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Moderators of exercise effects on cancer-related fatigue: a meta-analysis of individual patient data

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Moderators of Exercise Effects on Cancer-related Fatigue: A Meta-analysis of Individual Patient Data

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Abstract

Purpose - Fatigue is a common and potentially disabling symptom in patients with cancer. It can often be effectively reduced by exercise. Yet, effects of exercise interventions might differ across subgroups. We conducted a meta-analysis using individual patient data of randomized controlled trials (RCTs) to investigate moderators of exercise intervention effects on cancer-related fatigue. **Methods –** We used individual patient data from 31 exercise RCTs worldwide, representing 4,366 patients, of whom 3,846 had complete fatigue data. We performed a one-step individual patient data meta-analysis, using linear mixed-effect models to analyze the effects of exercise interventions on fatigue (z-score) and to identify demographic, clinical, intervention- and exercise-related moderators. Models were adjusted for baseline fatigue and included a random intercept on study level to account for clustering of patients within studies. We identified potential moderators by testing their interaction with group allocation, using a likelihood ratio test. **Results –** Exercise interventions had statistically significant beneficial effects on fatigue (β= -0.17 [95% confidence interval (CI) -0.22;-0.12]). There was no evidence of moderation by demographic or clinical characteristics. Supervised exercise interventions had significantly larger effects on fatigue than unsupervised exercise interventions ($\beta_{difference}$= -0.18 [95%CI -0.28;-0.08]). Supervised interventions with a duration ≤12 weeks showed larger effects on fatigue (β= -0.29 [95% CI -0.39;-0.20]) than supervised interventions with a longer duration. **Conclusions –** In this individual patient data meta-analysis, we found statistically significant beneficial effects of exercise interventions on fatigue, irrespective of demographic and clinical characteristics. These findings support a role for exercise, preferably supervised exercise interventions, in clinical practice. Reasons for differential effects in duration require further exploration.

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Registration - PROSPERO, CRD42013003805.

Key words - exercise; fatigue; cancer; individual patient data meta-analysis

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Introduction

With an estimated 22.2 million new cancer cases world-wide per year by 2030 (1), attention to cancer- and treatment-related symptoms is of great importance. Patients with cancer suffer from a variety of symptoms, of which cancer-related fatigue is one of the most frequently reported and disabling (2). Fatigue is a potential contributing factor to treatment noncompliance, treatment modifications and early discontinuation of treatment, which in turn might have negative impact on clinical outcomes (3). Although fatigue levels are typically highest during active treatment, elevated levels often persist, even up to 5 years after successful cancer treatment (2, 4). With its negative impact on work, daily activities, social activities and mood, fatigue causes significant impairment in quality of life among patients with cancer (5, 6).

Since the late 1980s, exercise has been proposed as a potential intervention for the prevention and reduction of cancer-related fatigue (7). An increasing number of randomized controlled trials (RCTs) in patients with cancer and survivors have evaluated the effects of exercise interventions, most of which have included fatigue as one of the main outcomes. Several meta-analyses have confirmed the beneficial effects of exercise interventions on fatigue, both during and after completion of primary cancer treatment (8-12). A recent meta-analysis, comparing effects of pharmaceuticals, exercise, psychological interventions, and combined exercise and psychological interventions, showed that the largest improvement in cancer-related fatigue was achieved by exercise interventions (weighted effect size: 0.30 [95% confidence interval (CI) 0.25; 0.36]) (9).

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With the availability of an effective intervention for diminishing fatigue, an important next step is to investigate: 1) whether or not exercise intervention effects are consistent across subgroups of patients with cancer; and 2) intervention characteristics with largest effect. Previous meta-analyses evaluated the overall exercise intervention effects on fatigue across a wide range of patient groups and interventions (8-12). It is important to determine if there is heterogeneity in responses to exercise interventions by investigating the potential moderating effects of sociodemographic and clinical characteristics. In addition, identifying characteristics of the exercise intervention that maximize the effect of exercise on fatigue will help to target and improve exercise programs. However, most RCTs are not adequately powered to identify differences in effects between subgroups with the use of interaction tests. Further, conventional meta-analyses lack the detailed information on individual patient characteristics that is needed for such analyses, resulting in potential ecological bias (i.e. bias that occurs when patient-level interactions are influenced by study-level interactions) (13, 14).

Individual patient data meta-analyses offer an opportunity to investigate moderators of intervention effects in a more thorough manner. By merging and synchronizing raw individual patient data from multiple RCTs, a large amount of detailed information on patient and intervention characteristics is available, which facilitates testing interactions at the patient-level (13, 14). In the current paper, we report the results of an analysis of individual patient data from RCTs in an effort to identify relevant moderators of the effects of exercise interventions on fatigue levels in patients with cancer.

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Methods

The current study is part of the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) project(15): an international infrastructure and shared database of RCTs investigating exercise and psychosocial intervention effects in patients with cancer (registered in PROSPERO, CRD42013003805). Effects and potential moderators of the effect of exercise on quality of life have been published previously (16). A detailed description of the POLARIS study design, including the method of study identification and selection, has been published (15). The meta-analysis was conducted in accordance with the PRISMA guidelines.

Briefly, principal investigators of 34 exercise RCTs worldwide have shared individual patient data. All principal investigators signed a data sharing agreement, stating that they agreed with the POLARIS policy document and were willing to share anonymized data of study participants. All individual studies had received approval from their local ethics committees. Datasets were imported into the POLARIS database and subsequently harmonized according to standardized protocols. Validity checks were performed on improbable or missing values. Details on requested variables, and data and project management can be found in the published study design (15). All exercise RCTs in POLARIS that reported fatigue outcomes were included in the current individual patient data meta-analysis.

Quality assessment

Methodological quality for each RCT included in the current analysis was assessed using the 'risk-of-bias' tool of the Cochrane Collaboration by two authors independently (MS and LB) (17). The following aspects were graded as high, low or unclear quality: random sequence

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generation (high quality if random component was used; 25 trials), allocation concealment (high quality if central, computerized allocation or sequentially numbered sealed envelopes were used; 24 trials), incomplete outcome (high quality if intention-to-treat analyses were performed and missing outcome data were <10% or adequate imputation techniques were used; 25 trials), and incomplete reporting (high quality if fatigue was reported such that data could be entered in an aggregate data meta-analysis; 24 trials). In addition, we assessed adherence (high quality if ≥80% of patients attended ≥80% of sessions; 12 trials) and contamination (high quality if no or limited exercise was present in the control group; 7 trials). For full quality assessment of the included trials, we refer to our previous publication (16).

Outcomes

The main outcome of our analysis was fatigue after the completion of the exercise intervention, measured with Multidimensional Fatigue Inventory (MFI) general fatigue scale(18) (six studies(19-26)), Fatigue Assessment Questionnaire (FAQ)(27) (two studies(28, 29)), Schwartz Cancer Fatigue Scale (SCFS-6)(30) (three studies(31-33)), revised Piper Fatigue Scale (PFS)(34) (two studies(35, 36)), Checklist Individual Strength (CIS)(37) (one study(38)), Functional Assessment of Cancer Therapy (FACT)/Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue scale(39) (eight studies(40-47)), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Fatigue subscale(48) (five studies(49-53)) and Short Form Health Survey (SF-36) Vitality subscale(54) (four studies(55-58)). If a study used multiple questionnaires to assess fatigue, we used data from 1) the fatigue-specific questionnaire or, 2) the fatigue scale of a cancer-specific quality of life questionnaire.

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Potential moderators

Potential moderators of the effects of exercise on fatigue were specified based on previous RCTs and meta-(regression) analyses(11, 24, 52, 59-61). Potential demographic moderators included age, sex, marital status, and education level (Table 1)(16). Potential clinical moderators included body mass index (BMI), cancer type, treatment type (surgery, chemotherapy, radiotherapy and hormone therapy), and presence of distant metastases.

A selection of intervention characteristics were identified as potential moderators of effective exercise programs(16): timing of intervention in relation to primary cancer treatment, delivery mode, and intervention duration (Table 1). Potential exercise-related moderators included: prescribed exercise frequency, exercise intensity, exercise type, exercise session time (i.e. FITT-factors) and exercise volume (i.e. frequency*time) (Table 1). Exercise intensity was scored according to the definitions of the American College of Sports Medicine (62). Exercise volume was dichotomized into <150 minutes versus ≥ 150 minutes per week, corresponding to ACSM's exercise guidelines for cancer survivors (63).

Statistical analysis

To allow pooling of the different fatigue questionnaires, we calculated z-scores for each individual by subtracting the mean score from the individual score at baseline per fatigue questionnaire and dividing the result by the mean standard deviation at baseline per questionnaire. Within our analyses, we used a one-step approach, i.e. simultaneously analyzing all observations while accounting for clustering of observations within studies (14). We conducted all analyses according to the intention-to-treat principle. We used linear mixed effects

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models to analyze the exercise intervention effect on fatigue. The models were adjusted for the baseline value of fatigue and included a random intercept on study level to take clustering of patients within studies into account. The result, a between-group difference in z-scores, corresponds to a Cohen's d effect size. Absolute effects of 0.2-0.5 were considered small, 0.5-0.8 as moderate and ≥0.8 as large (64).

To examine whether the effect of exercise interventions on fatigue was moderated by patient characteristics, the aforementioned models were extended with interaction terms of the group allocation with demographic and clinical characteristics. To prevent ecological bias for patient-level interactions, we centered the individual values of potential moderators around their mean study values (13). The independent variables in the models were random intercept, group allocation (exercise intervention or control), baseline value of fatigue, centered patient characteristic, and interaction term (centered patient characteristic*group allocation). The potential moderators were examined one-by-one in separate models. We considered a patient-characteristic to be a moderator if the likelihood ratio test (LRT) indicated a statistically significant improvement of the model fit by adding the interaction term.

To identify intervention- and exercise-related moderators, we did not center the characteristics, since these generally do not vary within studies. A similar method as described above was used, with an interaction term between group allocation and the non-centered intervention- or exercise-related characteristic. If this analysis yielded a statistically significant interaction, exercise intervention effects were reported per stratum. For studies with multiple intervention arms with different characteristics, interaction testing for these specific

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characteristics was not possible. In those situations, we applied a different approach: the main effect models were evaluated using dummy variables for the intervention- or exercise-related characteristics. Again, analyses were performed for each characteristic separately. Because of the statistically significant moderator effect of delivery mode and the differential exercise characteristics between supervised and unsupervised exercise interventions, we investigated exercise-related moderators stratified per delivery mode.

Since the majority of patients were women with breast cancer, we also tested overall effects on fatigue for patients with breast cancer versus other patients (dichotomized). Because no statistically significant interaction was found (p-value LRT 0.7) and effect sizes were similar, analyses are presented for all cancer types combined. Statistical significance was set at a probability of $p<0.05$ for all analyses. All statistical analyses were performed using IBM SPSS Statistics 21.0 and R version 3.1.1.

Results

Of the 34 exercise RCTs included in the POLARIS database, 31 evaluated the effect of exercise interventions on fatigue, representing 4,366 individual patients. Of these, 2,437 patients were randomized to an exercise intervention group and 1,929 to a control group. Baseline demographic and clinical characteristics of patients in the exercise intervention group and control group are presented separately in Table 2. Patients had a mean age of 54.5 (±11.4) years and a mean BMI of 27.2 (±5.2) kg/m^2. The majority of patients were female (78%) and diagnosed with breast cancer (70%). Only a small proportion of patients (2%) had distant metastases at baseline. Baseline variables were well balanced over the exercise intervention and control groups.

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Baseline and end of intervention values were available for analysis of fatigue scores for 3,846 patients.

Included exercise interventions

The studies included in the analysis, published between 2003-17, were carried out in the Netherlands (19-25, 38, 56), the United States (31-33, 36, 55, 57, 58), Australia (40, 45, 47, 49, 50, 52), Canada (41-44), Germany (26, 28, 29, 51), United Kingdom (35, 46), and Norway (53). Sample sizes ranged from 50 to 330 patients. Of the patients allocated to an exercise intervention group, a little over half (50.3%) participated in exercise during primary cancer treatment (Table 3 and Supplemental Digital Content 1, Appendix, http://links.lww.com/MSS/B757). For the majority of patients, the exercise intervention was (partly) supervised (65.3%). Duration of the exercise interventions varied between 8 and 52 weeks. Most patients participated in exercise interventions that prescribed exercising twice a week (53.6%) at a moderate-vigorous to vigorous intensity (48.9%), with session duration of 30-60 minutes (51.7%), and an exercise volume of <150 minutes per week (63.2%). A combination of aerobic and resistance exercise was the most common exercise type (50.7%). Of the patients allocated to a control group, the majority were assigned to a usual care group (63.9%).

Effects on fatigue and moderating effects by patient characteristics

Exercise interventions had statistically significant beneficial effects on fatigue (β=-0.17 [95% CI -0.22; -0.12]) compared to control (Table 4 and Figure 1). Our interaction analyses did not reveal statistically significant moderation of demographic or clinical characteristics on the intervention effect on fatigue (Table 4).

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Intervention- and exercise-related moderators

Timing of the intervention (i.e. during or post primary cancer treatment) was not found to influence the effect of exercise on fatigue (Table 5). Supervised exercise interventions had statistically significantly larger effects on fatigue than unsupervised exercise interventions (difference between subgroups: -0.18 [95% CI: -0.28;-0.08]). Compared to the control group, supervised exercise interventions showed statistically significant improvement of fatigue (β=-0.23 [95% CI: -0.29; -0.17]), while unsupervised exercise interventions did not (β=-0.04 [95%CI -0.13; 0.04]) (Table 5 and Figure 1). Within the supervised interventions, duration of the exercise intervention was found to moderate the effect of exercise on fatigue. Largest effects on fatigue were observed in the supervised exercise interventions with a duration ≤12 weeks (β=-0.29 [95%CI: -0.39;-0.20]) and smallest effects were observed in supervised exercise interventions with duration of >24 weeks (β=-0.11 [95%CI: -0.22; -0.0002]). No other intervention- or exercise-related characteristics were identified as moderators of supervised exercise interventions. Within the unsupervised interventions, neither duration of the intervention nor exercise-related characteristics moderated the effect of exercise interventions on fatigue (Table 5).

Discussion

The results of our individual patient data meta-analysis of 31 RCTs indicate that exercise interventions have statistically significant beneficial effects on fatigue in patients with cancer. For the populations studied, we found no indication that selection of patients based on their demographic or clinical characteristics would lead to different effects of exercise interventions on fatigue. Instead, beneficial effects on fatigue were observed across all subgroups of patients,

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supporting a role for exercise in clinical practice for patients with cancer. Strongest effects on fatigue were observed in supervised exercise interventions, whereas effects for non-supervised interventions were non-significant.

The beneficial effect of exercise interventions on fatigue that we observed in this study is in line with previous meta-analyses (8-12). The overall effect on fatigue in our study was statistically significant. Clinical relevance, however, was most pronounced for supervised interventions, that showed significant and small effects on fatigue (64). Despite this small clinically relevant effect, the clinical relevance is further underlined by the magnitude of the problem of fatigue, both in terms of the number of patients affected and the negative impact on patients' lives, combined with the lack of other, more effective treatment options (9).We recently showed that exercise intervention effects on fatigue are larger in patients with worse baseline fatigue levels . Exercise intervention effects on fatigue would possibly be larger in trials selecting patients based on their baseline fatigue level. Another explanation for the small effect may be the joint evaluation of different dimensions of fatigue, resulting in a dilution of the effect by the fatigue dimensions that may be less sensitive to exercise (e.g. mental fatigue) (66).

The availability of a large set of individual patient data in our study offered a unique opportunity to investigate if the effect of exercise interventions on fatigue differed significantly across subgroups of patients with cancer. In previous attempts to identify patient-level moderators using meta-regression analyses, chemotherapy and age were found to be statistically significant modifiers of the effect of exercise (59, 60). Importantly, in these studies, only published aggregate data (i.e., summary statistics, such as mean age) were available. Although

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meta-regression techniques can be used to explore moderation of exercise effects, they have several important disadvantages, including a high risk of bias due to the inability to disentangle patient-level heterogeneity from study-level heterogeneity (ecological bias) (13, 67). Therefore, the use of individual patient data to investigate the possible influence of patient-level characteristics is considered superior (67). In line with a previous single RCT exploring moderators of exercise effects on fatigue (19), and our individual patient data meta-analysis of moderators of exercise effects on quality of life (16), we did not identify any statistically significant demographic or clinical moderators of the effect of exercise on fatigue in patients with cancer. Accordingly, our findings support the use of exercise interventions for treatment of fatigue across subgroups of patients with cancer.

Of note, the largest group of patients included in the current individual patient data meta-analysis had breast cancer, followed by prostate cancer and hematological malignancies. Although we did not observe a moderating effect of cancer type in our study, the limited number of cancer sites included in the RCTs that were part of the present analysis precludes generalizing our results to all cancer types. Also, the large majority of patients were treated with curative intent. Therefore, the effects of exercise on fatigue in the metastatic setting requires further investigation.

We observed that supervised exercise interventions had a larger effect on fatigue than unsupervised interventions, which was both statistically significant and clinically relevant. The larger effects of supervised exercise interventions may be explained by psychosocial benefits due to attention and positive feedback on progress in fitness by the physiotherapist or exercise

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physiologist delivering the intervention. However, RCTs comparing a supervised exercise intervention with a supervised relaxation control group, and thus controlling for attention, also showed that effects on fatigue were significantly higher in the exercise group (28, 29). An additional feature that may explain the larger effect size of supervised exercise interventions is access to proper equipment, permitting appropriate overload, monitoring and feedback, hence appropriate intensity. As intensity is often higher in supervised programs (e.g. because of safety reasons), teasing out the relative benefit of delivery mode from that of intensity is difficult. In addition, the larger effects of supervised exercise interventions may be explained by better adherence, greater quality in performance of the exercises, selection of different patients and higher fidelity of patient exercise monitoring. Moreover, goals of a supervised exercise program may be different from goals of unsupervised exercise interventions (e.g. increasing physical fitness versus increasing level of daily physical activity).

Our findings suggest that in the patient groups represented in the included RCTs, supervised exercise interventions should be preferred over unsupervised interventions in the treatment of fatigue. However, it should be noted that home-based interventions might be preferred by some patients, because they are not able or willing to attend supervised interventions (68). Moreover, unsupervised interventions have been found to exert positive effects on other outcomes, such as physical functioning (16). We recommend that in general, patients with cancer should be prescribed a supervised exercise intervention, particularly prior to, during and the initial three months following cancer treatment when fatigue effects of treatment are greatest. For those who do not have access to a supervised exercise intervention, unsupervised exercise interventions could still be useful, and might be augmented with e-Health

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applications. Further investigation is needed to understand which components are the most critical for inclusion in home-based interventions (e.g. including more tailored exercise advice).

Incorporation of supervised exercise into standard care might possibly be more demanding in terms of resource allocation and costs. However, a recent trial showed that a home-based, low-intensity physical activity program was not likely to be cost-effective for fatigue in comparison with usual care, whereas a supervised, moderate-to-high intensity exercise program could be considered cost-effective for fatigue depending on the decision-makers' willingness-to-pay (69). Also, our finding that exercise interventions with a duration as short as 12 weeks already have clinically relevant effects on fatigue, may further support the feasibility of incorporating supervised exercise into standard care.

The largest effects of supervised interventions on fatigue were observed in the studies with shortest intervention duration. It is possible that adherence to the intervention, and consequently the effect of exercise on fatigue, decreases over time (70). At the same time, contamination (adoption of exercise by the control group) may increase over time as well (71). In addition, there may be a ceiling effect of exercise interventions on fatigue in cancer patients whereby 12 weeks or less is sufficient to counteract disease and treatment detriments and further duration provides maintenance. Furthermore, we cannot exclude the possibility that this finding is partly due to the distribution of other exercise-related characteristics over the duration strata. It would be interesting to compare the long-term fatigue outcomes between the interventions with different durations, but as only a few studies have examined maintenance of intervention effects in the long-term (21, 72-74), this remains to be investigated. In any case, it is an important

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finding that interventions with a duration as short as 12 weeks already have positive and clinically relevant effects.

Several methodological limitations of our study should be noted. First, our literature search was conducted in 2012 (15), but we also included published study designs in our literature search and contacted the principal investigators of these studies. Therefore, we included 13 studies that were completed after 2012. Although the literature search focused on quality of life as primary or secondary outcome, fatigue was assessed in most of the RCTs (31/34) in parallel with quality of life. Our main aim was to assess moderators of exercise effects on fatigue using individual patient data, and we have no reason to believe that adding more recent studies would significantly change our conclusions regarding patient- and disease-related moderators. As technology is continuously evolving, intervention characteristics of more recent studies might differ from studies conducted in the past. Although technology developments likely take place throughout the whole field of exercise interventions, we cannot exclude the possibility that adding more recent data could impact some intervention and exercise-related moderators.

Second, despite the inclusion of a large amount of individual patient data, the statistical power to detect intervention- and exercise-related moderators was limited because these variables are defined at the study-level (14). Especially the identification of significant exercise-related moderators (FITT-factors), which were stratified by delivery mode, may have been compromised by limited power or little variation across studies. Also, we only examined single interactions, but there may be more complex multilevel interactions. Furthermore, within meta-analyses, in general, both patient-level and study-level characteristics can be influenced by

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(other) study-level characteristics. Centering of patient-level characteristics enabled us to reduce the risk of ecological bias by separating patient-level heterogeneity from study-level heterogeneity when evaluating demographic and clinical moderators (13). This approach was not possible for the analyses on intervention- and exercise-related characteristics, making these analyses more prone to influences of other study-level characteristics. Thus, more RCTs that include head-to-head comparisons of intervention and exercise-related characteristics are warranted to confirm our findings and to better disentangle the effects of different study-level determinants, e.g. comparisons between exercise interventions with different exercise types (75, 76) or post-treatment exercise interventions with different timing in relation to cancer treatment.

Third, adherence to exercise interventions was unknown in the majority of included studies and consequently, patients in the exercise groups might have actually been exposed to different exercise-related characteristics than assumed. In addition, information on contamination was limited, hampering our ability to take the activity level of patients in the control group into account. Since adherence and contamination may affect intervention outcomes(41, 77), care should be taken to accurately registering both items in order to optimally interpret outcomes of exercise interventions.

The present study is the first to collect, synchronize, pool and analyze individual patient data on cancer-related fatigue from exercise RCTs worldwide. We applied a careful standardization of the outcome data and uniform analytic procedures across all studies. An important strength of the study is the availability of a large amount of individual patient data, which enabled us to study multiple demographic and clinical patient-level moderators.

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Conclusions

In conclusion, we found that exercise has statistically significant beneficial effects on fatigue in patients with cancer. These benefits are consistent across subgroups formed on the basis of demographic and clinical characteristics. The effect of exercise interventions on fatigue is significantly larger when performed under supervision. Differential effects of duration and potential roles of adherence and contamination in these findings need further exploration. Our results support implementation of exercise, preferably supervised exercise interventions, in clinical practice.

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The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and results of the present study do not constitute endorsement by ACSM.

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Figure legends

Figure 1 Forest plot of the effects of exercise interventions on fatigue.

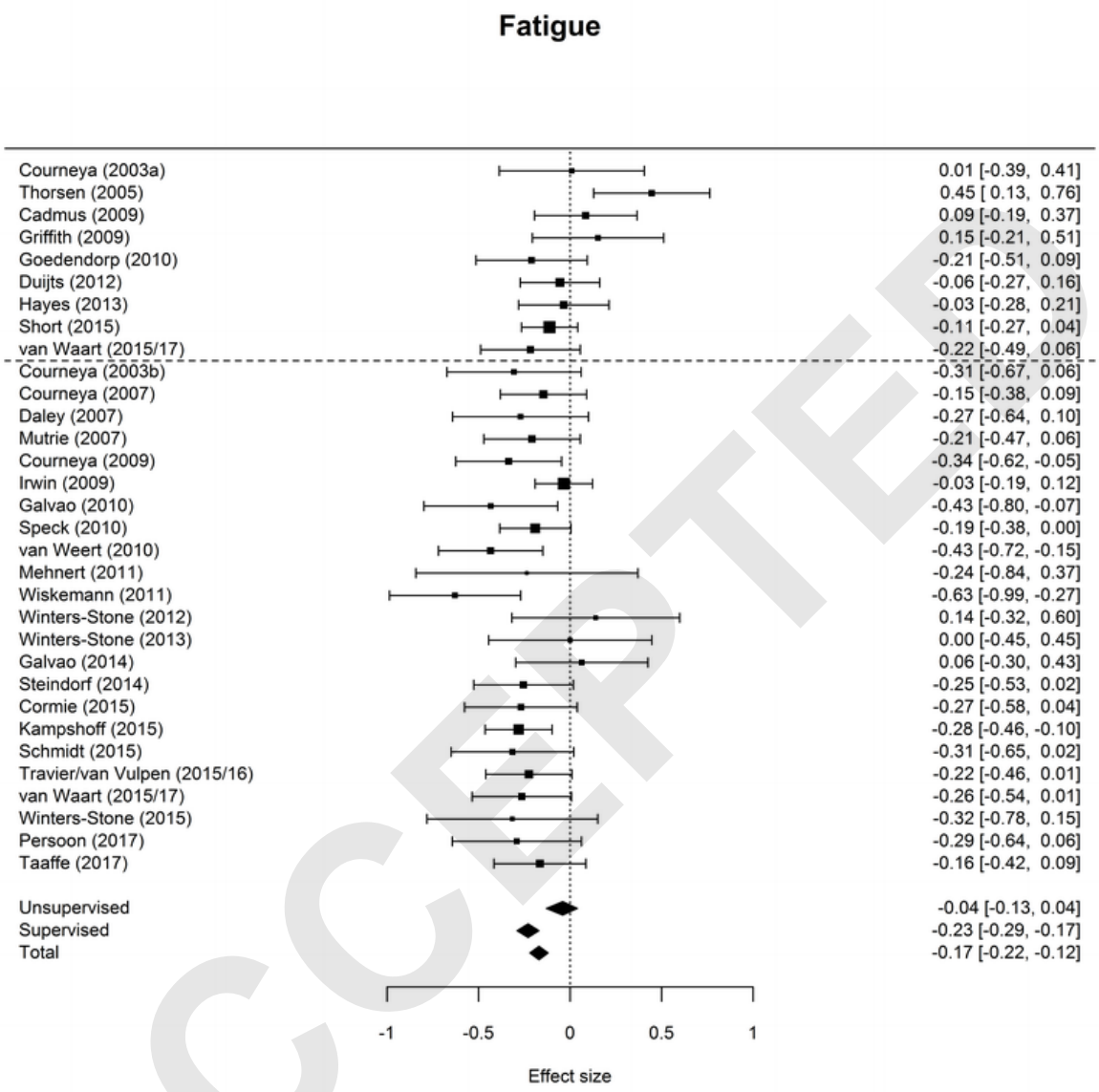
Exercise effects (between-group differences in z-scores) with 95% confidence intervals are presented per intervention, in alphabetical order of first author. Unsupervised interventions are presented above the dashed line, and supervised interventions below. Summary estimates for unsupervised interventions, supervised intervention and all interventions are provided.

Supplemental Digital Content 1 - Appendix 1: Descriptives of studies evaluating the effects of exercise interventions on fatigue (N=31)

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Figure 1



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Table 1 Potential moderators of exercise intervention effects on fatigue

Potential moderator	Subcategories
Demographic moderators	
Age	Continuous
Sex	Men Women
Marital status	Single Married or living with partner
Education level	Low-medium (elementary, primary or secondary school, or lower or secondary vocational education) High (higher vocational, college or university education)
Clinical moderators	
Body mass index	Continuous
Cancer type	Breast cancer Male genitourinary cancer Gastrointestinal cancer Hematological cancer Gynecological cancer Other types of cancer
Surgery	Previous or current treatment No such treatment
Chemotherapy	Previous or current treatment No such treatment
Radiotherapy	Previous or current treatment No such treatment
Hormone therapy	Previous or current treatment No such treatment
Presence of distant metastases	Yes No
Intervention-related moderators	
Timing of intervention	During primary cancer treatment Post primary cancer treatment
Delivery mode	Supervised exercise interventions ((part of) exercise sessions conducted under supervision) Unsupervised exercise interventions (exercise sessions performed unsupervised from or at home)
Intervention duration	≤12 weeks (median 12 weeks, range 3-12) >12-24 weeks (median 16 weeks) >24 weeks (median 32 weeks, range 26-52)
Exercise-related moderators	
Exercise frequency	Supervised: <3 sessions per week ≥3 sessions per week Unsupervised: <5 sessions per week ≥5 sessions per week
Exercise intensity	Low-moderate and moderate Moderate-vigorous and vigorous
Exercise type	Aerobic exercise (AE)

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	Resistance exercise (RE) Combined aerobic and resistance exercise (AE+RE) Combined resistance and impact loading exercise (RE+impact)
Exercise time per session	≤30 minutes >30-60 minutes >60 minutes
Exercise volume	<150 minutes per week ≥150 minutes per week

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Table 2 Demographic and clinical characteristics of individual patients from 31 exercise randomized controlled trials included in the meta-analysis

	Exercise (n=2437)	**Control (n=1929)**
Demographic characteristics		
Age, mean (SD) years	54.5 (11.5)	54.5 (11.2)
Age categories, n (%)		
< 50 years	831 (34.1)	644 (33.4)
50-70 years	1365 (56.0)	1102 (57.1)
≥ 70 years	239 (9.8)	177 (9.2)
Unknown	2 (0.1)	6 (0.3)
Sex, n (%)		
Men	539 (22.1)	426 (22.1)
Women	1898 (77.9)	1503 (77.9)
Married/living with partner, n (%)		
Yes	1587 (65.1)	1209 (62.7)
No	442 (18.1)	389 (20.2)
Unknown	408 (16.7)	331 (17.2)
Education level, n (%)		
Low/middle	1149 (47.1)	913 (47.3)
High	1033 (42.4)	746 (38.7)
Unknown	255 (10.5)	270 (14.0)
Clinical characteristics		
BMI, mean (SD) kg/m^2	27.1 (5.1)	27.3 (5.3)
BMI categories, n (%)		
Underweight (BMI <18.5 kg/m^2)	17 (0.7)	22 (1.1)
Normal weight (BMI 18.5 to < 25 kg/m^2)	823 (33.8)	616 (31.9)
Overweight (BMI 25 to <30 kg/m^2)	806 (33.1)	621 (32.2)
Obese (BMI ≥ 30 kg/m^2)	541 (22.2)	436 (22.6)
Unknown	250 (10.3)	234 (12.1)
Cancer Type, n (%)		
Breast	1706 (70.0)	1355 (70.2)
Male genitourinary	326 (13.4)	248 (12.9)
Hematological	199 (8.2)	195 (10.1)
Gastrointestinal	146 (6.0)	87 (4.5)
Gynecological	44 (1.8)	33 (1.7)
Other	16 (0.7)	11 (0.6)
Distant metastasis, n (%)		
No	2167 (88.9)	1696 (87.9)
Yes	47 (1.9)	28 (1.5)
N/A (hematological cancer)	199 (8.2)	195 (10.1)
Unknown	24 (1.0)	10 (0.5)
Surgery, n (%)		
No	299 (12.3)	242 (12.5)
Yes	1955 (80.2)	1519 (78.7)
N/A (non-solid tumor)	96 (3.9)	97 (5.0)
Unknown	87 (3.6)	71 (3.7)
Chemotherapy, n (%)		
No	653 (26.8)	526 (27.3)
Prior to intervention	954 (39.1)	826 (42.8)
During intervention	761 (31.2)	513 (26.6)
Unknown	69 (2.8)	64 (3.3)
Radiotherapy, n (%)		

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No	990 (40.6)	721 (37.4)
Prior to intervention	1004 (41.2)	841 (43.6)
During intervention	364 (14.9)	314 (16.3)
Unknown	79 (3.2)	53 (2.7)
Hormone therapy for breast cancer, n (%)		
No	860 (35.3)	671 (34.8)
Yes	631 (25.9)	481 (24.9)
N/A (no breast cancer)	731 (30.0)	574 (29.8)
Unknown	215 (8.8)	203 (10.5)

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Table 3 Intervention and exercise-related characteristics of individual patients from 31 exercise randomized controlled trials included in the meta-analysis

	All interventions (n=2437)	**Supervised interventions (n=1592)**	**Unsupervised interventions (n=845)**
	n (%)a	n (%)a	n (%)a
Intervention characteristics			
Timing of intervention			
Pre-during-post cancer treatment	40 (1.6)	40 (2.5)	-
During cancer treatment	1226 (50.3)	799 (50.2)	427 (50.7)
Post cancer treatment	1168 (47.9)	753 (47.3)	415 (49.3)
Mode of intervention delivery			
(Partly) Supervised	1592 (65.3)	1592 (100)	-
Unsupervised	845 (34.7)	-	845 (100)
Duration of intervention			
≤ 12 weeks	788 (32.3)	666 (41.8)	122 (14.1)
>12 - 24 weeks	751 (30.8)	261 (16.4)	490 (58.0)
>24 weeks	698 (28.6)	465 (29.2)	233 (27.6)
Unknowne	200 (8.2)	200 (12.6)	-
Type of control groupb			
Usual care control	1232 (63.9)	836 (59.8)	481 (78.0)
Wait list control	392 (20.3)	256 (18.3)	136 (22.0)
Attention control	305 (15.8)	305 (21.8)	-
Exercise-related characteristics			
Exercise frequency			
2 times per week	1306 (53.6)	1237 (77.7)	69 (8.2)
3 times per week	315 (12.9)	315 (19.8)	-
4 times per week	203 (8.3)	-	203 (24.0)
≥5 times per week	509 (20.9)	40 (2.5)	469 (55.5)
Unknown	104 (4.3)	-	104 (12.3)
Exercise intensity			
Low-moderate to moderate	1025 (42.1)	425 (26.7)	600 (71.0)
Moderate-vigorous to vigorous	1192 (48.9)	1019 (64.0)	173 (20.5)
Unknown	220 (9.0)	148 (9.3)	72 (8.5)
Exercise type			
AE	686 (28.1)	263 (16.5)	423 (50.1)
RE	342 (14.0)	342 (21.5)	-
AE + RE	1236 (50.7)	814 (51.1)	422 (49.9)
RE + Impact training	173 (7.1)	173 (10.9)	-
Exercise session duration			
≤ 30 min	928 (38.1)	321 (20.2)	607 (71.8)
>30 – 60 min	1260 (51.7)	1022 (64.2)	238 (28.2)
>60 min	249 (10.2)	249 (15.6)	-
Exercise volume			
<150 minutes/week	1541 (63.2)	1269 (79.7)	272 (32.2)
≥150 minutes/week	792 (32.5)	323 (20.3)	469 (55.5)
Unknown	104 (4.3)	-	104 (12.3)

Abbreviations: AE=aerobic exercise; RE=resistance exercise. [a]Proportion of patients from exercise groups. [b]Proportion of patients from control groups (n=1929 for all interventions, n=1397 for supervised interventions, n=617 for unsupervised interventions).

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Table 4 Effects and patient-level moderators of exercise interventions on fatigue

	Fatigue	**p-value LRT**
Effect of exercise (95% CI)	-0.17 (-0.22;-0.12)*	
	Interaction β (95% CI)	
Demographic moderators		
Age	0.00 (-0.01;0.01	0.9
Sex	0.01 (-0.19;0.21)	0.9
Marital status	0.06 (-0.07;0.20)	0.3
Education level	0.03 (-0.09;0.14)	0.6
Clinical moderators		
BMI	-0.00 (-0.02;0.01)	0.4
Cancer type		0.9
Breast	Reference	
Male genitourinary	0.11 (-0.25;0.46)	
Haematological	-0.06 (-0.48;0.37)	
Gastrointestinal	-0.14 (-0.45;0.17)	
Gynaecological	-0.04 (-0.48;0.40)	
Other	0.07 (-0.58;0.72)	
Surgery	-0.05 (-0.32;0.23)	0.7
Chemotherapy	-0.04 (-0.19;0.11)	0.6
Radiotherapy	0.04 (-0.09;0.16)	0.6
Hormone therapy for breast cancer	0.03 (-0.13;0.19)	0.7
Distant metastasis	0.28 (-0.18;0.73)	0.2

*p< 0.05. Betas for patient-level interactions are based on centered values of the potential moderators.
Abbreviations: LRT=likelihood ratio test; CI=confidence interval; BMI=body mass index.

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Table 5 Effects and intervention- and exercise-related moderators of exercise on fatigue

	Interaction β (95% CI)	Treatment effect on fatigue (95%CI)	p-value LRT
All exercise interventions		-0.17 (-0.22;-0.12)*	
Intervention characteristics		*Stratified analysis*	
Timing (post versus during cancer treatment)	0.04 (-0.07;0.14)		0.48
Delivery mode[$#]			0.003
Unsupervised exercise interventions	Reference	-0.04 (-0.13; 0.04)	
Supervised exercise interventions	-0.18 (-0.28;-0.08)*	-0.23 (-0.29; -0.17)*	
Supervised exercise interventions		-0.23 (-0.29; -0.17)*	
Intervention characteristics		*Stratified analysis*	
Duration[#]			0.048
≤ 12 weeks	Reference	-0.29 (-0.39;-0.20)*	
>12-24 weeks	0.04 (-0.13;0.21)	-0.25 (-0.41;-0.10)*	
>24 weeks	0.19 (0.04;0.34)	-0.11 (-0.22; -0.0002)*	
Exercise-related characteristics			
Frequency	-0.03 (-0.17; 0.11)		0.67
Duration of session			0.87
<30 minutes	Reference		
>30-60 minutes	0.04 (-0.12;0.19)		
>60 minutes	0.01 (-0.20;0.21)		
Exercise volume	-0.09 (-0.24;0.05)		0.22
Intensity[$]			0.93
Control	Reference		
Low-moderate and moderate	-0.25 (-0.36;-0.14)*		
Moderate-vigorous and vigorous	-0.24 (-0.32;-0.17)*		
Type[$]			0.63
Control	Reference		
AE	-0.23 (-0.36;-0.11)*		
AE+RE	-0.26 (-0.34 -0.18)*		
RE	-0.21 (-0.32;-0.09)*		
RE + impact training	-0.14 (-0.32;0.05)		
Unsupervised exercise interventions		-0.04 (-0.13; 0.04)	
Intervention characteristics			
Duration			0.23
≤ 12 weeks	Reference		
>12-24 weeks	0.14 (-0.12;0.40)		
>24 weeks	-0.03 (-0.32;0.25)		
Exercise-related characteristics			
Frequency	-0.20 (-0.42;0.01)		0.06
Duration of session	-0.02 (-0.23;0.19)		0.86
Exercise volume	-0.20 (-0.42;0.01)		0.06
Intensity[$]			0.15
Control	Reference		
Low-moderate and moderate	-0.06 (-0.17;0.06)		
Moderate-vigorous and vigorous	0.11 (-0.09; 0.31)		
Type[$]			0.80
Control	Reference		
AE	-0.05 (-0.17;0.07)		
AE+RE	-0.02 (-0.17;0.12)		

Abbreviations: CI=confidence interval; LRT=likelihood ratio test; AE=aerobic exercise; RE=resistance exercise.
*p< 0.05; [$]Interaction testing is not applicable, therefore differences between subgroups are reported. LRT of the model including the intervention or exercise-related characteristic versus the main model is presented. [#]Stratified analysis (significant interaction).

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Appendix 1 Descriptive characteristics of studies evaluating the effects of exercise interventions on fatigue (N=31)

						Intervention			Exercise	Control	
Author (year) *Acronym*	**Country**	**N**	**Age, mean (SD)**	**Sex (% female)**	**Diagnosis**	**Timing***	**Delivery mode**	**Duration (weeks)**	**FITT**		**Fatigue questionnaire**
Cadmus, (2009)(55) *IMPACT*	USA	50	54.2 (9.6)	100	Breast	During	Unsupervised	6 months	F: aim 5x/week I: moderate T: AE T: 30 min	Usual care	SF-36 vitality
Cormie (2015)(40)	AUS	64	68.4 (7.1)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	FACT-fatigue
Courneya (2003)(41) *CANHOPE*	CAN	102	60.2 (10.8)	41.2	Colorectal	During or post	Unsupervised	16	F: 3-5x/week I: moderate T: AE T: 20-30 min	Wait-list	FACT-fatigue
Courneya (2003)(42) *REHAB*	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-fatigue
Courneya (2007)(43) *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-fatigue
Courneya (2009)(44) *HELP*	CAN	122	53.2 (14.8)	41.0	Hematological	During or post	Supervised	12	F: 3x/week I: moderate-vigorous T: AE T: 15-45 min	Usual care	FACT-fatigue
Daley (2007)(35)	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	PFS
Duijts	NL	207	47.8	100	Breast	Post	Unsupervised	12	F: 5x per 2 weeks	Wait-list	SF-36 vitality

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						Intervention			Exercise	Control	
Author (year) *Acronym*	**Country**	**N**	**Age, mean (SD)**	**Sex (% female)**	**Diagnosis**	**Timing***	**Delivery mode**	**Duration (weeks)**	**FITT**		**Fatigue questionnaire**
(2012)(56) *EVA*			(5.8)						I: vigorous T: AE T: 45-60 min		
Galvão (2010)(50)	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	EORTC QLQ C30 fatigue
Galvão (2014)(49) *RADAR-exercise*	AUS	100	71.7 (6.4)	0	Prostate	Post ADT	Supervised	6 months	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care with PA brochure	EORTC QLQ C30 fatigue
Goedendorp (2010)(38)	NL	144	57.2 (10.5)	63.2	Mixed	During	Unsupervised	Mean: 31.7	F: towards 5d/week I: ? T: AE T: towards 60 min	Usual care	CIS
Griffith (2009)(36)	USA	126	60.2 (10.6)	38.9	Mixed	During CT, RT or both	Unsupervised	Mean: 12.8	F: 5x/week I: low-moderate T: AE T: 25-35min	Usual care	PFS
Hayes (2013)(45) *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-fatigue
Irwin (2009)(57) *YES*	USA	75	55.8 (8.7)	100	Breast	Post	Supervised	6 months	F: 3 supervised (+2 unsupervised) I: moderate T: AE (walking) T: 15-30 min	Usual care	SF-36 vitality
Kampshoff (2015)(19) *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	MFI
Mehnert	GER	58	51.9	100	Breast	Post	Supervised	10	F: 2x/week	Wait-list	EORTC QLQ

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						Intervention			Exercise	Control	
Author (year) *Acronym*	**Country**	**N**	**Age, mean (SD)**	**Sex (% female)**	**Diagnosis**	**Timing***	**Delivery mode**	**Duration (weeks)**	**FITT**		**Fatigue questionnaire**
(2011)(51)			(8.5)						I: moderate T: AE + gymnastics + movement games + relaxation T: 90 min		C30 fatigue
Mutrie (2007)(46)	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-fatigue
Persoon, (2017)(20) *EXIST*	NL	109	52.4 (11.2)	36.7	Hematological	Post SCT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	MFI[#]
Schmidt (2015)*(28)* *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	FAQ
Short (2015)(47) *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	FACIT-fatigue
Speck (2010)(58) 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 vitality
Steindorf (2014)(29) *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	FAQ
Taaffe (2017)(52)	AUS	154	69.0 (9.0)	0	Prostate	During ADT	Supervised	6 months	F: 2x/week I: moderate-vigorous	Wait-list	EORTC QLQ C30 fatigue

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						Intervention			Exercise	Control	
Author (year) *Acronym*	**Country**	**N**	**Age, mean (SD)**	**Sex (% female)**	**Diagnosis**	**Timing***	**Delivery mode**	**Duration (weeks)**	**FITT**		**Fatigue questionnaire**
									T: RE+AE vs RE+impact T: 60 min		
Thorsen (2005)(53)	NOR	139	39.4 (8.3)	66.9	Mixed	Post	Unsupervised	14	F: 2x/week or more I: moderate-vigorous T: RE+AE T: aim 30 min	Usual care	EORTC QLQ C30 fatigue
Travier (2015)(21); van Vulpen (2016)(22) *PACT*	NL	237	50.7 (8.8)	91.1	Breast and Colon	During CT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	MFI
Van Waart (2015)(24); van Waart (2017)(23) 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: 60min; unsupervised: aim 30 min	Usual care	MFI
Van Weert (2010)(25) *OncoRev*	NL	133	50.6 (10.2)	85.0	Mixed	Post	Supervised	12	F: 2x/week I: AE: moderate-vigorous, RE: low-moderate T: RE+AE T: 120 min	Wait-list	MFI
Winters-Stone (2012) (31)	USA	106	62.2 (6.7)	100	Breast	Post	Supervised	52	F: 2x/week supervised (+ 1x/week unsupervised) I: moderate-vigorous	Attention control	SCFS-6

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						Intervention			Exercise	Control	
Author (year) *Acronym*	**Country**	**N**	**Age, mean (SD)**	**Sex (% female)**	**Diagnosis**	**Timing***	**Delivery mode**	**Duration (weeks)**	**FITT**		**Fatigue questionnaire**
									T: RE+impact T: 60 min		
Winters-Stone (2013) (32)	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	SCFS-6
Winters-Stone (2015)(33)	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	SCFS-6
Wiskemann (2011)(26)	GER	80	48.4 (14.4)	31.3	Hematological	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	MFI

Descriptive characteristics are based on the data in the POLARIS database. Abbreviations: SD=standard deviation; ADT= androgen deprivation therapy; CT=chemotherapy; RT=radiotherapy; SCT=stem cell transplantation; AE=aerobic exercise; RE=resistance exercise; SF-36 vitality= Short Form-36 Item Health Survey vitality subscale; FACT-fatigue=Functional assessment of cancer treatment fatigue scale; PFS=revised Piper fatigue scale; EORTC QLQ C30 fatigue= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 fatigue subscale; CIS=Checklist individual strength; MFI=Multidimensional fatigue inventory; FAQ=Fatigue Assessment Questionnaire; SCFS-6=Schwartz Cancer Fatigue Scale. *Timing of the exercise intervention in relation to treatment.

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