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# Effects of exercise on physical outcomes of breast cancer survivors receiving hormone therapy – A systematic review and meta-analysis

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ABSTRACT

*Background:* Side-effects of hormone therapy can impair the physical health of breast cancer survivors. Exercise has been clearly shown to improve the quality of life of breast cancer survivors. Less is known about the effects of exercise on physical outcomes for breast cancer survivors receiving hormone therapy.
*Objective:* To investigate the effects of exercise on physical outcomes of breast cancer survivors receiving hormone therapy.
*Methods:* Five electronic databases were searched by two authors using the terms "Breast Neoplasms" [MeSH] and "Tamoxifen" [MeSH] and "Aromatase Inhibitors" [MeSH] and "Exercise" [MeSH]. Randomized and non-randomized clinical trials were included. Risk of bias was assessed by the Cochrane Collaboration tool and ROBINS-I, and the quality of evidence was evaluated using GRADE. Pooled effects were reported as standardized mean differences (SMDs) and 95 % confidence intervals (CIs) using a random effects model.
*Results:* Eleven studies were included in the meta-analysis. Two hundred and fourteen breast cancer survivors receiving hormone therapy, tamoxifen, or aromatase inhibitors participated in interventions based on aerobic plus resistance exercise or walking activity. The physical outcomes reported in the articles were: cardiorespiratory fitness, pain, bone mineral density, grip strength, and body fat percentage. Exercise effects were found only for cardiorespiratory fitness (SMD = 0.37; 95 % CI: 0.11; 0.63; $I^2$ = 93 %) and pain (SMD = −0.55; IC95 % −1.11; −0.00; $I^2$ = 80 %), with low quality of evidence. No effects were observed for the other variables.
*Conclusions:* Aerobic plus resistance exercise had positive effects on cardiorespiratory fitness and pain in breast cancer survivors receiving hormone therapy. However, high-quality randomized clinical trials are required to confirm this finding.

## 1. Introduction

Breast cancer is the most commonly diagnosed type of cancer in women worldwide. After diagnosis, women may undergo surgery, potentially followed by chemotherapy, radiotherapy, immunotherapy and/or hormone therapy. Treatment plans depend on the tumour and clinical characteristics of each patient [1].

Breast cancer survivors receiving hormone therapy can experience collateral effects. Tamoxifen users report an increased risk of endometrial cancer, vaginal dryness, hot flashes and non-alcoholic fatty liver disease [2]. Use of aromatase inhibitors is associated with decreased bone mineral density and an increased risk of bone fractures [3]. The acute drop in circulating estrogen caused by aromatase inhibitors may also lead to arthralgia (joint pain) [4–6]. Beyond the side-effects related specifically to hormone therapy, breast cancer survivors may experience decreased muscular strength [7–10], increased body mass and body fat percentage [11] and declines in cardiorespiratory fitness [12–17].

A number of systematic reviews and meta-analysis have found positive effects of exercise on the quality of life, psychological wellbeing and physical outcomes of breast cancer survivors [18–29]. However, these systematic reviews have not studied the effects of exercise exclusively amongst women undergoing hormone therapy; thus, the effects of exercise in this population are not well understood.

A systematic review on interventions for the treatment of arthralgia induced by aromatase inhibitors showed moderate to large effects on joint pain for pharmacological approaches, acupuncture, and relaxation techniques only [6]. Another systematic review investigated the effects

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of exercise on preventing or treating arthralgia induced by aromatase inhibitors- in breast cancer survivors, and demonstrated little or uncertain effect on pain, stiffness, grip strength, health-related quality of life and adherence to aromatase inhibitors [30]. These two systematic reviews [6,30] focussed solely on women receiving aromatase inhibitors. To our knowledge there has not been a systematic review of exercise effects on physical outcomes in breast cancer survivors receiving any modality of hormone therapy.

Most breast cancers are hormone receptor positive, resulting in women requiring adjuvant treatment with hormone therapy for at least ten years [31]. In light of this, it would be helpful to summarize the evidence on the role that exercise can play in minimizing the side-effects of hormone therapy, particularly the physical outcomes, which have received little research attention to date. Thus, the purpose of this systematic review and meta-analysis is to investigate the effects of exercise on physical outcomes in breast cancer women receiving any modality of hormone therapy.

## 2. Methods

### 2.1. Register and protocol

This systematic review and meta-analysis followed the recommendations of the *Preferred reporting Items for Systematic Reviews and Meta-analysis* – PRISMA [32] and was registered in PROSPERO (nº CRD42018099367).

### 2.2. Search strategy

We searched the following electronic databases from inception through to April 2019: *PubMed, Web of Science, Cinahl Database, Cochrane Library for Clinical Trials* and *Lilacs.* Keywords for this search included: (("Breast Neoplasms" [MeSH] OR "Breast Neoplasms" OR "Breast Neoplasm" OR "Breast Tumors" OR "Breast Tumor" OR "Breast Cancer" OR "Mammary Cancer" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Human Mammary Carcinomas" OR "Human Mammary Carcinoma" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Breast Carcinoma" OR "Breast Carcinomas") AND ("Tamoxifen" [MeSH] OR "Tamoxifen" OR "Aromatase Inhibitors" [MeSH] OR "Aromatase Inhibitors") AND ("Exercise" [MeSH] OR "Exercise" OR "Exercises" OR "Physical Activity" OR "Physical Activities" OR "Physical Exercise" OR "Physical Exercises" OR "Acute Exercise" OR "Acute Exercises" OR "Isometric Exercises" OR "Isometric Exercise" OR "Aerobic Exercise" OR "Aerobic Exercises" OR "Exercise Training" OR "Exercise Trainings")).

### 2.3. Trial selection

The first step of this review was to screen the titles and abstracts, by two independent authors from the Laboratory of Research in Leisure and Physical Activity LAPLAF/CNPq (LB and MSCV). Abstract information was downloaded from the electronic databases into Excel for this purpose. Articles deemed eligible after this screening were read in full by the same two authors independently, and eligibility was assessed for each paper. Conflicts were resolved through discussion with a third reviewer (JM).

### 2.4. Eligibility criteria

The inclusion criteria were: (i) randomized or non-randomized clinical trial, with or without a control group; (ii) published in English, Spanish or Portuguese; (iii) investigation of the effect of exercise on physical outcomes for breast cancer survivors receiving hormone therapy; (iv) sample aged above 18 years. The exclusion criteria were: (i) not reporting frequency, volume or intensity of the exercise intervention when applied; (ii) sample with other types of cancers, or including stage IV breast cancer; (iii) thesis, dissertations, abstracts, viability studies and protocol studies.

### 2.5. Outcomes

Physical outcomes were defined after reading the selected full text studies. During the title and abstract screening we included all studies that investigated exercise effects on any physical outcome amongst breast cancer survivors receiving hormone therapy. After full text review, we were able to extract data on five physical outcomes: (i) cardiorespiratory fitness, (ii) pain, (iii) bone mineral density, (iv) grip strength and (v) body fat percentage. In this systematic review, we use the following operational definitions to define the physical outcomes and tools acceptable for their measurement:

(i) Cardiorespiratory fitness: the ability of the circulatory and respiratory systems to supply oxygen to muscles during exercise of moderate to high intensity, measured as maximal oxygen consumption ($\dot{V}O_2$ max) by a cycle ergometer or treadmill exercise test [33].
(ii) Pain: "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*" [34]. A pain scale (zero to ten) is an accepted tool for the evaluation of pain [35].
(iii) Bone mineral density: "*a measure of the amount of minerals (mostly calcium and phosphorous) contained in a certain volume of bone"* [36]. The most widely validated technique to measure bone mineral density is dual energy X-ray absorptiometry (DXA) [37].
(iv) Grip strength: the strength that a muscle group applies against resistance at maximum effort [38]. Grip strength is a commonly used test to verify muscular strength and correlated health in breast cancer survivors [39].
(v) Body fat percentage: a measurement of adiposity and metabolic health [40], measured using DXA [41].

### 2.6. Data extraction

Data extraction was undertaken by the same two independent authors (LB and MCSV) who performed the study screening. The data extracted included: participants' characteristics (age, country, modality of hormone therapy), study sample size, control group strategies, physical outcomes, details of the exercise intervention (modality of exercise, duration and number of sessions, session per week and intensity).

### 2.7. Risk of bias assessment

To evaluate the risk of bias of the randomized clinical trials, we used the Cochrane Collaboration's tool [42], and for non-randomized clinical trials we applied the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) [43].

The following criteria of the Cochrane Collaboration's tool were evaluated: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and researchers, (4) Blinding of outcome assessment, (5) Incomplete outcome data, (6) Selective reporting, and (7) Other bias. The review authors categorized studies as having a low, unclear, or high risk of bias. The ROBINS-I includes (1) Bias due to confounding, (2) Bias in selection of participants into the study, (3) Bias in classification of interventions, (4) Bias due to departures from intended interventions, (5) Bias due to missing data, (6) Bias in measurement of outcomes, (7) Bias in selection of the reported result, and (8) Overall judgment.

### 2.8. Quality of evidence

To evaluate the quality of evidence and the strength of findings, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used [44]. This system gives a score for the quality of evidence of each outcome, which ranges between very low to high. Outcomes with evidence from RCTs start with a high level of evidence and are graded down for high risk of bias, consistency of findings, directness, publication bias and imprecision. Studies may be graded up if there is a large effect, a dose-response relationship, or when all plausible confounders or other biases increase confidence in the estimated effect [44].

### 2.9. Data synthesis and analysis

Eleven articles were eligible for the meta-analysis. The effect size of each study included in the meta-analysis was calculated by the mean of the pre and post intervention, change standard deviation (SD) and sample size of each group (intervention). Statistical heterogeneity was examined using the Q statistic, and quantified with the I-square test [45]. The random effects with 95 % confidence interval (CI) was used, considering that heterogeneity for all outcomes were higher than 20 %. All analysis was conducted using the Comprehensive Metanalysis Software (version 3, Biostat Inc, Englewood, NJ, EUA).

## 3. Results

### 3.1. Study selection

A total of 471 article titles and abstracts were screened, 155 from PubMed, 143 from Web of Science, 69 from CINAHL, 96 from Cochrane database and eight from Lilacs. We excluded 413 studies after screening titles and abstracts. After exclusion of duplicates, 29 articles were eligible for full text screening. The details of the selection process are presented in Fig. 1.

We excluded 18 articles, for the follow reasons: (i) thirteen studies included women in other clinical treatment or after completing hormone therapy [46–58], (ii) one reported an adherence study [59], (iii) one was a viability study presenting only qualitative results from the intervention [60], (iv) one investigated the effect of a whole vibration instrument, rather than an exercise intervention per se [61], (v) one did not assess a physical outcome selected for inclusion in this review [62] and (vi) one did not provide enough information for inclusion in the meta-analysis [63]. After this step, 11 articles were eligible and able to be included in the systematic review and meta-analysis.

### 3.2. Study characteristics

From the 11 studies included in this systematic review and meta-analysis, five were randomized clinical trials [64–67], three were non-randomized clinical trials [68–70], two were pilot studies of a non-randomized clinical trial [71,72] and one a pilot study of a randomized clinical trial [73]. Two trials had more than one paper published, which means that the results were from the same exercise intervention; two papers used one same sample [66,67] and three papers used another same sample [68–70]. Different physical outcomes were examined across the different papers from the same trial.

Five studies were conducted in the United States of America [64,66,67,71,73], three in Poland [68–70], and one each in Austria [65], Colombia [72] and Brazil [74].

### 3.3. Participants characteristics

The 11 eligible trials involved 368 women aged 57.5 ( ± 8.1) years (we counted just once for the papers that used the same sample). Of these, 241 women were allocated to an exercise intervention and 127 were allocated to a control group. The mean sample size was 46 (range 8–121) across the trials, with mean group sizes of 32 (range 8–61) for the interventions and 30 (18–60) for the control conditions. Seven studies investigated women taking aromatase inhibitors [64–67,71,73,74] and four studies had participants using tamoxifen [68–70,72]. Detailed information is provided in Table 1.

### 3.4. Control groups

Five studies included a control group [64,66,67,73,74]. Three studies asked women allocated to control groups to maintain their usual activity routine during the study [66,67,73], another allocated them to

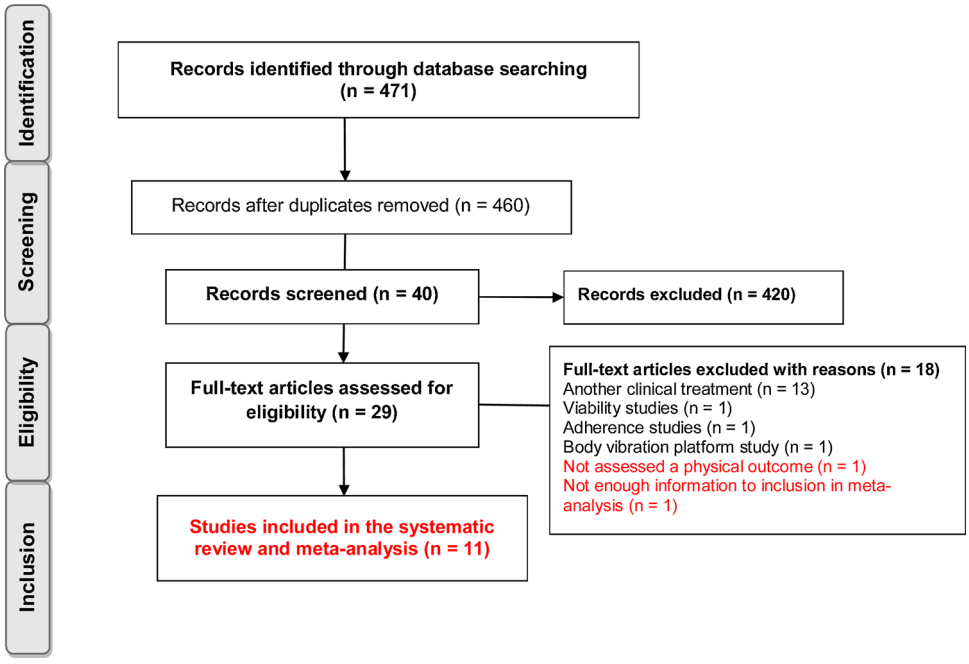


**Fig. 1.** Study selection strategy flowchart.

**Table 1**
Participant characteristics, exercise interventions and physical outcomes reported in the selected studies.

| | Study | HMT | Country | N | CG N – age (SD or IC) CG strategies | IG N – age (SD or range) | Exercise | Weeks | Intensity | Frequency/duration | Physical ouctomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | DeNysschen et al., 2014 [71] | AI | USA | 26 | – | 26 – 52–72 years | Aerobic and resistance exercise (TheraBand®) - (*home-based*) | 8 | 55 − 65% HRmax | 15 − 30 min/session; 2 to 3x/week | Pain, grip strength and biceps strength. |
| 2 | Hojan et al., 2013 (a) [69] | TMX | Poland | 41 | – | 41 – 44.3(4.9) years | Aerobic exercise - (*home-based*) | 24 | 65 − 75% HRmax | 40 − 45 min/session; 5x/week | BMD |
| 3 | Hojan et al., 2013 (b) [70] | TMX | Poland | 41 | – | 41 – 44.3(4.9) years | Six months of aerobic exercise (*home-based*) + Six months of concurrent exercise | 48 | Aerobic - 65 − 75% HRmax; Resistance (every six weeks increase the training load) | 40 − 45 min/session; 5x/week (aerobic); 3x/week; 40 − 45 min/session (resistance) | BMD, BMI and %BF |
| 4 | Hojan et al., 2013 (c) [68] | TMX | Poland | 41 | – | 41 – 44.3(4.9) years | Six months of aerobic exercise (*home-based*) + Six months of concurrent exercise | 48 | Aerobic - 65 − 75% HRmax; Resistance (every six weeks increase the training load) | 40 − 45 min/session; 5x/week (aerobic); 3x/week; 40 − 45 min/session (resistance) | BMD |
| 5 | Irwin et al., 2015 [66] | AI | USA | 121 | 60 – 60.5(7.0) Daily activities and educative brochures. Contact by phone monthly. | 61 – 62.0(7.0) years | Aerobic (walking *home-based*) + Resistance (bench press, latissimus pull down, seated row, leg press, leg extension and leg curl) (Supervised) | 48 | Aerobic (50 − 80% HRmax;); Resistance (six exercises) | 150 min/week; 5x/week (aerobic) and 2x/week 8 − 12 rep for 3 sets (resistance) | Vo2max, grip strength, and pain |
| 6 | Nyrop et al., 2017 [64] | AI | USA | 53 | 29 – 64.4(9.7) Waiting list | 24 – 63.3(6.9) years | Walking - Aerobic exercise (*home-based*) | 6 | – | 150 min/week; 3x/week | Pain |
| 7 | Ortega; Fernández, 2016 [72] | TMX | Colombia | 8 | – | 8 – 45.63(8.1) years | Aerobic (supervised treadmill) + resistance (sitting arm extension, bench press and fly) | 22 | 80 % da HRmax + 1RM | 20 − 50 min/session; 2 × 12 rep; 3x/week | Strength, VO2max, BMI and %BF |
| 8 | Paulo et al., 2018 [74] | AI | Brazil | 36 | 18 –63.2(7.1) Low intensity stretching classes, twice per week, 45 min. | 18 – 66.6(9.6) years | Concurrent exercise (Supervised) + educational lectures weekly.(Aerobic exercise: treadmill; Resistance exercise: seated cable row, bench press, leg extension, leg press, and leg curl, as well as bridge, abdominal, and standard plank exercises) | 36 | 50 − 80% HRmax; + 55 − 75% of 1RM | 100 min/session e 10 − 12 rep; 3x/week | BMD and %BF |
| 9 | Thomas et al., 2017 [67] | AI | USA | 121 | 60 – 60.5(7.0) Daily activities and educative brochures, contact by phone monthly. | 61 – 62.0(7.0) years | Resistance (bench press, latissimus pull down, seated row, leg press, leg extension and leg curl) (Supervised) + Aerobic (walking *home-based*) | 48 | Aerobic (50 − 80% HRmax); Resistance (six exercises) | 150 min/week; 5x/week (aerobic) and 2x/week 8 − 12 rep for 3 sets (resistance) | BMD, BMI and %BF |
| 10 | Westphal et al., 2018 [65] | AI | Austria | 42 | – | *Home-based* n = 23; 60.7 (49–74 years); Supervised n = 19; 61.0 (48–81 years) | Aerobic (*home-based* e supervised) + resistance (supervised) (Latissimus pull down, back extension, chest press, leg press, leg extension, leg flexion, dips, rowing, abdominal crunches, cable pull) | 48 | Supervised (aerobic - 70 % of HRmax + 10RM of each exercise. | *Home-based* (150 min/week aerobic + 2x/week resistance). Supervised (24 weeks – 45 min/session cycle ergometer e 30 min/session resistance 2x/week + 24 weeks *home-based*). | VO2max and BMI |
| 11 | Rogers et al., 2009 [73] | AI | USA | 41 | 20 – 54(8) Daily activities, educative brochures, and payment fee | 21 – 52(15) years | BEAT Cancer Program -Aerobic (twelve sessions of supervised walking + flexibility exercise) followed by walking in *home-based* + six group therapy sessions with a psychologist | 12 | – | Walking *home-based* 2x/week. | $VO_2$max, muscle strength, BMI and %BF |

Abbreviations: AI – Aromatase inhibitors; TMX – Tamoxifen. IG – Intervention group; CG – Control group. BMI – Body Mass Index. %BF – Body fat percentage. BMD – Bone mineral density. Min.- minutes. USA – United States of America. Rep – repetitions. RM – repetition maximum.

a wait list control [64], and one provided low-intensity stretching classes [74]. Other initiatives provided to participants of control conditions included a booklet with educational information regarding physical activity benefits [66,67,73], phone calls [66,67], and a payment fee [73]. Detailed information is provided in Table 1.

### 3.5. Exercise interventions

#### 3.5.1. Materials

Equipment used included machines and weights for resistance training, and for aerobic exercise a treadmill [72,74], cycle ergometers [65] or patients could choose between treadmill, outside or stationary cycling [66,67]. Thera-Band® exercise bands were also used [68–71].

#### 3.5.2. Providers

Most of the exercise interventions were delivered by health professionals, including American College of Sports Medicine certified cancer exercise trainers [66,67,73], exercise specialists [71,72,74] and physiotherapists [68–70].

#### 3.5.3. Delivery

Exercise was individually performed in most of the studies [66,67,71–74]. However, in some studies patients participated in the interventions either alone or in groups depending on the type of exercise [68–70]. In one study, participants could choose to walk alone or in groups [64].

Three studies included fully home-based intervention models [64,69,71], two studies included fully supervised interventions [72,74] and six studies included both home-based and supervised interventions [65–68,70,73].

In order to verify adherence during the trials, patients wore heart-rate monitors during each workout, and after each exercise session they recorded the type, duration, and average heart rate during exercise in physical activity logs [66,67], received a printed physical activity log to record daily minutes of walking for leisure, pleasure or recreation [64,73], or received a pedometer to monitor the number of daily steps and registered in the daily exercise log [71]. For fully supervised exercise sessions, adherence was evaluated by attendance in sessions [74].

Some studies provided information regarding strategies to motivate participants in the exercise intervention, such as using pedometers and receiving phone calls once a week to provide support and encouragement [71]; some women allocated to the intervention group also received lectures and group meetings with psychologists [73,74] or received a booklet [64]. Likewise, in order to motivate participants receiving home-based interventions, one study provided a video that illustrated each of the upper- and lower-body exercises, hand exercises as well as flexibility exercises and instruction for warming up and cooling down [71].

In five of the studies no adverse events occurred during the intervention [64,66,71–73]. The other six studies did not report the presence or absence of adverse effects [65,67–70,74].

#### 3.5.4. Location

The exercise interventions were delivered in a variety of settings, including a local health club [66,67], exercise physiology laboratory [72], university gym [65,74], hospital medical fitness center [65], rehabilitation ward [68–70] and home [64,71].

#### 3.5.5. Dosage

The duration of the intervention ranged from eight to 48 weeks, with an average of 28 ± 19 weeks. The frequency per week of aerobic exercise ranged from twice to five days, with an average of 4 ± 1 day per week, and resistance exercise ranged from twice to three sessions per week, with an average of 3 ± 0.5 sessions. The duration of the total sessions ranged from 15 to 100 min, with an average of 47 ± 25 min.

Most of the studies investigated aerobic exercise plus resistance training [65–68,70–72,74], one investigated only aerobic activity [69] and two investigated only walking activity at home [64,73].

The intensity of the aerobic exercise intervention was controlled by maximum heart rate, which ranged between 50%–80% of the HRmax and was progressively increased during the weeks of intervention [65–72,74].

The intensity of resistance exercise varied across the studies. Two studies reported that intensity was progressively increased by enlarging the amplitude of the movement, changing the velocity of the concentric execution, and introducing more strenuous exercises [68,70]. Another study reported intensity progression by increasing the number of sets per exercise after the first month, and the weight was increased by the smallest possible increment after two sessions lifting the same weight 12 times [66]. In other trials the progression was evaluated by a predicted one repetition maximum (1-RM) test, performed by bench press and leg press exercises [74], or by 10 repetition maximum (10-RM) test, and the intensity was calculated to initially permit not more than 30 repetitions to failure (T Westphal et al. 2018). Whenever more than 30 repetitions could be performed, weight was increased.

#### 3.5.6. Tailoring

Progression was individualized using maximum heart rate for aerobic exercise [65–67,74] and 1-RM [74] or 10-RM [65] for resistance exercise. One study based the exercise program on the American College of Sports Medicine (ACSM) Risk Stratification Guidelines for participating in low-intensity exercise programs. The patients received their workout schedules based on their initial fitness levels; three tests (hand grip, step test and sit-to-stand) were performed to determine the appropriate training level for the home-based exercise [71].

Detailed information is provided in Table 1.

### 3.6. Physical outcomes

#### 3.6.1. Cardiorespiratory fitness

Cardiorespiratory fitness was examined in four trials [65,66,72,73], and was measured using a treadmill test [66,73], a submaximal treadmill test [72] and cycle ergometer test [65].

#### 3.6.2. Pain

Pain was assessed in three studies [64,66,71], and was measured using the Arthritis Impact Measurement Scale (AIMS2) [71], the Brief Pain Inventory [66] and the Visual Analogue Scale [64].

#### 3.6.3. Muscle strength

Muscle strength of the upper arm was investigated in four trials [66,71–73]. Three studies evaluated grip strength using a dynamometer [66,71,73] and one trial used the 1RM test in the movements of sitting arm extension, bench press and fly with free weights for each arm [72].

#### 3.6.4. Body fat percentage

Body fat percentage was investigated in six studies [67–70,72–74]. Most of them used DXA to measure body fat percentage [67–70,73,74]. Only one trial estimated body fat percentage using the Harpenden skinfold caliper [72].

#### 3.6.5. Bone mineral density

Bone mineral density was included in five studies [67–70,74] and measured exclusively by DXA.

## 4. Meta-analysis

Eleven studies were included in the meta-analyses investigating cardiorespiratory fitness, pain, bone mineral density, grip strength and body fat percentage. Results are presented in Figs. 2–6, respectively. Not all studies included a control group; thus, our meta-analyses only provide results based on within-group changes (pre and post

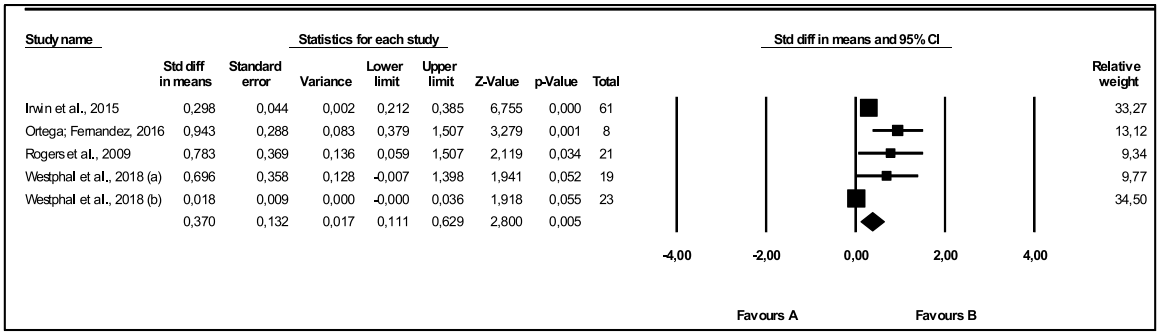


**Fig. 2.** Meta-analysis of cardiorespiratory fitness after exercise intervention in breast cancer survivors undergoing hormone therapy.

intervention).

The grip strength data from the study by DeNysschen et al. [71] was only available in graphs, and the program WebPlotDigitizer was used for extraction of the values. The study by Westphal et al. (2018) [65] presented the cardiorespiratory fitness in watts from the cycle ergometer exercise test. For inclusion in meta-analysis the values were transformed to maximum oxygen consumption, estimated by the Balke formula (200 + (12*Watts))/body mass). The same study included two groups of exercise intervention, and both were considered, being (i) with supervised intervention and (ii) home-based model.

### 4.1. Cardiorespiratory fitness

For cardiorespiratory fitness four studies were analysed [65,66,72,73]; however, for this meta-analysis five groups of exercise were included, given that the study by Westphal et al. [65] examined two exercise groups. Three of the five trials demonstrated significant effects separately in improving VO2max, and this trend was reflected in the meta-analysis (SMD = 0.37; p = 0.00).

### 4.2. Pain

Three studies were included in the meta-analysis of pain. Although only two of the three studies demonstrated effects separately [66,71], the meta-analysis suggested that exercise in decreasing pain in breast cancer survivors undergoing hormone therapy, in this case receiving aromatase inhibitors (SMD = -0.55; p = 0.05).

### 4.3. Bone mineral density

Only one trial showed significant effects separately [68–70]. Beyond that, the meta-analysis did not suggest a meaningful effect on bone mineral density after the exercise intervention.

### 4.4. Grip strength

Two of three studies [71,73] that investigated grip strength showed exercise effects separately; the meta-analysis suggests only a marginal improvement on grip strength.

### 4.5. Body fat percentage

Six studies were included [67,68,70,72–74], but only four trials were evaluated in the meta-analysis, because Ortega and Fernandez [72] provided the body fat as sum of the skinfold, and Hojan et al. [68,70] were the same trial. This meta-analysis suggested an overall reduction on body fat post intervention, although this was not statistically significant.

### 4.6. Heterogeneity

For all the outcomes analysed in our meta-analysis the statistical heterogeneity ranged between 80 % and 95 %, as shown in Table 2. Clinical heterogeneity is also noted in this meta-analysis, due to the lack of similarity in the exercise interventions. Also, as a limitation of our meta-analysis, the inclusion of non-randomized clinical trials could increase the heterogeneity between studies, representing the methodological heterogeneity.

### 4.7. Risk of bias assessment

Tables 3 and 4 evaluate the risk of bias of randomized and non-randomized studies included in the meta-analysis. For randomized clinical studies the categories "blindness of participants and researches" and "blinding assessment of the outcomes" are more likely to present a risk of bias, as they were mostly classified as unclear, for not presenting enough information for evaluation. On the other hand, the category that presented low risk of bias was “random sequence generation”. For non-randomized studies, presented in Table 4, high risk of bias was observed in “bias due to departures from intended interventions”, in which all studies were classified as serious risk of bias, and the category that presented low risk was “bias in selection of participants into the study”.

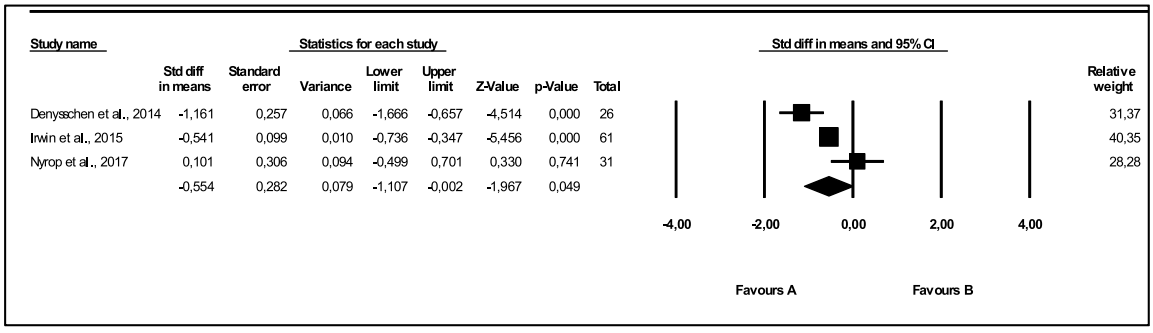


**Fig. 3.** Meta-analysis of pain after exercise intervention in breast cancer survivors undergoing hormone therapy.

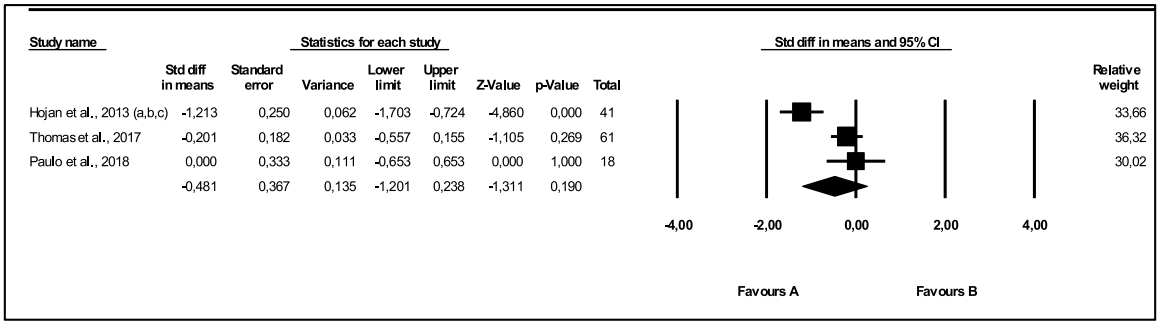


**Fig. 4.** Meta-analysis of bone mineral density after exercise intervention in breast cancer survivors undergoing hormone therapy.

### *4.8. Quality of evidence*

A summary of the quality of evidence according to the GRADE system for each outcome is presented in Table 5. The quality of the evidence was graded as either low (cardiorespiratory fitness, pain, grip strength) or very low (bone mineral density, body fat percentage). Although RCTs were used to address each outcome, these contained unclear or high risk of bias for select criteria, and in the pre and post studies risk of bias ranged from moderate to serious. Results between studies were inconsistent, as indicated by the high statistical heterogeneity identified in the meta-analysis. For bone mineral density and body fat percentage, a further downgrade in score was applied due to imprecision indicated by wide confidence intervals. No outcome met the criteria to be graded up.

## 5. Discussion

### *5.1. Summary of evidence*

The main objective of this study was to investigate the effects of exercise on physical outcomes of breast cancer survivors receiving hormone therapy. Exercise effects were found for cardiorespiratory fitness and pain. For the other physical outcomes, bone mineral density, body fat percentage and grip strength, there was no strong or statistically significant exercise effect.

VO2max has been used as a standard measure to identify risk of mortality in breast cancer survivors, and poorer VO2max have been associated with higher risk of death after breast cancer [75]. Other meta-analysis identified that the $VO_2$max (22.2 mL/kg min) of breast cancer survivors after treatment were 25 % lower when compared with healthy women of the same age [15]. The results from our meta-analysis suggests an increase in $VO_2$max after exercise, specifically, 12–48 weeks of aerobic plus resistance exercise (50–80% HRmax) or with walking activity for 150 min per week in women receiving either aromatase inhibitors or tamoxifen [65,66,72,73]. The findings from our study agree with other meta-analyses that showed exercise benefits in cardiorespiratory fitness of breast cancer survivors during chemotherapy, radiotherapy or after treatment [18,76,77]. Our results should be assessed with caution as the heterogeneity from the studies was high ($I^2$ = 93 %), which can be explained by the variety in intensity, duration, and type of exercise interventions, and in the measure of VO2max.

Our meta-analysis showed that pain can be decreased by exercise in breast cancer survivors receiving aromatase inhibitors. Exercise effects showed a decrease of 1.52 points on a zero to 10-point scale of pain. The exercise intervention ranged from six to 48 weeks, delivering aerobic plus resistance exercise or home-based walking activity to 118 breast cancer survivors undergoing aromatase inhibitors [64,66,71]. It is known that women using aromatase inhibitors report arthralgia [4–6]. These symptoms can lead women to discontinuing use of aromatase inhibitors and therefore increasing the chance of cancer recurring and a poorer prognosis [5,6].

Systematic reviews that investigated arthralgia in breast cancer survivors revealed that alternative and complementary therapies are important, such as acupuncture, relaxation techniques and nutritional supplements [18,78]. Considering the findings from our meta-analysis, exercise should also be recommended for breast cancer survivors receiving aromatase inhibitors. Benefits were identified after different exercise interventions, ranging from home-based walking activity for six weeks [64], resistance exercise using TheraBand® plus home-based aerobic activity for eight weeks [71] and supervised resistance exercise and home-based aerobic activity for 48 weeks [66].

Other side-effects of receiving hormone therapy are effects on bone health. The use of tamoxifen can lead to an accelerated bone loss in premenopausal women, but it is bone protective for postmenopausal women. In contrast, aromatase inhibitors can accelerate the decline in bone health and increase the chance of fractures for pre- and postmenopausal breast cancer survivors [79]. Thus, therapeutic options to minimize these side-effects in bone health are essential. Our meta-analysis showed evidence of a small protective effect of exercise on bone mineral density, but this was not statistically significant. Similarly, for grip strength the results of our meta-analysis revealed only a small beneficial effect of exercise, which was not statistically significant. Only three trials were included in this analysis, all of which

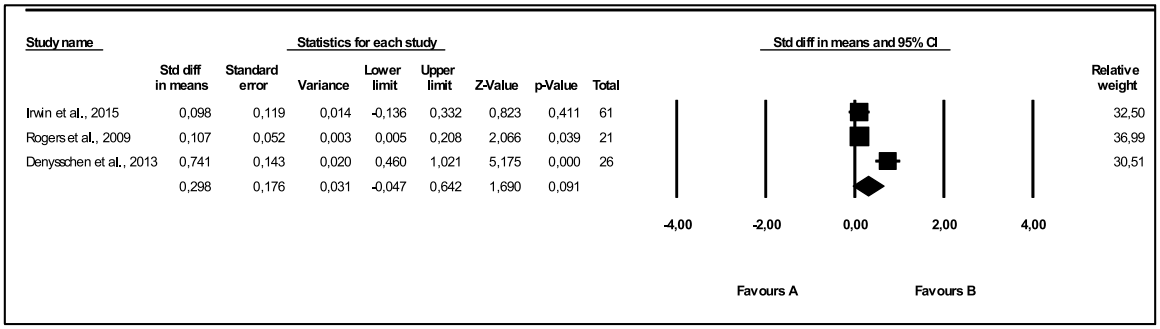


**Fig. 5.** Meta-analysis of grip strength after exercise intervention in breast cancer survivors undergoing hormone therapy.

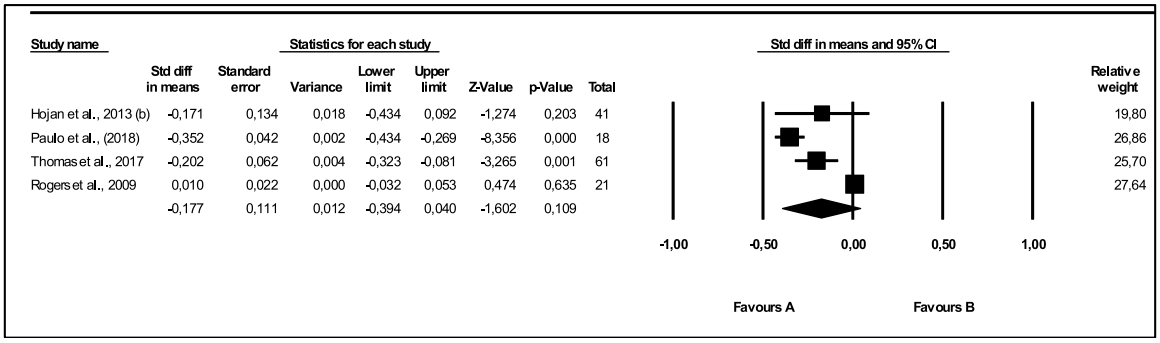


**Fig. 6.** Meta-analysis of body fat percentage after exercise intervention in breast cancer survivors undergoing hormone therapy (Florianopolis, 2019).

**Table 2**
Statistical heterogeneity ($I^2$) of the standardized mean differences for physical outcomes after exercise intervention.

| Outcomes | No. of Interventions | SMD | 95 % CI | Q-value | df(Q) | p value | $I^2$ (%) |
|---|---|---|---|---|---|---|---|
| Cardiorespiratory fitness | 5 | 0.37 | 0.11;0.62 | 56.25 | 4 | < 0.00 | 93 % |
| Pain | 3 | −0.55 | −1.10; −0.00 | 10.15 | 2 | 0.01 | 80 % |
| Bone mineral density | 3 | −0.48 | −1.20;0.23 | 13.04 | 2 | 0.00 | 85% |
| Grip strength | 3 | 0.29 | −0.04;0.64 | 13.84 | 2 | < 0.00 | 89% |
| Body fat percentage | 4 | −0.17 | −0.39;0.04 | 63.14 | 3 | < 0.00 | 95 % |

Abbreviations: $I^2$, Heterogeneity; SMD, Standardized mean difference; df, degree of freedom.

**Table 3**
Summary table of the risk of bias using Cochrane Collaboration tool for randomized clinical trials.

| | Random sequence generation | Allocation concealment | Blinding of participants and researchers | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Irwin, 2015 [66] | low | low | unclear | unclear | unclear | unclear | low |
| Nyrop, 2017 [64] | low | unclear | unclear | unclear | low | low | low |
| Paulo, 2018 [74] | low | low | unclear | unclear | low | low | low |
| Thomas, 2017 [67] | low | low | unclear | unclear | low | unclear | low |
| Westphal, 2018 [65] | low | low | high | high | unclear | unclear | low |
| Rogers, 2009 [73] | low | low | unclear | unclear | low | low | low |

included women receiving aromatase inhibitors.

Exercise demonstrated a small effect on body fat percentage in our meta-analysis. These results were not as striking as those from the meta-analysis of Kim, Kang, and Park [18], who investigated the effects of aerobic exercise on breast cancer survivors during and after adjuvant treatment, and found large and significant effects of exercise in reducing the body fat percentage. Our review did not include studies that offered nutritional monitoring, and this may be a reason for our result, as this intervention component is essential for a large decrease in body fat percentage. In addition, the characteristics of the exercise intervention can affect the extent of the change in body fat percentage. Although only aerobic exercise was included in our meta-analysis, the intensity ranged from 50 to 80 % of heart rate, and this interval may not have been sufficient to significantly reduce body fat percentage. In addition, two of the three studies delivered a home-based intervention [67,68], which make it difficult to control the intensity and accuracy of the exercise.

It is essential that breast cancer survivors try to reduce their body mass, particularly postmenopausal women who demonstrate increasing body fat percentage six months after surgery. This scenario has been associated with metastasis [80]. Additionally, receiving aromatase inhibitors could be associated with an increase in body mass [11]. Therefore, intervening in order to help maintain a healthy body composition is important for postmenopausal breast cancer survivors, especially those receiving hormone therapy.

### 5.2. Limitations

The results found in this meta-analysis are promising; however, some limitations are presented, such as the inclusion of non-randomized clinical trials without a control group, which meant we only analysed within-group change (pre- and post-intervention). Our decision to maintain these studies in the systematic review and meta-analysis was guided by the need to answer the questions posed by the study. The lack of studies focussing solely on women receiving hormone therapy limited our ability to draw firm conclusions from our findings. The small number of studies meant that we could not conduct meta-regression to verify the dose-response of intensity and volume exercise. Some measurements were not standardized between the studies, which complicated the analysis and increased the heterogeneity between the studies.

### 5.3. Conclusion

The findings of this meta-analysis suggest that exercise has clear positive effects on cardiorespiratory fitness and pain, as well possible positive effects on bone mineral density, grip strength and body fat percentage, in breast cancer survivors undergoing adjuvant treatment with hormone therapy. The small number of studies included in each outcome and their difference in type, volume, intensity of exercise and outcomes measurements resulted high heterogeneity, which downgraded the quality of evidence to very low. However, the clinical and practical implications of the findings support the importance of exercise

**Table 4**
Summary table of the risk of bias using ROBINS-I for non-randomized studies of interventions.

| | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall judgment |
|---|---|---|---|---|---|---|---|---|
| DeNysschen, 2014 [71] | NI | low | low | Serious* | NI | low | low | mod |
| Hojan, 2013a [69] | NI | low | mod | Serious* | NI | low | low | serious |
| Hojan, 2013b [70] | NI | low | mod | Serious* | NI | low | mod | serious |
| Hojan, 2013c [68] | NI | low | mod | Serious* | NI | low | mod | serious |
| Ortega, 2016 [72] | NI | low | low | Serious* | low | low | low | mod |

Abbreviations: NI, no information available; Mod, moderate.

**Table 5**
Quality of evidence: Physical outcomes after exercise intervention in breast cancer women receiving hormone therapy.

| Outcome: Study type (No. of participants) | Meta-analysis effect estimates SMD [p value] | Quality of evidence |
|---|---|---|
| Cardiorespiratory fitness<br>3 RCT (124 patients)<br>1 pilot study (8 patients) | 0.37 [0.00] | Low |
| Pain<br>2 RCT (92 patients)<br>1 pilot study (26 patients) | −0.55 [0.05] | Low |
| BMD<br>2 RCT (79 patients)<br>1 NRCT (41 patients) | −0.48 [0.19] | Very low |
| Grip strength<br>2 RCT (82 patients)<br>1 pilot study (26 patients) | 1.08 [0.05] | Low |
| Body fat percentage<br>3 RCT (100 patients)<br>1 NRCT (41 patients) | −1.18 [0.09] | Very low |

Abbreviations: RCT, randomized clinical trial; NCRT, non-randomized clinical trial; BMC, bone mineral density.

during adjuvant treatment of hormone therapy. There appears to be benefit from both aerobic and resistance exercise; even 150 min per week of walking activity, as recommended by the World Health Organization, has been shown to have positive effects.

## Contributors

Leonessa Boing contributed to the search of the databases, the meta-analysis, and the drafting of the manuscript.

Melissa de Carvalho Souza Vieira contributed to the search of the databases, the meta-analysis, and the drafting of the manuscript.

Jéssica Moratelli contributed to the meta-analysis and the drafting of the manuscript.

Anke Bergmann contributed to drafting of the manuscript.

Adriana Coutinho de Azevedo Guimarães contributed to the drafting of the manuscript.

All authors read and approved the final manuscript.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## Provenance and peer review

This article has undergone peer review.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2020.06.022.

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