of 0–30 min (β=0.28, 95% CI 0.13 to 0.42) than for a session duration of >30–60 min (β=−0.14, 95% CI −0.39 to 0.11). Weekly exercise volume did not moderate the exercise intervention effect on aerobic fitness. No other exercise characteristics moderated the effects of unsupervised exercise on UBMS, LBMS, LBMF and aerobic fitness.

DISCUSSION

Based on IPD meta-analyses of 28 RCTs, there were small effects of exercise interventions on UBMS, LBMS, LBMF and aerobic fitness in patients with cancer. The effect on physical fitness was moderated by age, marital status, intervention timing, delivery mode, exercise frequency, type and time, with differences in moderator effects between the different physical fitness outcomes. Effects of exercise interventions in subgroups of patients with different demographic and clinical characteristics or studies with different intervention-related or exercise-related characteristics were small to moderate.

The beneficial effects on UBMS and LBMS correspond to the results reported in a previous systematic review[65] but are smaller than reported in a previous aggregate meta-analysis.[5] One explanation could be that we included more recent studies in our analysis. Another could be that the previous aggregate meta-analysis selected only high-quality RCTs based on the validity criteria from the Amsterdam-Maastricht Consensus List for Quality Assessment. Using this tool, studies with five or more internal validity characteristics were classified as high-quality RCTs. In our meta-analysis, we included all studies as the Cochrane risk of bias tool used in this study does not provide a cut-off for high-quality RCTs. In addition, the effects might be influenced by the methods used to measure muscle strength, as we found statistically significant beneficial effects on 1RM chest press but not on grip strength. This indicates that grip strength—despite being often used as indicator of UBMS—may not be reflective of changes in UBMS as strength of the finger flexor muscles do not reflect general UBMS. The resistance training interventions of the included studies do not list specific training of these muscle groups, and absence of change is not unexpected. Finally, variation in the protocol used to measure grip strength could affect the results.[66]

Demographic and clinical moderators

The exercise intervention effects on LBMS were larger for patients who were unmarried or living alone than for those who were married. These results correspond to previous findings of single RCTs.[8 27 52] Patients who are unmarried or living alone may benefit more from supervised or guided exercise because they may have a higher adherence to the exercise programme because of less time constraints than married patients with children.[27] However, being unmarried does not necessarily reflect household composition, and results were not consistent for all outcomes.

Our finding that exercise interventions were more effective in improving aerobic fitness of younger patients confirms the results reported in a single RCT.[27] This could be explained by higher exercise adherence in younger patients[67 68] or inadequate training regimes targeting aerobic fitness in older adults.[69] For example, older adults experienced larger improvements in aerobic fitness from high-intensity interval training than moderate-intensity continuous training.[69] However, a systematic review investigating determinants of exercise adherence in patients with cancer reported inconsistent findings for age,[70] and supervised exercise interventions during and following cancer treatment can improve muscle strength and aerobic fitness in older patients with prostate or breast cancer.[33 38 71 72]

Intervention-related moderators

Our finding that exercise intervention effects on UBMS were larger during than after treatment has not been reported in previous studies. The moderator effect remained significant after adjusting for intervention delivery mode and methods used to measure UBMS did not differ between studies during or following cancer treatment. Upper extremities may be particularly susceptible to a decrease in muscle strength due to physical inactivity during treatment. Thus, offering exercise intervention during treatment may be particularly important for maintaining UBMS.[73 74] In contrast, daily activities, such as walking and cycling, may attenuate the decrease in LBMS, LBMF and aerobic fitness during treatment, which could

explain why the timing of the intervention did not moderate the effect on these outcomes.

Our finding that supervised exercise interventions had larger effects on UBMS, LBMS and aerobic fitness than unsupervised exercise interventions is in line with previous IPD and aggregate meta-analyses investigating the exercise effects on self-reported QoL and self-reported physical function.[29 75] The larger effects of supervised exercise may have resulted from better session attendance and guidance from a physiotherapist or exercise specialist, access to better training facilities, higher fidelity of patient exercise monitoring or better adherence to the prescribed exercise programme.[70] The delivery mode did not moderate the effects on LBMF. However, this finding was based on one study, with a large CI around the effect. Furthermore, the methods used to measure LBMF may not be sensitive enough to detect change over time[76] or may be vulnerable to ceiling effects.[77]

Exercise-related moderators

The exercise intervention effects on physical fitness were significantly moderated by different exercise FITT-factors. When aiming to improve UBMS, the ideal frequency of supervised exercise interventions appears to be at least three times per week. The significantly larger exercise effects of 0–30 min of exercise per session than >30–60 min per session on UBMS was unexpected and most likely resulted from the specific combinations of exercise FITT-factors rather than session duration alone. We found no moderator effect of weekly exercise volume on UBMS. This confirms the results of a single RCT in patients during chemotherapy treatment for breast cancer,[78] where no difference in effect on UBMS was reported between a dose of three times 25–30 min/week of AE and three times 50–60 min/week of AE. However, these results should be interpreted with caution given the exercise intervention focused on AE, which is expected to provide minimal strength adaptation. Only one study included in our analysis prescribed a session duration of >60 min, which was a RE-only study.[34] This makes it difficult to disentangle whether differences in effect result from differences in exercise type or session duration.

There were larger beneficial effects of exercise on UBMS and LBMS of exercise interventions that included an RE component and larger beneficial effects on aerobic fitness of exercise interventions that included an AE component. This confirms previous findings from a single RCT in patients with breast cancer[8] and corresponds to the aim of the specific exercise intervention. Therefore, general training principles can be applied with patients with cancer. Most importantly, exercise prescriptions must be tailored to maximise training effects.[79 80]

We found that the effect of unsupervised exercise on aerobic fitness was moderated by session duration, but weekly exercise volume did not moderate the effects on aerobic fitness. Our findings for unsupervised exercise should be interpreted with caution due to the small number of studies investigating the effect of an unsupervised exercise intervention on UBMS, LBMS, LBF and aerobic fitness. The difference in effect on aerobic fitness for studies with different session duration could be explained by specific combinations of intervention-related or exercise-related characteristics.

Because FITT-factors are defined at the study level, there may be less variation in these variables, and the power to detect moderator effects is smaller than for variables at the patient level.[81] To further disentangle the effects of different intervention-related or exercise-related characteristics, it is necessary to conduct second-generation studies that directly compare different exercise-related characteristics focusing on one FITT-factor while keeping others similar.[8 24 71]

Study limitations and strengths

A limitation of this IPD meta-analysis is that the literature search was conducted in 2012, focused on QoL outcomes, and only articles published in English, German or Dutch were included. Therefore, we may not have included all recent RCTs evaluating physical fitness.[29] However, we also prepared for including data from studies to be published in the years after 2012 by identifying protocol papers describing such ongoing trials and approaching the principal investigators from these studies to discuss transfer of data as soon as possible after completion of data collection. This resulted in further inclusion of data from 12 studies published up to 2017 (48% of included studies were published between 2013 and 2017). The focus on moderators of the exercise effect on physical fitness is novel, and these results are less likely to be influenced by recent studies currently not included in the IPD meta-analysis.

There were significantly larger effects on UBMS and aerobic fitness in studies where the outcome assessor was not blinded. However, intervention characteristics differed across studies judged as being at high risk for detection bias. Therefore, we expect this influence to be minimal on our results regarding moderator effects of study level characteristics.

We did not investigate the moderator effect of combinations of anticancer treatments of the exercise effect on UBMS, LBMS, LBMF or aerobic fitness because treatment is highly correlated with cancer type. Future research should investigate the moderator effect of different anticancer treatments in more homogeneous groups of patients. Strengths of the current IPD meta-analysis are the large number of included RCTs and patients, allowing the testing of moderator effects,

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What is already known?

► Previous randomised controlled trials and meta-analyses have reported beneficial effects of exercise on physical fitness in patients with cancer.
► Maintaining and improving upper and lower body muscle strength, lower body muscle function and aerobic fitness may be important during and following cancer treatment for functional independence and to improve quality of life and potentially survival.

What are the new findings?

► We found statistically significant small effects of exercise interventions on upper and lower body muscle strength, lower body muscle function and aerobic fitness in patients with cancer, with significantly higher effects on upper and lower body muscle strength and aerobic fitness for supervised exercise interventions compared with unsupervised exercise interventions.
► The effects on upper and lower body muscle strength, lower body muscle function and aerobic fitness were moderated by age, marital status, intervention timing, delivery mode, exercise frequency, type and time, with differences in moderator effects between the different physical fitness outcomes.

using uniform analytic procedures across all RCTs. In addition, the POLARIS database is, to date, the most comprehensive IPD dataset with exercise oncology RCTs.

CONCLUSION

Exercise interventions, particularly those with a supervised component, had beneficial effects on UBMS, LBMS, LBMF and aerobic fitness in patients with cancer with different demographic and clinical characteristics, both during and following treatment. Exercise intervention effects on aerobic fitness were larger for younger patients, and the effects on LBMS were larger for patients who are unmarried or living alone. Exercise intervention effects on UBMS were larger during than after treatment and for supervised exercise with ≥3 versus less sessions per week.

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