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REVIEW

Effects of physical exercise after treatment of early breast cancer: systematic review and meta-analysis

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Abstract

Purpose Randomized clinical trials are inconclusive regarding the role of physical exercise in anthropometric measurements, quality of life, and survival in breast cancer patients. Our aim was to conduct a systematic review and meta-analysis to assess the effects of physical exercise on these outcomes in women who went through curative treatment of early-stage breast cancer.

Methods Pubmed, Embase, Cochrane Library were searched for randomized clinical trial comparing physical exercise (counseling or structured programs with supervised/individualized exercise sessions) with usual care in women that went through for breast cancer treatment. Primary outcomes were overall survival and disease-free survival, while secondary outcomes were weight loss, body mass index, waist–hip ratio, percentage of body fat, and quality of life.

Results We found 60 randomized clinical trials, only one of them showed mortality data; the HR for mortality was 0.45 (95% CI 0.21–0.97) for the intervention group when compared to the control group. Physical exercise was associated with weight reduction (− 1.36 kg, 95% CI − 2.51 to − 0.21, $p = 0.02$), lower body mass index (− 0.89 kg/m^2, 95% CI − 1.50 to − 0.28, $p < 0.01$), and lower percentage of body fat (− 1.60 percentage points, 95% CI − 2.31 to − 0.88, $p < 0.01$). There was an increase in the quality of life (standardized mean difference of 0.45, 95% CI 0.20–0.69, $p < 0.01$).

Conclusions The articles found had heterogeneous types of intervention, but they showed significant effects on anthropometric measures and quality of life. Among them, only one study had mortality as outcome and it showed physical exercise as a protective intervention. Despite these findings, publication bias and poor methodological quality were presented. Physical exercise should be advised for breast cancer survivors since it has no adverse effects and can improve anthropometrics measures and quality of life. PROSPERO registry: CRD42014008743.

Keywords Breast cancer · Meta-analysis · Physical exercise · Quality of life

Introduction

Breast cancer is the most common malignant neoplasm among women in much of the world, even in more developed countries, when cases of non-melanoma skin cancer are excluded. Incidence and mortality make breast cancer a very important health problem. This is associated with the fact that the majority of newly diagnosed cases are in early stages, which are highly curable with surgical and adjuvant treatment. This is the result of significant advances in the diagnosis and treatment of the disease. At the same time, high rates of cure lead to a growing contingent of women survivors of breast cancer [1]. This is a population with different medical and social needs, to which the different health systems are neither trained nor prepared to attend [2]. Caring

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for breast cancer survivors is therefore a matter of growing importance for health professionals.

Obesity is also a growing problem that requires attention from multiple healthcare professionals. There is evidence that obese women and women who gain weight after breast cancer diagnosis have twice the risk of recurrence and death from breast cancer in 5 years and 60% higher risk of death over 10 years, when compared to women normal weight [3, 4]. More than half of women diagnosed with breast cancer experience an increase in body weight associated with menopause and related to chemotherapy and hormonal treatment [5]. In this setting, regular physical activity can help control body weight and has already been shown to reduce the risk of breast cancer [6, 7]. Recent studies suggest that physical activity can also halve the risk of death in patients with breast cancer [8]. The Nurses' Health Study, one of the largest cohorts in the field, showed that physically active women (from 2987 patients with early breast cancer) had half the risk of recurrence and death when compared to sedentary women [8].

Unlike studies involving chemotherapeutic treatments, physical exercise studies are consistently smaller, with shorter follow-up and different assessments regarding the type of physical exercises whether aerobic or strength exercises. In addition, the existing randomized clinical trials were inconclusive regarding the role of this intervention in anthropometric measurements or quality-of-life outcomes [9].

In this study, we aim to conduct a systematic review and meta-analysis to assess the effects of physical exercise (with or without dietary interventions) in body composition, quality of life, and survival in women after treatment of early-stage breast cancer.

Methods

Protocol and registration

We conducted this systematic review and meta-analysis using a previously published protocol [10] (PROSPERO registry number CRD42014008743) for the research question related to physical activity. We conducted this systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions [11] and reported the manuscript according to PRISMA recommendations [12].

Data sources and searches

The following electronic databases were used to evaluate the indexed literature: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. We conducted the electronic search and up to July 2017; it was limited to papers in English (see Supplementary Material). We have also searched gray literature in annals of major meetings and ongoing studies at ClinicalTrials.gov.

Study selection

We included randomized trials that evaluated physical exercise interventions (counseling or structured programs with supervised/individualized exercise sessions). The intervention should have been compared with usual care in women treated for stage I–III breast cancer. We included studies that performed the intervention after the end of adjuvant treatment (excluding hormone therapy) and excluded studies that applied the intervention after 5 years from the diagnosis.

The following primary outcomes were considered in the evaluation of the studies: overall survival and disease-free survival (5 years after treatment or until the maximum follow-up study). The secondary endpoints were weight loss (kg), BMI (kg/m^2), waist–hip ratio, percentage body fat (%), and quality of life. Adverse events, such as exercise-induced lesions, were also been considered.

The evaluation of titles and abstracts for potentially eligible studies was conducted in paired and independently. Inclusion and data extraction were conducted for the full texts in the same manner, using a standardized form. Disagreement was solved through discussion.

Data extraction

The data used for meta-analysis and comparison between usual care and intervention were the final values of the groups after the intervention, since these were the data most frequently found. This method was used to minimize the number of errors and minimize the need for imputations. In the studies that presented only the values of the difference between final results and initial results, the final values were calculated from a simple sum of the variation with the initial value. In this case, the values of the standard deviations used were the same as the initial values of the variables. We preferred the EORTC QLQ-C30 quality-of-life score, since this was the most frequently used instrument among the studies. For studies such as Harrigan 2016 [13], Demark-Wahnefried 2014 [14], and Vallance 2007 [15] with two or more intervention groups, the data from all intervention groups were combined into a single group. Finally, some values of standard deviation of the quality-of-life data were not described by the authors in their works (Herrero 2006 [16], Lee 2014 [17], Heim 2007 [18], Rogers 2009 [19], Baruth 2015 [20] and Fields 2016 [21]); in these cases, the standard deviation was used as a weighted mean of the other studies that used the same scale.

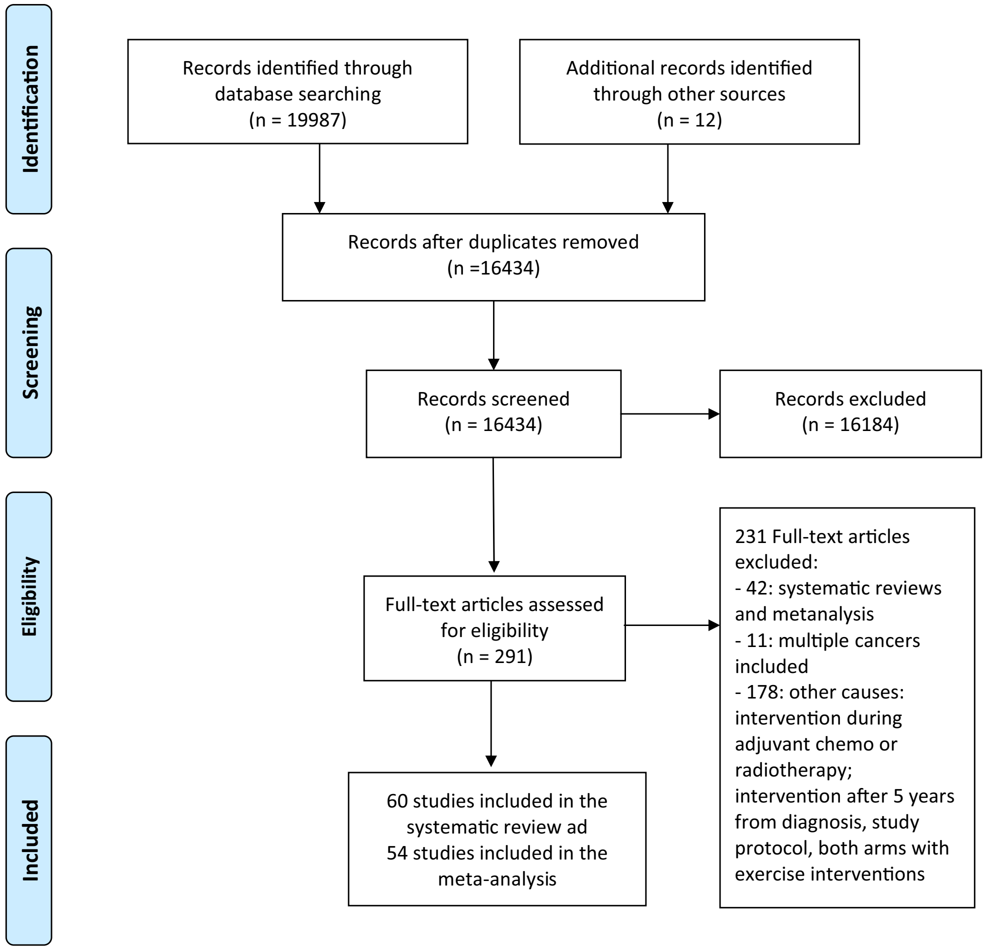

Fig. 1 Prisma flow diagram

Quality assessment

We also carried out a paired methodological quality evaluation of the individual studies, according to the Cochrane Handbook of Systematic Reviews [11] using the Cochrane risk of bias tool. Disagreement was solved through discussion. The overall quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [22], and verified by a third reviewer. The quality of evidence was classified as 'high,' 'moderate,' 'low,' or 'very low.'

Data synthesis and analysis

The data were combined using the random-effect meta-analysis model, with DerSimonian–Laird estimator as variance estimator. We estimated the treatment effect using the mean difference (MD) as summary measure for continuous outcomes. For continuous outcomes presented in different scales, we used the standardized mean difference (SMD). Data were presented with 95% confidence intervals (CI). All analyzes were performed using software R, version 3.3.2, *meta* packages version 4.8-4.

Statistical heterogeneity was assessed in each meta-analysis using the statistics I^2. Heterogeneity was considered substantial if the I^2 was greater than 50%. Heterogeneity was explored through subgroup analysis. We assessed publication bias using funnel plot and the Egger test. A significant publication bias was considered if $p < 0.10$. We estimated the effect of publication bias on the interpretation of results by a trim-and-fill computation.

Results

Literature search

In total, 19,987 titles were located, of which 3553 were duplicates. In the review of titles and abstracts 16,434 studies were excluded 291 were fully read for assessment

Table 1 Characteristics of the included studies

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Anderson 2015 (Australia) [27]	12-Week program instructions and healthy lifestyle readings, with a book containing weekly exercise planning and special parts to record data on diet, aerobic exercise, strength exercises, pelvic floor exercises, weight, waist circumference, and climacteric symptoms and diary supply to help participants achieve their goals	3	3	51	48.9
Baruth 2015 (USA) [20]	Home walking program for 12 weeks. First a face-to-face orientation session on exercise and week 1, 2, 4, and 10-week guidelines	3	3	32	56.7
Cadmus 2009 (USA) [28]	Supervised exercises 3×/week plus exercises on their own 2×/week; heart rate monitoring during sessions with a goal of maintaining between 60 and 80% of the expected maximum frequency	6	6	75	56.0
Campbell 2017 (Canada) [29]	150 min per week of aerobic activity (moderate to vigorous): two 45-min sessions at a research facility gym and 2 30-min sessions of unsupervised exercise of patient preference	6	6	19	52.6
Casla 2015 (Spain) [30]	Exercise program consisted of supervised exercise sessions twice a week (aerobic + resistance) with progressive increase of intensity. Patients also received nutritional guidance	3	3	94	47.9
Courneya 2003 (Canada) [31]	Training 3×/week on ergonomic bikes for 15 weeks. Duration of training gradually increased and intensity was adjusted according to the ventilatory equivalent for carbon dioxide	3.75	3.75	52	58.7
Daley 2007 (UK) [32]	Moderate-intensity exercises 3×/week for 8 weeks lasting 50 min under the supervision of a specialist	2	2	72	51.4
De Luca 2016 (Italy) [33]	Two weekly sessions of 90 min, corresponding to 10 min of warm-up (onset) and cooling (final) followed by 40 min of resistance exercise followed by 30 min of aerobic exercise for 24 weeks. The exercises were progressive during the protocol	6	6	20	48.8

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Demark-Wahnefried 2014 (USA) [14]	Individualized books with guidelines for weight loss and dietary changes followed by six leaflets over a year. Patients in the two intervention groups received individualized information or individualized information plus information about other participants in the group	12	12	68	61.3
Demark-Wahnenfried 2015 (USA) [34]	Physical exercise group sessions of 1 h/week for 4 months, then sessions of 15/15 days and then monthly for 1 year, as well as telephone and e-mail between sessions. They also received dietary information on diet to physical exercise	12	24	692	56.1
Do 2015 (South Korea) [35]	Heating, aerobic exercise, strength exercise, core stability exercise, and cooling 5×/week for 4 weeks under the supervision of a physical therapist	1	1	62	47.5
Duijts 2012 (Netherlands) [36]	Unsupervised exercises, at home, lasting 2.5–3 h per week for 12 weeks aiming to achieve 60–80% Karvonen (Max heart rate equivalent). Physiotherapist assisted the patient to choose the most appropriate exercise modality (bicycle, running, swimming)	3	6	207	47.7
Fairey 2003 (Canada) [37]	Treadmill 3×/week in ergometers at a VO2 of 70–75%. Exercise started for 15 min in the first 3 weeks and progressed in 5 min every 3 weeks to 35 min	3.75	3.75	52	58.7
Fields 2016 (UK) [21]	Nordic walks (two-stick walk) supervised by the first ones for 12 weeks. Exercise was a group under supervision at weeks 1–6 with gradual increase in frequency, in weeks 7–12 the patients were instructed to perform 4 sessions of 30 min per week on their own	3	3	40	62.0
Fillion 2008 (Canada) [38]	Supervised walk for 1 h associated with management sessions for fatigue symptoms once a week for 4 weeks. Patients were given a heart monitor (Polar) to receive objective feedback from walking	1	4	87	52.7
Galiano-Castillo 2016 (Spain) [39]	Three sessions of 90 min per week on non-consecutive days for 8 weeks. Exercises consisted of an aerobic part and a part of resistance	2	6	81	48.0

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Ghavami 2017 (Turkey) [40]	Moderate-intensity aerobic exercise sessions under supervision 3–5 days per week throughout 24 weeks. Each session comprised a 10-min light aerobic exercise and a gentle range of motion exercises (warm-up period), followed by 30 min of aerobic exercise at an intensity of 70–85% of maximum heart rate and a reduction of caloric intake to 600 kcal below calculated energy requirements	6	6	80	49
Giallauria 2015 (Italy) [41]	Aerobic training with treadmill or bicycle 3×/week for 3 months and after 1×/week for another 9 months; patients also received information leaflets on exercise, diet, and weight loss with a goal of performing exercises for 210 min per week. Patients also participated in feeding classes and meetings	12	12	51	52.5
Goodwin 2014 (USA, Canada) [42]	Patients received in the whole 19 connections over 24 months with guidelines on reduction of caloric intake, weight loss, increase in the amount of vegetables and fruits consumed, and reduction in fats; goal of gradual increase in the practice of aerobic physical exercises to a goal of 150–200 min per week; between 30 and 60 min	24	24	338	61.2
Greenlee 2013 (USA) [43]	Patients were enrolled in a physical training center where they were recommended to attend 5×/week; strength and aerobic exercises for 15–30 min per session; also received dietary recommendations in a nutrition course	6	12	42	51.3
Guinan 2013 (Ireland) [44]	Aerobic exercises (biking, treadmill, rowing) supervised 2×/week + exercises at home up to 5×/week. Lesson duration and intensity increased every two weeks	2	3	26	48.7
Hagstrom 2016 (Australia) [45]	Resistance training 3×/week for 60 min for 16 weeks; movements with the use of machines in the first 8 weeks and movements without weights in the last 8 weeks	4	4	39	51.7

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Harrigan 2016 (USA) [13]	Counseling by telephone [1] or live [2] focusing on weight loss: reduced caloric intake and moderate-intensity exercise for 150 min/week; also received a book on the LEAN method of weight loss. Weekly meetings in the first month; biweekly in the second and third months; monthly thereafter	6	6	66	58.6
Hayes 2017 (Australia, New Zealand) [23]	Described as a translational exercise intervention delivered either face-to-face or over the telephone	8	101	337	Not described
Heim 2007 (Germany) [18]	Brochure and guidelines on stretching and muscle exercises; instructions for aerobic (walking), coordination, and relaxation	During rehabilitation	3 months after finishing rehabilitation	63	Not described
Herrero 2006 (Spain) [16]	Three weekly sessions of 90 min with endurance and aerobic exercises	2	2	20	50.3
Irwin 2009 (USA) [46]	Supervised aerobic exercise 3×/week plus home exercise 2×/week; duration of 15–30 min according to tolerance; mode of exercise of the patient's preference	6	6	75	56.0
Irwin 2013 (USA) [47]	Supervised aerobic and strength exercises 2×/week plus home exercises for 150 min/week. Intensity of the exercise was adjusted according to heart rate	12	12	121	61.5
Karimi 2013 (Iran) [48]	Aquatic aerobic exercises 4×/week lasting 40–80 min per session	1.5	1.5	20	Not described
Kim 2011 (South Korea) [49]	Patients received counseling by phone, book, and a prescription of diet and exercise. The goal was to perform exercises 5×/week for at least 30 min	3	6	45	45.4
Kim 2017 (South Korea) [50]	Three times a week of warm-up consisting whole body stretching and flexibility exercises for 10 min followed by step aerobics for 20 min followed by the strength training using body weight and elastic bands for 20 min. The exercise intensity and the resistance of elastic band were progressively increased. At the end of the session, subjects performed cool-down involving easy walking and stretching exercises for 10 min	3	3	24	52

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Kwiatkowski 2013 (France) [51]	Admission to a SPA for 2 weeks, where 2 h of physical activity (strength, resistance, elasticity, and water aerobics) were performed daily. They also received baths, massages, prepared diet, and esthetic care	0.5	12	222	52.0
Lahart 2016 (UK) [52]	Stimulating exercise; phone call at the end of the first, second, and third month to maintain exercise; leaflet by mail at the end of the fourth and the fifth month with encouragement to practice. Order to maintain the practice of exercises 3–5×/week for 30 min at least. Patients also received a brochure with information and a DVD.	6	6	80	53.2
Lee 2014 (South Korea) [17]	Self-management web-based exercise and diet program. The intervention incorporates strategies of transtheoretical model as stage of change, process of change, balance of decision, or self-efficiency	3	3	59	42.1
Ligibel 2008 (USA) [53]	Strength and cardiovascular training at home for 16 weeks. Two weekly training sessions of 50 min supervised strength + 1 cardiovascular training of 90 min weekly at home	4	4	100	52.3
Matthews 2007 (USA) [54]	Guided home walks on a 30-min visit, followed by short phone calls after 1, 2, 4, 7, and 10 weeks. Hiking in the first 4 weeks 3×/week (20–30 min/session); at weeks 5–7, 4×/week (30–40 min/session); in the last 5 weeks, 5×/week (30–40 min/session) at moderate intensity	3	3	36	52.9
Mefferd 2007 (USA) [55]	Cognitive-behavioral group therapy, physical activity, and dietary guidelines. Physical activity: promotion and encouragement of daily aerobic exercises, with progression of time and intensity. Strength exercises 2–3× per week. Providing a pedometer to encourage and record physical activity on a daily basis	4	4	76	56.3
Milne 2008 (Australia) [56]	3 times per week supervised physical activity sessions in rehabilitation clinic. The program contains aerobic/cardiovascular and endurance, as well as stretching	3	6	58	55.2

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Nuri 2012 (Iran) [57]	Supervised walking program for two times per week in a time-progressive duration protocol plus 60 min resistance training during the 15 weeks of intervention	3.75	3.75	29	58.3
Nyrop 2017 (USA) [26]	Participants were asked to walk on their own or with others at a pace that was safe, comfortable, and sustainable for 150 min per week	1.5	1.2	29	63.8
Ohira 2006 (USA) [58]	Supervised strength and resistance training exercises using resistance machines and free weights for thorax muscles, back, shoulders, and arms as well as the buttocks, hips, and thighs. In addition, participants were taught stretching exercises to perform before and after each weight training session	6	6	81	53.1
Pakiz 2011 (USA) [59]	Cognitive-behavioral therapy based on 24 group sessions for weight loss. Weekly for 4 months and monthly up to 12 months. Aim to promote regular physical activity and reduce caloric intake to facilitate weight loss	4	4	68	56.0
Pinto 2005 (USA) [60]	Participants received instructions on how to exercise at moderate intensity, heart rate monitoring, and how to perform warm-up and cooling after exercise. Received pedometer and exercise table. Oriented to exercise for at least 10 min 2× per week, with gradual increase up to 30 min 5× per week at the end of 12 weeks. Weekly phone calls from the team to monitor. They received weekly workout tips	3	9	86	53.2
Rahnama 2010 (Iran) [61]	60 min of resistance exercise (weight lifting) 2× in the week + walks (minimum time 25 min) 2× in the week (alternate days)	3.75	3.75	29	Not described
Reeves 2017 (Australia, USA) [62]	Participants received detailed workbook of lifestyle recommendations, monitoring diary, digital scales, calorie count book, and 16 phone calls (by lifestyle coaches, nutritionists specializing in motivation for physical training), calorie deficit diet of 2000 kJ, orientation for increase walks to at least 30 min/day, and a pedometer	6.5	6	90	55.7

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Rock 2015 (USA) [63]	Weekly meetings of 1 h in the first 4 months, then every 15 days for another 2 months and after monthly; in the meetings were taught exercises and provided guidance as to achievement. Orientation of 60 min/day. Diet recommendation with caloric deficit of 500–1000 kcal	24	24	692	56.0
Rogers 2009 (USA) [19]	Goal of reaching 150 min of moderate-intensity walking per week. Participants attended 6 group sessions for time management, importance of physical activity, and behavioral change and goals. They also attended 12 supervised exercise sessions and 3 session sessions with exercise specialists	3	3	41	52.7
Roveda 2016 (Italy) [64]	A program conducted by 2 sport therapy experts and included 2 sessions of 1-h brisk walking per week for 3 months	3	3	40	56.8
Saarto 2012 (Finland) [65]	Supervised on-site training and home-based exercise counseling. The supervised training was 1×/week, with up to 15 individuals and was performed circuit training and aerobic with walking, with progressive intensity. The home part could be walks, Nordic walks, step exercises or jump (patient preference), oriented to perform preferably 3×/week and at least 2×/week	12	12	473	52.3
Schmitz 2005 (USA) [66]	In the first 3 months of intervention: supervised exercises with trainer enabled in groups of maximum 4 people. In the other 3 months, participants were encouraged to continue performing physical activity on their own	6	12	81	53.1
Scott 2013 (UK) [67]	Three sessions per week supervised 30 min of aerobic exercise plus 10–15 min of muscle strengthening, using free weight. In addition, consultation with nutritionist for a caloric deficit of 600 kcal/day	6	6	90	55.7
Sheppard 2016 (USA) [68]	Supervised 30-min physical activity group sessions and 60 min educational sessions every 2 weeks comprising. On weeks when participants did not meet as a group they had individual telephone coaching sessions led by a trained survivor coach.	3	3	22	54.7

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Shobeiri 2016 (Iran) [69]	Exercises of 40–60 min 2× per week for 10 weeks involving the HEATING (5–10 min walk slow and moderate stretching), moderate aerobic exercise (15 min of slow walking, stretching, and specific movements of the arms and shoulders), and 5 min of cooling down (slow walk). Increase of 2% of aerobic exercise time each week, resulting in 35 min in the tenth week	2.5	2.5	53	43.0
Speck 2010 (USA) [70]	Group instructions 2×/week for 90 min for 13 weeks followed by a further 13 weeks of 2×/week exercises without supervision. Sessions included stretching, cardiovascular warm-up, abdominal and back strengthening exercises, and weight lifting	12	12	234	56.5
Sturgeon 2016 (USA) [71]	The exercise component required 160 min/week of exercise (3 days/week of progressive resistance exercise, 2 days/week of interval aerobic exercise, and 1 day/week of active recovery aerobic exercise)	12	12	35	46.1
Swisher 2015 (USA) [72]	Supervised exercise of moderate intensity for 3×/week in physical activity environment and other 2×/week in home environment without supervision. Consultation with nutritionist with dietary guidelines of caloric reduction	3	3	28	53.7
Thomas 2017 (USA) [73]	Twice-weekly supervised resistance training (total body program for the lower and upper extremities) and 150 min of moderate-intensity aerobic at home (brisk walking on a treadmill or outside, but cycle ergometers and elliptical trainers were permitted). Exercise started at 50% of predicted maximal heart rate (220-age) and was gradually increased to approximately 60–80% of predicted maximal heart rate (verified by heart rate monitors)	12	12	121	61.2
Tirado-Gomez 2015 (Spain) [74]	Study of three groups in which one received written materials adapted to the culture of the patient with orientation of physical exercise, another group receiving materials not adapted to their culture and a placebo group	4	4	38	58.0

Table 1 (continued)

Study ID	Description of intervention	Duration of intervention (months)	Follow-up (months)	Number of participants	Mean age
Vallance 2007 (Canada) [15]	The participants received a standard public health recommendation for physical activity (PA), previously developed breast cancer-specific PA print materials, a step pedometer, or a combination of breast cancer-specific print materials and step pedometers	3	3	190	57.0
Winters-Stone 2013 (USA) [75]	Participants received supervised classes (30–60/min) 2 days/week and were instructed to repeat at home 1×/week for 12 months. The intervention group performed resistance activities with weights (shin guards and weight vests, dumbbell, kettlebell, barbells) with 8–15× repetition orientation and modulation of weight depending on individual capacity	12	12	71	46.6

of eligibility. After that, 169 studies were excluded, and 60 studies entered the phase of data extraction, of those *54 studies provided quantitative data for meta-analysis.* The flowchart of the search is presented in Fig. 1, and the initial characteristics of the studies are presented in Table 1.

Study characteristics

The total number of patients in all of the studies was 6303. The follow-up ranged from 1 to 101 months and the duration of the intervention ranged from 4 weeks to 24 months. The mean age of the patients across the trials was 47.4 years, and the time from breast cancer surgery or from finishing the adjuvant treatment to intervention ranged from 1 month to 4 years. We found multiple types of physical exercise interventions but the most frequent modality was structured or individualized programs (found in 41 trials).

Outcomes

We found only one trial that reported disease-free survival in an abstract. This was an Australian trial that randomized 337 women 6 weeks after surgery for breast cancer to 8 months of physical exercise counseling (either in person or by telephone) or to usual care. After a follow-up of 101 months, the HR for overall survival in the intervention groups compared to placebo was 0.45 (95% CI 0.21–0.97); there was no difference in disease-free survival between the groups (HR 0.66 [95% CI 0.38–1.17]). Despite not establishing causality, the study suggests the potential of physical activity to influence survival.

For the secondary outcomes we found that physical exercise interventions, whether by orientation or by structured programs, promote statistically significant weight reduction in breast cancer patients (− 1.36 kg; 95% CI − 2.51 to − 0.21; $p = 0.02$; $I^2 = 17\%$; very low quality of evidence) (Fig. 2) and BMI reduction (− 0.89; CI 95% − 1.50 to − 0.28; $p < 0.01$; $I^2 = 51\%$; low quality of evidence) especially for the diet and exercise counseling group (Fig. 3). Physical exercise also showed a statistically significant decrease of − 1.60 in body fat percentage points (95% CI − 2.31 to − 0.88; $p < 0.01$; $I^2 = 28\%$; low quality of evidence) especially in the structured or individualized exercise program (Fig. 4).

The overall quality of life was significantly modified by physical exercise interventions showing a standardized mean difference of 0.45 (95% CI 0.20–0.69, $p < 0.01$; $I^2 = 83\%$; very low quality of evidence) (Fig. 5). The same can be said about the effect on the physical domain of quality

Study	Experimental Total	Experimental Mean	Experimental SD	Contol Total	Contol Mean	Contol SD	MD	95%–CI	Weight
Structured or individualized exercise programs									
Herrero 2006	8	65.60	8.70	8	67.30	8.90	−1.70	[−10.32; 6.92]	1.7%
Irwin 2009	26	81.60	18.97	23	76.58	17.41	5.02	[−5.17; 15.21]	1.2%
Irwin 2013	61	76.40	18.10	60	75.60	14.50	0.80	[−5.04; 6.64]	3.4%
Casla 2015	45	66.78	8.64	44	65.49	12.29	1.29	[−3.13; 5.71]	5.4%
Courneya 2003	24	78.20	20.50	28	80.10	16.20	−1.90	[−12.06; 8.26]	1.2%
Campbell 2017	10	70.90	15.90	9	66.80	16.70	4.10	[−10.60; 18.80]	0.6%
Matthews 2007	22	74.90	15.20	14	78.90	20.30	−4.00	[−16.39; 8.39]	0.8%
Mefferd 2007	47	78.20	12.60	29	85.80	15.00	−7.60	[−14.14; −1.06]	2.8%
Ligibel 2008	51	80.00	17.50	42	83.30	18.70	−3.30	[−10.72; 4.12]	2.2%
Nuri 2012	14	69.40	13.50	15	71.60	9.20	−2.20	[−10.67; 6.27]	1.7%
Rahnama 2010	14	69.40	13.51	15	71.60	9.28	−2.20	[−10.69; 6.29]	1.7%
Rock 2015	300	81.40	15.58	287	83.80	15.24	−2.40	[−4.89; 0.09]	11.8%
Schmitz 2005	39	69.54	2.22	40	69.16	2.20	0.38	[−0.59; 1.35]	22.4%
Winters−Stone 2012	23	73.60	14.90	25	72.30	13.30	1.30	[−6.72; 9.32]	1.9%
Scott 2013	41	76.91	10.00	38	82.80	17.00	−5.89	[−12.10; 0.32]	3.0%
Thomas 2017	61	77.32	18.00	60	75.58	14.80	1.74	[−4.13; 7.61]	3.4%
Sturgeon 2016	19	71.35	11.80	16	71.75	15.54	−0.40	[−9.68; 8.88]	1.4%
Roveda 2016	19	67.10	11.90	21	63.70	9.50	3.40	[−3.32; 10.12]	2.6%
Kim 2017	11	58.40	8.00	13	61.60	12.10	−3.20	[−11.30; 4.90]	1.9%
Random effects model	**835**			**787**			**−0.27**	**[−1.16; 0.63]**	**71.2%**
Heterogeneity: $I^2 = 1\%$									
Diet and exercise counseling									
Greenlee 2013	21	83.34	12.50	17	81.66	15.30	1.68	[−7.35; 10.71]	1.5%
Harrigan 2016	67	82.91	13.40	33	88.70	13.51	−5.79	[−11.41; −0.17]	3.6%
Goodwin 2014	171	79.60	15.30	167	80.90	14.50	−1.30	[−4.48; 1.88]	8.8%
Demark−Wahnefried 2014	46	79.25	9.80	18	80.70	10.10	−1.45	[−6.91; 4.01]	3.8%
Pakiz 2011	44	78.20	11.80	24	87.00	14.70	−8.80	[−15.64; −1.96]	2.6%
Swisher 2015	18	77.20	10.30	10	85.00	21.50	−7.80	[−21.95; 6.35]	0.6%
Random effects model	**367**			**269**			**−3.15**	**[−5.95; −0.36]**	**20.9%**
Heterogeneity: $I^2 = 24\%$									
Exercise counseling									
Lahart 2016	40	69.43	12.46	40	69.19	12.36	0.24	[−5.20; 5.68]	3.8%
Reeves 2017	40	77.60	12.80	45	83.10	13.40	−5.50	[−11.07; 0.07]	3.7%
Sheppard 2016	10	97.38	20.00	12	98.97	21.45	−1.59	[−18.94; 15.76]	0.4%
Random effects model	**90**			**97**			**−2.52**	**[−6.47; 1.44]**	**7.9%**
Heterogeneity: $I^2 = 5\%$									
Random effects model	**1292**			**1153**			**−1.36**	**[−2.51; −0.21]**	**100.0%**
Heterogeneity: $I^2 = 17\%$									

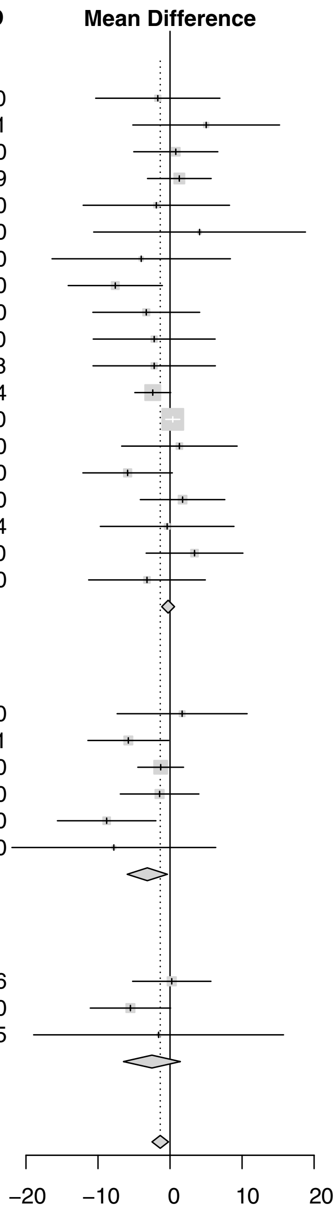

Fig. 2 Forest plot for weight reduction

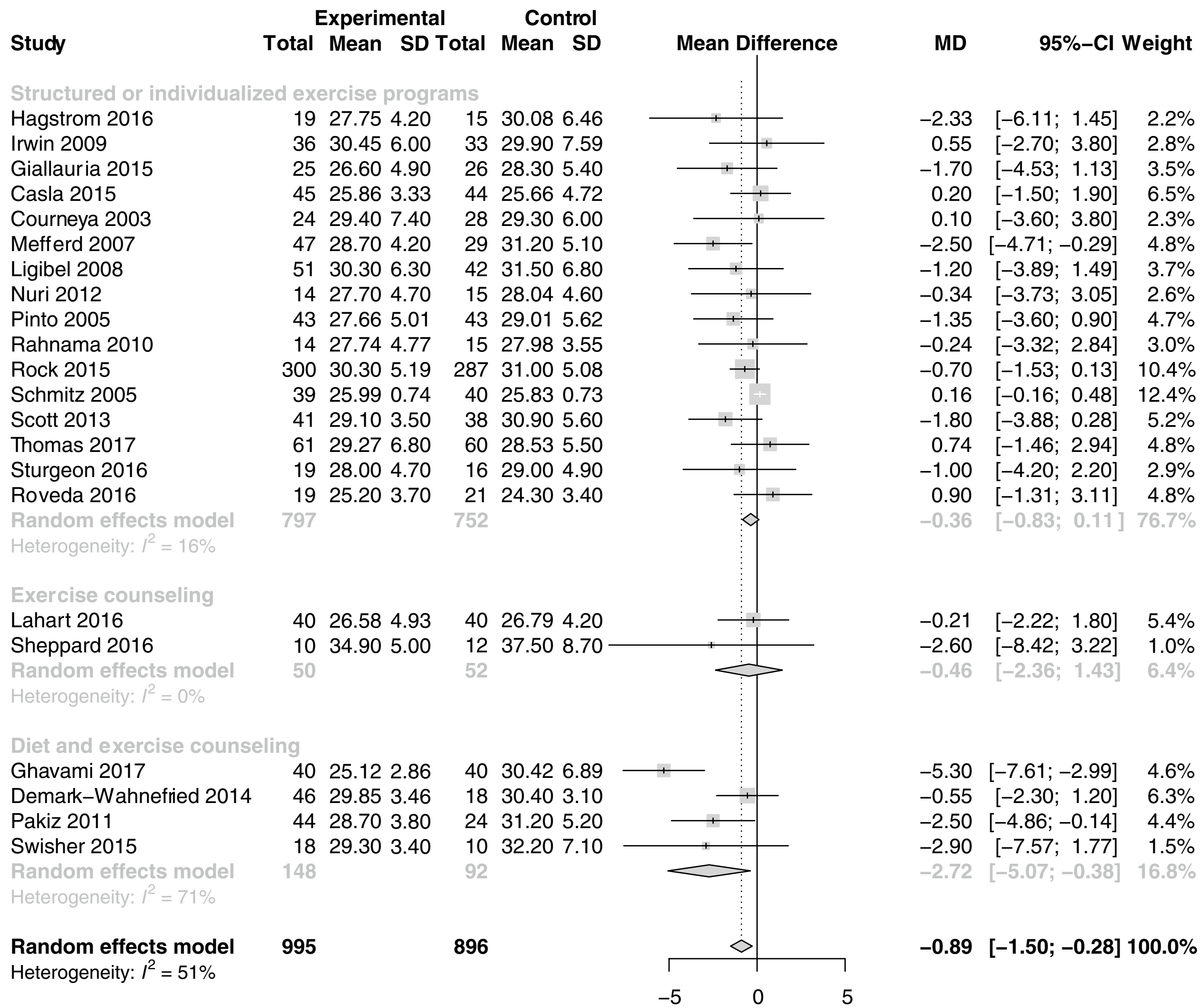

Fig. 3 Forest plot for BMI reduction

of life, showing a standardized mean difference of 0.51 (95% CI 0.23–0.79; $p<0.01$; $I^2=86\%$; very low quality of evidence) (Supplementary Material) and the mental domain, showing a standardized mean difference of 0.28 (95% CI 0.06–0.50; $p=0.013$; $I^2=71\%$; very low quality of evidence) in favor of the intervention groups (Supplementary Material). No significant effect of physical exercise could be seen on HOMA-IR (−0.03; 95% CI −0.20 to 0.13; $p=0.68$) (see Supplementary Material).

We performed subgroup analysis for all the anthropometric outcomes according to type of intervention and for the different quality-of-life scales (as seen in Figs. 2, 3, 4, 5, and

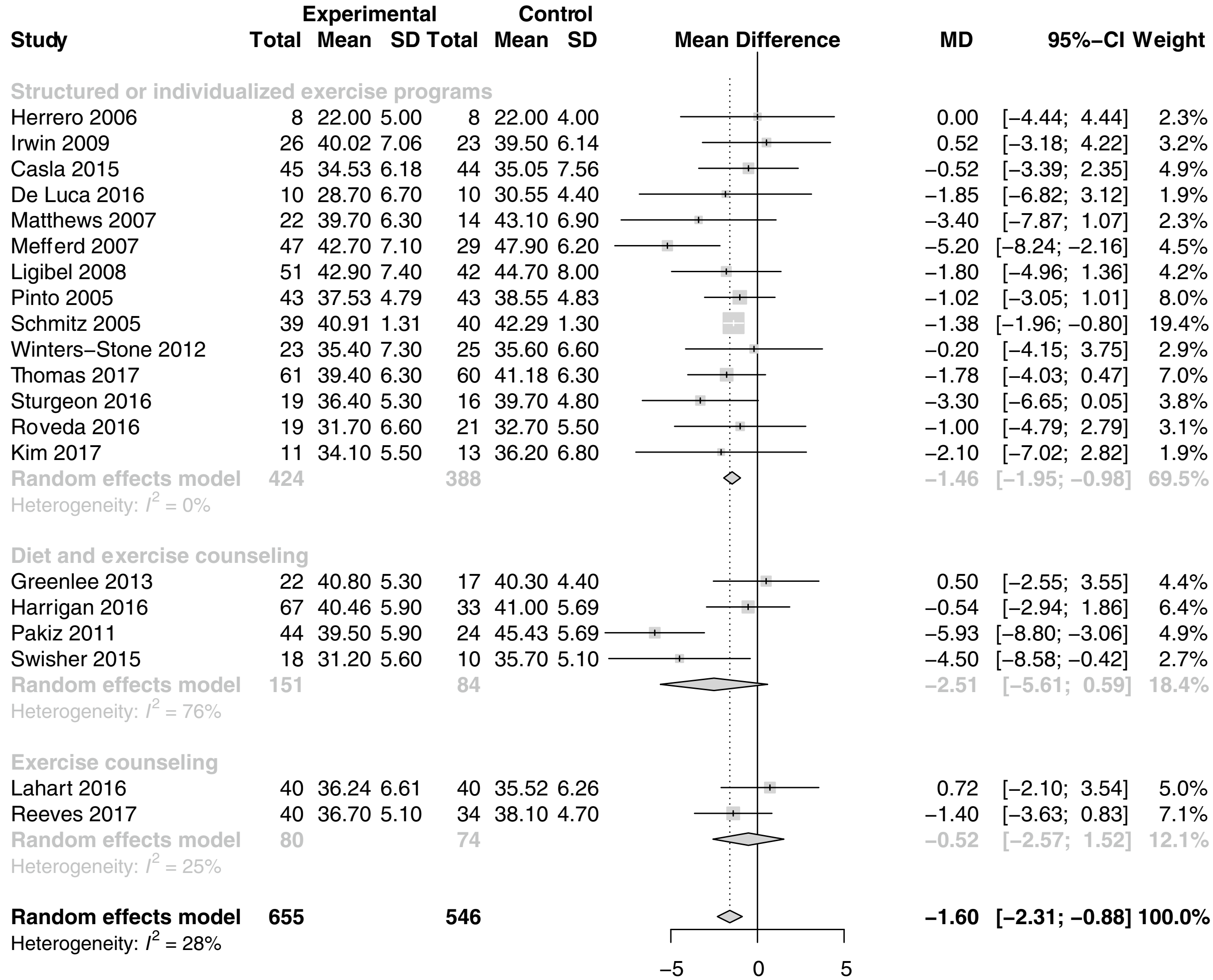

Fig. 4 Forest plot for fat percentage reduction

in the Supplementary Material). Meta-regression analysis showed no association between duration of intervention and all outcomes.

The Egger test showed significant publication bias for all outcomes, except for fat percentage reduction or the mental domain of quality of life. Funnel plots for all the outcomes can be seen in the Supplementary Material. Trim-and-fill computation resulted in loss of statistical significance when publication bias was corrected. After this correction, the effect of the intervention on weight was − 0.18 (95% CI − 1.52 to 1.15), on BMI was − 0.04 (95% CI − 0.67 to 0.60), on the general quality of life was 0.08 (95% CI − 0.2 to 0.36), and on physical quality of life was 0.09 (95% CI − 0.22 to 0.40).

Quality evaluation

The risk of bias according to Cochrane risk of bias tool is presented in Figs. 6 and 7. Serious methodological flaws were found such as poor randomization methods and poor outcome assessments. Noteworthy, most of the studies

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	SMD	95%-CI	Weight
EORTC QLQ−C30									
Herrero 2006	8	92.00	17.71	8	63.00	19.34	1.48	[0.33; 2.62]	2.6%
Kim 2011	23	73.33	17.67	22	68.02	16.18	0.31	[−0.28; 0.90]	4.3%
Do 2015	32	80.20	15.50	30	58.00	18.50	1.29	[0.74; 1.84]	4.4%
Galiano−Castillo 2016	39	72.86	19.93	37	57.21	21.71	0.74	[0.28; 1.21]	4.7%
Shobeiri 2016	27	81.79	16.34	26	52.88	14.51	1.84	[1.19; 2.49]	4.1%
Lee 2014	29	56.40	17.71	28	53.10	19.34	0.18	[−0.34; 0.70]	4.5%
Saarto 2012	263	74.00	17.80	237	75.80	19.90	−0.10	[−0.27; 0.08]	5.5%
Random effects model	421			388			0.76	[0.19; 1.34]	30.2%
Heterogeneity: I^2 = 90%									
FACT−G									
Heim 2007	32	81.00	13.11	31	70.00	14.72	0.78	[0.27; 1.29]	4.6%
Lahart 2016	40	88.03	18.53	40	89.59	16.84	−0.09	[−0.53; 0.35]	4.8%
Courneya 2003	24	91.30	11.00	28	89.30	10.90	0.18	[−0.37; 0.73]	4.4%
Daley 2007	34	87.68	13.57	38	80.41	14.76	0.51	[0.04; 0.98]	4.7%
De Luca 2016	10	87.00	12.30	10	65.90	14.70	1.49	[0.47; 2.51]	2.9%
Milne 2008	29	86.40	8.30	29	64.10	10.80	2.28	[1.61; 2.96]	4.0%
Anderson 2015	26	81.10	12.40	25	78.90	20.20	0.13	[−0.42; 0.68]	4.4%
Rogers 2009	21	86.20	13.11	20	85.80	14.72	0.03	[−0.58; 0.64]	4.2%
Nyrop 2017	24	79.90	14.36	29	81.02	15.00	−0.07	[−0.62; 0.47]	4.5%
Random effects model	240			250			0.54	[0.08; 0.99]	38.6%
Heterogeneity: I^2 = 83%									
SF−36									
Kwiatkowski 2013	113	70.80	20.30	107	64.34	22.07	0.30	[0.04; 0.57]	5.3%
Cadmus 2009	37	50.00	8.80	37	51.70	8.40	−0.20	[−0.65; 0.26]	4.8%
Casla 2015	45	51.11	9.93	44	46.37	9.70	0.48	[0.06; 0.90]	4.9%
Fields 2016	20	58.00	15.72	20	70.00	16.48	−0.73	[−1.37; −0.09]	4.1%
Baruth 2015	20	68.10	15.72	12	61.60	16.48	0.40	[−0.33; 1.12]	3.8%
Random effects model	235			220			0.08	[−0.30; 0.46]	22.9%
Heterogeneity: I^2 = 70%									
CARES−SF									
Ohira 2006	39	44.20	8.70	40	47.40	9.40	−0.35	[−0.79; 0.09]	4.8%
Random effects model	39			40			−0.35	[−0.79; 0.09]	4.8%
Heterogeneity: not applicable									
FACT−B									
Swisher 2015	18	119.60	14.60	10	104.60	30.60	0.68	[−0.12; 1.47]	3.6%
Random effects model	18			10			0.68	[−0.12; 1.47]	3.6%
Heterogeneity: not applicable									
Random effects model	**953**			**908**			**0.45**	**[0.20; 0.69]**	**100.0%**
Heterogeneity: I^2 = 83%									

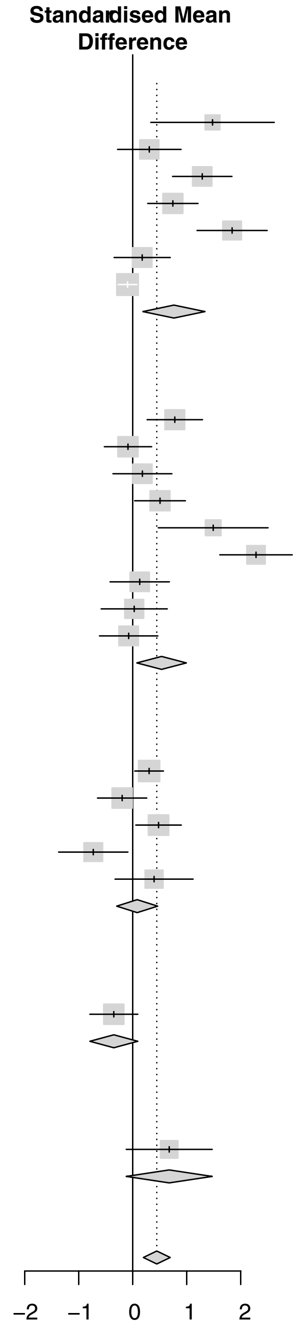

Fig. 5 Forest plot for quality of life (general) for different scales

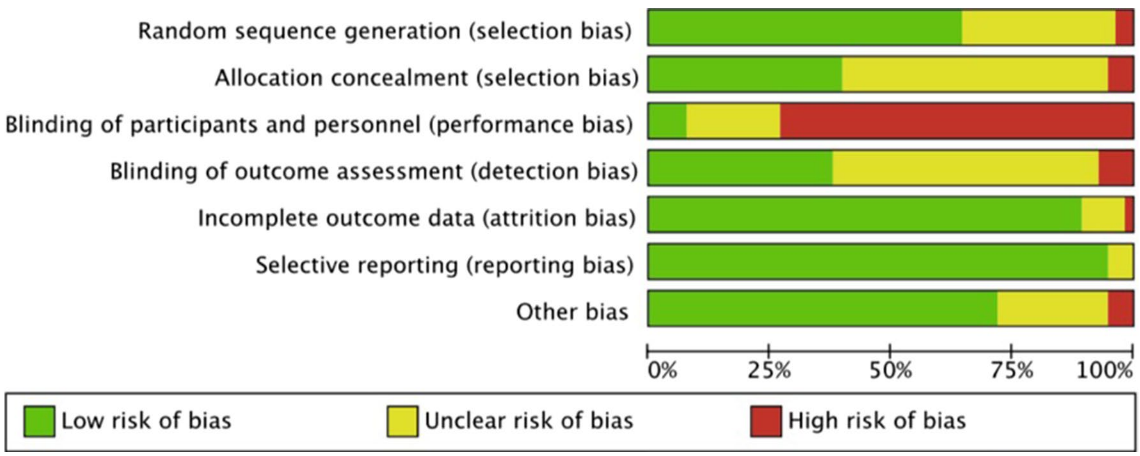

Fig. 6 Risk of bias graph

were relatively small and just one study, published as an abstract, evaluated outcomes such as overall mortality or disease-free survival [23]. The GRADE summary of findings table is shown in Fig. 8.

Discussion

The diagnosis of breast cancer affects patients' quality of life and has long-lasting consequences. Both the diagnosis itself and the treatments that those patients are submitted to have significant influence in mental and physical health for years to come. The incidence of breast cancer in its earlier stages is increasing due to improved screening. In the same way, treatments for the disease are becoming more effective, and so the number of survivors is expected to increase in the next years [24]. Many of these women might live for many years and have time to develop chronic conditions just as the general population [25]. Therefore, high-quality evidence for survivorship guidance will be necessary. Physical activity is key to improve health and quality of life in any population, and here it is not an exception.

Our goal was to collect the best evidence regarding the impact of physical activity on the body composition and quality of life of patients who had been treated for breast cancer with curative intent. We have searched for randomized clinical trials only, considering them to be the best source of evidence for the question. To avoid confusion regarding quality of life, we exclude trials that assessed patients during treatment with chemotherapy or radiation; the included patients may have been receiving adjuvant hormone therapy. Also, trials evaluating patients with metastatic disease were not included, since treatment goals and prognosis are significantly different in more advanced stages of the disease. We may say that we have collected the best evidence about this issue.

The results of this meta-analysis demonstrated a significant decrease in body weight and BMI and an improvement in quality-of-life outcomes, but a serious bias effect was demonstrated. Publication bias was found in almost all

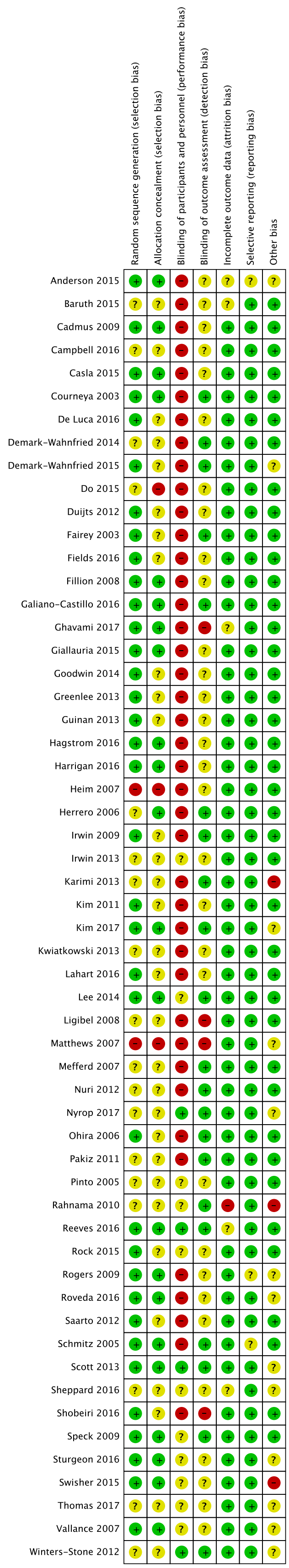

Fig. 7 Risk of bias summary

outcomes and is a concern regarding physical activity trials, since all of them lost statistical significance after correction.

We found only one study that described overall survival and progression-free survival: it was from an Australian population of 337 newly diagnosed breast cancer women showing lower mortality rates in the physical activity group [23].

Nonetheless, our meta-analysis has several limitations. First, most of the included studies were small and many of them had significant methodological flaws. In some studies reducing pain was the main outcome in aromatase inhibitors users, such as Nyrop 2017 [26] and Fields 2016 [21], so some selection bias was expected from this population. Second, the interventions were very different among the studies, making it very difficult to select any one of them as the best. The interventions varied in duration and quality, since they comprised from exercise counseling to structured and supervised exercise programs. Because of this we chose to compare exercise interventions as a single group. It was also not possible to determine if any of the interventions should have been considered ineffective at all. Third, quality of life was assessed using different scales, which may have influenced the results, since these scales correspond to different metrics assessing the same underlying outcome. Finally, long-term data are seldom available, and conclusions about the possible impact in outcomes such as overall survival or disease-free survival were not possible. High-quality randomized trials with larger numbers of patients are required, and patients should be followed for longer periods of time to assess if the benefits of the interventions are long lasting or temporary.

It is also worth commenting that the studies included were broadly heterogeneous, with variations in the type of intervention (counseling, face-to-face orientation, practicing, phone call orientation), therefore we cannot classify all these interventions under the same label, once they are not equivalent. This study shows that any intervention towards encouraging physical activity is valid and promotes good life habits that might affect the quality of life, the metabolic profile, and mortality.

With all the limitations considered, clinical trials of physical activity as an intervention for breast cancer survivors are highly justifiable, especially because exercise is a cheap intervention, is easy to apply, and practically has no contraindications or adverse effects. Even though a strong and solid evidence relating physical activity and reduced risk of recurrence and death from breast cancer is lacking, survivors are oriented to avoid a sedentary lifestyle and seek to exercise regularly. The potential benefits of this practice can help maintaining a healthy weight, improve fitness and tolerance to treatment, stimulate healthy lifestyles, and prevent other chronic diseases for which this population is particularly vulnerable.

Physical exercise compared to not realize physical exercise for breast cancer

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Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with not realize physical exercise	Risk difference with Physical exercise
Weight	2445 (24 RCTs)	⊕◯◯◯ VERY LOW a,b,c,d	-	The mean weight was **0** kg	MD **1.36 kg lower** (2.51 lower to 0.21 lower)
Body mass index	1891 (19 RCTs)	⊕⊕◯◯ LOW d	-	The mean body mass index was **0**	MD **0.89 lower** (1.5 lower to 0.28 lower)
Body fat percentage	1201 (16 RCTs)	⊕⊕◯◯ LOW b,e	-	The mean body fat percentage was **0** % points	MD **1.6 % points lower** (2.31 lower to 0.88 lower)
Quality of life - General	1861 (22 RCTs)	⊕◯◯◯ VERY LOW a,d,f	-	-	SMD **0.45 SD higher** (0.2 higher to 0.69 higher)
Quality of life - physical	1716 (20 RCTs)	⊕◯◯◯ VERY LOW a,d,f,g	-	-	SMD **0.51 SD higher** (0.23 higher to 0.79 higher)
Quality of life - mental	1326 (14 RCTs)	⊕◯◯◯ VERY LOW a,f,g	-	-	SMD **0.28 SD higher** (0.06 higher to 0.5 higher)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **HR:** Hazard Ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Impact on outcome varied greatly across studies.
b. Interventions varied widely across different studies. Interventions, in general, not tailored for the target patients. Excercise adherence unknown.
c. Confidence interval ranging from important effect (-1.5) to no clinical significant effect (-0.28)
d. Publication bias detected through Egger test. Trim and fill computation resulted in loss of statistical significance.
e. Confidence interval ranging from important effect (-2.31) to no clinical significant effect (-0.88)
f. Confidence intervals varied greatly across studies and across the different quality of life scales
g. Outcome assessed through different quality of life scales

Fig. 8 GRADE summary

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest to carry out this work.

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