Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis

Laurien M Buffart[1,2], Maike G Sweegers[1], Anne M May[3], Mai J Chinapaw[4], Jonna K van Vulpen[3], Rob U Newton[5], Daniel A Galvão[5], Neil K Aaronson[6], Martijn M Stuiver[7], Paul B Jacobsen[8], Irma M Verdonck-de Leeuw[9,10], Karen Steindorf[11], Melinda L Irwin,[12] Sandi Hayes[13], Kathleen A Griffith[14], Alejandro Lucia[15], Fernando Herrero-Roman[16], Ilse Mesters[17], Ellen van Weert[18], Hans Knoop[19], Martine M Goedendorp[20,21], Nanette Mutrie[22], Amanda J Daley[23], Alex McConnachie[24], Martin Bohus[25,26], Lene Thorsen[27,28], Karl-Heinz Schulz[29], Camille E Short[30], Erica L James[31], Ronald C Plotnikoff[32], Gill Arbane[33], Martina E Schmidt[11], Karin Potthoff[34,35], Marc van Beurden[36], Hester S Oldenburg[36], Gabe S Sonke[36], Wim H van Harten[7,37], Rachel Garrod[38], Kathryn H Schmitz[39], Kerri M Winters-Stone[40], Miranda J Velthuis[41], Dennis R Taaffe[5], Willem van Mechelen[4], Marie José Kersten[42], Frans Nollet[43], Jennifer Wenzel[44], Joachim Wiskemann[34,39], Johannes Brug[45], Kerry S Courneya[46]

Authors' affiliations:

1. Department of Epidemiology and Biostatistics, Amsterdam University Medical Center, Amsterdam Public Health research institute, Amsterdam, The Netherlands
2. Department of Medical Oncology, Amsterdam University Medical Center, Cancer Center Amsterdam, Amsterdam, The Netherlands
3. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands
4. Department of Public and Occupational health, Amsterdam Public Health research institute, Amsterdam University Medical Center, Amsterdam, The Netherlands
5. Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia
6. Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands
7. Center for Quality of life, Netherlands Cancer Institute, Amsterdam, The Netherlands
8. Division of Cancer Control and Population Science, National Cancer Institute, Bethesda, Maryland, USA.
9. Department of Clinical Psychology, VU University Amsterdam, The Netherlands
10. Department of Otolaryngology-Head and Neck Surgery, Amsterdam Public Health research institute and Cancer Center Amsterdam, Amsterdam University Medical Center, Amsterdam, The Netherlands

11. Division of Physical Activity, Prevention and Cancer, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany
12. Yale School of Public Health, New Haven, USA
13. School of Public Health and Social Work, Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, QLD, Australia.
14. The George Washington University School of Nursing, Washington, DC, USA
15. European University and Research Institute, Madrid, Spain
16. Fundación GIAFyS Cancer, Miranda de Ebro, Spain
17. Department of Epidemiology, Maastricht University, The Netherlands
18. University Medical Centre Groningen, University of Groningen, Center for Rehabilitation, Groningen, The Netherlands
19. Department of Medical Psychology, Academic Medical Center, Amsterdam, The Netherlands.
20. Department of Health Psychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
21. Department of Health Sciences, Faculty of Science, Vrije Universiteit Amsterdam, Amsterdam Public Health research institute, The Netherlands.
22. Physical Activity for Health Research Center, University of Edinburgh, Edinburgh, UK.
23. School of Sports, Exercise and Health Sciences, University of Loughborough, Loughborough, UK.
24. Robertson Centre for biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
25. Institute of Psychiatric and Psychosomatic Psychotherapy, Central Institute of Mental Health, Mannheim, Heidelberg University, Germany.
26. Faculty of Health, University of Antwerp, Belgium.
27. National Advisory Unit on Late Effects after Cancer Treatment, Department of Oncology, Oslo University Hospital, Oslo, Norway
28. Department of Clinical Service, Oslo University Hospital, Oslo, Norway
29. Athleticum – Competence Center for Sports- and Exercise Medicine and Institute for Medical Psychology, University Medical Center Hamburg-Eppendorf, Germany.
30. Freemasons Foundation Centre of Men's Health, School of Medicine, University of Adelaide, SA, Australia
31. School of Medicine & Public Health, the University of Newcastle, Callaghan, NSW, Australia.
32. Priority Research Centre for Physical Activity and Nutrition, the University of Newcastle, Callaghan, NSW, Australia.
33. Lane Fox Respiratory Research Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK
34. Department of Medical Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Heidelberg, Germany
35. Department of Radiation Oncology, National Center for Tumor Diseases (NCT) and Heidelberg University Hospital, Heidelberg, Germany
36. Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
37. University of Twente, Enschede, The Netherlands
38. Department of Respiratory Medicine, Kings College London, London, UK.
39. Department of Public Health Science, College of Medicine and Cancer Institute, Pennsylvania State University, Hershey, PA, USA.

40. Knight Cancer Institute and School of Nursing, Oregon Health & Science University, Portland, USA
41. Netherlands comprehensive cancer organisation (IKNL), Utrecht, the Netherlands.
42. Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands.
43. Department of Rehabilitation, Academic Medical Center, University of Amsterdam, Amsterdam Movement Sciences research institute, Amsterdam, The Netherlands.
44. Johns Hopkins School of Nursing, Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, USA.
45. Amsterdam School of Communication Research (ASCoR), University of Amsterdam, Amsterdam, The Netherlands
46. Faculty of Kinesiology, Sport, and Recreation, University of Alberta, Edmonton, Alberta, Canada

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the (U.S.) National Institutes of Health.

Corresponding author:

Laurien M Buffart
Amsterdam University Medical Center, Department of Epidemiology and Biostatistics and Medical Oncology
De Boelelaan 1089a
1081 HV Amsterdam
The Netherlands
Phone: +31 (0)20 444 9931
Email: l.buffart@vumc.nl

Running head: Targeting exercise to patients with cancer: an IPD-meta-analysis

Keywords: neoplasm; exercise; quality of life; fatigue; muscle strength; aerobic capacity; physical function; physical activity

ABSTRACT

Background Exercise effects in cancer patients often appear modest, possibly because interventions rarely target patients most in need. This study investigated the moderator effects of baseline values on the exercise outcomes of fatigue, aerobic fitness, muscle strength, quality of life (QoL) and self-reported physical function (PF) in cancer patients during and post-treatment.

Methods Individual patient data from 34 randomized exercise trials (n=4,519) were pooled. Linear mixed-effect models were used to study moderator effects of baseline values on exercise intervention outcomes, and to determine whether these moderator effects differed by intervention timing (during versus post-treatment).

Results Moderator effects of baseline fatigue and PF were consistent across intervention timing, with larger effects in patients with worse fatigue ($p=0.05$) and worse PF ($p=0.003$). Moderator effects of baseline aerobic fitness, muscle strength and QoL differed by intervention timing. During treatment, effects on aerobic fitness were larger for patients with better baseline aerobic fitness ($p=0.002$). Post-treatment, effects on upper ($p<0.001$) and lower ($p=0.01$) body muscle strength and QoL ($p<0.001$) were larger in patients with worse baseline values.

Conclusion Although exercise should be encouraged for most cancer patients during and post treatments, targeting specific subgroups may be especially beneficial and cost-effective. For fatigue and PF, interventions during and post-treatment should target patients with high fatigue and low PF. During treatment, patients experience benefit for muscle strength and QoL regardless of baseline values, however, only patients with low baseline values benefit post-treatment. For aerobic fitness, patients with low baseline values do not appear to benefit from exercise during treatment.

INTRODUCTION

There is evidence from randomized controlled trials (RCTs) that exercise has beneficial effects on fatigue, physical fitness, quality of life (QoL) and self-reported physical function (PF) during and post cancer treatment(1-7). The magnitude of these effects, however, is often small to moderate(2, 3, 8-10). One explanation for these modest effects may be the lack of specifically targeting those patients who are most likely to benefit from exercise interventions. For other types of supportive care interventions, such as psychosocial interventions, larger effects on distress and QoL are often found in patients with higher distress(11-13) and lower QoL(14). Consequently, some RCTs have screened for distress prior to enrolling patients into a psychosocial intervention(15-18). In our previous meta-analysis on individual patient data (IPD), we found that 36% of RCTs evaluating the effects of psychosocial interventions specifically targeted patients with psychosocial symptoms and, in general, these RCTs showed larger intervention benefits(19). Thus, targeting psychosocial interventions to patients with worse symptoms and QoL seems useful and economical. Whether this principle is also the case for exercise interventions is unknown.

Only a limited number of exercise intervention studies have evaluated the moderator effect of baseline fatigue, physical fitness (i.e. aerobic fitness and muscle strength), QoL and PF on intervention effects in patients with cancer(20-24). Studying these moderator effects may help to identify subgroup of patients *for whom* exercise interventions are especially beneficial or futile(25, 26). Results from previous RCTs have shown that the effects of exercise interventions on fatigue were larger in patients with higher baseline fatigue(22, 23). Also, exercise intervention effects on QoL were larger in patients who had completed chemotherapy with higher baseline fatigue(20), and in patients with lymphoma with lower baseline QoL(21). Comparably, in patients undergoing allogeneic stem cell transplantations, larger effects on physical fitness were found in unfit patients compared with fit patients(27).

The aims of exercise interventions differ across the cancer continuum. Exercise interventions during primary cancer treatment, especially chemotherapy, typically aim to prevent declines in functioning and to ameliorate treatment side-effects, while exercise interventions post-treatment aim to improve functioning(28). Therefore, it may also be important to identify *when* targeting exercise interventions to baseline values of fatigue, physical fitness, QoL and PF would be most useful. Since it may be important to prevent declines in functioning during primary cancer treatment in all patients regardless of baseline functioning, we studied whether the benefit from exercise during cancer treatment was independent of baseline value. Conversely, post-treatment, we hypothesized larger benefits on fatigue, physical fitness, QoL and PF in patients with worse baseline values.

Using data collected in the Predicting OptimaL cAncer RehabIlition and Supportive care (POLARIS) study(26), this IPD meta-analysis aimed to study the moderator effects of baseline values on the exercise response for fatigue, physical fitness, QoL and PF, and to examine whether these moderator effects differ by intervention timing (during versus post-treatment).

METHODS

Study inclusion and characteristics

The POLARIS study is an international collaboration in which IPD of RCTs were harmonized for pooled analyses(26). POLARIS included RCTs that evaluated the effects of exercise and/or psychosocial interventions on QoL compared to a wait-list, usual care or attention control group in adult (≥18 years) patients with cancer. Eligible studies were identified via systematic searches in electronic databases, reference checking of systematic reviews, meta-analyses and via personal communication with collaborators, colleagues and other experts in the field. Details of the study design, procedures, search strategies, study inclusion, sample and quality have been published previously(4, 26). The study protocol was registered in PROSPERO in February 2013 (CRD42013003805).

IPD from 34 (n= 4,519 patients) of 69 RCTs (response 49%) evaluating the effects of exercise were included(4). These 34 RCTs were a representative sample of the published RCTs evaluating exercise intervention effects on QoL and PF(4). The moderator effects of demographic, clinical, and intervention-related variables for QoL(4), physical fitness(6), and fatigue(7) are reported elsewhere.

Exercise interventions

Details of the different exercise interventions have been published previously(4). Study-, intervention-, and exercise-characteristics of included studies and pre-intervention values of fatigue, physical fitness, QoL, and PF are presented in Table 1. Of 34 RCTs, 17(29-45) focused on patients with breast cancer, five(46-50) on various cancer types, five(23, 51-54) on prostate cancer, three(55-57) on hematological cancer, one(58) on colorectal cancer, and one(59) on lung cancer. Two RCTs(60-63) included patients with breast and colon cancer, of which results were published in separate reports. Three RCTs specifically targeted patients with menopausal symptoms(33), lymphedema (risk)(42) or multiple physical or psychosocial problems(49), but no studies specifically targeted patients with fatigue, low fitness, or poor QoL. Fourteen(23, 32, 35, 36, 38-40, 43-45, 47, 52-54) RCTs excluded patients who participated in regular physical activity or exercise.

Outcome variables

The current analyses used outcomes assessed at pre- and post-intervention. Table 2 presents the different measures used to assess the outcomes. Fatigue, QoL and PF were assessed by self-report. Physical fitness was measured objectively by assessing aerobic fitness, upper

(UBMS) and lower body muscle strength (LBMS). To allow pooling of the different measures or questionnaires, we recoded the individual scores (pre- and post-intervention) into z-scores by subtracting the mean pre-intervention score from the individual score and dividing the result by the standard deviation (SD) pre-intervention per measurement instrument. Subsequently, the pooled z-scores were used for further analyses.

Statistical analysis

Moderator effects of the baseline value of the outcome were studied using a one-step approach. Linear mixed model analyses with a two-level structure (1:patient, 2:study) were used to consider the clustering of patients within studies by using a random intercept on study level. The post-intervention value (z-score) of the outcome was regressed on the intervention, and adjusted for the baseline value (z-score) to limit regression to the mean(64, 65). Moderator effects were examined by adding the interaction term of the moderator variable with the intervention into the regression model. We added a 3-way interaction of intervention×baseline value×intervention timing, along with the three corresponding 2-way interactions to the model, and intervention timing. A significant 3-way interaction indicates that the moderator effects of the baseline value of the outcome differ between interventions offered during versus post cancer treatment. In this case, we tested the moderator effects separately for interventions during and post cancer treatment. In case the 3-way interaction was not significant, the moderator effect of the baseline value (baseline value×intervention) was tested in the total group (i.e. both during and post-treatment). We used the likelihood ratio test to compare models with and without interaction terms. Additionally, regression coefficients, 95% confidence intervals (CI), and corresponding p-values of the interaction term were examined. In case the model improved significantly by adding the interaction term or in case the interaction term was significant, stratified analyses were conducted for intervention timing, and for subgroups of baseline fatigue, aerobic fitness, UBMS, LBMS, QoL and PF. For 2-way interactions, we considered $p \leq 0.05$ as significant. For 3-way interactions, we chose a cut-off of $p \leq 0.10$ to reduce the risk for missing potential moderator effects. For the stratified analyses, we categorised the baseline values into four groups of SD scores (<-1SD *vs*.-1SD to mean *vs.* ≥mean to 1SD *vs.*>1SD). The SD scores can be translated to the scores of the original measurement instrument of interest. All analyses were adjusted for age, sex and cancer type. Because supervised exercise showed to have larger effects on all outcomes compared to unsupervised exercise(4, 6, 7), we conducted sensitivity analyses in the subgroup of patients that had received a supervised exercise intervention.

RESULTS

Baseline values of fatigue, physical fitness, QoL, and PF are presented in Table 2. As also reported previously(4, 6, 7), linear mixed model analyses showed that exercise significantly reduced fatigue (β=-0.17,95%CI=-0.22;-0.12,$p<0.001$; I^2 for heterogeneity=37.83,p=0.02) and improved aerobic fitness (β=0.28,95%CI=0.22;0.33,$p<0.001$;I^2=81.02,$p<0.001$), UBMS (β=0.18,95%CI=0.13;0.24,$p<0.001$;I^2=65.58,$p<0.001$), LBMS (β=0.27,95%CI=0.22;0.33,$p<0.001$;I^2=84.69,$p<0.001$), QoL (β=0.15,95%CI=0.10;0.19,$p<0.001$;I^2=18.07,p=0.18) and PF (β=0.18,95%CI=0.13;0.23,$p<0.001$;I^2=38.10,p=0.01) overall, compared to the control condition.

Three-way interactions were (borderline) significant for aerobic fitness ($p_{interaction}$=0.04), UBMS ($p_{interaction}$=0.10), LBMS ($p_{interaction}$=0.05) and QoL ($p_{interaction}$=0.07), but not for fatigue ($p_{interaction}$=0.89) and PF ($p_{interaction}$=0.65). These interactions indicate that the moderator effects of the baseline values of aerobic fitness, UBMS, LBMS, and QoL differed between exercise interventions offered during versus post cancer treatment, whereas they did not differ for fatigue and PF (Table 3).

Across intervention timing, baseline PF significantly moderated the exercise intervention effect on PF ($p_{interaction}$=0.003) and baseline fatigue moderated the exercise intervention effects on fatigue ($p_{interaction}$=0.05). The exercise intervention effect on PF was significant when baseline PF was less than 1SD above the mean (Table 4;Figure 1). The exercise intervention effect on fatigue was significant when baseline values of fatigue were equal or larger than 1SD below the mean (Table 4;Figure 1).

For exercise interventions during treatment, we found that the exercise intervention effect on aerobic fitness was moderated significantly by its baseline value ($p_{interaction}$=0.002, Table 2), such that patients with low baseline aerobic fitness (<-1 SD below mean) did not significantly benefit from the exercise intervention, whereas larger benefits were found in patients with higher aerobic fitness at baseline (Table 4;Figure 2).

For exercise interventions post-treatment, baseline values of UBMS ($p_{interaction}$ <0.001), LBMS (p=0.01), and QoL ($p_{interaction}$<0.001) significantly moderated the exercise intervention effects (Table 3). Stratified analyses of the exercise intervention effects post-treatment showed larger effects on UBMS and LBMS for patients with baseline values below the mean, whereas effects on QoL were particularly pronounced for patients with baseline values of at least 1SD below the mean (Table 4;Figure 3).

Results of the sensitivity analyses in patients who had received supervised exercise interventions were only slightly different. The moderator effect of the baseline value of aerobic fitness during cancer treatment was less pronounced ($\beta_{interaction}$=0.07, 95%CI=-0.01;0.16,p=0.08). Additionally, for UBMS, the difference in the moderator effect of baseline values between interventions during and post cancer treatment was larger ($\beta_{3\text{-way interaction}}$=-0.21,95%CI=-0.32;-0.09,p<0.001), but it did not change the conclusions.

DISCUSSION

In this IPD-meta-analysis, we investigated whether the effects of exercise interventions during treatment on fatigue, physical fitness, QoL and PF were equally effective across patients with different baseline values, and whether the effects of exercise interventions on these outcomes post-treatment were larger in patients with worse baseline values. We found that baseline values did not significantly moderate the exercise intervention effect on these outcomes during cancer treatment except for aerobic fitness. For exercise interventions post cancer treatment, baseline values of UBMS, LBMS, and QoL moderated the exercise intervention effect on these outcomes, with stronger effects in patients with worse baseline values, and no significant benefits for patients with baseline values >1 SD above the mean. For aerobic fitness, we found larger effects of exercise interventions during treatment in patients with higher baseline aerobic fitness, whereas baseline values did not moderate the exercise intervention effects post-treatment. Larger effects on fatigue and PF were found for patients with worse baseline fatigue and PF, both during and post-treatment.

Our findings may have important clinical implications for identifying which subgroups of patients may benefit the most or the least from exercise during and post cancer treatment for these specific outcomes. Although exercise should be encouraged for most patients with cancer(66), our results indicate that depending on the aim of the exercise intervention, certain subgroups of patients may not gain benefits for certain outcomes. Exercise interventions during treatment are effective in maintaining UBMS, LBMS, and QoL, regardless of the baseline value. Offering exercise interventions post-treatment to patients with a relatively high UBMS, LBMS and QoL (>1 SD above the mean on respective measures) does not appear to further improve these outcomes. A previous RCT in patients with lymphoma during or post chemotherapy also found larger effects on QoL in patients with lower baseline values(21), but this study did not disentangle differences in the moderator effects across timing of intervention delivery.

Our finding that exercise interventions during cancer treatment showed better effects on aerobic fitness in patients with higher baseline aerobic fitness was unexpected and counterintuitive. The stratified analysis showed, however, that it was only patients with values lower than 1 SD below the mean who did not benefit significantly. This finding suggests that a minimum level of aerobic fitness may be needed to obtain an aerobic fitness response to an exercise intervention during cancer treatment. Perhaps, despite often being tailored to an individual's capacity, exercise interventions during intensive cancer treatments may be too difficult for patients with low aerobic fitness, resulting in lower adherence. Previous studies have found aerobic fitness to be a predictor of exercise adherence during chemotherapy(67-69). Lower adherence to exercise during chemotherapy in patients with lower aerobic fitness may be caused by more comorbidities, toxicities, illness or fatigue(67, 69, 70), as well as by limited exercise history(71) or low muscle strength(69). This may particularly be the case for unsupervised exercise, as our sensitivity analyses indicated that the moderator effect of baseline aerobic fitness was less pronounced for supervised exercise. A second possible explanation may be an inadequate exercise stimulus to improve aerobic fitness, either because exercise specialists may be too conservative when tailoring the exercise intervention to patients with low fitness during treatment, or that, related to variations in methods used to prescribe exercise intensity, patients may not be able to reach prescribed intensity targets(72, 73). Future studies should clarify if and how patients with low aerobic fitness can adhere and benefit from exercise interventions during cancer treatment. They should study how to better tailor exercise interventions during treatment to patients with low aerobic fitness, or whether it is better to offer these patients an aerobic exercise intervention after completion of cancer treatment, as this was shown to be effective for patients with various baseline fitness levels in the current meta-analysis. The discrepancy between findings for muscle strength and aerobic fitness may indicate that it is more feasible for patients with low muscle strength to perform resistance exercises during cancer treatment than for patients with low aerobic fitness to perform aerobic exercises.

In contrast to objective measures of physical fitness, larger exercise intervention effects were found for self-reported PF for patients with worse baseline values, regardless of intervention timing. Although physical fitness and PF are related, they are not the same constructs, and may therefore produce different results(74). Our data suggest that exercise interventions may improve patient reports of PF during and post cancer treatment in patients with low PF, whereas the influence of the patient's objectively assessed baseline muscle strength and aerobic fitness on the intervention effects on these outcomes differed across intervention timing. This non-linear relationship between objective functional capacity (i.e. physical fitness) and patient-reported performance (i.e. physical function) indicates that improved capacity is not necessarily a prerequisite for improved patient-reported functioning(75), and that improving PF may also require behavioral changes, adaptations to the physical environment or support from the social environment(76). Additionally, symptoms such as fatigue may also influence self-reported functioning, regardless of physical fitness(77).

Our finding that patients with worse baseline fatigue had larger fatigue reductions supports results of previous explorative studies in patients who completed cancer treatment(20, 22), and in patients during androgen deprivation therapy(23). This finding highlights the importance of targeting subgroups of patients whose fatigue is 1SD worse than the mean value, as they may benefit the most from exercise with respect to fatigue. Results showed that exercise will neither benefit PF of patients with high baseline values (>1SD above mean), nor will it benefit fatigue in patients with low symptoms of fatigue (<1SD below mean). Obviously, post cancer treatment, there is no or little room for improvement in these symptoms if they are not present or only marginally present. Perhaps during treatment, patients with no or minimal symptoms (often post-surgery) are not prone to developing them, and therefore, no significant preventive effects of exercise are found for these measures. The lack of appropriately targeted interventions in previous studies may have underestimated the effects of exercise, particularly on fatigue and PF, and post-treatment. Future studies should therefore consider targeting exercise interventions to specific subgroups of patients. More recent exercise studies have begun to target patients with symptoms such as arthralgia(78), and fatigue(79), and to tailor exercise prescriptions to key physiological characteristics, such as bone health and muscle strength(80).

Strengths of this IPD meta-analyses include the large sample size, allowing us to assess the moderator effects with interaction tests, using uniform analytic procedures across all RCTs, and to conduct subsequent stratified analyses. However, some caution is warranted in generalizing these results to all patients with cancer. The IPD study population may be somewhat biased towards patients with breast cancer and to those who are more interested in exercise and may have fewer comorbidities(81), less fatigue(63, 81, 82) and distress(83), and higher QoL(82). Additionally, this paper focused exclusively on fatigue, physical fitness, QoL and PF. Moderator effects of baseline values of other relevant outcomes, including depression, sleep, and menopausal symptoms, and long term health outcomes (e.g. cardiovascular risk, cancer recurrence, and survival) should be investigated in future studies. Finally, there was considerable heterogeneity in the content of the exercise interventions, the measures to assess the outcomes with potentially different psychometric properties and responsiveness, and the types of cancer treatments. Therefore, our findings on moderator effects of baseline values should be confirmed in large single studies with homogeneous patient populations, uniform treatment protocols, and validated outcome measures.

In conclusion, the effects of exercise interventions post cancer treatment on UBMS, LBMS and QoL appear to be larger in patients with worse baseline values, whereas exercise interventions during cancer treatment are equally effective for these outcomes, regardless of baseline values. This finding indicates that, when using exercise for rehabilitation after cancer treatments, it may be useful to target specific exercise interventions to patients with low muscle strength and poor QoL. Likewise, when aiming to benefit fatigue and PF during and post cancer treatment, exercise interventions should be targeted to patients with high levels of fatigue and low levels of PF, as they show the most benefits on these outcomes. Further research is necessary to identify how to improve aerobic fitness in patients with low aerobic fitness during cancer treatment. Although exercise is likely beneficial for most patients with cancer, exercise interventions targeted to specific subgroup of patients stand to have the largest impact on patient outcomes and the highest cost-effectiveness.

FUNDING

This work was supported by the Alpe d'HuZes foundation/Dutch Cancer Society (VU 2011-5045), via the ''Bas Mulder Award" granted to L.M. Buffart

CONFLICTS OF INTEREST

none

REFERENCES

1. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2012;11:CD006145.

2. Mishra SI, Scherer RW, Geigle PM, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev* 2012;8:CD007566.
3. Mishra SI, Scherer RW, Snyder C, et al. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;8:CD008465.
4. Buffart LM, Kalter J, Sweegers MG, et al. 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. *Cancer Treat Rev* 2017;52:91-104.
5. Sweegers MG, Altenburg TM, Chinapaw MJ, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med* 2018;52:505-513.
6. Sweegers MG, Altenburg TM, Van Vulpen JK, et al. Moderators of the exercise intervention effects on physical fitness in patients with cancer: a meta-analysis of individual patient data. *submitted* 2018.
7. Van Vulpen JK, Sweegers MG, Peeters PH, et al. Moderators of exercise on fatigue in patients with cancer: meta-analysis of individual patient data. *submitted* 2018.
8. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2016;9:CD005001.
9. Galway K, Black A, Cantwell M, et al. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. *Cochrane Database Syst Rev* 2012;11:CD007064.
10. Jassim GA, Whitford DL, Hickey A, et al. Psychological interventions for women with non-metastatic breast cancer. *Cochrane Database Syst Rev* 2015; 10.1002/14651858.CD008729.pub2(5):CD008729.

11. Heron-Speirs HA, Baken DM, Harvey ST. Moderators of psycho-oncology therapy effectiveness: meta-analysis of socio-demographic and medical patient characteristics. *Clinical Psychology: Science and Practice* 2012;19:402-416.

12. Faller H, Schuler M, Richard M, et al. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. *J Clin Oncol* 2013;31(6):782-93.

13. Schneider S, Moyer A, Knapp-Oliver S, et al. Pre-intervention distress moderates the efficacy of psychosocial treatment for cancer patients: a meta-analysis. *J Behav Med* 2010;33(1):1-14.

14. Tamagawa R, Garland S, Vaska M, et al. Who benefits from psychosocial interventions in oncology? A systematic review of psychological moderators of treatment outcome. *J Behav Med* 2012;35(6):658-73.

15. Fann JR, Fan MY, Unutzer J. Improving primary care for older adults with cancer and depression. *J Gen Intern Med* 2009;24 Suppl 2:S417-24.

16. Savard J, Simard S, Giguere I, et al. Randomized clinical trial on cognitive therapy for depression in women with metastatic breast cancer: psychological and immunological effects. *Palliat Support Care* 2006;4(3):219-37.

17. Ell K, Xie B, Quon B, et al. Randomized controlled trial of collaborative care management of depression among low-income patients with cancer. *J Clin Oncol* 2008;26(27):4488-96.

18. Kroenke K, Theobald D, Wu J, et al. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA* 2010;304(2):163-71.

19. Kalter J, Verdonck-de Leeuw IM, Sweegers MG, et al. Effects and moderators of psychosocial interventions on quality of life, and emotional and social function in

patients with cancer: an individual patient data meta-analysis of 22 RCTs. *Psychooncology* 2018; 10.1002/pon.4648.

20. Kalter J, Buffart LM, Korstjens I, et al. Moderators of the effects of group-based physical exercise on cancer survivors' quality of life. *Support Care Cancer* 2015;23(9):2623-31.

21. Courneya KS, Sellar CM, Stevinson C, et al. Moderator effects in a randomized controlled trial of exercise training in lymphoma patients. *Cancer Epidemiol Biomarkers Prev* 2009;18(10):2600-7.

22. Adams SC, DeLorey DS, Davenport MH, et al. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer* 2018 (in press).

23. Taaffe DR, Newton RU, Spry N, et al. Effects of different exercise modalities on fatigue in prostate cancer patients undergoing androgen deprivation therapy: A year-long randomised controlled trial. *Eur Urol* 2017;72(2):293-299.

24. Puetz TW, Herring MP. Differential effects of exercise on cancer-related fatigue during and following treatment: a meta-analysis. *Am J Prev Med* 2012;43(2):e1-24.

25. Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry* 2002;59(10):877-83.

26. Buffart LM, Kalter J, Chinapaw MJ, 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.

27. Wiskemann J, Kuehl R, Dreger P, et al. Efficacy of exercise training in SCT patients--who benefits most? *Bone Marrow Transplant* 2014;49(3):443-8.

28. Courneya KS, Friedenreich CM. Physical activity and cancer control. *Semin Oncol Nurs* 2007;23(4):242-52.

29. Cadmus LA, Salovey P, Yu H, et al. Exercise and quality of life during and after treatment for breast cancer: results of two randomized controlled trials. *Psychooncology* 2009;18(4):343-52.

30. Courneya KS, Mackey JR, Bell GJ, et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *J Clin Oncol* 2003;21(9):1660-8.

31. Courneya KS, Segal RJ, Mackey JR, 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(28):4396-404.

32. Daley AJ, Crank H, Saxton JM, et al. Randomized trial of exercise therapy in women treated for breast cancer. *J Clin Oncol* 2007;25(13):1713-21.

33. Duijts SF, van Beurden M, Oldenburg HS, 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(33):4124-33.

34. Hayes SC, Rye S, Disipio T, 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(1):175-86.

35. Herrero F, San Juan AF, Fleck SJ, et al. Combined aerobic and resistance training in breast cancer survivors: A randomized, controlled pilot trial. *Int J Sports Med* 2006;27(7):573-80.

36. Irwin ML, Varma K, Alvarez-Reeves M, 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(1):306-13.

37. Mehnert A, Veers S, Howaldt D, et al. 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(5):248-53.

38. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. *BMJ* 2007;334(7592):517.

39. Ohira T, Schmitz KH, Ahmed RL, et al. 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(9):2076-83.

40. Schmidt ME, Wiskemann J, Armbrust P, et al. 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(2):471-80.

41. Short CE, James EL, Girgis A, et al. 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(7):771-8.

42. Speck RM, Gross CR, Hormes JM, 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(2):421-30.

43. Steindorf K, Schmidt ME, Klassen O, 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(11):2237-43.

44. Winters-Stone KM, Dobek J, Bennett JA, et al. 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(2):189-99.

45. Winters-Stone KM, Dobek J, Nail LM, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteoporos Int* 2013;24(5):1637-46.

46. Goedendorp MM, Peters ME, Gielissen MF, 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(10):1122-32.

47. Griffith K, Wenzel J, Shang J, et al. Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors. *Cancer* 2009;115(20):4874-84.

48. Kampshoff CS, Chinapaw MJ, Brug J, 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.

49. Korstjens I, May AM, van Weert E, 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(4):422-9.

50. Thorsen L, Skovlund E, Stromme SB, et al. 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(10):2378-88.

51. Cormie P, Galvao DA, Spry N, 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(2):256-66.

52. Galvao DA, Spry N, Denham J, 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(5):856-64.

53. Galvao DA, Taaffe DR, Spry N, et al. 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(2):340-7.

54. Winters-Stone KM, Dobek JC, Bennett JA, 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(1):7-14.

55. Courneya KS, Sellar CM, Stevinson C, 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(27):4605-12.

56. Persoon S, Chin AMJM, Buffart LM, et al. Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: Results from the EXIST study. *PLoS One* 2017;12(7):e0181313.

57. Wiskemann J, Dreger P, Schwerdtfeger R, et al. Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood* 2011;117(9):2604-13.

58. Courneya KS, Friedenreich CM, Quinney HA, et al. A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl)* 2003;12(4):347-57.

59. Arbane G, Tropman D, Jackson D, et al. 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(2):229-34.

60. Travier N, Velthuis MJ, Steins Bisschop CN, et al. Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. *BMC Med* 2015;13:121.

61. van Vulpen JK, Velthuis MJ, Steins Bisschop CN, et al. Effects of an Exercise Program in Colon Cancer Patients undergoing Chemotherapy. *Med Sci Sports Exerc* 2016;48(5):767-75.

62. van Waart H, Stuiver MM, van Harten WH, 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(17):1918-27.

63. van Waart H, Stuiver MM, van Harten WH, et al. Recruitment to and pilot results of the PACES randomized trial of physical exercise during adjuvant chemotherapy for colon cancer. *Int J Colorectal Dis* 2018;33(1):29-40.

64. Twisk J, Proper K. Evaluation of the results of a randomized controlled trial: how to define changes between baseline and follow-up. *J Clin Epidemiol* 2004;57(3):223-8.

65. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;323(7321):1123-4.

66. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42(7):1409-26.

67. Van Waart H, Buffart LM, Stuiver MM, et al. Adherence to and satisfaction with low-intensity physical activity and supervised moderate-high intensity exercise during chemotherapy for breast cancer. *Submitted* 2018.

68. Courneya KS, Segal RJ, Gelmon K, et al. Predictors of adherence to different types and doses of supervised exercise during breast cancer chemotherapy. *Int J Behav Nutr Phys Act* 2014;11:85.

69. Courneya KS, Segal RJ, Gelmon K, et al. Predictors of supervised exercise adherence during breast cancer chemotherapy. *Med Sci Sports Exerc* 2008;40(6):1180-7.

70. Courneya KS, McKenzie DC, Reid RD, et al. Barriers to supervised exercise training in a randomized controlled trial of breast cancer patients receiving chemotherapy. *Ann Behav Med* 2008;35(1):116-22.

71. Kampshoff CS, Jansen F, van Mechelen W, et al. Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. *Int J Behav Nutr Phys Act* 2014;11:80.

72. Kuehl R, Scharhag-Rosenberger F, Schommer K, et al. Exercise intensity classification in cancer patients undergoing allogeneic HCT. *Med Sci Sports Exerc* 2015;47(5):889-95.

73. Scharhag-Rosenberger F, Kuehl R, Klassen O, et al. Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations. *J Cancer Surviv* 2015;9(4):612-9.

74. Douma JA, Verheul HM, Buffart LM. Patient-reported outcomes or objective measurements to assess physical function? . *Submitted* 2018.

75. WHO. *International Classification of Function, Disability and Health (ICF)*. Geneva: World Health Organization; 2001.

76. Rijpkema C, Van Hartingsveldt M, Stuiver MM. Occupational therapy in cancer rehabilitation: going beyond physical function in enabling activity and participation *Expert Review of Quality of Life in Cancer Care* 2018;in press.

77. van Weert E, Hoekstra-Weebers J, Otter R, et al. Cancer-related fatigue: predictors and effects of rehabilitation. *Oncologist* 2006;11(2):184-96.

78. Nyrop KA, Callahan LF, Cleveland RJ, et al. Randomized controlled trial of a home-based walking program to reduce moderate to severe aromatase inhibitor-associated arthralgia in breast cancer survivors. *Oncologist* 2017;22(10):1238-1249.

79. Pyszora A, Budzynski J, Wojcik A, et al. Physiotherapy programme reduces fatigue in patients with advanced cancer receiving palliative care: randomized controlled trial. *Support Care Cancer* 2017;25(9):2899-2908.

80. Galvao DA, Taaffe DR, Spry N, et al. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. *Med Sci Sports Exerc* 2018;50(3):393-399.

81. Gollhofer SM, Wiskemann J, Schmidt ME, et al. Factors influencing participation in a randomized controlled resistance exercise intervention study in breast cancer patients during radiotherapy. *BMC Cancer* 2015;15:186.

82. van Waart H, van Harten WH, Buffart LM, et al. Why do patients choose (not) to participate in an exercise trial during adjuvant chemotherapy for breast cancer? *Psychooncology* 2016;25(8):964-70.

83. Kampshoff CS, van Mechelen W, Schep G, et al. Participation in and adherence to physical exercise after completion of primary cancer treatment. *Int J Behav Nutr Phys Act* 2016;13(1):100.

Table 1. Descriptives of study-, intervention-, and exercise-characteristics of included studies (n=34), and baseline values of outcomes of participants (n=4,519).

	Number of studies	**Number of participants in these studies**
Study characteristics		
Country		
United States	8	860
The Netherlands	7	1360
Australia	6	899
Canada	4	518
Germany	4	367
United Kingdom	3	360
Spain	1	16
Norway	1	139
Sample size		
0 – 100	13	799
>100 – 200	13	1678
>200 – 300	7	1712
>300	1	330
Cancer type[a]		
Breast cancer	19	2754
Mixed cancer types	5	819
Prostate cancer	5	426
Haematological	3	311
Colon cancer	3	158
Lung cancer	1	51
Intervention characteristics		
Intervention timing		
Pre-during-post cancer treatment	1	80
During and/or post cancer treatment	3	418
During cancer treatment	13	1808
During chemotherapy	4	820
During radiotherapy	1	141
During chemotherapy and/or radiotherapy	4	524
During androgen deprivation therapy	4	326
Post cancer treatment	17	2213
Intervention delivery mode[b]		
Supervised	25	3091
Unsupervised	10	1513
Intervention Duration		
≤ 12 weeks	13	1523
12 – 24 weeks	11	1824
>24 weeks	10	1172
Type of control group[c]		
Usual care	19	2582
Wait-list	9	1364
Attention Control	7	607
Exercise characteristics		
Frequency, times per week[b]		
2	19	2742
3 – 4	8	1081
≥ 5	6	730
Unknown	1	51
Intensity[d]		
Low-moderate	2	327
Moderate	13	1528
Moderate-high	16	1926
High	2	389
Unknown	3	525
Type[e]		

Aerobic exercise	12	1374
Aerobic + resistance exercise	16	2253
Resistance exercise	5	774
Resistance + impact exercise	4	332
Mean session duration[f]		
0 – 30 min	10	1486
>30 – 60 min	19	2479
>60 min	4	502
Unknown	2	137
Outcome measure		
Fatigue	31	4366
Aerobic fitness	21	2742
Upper body muscle strength	19	2546
Lower body muscle strength	18	2258
Quality of life	34	4519
Physical function	34	4519

[a]n+2, because two(60-63)RCTs included patients with breast and colon cancer with separate reports. [b]n+1, because one RCT(62) included both a supervised (2 times per week) and an unsupervised (5 times per week) exercise study arm. [c]n+1 because one RCT(32) included both a usual care and an attention control group. [d]n+2, because one RCT(62) included a moderate intensity and moderate-high intensity study arm, and another RCT(48) included both a moderate and a vigorous intensity exercise study arm.[e]n+3, because one RCT(62) had combined aerobic and resistance exercise study arm and an aerobic exercise study arm, one RCT(31) had an aerobic exercise and a resistance exercise study arm, and one RCT(23) had a combined resistance and aerobic exercise study arm and a combined resistance and impact loading exercise arm.[f]n+1 because one RCT(62) had a study arm with 30 min/session and one with 60min/session.

Table 2. Instruments used to assess the outcome measures and the baseline values.

	Number of studies (references)	Mean (SD) total sample[a]	Mean (SD) during treatment	Mean (SD) post-treatment
Fatigue (n=4,272)				
FACIT	8 (30, 31, 34, 38, 41, 51, 55, 58)	37.1 (11.0)	36.0 (11.5)	39.1 (9.6)
MFI, general fatigue	6 (48, 49, 56, 57, 60-62)	12.1 (4.3)	10.7 (4.1)	13.5 (4.0)
EORTC QLQ-C30, fatigue	5 (23, 37, 50, 52, 53)	29.1 (22.3)	24.9 (19.3)	32.3 (23.8)
SF-36, vitality	4 (29, 33, 36, 42)	55.3 (18.7)	50.0 (9.5)	55.7 (19.2)
Schwartz Cancer Fatigue Scale	3 (44, 45, 54)	10.4 (3.9)	9.8 (4.0)	10.6 (3.9)
FAQ, total	2 (40, 43)	38.4 (21.8)	38.4 (21.8)	N/A
Revised Piper Fatigue Scale	2 (32, 47)	2.7 (1.9)	2.4 (2.0)	3.1 (1.8)
CIS, total	1 (46)	57.0 (26.1)	57.0 (26.1)	N/A
Missing, n=94				
Aerobic fitness (n=2,322)				
PeakVO$_2$, ml/kg/min	11	23.5 (7.2)	22.4 (7.1)	24.2(7.0)
Directly	8 (30, 31, 37, 48, 55, 56, 58, 60, 61)			
Indirectly via a submaximal exercise test	2 (32, 50)			
Directly or indirectly, based on patient's Preference	1 (47)			
400 meter walk test, s	4 (23, 51-53)	272.6 (49.4)	268.4 (50.4)	282.3 (53.8)
6 minute walk test, m	2 (57, 59)	441.9 (109.2)	N/A	441.9 (109.2)
12 minute walk test, m	1 (38)	986.3 (222.8)	986.3 (222.8)	N/A
Endurance test at 70% of Wmax, s	1 (62)	743.7 (530.0)	743.7 (530.0)	N/A
Modified Balke test, s	1 (58)	367.3 (291.1)	364.0 (300.1)	383.2 (269.5)
Steptest, heartrate in beats per minute	1 (34)	120.4 (16.0)	120.4 (16.0)	N/A
Missing: n=2				
Upper body muscle strength (n=2,255)				
Chest press, 1 repetition maximum in kg	10 (23, 31, 39, 42, 51-54)	34.0 (16.4)	44.2 (16.1)	24.5 (9.5)
Handgrip strength, in kg	4 (30, 48, 56, 60, 61)	35.8 (10.3)	32.9 (7.4)	37.3 (11.2)
Elbow flexion with handheld dynamometer, in Nm	1 (62)	29.9 (12.4)	29.9 (12.4)	N/A
Chest press, number of repetitions at 30-35% body mass	1 (35)	0.1 (0.5)	N/A	0.1 (0.5)
Sum upper body muscle strength (4 groups), in N	1 (57)	154.1 (50.6)	N/A	N/A
Sum of left and right grip strength, kg	1 (58)	70.5 (22.5)	71.9 (21.8)	68.9 (23.6)
Upright row and shoulder press, stage	1 (34)	6.8 (3.1)	6.8 (3.1)	N/A
Missing, n=79				
Lower body muscle strength (n=2,056)				
Leg press, 1 repetition maximum in kg	9 (23, 39, 42, 44, 45, 51-54)	101.9 (43.6)	124 (51.6)	89.8 (32.7)
Quadriceps torque, in Nm	5 (32, 40, 43, 56, 60, 61)	104.6 (35.7)	103.3 (28.5)	107.5 (47.8)

Leg extension, 1 repetition maximum in kg	1 (31)	54.9 (26.6)	54.9 (26.6)	N/A
Knee extension with handheld dynamometer, in Nm	1 (62)	67.6 (19.1)	67.6 (19.1)	N/A
Leg press, number of repetitions at 100-110% body mass	1 (35)	13.5 (7.2)	N/A	13.5 (7.2)
Sum of lower body muscle strength (4 groups), in N	1 (57)	186.1 (58.7)	N/A	N/A
Missing: n= 107				
Quality of life (n=4,419)				
EORTC-QLQ-C30, global QoL	17 (23, 35, 40, 43-46, 48-54, 56, 59-61)	69.6 (19.0)	71.7 (18.7)	67.8 (18.7)
FACT-G, total score	10 (29-32, 34, 36, 38, 41, 55, 58)	81.3 (14.3)	79.2 (14.6)	84.1 (13.5)
SF-36, general health	6 (33, 37, 42, 44, 45, 47)	66.3 (19.6)	52.6 (13.9)	68.7 (19.8)
Cares-SF, global QoL	1 (39)	48.2 (9.1)	N/A	48.2 (9.1)
Missing, n=100				
Physical Function (n=4,433)				
EORTC-QLQ-C30, physical function	17 (23, 35, 40, 43-46, 48-54, 56, 59-61)	83.4 (16.1)	86.7 (14.5)	79.6 (16.5)
FACT-G, physical well-being	10 (29-32, 34, 36, 38, 41, 55, 58)	21.9 (5.4)	20.6 (5.9)	23.7 (3.9)
SF-36, physical function	6 (33, 37, 42, 44, 45, 47)	81.6 (17.6)	85.6 (14.4)	80.9 (18.0)
Cares-SF, physical function	1 (39)	46.6 (7.0)	N/A	46.6 (7.0)
Missing, n= 86				

[a]The SD values of the total group can be used to interpret the effect sizes, which are expressed in SD scores.

Abbreviations: CARES-SF=Cancer Rehabilitation Evaluation System-Short Form; CIS=Checklist Individual Strength; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FACIT= Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-G= Functional Assessment of Cancer Therapy-General; FAQ= Fatigue Assessment Questionnaire; MFI= Multidimensional Fatigue Inventory; N/A= not applicable; peakVO_2= peak oxygen uptake; SF-36= Short Form-36 Health Survey.

Table 3. Moderator effects of baseline values for the total group or stratified for interventions during and post cancer treatment in case of significant moderator effect of timing.

Variable	3-way interaction		Moderator effect in total group		Moderator effect during cancer treatment		Moderator effect post cancer treatment	
	p of LR test	**$\beta_{interaction}$ (95%CI)**	**P of LR test**	**$\beta_{interaction}$ (95%CI)**	**P of LR test**	**$\beta_{interaction}$ (95%CI)**	**P of LR test**	**$\beta_{interaction}$ (95%CI)**
Fatigue	0.89	0.007 (-0.10; 0.11)	0.05#	-0.05 (-0.10; 0.000)	-	-	-	-
Aerobic fitness	0.04*	-0.11 (-0.22; -0.004)*	-	-	0.002*	0.11 (0.04;0.18)	0.95	0.002 (-0.08;0.08)
UBMS	0.10#	-0.10 (-0.21; 0.02)	-	-	1.00	-0.00 (-0.09;0.09)	<0.001*	-0.11 (-0.17;-0.05)
LBMS	0.05#	-0.12 (-0.24; 0.002)	-	-	0.57	0.02 (-0.06;0.10)	0.01*	-0.10 (-0.18;-0.02)
QoL	0.07#	-0.09 (-0.19;0.006)	-	-	0.38	-0.03 (-0.11;0.04)	<0.001*	-0.13 (-0.19;-0.06)
PF	0.65	-0.02 (-0.12;0.08)	0.003*	-0.07 (-0.12;-0.03)	-	-	-	-

*p≤0.05, #0.05 <p≤ 0.10. Analyses are adjusted for age, sex and cancer type.

Abbreviations: CI= confidence intervals; LBMS= lower body muscle strength; LR= likelihood ratio; PF= physical function; QoL= quality of life; UBMS= upper body muscle strength

Table 4. Exercise intervention effects on outcomes for the total group and stratified per subgroup based on baseline standard deviation score, in case of significant moderator effects of the baseline values.

	Overall effect	**<1 SD below mean**	**1 SD below mean to mean**	**mean to 1SD above mean**	**>1 SD above mean**	**P for trend**
	β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	
All studies						
Fatigue[a]	-0.17 (-0.22; -0.12)* (n=3846)	-0.03 (-0.13; 0.08) (n=649)	-0.17 (-0.25; -0.09)* (n=1430)	-0.20 (-0.30; -0.11)* (n=1124)	-0.22 (-0.37; -0.07)* (n=643)	<0.001
PF	0.18 (0.13; 0.23)* (n=3984)	0.27 (0.11; 0.42)* (n=649)	0.22 (0.11; 0.34)* (n=890)	0.19 (0.12; 0.25)* (n=1727)	0.03 (-0.07; 0.12) (n=718)	<0.001
During cancer treatment						
Aerobic fitness	0.25 (0.18; 0.33)* (n= 1374)	0.07 (-0.12; 0.26) (n=211)	0.20 (0.09 0.31)* (n=510)	0.32 (0.22; 0.43)* (n=453)	0.38 (0.15; 0.60)* (n=200)	<0.001
UBMS	0.25 (0.16; 0.35)* (n=1106)	-	-	-		
LBMS	0.29 (0.20; 0.37)* (n=1019)	-	-	-		
QoL	0.15 (0.07; 0.22)* (n=1914)	-	-	-		
Post cancer treatment						
Aerobic fitness	0.33 (0.24; 0.41)* (n=843)	-	-	-		
UBMS	0.10 (0.04; 0.15)* (n=904)	0.21 (0.12; 0.30)* (n=168)	0.19 (0.13; 0.25)* (n=458)	-0.04 (-0.16; 0.08) (n=180)	-0.06 (-0.17; 0.06) (n=98)	<0.001
LBMS	0.26 (0.18; 0.34)* (n=646)	0.38 (0.25; 0.51)* (n=89)	0.30 (0.21; 0.39)* (n=363)	0.20 (-0.01;0.40)# (n=129)	0.03 (-0.33; 0.40) (n=65)	<0.001
QoL	0.15 (0.09; 0.21)* (n=1960)	0.36 (0.17; 0.55)* (n=311)	0.19 (0.06; 0.32)* (n=538)	0.12 (0.03; 0.21)* (n=741)	-0.02 (-0.13; 0.08) (n=370)	0.012

*p≤0.05, #0.05 <p≤ 0.10. Analyses are adjusted for age, gender and cancer type

[a]Higher scores on the fatigue scale indicate more fatigue

Abbreviations: CI= confidence intervals; df= degrees of freedom; LBMS= lower body muscle strength; PF= physical function; QoL= quality of life; SD= standard deviation; UBMS= upper body muscle strength

Figure 1. Stratified subgroup effect of exercise interventions based on pre-intervention standard deviation (SD) score for baseline values of physical function (black bars) and fatigue (white bars) during and post cancer treatment.

Figure 2. Stratified subgroup effects of exercise interventions based on pre-intervention standard deviation (SD) score for the baseline value of aerobic fitness during treatment.

Figure 3. Stratified subgroup effects of exercise interventions based on pre-intervention standard deviation (SD) score for baseline values of upper body muscle strength (black bars), lower body muscle strength (white bars) and quality of life (dashed bars) post cancer treatment.