Psycho-Oncology
Psycho-Oncology **24**: 737–747 (2015)
Published online 8 December 2014 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3727

Review

Population-, intervention- and methodology-related characteristics of clinical trials impact exercise efficacy during adjuvant therapy for breast cancer: a meta-regression analysis

Marion Carayol[1,2]*, Cyrille Delpierre[2], Paquito Bernard[1] and Grégory Ninot[1]
[1]*Laboratory Epsylon EA 4556 Dynamics of Human Abilities and Health Behaviors, University of Montpellier, Montpellier, France*
[2]*INSERM UMR 1027, Paul Sabatier University, Toulouse, France*

Correspondence to: INSERM UMR 1027, Paul Sabatier University, 37 allées Jules Guesde, F-31073 Toulouse, France. E-mail: marioncarayol@yahoo.fr

Received: 20 March 2014
Revised: 20 October 2014
Accepted: 27 October 2014

Abstract

Objective: **Significant heterogeneity was highlighted in recent meta-analyses examining exercise effects in cancer patients, suggesting that some characteristics may moderate exercise efficacy. The objectives of this meta-analysis are (1) to investigate the influence of methodology, population and intervention studies' characteristics on the association of exercise with fatigue, quality-of-life (QoL), anxiety and depression; (2) to identify exercise intervention characteristics that may maximize efficacy and evaluate the level of evidence about exercise efficacy in breast cancer patients receiving chemotherapy and/or radiotherapy.**

Methods: **Thirty-three randomized controlled trials (RCTs) evaluating exercise were systematically identified. Population, intervention and methodology characteristics were extracted, coded by two independent investigators and tested as moderators of exercise effect in meta-regression models. Psychological outcomes summary effects were then computed by pooling subgroup of RCTs based on categorized moderators.**

Results: **Indications of selection bias (random sequence generation) or attrition bias (high attrition rate, no intent-to-treat analysis) were associated with better exercise efficacy on QoL, anxiety and depression. Low total prescribed exercise doses (<140 METs.h) or short duration (<16 weeks) interventions yielded fatigue, anxiety and depression reductions whereas higher doses or duration did not. Mind–body interventions led to greater decrease of fatigue and anxiety rather than aerobic/resistance-based interventions.**

Conclusion: **Our findings indicated that exercise-based interventions may improve fatigue, QoL, anxiety and depression, but the evidence mainly rely on studies prone to methodological biases. A prescription of approximately 100 MET.h, e.g. ~120 min of weekly moderate physical exercise for 10 weeks involving mind–body activities, could be advised to maximize fatigue reduction.**

Introduction

Breast cancer is the most frequent cancer affecting more than 1 million women per year worldwide [1] who have to face up to adjuvant cancer therapy related side-effects. Fatigue is one of the most common symptoms experienced by patients receiving cancer adjuvant therapy [2] and has been reported by 80% of the patients in a large population-based survey [3]. Cancer-related fatigue has been associated with anxiety and depression burden [3], affecting quality-of-life (QoL), particularly in patients treated for breast cancer [4,5]. The importance to relieve these psychological symptoms has been emphasized in literature reviews [6,7] suggesting QoL, fatigue and psychosocial factors to be associated with cancer prognosis.

Exercise has been recently advanced by the National Comprehensive Cancer Network (NCCN) as one of the specific nonpharmacologic interventions that have the strongest evidence base (category 1) for treating cancer-related fatigue in cancer patients (without localization differentiation) undergoing active treatment, meaning that 'the recommendation is based on high-level evidence, e.g. randomized controlled trials (RCTs), and there is a uniform NCCN consensus' [8]. In breast cancer patients undergoing chemotherapy and/or radiotherapy, we carried out a previous meta-analysis of 17 randomized controlled trials (RCTs) testing exercise-based interventions that examined exercise interventions to relieve fatigue, anxiety, depression and QoL by evaluating exercise impact and dose–response relationship [9]. Significant improvements of fatigue, QoL, anxiety and depression (borderline for anxiety) were observed in favor of intervention compared to control. However, the validity of the observed associations was limited by the detection of significant heterogeneity in pooled analyses that assessed fatigue, QoL and anxiety. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance and ranges from 0% to 100%, with 0% indicating no observed heterogeneity and larger values increasing heterogeneity [10,11]. In our previous study, I^2 was estimated to 72% in fatigue, 73% in QoL, 91% in anxiety and 39% in depression analyses, respectively, indicating a high degree of dissimilarity and inconsistencies in the results of individual studies [12] and preventing uniformity of exercise effect across included studies. Yet, consistency of individual studies results is a key factor to determine the generalizability of the findings [13], the strength of the evidence [14–16] and the recommendation of a therapy for clinical practice [16].

The present meta-regression analysis firstly intends to characterize this high degree of heterogeneity. Many sources of variation could explain some heterogeneity seen across exercise-based RCTs such as variability in socio-demographic or clinical population characteristics (age, stage, corpulence, etc.), in exercise intervention characteristics (activity, frequency, intensity, duration, etc.) and in methodological characteristics [17]. The identification of characteristics related to exercise efficacy may indicate (a) subgroups of population more receptive to exercise effects that should be primarily targeted, (b) more efficient intervention modalities that should be implemented to maximize efficacy and, (c) methodological standards or weaknesses associated with exercise efficacy. Methodological standards are of particular interest in the evaluation of the quality and the strength of evidence because they indicate the level of confidence the evidence and the recommendations rely on. Although they did not differentiate cancer sites and included post-treatment cancer patients, a few meta-analyses of exercise-based RCTs have investigated the variables that may influence exercise efficacy, usually called 'moderators' [18–21]. The following characteristics related to population, intervention and methodological quality were associated with exercise efficacy on fatigue, QoL, anxiety or depression: age, supervised exercise sessions, exercise weekly dose, moderate exercise intensity and motivation theory-based intervention were positively associated with exercise efficacy, whereas length of exercise intervention, sample size and methodological quality score were negatively associated with exercise efficacy.

To date, no investigation has specifically explored the sources of heterogeneity of exercise efficacy in the adjuvant therapy period of breast cancer. Therefore, in patients with breast cancer undergoing chemotherapy and/or radiotherapy, the objectives of this systematic review and meta-analysis are (a) to investigate heterogeneity sources and, more particularly, the influence of studies characteristics regarding methodology, population and intervention on the association of exercise with fatigue, QoL, anxiety and depression; and based on these findings, (b) to identify exercise intervention characteristics that may maximize efficacy and evaluate the implications for the level of evidence about exercise efficacy to relieve these psychological outcomes.

Materials and methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

Literature search

Studies were identified by searching MEDLINE, PsycINFO, Francis, PSYarticles and the Cochrane Central Register for Controlled Trials electronic databases until 16 June 2014 with no language restriction by using the following Medical Subject Headings (Mesh) in MEDLINE: 'Breast Neoplasms' AND ('Motor Activity' OR 'Exercise' OR 'Exercise Movement Techniques' OR 'Plyometric Exercise' OR 'Exercise Tolerance' OR 'Exercise Therapy' OR 'Resistance Training' OR 'Muscle Stretching Exercises' OR 'Breathing Exercises') and, in Cochrane: 'Breast Neoplasms' AND ('Exercise' OR 'Exercise Therapy' OR 'Physical Exertion' OR 'Leisure Activities' OR 'Sports' OR 'Exercise Movement Techniques'). The other databases were searched by using: 'breast cancer' AND ('Exercise' OR 'Exercise Therapy' OR 'Exercise Movement Techniques' OR 'Resistance Training' OR 'Muscle Stretching Exercises' OR 'Breathing Exercises' OR 'Sports' OR 'Motor Activity' OR 'Relaxation' OR 'Physical Fitness' OR 'Physical activity'). These research algorithms were combined with filters for RCT, and human studies when available. In addition, references of relevant reviews and meta-analyses were scanned [18–21,23–34].

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria (according to PICOS [35]):

1. Participants. Participants were adult women diagnosed with breast cancer, any tumor stage, any time since diagnosis, undergoing chemotherapy and/or radiotherapy during the time of intervention. Trials involving participants undergoing hormone therapy alone were not included.
2. Interventions. Included trials examined the effects of an exercise intervention involving planned, structured, and repetitive movements to improve or maintain one or more components of physical fitness. The nature of the prescribed exercise was not limited to specific activities and included the following practice: walking programs, running, sports, resistance training, dance, yoga, tai chi and pilates. Strict relaxation interventions were excluded.
3. Controls. Included trials compared exercise with no exercise, usual care (e.g. no specific exercise program prescribed) or active (attention placebo) control condition.

DOI: 10.1002/pon

4. Outcomes. The included trials measured at least one self-reported participant measures among cancer-related fatigue, health-related QoL, anxiety and depression as primary or secondary end points at post-intervention time.
5. Studies. Only RCTs were included.

Data extraction

A standardized data extraction sheet derived from one developed for a previous meta-analysis [9] was used by two independent reviewers (M.C., PhD; P.B., PhD) who systematically recorded data and any discrepancies were resolved by discussion. Descriptive data were extracted regarding (a) study population and design: year, country, number of participants randomly assigned, demographics, tumor stage, treatment status, control condition and special design features; (b) exercise intervention: nature, intensity, duration and frequency of sessions, intervention length, adherence rate, delivery modes (supervision, group and individual) and motivation theory; and (c) outcomes: assessment tools, number of subjects assessed in each randomization group, mean and standard deviation at post-intervention time. When several tools were used to measure the same outcome in a study, validated and specific cancer tools were favored. Regarding QoL evaluation, in order of preference, total Functional Assessment Cancer Therapy (FACT)-B, total FACT-G, total FACT-An and General Health SF-36 subscale scores were extracted. Vitality SF-36 subscale was considered as a measure of fatigue (reversed score). When the State Trait Anxiety Inventory was used, the state scale score was recorded. Unreported data were requested to the corresponding authors by e-mail communication and six provided it [36–41].

Methodological assessment

A 12-point quality score based on 12 methodological criteria was calculated. Mostly derived from PEDro Scale [42] and Cochrane reviews [30], the criteria have been specifically chosen to assess risk of bias in RCTs testing nonpharmacologic interventions and involved selection, performance, detection, attrition and reporting bias (see detailed criteria in supplemental Appendix Table 2). Two investigators (M.C. and P.B.) independently scored the studies and any disagreements were resolved by discussion.

Exercise dose calculation

Prescribed volumes of exercise were estimated (see Carayol *et al.* [9] for more details): (a) Weekly exercise dose $= \sum_{i=1}^{n} (\text{METs})_i \times (\text{bout duration})_i \times (\text{frequency})_i$, where one exercise session is composed of i physical activities and intensity of activity i is in metabolic equivalent for task (METs); (b) total exercise dose = weekly exercise dose × intervention length.

Analytic and statistical process

We planned to assess exercise intervention effects on fatigue, QoL, anxiety and depression. Pre- and post-intervention mean scores and standard deviations (SDs) of outcomes as well as number of subjects in experimental and control groups were used to calculate Hedges' g [43] as the measure of standardized mean difference (SMD), difference between the outcome mean values of the intervention and control groups divided by the pooled standard deviation [43,44]. Signs of effect sizes were set so that positive effect sizes for fatigue, QoL, anxiety and depression indicated improvements in favor of intervention. Heterogeneity was tested with Q test, and residual between-variance study was quantified through I^2 statistic [10,11], ranging from 0% to 100%, with 0% indicating no observed heterogeneity and larger values increasing heterogeneity.

To meet the first objective, two types of heterogeneity sources were searched: (a) outlier studies were identified with sensitivity analyses when the 95% confidence intervals (CIs) of individual studies SMDs were completely disjoined from the 95%CI of the summary effect estimate, and (b) moderators of exercise effect were tested in single covariate random effects meta-regression models [45,46]. The following study characteristics were chosen for testing according to clinical experience, literature background [18–21] and distribution in our sample: (a) population-related characteristics: proportion of patients undergoing chemotherapy, age, body mass index (BMI), education and outcome baseline level; (b) intervention related-characteristics: intervention length, total and weekly exercise doses, exercise nature, adherence and delivery modes and motivation theory-based intervention; and (c) methodology related-characteristics: control condition, number of experimental patients, random sequence generation, concealed allocation, baseline comparability of groups, attrition rate, intention-to-treat (ITT) analysis and total quality score. In order to decrease the risk of false positive conclusions, meta-regression analyses were run after the exclusion of outliers and their estimates were obtained using the t-test described by Knapp and Hartung [47] that has been stated to decrease false-positive rates related to multiple testing when there are few studies and little heterogeneity [48]. All continuous variables were zero centered based on their means; categorical variables were contrast coded (−1/+1) (as done by Brown *et al.* [19]). Beta-values (β) quantify the amount of variability in SMDs associated with 1 unit increase of each moderator of interest.

DOI: 10.1002/pon

To meet the second objective, summary measures were computed for all and subgroups of included studies (excluding outliers) based on dichotomized identified moderators according to their median value. Psychological outcome summary effect estimates were obtained by pooling weighted SMDs based up on random effects methods, or on fixed effects models in the absence of heterogeneity ($I^2 = 0\%$).

Publication bias was searched by using funnel plot representations and Egger's [49] test with $P < .10$ taken as an indication of publication bias.

Statistical analyses were conducted in Stata version 11.2 (StatCorp, TX). The nominal level of significance was 5% in all tests except otherwise specified.

Results

Of 629 identified records from databases and 11 from references lists of relevant reviews, 36 RCTs involving a total of 42 intervention groups met our inclusion criteria [36–41,50–82] (see the flow diagram in supplemental Appendix Figure 1). Two articles [41,83] were considered as duplicates of the same study as they presented similar interventions and flow charts; only data from the publication of Raghavendra *et al*. [41] was included. Population, intervention and methodological characteristics of included studies are summarized in supplemental Appendix Tables 1 and 2. All studies involved a total of 1479 experimental and 1244 control patients with non metastatic breast cancer and median age of 51 years old. A large number of studies were pilot RCTs with 19 intervention groups including <30 patients (Appendix Table 1). Out of the 12 methodological criteria, median quality score was 7 (interquartile range: 3). More than half of the studies used random sequence generation, reported exercise session adherence >60% and drop-out <15% with reasons of drop-out, but less than half reported concealed allocation of subjects, sample size calculation with target achievement and comparability of randomization groups upon cancer stage, age and BMI. Only five studies (14%) reported that assessors were blinded to patients' allocation group and nine studies (25%) used ITT analysis with imputation or statistical modelization accounting for missing data (Appendix Table 2). Risks of bias are represented in supplemental Appendix Figure 2. Among all included intervention groups, mean length of interventions was 16 (±9) weeks, ranging from 5 [67] to 34 [39,40] and mean prescribed exercise dose was 11 (±5) MET.h a week ranging from 2.5 [68] to 25.5 [38]. After request for unreported information, data of interest were available for 30 studies and 36 intervention groups that were included in the quantitative meta-analysis. Compared to those with reported data, intervention groups without available data were older: 2008 (±4) vs. 2003 (±6), respectively ($t = -2.7$; $P = 0.01$), presented fewer experimental patients: 44 (±26) vs. 18 (±7), respectively ($t = -2.2$; $P = 0.03$) and a higher attrition: 31% vs. 83% reported drop-out rate >15% ($X^2 = 6.1$; $P = 0.01$).

Heterogeneity sources

Significant heterogeneity was observed among included RCTs in all outcomes of interest (Table 1), with between-variance study ranging from very large values in anxiety (87%) and QoL (76%) and moderate to large values in fatigue (50%) and depression (58%).

Outliers

Sensitivity analyses pointed out six outliers that were excluded in meta-regression analyses (Table 1). Four of these studies [37,50,55,76,81] reported heterogeneous SMDs in the sense of larger improvements of psychological outcomes, as compared to the pooled effect estimate (see supplemental Appendix Figure 3). In contrast, two studies [54,76] reported higher post-intervention deteriorations of QoL or depression due to intervention, as compared to the pooled effect estimate; it should be noted that the study of Rausch *et al.* [76] has been extracted from a thesis report and that only the intervention group of stretching (not the one of yoga) was found as an outlier for depression, in the study of Chandwani *et al.* [54] (see supplemental Appendix Figure 3).

Compared to included groups, outlier groups presented shorter interventions: 17 (±10) vs. 9 (±6), respectively ($t = 2.6$; $P = 0.01$), fewer experimental patients: 51 (±28) vs. 29 (±14), respectively ($t = 2.3$; $P = 0.03$), lower methodological quality score: 7 (±2) vs. 4 (±3), respectively ($t = 4.2$; $P = 0.0001$), lower retention rate: 88% (±8) vs. 82% (±6), respectively ($t = 2.1$; $P = 0.04$). Compared to included groups, outliers less frequently reported random sequence generation: 82% vs. 33%, respectively ($X^2 = 10.8$; $P = 0.001$), concealed allocation: 39% vs. 0%, respectively ($X^2 = 5.4$; $P = 0.02$), ITT analysis: 46% vs. 11%, respectively ($X^2 = 4.0$; $P = 0.04$) and more frequently involved mind–body activities: 23% vs. 55% ($X^2 = 4.5$; $P = 0.03$).

Population-related moderators

The effect of exercise on fatigue was negatively associated with the proportion of patients receiving chemotherapy during exercise intervention (Table 1).

Intervention-related moderators

The effect of exercise on fatigue and depression was negatively associated with total prescribed dose of exercise. Exercise effect on fatigue, anxiety and depression was negatively associated with duration of intervention. Interventions involving mind–body activities were associated

DOI: 10.1002/pon

Table 1. Quantification of heterogeneity among pooled studies and identification of sources of heterogeneity

Outcome	Heterogeneity			Sources of heterogeneity					
				Outliers		Meta-regression (outliers excluded)			
	k	I^2	*P*	Author, year	Res. I^2 [a]	Moderators	β	*P*	Res. I^2 [b]
Fatigue	28	50%	0.001	Battaglini [37]	35%	Proportion of patients undergoing chemotherapy (%)	−0.13	0.009	0%
				Wang [81]	35%	Total prescribed exercise dose: ≥140 vs. <140 MET.h	−0.21	0.028	0%
						Intervention length (weeks)	−0.10	0.034	0%
						Exercise nature: yoga, tai chi or qi gong *v* aerobic and/or resistance	0.26	0.019	0%
QoL	26	76%	<0.0001	Chandwani [55]	54%	Random sequence generation: yes vs. no	−0.54	0.011	0%
				Wangb [81]	72%	Sample size ($N_{\text{experimental group}}$)	−0.10	0.049	11%
				Rausch [76]	76%				
Anxiety	18	87%	<0.0001	Badger [50]	73%	Intervention length: ≥16 vs. <16 weeks	−0.28	0.099	4%
				Chandwani [55]	81%	Exercise nature: yoga, tai chi or qi gong vs. aerobic and/or resistance	0.41	0.018	0%
						Intention-to-treat analysis: yes vs. no	−0.25	0.048	0%
						Retention rate (%)	−0.11	0.029	0%
Depression	23	58%	<0.0001	Rausch [76]	53%	Total prescribed exercise dose (MET.h)	−0.16	0.031	23%
				Chandwani [54]	46%	Intervention length (wk)	−0.16	0.012	15%
						Methodological quality score: ≥7 vs. <7	−0.29	0.033	21%
						Random sequence generation: yes vs. no	−0.49	0.008	10%
						Intention-to-treat analysis: yes vs. no	−0.27	0.030	22%
						Retention rate: ≥90% vs. <90%	−0.28	0.030	21%

[a]Residual I^2 after the deletion of each outlier.
[b]Residual I^2 after the introduction of each moderator in the meta-regression model (outliers excluded).
Continuous moderators were all tested as continuous variables; if significance was not reached, moderators were tested as categorical (+1/−1). ^{2}, measure of heterogeneity; *k*, number of intervention groups; QoL, quality-of-life.

with greater impact of exercise on fatigue and anxiety rather than aerobic and/or resistance activities.

Methodology-related moderators

The absence of random sequence generation in RCTs was associated with greater effect of exercise on QoL and depression. The effect of exercise on anxiety and depression was negatively associated with retention rate and was better in RCTs that did not use ITT analysis. Exercise effect on depression was negatively associated with methodological quality score. The effect of exercise on QoL was negatively related to sample size.

Meta-regression models generally resulted in null to small unexplained heterogeneity in all outcomes of interest, with I^2 ranging from 0% to 23% (outliers excluded) (Table 1).

Exercise intervention efficacy

All included studies

The large amount of heterogeneity detected in all outcomes did not allow us to compute summary effect sizes by pooling all included studies (supplemental Appendix Figure 3). After the exclusion of outliers, exercise based-interventions had a significant beneficial impact on fatigue, QoL, anxiety and depression with respective summary SMDs (95%CI) of 0.17 (0.08 to 0.25), 0.16 (0.05 to 0.26), 0.16 (0.04 to 0.28) and 0.20 (0.08 to 0.33) at the end of intervention (see supplemental Appendix Figure 4); small heterogeneity persisted with respective I^2 values of 1%, 23%, 16% and 35%. Subgroup meta-analyses were carried out according to dichotomized moderators (outliers excluded); results are detailed in Table 2.

Population-related subgroups

In RCTs with less than 75% of patients undergoing chemotherapy, exercise interventions resulted in small significant decrease of fatigue (without detected heterogeneity) whereas no beneficial effect was observed in RCTs with (almost) all patients receiving chemotherapy (Table 2).

Intervention-related subgroups

Yoga, tai chi and qi gong interventions significantly reduced anxiety and fatigue with a medium size of effect (without detected heterogeneity), whereas aerobic and/or resistance interventions studies only improved fatigue with a very small effect size (Table 2 and Figure 1). Pooled studies with long exercise intervention (≥16 weeks) or high targeted exercise doses (≥140 MET.h in total) showed no heterogeneity but did not reduce fatigue, anxiety or depression. Conversely, subgroups of interventions with lower doses and duration (<16 weeks of intervention, <140 MET.h) revealed systematically significant medium decreases of fatigue, anxiety or depression; no heterogeneity was detected in these associations, except for the associations with depression.

Methodology-related subgroups

In RCTs with random sequence generation, exercise interventions resulted in small non heterogeneous benefits on

DOI: 10.1002/pon

Table 2. Summary effect sizes of exercise according to identified sources of heterogeneity

Outcome	Pooled studies	k	Ne	Nc	SMD	95%CI	P	Size of effect[a]	Heterogeneity I^2	Heterogeneity P
Fatigue										
	≥75% of study sample undergoing chemotherapy	10	502	369	0.07	−0.06 to 0.21	0.28	—	0%	0.74
	<75% of study sample undergoing chemotherapy	16	695	615	0.23	0.11 to 0.35	<0.0001	Small	9%	0.35
	≥140 total prescribed METs.h	13	717	542	0.08	−0.04 to 0.19	0.17	—	0%	0.83
	<140 total prescribed METs.h	12	472	433	0.30	0.15 to 0.44	<0.0001	Medium	11%	0.34
	Exercise intervention ≥16 weeks	14	799	583	0.09	−0.02 to 0.19	0.12	—	0%	0.87
	Exercise intervention <16 weeks	12	398	401	0.31	0.16 to 0.46	<0.0001	Medium	8%	0.37
	Aerobic and/or resistance exercise	20	951	745	0.11	0.01 to 0.20	0.03	Small	0%	0.91
	Yoga, tai chi or qi gong	6	246	239	0.37	0.16 to 0.60	0.001	Medium	33%	0.19
QoL										
	Random sequence generation	20	1079	831	0.11	0.02 to 0.20	0.02	Small	0%	0.52
	No/unstated random sequence generation	3	66	57	0.72	0.21 to 1.23	0.006	High	39%	0.19
	Sample size ≥40 experimental patients	15	962	739	0.09	−0.01 to 0.19	0.07	—	0%	0.97
	Sample size <40 experimental patients	8	183	149	0.43	0.09 to 0.79	0.01	—	55%	0.03
Anxiety										
	Exercise intervention ≥16 weeks	12	671	479	0.11	−0.01 to 0.24	0.07	—	5%	0.40
	Exercise intervention <16 weeks	4	116	96	0.39	0.11 to 0.66	0.006	Medium	2%	0.38
	Aerobic and/or resistance exercise	12	678	477	0.09	−0.03 to 0.21	0.12	—	0%	0.59
	Yoga, tai chi or qi gong	3	109	98	0.51	0.23 to 0.79	<0.0001	Medium	0%	0.80
	Intention-to-treat analysis	7	520	357	0.07	−0.07 to 0.20	0.34	—	0%	0.66
	No intention-to-treat analysis	9	267	218	0.31	0.11 to 0.51	0.003	Medium	15%	0.31
	≥90% retention	10	579	390	0.08	−0.05 to 0.21	0.24	—	0%	0.74
	<90% retention	6	208	185	0.34	0.10 to 0.58	0.006	Medium	28%	0.22
Depression										
	≥ 140 total prescribed METs.h	9	525	383	0.10	−0.04 to 0.23	0.16	—	0%	0.81
	< 140 total prescribed METs.h	11	447	413	0.34	0.14 to 0.56	0.001	—	53%	0.02
	Exercise intervention ≥16 weeks	11	607	424	0.09	−0.04 to 0.21	0.17	—	0%	0.86
	Exercise intervention <16 weeks	10	365	372	0.39	0.17 to 0.61	0.001	—	52%	0.03
	Scored ≥7 methodological criteria	11	719	565	0.11	0.00 to 0.23	0.05	Small	5%	0.39
	Scored <7 methodological criteria	10	253	231	0.38	0.15 to 0.61	0.001	Medium	33%	0.14
	Random sequence generation	17	878	697	0.14	0.03 to 0.25	0.01	Small	15%	0.27
	No/unstated random sequence generation	4	94	99	0.64	0.34 to 0.93	<0.0001	Medium	0%	0.52
	Intention-to-treat analysis	8	569	405	0.08	−0.05 to 0.21	0.21	—	0%	0.56
	No intention-to-treat analysis	13	403	391	0.34	0.16 to 0.53	<0.0001	Medium	35%	0.10
	≥90% retention	11	696	506	0.11	−0.02 to 0.23	0.39	—	6%	0.12
	<90% retention	7	276	290	0.40	0.17 to 0.62	0.001	Medium	38%	0.12

[a]Effect sizes that reach level of significance without detected heterogeneity were interpreted as 'small' effects for SMDs <0.3, 'medium' effects when SMDs ranged from 0.3 to 0.8 and 'large' effects if SMDs were larger than 0.8.
Subgroup of studies showing a significant impact of exercise ($P < .05$) without detected heterogeneity ($P < .10$) are highlighted in bold.
SMD, standardized mean difference; I^2, measure of heterogeneity; k, number of intervention groups; Ne, number of experimental patients; Nc, number of control patients; QoL, quality-of-life; 95%CI, 95% confidence interval.

QoL and depression; medium to high effect sizes (without detected heterogeneity) were observed in RCTs that did not meet this quality criteria (Table 2 and Figure 2). No effect of exercise was observed on anxiety and depression among studies reporting ITT analyses or high retention rate (>90%). On the other hand, pooling studies of opposite categories (i.e. no ITT analyses and low retention rate) led systematically to significant beneficial impact on anxiety and depression with medium sizes of effects; no heterogeneity was detected in these associations. Low (score <7) and higher (score ≥7) methodological quality studies showed both significant effect of exercise on depression (without detected heterogeneity), with very small size of effect in low quality RCTs and medium size of effect in higher quality RCTs, respectively. In addition, exercise effect on QoL did not reach significance in small sample size studies (<40 experimental patients), whereas significant benefits were seen in larger sample size studies (with detected heterogeneity).

Publication bias

Egger's test indicated evidence for small study-effects in fatigue ($P = .09$), QoL ($P = .04$) and anxiety ($P = .08$) but not in depression ($P = .71$). Funnel plot representations (see supplemental Appendix Figure 5) showed asymmetry with a few studies with relatively small sample size reporting very large effects on fatigue, QoL and anxiety compared to others. Most of these studies were identified as outliers as no evidence of publication bias persisted on fatigue ($P = .71$) and anxiety ($P = .71$) after the exclusion of outliers; however, a

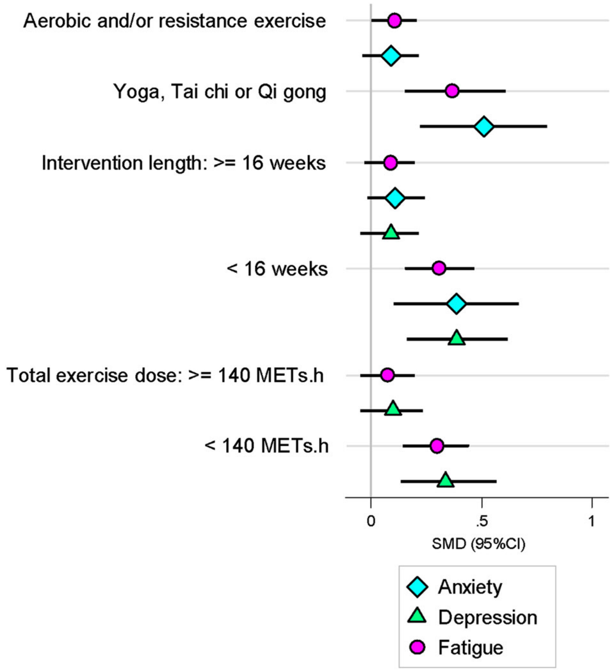

Figure 1. Post-intervention summary effects of exercise on psychological outcomes according to categorized intervention related-moderators. Medium value was used for the categorization of continuous moderators

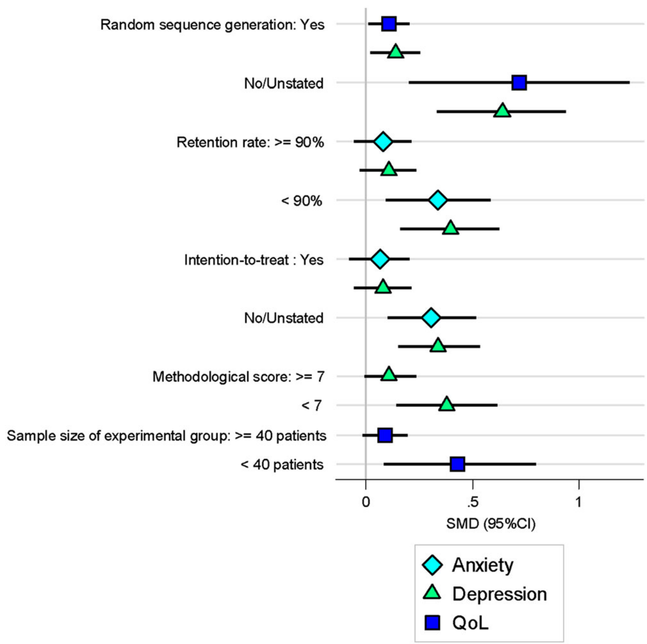

Figure 2. Post-intervention summary effects of exercise on psychological outcomes according to categorized methodology related-moderators. Medium value was used for the categorization of continuous moderators

publication bias persisted for QoL suggesting that our analyses may be biased in the sense of an overestimation of exercise effect on QoL.

Discussion

In patients undergoing chemotherapy and/or radiotherapy for breast cancer, substantial heterogeneity was observed among the RCTs testing the effect of exercise interventions on fatigue, QoL, anxiety and depression. The exclusion of outliers reduced heterogeneity to small or moderate levels ($I^2 \leq 35\%$), and the identification of moderators further decreased heterogeneity to null or small levels ($I^2 \leq 23\%$). Shorter exercise interventions or lower targeted exercise doses were consistently associated with higher improvements of fatigue, anxiety and depression due to exercise, whereas interventions ≥16 weeks and exercise dose ≥140 MET.h did not show any significant benefits. These findings suggest that an exercise intervention targeting less than 140 MET.h on a 5 to 16-week period may yield the largest improvements of fatigue, anxiety and depression. Fatigue and anxiety were more particularly reduced in RCTs with yoga, tai chi or qi gong based interventions whereas interventions involving traditional aerobic and/or resistance activities led to no or very small reduction, suggesting that the implementation of mind–body therapies should be particularly considered to relieve fatigue and anxiety symptoms in interventions targeting adjuvant breast cancer patients. In addition, RCTs rated at high risk of selection bias with the absence of random sequence generation, or at high risk of attrition bias with large attrition rate or the absence of ITT analysis, resulted in greater efficacy of exercise on either QoL, anxiety or depression at the end of intervention in experimental group vs. control. In contrast, retention rate ≥90% and ITT analyses were not associated with any significant effect of exercise. Sample size was identified as a moderator of exercise effect on QoL (negative association). This finding is consistent with the suggestion of small-study effects in the exploration of publication bias implying that negative small studies may remain unpublished and then, exercise effect on QoL may be overestimated.

Some of our findings are in accordance with other meta-regression studies of RCTs on exercise and cancer: methodological quality has been reported to negatively moderate exercise effect on QoL in cancer patients after adjuvant therapy [20], a notably stronger fatigue reduction has been observed in exercise-based RCTs including cancer survivors that did not explicitly report the use of ITT analyses compared with studies that did report the information [21]. In addition, intervention length has been negatively related to QoL increase in breast cancer patient after adjuvant therapy [20]. However, although our findings did not indicate any moderation effect of weekly exercise dose, the use of theoretical model and age, other meta-regression analyses including mixed cancer survivors during and after adjuvant therapy highlighted these moderators: weekly volume of aerobic exercise reduced depression in higher quality trials [19]; reductions in

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fatigue were greater when interventions adhered to a theoretical model, sampled older cancer survivors and occurred preferentially with moderate-intensity resistance exercise [18]. When investigated, no clear evidence of publication bias was pointed out in these meta-analyses [18–20].

Exercise intervention efficacy versus exercise benefits: a matter of adherence?

RCTs' attrition bias has been associated with differential exercise intervention effects; no effect on psychological outcomes was seen in pooled RCTs with attrition rate ≤10% (i.e. retention rate >90%) or ITT analyses, whereas significant improvements were found in those with higher attrition rate or no ITT analyses. An ITT comparison is a conservative approach protecting against type I error as it underestimates the treatment effect when experimental patients do not fully adhere to their assigned treatment. On the other hand, studies with per protocol analyses or low retention rate may indirectly select patients with better compliance (and maybe, better physical aptitude, motivation and adherence) and could be prone to selection bias. ITT and per protocol analyses may lead to different findings. For instance, the ITT analysis of two included studies of Mock *et al.* [71,72] did not reveal any exercise intervention efficacy, whereas in both cases, stratification on exercise practice showed exercise efficacy on fatigue. In addition, ITT analysis remains an anticonservative approach regarding type II error, i.e. the risk of false negative conclusions, especially with poor adherence rate of experimental group and dilution of treatment effect by contamination of control group (contamination occurs when controls reach exercise intervention goals) [84]. Therefore, ITT analyses actually assess the intervention efficacy rather than the efficacy of exercise itself. In the studies of Mock *et al.* [71,72], dilution of treatment effect was an important issue as adherence rates were ~70% [72] and 72% [71] and contamination rates were 50% [72] and 61% [71], respectively. Contamination is a limitation of primary interest in such exercise-based RCTs. Individuals who gave their informed consent generally want to practice exercise; as participants are not blinded to group assignment and taking on physical activity is easily accessible in everyday life. Contamination could be an important moderator of exercise intervention efficacy; however, only a very few studies have measured it [38,57,58,71,72]. Adherence to exercise intervention did not moderate exercise effect in our analyses. However, these findings are approximate as adherence was missing in nine studies, and only average adherence was available at the study level. To assess if exercise practice is a determinant of psychological symptoms improvement, testing individual level adherence would be more informative.

Poorer efficacy in longer interventions: increased burden, decreased feeling?

RCTs with long interventions and high total targeted doses showed benefits on fatigue, anxiety and depression whereas RCTs with lower dose and duration did not. First, adjuvant chemotherapy of breast cancer leads to gradually fatigue accumulation through chemotherapy cycles [85] and could constitute a barrier to patient's implication and adherence to the intervention at long term rather than in the first weeks of the treatment. Our results indicated that the higher the proportion of patients receiving chemotherapy, the worst the efficacy of exercise interventions was on fatigue.

Weekly prescribed exercise dose did not moderate our analyses, suggesting that the moderation effect of total exercise dose may particularly rely on duration of intervention. This finding is contra-intuitive, and we cannot exclude a potential confounding effect of methodological biases. However, the consistency of the association of intervention length as a moderator of exercise effect across three outcomes of interest suggests that a routine could gradually settle in physical activity practice and alter general well-being feeling reported by patients due to intervention.

Limitations

The heterogeneity sources identified in our analyses do not exclude that other confounding factors may explain differential efficacy of exercise on psychological outcomes. The relatively low number of studies included for each outcome of interest did not result in sufficient statistical power to conduct multivariate meta-regression. The performed univariate analyses may be highly related and did not enable to disentangle moderators. Indeed, mind–body interventions were inversely correlated with dose ($r = -0.36$) and duration ($r = -0.43$); however, methodological quality was not correlated with exercise nature, dose or duration ($r < 0.20$). Our meta-analysis is not free from risk of false positive conclusions although the pre-specification of moderators to be tested, the exclusion of outliers and the use of Knapp and Hartung estimates [47] in meta-regression models may have protect against it [86]. The large number of different assessment tools used may have increased heterogeneity. However, a recent meta-analysis that combined subgroups of studies according to questionnaires dimensions did not eliminate heterogeneity [20]. In the present meta-analysis, SMDs were used to standardize change units across different scales.

Six studies included in the systematic review did not provide data of interest and thus were not involved in the quantitative analysis which may have biased our findings. Comparing the characteristics of these studies with missing data to those of the included studies, they appeared to present lower sample size, lower quality score

DOI: 10.1002/pon

and higher attrition rate and to report 9 associations in favor of intervention of which 7 were significant out of 14 described findings about fatigue, QoL, anxiety and depression [60,62,64,69,72,75].

Conclusion

In summary, in adjuvant breast cancer patients, our findings indicate that, on a whole, exercise-based interventions may result in significant improvements of fatigue, QoL, anxiety and depression, with small sizes of effect. However, the evidence mainly rely on studies that are prone to methodological bias, particularly regarding selection or attrition, and studies with low prescribed exercise doses, short interventions or mind–body activity-based interventions.

According to our findings, a prescription of approximately 100 MET.h, e.g. ~120 min of weekly moderate physical exercise for 10 weeks, could be advised to maximize fatigue and depression reductions. In addition, the choice of mind–body activities such as yoga, tai chi or qi gong may be favored to decrease fatigue and anxiety. The lack of effect of exercise interventions on psychological outcomes in studies with low risk of attrition bias (small attrition rate and use of ITT analysis) and high exercise dose or duration promotes the necessity of subsequent high methodological standards RCTs and addresses methodological issues in nonpharmacological RCTs such as exercise adherence of experimental patients, contamination between randomization groups and statistical treatment of patient's drop-out. Our findings highlighted that the high degree of heterogeneity among reviewed RCTs in systematic or meta-analytic reports should be taken into consideration in the establishment of evidence-based conclusions.

Acknowledgements

This work was supported by project grants from the national French Cancer League [Ligue contre le Cancer], the regional French Cancer League of Hérault and Languedoc-Roussillon (No. 8FI10347LQOP) and the French Food and Health Fund [Fonds Français pour l'Alimentation et la Santé]. We thank Zong Zhao for its translation of the Chinese written article of Hu *et al.* [65].

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DOI: 10.1002/pon