Effect of physical activity on depression, anxiety, and stress in women surviving breast cancer: A systematic review and meta-analysis of randomized clinical trials

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Abstract

Breast cancer treatment can lead to psychological distress, including depression, anxiety, and stress. We systematically investigated the effect of physical exercise on these factors in women surviving breast cancer (WSBC). Eight databases were searched to identify eligible randomized controlled trials (RCTs). Data extraction and bias risk analysis were conducted using standardized tools, with meta-analysis performed using RevMan® software. Out of 3,529 documents initially identified, 15 RCTs were included, comprising 2,756 WSBC (1,284 in intervention groups and 1,472 in control groups), with 2,082 participants in depression analyses, 513 in anxiety analyses, and 161 in stress analyses. Meta-analyses showed that physical exercise promoted significant reduction in depression and anxiety. Subgroup analyses showed greater reduction in anxiety when aerobic and resistance exercise were combined. Only two studies investigated stress, with less robust data suggesting improvement when combining aerobic and resistance interventions. Future RCTs with standardized intervention protocols are needed to confirm these findings.

Keywords: Physical Exercise; Breast cancer; Depression; Anxiety; Stress

Introduction

Breast cancer is the most common cancer among women globally. It poses a significant public health challenge, with an increasing number of survivors (INCA, 2020; WHO, 2020). Survival can range from the active treatment phase to complete recovery and the absence of cancer signs (Miller et al., 2022). However, even after treatment completion, many women surviving breast cancer (WSBC) experience emotional vulnerabilities that significantly impact their quality of life, including physical and emotional issues such as fatigue, functional limitations, depression, anxiety, and stress (Cortiana et al., 2024; Biparva et al., 2022; Heidary et al., 2023; Gershfeld-Litvin et al., 2024).).

Among those emotional vulnerabilities, depression is a mental disorder characterized by persistent sadness and loss of interest in activities, along with changes in sleep and appetite. Anxiety, on the other hand, involves intense emotional responses to perceived threats, leading to increased heart rate and tremors. Stress, a bodily response to external demands, can be acute or chronic and is often associated with heightened anxiety and depression (American Psychiatric Association, 2023; National Institute of Mental Health, 2023). These emotional issues significantly affect the mental health of WSBC (Avital et al., 2024; Kuswanto et al., 2024; Biparva et al., 2022; Heidary et al., 2023; When et al., 2016).

Among available treatments, physical exercise stands out as a promising alternative. Defined as any planned, structured, and repetitive movement aimed at improving physical condition (WHO, 2024), physical exercise can include aerobic exercises such as walking, running, dancing, swimming, cycling, and group fitness classes, as well as resistance exercises, or a combination of both (ACSM, 2018; ACSM, 2021). Studies show that physical exercise can improve overall quality of life, social aspects, cardiorespiratory capacity (Farajivafa et al., 2023), and increase muscular strength as well as functional independence (Batalik et al., 2021). Furthermore, available evidence suggests that exercise can reduce depression and anxiety, promoting better mental health (Aydin et al., 2021; Maldonado et al., 2022; Moraes et al., 2021). Despite evidence suggesting benefits of physical exercise for the mental health of WSBC, particularly in reducing stress, depression, and anxiety, there remains a lack of comprehensive studies that have investigated in an integrated manner the effects of different types of exercise (aerobic, resistance, and/or combined) on these emotional challenges (Patsou et al., 2017; Salam et al., 2022; Sun et al., 2023).

The present systematic review and meta-analysis investigated the effects of physical exercise on depression, anxiety, and stress, based on findings of RCTs. Specifically, we focused on aerobic, resistance, and combined exercise types because existing literature suggests that each modality may offer unique benefits for managing emotional vulnerabilities (ACSM, 2021). Aerobic exercise has been associated with improved cardiovascular health and mood enhancement (Demark-Wahnefried et al., 2015), while resistance training has been associated with increased strength and functional independence (Moraes et al., 2021). Combining both types may maximize mental health benefits (Aydin et al., 2021), thus providing a more comprehensive understanding of how various exercise approaches impact the mental health of WSBC.

Methods

This systematic review with meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) and is registered on the PROSPERO platform (registration number omitted for review purposes).

The structured research question 'In women surviving breast cancer, does physical exercise, compared to physical inactivity, affect depression, anxiety, and stress?' was guided by the PICO acronym, with P for population (WSBC), I for intervention (physical exercise programs), C for comparison (no regular or guided physical exercise), and O for outcomes (depression, anxiety, and stress). Search terms and their synonyms were defined based on descriptors indexed in Medical Subject Headings (MeSH), Embase Subject Headings (EMTREE), and Descritores em Ciências da Saúde (DeCS). The search terms included "Breast Cancer", "Breast Tumors", "Breast Neoplasm", "Breast Mammary", "Cancer; Breast Neoplasm", "Unilateral Exercise, Physical", "Exercise, Muscle", "Training, Resistance", "Lifting, Weight", "Conditioning, Human Physical", "Resistance Training", "Depression", "Anxiety" and "Stress, Psychological" and their synonyms. Search strategies were developed using the Boolean operators AND and OR (Supplementary Table 1).

The databases searched included LILACS, Medline via PubMed, PsycInfo, Embase, Web of Science, Cochrane CENTRAL, Scopus, and Google Scholar. The reference lists of eligible studies were also consulted. Searches were conducted in November 2022 and updated in August 2024. Search terms were applied in English, except in LILACS, where Portuguese, French, and Spanish were also used. Study inclusion was independent of the language of publication.

Inclusion and Exclusion Criteria

For this systematic review and meta-analysis, we included studies involving adult women (≥18 years) who have survived breast cancer and had completed primary oncological treatment (chemotherapy, radiotherapy, surgery) at least 1 month prior. Interventions considered were physical exercise programs, such as aerobic training (walking, running, dancing, group fitness classes, aquatic activities, and cycling), resistance training, and combined resistance and aerobic training, that reported outcomes related to quality of life, physical recovery, and mental health. Only randomized controlled trials with quantitative data were accepted. We excluded studies involving women under 18 years of age, those still undergoing oncological treatment or with metastases. Additionally, interventions not relevant to the post-treatment breast cancer context, irrelevant outcomes, and relaxation activities such as Tai Chi and yoga were excluded. Also excluded were qualitative studies, narrative reviews, editorials, opinions, and single case studies.

Eligibility Criteria

Included were RCTs conducted with women aged 18 years or older who were breast cancer survivors and had completed treatment with surgery (total or partial mastectomy), chemotherapy, and/or radiotherapy. The intervention analyzed was defined as any structured physical exercise program that promoted energy expenditure beyond resting,

including aerobic, resistance, or combined aerobic and resistance exercises (Carvalho et al., 2021).

Study selection process

The database search results were exported to Endnote® web version software to remove duplicates, and subsequently exported to Rayyan® software (Qatar Computing Research Institute). The article selection process by titles and abstracts (phase I - identification), and subsequent reading in full (phase II - screening) was carried out independently by two reviewers (DSMN and CRNL). Differences of opinion were resolved with the intervention of a third reviewer (LPMO) when necessary. For studies whose full access was not possible, or where there was a need to obtain additional information not available within the publication, the authors were contacted by email. The data collection protocol is presented in a PRISMA flowchart (Figure 1).

Risk of Bias Assessment

The Risk of Bias 2 (RoB 2) tool from Cochrane was used to systematically assess bias risk in the RCTs included in this review (Brasil, 2021). RoB 2 evaluates five key domains: (1) bias in the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in outcome measurement; and (5) bias in the selection of reported results (Sterne et al., 2019).

The assessment was conducted by two independent reviewers (DSMN and CRNL), with a third reviewer consulted (LPMO) when necessary to resolve any disagreements. The risk of bias for each study was evaluated based on the outcomes of interest and categorized as follows: “low risk” if all domains were rated as “low risk”; “some concerns” if at least one domain was rated as “some concerns” but none were rated as “high risk”; and “high risk” if at least one domain was rated as “high risk” or if multiple domains were rated as “some concerns” (Sterne et al., 2019).

None of the studies included in this review were classified as having a high risk of bias. All studies included were rated either as having a low risk of bias or raising some concerns in certain domains. Specifically, studies were classified as having “some concerns” if one or more domains were rated as such, but no study included in our analysis reached the threshold for “high risk” in any domain. A comprehensive overview of the risk of bias assessment for all included studies is presented in Supplementary Table 2.

Data Extraction and Analysis

Data were recorded in a Microsoft® Excel spreadsheet. Extracted data included: author, year of publication, country, study objective, study design, sample size, age range, time since diagnosis, type of exercise performed, exercise frequency, duration of the intervention, instruments used to assess outcomes, primary results, and key conclusions.

Qualitative synthesis was conducted with information from eligible RCTs. For studies suitable for meta-analysis, data were aggregated. Analyses were performed under two intervention conditions: (a) studies evaluating the effect of aerobic exercise only, and (b) studies evaluating the effect of combined aerobic and resistance exercise.

Meta-analysis used the changes in measures from baseline to the end of the intervention, along with their standard deviations. This method was chosen because the studies reported changes in indicators, rather than initial and final values. For studies reporting outcomes as median, minimum, and maximum values, or mean with confidence intervals or standard errors, the mean and standard deviation were derived from these details (McGrath et al., 2020; Higgins, Li, & Deeks, 2021). For studies with missing data, the mean and standard deviation were estimated from median values and ranges, or from means with confidence intervals or standard errors, when available (McGrath et al., 2020; Higgins, Li, & Deeks, 2021).

Effect sizes of exercise on depression, anxiety, and stress, were calculated using the Standardized Mean Difference (SMD) due to the variation in outcome scales. Results were combined using the generic inverse variance method with a random-effects model (Deeks, Higgins, & Altman, 2021).

Sensitivity analysis identified potential issues related to study bias risk classification, publication bias using funnel plots, and data imputation needs, which could affect the results and interpretation of the meta-analysis. Subgroup analyses were performed based on exercise modality and type of instrument used. However, meta-regression was not feasible due to the number of studies included in the meta-analyses being fewer than 10 RCTs per outcome.

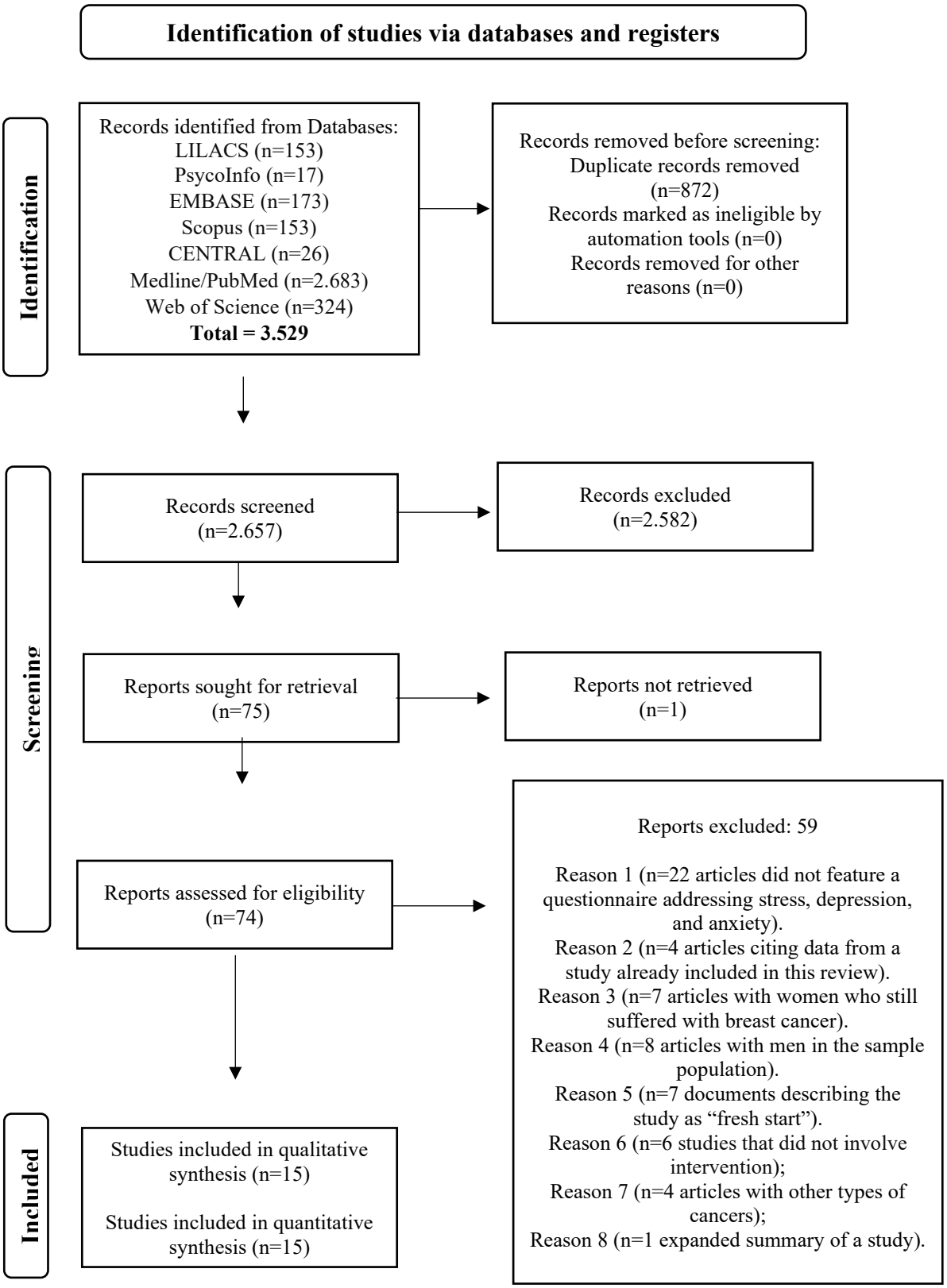
The magnitude of heterogeneity was quantified using the I^2 statistic, ranging from 0 to 100% (Deeks, Higgins, & Altman, 2019; Higgins, Li, & Deeks, 2021). An I^2 value close to zero suggests that all dispersion can be attributed to random error, indicating no heterogeneity. An I^2 value near 25% indicates low heterogeneity; >50% indicates moderate heterogeneity; and >75% indicates high heterogeneity (Deeks, Higgins, & Altman, 2019; Higgins, Li, & Deeks, 2021). For all analyses, a two-tailed p-value <0.05 was considered statistically significant, and analyses were performed using Review Manager software, version 5.0 (The Cochrane Collaboration).

Additionally, evidence certainty was assessed using the GRADE approach (The Grading of Recommendations Assessment, Development, and Evaluation) according to the outcomes of interest.

Results

This review identified 3,529 documents. After the initial screening, 872 duplicate studies were excluded. After title and abstract selection, 2,657 papers were excluded, leaving 75 studies for full-text review. Of these, only one document could not be accessed due to an incorrect DOI, and no response was received from the authors. Thus, 74 studies were examined in full, and 59 were excluded for not meeting the eligibility criteria (Figure 1).

Figure 1: Flow diagram for the study selection process for this systematic review:



Selected Studies and Outcome Synthesis

Fifteen RCTs (Aydin et al., 2021; Cadmus et al., 2009; Daley et al., 2007; Demark-Wahnefried et al., 2015; Dieli-Conwright et al., 2018; Fields et al., 2016; Fillion et al., 2008; Kaltsatou, Mameletzi & Douka, 2011; Kim et al., 2011; Kwiatkowski et al., 2013; Lee et al., 2014; Saarto et al., 2012; Maldonado et al., 2022; Moraes et al., 2021; Milne et al., 2007) were included in this systematic review, providing data on the three outcomes of interest.

Among the outcomes of interest, depression was assessed in 12 studies (Aydin et al., 2021; Cadmus et al., 2009; Daley et al., 2007; Demark-Wahnefried et al., 2015; Fields et al., 2016; Kim et al., 2011; Lee et al., 2014; Saarto et al., 2012; Dieli-Conwright et al., 2018; Kaltsatou, Mameletzi & Douka, 2011; Kwiatkowski et al., 2013; Maldonado et al., 2022), six studies assessed anxiety (Cadmus et al., 2009; Kim et al., 2011; Lee et al., 2014; Kwiatkowski et al., 2013; Moraes et al., 2021; Milne et al., 2007), and two studies assessed stress (Cadmus et al., 2009; Fillion et al., 2008) (Table 1).

The present systematic review includes a total of 2,756 WSBC (1,284 in intervention groups and 1,472 controls), with 2,082 WSBC participating in analyses evaluating the effect of physical exercise on depression, 513 on anxiety, and 161 on stress. Of the 15 included studies, five (33.33%) were conducted in Europe (Kaltsatou, Mameletzi & Douka, 2011; Kwiatkowski et al., 2013; Daley et al., 2007; Fields et al., 2016; Saarto et al., 2012), four (26.66%) in North America (Dieli-Conwright et al., 2018; Cadmus et al., 2009; Demark-Wahnefried et al., 2015; Fillion et al., 2008), three (20%) in Asia (Kim et al., 2011; Lee et al., 2014; Aydin et al., 2021), two (13.33%) in South America (Maldonado et al., 2022; Moraes et al., 2021), and one (6.66%) in Oceania (Milne et al., 2007) (Table 1).

For the assessment of depression, the instruments employed included the Center for Epidemiological Studies Depression Scale (CES-D) (Dieli-Conwright et al., 2018; Cadmus et al., 2009; Demark-Wahnefried et al., 2015; Fields et al., 2016; Maldonado et al., 2022), the Hospital Anxiety and Depression Scale – Depression (HADS-D) (Kim et al., 2011; Kwiatkowski et al., 2013; Lee et al., 2014), and the Beck Depression Inventory (BDI) (Aydin et al., 2021; Daley et al., 2007; Kaltsatou, Mameletzi & Douka, 2011; Saarto et al., 2012) (Table 1). For the assessment of depression, three studies employed the Hospital Anxiety and Depression Scale – Anxiety (HADS-A) (Kwiatkowski et al., 2013; Kim et al., 2011; Lee et al., 2014), two employed the State-Trait Anxiety Index (STAI) (Cadmus et al., 2009; Moraes et al., 2021), and one employed the Social Physique Anxiety Scale (SPA) (Milne et al., 2007). For the assessment of stress, the Inventory of Recent Life Experiences for Cancer Patients (IRLE-C) (Fillion et al., 2008) and the Perceived Stress Scale (PSS) (Cadmus et al., 2009) were employed (Table 1).

Table 1: Summary of the characteristics of studies included in this systematic review for the outcomes depression, anxiety, and stress in women surviving breast cancer.

Author, Year	Country	Intervention/control (n)	Intervention / Frequency / Time	Intervention duration	Instrument for the outcome	Key results
DEPRESSION						
AEROBIC EXERCISE						
Cadmus et al., 2009	USA	74 / 37	Walking in a gym and supervised by exercise physiologists / 5x in the week / 30 minutes.	26 weeks	CES-D	The groups showed no improvement, with an increase of 0.3 vs. 1.7 points on the score ($p < 0,05$).
Daley et al., 2007	England	108 / 38	Moderate intensity walking at a university center, with an exercise specialist. Cognitive-behavioral techniques were also explored / 3x in the week / 50 minutes.	8 weeks	BDI	The intervention group showed improvement, with a greater reduction in the score (difference of -6.01 points, $p=0,001$) compared to the control group.
Demark-Wahnefried et al., 2015	USA	697 / 348	Walking, group and personalized guidance; and update provided by phone and/or E-mail between each group session / weekly sessions / 60 minutes.	108 weeks	CES-D	The intervention group did not show improvement, there was an increase in the score (1,9 vs. 0,2 points; $p=0,30$).
Fields et al. 2016	United Kingdom	40 /20	Group training supervised by an instructor with Nordic walking outdoors / 1x per week / 60 minutes.	12 weeks	CES-D	The intervention group showed improvement, there was a reduction in the score (3 vs. 1 control point; p-value not reported).
Kim et al., 2011	South Korea	45 / 22	Telephone counselling combined with an e-book containing moderate intensity exercise guidelines / 5x a week / 30 minutes daily.	12 weeks	HADS	The intervention group showed improvement, with a reduction of 2.48 vs. 0.1 control points ($p=0,03$).
Lee et al., 2014	South Korea	59 / 28	Guidance from web-based self-management platform, with guidance on how to improve and plan exercise, eating behavior, importance of weight management,	12 weeks	HADS	The intervention group showed no improvement, there was an increase of 0.8

			etc. Participants recorded the type, intensity, and duration of exercise, and were to access the platform 2x per week / recommended 30 minutes of exercise per day/ or at least 150 minutes per week.			points vs. 1.6 points in the control group (p=0.27).
Saarto et al., 2012	Finland	573 / 237	Supervised and/or home training with the help of a physical therapist. Supervised training consisted of different classes (step aerobics and circuit class). Home training was optional (walking, Nordic walking or aerobic training, jumping and step aerobics-like jumping)/ 2x a week for home training / 1x a week for supervised training / for 30 minutes.	52 weeks	BDI	The intervention group did not show significant improvement, with a reduction of 0.3 points vs. 0.5 points in the control group (p=0.50).
RESISTANCE EXERCISE + AEROBICS						
Aydin et al., 2021	Turquia Região da Asia	24/24	Aerobic exercise (walking and cycling) 5x in the week, 50 minutes at 50-60% of maximum heart rate + resistance training 2x in the week, 60 minutes	12 weeks	BDI	The intervention group showed improvement, with a reduction of 10,5 vs. 0,5 points on the score (p < 0,001).
Dieli-Conwright et al., 2018	USA	100 / 50	Walking, running on treadmill, rowing machine and stationary bike / resistance training on machines with three sets of 10 repetitions with 80% intensity for upper limbs and 60% for lower limbs / 80 minutes of aerobic 2x a week and 50 minutes of resistance training 1x a week. With certified professional.	16 weeks	CES-D	The intervention group showed improvement, with a 5.4 point reduction vs. a 1.5 point increase in the control group (p<0.001).
Kaltsatou, Mameletzi e Douka 2011	Greece	27 / 13	Greek dance (low intensity at the beginning and high from the 15th week on) and resistance training with varied resistance machines /3x per week /10 minutes of warm up, 25 minutes of dance and 25 minutes of resistance training. With a professional specialized in dance.	24 weeks	BDI	The intervention group showed improvement, a reduction of 5.97 points vs. 4.94 points in the control group (p=0.001).
Kwiatkowski et al., 2013	France	251 / 115	Walking on level ground or cycling on a cycle ergometer and strength training for lower and upper limbs supervised by a physical therapist 5x a week / 120 minutes per session.	2 weeks	HADS	The intervention group had an improvement, a reduction of – 17,61 points vs. – 5,82 points in the control group (p=0.03).
RESISTANCE EXERCISE						
Maldonado et al., 2022	Espanha	32/28	Training with load progression starting at 40% and going up to 70% moderate intensity exercise guidelines / 2x a week / 60 minutes daily.	12 weeks	CES-D	The intervention group had an improvement, a reduction of –

						2,4 points vs. 0 points in the control group (p= 0,235).
ANXIETY						
AEROBIC EXERCISE						
Cadmus et al., 2009	USA	74 / 37	Walking in a gym and supervised by exercise physiologists / 5x a week / 30 minutes.	26 weeks	STAI	The intervention group showed an improvement in anxiety (reduction of 0.7 vs. increase 0.5 points; p<0.05).
Kim et al., 2011	South Korea	45 / 22	Telephone counselling combined with an e-book containing moderate intensity exercise guidelines / 5x a week / 30 minutes daily.	12 weeks	HADS	The intervention and control group showed improvement in anxiety, (reduction of 2.13 vs. 0.81 points; p=0.123) with greater reduction in the intervention group, but no significant difference.
Lee et al., 2014	South Korea	59 / 28	Guidance from web-based self-management platform, with guidance on how to improve and plan exercise, eating behavior, importance of weight management, etc. Participants recorded the type, intensity, and duration of exercise, and were to access the platform 2x per week / recommended 30 minutes of exercise per day/ or at least 150 minutes per week.	12 weeks	HADS	The intervention group showed no improvement in score and the control group showed an increase (reduction of 0.1 point vs. increase of 1.5 points; p=0.14).
RESISTANCE EXERCISE + AEROBICS						
Kwiatkowski et al., 2013	France	251 / 115	Walking on level ground or cycling on a cycle ergometer and strength training for lower and upper limbs supervised by a physical therapist / 5x a week / 120 minutes per session.	2 weeks	HADS	The intervention group showed improvement, with a reduction in the score (reduction of – 7,75 vs. increase of + 0.79 points); p=0.00002).
Milne et al., 2007	Australia	58 / 29	Sessions supervised by exercise physiologists for stationary bike and trampoline. The resistance training consisted of 12 different exercises / 2 sets of 10 to 15 repetitions / 25 minutes of aerobic and no identified time for resistance training / 3x a week.	12 weeks	SPA	The intervention group showed improvement, with a reduction in the scale (4.2 points vs. an increase of 0.9 points in the control group; p=0.03).
RESISTANCE EXERCISE						

Moraes et al., 2021	Brazil	26/12	Resistance Training Session: 1 session per week / 3 sets / 8-12 repetitions / with 2 minutes rest. Exercises: 45° leg press, stiff-legged deadlifts, bench press, lat pulldown and sit-ups. And 20 repetitions for the abdominal exercise, with a rest interval of 1 minute between sets.	8 weeks	STAI	The intervention group had an improvement, a reduction of 9.1 vs. 1.0 point in the control group ($p<0.05$).
STRESS						
AEROBIC EXERCISE						
Cadmus et al., 2009	USA	74 / 37	Walking in a gym and supervised by exercise physiologists / 5x a week / 30 minutes.	26 weeks	PSS	The groups showed no improvement, with an increase of 0.2 points vs. 0.8 points in the control group ($p < 0.05$).
Fillion et al., 2008	Canada	87 / 43	A kinesiologist or a nurse provided guidance on relaxation and walking practice at home according to physical condition and personal goals. They also received 20-minute muscle relaxation recordings to listen to daily / 44 minutes / orientation 4 x a week / 1 hour.	12 weeks	IRLE-C	The intervention group showed no improvement, a reduction of 0.10 points vs. 0.06 points in the control group ($p=0.55$).

Legend: PSS: Perceived Stress Scale; IRLE-C: Inventory of Recent Life Experiences for Cancer Patients; HADS: Hospital Anxiety and Depression Scale; SPA: Social Physique Anxiety; STAI: State-Trait Anxiety Index; CES-D: Center for Epidemiological Studies Depression Scale; BDI: Beck Depression Inventory.

Impact of Physical Activity on Depression

Among the 12 RCTs that assessed depression, seven observed a significant reduction in scale scores, indicating improvement in depression following the intervention (Aydin et al., 2021; Daley et al., 2007; Fields et al., 2016; Kim et al., 2011; Dieli-Conwright et al., 2018; Kaltsatou, Mameletzi & Douka, 2011; Kwiatkowski et al., 2013) (Table 1). Regarding the intervention protocols used, seven studies implemented aerobic exercises (Cadmus et al., 2009; Daley et al., 2007; Demark-Wahnefried et al., 2015; Fields et al., 2016; Kim et al., 2011; Lee et al., 2014; Saarto et al., 2012), four combined aerobic and resistance exercises (Aydin et al., 2021; Dieli-Conwright et al., 2018; Kaltsatou, Mameletzi & Douka, 2011; Kwiatkowski et al., 2013), and one used resistance exercise (Moraes et al., 2021). The longest intervention lasted 108 weeks (Demark-Wahnefried et al., 2015) and the shortest lasted two weeks (Kwiatkowski et al., 2013).

Among the RCTs with aerobic exercise interventions, four showed positive results on depression (Aydin et al., 2021; Daley et al., 2007; Fields et al., 2016; Kim et al., 2011). Different intervention strategies were observed, both in-person and remote, and various scales were used to assess depression.

Aydin et al. (2021) observed a reduction of 10.5 points in the intervention group vs. 0.5 points in the control group on the CES-D scale over 12 weeks ($p<0.001$), while Daley et al. (2007) noted a decrease of 6.01 points on the BDI scale between the intervention and control groups ($p=0.001$). Fields et al. (2016) observed a decrease in CES-D scores, with the intervention group showing a reduction of 3 points vs. 1 point in the control group (p-value not reported). Kim et al. (2011) found a decrease in HADS-D scores, with the intervention group improving by 2.48 points vs. the control group's 0.1 point ($p=0.03$).

Four studies did not find improvement following aerobic exercise interventions (Cadmus et al., 2009; Demark-Wahnefried et al., 2015; Lee et al., 2014; Saarto et al., 2012). Cadmus et al. (2009) observed an increase in CES-D scores (0.3 vs. 1.7 points, $p<0.05$), with a greater increase in the control group. Lee et al. (2014) observed an increase in HADS-D scores (0.8 vs. 1.6 points; $p=0.27$), higher in the control group. Demark-Wahnefried et al. (2015) observed an increase in CES-D scores in the intervention group after 24 months (1.9 vs. 0.2 points, $p=0.30$). Saarto et al. (2012) observed a small reduction in BDI scores, with the intervention group decreasing by 0.3 point and the control group by 0.5 point, with no significant difference between groups ($p=0.50$). Interventions included guidance provided via phone, e-mail (Demark-Wahnefried et al., 2015), or web platform (Lee et al., 2014), as well as in-person follow-up (Saarto et al., 2012). One study using resistance exercise (Maldonado et al., 2022) did not show a significant effect, with a reduction of 2.4 points vs. 0 point in the control group ($p=0.235$).

The four RCTs that combined aerobic and resistance exercises all showed positive results, regardless of instrument used (CES-D, BDI, or HADS) and intervention protocol (Aydin et al., 2021; Dieli-Conwright et al., 2018; Kaltsatou, Mameletzi & Douka, 2011; Kwiatkowski et al., 2013). Dieli-Conwright et al. (2018) observed a decrease in CES-D scores with the intervention group reducing by 5.4 points vs. an increase of 1.5 points in the control group ($p<0.001$). Kaltsatou, Mameletzi & Douka (2011) observed a decrease in BDI scores, with the intervention group reducing by 5.97 points and the control group by 4.94 points ($p=0.00$). Kwiatkowski et al. (2013) also observed a decrease in HADS-D

scores, with the intervention group improving by -23.8% ± 56.4 points vs. the control group -9.7% ± 54.1 points (p=0.03).

Impact of Physical Activity on Anxiety

Among the eligible RCTs, six studies provided data on anxiety outcomes. Four studies observed a reduction in scores following intervention (Cadmus et al., 2009; Kwiatkowski et al., 2013; Moraes et al., 2021; Milne et al., 2007), one showed a reduction in scores for both intervention and control groups (Kim et al., 2011), and one did not observe a reduction in anxiety scores after intervention (Lee et al., 2014) (Table 1).

Of the RCTs that assessed anxiety, three used aerobic exercise as intervention (Cadmus et al., 2009; Kim et al., 2011; Lee et al., 2014). Cadmus et al. (2009), using the STI scale, found a significant improvement in anxiety in the intervention group, with a reduction of 0.7 points vs. a 0.5-point increase in the control group ($p<0.05$). In Kim et al. (2011), the average HADS-A score decreased by 2.13 points in the intervention group and 0.81 point in the control group, but with no significant difference between groups (p=0.123). Meanwhile, Lee et al. (2014), using the same scale, found a slight reduction (-0.1 point) in the intervention group, while the control group increased by 1.5 points in average anxiety scores (p=0.14).

RCTs that combined aerobic and resistance exercises demonstrated significant reductions in anxiety, regardless of the scales used (HADS and SPA). Kwiatkowski et al. (2013) showed that the intervention group had an 18.0% reduction in anxiety (-7.75 points) vs. a 2.1% increase (0.79 points) in the control group (p=0.00002). Similarly, Milne et al. (2007) reported an improvement in the intervention group, with a reduction of 4.2 points in anxiety vs. an increase of 0.9 points in the control group (p=0.03).

A notable difference in intervention protocols was observed, with more prominent results in RCTs which had included in-person supervision by a physiotherapist or exercise physiologist (Kwiatkowski et al., 2013; Milne et al., 2007). The longest intervention was 26 weeks (Cadmus et al., 2009) and the shortest was two weeks (Kwiatkowski et al., 2013). A study using resistance exercise (Moraes et al., 2021) also showed significant effects, with a reduction of 9.1 points in the intervention group vs. 1.0 point in the control group ($p<0.05$).

Impact of Physical Activity on Stress

In this review, only two RCTs assessed the impact of aerobic exercise on WSBC (Cadmus et al., 2009; Fillion et al., 2008). Cadmus et al. (2009), using the Perceived Stress Scale (PSS), found that the intervention group had an smaller increase of 0.2 points vs. 1.0 point in the control group ($p<0.05$). Fillion et al. (2008), using the Inventory of Recent Life Experiences for Cancer patients (IRLE-C), reported a small reduction of 0.1 point in the intervention group vs. 0.06 point in the control group, with no statistically significant difference (p=0.55).

Methodological Quality and Risk of Bias Assessment

The risk of bias analysis for the eligible studies considered the different outcomes studied, as recommended by Cochrane (Higgins et al., 2022). The RoB 2 tool identified that

studies evaluating depression and anxiety outcomes had some concerns, while studies evaluating stress had a low risk of bias. No study was found to have a high risk of bias, as shown in supplementary Figure 1.

Among the twelve studies assessed for risk of bias with depression outcomes, six (Cadmus et al., 2009; Daley et al., 2007; Dieli-Conwright et al., 2018; Lee et al., 2014; Maldonado et al., 2022; Saarto et al., 2012) had a low risk of bias, while the remaining six (Aydin et al., 2021; Demark-Wahnefried et al., 2015; Fields et al., 2016; Kaltsatou, Mameletzi, and Douka, 2011; Kim et al., 2011; Kwiatkowski et al., 2013) had some level of risk or moderate risk of bias, primarily due to lack of information, methodological flaws such as details of randomization, participant blinding issues, and problems in the randomization process (D1: Randomization process).

Among the six studies assessed for risk of bias with anxiety outcomes, 50% (n=3) showed a low risk of bias, and 50% (n=3) showed some level of risk or moderate risk. For the two studies assessing stress, both had a low risk of bias.

Meta-analysis of the Effect of Physical Exercise on Depression, Anxiety, and Stress

When assessing the overall effect of physical exercise, a significant reduction in scores of depression was observed (SMD = -0.46; 95% CI: -0.78 to -0.15; p = 0.004). In analysis by exercise modality, interventions involving only aerobic exercise resulted in a small reduction in depression scores (SMD = -0.10; 95% CI: -0.30 to 0.09; p = 0.31), while interventions combining strength and aerobic exercises led to greater reduction in scores (SMD = -1.18; 95% CI: -2.21 to -0.14; p = 0.03) with statistical significance. Strength training alone showed no significant effect (SMD = -0.30; 95% CI: -0.81 to 0.21; p = 0.25) (supplementary Figure 2).

For the outcome anxiety, physical exercise, regardless of modality, significantly reduced scores for these (SMD = -0.52; 95% CI: -0.71 to -0.33; p < 0.001). Similarly, in subgroup analyses, both aerobic exercise (SMD = -0.36; 95% CI: -0.66 to -0.06; p = 0.02) and combined strength and aerobic exercise (SMD = -0.68; 95% CI: -1.07 to -0.29; p = 0.0007) led to significant reductions in anxiety scores. Strength training alone also showed a significant reduction (SMD = -0.63; 95% CI: -1.43 to -0.18; p = 0.13) (supplementary Figure 3).

Regarding the outcome stress, a small increase in scale scores was observed for the intervention group compared to the control group (SMD = 0.06; 95% CI: -0.27 to 0.39; p = 0.72), but without statistical significance (supplementary Figure 4).

Subgroup and Sensitivity Analysis

Subgroup analyses were conducted to investigate heterogeneity based on the type of exercise and instruments used to assess depression and anxiety. For the stress outcome, analysis was not necessary, as only two studies showed low heterogeneity (I^2 = 11%) (supplementary Figure 4). For depression, overall heterogeneity (I^2 = 89%) was reduced in the aerobic exercise subgroup (I^2 = 55%) (supplementary Figure 2). For anxiety, the overall analysis showed low heterogeneity (I^2 = 5%), which was eliminated in the aerobic exercise subgroup (I^2 = 0%) (supplementary Figure 3). The use of different scales, such as the BDI, reduced heterogeneity for depression (from I^2 = 96% to I^2 = 0%)

(supplementary Figure 5) and for anxiety (from $I^2 = 23\%$ to $I^2 = 0\%$) (supplementary Figure 6).

Sensitivity analysis, considering risk of bias and data imputation, revealed that risk of bias did not explain the heterogeneity in results related to depression (supplementary Figure 7), but eliminated heterogeneity for anxiety when analyzing only studies with low risk of bias (supplementary Figure 8). Data imputation did not significantly influence the results (supplementary Figure 9). Publication bias analysis, conducted using a funnel plot, was possible only for the depression outcome and did not show significant bias ($p = 0.36$) (supplementary Figure 10). Meta-regression was not possible due to the limited number of studies included in this systematic review.

Analysis of Evidence Certainty

According to the GRADE criteria, the certainty of evidence was considered very low for depression, moderate for anxiety, and low for stress (supplementary Table 3). Among the four GRADE assessment criteria (risk of bias, inconsistency, indirect evidence, imprecision), the main reasons for the very low certainty of evidence for studies evaluating depression symptoms were inconsistency of findings due to heterogeneity and imprecision due to the magnitude of the effect and confidence interval width. Moderate certainty of evidence for anxiety was primarily attributed to imprecision in the findings. Low certainty of evidence for studies on stress was also due to imprecision and study limitations.

The present systematic review and meta-analysis, assessed using the GRADE system, showed that physical exercise has a variable impact on stress, anxiety, and depression in WSBC. For stress, there was little difference compared to usual care (MD 0.03 points), with low quality of evidence. For depression, exercise reduced scores by an average of 6 points (95% CI: -11 to -2), also with low quality of evidence. For anxiety, there was an average reduction of 7 points (95% CI: -9.5 to -4.4), with low confidence in estimates due to study imprecision. Although the results are promising, more research is needed to increase confidence in the evidence.

Discussion

The present systematic review and meta-analysis investigated the effects of physical exercise on depression, anxiety, and stress in WSBC. The results herein presented suggest that physical exercise, regardless of modality, has a favorable impact on reducing depression and anxiety. A more pronounced effect was observed in reducing anxiety when aerobic exercise was combined with strength training.

Despite the relatively high remission and survival rates for breast cancer (INCA, 2021), the disease is still accompanied by stigma and emotional difficulties such as depression, anxiety, and stress (Biparva et al., 2022; Heidary et al., 2023). International guidelines recommend that physical exercise be a relevant and crucial lifestyle factor for improving the overall health of the affected population (INCA, 2021; ACSM, 2021; WHO, 2019).

Our study confirms that physical exercise has a significant impact on improving depression, corroborating systematic reviews by Patsou et al. (2017), Salam et al. (2022), and Sun et al. (2023). However, our findings expand the previously observed perspective by demonstrating the efficacy of exercise combinations, especially for anxiety. This may suggest that mixed interventions, including both aerobic and strength exercises, are particularly beneficial for WSBC.

Exercise protocols varied widely between studies, including in-person, online, and e-book approaches, with distinct durations and frequencies. Such variability makes it more difficult to determine the most effective protocol. Additionally, the lack of consensus on diagnostic tools for psychological symptoms may limit the interpretation of our results. It is important for future studies to consider standardizing exercise protocols and using more consistent diagnostic instruments.

The recommendation for WSBC to engage in physical exercise three to five times per week, with moderate to vigorous intensity, aligns with the guidelines from the American College of Sports Medicine and the American Cancer Society (ACSM, 2021). Healthcare professionals should consider these guidelines when prescribing exercise programs and ensure patient motivation, which may be influenced by the exercise environment and social support (Rocha et al., 2019).

Improvements in psychological symptoms associated with physical exercise may be attributed to various mechanisms, both psychological and physiological. Psychological models, such as the distraction hypothesis and the importance of social interactions, offer valuable insights into the effects of exercise on mental well-being (Alizadeh, 2024; Di Bartolomeo & Papa, 2019). Physiological models suggest that exercise promotes the release of endorphins and neurotransmitters that enhance mood and reduce stress (de Oliveira et al., 2019; Guszkowska, 2004). However, the exact mechanisms are not yet fully understood and should be more thoroughly explored in future research.

A total of 15 studies were assessed in the present systematic review, revealing a range of risk levels, with six studies rated as low risk of bias, and five rated as some concerns. Notably, although some studies exhibited concerns regarding randomization and blinding, particularly Demark-Wahnefried et al. (2015) and Fields et al. (2016), no included study were classified as high risk according to RoB 2. Sensitivity analyses were conducted to assess the robustness of the findings by excluding studies rated as some concerns. Nonetheless, the studies rated as some concerns which were eventually included in our analysis provide critical data on outcomes that were less explored by other studies. The primary outcome results, such as quality of life, stress, and sleep quality, remained consistent, showing that the overall conclusions were not significantly influenced by the inclusion of said studies. Thus, while a few studies presented some concerns, their contribution to the evidence herein presented warranted their retention in the analysis.

This systematic review has shown that physical exercise is effective in reducing depression and anxiety in WSBC, with an additional effect when combining aerobic and strength exercises. Interpretation of the findings should be cautious due to variability in exercise protocols and diversity in diagnostic tools. Future studies should focus on

standardizing exercise protocols and using more consistent assessment instruments to provide a clearer and more applicable understanding of the benefits of physical exercise.

Strengths of this systematic review include the comprehensive methodology in data search and analysis, stringent risk of bias assessment, and evaluation of evidence certainty. Only RCTs were included, providing a solid foundation for result interpretation (Gordis, 2013).

Conclusion

Based on the literature currently available, RCTs indicate a positive effect of physical exercise on symptoms of depression and anxiety, and possibly stress, in WSBC. It has been observed that combining aerobic and strength exercises offers superior benefits for anxiety. Therefore, it is suggested that engagement in physical activity can lead to significant improvements in emotional symptoms and overall well-being for WSBC.

However, due to the methodological diversity of the studies included in this systematic review, it is difficult to precisely recommend a specific modality, duration, or intensity of exercise for WSBC. Adherence to internationally validated exercise guidelines, preferably under the guidance of a specialized professional, is recommended.

The results of this meta-analysis should be interpreted with caution, considering the heterogeneity of the studies included. Future studies with more rigorous methodologies, uniform exercise protocols, and larger sample sizes could more precisely define the most effective approach for WSBC.

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