Effects and moderators of exercise on quality of life and physical function in patients with cancer

Cancer Treatment Reviews 52 (2017) 91–104

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Systematic or Meta-analysis Studies

Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs

Laurien M. Buffart [a,b,*], Joeri Kalter [a], Maike G. Sweegers [a], Kerry S. Courneya [c], Robert U. Newton [d], Neil K. Aaronson [e], Paul B. Jacobsen [f], Anne M. May [g], Daniel A. Galvão [d], Mai J. Chinapaw [h], Karen Steindorf [i], Melinda L. Irwin [j], Martijn M. Stuiver [k], Sandi Hayes [l], Kathleen A. Griffith [m], Alejandro Lucia [n], Ilse Mesters [o], Ellen van Weert [p], Hans Knoop [q], Martine M. Goedendorp [r], Nanette Mutrie [s], Amanda J. Daley [t], Alex McConnachie [u], Martin Bohus [v,w], Lene Thorsen [x], Karl-Heinz Schulz [y], Camille E. Short [z], Erica L. James [aa], Ron C. Plotnikoff [ab], Gill Arbane [ac], Martina E. Schmidt [i], Karin Potthoff [ad,ae], Marc van Beurden [af], Hester S. Oldenburg [af], Gabe S. Sonke [af], Wim H. van Harten [e,ag], Rachel Garrod [ah], Kathryn H. Schmitz [ai], Kerri M. Winters-Stone [aj], Miranda J. Velthuis [ak], Dennis R. Taaffe [d], Willem van Mechelen [h], Marie-José Kersten [al], Frans Nollet [am], Jennifer Wenzel [an], Joachim Wiskemann [ac], Irma M. Verdonck-de Leeuw [ao,ap], Johannes Brug [a,aq]

[a] Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands
[c] Faculty of Physical Education and Recreation, University of Alberta, Edmonton, Canada
[d] Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia
[e] Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[f] Division of Population Science, Moffitt Cancer Center and Research Institute, Tampa, FL, USA
[g] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[h] Department of Public and Occupational Health, VU University Medical Center, Amsterdam, The Netherlands
[i] Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Disease (NCT), Heidelberg, Germany
[j] Yale School of Public Health, New Haven, USA
[k] Department of Physiotherapy, Netherlands Cancer Institute, Amsterdam, The Netherlands
[l] School of Public Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, QLD, Australia
[m] School of Nursing, University of Maryland, Baltimore, USA
[n] European University, Madrid, Spain
[o] Department of Epidemiology, Maastricht University, The Netherlands
[p] University Medical Centre Groningen, University of Groningen, Center for Rehabilitation, Groningen, The Netherlands
[q] Department of Medical Psychology, Academic Medical Center, Amsterdam, The Netherlands
[r] Department of Health Psychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[s] Physical Activity for Health Research Center, University of Edinburgh, Edinburgh, UK
[t] Primary Care Clinical Sciences, School of Health and Population Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
[u] Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[v] Institute of Psychiatric and Psychosomatic Psychotherapy, Central Institute of Mental Health, Heidelberg University, Mannheim, Germany
[w] Faculty of Health, University of Antwerp, Belgium
[x] National Advisory Unit on Late Effects after Cancer, Department of Oncology, Oslo University Hospital, Oslo, Norway
[y] Athleticum – Competence Center for Sports- and Exercise Medicine and Institute for Medical Psychology, University Medical Center Hamburg-Eppendorf, Germany
[z] Freemasons Foundation Centre of Men's Health, School of Medicine, University of Adelaide, SA, Australia
[aa] School of Medicine & Public Health, the University of Newcastle, Callaghan, NSW, Australia
[ab] Priority Research Centre for Physical Activity and Nutrition, the University of Newcastle, Callaghan, NSW, Australia
[ac] Lane Fox Respiratory Research Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
[ad] Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Heidelberg, Germany
[ae] Department of Radiation Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Heidelberg, Germany
[af] Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[ag] University of Twente, Enschede, The Netherlands
[ah] Department of Respiratory Medicine, Kings College London, London, UK
[ai] Penn State Health, College of Medicine, and Cancer Institute, Hershey, PA, USA
[aj] Oregon Health & Science University, Portland, USA
[ak] Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands
[al] Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands
[am] Department of Rehabilitation Medicine, Academic Medical Center, Amsterdam, The Netherlands
[an] Johns Hopkins School of Nursing, Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, USA

http://dx.doi.org/10.1016/j.ctrv.2016.11.010
0305-7372/

[ao] Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands
[ap] Department of Clinical Psychology, Vrije Universiteit Amsterdam, The Netherlands
[aq] Amsterdam School of Communication Research (ASCoR), University of Amsterdam, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 7 October 2016
Received in revised form 24 November 2016
Accepted 25 November 2016

Keywords:
Exercise
Quality of life
Physical function
Neoplasm
Individual patient data meta-analysis

ABSTRACT

This individual patient data meta-analysis aimed to evaluate the effects of exercise on quality of life (QoL) and physical function (PF) in patients with cancer, and to identify moderator effects of demographic (age, sex, marital status, education), clinical (body mass index, cancer type, presence of metastasis), intervention-related (intervention timing, delivery mode and duration, and type of control group), and exercise-related (exercise frequency, intensity, type, time) characteristics.

Relevant published and unpublished studies were identified in September 2012 via PubMed, EMBASE, PsycINFO, and CINAHL, reference checking and personal communications. Principle investigators of all 69 eligible trials were requested to share IPD from their study. IPD from 34 randomised controlled trials (n = 4519 patients) that evaluated the effects of exercise compared to a usual care, wait-list or attention control group on QoL and PF in adult patients with cancer were retrieved and pooled. Linear mixed-effect models were used to evaluate the effects of the exercise on post-intervention outcome values (z-score) adjusting for baseline values. Moderator effects were studies by testing interactions.

Exercise significantly improved QoL (β = 0.15, 95%CI = 0.10;0.20) and PF (β = 0.18, 95%CI = 0.13;0.23). The effects were not moderated by demographic, clinical or exercise characteristics. Effects on QoL ($\beta_{difference\_in\_effect}$ = 0.13, 95%CI = 0.03;0.22) and PF ($\beta_{difference\_in\_effect}$ = 0.10, 95%CI = 0.01;0.20) were significantly larger for supervised than unsupervised interventions.

In conclusion, exercise, and particularly supervised exercise, effectively improves QoL and PF in patients with cancer with different demographic and clinical characteristics during and following treatment. Although effect sizes are small, there is consistent empirical evidence to support implementation of exercise as part of cancer care.

Introduction

As a consequence of the increased number of cancer diagnoses, and concomitant mortality reductions for most types of cancer [1–3], many patients live with physical and psychosocial problems associated with the disease and its treatment that may compromise their quality of life (QoL). Exercise has been recommended as part of standard care for patients with cancer to help prevent and manage physical and psychosocial problems, and improve QoL [4,5].

Previous meta-analyses of randomised controlled trials (RCT) reported benefits of exercise during and following cancer treatment [6]. Benefits include improved physical fitness, function, and quality of life (QoL), and reduced fatigue, and depression [6–9]. However, average reported effect sizes on these outcomes were small to moderate.

To maximize benefits of exercise, it is important to target subgroups of patients that respond best to a particular intervention [10]. A number of RCTs showed that demographic, clinical, and personal factors, such as age, marital status, disease stage and type of treatment, moderate the effects of exercise in patients with cancer [11–15]. However, these single studies are generally underpowered to analyse moderators of intervention effects and conduct subsequent stratified analysis. Meta-analyses based on aggregate data are limited to using summary data, such as the mean age of the patients or the proportion of men in a study, and they are unable to investigate intervention-covariate interactions at the level of the patient [16,17].

Optimizing benefits of exercise also requires a better understanding of important intervention-related characteristics, including the timing and mode of intervention delivery, intervention duration, and exercise dimensions, in terms of frequency, intensity, type and time (FITT factors).

Meta-analyses of raw individual patient data (IPD) are suggested as the preferred method to evaluate moderators of intervention effects, since the large number of raw data points facilitates testing of interactions at the patient level, conducting subsequent stratified analyses, and standardizing analytic techniques across the included studies [18,19]. In the current IPD meta-analysis we used data collected in the Predicting OptimaL Cancer RehabIlitation and Supportive care (POLARIS) study [20]. The aims were to evaluate the effects of exercise on QoL and physical function (PF) in patients with cancer, and to identify demographic, clinical, intervention-, and exercise-related moderators of intervention effects.

* Corresponding author at: VU University Medical Center, Departments of Epidemiology and Biostatistics and Medical Oncology, De Boelelaan 1089a, 1081 HV Amsterdam, The Netherlands.

E-mail addresses: l.buffart@vumc.nl (L.M. Buffart), j.kalter@vumc.nl (J. Kalter), m.sweegers@vumc.nl (M.G. Sweegers), kerry.courneya@ualberta.ca (K.S. Courneya), r.newton@ecu.edu.au (R.U. Newton), n.aaronson@nki.nl (N.K. Aaronson), Paul.Jacobsen@moffitt.org (P.B. Jacobsen), a.m.may@umcutrecht.nl (A.M. May), d.galvao@ecu.edu.au (D.A. Galvão), m.chinapaw@vumc.nl (M.J. Chinapaw), k.steindorf@dkfz-heidelberg.de (K. Steindorf), melinda.irwin@yale.edu (M.L. Irwin), m.stuiver@nki.nl (M.M. Stuiver), sc.hayes@qut.edu.au (S. Hayes), Griffith@son.umaryland.edu (K.A. Griffith), alejandro.lucia@uem.es (A. Lucia), ilse.mesters@maastrichtuniversity.nl (I. Mesters), e.van.weert@rev.umcg.nl (E. van Weert), hans.knoop@amc.uva.nl (H. Knoop), m.m.goedendorp@med.umcg.nl (M.M. Goedendorp), nanette.mutrie@ed.ac.uk (N. Mutrie), a.daley@bham.ac.uk (A.J. Daley), alex.mcconnachie@glasgow.ac.uk (A. McConnachie), martin.bohus@zi-mannheim.de (M. Bohus), LKA@ous-hf.no (L. Thorsen), khschulz@uke.uni-hamburg.de (K.-H. Schulz), camille.short@adelaide.edu.au (C.E. Short), erica.james@newcastle.edu.au (E.L. James), erica.james@newcastle.edu.au (R.C. James), erica.james@newcastle.edu.au (R.C. James), erica.james@newcastle.edu.au (R.C. James), erica.james@newcastle.edu.au (R.C. James), ron.plotnikoff@newcastle.edu.au (R.C. Plotnikoff), Gill.Arbane@gstt.nhs.uk (G. Arbane), m.schmidt@dkfz.de (M.E. Schmidt), karin_potthoff@gmx.de (K. Potthoff), m.v.beurden@nki.nlm (M. van Beurden), h.oldenburg@nki.nl (H.S. Oldenburg), g.sonke@nki.nl (G.S. Sonke), w.v.harten@nki.nl (W.H. van Harten), rachelgarrod1@gmail.com (R. Garrod), kschmitz@phs.psu.edu (K.H. Schmitz), wintersk@ohsu.edu (Kerri M. Winters-Stone), M.Velthuis@iknl.nl (M.J. Velthuis), d.taaffe@ecu.edu.au (D.R. Taaffe), w.vanmechelen@vumc.nl (W. van Mechelen), m.j.kersten@amc.uva.nl (M.-J. Kersten), f.nollet@amc.uva.nl (F. Nollet), jwenzel@jhu.edu (J. Wenzel), joachim.wiskemann@nct-heidelberg.de (J. Wiskemann), im.verdonck@vumc.nl (I.M. Verdonck-de Leeuw), j.brug@uva.n.

Methods

The conduct and reporting of this IPD meta-analysis is based on the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement [21].

Identification and inclusion of studies

Detailed descriptions of the design and procedures of the POLARIS study were published previously [20]. In short, relevant published and unpublished studies (e.g. study protocol papers) were identified in September 2012 via systematic searches in four electronic databases (PubMed, EMBASE, PsycINFO, and CINAHL), reference checking of systematic reviews, meta-analyses, and personal communication with collaborators, colleagues, and other experts in the field [20]. POLARIS included RCTs that evaluated the effects of exercise interventions and/or psychosocial interventions on QoL compared to a wait-list, usual care or attention control group in adult patients with cancer. We excluded studies focusing on spiritual or existential therapy, yoga, and diet or multimodal lifestyle interventions. The study protocol was registered in PROSPERO in February 2013 (CRD42013003805) [20].

A letter of invitation to join the POLARIS consortium and share data was sent to the principal investigator (PI) of eligible RCTs. In case of no response, we sent reminders or contacted another PI. In case the study was not yet published, we maintained contact about the study completion date, to allow inclusion at a later stage during the data collection process of approximately 3 years. After PI's expressed interest in data sharing, they were requested to sign a data sharing agreement stating that they agreed with the POLARIS policy document, and were willing to share and transform anonymised data of study participants who were randomised. Data could be sent in various formats, were re-coded according to standardised protocols, and were checked for completeness, improbable values, consistency with published articles, and missing items. Subsequently, datasets were imported into the POLARIS database where they were harmonized [20].

Data extraction and quality assessment

Two independent researchers (LB and MS) extracted study characteristics and rated the quality of included studies from published papers, using the 'risk-of-bias' assessment tool of the Cochrane Collaboration. The quality of following aspects was graded as high ('+'), low ('−') or unclear ('?') quality: random sequence generation (high quality if random component was used), allocation concealment (high quality if central, computerized allocation or sequentially numbered sealed envelopes were used), incomplete outcome (high quality if intention-to-treat analyses were performed and missing outcome data were <10% or adequate imputation techniques were used), and incomplete reporting (high quality if QoL or PF was reported such that data could be entered in an aggregate data meta-analysis). We also included ratings of adherence (high quality if $\geqslant$80% of patients had high attendance, defined as $\geqslant$80% of sessions attended [22,23]) and contamination (high quality if no or limited exercise was present in the control group, i.e. moderate to vigorous exercise was present in <25% of patients or increased less than 60 min [24]). Items related to blinding were omitted because blinding of patients and personnel is difficult in the case of exercise interventions, and QoL and PF were assessed using patient-reported outcomes. Quality assessments of both reviewers were compared and disagreements in the scores were resolved by discussion.

Representativeness of included studies

To examine whether the included RCTs were a representative sample of all eligible RCTs, we compared pooled effect sizes of RCTs included versus those not included. Effect sizes per RCT were calculated by subtracting the published average post-intervention value of QoL or PF of the control group from that of the intervention group, and dividing the result by the pooled standard deviation. We corrected effect sizes for small samples as suggested by Hedges and Olkin. Effect sizes (Hedges' g) were pooled with a random effects model and differences in effects between studies providing data and those that did not were examined using Comprehensive Meta-analysis software (version 2.2.064).

We evaluated publication bias for all eligible studies and for studies providing data by inspecting the funnel plot and by the Duval and Tweedie's trim and fill procedure [25,26]. The procedure provides estimates of the number of missing studies and the effect size after the publication bias has been taken into account. The Egger's test was used to test whether the bias captured by the funnel plot was significant.

Outcome variables

QoL and PF were assessed with patient reported outcomes (PRO, Table 1). In the present paper, we used baseline (pre-intervention) and post-intervention values. To allow pooling of the different PROs, we recoded the individual scores into *z*-scores by subtracting the individual score from the mean score at baseline, and dividing the result by the mean standard deviation at baseline. Subsequently, the pooled *z*-scores were used for further analyses. If studies used both a cancer-specific and a generic QoL PRO, data from the cancer-specific PRO were used.

Possible moderators

Potential demographic and clinical moderators were identified from single studies that reported on the moderating effects with some inconsistent findings [11–14,27].

Potential demographic moderators included baseline age, sex, marital status, and education level. Marital status was dichotomised into single versus married or living with partner. As a consequence of different coding schemes of the original RCTs, education level was dichotomised into low-medium (elementary, primary, or secondary school, lower or secondary vocational education) or high (higher vocational, college, or university education). Potential clinical moderators included body mass index (BMI), type of cancer, the presence of distant metastases, and type of treatment. BMI was categorised into underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–<30 kg/m^2) and obese ($\geqslant$30 kg/m^2) according to the World Health Organization. The type of cancer was categorised into breast, male genitourinary, gastrointestinal, haematological, gynaecological, respiratory tract, and other types. Treatment with surgery, chemotherapy, radiotherapy, hormone therapy or stem cell transplantation were each dichotomised into previous or current treatment versus no such treatment. As the majority of men diagnosed with prostate cancer received androgen deprivation therapy, we were unable to study the moderating effects of hormone therapy in prostate cancer.

Timing of intervention delivery in relation to primary cancer treatment was categorised into pre-treatment, during treatment, post-treatment and end-of-life, according to the Physical Activity and Cancer Control (PACC) framework [28]. Because interventions pre-treatment and during end-of-life were not available, we tested differences in intervention effects between those delivered during treatment versus post-treatment. As hormone therapy for breast cancer may continue for five years post-treatment, we considered

Table 1
Descriptives of studies evaluating the effects of exercise on quality of life and physical function included in the database ($n = 34$), in alphabetical order of first author.

Author (year) *Acronym*	Country	N	Age, mean (SD)	Gender (% female)	Cancer type	Intervention			Exercise	Control	Quality						
						Timing	Delivery mode	Duration (weeks)	FITT		PRO	RSG	AC	IO	IR	Adh	Con
Arbane (2011) [52]	UK	51	64.0 (11.0)	48.1	Lung	Post	Unsupervised	12	F: ? I: moderate T: RE + AE T: ?	Usual care	C30	+	+	-	+	?	?
Cadmus, (2009) [53] *IMPACT*	USA	50	54.2 (9.6)	100	Breast	During	Unsupervised	26	F: aim 5x/week I: moderate T: AE T: 30 min	Usual care	FACT	+	+	+	+	-	?
Cormie (2015) [54]	AUS	64	67.9 (7.1)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE + AE T: 60 min	Usual care	C30	+	+	+	+	?	?
Couneya (2003) [55] *CANHOPE*	CAN	93	60.3 (10.4)	41.9	Colorectal	During or post	Unsupervised	16	F: 3-5x/week I: moderate T: AE T: 20–30 min	Wait-list	FACT	+	?	+	+	-	-
Courneya (2003) [56] *RE-HAB*	CAN	52	58.6 (5.7)	100	Breast	Post	Supervised	15	F: 3x/week I: moderate-vigorous T: AE T: 15–35 min	Wait-list	FACT	+	+	+	+	+	+
Courneya (2007) [33] *START*	CAN	242	49.2 (9.3)	100	Breast	During CT	Supervised	Median: 17	F: 3x/week I: moderate-vigorous T: AE vs RE T: AE: 15–45 min	Usual care	FACT	+	+	+	+	-	+
Courneya (2009) [57] *HELP*	CAN	122	53.2 (14.8)	41.0	Haematological	During or post	Supervised	12	F: 3x/week I: moderate-vigorous T: AE T: 15–45 min	Usual care	FACT	+	+	+	+	+	-
Daley (2007) [58]	UK	108	51.1 (8.6)	100	Breast	Post	Supervised	8	F: 3x/week I: moderate-vigorous T: AE T: 50 min	Attention control vs usual care	FACT	+	+	+	+	-	-
Duijts (2012) [31] *EVA*	NL	207	47.8 (5.8)	100	Breast	Post	Unsupervised	12	F: 5x per 2 weeks I: vigorous T: AE T: 45–60 min*	Wait-list	SF-36	+	+	-	+	-	?
Galvão (2010) [59]	AUS	57	69.8 (7.3)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate T: RE + AE T: 60 min	Usual Care	C30	+	+	+	+	?	?
Galvão (2014) [60] *RA-DAR-exercise*	AUS	100	71.7 (6.4)	0	Prostate	Post ADT	Supervised	26	F: 2x/week I: moderate-vigorous T: RE + AE T: 60 min	Usual care with PA brochure	C30	+	+	+	+	-	?
Goedendorp (2010) [32]	NL	144	57.2 (10.5)	63.2	Mixed	During	Home-based	Mean: 31.7	F: towards 5d/week I: ? T: AE T: towards 60 min	Usual care	C30	+	+	+	-	?	?
Griffith (2009) [61]	USA	126	60.2 (10.6)	38.9	Mixed	During CT, RT or both	Home-based	Mean: 12.8	F: 5x/week I: low-moderate T: AE T: 25-35 min	Usual care	SF-36	?	?	+	-	-	-

Hayes (2013) [34] *Exercise for Health*	AUS	194	52.4 (8.5)	100	Breast	During and/or post	Unsupervised	35	F: aim: ⩾ 4x/week I: moderate T: RE + AE T: 20–45 min	Usual care	FACT	+	+	+	+	+	-
Herrero (2006) [62]	Spain	16	?	100	Breast	Post	Supervised	8	F: 3x/week I: moderate-vigorous T: RE + AE T: 90 min	Usual care	C30	?	+	-	-	+	?
Irwin (2009) [63] *YES*	USA	75	55.8 (8.7)	100	Breast	Post	Supervised	26	F: 3 supervised (+ 2 unsupervised) I: moderate T: AE (walking) T: 15–30 min	Usual care	FACT	+	?	-	+	-	+
Kampshoff (2015) [27] *REACT*	NL	277	53.5 (11.0)	80.1	Mixed	Post	Supervised	12	F: 2x/week I: moderate vs vigorous T: RE + AE T: 60 min	Wait-list	C30	+	+	+	+	-	+
Korstjens (2008) [30] *OncoRev*	NL	133	50.6 (10.2)	85	Mixed	Post	Supervised	12	F: 2x/week I: AE: moderate-vigorous, RE: low-moderate T: RE + AE T: 120 min	Wait-list	C30	+	?	+	+	+	?
Mehnert (2011) [64]	GER	58	51.9 (8.5)	100	Breast	Post	Supervised	10	F: 2x/week I: moderate T: AE + gymnastics + movement games + relaxation T: 90 min	Wait-list	SF-36	?	+	+	-	+	?
Mutrie (2007) [65]	UK	201	51.6 (9.5)	100	Breast	During CT and/or RT	Supervised	12	F: 2 supervised (+1 unsupervised) I: low-moderate T: RE + AE T: 45 min	Usual care	FACT	+	+	+	+	?	?
Newton (2009) [66]	AUS	154	69.0 (9.0)	0	Prostate	During ADT	Supervised	24	F: 2x/week I: moderate-vigorous T: RE + AE vs RE + impact T: 60 min	Wait-list	C30	‡					
Ohira (2006) [67] *WTBS*	USA	86	52.7 (8.3)	100	Breast	Post	Supervised	26 (13 super-vised)	F: 2x/week I: ? T: RE T: ?	Wait-list	Cares-SF	+	?	+	+	?	?
Persoon, (2010) [68] *EXIST*	NL	109	52.4 (11.2)	36.7	Haematological	Post SCT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE + AE T: 60 min	Usual care	C30	‡					
Schmidt (2015) [69] *BEATE*	GER	88	52.5 (10.0)	100	Breast	During CT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE T: 60 min	Attention control	C30	+	+	+	+	-	?
Short (2015) [35] *MM4L*	AUS	330	55.9 (8.3)	100	Breast	Post	Unsupervised	16	F: AE: 5x/week; RE: 1-3x/week I: moderate T: RE + AE T: AE: 30 min	Usual care	FACT	+	+	+	+	+	?

(*continued on next page*)

Table 1 (*continued*)

Author (year) *Acronym*	Country	N	Age, mean (SD)	Gender (% female)	Cancer type	Intervention			Exercise	Control	Quality						
						Timing	Delivery mode	Duration (weeks)	FITT		PRO	RSG	AC	IO	IR	Adh	Con
Speck (2010) [70] PAL	USA	295	56.0 (8.8)	100	Breast	Post	Supervised	52 (13 super-vised	F: 2x/week I: ? T: RE T: 90 min	Wait-list	SF-36	+	+	-	+	+	?
Steindorf (2014) [71] *BEST*	GER	141	56.3 (8.9)	100	Breast	During RT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE T: 60 min	Attention control	C30	+	+	+	+	-	?
Thorsen (2005) [72]	NOR	139	39.4 (8.3)	67.1	Mixed	Post	Unsupervised	14	F: 2x/week or more I: moderate-vigorous T: RE + AE T: 30 min or more	Usual care	C30	+	+	+	-	+	-
Travier (2015) [73]; van Vulpen (2015) [74] *PACT*	NL	237	50.7 (8.8)	100	Breast and Colon	During CT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE + AE T: 60 min	Usual care	C30	+	+	+	+	+	?
Van Waart (2015) [37] PACES	NL	253	51.4 (9.5)	95.7	Breast and Colon	During CT	Unsupervised vs supervised	Mean: 15.9	F: supervised: 2x/week; unsupervised towards 5x/week I: supervised: moderate-vigorous Unsupervised: moderate T: supervised: RE + AE; unsupervised: AE T: supervised: 60 min; unsupervised: aim 30 min	Usual care	C30	+	+	+	+	-	?
Winters-Stone (2012) [75]	USA	106	62.2 (6.7)	100	Breast	Post	Supervised	52	F: 2x/week supervised (+ 1x/week unsupervised) I: moderate-vigorous T: RE + impact T: 60 min	Attention control	SF-36	+	+	+	+	+	+
Winters-Stone (2013) [76]	USA	71	46.4 (4.9)	100	Breast	Post	Supervised	52	F: 2x/week supervised + 1x/week unsupervised I: moderate T: RE + impact T: 60 min	Attention control	SF-36	+	+	+	-	-	+
Winters-Stone (2015) [77]	USA	51	70.1 (8.6)	0	Prostate	During ADT	Supervised	52	F: 2x/wk supervised (+1x/week unsupervised) I: moderate T: RE + impact T: 60 min	Attention control	C30	?	?	+	+	+	+
Wiskemann (2011) [78]	GER	80	48.4 (14.4)	31.3	Haematological	Pre-during-post	Supervised	Median exercise: 16.4 Control: 15.7	F: 5x/week I: moderate-vigorous T: RE + AE T: AE: 20–40 min	Attention control	C30	+	+	-	+	+	?

* Personal communication with authors.

‡ quality rating could not be performed because papers are not yet published. ADT = androgen deprivation therapy; AE = Aerobic exercise training; CARES-SF = cancer rehabilitation evaluation system short form; C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; CT = chemotherapy; FACT = Functional Assessment of Cancer Therapy; PRO = patient reported outcome; RE = Resistance exercise training; RT = radiotherapy; SF36 = Short Form-36 Item Health Survey. *Quality assessment*: + = high quality; – = low quality; ? = unclear quality; RSG = random sequence generation; AC = allocation concealment; IO = incomplete outcome; IR = incomplete reporting; Adh = adherence; Con = contamination.

women on hormone therapy who completed other primary cancer treatments as being post-treatment. Men receiving androgen deprivation therapy for prostate cancer were considered as being during treatment. Delivery mode of intervention was dichotomized into supervised (in case (part of) the weekly exercise sessions were conducted under supervision) versus unsupervised (in case exercise sessions were performed unsupervised from or at home). Intervention duration was categorised based on tertiles (⩽12 weeks; >12–24 weeks; >24 weeks). Exercise frequency was dichotomised based on the median, into ⩽2 versus >2 supervised sessions per week for supervised exercise and into <5 versus ⩾5 sessions per week for unsupervised exercise. Exercise intensity was categorised from low to high intensity using the definitions of the American College of Sports Medicine [29]. Exercise type was categorised into aerobic, resistance, combined aerobic and resistance and combined resistance and impact loading (e.g. skipping, jumping) exercise. Exercise time per session was categorised into ⩽30 min, >30–60 min and >60 min.

Statistical analysis

We conducted one-step IPD meta-analyses to study the effects and moderators of exercise on QoL and PF. The effects were evaluated by regressing the intervention on the post-intervention value (*z*-score) of the outcome adjusted for the baseline value (*z*-score) using linear mixed model analyses with a two-level structure (1: patient; 2: study) to take into account the clustering of patients within studies by using a random intercept on study level. Moderators of exercise effects were examined by adding the moderator and its interaction term with the intervention into the regression model, for each moderator separately. To reduce ecological bias for patient-level interactions, we separated within-trial interaction from between-trial interaction by centring the individual value of the covariate around the mean study value of that covariate [19]. If interaction terms were significant ($p < 0.05$), stratified analyses were performed. In case a RCT had three study arms with different study-level moderators across study arms, interaction testing for a study-level moderator was not possible. Therefore, in those situations, we tested differences between subgroups using dummy variables. Regression coefficients and 95% confidence intervals (CI) were reported, which represent the between group difference in *z*-scores of QoL and PF, and correspond to a Cohen's d effect size. Effects of 0.2 were considered small, 0.50 as moderate and at or above 0.8 as large.

Since the majority of patients were women with breast cancer, we performed a sensitivity analysis to check robustness of findings in the subgroup of patients that were not women with breast cancer, despite non-significant overall interaction effects for women with breast cancer vs other ($\beta = 0.09$, 95%CI = −0.12; 0.29 for QoL; $\beta = -0.06$, 95%CI = −0.27;0.14 for PF). Statistical analyses were performed using SPSS 22.0 and R Studio.

Results

Characteristics of studies and patients

Of the 136 RCTs that met the inclusion criteria (Fig. 1), 66 evaluated the effects of exercise and three [30–32] evaluated the effects of a combined exercise and psychosocial intervention and also included a third arm with exercise only. Principal investigators of 34 of these 69 RCTs (response 49%) shared IPD. In total, 27 RCTs reported adequate random sequence generation, 26 studies

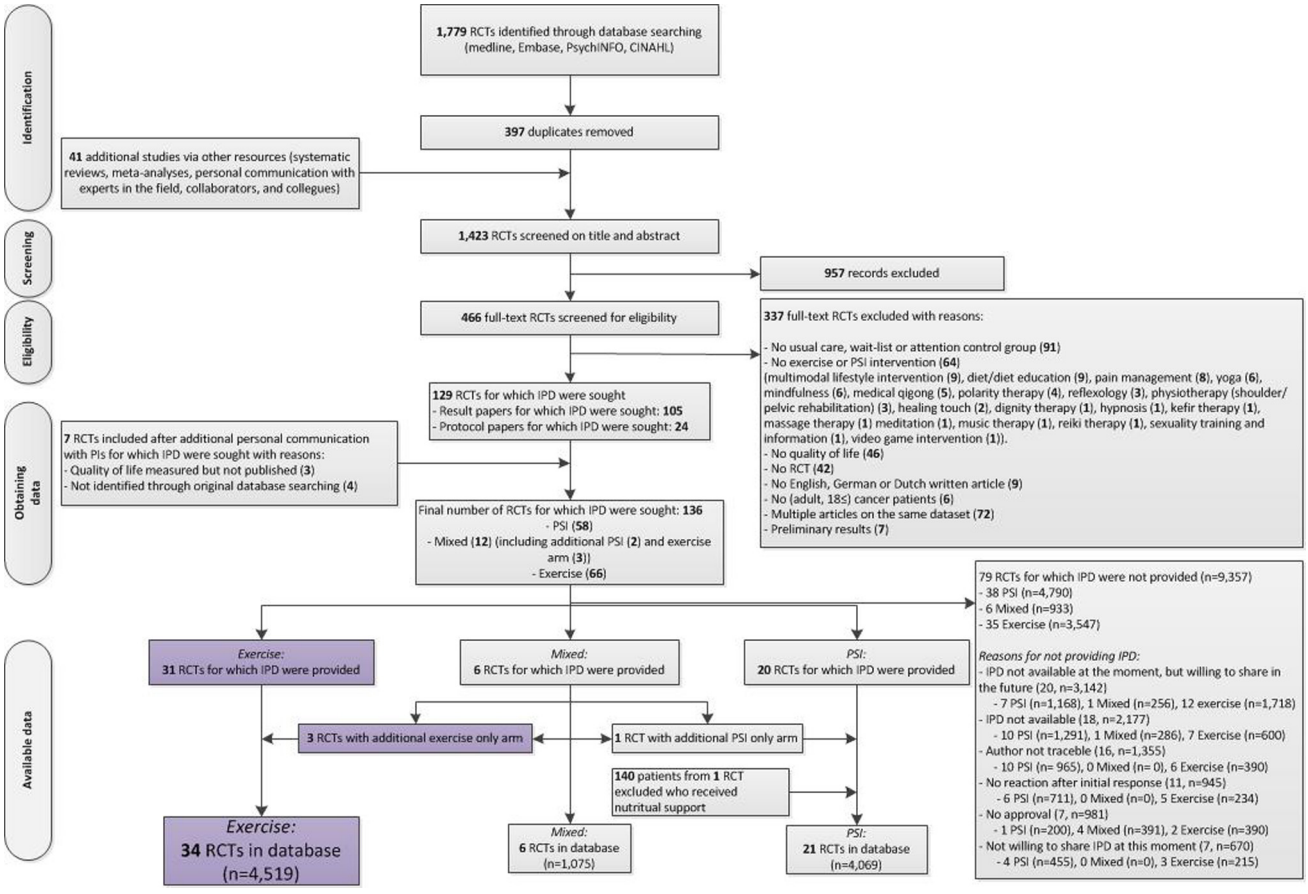

Fig. 1. Flow chart of study inclusion IPD = individual patient data; PSI = psychosocial interventions; RCT = randomised controlled trial.

reported adequate allocation concealment, 26 RCTs had adequate completeness of outcome data, and 26 RCTs had complete outcome reporting (Table 1). Intervention adherence was reported in 26 RCTs, and was of high quality in 13 RCTs, and 7 of the 13 RCTs that

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

	Exercise (n = 2514)	Control (n = 2005)
Demographic		
Age, mean (SD) years	54.6 (11.5)	54.5 (11.2)
Age categories, n (%)		
<50 years	850 (33.8)	663 (33.1)
50–70 years	1405 (55.9)	1143 (57.0)
⩾70 years	249 (9.9)	185 (9.2)
Unknown	10 (0.4)	14 (0.7)
Sex, n (%)		
Men	553 (22.0)	438 (21.8)
Women	1961 (78.0)	1567 (78.2)
Married/living with partner, n (%)		
Yes	1587 (63.1)	1209 (60.3)
No	442 (17.6)	389 (19.4)
Unknown	485 (19.3)	407 (20.3)
Education level, n (%)		
Low/middle	1095 (43.6)	857 (42.7)
High	1018 (40.5)	728 (36.3)
Unknown	401 (16.0)	420 (20.9)
Clinical		
BMI, mean (SD) kg/m^2	27.1 (5.1)	27.2 (5.3)
BMI categories, n (%)		
Underweight (BMI <18.5 kg/m^2)	18 (0.7)	23 (1.1)
Normal weight (BMI 18.5 to <25 kg/m^2)	859 (34.2)	651 (32.5)
Overweight (BMI 25 to <30 kg/m^2)	827 (32.9)	639 (31.9)
Obese (BMI ⩾ 30 kg/m^2)	551 (21.9)	450 (22.4)
Unknown	259 (10.3)	242 (12.1)
Cancer type, n (%)		
Breast	1757 (69.9)	1406 (70.1)
Male genitourinary	326 (13.0)	248 (12.4)
Haematological	199 (7.9)	195 (9.7)
Gastrointestinal	146 (5.8)	87 (4.3)
Gynaecological	44 (1.8)	33 (1.6)
Respiratory track	28 (1.1)	29 (1.4)
Other	14 (0.6)	7 (0.3)
Distant metastasis at baseline, n (%)[a]		
No	2241 (96.8)	1762 (97.3)
Yes	47 (2.0)	33 (1.8)
Unknown	27 (1.2)	15 (0.8)
Surgery, n (%) yes[b]		
No	299 (12.4)	242 (12.7)
Yes	1989 (82.3)	1552 (81.3)
Unknown	130 (5.4)	114 (6.0)
Chemotherapy, n (%)		
No	692 (27.5)	562 (28.0)
Prior to intervention	988 (39.3)	866 (43.2)
During intervention	761 (30.3)	513 (25.6)
Unknown	73 (2.9)	64 (3.2)
Radiotherapy, n (%)		
No	1030 (41.0)	760 (37.9)
Prior to intervention	1037 (41.2)	877 (43.7)
During intervention	364 (14.5)	314 (15.7)
Unknown	83 (3.3)	54 (2.7)
Hormone therapy		
Breast cancer (n = 3163), n (%)		
No	860 (48.9)	671 (47.7)
Yes	631 (35.9)	481 (34.2)
Unknown	266 (15.1)	254 (18.1)
Prostate cancer (n = 536), n (%)		
No	16 (5.2)	11 (4.8)
Prior to intervention	50 (16.2)	50 (21.9)
During intervention	204 (66.2)	135 (59.2)
Unknown	38 (12.3)	32 (14.0)
SCT, n (%)[c]		
Allogeneic	42 (43.7)	42 (43.3)
Autologous	54 (56.3)	55 (56.7)
Intervention-related[d]		
Timing of intervention, n (%)		
Pre-during-post treatment	80 (1.8)	
During treatment	2122 (47.0)	
Post treatment	2314 (51.2)	
Mode of intervention delivery, n (%)		
(partly) Supervised	1643 (65.4)	
Unsupervised	871 (34.6)	
Duration of intervention, n (%)		
⩽12 weeks	822 (32.7)	
12–24 weeks	683 (27.2)	
>24 weeks	741 (29.5)	
Unknown[e]	268 (10.7)	
Exercise frequency, n (%)		
2 times per week	1349 (53.7)	
3 times per week	323 (12.8)	
4 times per week	203 (8.1)	
⩾5 times per week	509 (20.2)	
Unknown	130 (5.2)	
Exercise Intensity, n (%)		
Low	0 (0)	
Low-moderate	167 (6.6)	
Moderate	884 (35.2)	
Moderate-vigorous	1005 (40.0)	
High	195 (7.8)	
Unknown	263 (10.5)	
Exercise type, n (%)		
AE	686 (27.3)	
RE	385 (15.3)	
AE + RE	1270 (50.5)	
RE + Impact training	173 (6.9)	
Exercise session duration, n (%)		
⩽30 min	928 (36.9)	
>30–60 min	1260 (50.1)	
>60 min	257 (10.2)	
Unknown	69 (2.7)	
Type of control group, n (%)[f]		
Usual care control	1265 (63.1)	
Wait list control	435 (21.7)	
Attention control	305 (15.2)	

Baseline values[g]	Intervention (n = 2514)		Control (n = 2005)	
	pre Mean (SD)	post Mean (SD)	pre Mean (SD)	post Mean (SD)
QoL, mean (SD)				
FACT-G, total score	81.3 (13.6)	85.6 (13.4)	82.2 (14.9)	84.3 (14.9)
EORTC QLQ-C30, subscale global QoL	70.4 (18.4)	73.2 (18.5)	68.8 (19.6)	69.0 (19.9)
CARES-SF, subscale global QoL	47.2 (9.3)	43.6 (9.0)	48.5 (9.1)	46.8 (9.5)
SF-36, subscale general health	66.4 (19.0)	69.5 (18.2)	66.6 (19.2)	68.3 (19.4)
PF, mean (SD)				
FACT-G, subscale PWB	21.9 (5.3)	23.7 (4.2)	22.2 (5.4)	23.2 (4.6)
EORTC QLQ-C30, subscale PF	84.1 (15.4)	85.0 (15.6)	82.7 (16.8)	80.8 (18.1)

Table 2 (*continued*)

Baseline values[g]	pre Mean (SD)	post Mean (SD)	pre Mean (SD)	post Mean (SD)
CARES-SF, subscale PF	46.0 (7.4)	43.8 (5.7)	46.8 (6.8)	48.0 (7.7)
SF-36, subscale PF	82.7 (15.9)	85.0 (16.9)	82.9 (16.7)	82.4 (19.0)

AE = aerobic exercise; CARES-SF = cancer rehabilitation evaluation system short form; EORTC QLQ-C30 = European Organisation Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACT = Functional Assessment of Cancer Therapy; FACT-G = FACT-General; PF = physical function; PWB = physical well-being; RE = resistance exercise; SCT = stem cell transplantation; SF-36 = Short Form-36 Health survey.

[a] Proportion of survivors of solid tumors (n = 4124).

[b] Proportion of survivors without SCT (n = 4326).

[c] Proportion of survivors with SCT (n = 193).

[d] Proportion of survivors from intervention groups (n = 2514).

[e] Intervention duration of individual patients unknown for three studies, but mean or median was reported.

[f] Proportion of survivors from the control groups (n = 2005).

[g] Scores are from 0 to 100 with higher scores representing higher QoL and PF for FACT-G, EORTC QLQ-C30 and SF-36, and lower QoL and PF for CARES-SF.

provided information on contamination met the criteria for high quality.

The sample included 4519 patients with cancer, of whom 2514 were randomized to the intervention group and 2005 to the control group. The mean age was 54.6 (SD 11.3) years, 78% were women, 70% were diagnosed with breast cancer, 2% had metastatic disease, 51% exercised following cancer treatment, and 65% received supervised exercise (Table 2).

Representativeness and publication bias

Published summary data for QoL were available for 36 out of 69 RCTs, of which five [27,33–36] included two exercise arms. Consequently, 41 exercise arms were included in the analyses of representativeness. For PF, summary data were published for 30 RCTs, with two [27,37] evaluating two exercise arms, resulting in 32 exercise arms. We found no significant differences in effects on QoL (p = 0.25) and PF (p = 0.25) between RCTs of which IPD were shared and those of which were not (Table 3). The trim and fill procedures showed significant publication bias for all eligible RCTs reporting on QoL, but not between RCTs included and those not included (Table 3).

Effects and moderators of exercise on QoL and PF

Exercise effects on QoL (β = 0.15, 95%CI = 0.10;0.20) and PF (β = 0.18, 95%CI = 0.13;0.23, Table 4, Fig. 2) were significant. Patients' demographic and clinical characteristics, intervention timing and duration, and exercise FITT factors did not significantly moderate the effects on QoL or PF (Table 4). Supervised exercise had significantly larger effects on QoL ($\beta_{difference\_in\_effect}$ = 0.13, 95%CI = 0.04;0.23) and PF ($\beta_{difference\_in\_effect}$ = 0.11, 95% CI = 0.01;0.20) than unsupervised exercise. Compared to the control group, supervised exercise significantly improved both QoL (β = 0.20, 95%CI = 0.14;0.25) and PF (β = 0.22, 95%CI = 0.16;0.27), while unsupervised exercise significantly improved PF (β = 0.11, 95%CI = 0.03;0.19). Effects on PF were significantly larger in RCTs with a usual care control group than those with an attention control group ($\beta_{difference\_in\_effect}$ = 0.12, 95%CI = 0.002;0.23).

Sensitivity analyses among patients other than women with breast cancer (n = 1360, originating from 17 RCTs) showed slight differences in regression coefficients with larger confidence intervals, but the conclusions on moderator effects were similar.

Discussion

Based on IPD meta-analyses of 34 RCTs including data from 4519 individual patients with cancer, we found that exercise significantly improved their QoL and PF. The IPD meta-analytical approach of the present paper enabled the testing of potential moderators in a large sample. The exercise effects did not differ significantly across subgroups of age, sex, education level, marital status, BMI, cancer type, metastatic stage or treatment. Further, exercise was equally effective during and following cancer treatment. These findings support and strengthen the evidence base

Table 3
Representativeness and publication bias of the pooled effects of studies providing data for the POLARIS study and those not providing data.

Representativeness	*N*	Pooled effect	Test of heterogeneity			Between group differences *P*-value
		g (95%CI)	Q	I^2	*P*-value	
Quality of life						
All eligible studies	41	0.22 (0.14; 0.31)	71.96	44.42	0.001	
All eligible studies, excluding one outlier	40	0.18 (0.12; 0.24)	32.90	0	0.74	
Studies providing data	27	0.16 (0.09; 0.23)	22.22	0	0.68	
Studies not providing data	14	0.42 (0.17; 0.67)	45.06	71.15	<0.001	0.05
Studies not providing data, excluding one outlier	13	0.25 (0.12; 0.37)	9.35	0	0.67	0.25
Physical function						
All eligible studies	32	0.32 (0.20; 0.44)	86.06	63.98	<0.001	
All eligible studies, excluding two outliers	30	0.27 (0.18; 0.35)	36.12	19.72	0.17	
Studies providing data	24	0.28 (0.19; 0.37)	30.87	25.50	0.13	
Studies not providing data	8	0.54 (0.05; 1.03)	53.44	86.70	<0.001	0.31
Studies not providing data, excluding two outliers	6	0.17 (-0.01; 0.34)	3.84	0.00	0.59	0.25
Publication bias using trim and fill procedure	$N_{missing}$	Adjusted effect			P_{Egger}	
Quality of life						
All eligible studies, excluding one outlier	10	0.13 (0.07; 0.20)			0.02	
Studies providing data	6	0.12 (0.05; 0.19)			0.20	
Physical function						
All eligible studies, excluding two outliers	3	0.29 (0.20; 0.37)			0.26	
Studies providing data	2	0.31 (0.21; 0.40)			0.33	

CI = confidence interval; g = Hedges' g effect size; I^2 = I^2 statistic, which is the percentage of total variance that can be explained by heterogeneity, and 25% is considered low, 50% moderate, and 75% high heterogeneity; n = number of exercise intervention arms; Q = Q-test for heterogeneity, which is significant if there is evidence for heterogeneity.

Table 4
Effects and moderators of the effects of exercise on quality of life and physical function.

	Quality of life β (95%CI)	Physical function β (95%CI)
Effect of exercise	0.15 (0.10; 0.20)*	0.18 (0.13; 0.23)*
Demographic moderators		
Interaction age categories		
<50 years	Reference	Reference
50–70 years	0.06 (−0.06; 0.17)	−0.01 (−0.12; 0.10)
⩾70 years	−0.06 (−0.28; 0.16)	−0.04 (−0.26; 0.17)
Interaction women vs. men	0.14 (−0.05; 0.32)	0.08 (−0.11; 0.26)
Interaction partner vs. single	−0.11 (−0.24; 0.02)	−0.07 (−0.22; 0.08)
Interaction high vs. low-middle education	−0.06 (−0.17; 0.05)	−0.01 (−0.12; 0.10)
Clinical moderators		
Interaction BMI categories		
Underweight (BMI <18.5 kg/m^2)	0.28 (−0.24; 0.81)	0.28 (−0.15; 0.88)
Normal weight (BMI 18.5–<25 kg/m^2)	Reference	Reference
Overweight (BMI 25 to <30 kg/m^2)	−0.03 (−0.15; 0.09)	−0.03 (−0.06; 0.17)
Obese (BMI ⩾30 kg/m^2)	−0.02 (−0.16; 0.11)	−0.02 (−0.08; 0.19)
Interaction cancer type		
Breast	Reference	Reference
Male genitourinary	−0.25 (−0.58; 0.07)	0.02 (−0.31; 0.35)
Haematological	0.03 (−0.41; 0.47)	0.14 (−0.30; 0.59)
Gastrointestinal	0.23 (−0.09; 0.55)	0.08 (−0.24; 0.40)
Gynaecological	0.10 (−1.00; 1.18)	0.45 (−0.66; 1.55)
Respiratory tract	0.06 (−0.40; 0.52)	0.03 (−0.43; 0.49)
Other	−0.43 (−1.65; 0.80)	−0.52 (−1.75; 0.72)
Interaction distant metastasis	−0.21 (−0.64; 0.22)	−0.06 (−0. 49; 0.37)
Interaction surgery	0.008 (−0.26; 0.28)	−0.05 (−0.32; 0.21)
Interaction chemotherapy	0.07 (−0.07; 0.22)	0.02 (−0.13; 0.16)
Interaction radiotherapy	−0.02 (−0.14; 0.10)	0.04 (−0.08; 0.16)
Interaction hormone therapy for breast cancer	−0.01 (−0.17; 0.14)	−0.07 (−0.23; 0.08)
Intervention-related moderators		
Interaction post vs. during treatment	0.02 (−0.08; 0.12)	0.04 (−0.39; 0.46)
Intervention delivery mode		
Effect supervised vs. unsupervised	0.13 (0.04; 0.23)*	0.11 (0.01; 0.20)*
Effect supervised vs. control	0.20 (0.14; 0.25)*	0.22 (0.16; 0.27)*
Effect unsupervised vs. control	0.06 (−0.02; 0.14)	0.11 (0.03; 0.19)*
Interaction intervention duration		
⩽12 weeks	Reference	Reference
12–24 weeks	−0.19 (−0.32; −0.07)*[a]	−0.12 (−0.24; 0.00)#[a]
>24 weeks	−0.09 (−0.21; 0.03)	−0.05 (−0.16; 0.07)
FITT factors for supervised exercise		
Frequency		
Interaction 3 times/week vs. 2 times/week	0.04 (−0.10; 0.18)	0.01 (−0.12; 0.15)
Intensity		
Effect low-moderate and moderate vs. control	0.23 (0.12; 0.34)*	0.22 (0.12; 0.33)*
Effect moderate-vigorous and vigorous vs. control	0.21 (0.13; 0.28)*	0.22 (0.15; 0.29)*
Effect moderate-vigorous and vigorous vs. low-moderate and moderate	−0.03 (−0.15; 0.10)	−0.007 (−0.13; 0.11)
Type[b]		
Control	Reference	Reference
AE	0.25 (0.13; 0.38)*	0.21 (0.10; 0.34)
AE + RE	0.21 (0.13; 0.30)*	0.22 (0.14; 0.30)
RE	0.15 (0.04; 0.26)*	0.26 (0.16; 0.37)*
RE + impact training	0.16 (−0.02; 0.34)	0.16 (−0.02; 0.34)
Time of session		
Interaction >30–60 min vs. 0–30 min	0.03 (−0.12; 0.19)	−0.05 (−0.20; 0.10)
Interaction >60 vs. 0–30 min	0.10 (−0.10; 0.29)	0.02 (−0.17; 0.20)
Interaction >60 min vs. >30–60 min	0.06 (−0.10; 0.23)	0.07 (−0.09; 0.23)
FITT factors for unsupervised exercise		
Frequency		
Interaction ⩾5 times/week vs. <5 times/week	−0.06 (−0.24; 0.12)	−0.01 (−0.20; 0.18)
Intensity		
Interaction moderate-vigorous and vigorous vs. low-moderate and moderate	0.003 (−0.20; 0.21)	0.09 (−0.14; 0.31)
Type		
Interaction RE + AE vs. AE	−0.01 (−0.18; 0.16)	−0.17 (−0.36; 0.01)#
Time		
Interaction >30 min vs.⩽30 min	0.18 (−0.02; 0.37)*	0.14 (−0.08; 0.37)

* $p < 0.05$.
\# $0.05 \leqslant p < 0.10$.
[a] Interaction term not significant after adjusting for delivery mode.
[b] Significantly larger effects of AE, AE + RE and RE than the control group, no significant differences in effects between different exercise types. AE = aerobic exercise; BMI = body mass index; CI = confidence interval; RE = resistance exercise.

for current exercise recommendations that all patients with cancer should be physically active during and following cancer treatment [4]. However, the effects were stronger for supervised exercise. We found no significant moderating effects of intervention timing, duration, and exercise FITT factors.

The exercise effects were significant, but small in general, and comparable across the different subgroups. The lack of demographic and clinical moderators suggests that targeting exercise, based on demographic and clinical characteristics may not be useful for improving QoL and PF.

The moderating effects of sex, age, education, marital status, BMI and cancer type have been explored in previous single studies reporting inconsistent findings [11–14,27]. It has been hypothesized that patients without a partner have less social support at home [38,39] and may therefore either benefit more from the support associated with supervised or guided exercise [13,14], or may be less likely to adhere to the exercise intervention [23]. We analysed the potential moderating effect of being married/having a partner, although this does not necessarily reflect partner support, and found no moderator effect on QoL and PF.

Additionally, we found no moderator effect of BMI. However, due to the higher likelihood of sarcopenic obesity (i.e. increased fat mass in combination with reduced muscle mass) caused by cancer and its treatment [40], BMI may not adequately reflect adiposity in patients with cancer. Additional studies are needed to investigate the moderator effects of muscle and fat mass.

We found no significant differences in effects on QoL and PF across cancer types or between patients with metastatic and non-metastatic disease. However, sample sizes of some subgroups were small, and due to different coding schemes or lack of information on disease stage we were limited to studying differences in intervention effects between patients with metastatic and

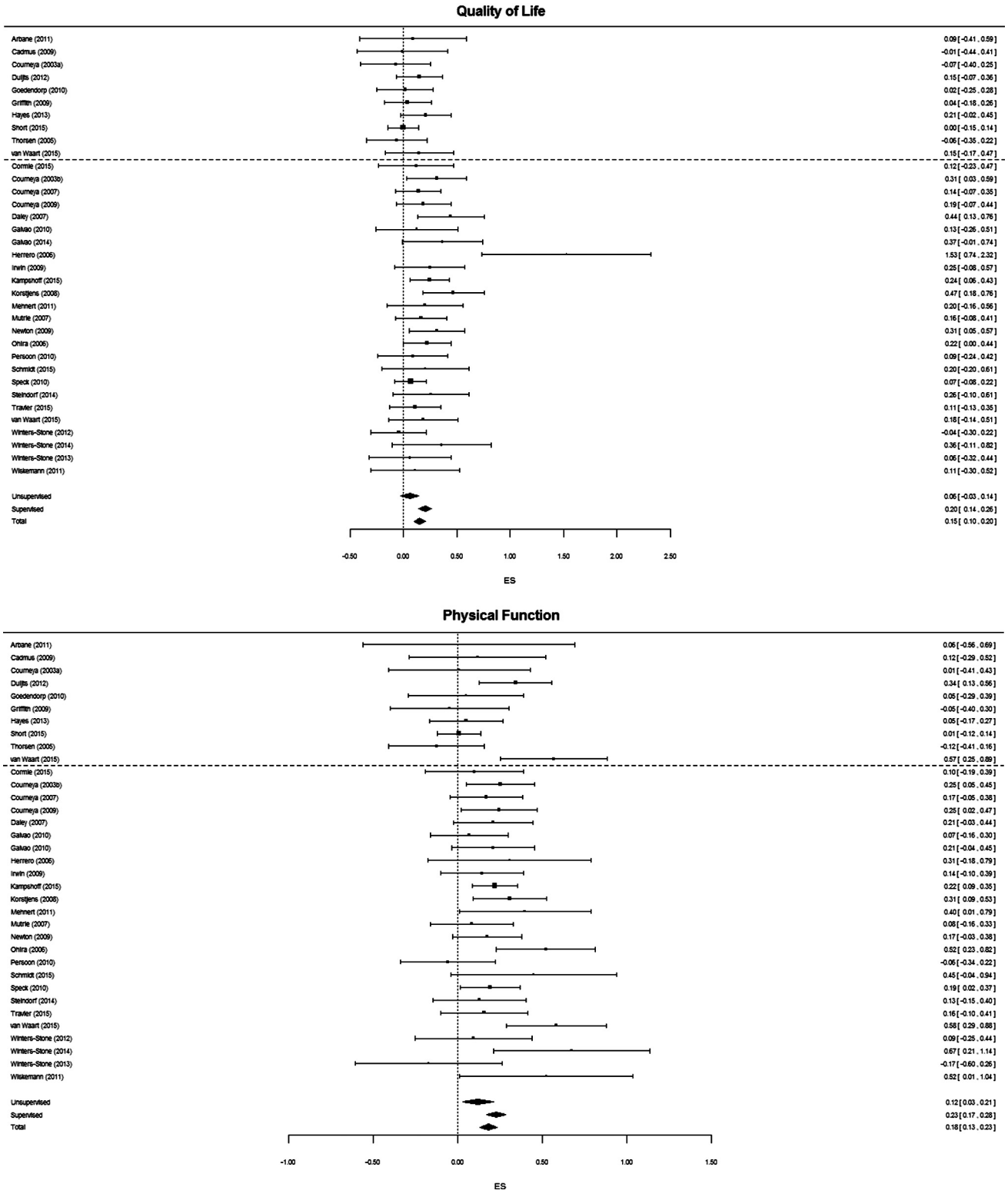

Fig. 2. Forest plots of the effects of exercise on quality of life (a) and physical function (b). Data represent the regression coefficients [95% confidence intervals] of the effects of exercise on quality of life and physical function (in *z*-scores). Unsupervised interventions are presented above the dashed line, and supervised interventions below.

non-metastatic disease, and were unable to further disentangle differences in effects between patients with disease stages I, II and III. Furthermore, the majority of studies evaluating the effects of exercise have been conducted in patients with breast cancer, and prostate cancer who were treated with curative intent [4,7]. Therefore exercise effects on QoL and PF remain unclear in understudied cancer populations, such as head and neck, lung, and gynaecological cancers, and in patients with metastatic disease, and they may differ from those with breast and prostate cancer due to differences in treatment trajectories. We were unable to confirm previous findings that radiotherapy [12] or chemotherapy [13] moderate exercise effects, which may be related to the

heterogeneous study population. As treatment types are related to cancer types, the moderator effects of treatment should perhaps be investigated separately within each cancer type.

Intervention goals are likely to differ across phases of the cancer continuum. Exercise during cancer treatment typically seeks to influence treatment effectiveness and coping by managing side effects, maintaining physical fitness, and preventing muscle loss, fat gain, fatigue, and deterioration in QoL [28]. Exercise post-treatment typically aims to speed recovery, improve physical fitness and QoL, reduce fatigue, distress and the risk of developing chronic diseases or secondary cancers [28]. Nevertheless, the exercise effects on QoL and PF were similar, and clearly demonstrate significant benefits both during and post cancer treatment, which is consistent with previous meta-analyses based on aggregate data [6,8,9].

Effects of supervised exercise were twice as large as those of unsupervised exercise, which is consistent with a previous systematic review [41]. The larger effects of supervised exercise may be explained by the attention of the physiotherapist or exercise physiologist delivering the intervention, access to better equipment, more challenging exercise prescriptions, or by better adherence to the prescribed exercise protocol. Reporting adherence and identifying determinants of adherence to unsupervised interventions is important to identify patients who do not need supervision.

The lack of significant differences in exercise effects across different FITT factors might have resulted from little variation in these factors across studies, or the limited power since FITT factors are moderators at the intervention level instead of the patient level. Previous head-to-head comparisons of exercise FITT factors indicated a dose response effect of aerobic exercise on PF during cancer treatment in patients with breast cancer [42] and larger effects of high intensity compared to moderate intensity exercise post treatment in a population with mixed cancer types [27]. More RCTs that directly compare exercise FITT factors are warranted to define optimal exercise prescriptions. Also, specific intervention components, including goal-setting, social support and exercise instructions and monitoring, may differ across interventions, and explain differences in effects.

The effects on QoL and PF were significant, but smaller than expected. There may be several explanations for the smaller effects. First, exercise interventions generally aim to improve exercise behaviour or health-related physical fitness, and probably not all dimensions of QoL (i.e. physical, emotional and social well-being) [43] were affected to the same extent. Second, QoL is susceptible to response shift [44,45], i.e., a change in the meaning of one's self-evaluation of QoL over time as a result of changes in internal standards, values and the conceptualization of QoL [46]. Third, results may have been contaminated by the adoption of exercise by patients in the control group. The limited information on contamination hampered us to evaluate its influence on the effects. Fourth, our analyses were based on patients participating in RCTs. Median (interquartile range) participation rates in exercise trails were found to be 63% (33–80) of eligible patients [47]. Patients who decline participation may be less motivated for exercise and have lower exercise levels, thus we may not reach patients who may benefit the most. However, studies comparing exercise of participants and non-participants found no differences [23,48,49]. Nevertheless, demographics may differ between participants and nonparticipants, with the latter more likely to be older [48] and to have lower education levels [23,49]. Therefore, results may not be fully generalizable to all patients with cancer. Future IPD meta-analyses should also study the moderator effects of baseline QoL, PF and fitness [50], and specific symptoms as fatigue and distress [12] and the moderator effects on other physical, psychosocial and clinical outcomes, as they may differ [13,14].

Study strengths are the large number of included RCTs from multiple countries, the consequent large sample size, and the uniform analytical procedures across all studies. Limitations are the following: first, there was considerable publication bias in studies that met our inclusion criteria, overestimating the intervention effects, particularly for studies reporting on QoL. However, no significant differences in effect sizes were found between studies providing data and those that did not, indicating that the 34 RCTs included in the analyses were a representative sample of the published literature. Second, not all RCTs met all quality criteria. In particular, information on exercise adherence and contamination was limited, hampering the ability to check whether adherence was similar across moderator subgroups. However, a previous review on determinants of exercise adherence in patients with cancer concluded that the majority of studies showed no significant association of demographic and clinical factors with adherence [51]. Finally, we focused on short term intervention effects as very few studies have examined maintenance of intervention effects into the long term.

In conclusion, exercise, and particularly those with a supervised component, effectively improves QoL and PF across subgroups of patients with cancer with different demographic and clinical characteristics, both during and following treatment. Although effect sizes were small, our study provides additional evidence to support the implementation of exercise as part of standard care to improve QoL and PF. Current knowledge on the exercise effects on QoL and PF is primarily based on studies in patients with non-metastasised breast or prostate cancer. Future studies should therefore shift the focus to understanding the exercise effects in understudied and advanced cancer populations; on clinical outcomes including specific symptoms, cancer treatment completion, and survival; and on how to optimize exercise participation, adherence, and prescriptions.

Funding

Via "Bas Mulder Award" granted to L.M. Buffart by the Alpe d'HuZes foundation/Dutch Cancer Society (VU 2011-5045).

Author contributions

Buffart, Brug, Verdonck-de Leeuw are members of the steering committee of POLARIS. Courneya, Newton, Jacobsen and Aaronson are members of the international advisory board of POLARIS. These authors contributed to the concept and design of the study. Buffart, Kalter and Sweegers gathered, pooled and analyzed the data. Buffart, Brug, Verdonck-de Leeuw drafted the manuscript. Buffart, Courneya, Newton, Aaronson, May, Galvão, Chinapaw, Steindorf, Irwin, Stuiver, Hayes, Griffith, Lucia, Mesters, van Weert, Knoop, Goedendorp, Mutrie, Daley, McConnachie, Bohus, Thorsen, Schulz, Short, James, Plotnikoff, Arbane, Schmidt, Potthoff, van Beurden, Oldenburg, Sonke, van Harten, Garrod, Schmitz, Winters-Stone, Velthuis, Taaffe, van Mechelen, Kersten, Nollet, Wenzel, Wiskemann, Brug are principal investigators of the randomised controlled trials of which the data are pooled for the current study, and have consequently contributed to the study concept, design and conduct of the trial that they were responsible for. All authors have critically revised the manuscript and approved the final version.

Authors' disclosures of potential conflicts of interest

Dr. Steindorf reports personal fees from Lilly Deutschland (Award), outside the submitted work; Dr. Bohus reports grants from Josse Carreras Foundation, during the conduct of the study;

Dr. van Mechelen reports to be shareholder-director of VU University Medical Center Amsterdam spin-off company Evalua Nederland B.V. (www.evalua.nl) and non-executive board member of Arbo Unie B.V. (www.arbounie.nl). Both companies are active in the Dutch occupational health care sector.

Dr. Nollet reports grants from Dutch Cancer Society, during the conduct of the study. Dr. Brug reports grants from Dutch Cancer Society, during the conduct of the study.

Acknowledgements

The POLARIS study was supported by the "Bas Mulder Award" granted to L.M. Buffart by the Alpe d'HuZes foundation, part of the Dutch Cancer Society (VU 2011-5045).

References

[1] Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends–an update. Cancer Epidemiol Biomarkers Prev 2016;25:16–27.
[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[3] Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezzi M, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol 2016.
[4] Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409–26.
[5] Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:243–74.
[6] Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J Cancer Surviv 2010;4:87–100.
[7] Buffart LM, Galvao DA, Brug J, Chinapaw MJ, Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treat Rev 2014;40:327–40.
[8] Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al. Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev 2012;8:CD007566.
[9] Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst Rev 2012;8:CD008465.
[10] Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry 2002;59:877–83.
[11] Buffart LM, Newton RU, Chinapaw MJ, Taaffe DR, Spry NA, Denham JW, et al. The effect, moderators, and mediators of resistance and aerobic exercise on health-related quality of life in older long-term survivors of prostate cancer. Cancer 2015;121:2821–30.
[12] Kalter J, Buffart LM, Korstjens I, van Weert E, Brug J, Verdonck-de Leeuw IM, et al. Moderators of the effects of group-based physical exercise on cancer survivors' quality of life. Support Care Cancer 2015;23:2623–31.
[13] Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. Cancer 2008;112:1845–53.
[14] Courneya KS, Sellar CM, Stevinson C, McNeely ML, Friedenreich CM, Peddle CJ, et al. Moderator effects in a randomized controlled trial of exercise training in lymphoma patients. Cancer Epidemiol Biomarkers Prev 2009;18:2600–7.
[15] Carmack Taylor CL, de Moor C, Basen-Engquist K, Smith MA, Dunn AL, Badr H, et al. Moderator analyses of participants in the Active for Life after cancer trial: implications for physical activity group intervention studies. Ann Behav Med 2007;33:99–104.
[16] Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, et al. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. PLoS Med 2015;12:e1001855.
[17] Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221.
[18] Teramukai S, Matsuyama Y, Mizuno S, Sakamoto J. Individual patient-level and study-level meta-analysis for investigating modifiers of treatment effect. Jpn J Clin Oncol 2004;34:717–21.
[19] Fisher DJ, Copas AJ, Tierney JF, Parmar MK. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011;64:949–67.
[20] Buffart LM, Kalter J, Chinapaw MJ, Heymans MW, Aaronson NK, Courneya KS, et al. Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS): rationale and design for meta-analyses of individual patient data of randomized controlled trials that evaluate the effect of physical activity and psychosocial interventions on health-related quality of life in cancer survivors. Syst Rev 2013;2:75.
[21] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657–65.
[22] Courneya KS, Segal RJ, Gelmon K, Reid RD, Mackey JR, Friedenreich CM, et al. Predictors of supervised exercise adherence during breast cancer chemotherapy. Med Sci Sports Exerc 2008;40:1180–7.
[23] Kampshoff CS, van Mechelen W, Schep G, Nijziel MR, Witlox L, Bosman L, et al. Participation in and adherence to physical exercise after completion of primary cancer treatment. Int J Behav Nutr Phys Act 2016;13:100.
[24] Steins Bisschop CN, Courneya KS, Velthuis MJ, Monninkhof EM, Jones LW, Friedenreich C, et al. Control group design, contamination and drop-out in exercise oncology trials: a systematic review. PLoS One 2015;10:e0120996.
[25] Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. BMJ 2012;344:d7762.
[26] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[27] Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the Resistance and Endurance exercise After ChemoTherapy (REACT) study. BMC Med 2015;13:275.
[28] Courneya KS, Friedenreich CM. Physical activity and cancer control. Semin Oncol Nurs 2007;23:242–52.
[29] American Collega of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 9th ed. Philadelphia: Lippincot Williams and Wilkins; 2014.
[30] Korstjens I, May AM, van Weert E, Mesters I, Tan F, Ros WJ, et al. Quality of life after self-management cancer rehabilitation: a randomized controlled trial comparing physical and cognitive-behavioral training versus physical training. Psychosom Med 2008;70:422–9.
[31] Duijts SF, van Beurden M, Oldenburg HS, Hunter MS, Kieffer JM, Stuiver MM, et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. J Clin Oncol 2012;30:4124–33.
[32] Goedendorp MM, Peters ME, Gielissen MF, Witjes JA, Leer JW, Verhagen CA, et al. Is increasing physical activity necessary to diminish fatigue during cancer treatment? Comparing cognitive behavior therapy and a brief nursing intervention with usual care in a multicenter randomized controlled trial. Oncologist 2010;15:1122–32.
[33] Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol 2007;25:4396–404.
[34] Hayes SC, Rye S, Disipio T, Yates P, Bashford J, Pyke C, et al. Exercise for health: a randomized, controlled trial evaluating the impact of a pragmatic, translational exercise intervention on the quality of life, function and treatment-related side effects following breast cancer. Breast Cancer Res Treat 2013;137:175–86.
[35] Short CE, James EL, Girgis A, D'Souza MI, Plotnikoff RC. Main outcomes of the Move More for Life Trial: a randomised controlled trial examining the effects of tailored-print and targeted-print materials for promoting physical activity among post-treatment breast cancer survivors. Psychooncology 2015;24:771–8.
[36] Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol 2009;27:344–51.
[37] van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. J Clin Oncol 2015;33:1918–27.
[38] Zhang J, Gan L, Wu Z, Yan S, Liu X, Guo W. The influence of marital status on the stage at diagnosis, treatment, and survival of adult patients with gastric cancer: a population-based study. Oncotarget 2016.
[39] Aizer AA, Chen MH, McCarthy EP, Mendu ML, Koo S, Wilhite TJ, et al. Marital status and survival in patients with cancer. J Clin Oncol 2013;31:3869–76.
[40] Jones LW, Demark-Wahnefried W. Diet, exercise, and complementary therapies after primary treatment for cancer. Lancet Oncol 2006;7:1017–26.
[41] Baumann FT, Zopf EM, Bloch W. Clinical exercise interventions in prostate cancer patients–a systematic review of randomized controlled trials. Support Care Cancer 2012;20:221–33.
[42] Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. J Natl Cancer Inst 2013;105:1821–32.
[43] The World Health Organization Quality of Life Assessment. (WHOQOL): development and general psychometric properties. Soc Sci Med 1998;46:1569–85.
[44] Gerlich C, Schuler M, Jelitte M, Neuderth S, Flentje M, Graefen M, et al. Prostate cancer patients' quality of life assessments across the primary treatment trajectory: 'True' change or response shift? Acta Oncol 2016;1–7.

[45] Anota A, Bascoul-Mollevi C, Conroy T, Guillemin F, Velten M, Jolly D, et al. Item response theory and factor analysis as a mean to characterize occurrence of response shift in a longitudinal quality of life study in breast cancer patients. Health Qual Life Outcomes 2014;12:32.
[46] Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507–15.
[47] Maddocks M, Mockett S, Wilcock A. Is exercise an acceptable and practical therapy for people with or cured of cancer? A systematic review. Cancer Treat Rev 2009;35:383–90.
[48] Gollhofer SM, Wiskemann J, Schmidt ME, Klassen O, Ulrich CM, Oelmann J, et al. Factors influencing participation in a randomized controlled resistance exercise intervention study in breast cancer patients during radiotherapy. BMC Cancer 2015;15:186.
[49] van Waart H, van Harten WH, Buffart LM, Sonke GS, Stuiver MM, Aaronson NK. Why do patients choose (not) to participate in an exercise trial during adjuvant chemotherapy for breast cancer? Psychooncology 2015.
[50] Wiskemann J, Kuehl R, Dreger P, Schwerdtfeger R, Huber G, Ulrich CM, et al. Efficacy of exercise training in SCT patients–who benefits most? Bone Marrow Transplant 2014;49:443–8.
[51] Kampshoff CS, Jansen F, van Mechelen W, May AM, Brug J, Chinapaw MJ, et al. Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. Int J Behav Nutr Phys Act 2014;11:80.
[52] Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 2011;71:229–34.
[53] Cadmus LA, Salovey P, Yu H, Chung G, Kasl S, Irwin ML. Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. Psychooncology 2009;18:343–52.
[54] Cormie P, Galvao DA, Spry N, Joseph D, Chee R, Taaffe DR, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int 2015;115:256–66.
[55] Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, Fairey AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. Eur J Cancer Care (Engl) 2003;12:347–57.
[56] Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003;21:1660–8.
[57] Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. J Clin Oncol 2009;27:4605–12.
[58] Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A. Randomized trial of exercise therapy in women treated for breast cancer. J Clin Oncol 2007;25:1713–21.
[59] Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol 2010;28:340–7.
[60] Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol 2014;65:856–64.
[61] Griffith K, Wenzel J, Shang J, Thompson C, Stewart K, Mock V. Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors. Cancer 2009;115:4874–84.
[62] Herrero F, San Juan AF, Fleck SJ, Balmer J, Perez M, Canete S, et al. Combined aerobic and resistance training in breast cancer survivors: a randomized, controlled pilot trial. Int J Sports Med 2006;27:573–80.
[63] Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GG, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. Cancer Epidemiol Biomarkers Prev 2009;18:306–13.
[64] Mehnert A, Veers S, Howaldt D, Braumann KM, Koch U, Schulz KH. Effects of a physical exercise rehabilitation group program on anxiety, depression, body image, and health-related quality of life among breast cancer patients. Onkologie 2011;34:248–53.
[65] Mutrie N, Campbell AM, Whyte F, McConnachie A, Emslie C, Lee L, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. BMJ 2007;334:517.
[66] Newton RU, Taaffe DR, Spry N, Gardiner RA, Levin G, Wall B, et al. A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer. BMC Cancer 2009;9:210.
[67] Ohira T, Schmitz KH, Ahmed RL, Yee D. Effects of weight training on quality of life in recent breast cancer survivors: the Weight Training for Breast Cancer Survivors (WTBS) study. Cancer 2006;106:2076–83.
[68] Persoon S, Kersten MJ, Chinapaw MJ, Buffart LM, Burghout H, Schep G, et al. Design of the EXercise Intervention after Stem cell Transplantation (EXIST) study: a randomized controlled trial to evaluate the effectiveness and cost-effectiveness of an individualized high intensity physical exercise program on fitness and fatigue in patients with multiple myeloma or (non-) Hodgkin's lymphoma treated with high dose chemotherapy and autologous stem cell transplantation. BMC Cancer 2010;10:671.
[69] Schmidt ME, Wiskemann J, Armbrust P, Schneeweiss A, Ulrich CM, Steindorf K. Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: a randomized controlled trial. Int J Cancer 2015;137:471–80.
[70] Speck RM, Gross CR, Hormes JM, Ahmed RL, Lytle LA, Hwang WT, et al. Changes in the Body Image and Relationship Scale following a one-year strength training trial for breast cancer survivors with or at risk for lymphedema. Breast Cancer Res Treat 2010;121:421–30.
[71] Steindorf K, Schmidt ME, Klassen O, Ulrich CM, Oelmann J, Habermann N, et al. Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life. Ann Oncol 2014;25:2237–43.
[72] Thorsen L, Skovlund E, Stromme SB, Hornslien K, Dahl AA, Fossa SD. Effectiveness of physical activity on cardiorespiratory fitness and health-related quality of life in young and middle-aged cancer patients shortly after chemotherapy. J Clin Oncol 2005;23:2378–88.
[73] Travier N, Velthuis MJ, Steins Bisschop CN, van den Buijs B, Monninkhof EM, Backx F, et al. Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. BMC Med 2015;13:121.
[74] van Vulpen JK, Velthuis MJ, Steins Bisschop CN, Travier N, VDB BJ, Backx FJ, et al. Effects of an exercise program in colon cancer patients undergoing chemotherapy. Med Sci Sports Exerc 2016;48:767–75.
[75] Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. J Cancer Surviv 2012;6:189–99.
[76] Winters-Stone KM, Dobek J, Nail LM, Bennett JA, Leo MC, Torgrimson-Ojerio B, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. Osteoporosis Int 2013;24:1637–46.
[77] Winters-Stone KM, Dobek JC, Bennett JA, Dieckmann NF, Maddalozzo GF, Ryan CW, et al. Resistance training reduces disability in prostate cancer survivors on androgen deprivation therapy: evidence from a randomized controlled trial. Arch Phys Med Rehabil 2015;96:7–14.
[78] Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. Blood 2011;117:2604–13.