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Effectiveness of aerobic exercise intervention on cardiovascular disease risk in female breast cancer: a systematic review with meta-analyses

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Abstract

Background Cardiovascular disease (CVD) has become the leading cause of competitive mortality in female breast cancer (BC). Regular aerobic exercise (AE) has been widely accepted as an effective intervention to reduce cardiovascular risk in a variety of different clinical conditions. This study is aimed at evaluating the efficacy and safety of AE on cardiovascular risk factors in female BC and assessing the quality of the synthesized evidence.

Methods We searched five English databases (Cochrane Library, PubMed, Embase, Scopus, and Web of Science) from inception to January 2023. Randomized controlled trials (RCTs) and cohort trials studying the effects of AE intervention on cardiovascular disease risk in female breast cancer were included. We used Stata 16 for data synthesis, Risk of Bias 2, and the Newcastle–Ottawa Scale for methodological quality evaluation and assessed the certainty of the synthesized evidence in the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results Forty RCTs and 6 cohort trials involving 44,877 BC patients showed AE reduced the incidence of CVD events by 29.4% [risk ratio (RR) = 0.706, 95% confidence interval (CI) (0.659, 0.757), low certainty] and coronary artery disease events by 36% [RR = 0.640, 95% CI (0.561, 0.729), low certainty]. AE improved LVEF, and reduced weight and hip circumference. The subgroup analysis results showed that nonlinear AE increased VO_2max by 5.354 ml·kg·min^{-1} [mean difference (MD) = 5.354, 95% CI (2.645, 8.062), very low certainty] and reduced fat mass by 4.256 kg [MD = 4.256, 95% CI (-3.839, -0.094), very low certainty]. While linear AE reduced low-density lipoprotein cholesterol (LDL-C) by 8.534 mg/dL [MD = -8.534, 95% CI (-15.511, -1.557), low certainty]. The sensitivity analysis results showed that each trial did not affect the impact index of the highly heterogeneous outcomes.

Conclusions Our study indicates that AE has a positive effect in reducing cardiovascular risk factors. The individualization principle of AE deserves more attention in the future. This will provide new ideas to reduce CVD events and improve the quality of life in female BC patients. However, further research on AE in female BC should take into account long-term and well-designed administration to draw definitive conclusions.

Keywords Breast cancer, Aerobic exercise, Cardiovascular disease risk, Systematic review

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Introduction

According to the latest global cancer statistics, female breast cancer (BC) has become the most prevalent cancer, with an estimated 2.3 million new cases, accounting for 11.7% of all cancer cases [1]. With the development and advancement of medical technology, the use of immune and endocrine therapy has increased the 5-year survival rate of BC by 10%- 20% [2, 3]. However, it is accompanied by a significantly higher risk of cardiovascular disease (CVD) with approximately 9.4% [4] compared with people who did not have BC [5, 6]. Deaths due to CVD accounted for 16.3% of deaths in BC patients [7] and all-cause mortality increased 3.8-fold in breast cancer patients who developed CVD compared to breast cancer patients who did not develop CVD [8]. CVD has become the leading cause of competitive mortality in BC women [9], due to the cardiotoxic effects of BC treatments (anthracycline chemotherapy, radiotherapy, and biotherapy) and overlapping risk factors for breast cancer and CVD (lack of exercise, obesity) [10]. Therefore, strategies to reduce the risk of CVD should ideally target both treatment- and patient-related factors [11].

Regular aerobic exercise (AE) has been widely accepted as an effective intervention to reduce cardiovascular risk in a variety of different clinical conditions [12]. It has been shown in preclinical studies that AE exerts cardioprotective effects in a model of chemotherapy-induced cardiotoxicity by being able to attenuate chemotherapeutic drug-induced oxidative stress and apoptosis [13, 14]. Lack of physical activity and poor cardiorespiratory fitness in BC patients is well documented [15]. To date, some systematic reviews and meta-analyses have been published about this topic [16–19]. These studies have mainly focused on chemotherapy-related cardiotoxicity and used VO_2max and LVEF as the tools of measurement. In addition, one systematic review [16] suggested that vigorous aerobic training performed with continuous or interval training mode should be considered. Furthermore, there are no reviews of body composition in previous literature. The linear aerobic exercise approach utilizes standard intensity, frequency, and duration parameters after an initial lead in period, with static increases in session duration [20]. The non-linear aerobic exercise approach considers the principles of exercise training in order to optimize the adaptations to the exercise stimulus. Sessions and weeks progress over the course of the prescription and vary between low intensity and moderate and high intensity training in order to target various physiological systems involved in the cardiopulmonary response to non-linear aerobic exercise approach [20]. Therefore this study is aimed to seek effective exercise strategies for reducing cardiovascular risk factors in BC patients through a systematic review and meta-analysis of AE intervention on cardiovascular risk factors in female BC. We also aimed to identify the appropriate exercise approach through analyzing the linear or non-linear approach to provide information on exercise prescriptions best suited for patients scheduled to receive BC therapy.

Methods

We performed this study in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. PRISMA checklist and abstract checklist were attached to Supplementary Materials 1 and 2. The systematic review was registered with PROSPERO (CRD42022342396).

Search strategy

We systematically searched five databases including PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science from their inception up to January 31st, 2023. We referred to the retrieval method of "P + I" and searched with "MeSH terms and Emtree terms + Entry terms". The search terms included "Breast Neoplasms", "Breast Cancer", "Exercise", "Aerobic Exercise", "training exercise", "endurance exercise" and so on. The search strategy without limits to publication year, type, and status was described in detail in Supplementary Material 3.

Inclusion and exclusion criteria of the study

Types of studies

To collect additional data to explore the relevance of AE on cardiovascular events in BC patients, randomized controlled trials (RCTs) and cohort studies (CSs) were included. Trials that did not describe the randomization method in detail were considered non-randomized studies of interventions and were excluded. Animal studies were also excluded.

Types of participants

Studies that included participants of any age with histologically confirmed non-metastatic breast cancer. We did not restrict the type of treatment (chemotherapy, radiotherapy, or surgery). Studies that evaluated different types of cancer (breast, ovarian, rectal.) were only included if data from a breast cancer-only group were provided.

Types of interventions and control

Patients in the intervention group were treated with AE (continuous or interval; home-based or under professional supervision). Patients in the control group were asked to only perform their daily activities and not to begin any formal exercise training. Studies with the intervention involving diet or acute exercise were excluded.

Types of outcome measures

Primary outcomes

(1) Incidence of CVD events. CVD events were defined as coronary artery disease (CAD), heart failure, valve abnormality, arrhythmia, stroke, pericardial complications, pulmonary hypertension, thromboembolic disease, or CVD death, occurring after study enrollment.
(2) Changes in cardiopulmonary endurance. Cardiopulmonary endurance was measured by the maximum oxygen uptake (VO2 max). Training types (linear aerobic exercise or nonlinear aerobic exercise) were used as moderator variables.

Secondary outcomes

(1) Cardiovascular risk score.
(2) Lipid profile. Lipid profile includes low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and total cholesterol (TC).
(3) Body Composition. Body composition includes body mass index (BMI), body weight, waist circumference (WC), hip circumference (HC), lean mass, fat mass, body fat percentage (BF%), and waist-to-hip ratio.
(4) Left ventricular ejection fraction (LVEF).
(5) C-Reactive Protein (CRP).

Study selection and data extraction

Search results were imported to EndNote X9. The eligibility of retrieved studies was evaluated using the established inclusion and exclusion criteria. The contents of data extraction include first author, publication year, sample size, treatment received for breast cancer, basic characteristics (age, clinical type) of the included patients, duration and frequency of aerobic exercise, outcome measures. Studies without detailed information on outcome measures were excluded. The screening of studies and data extraction were performed independently by two reviewers (QJ and CM), and any differences were resolved by discussion or the decision of the third reviewer (JL).

Quality assessment

The Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool was used to assess the methodological quality of the included RCT [22]. The following five domains were assessed: bias in the randomization process; bias from the intended intervention; missing outcome data; bias in outcome measures; and selective reporting of outcomes. Each domain was classified as low, some concern, and high risk of bias. The risk assessment for each entry using this tool finally resulted in a study quality assessment.

The quality of CS was evaluated using the corresponding Newcastle–Ottawa Scale (NOS, range 0–9) [23]. The study was scored based on 8 items in three categories: selection of participants, comparability between study groups, and measurement of exposure factors or results. Each entry is scored accordingly, with a total scale score of 9. A study scoring 7–9 is considered a high-quality study, 4–6 is a medium-quality study, and less than 4 is considered a low-quality study.

The quality assessment of each included study was performed independently by two reviewers (QJ and CM), and any disagreements were resolved by discussion or the decision of the third reviewer (BX).

Evidence synthesis

We used Stata 16 (Stata Corp LLC, College Station, TX, USA) for all statistical analyses. Continuous variable's effect estimates were expressed as weighted mean differences (WMD) with a 95% confidence interval (CI). We did I^2 testing to assess the magnitude of the heterogeneity between studies, a value of $I^2 > 50\%$ was considered substantial heterogeneity [24]. The random-effects model was used when synthesizing data with high heterogeneity.

Additional analyses

Subgroup analysis

Subgroup analyses were performed, based on whether patients received linear or nonlinear aerobic exercise in the intervention group. Aerobic exercise was distinguished as a linear or non-linear exercise group based on the intensity, frequency and duration parameters of the exercise. If substantial heterogeneity existed, the source of heterogeneity was explored.

Sensitivity analysis

According to the Cochrane Handbook for Systematic Reviews of Interventions [24], I^2 values between 0 and 50% indicated that heterogeneity might not be important. Therefore, we eliminated the included studies with $I^2 > 50\%$ one by one and performed sensitivity analysis to identify possible highly influential studies. Studies were considered influential if the removal significantly changed the summary effect (i.e., change going from significant to non-significant).

Publication bias

Publication bias of the cumulative evidence among individual studies was evaluated using a graphical method of funnel plot and Egger's test if at least 10 trials were included for the synthesized outcome [25]. If publication bias existed, the meta-trim-fill method was employed

using Stata 16 to assess the potential impacts of publication bias of cumulative evidence.

Certainty of evidence

We assessed the certainty of the cumulative evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system [26], where the certainty of the evidence was classified as high, moderate, low, or very low. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were assessed. We present our findings in a summary of findings (SoF) table.

Results

Details of included trials

We obtained 12,678 records from the database search, and after the selection process, a total of 40 RCTs involving 2,129 participants were enrolled and 6 cohort trials involving 42,748 participants were enrolled. The selection process was summarized in the flowchart shown in Fig. 1.

General and intervention information of the cohort trials

The two reports included were a retrospective cohort trial report [27] and a prospective cohort trial report [28]. For the reporting of CVD events, the retrospective cohort trials reported stroke events and the prospective cohort trials reported heart failure events, and all trials reported the occurrence of CAD events. In the two cohort trial reports, the intervention groups were all set up respectively with AE intervention of different intensities in the low, medium, and high groups, and the control groups were all asked to only perform their daily activities and not to begin any formal exercise training.

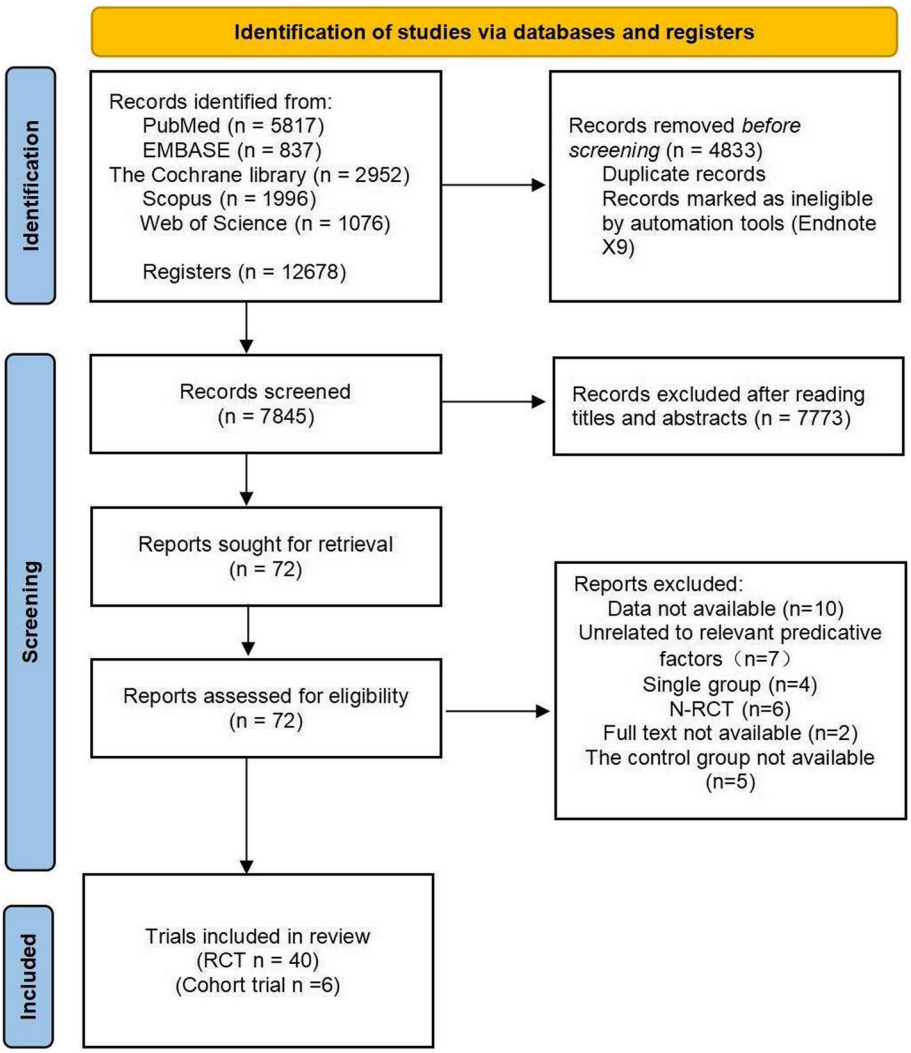

Fig. 1 Flowchart of the selection process

Therefore, we conducted a meta-analysis of 6 trials from 2 cohort reports based on exercise intensity to investigate the relevance of AE intervention on the occurrence of CVD and CAD events in BC patients. The characteristics of the 6 cohort trials were summarized in Table 1.

General and intervention information of the RCTs

The three reports [39, 46, 50] contained 2 intervention groups respectively. Although both intervention groups were aerobic, the exercise protocols had slightly different. One group was a continuous AE with a continuous increase in exercise duration and intensity, which meets the definition of linear AE. While the other group was an intermittent AE with alternating intensity and duration, which meets the definition of nonlinear AE. So we divided each of the three reports into 2 trials for inclusion in the meta-analysis. The intervention group of one report [55] had the same intervention protocol for AE but was divided into Hispanic and non-Hispanic groups based on the race of the BC patients, so we extracted 2 trials from this study for inclusion in the meta-analysis. A total of 2,129 participants were randomized in the AE intervention group (n = 1,094) and the control group (n = 1,035). The characteristics of 40 RCTs were summarized in Table 1.

The current exercise oncology prescription design follows the design principles of linear and nonlinear exercise prescriptions [20]. The linear prescription design approach utilizes standard intensity, frequency, and duration parameters with static increases in session duration after an initial lead cycle. The nonlinear prescription design approach considered the principles of exercise training, tailored to the relative intensity of the individual, varying between low, moderate, and high intensity training. Fifteen RCTs of AE design followed linear design principles, and the other 25 trials followed nonlinear design principles.

Quality assessment of studies

Cohort studies

Since the 6 observational trials included were all cohort studies, the NOS corresponding to the cohort study was used to evaluate their quality. Three studies scored 9 and the other scored 8. Overall, the 6 cohort trials were high quality. Details of the NOS evaluation of the 6 cohort trials were provided in Supplementary Material 4.

Risk of bias of RCTs

We assessed the risk of bias in 40 included trials with the RoB 2 tool. Only one trial was assessed as 'Low' risk of bias, and other 39 trials were assessed as 'Some concerns'. Most concerns were caused by the measurement of the outcomes, since the assessment of outcomes could be influenced by knowledge of interventions that patients received. The summary of the risk of bias is shown in Fig. 2.

Primary outcomes

Effect of AE on CVD

Six cohort trials reported the occurrence of CVD and CAD events in BC patients. The meta-analysis showed that compared to the control group, AE reduced the incidence of CVD events by 29.4% [RR = 0.706, 95% CI (0.659, 0.757), $P < 0.05$] and CAD events by 36% [RR = 0.640, 95% CI (0.561, 0.729), $P < 0.05$] in female BC. There was high effect heterogeneity among the CVD trials ($I^2 = 81.2\%$, $p < 0.05$), as shown in Fig. 3. While there was low effect heterogeneity among the CAD trials ($I^2 = 14.7\%$, $p = 0.32$), as shown in Fig. 4.

Effect of AE on cardiopulmonary endurance

Cardiopulmonary endurance is expressed as the VO_2max. Pooled data from 26 RCTs (1216 participants: cases = 625, controls = 591) showed that compared to the control group, AE elevated VO_2max by 3.86 ml·kg·min^{-1} [95% CI (2.107, 5.613), $p < 0.05$)] in BC patients. There was high effect heterogeneity among the studies ($I^2 = 90.9\%$, $p = 0.000$), as shown in Fig. 5.

The heterogeneity between trials was large, and to elucidate the sources of heterogeneity, subgroup analyses were performed according to AE design principles: classification into linear AE and nonlinear AE. We used a random effects model for subgroup analysis in Fig. 6. (1) Linear AE group: eleven RCTs [29, 30, 35, 37, 39, 40, 46, 48, 50, 51, 58] were included, and the results showed that linear AE treatment was significantly better than the control group in increasing VO_2max, with no statistically significant difference [WMD = 1.884, 95% CI (-0.154, 4.283), $p = 0.124$]. (2) Nonlinear AE group: fifteen RCTs [32, 34, 36, 38, 39, 43, 44, 46, 50, 52, 55–57, 60] were included and the results showed that nonlinear AE treatment was significantly better than the control group, which could significantly improve VO_2max by 5.354 ml·kg·min^{-1}, with a statistically significant difference [95% CI (2.645, 8.062), $p = 0.000$].

Secondary outcomes

Effect of AE on the cardiovascular risk score

Cardiovascular scores were used in 3 RCTs to measure the effects of AE intervention: the Reynolds risk score (RRS) [31], the metabolic syndrome z-score [33], and the Framingham Risk Score (FRS) [35]. The results showed that AE significantly reduced cardiovascular risk scores compared with the control group. But the meta-analysis could not be performed because each score involved only one trial.

Table 1 Characteristics of included trails

Study	Study design	Stage	Sample size		Age (years)	Cancer Treatment	Aerobic exercise protocol in Intervention Group	Principles of exercise	Outcomes
			T	C					
Chung et al. [29] (2021)	RCT. Single-center	I—III	16	13	T 52.4 ± 8.9 C: 50.3 ± 7.7	AC	**Aerobic exercise modality:** Continuous. **Time:** 40 min/ sessions. **Frequency:** 2–3 sessions /w. **Duration:** 3m. **Intensity:70%-75%** VO_2max	Linear	(5)(22)
De Luca et al. [30] (2016)	RCT. Single-center	I—III	10	10	T: 50.2 ± 9.7 C:46.0 ± 2.8	Chemotherapy, radiation, hormonal therapy	**Aerobic exercise modality:** Continuous. **Time:** 30 min/ sessions. **Frequency:** 2 sessions /w. **Duration:** 24w. **Intensity:70%-75%** HR max	Linear	(5)(12)
Lee et al. [31] (2020)	RCT. Single-center	0 to 3	48	45	T: 52.8 ± 10.6 C: 53.6 ± 10.1	Chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 5 min every 3–4 weeks resulting in a total of 45 min per session by week 16. **Frequency:** 3 sessions /w. **Duration:** 16w. **Intensity:65%-80%** HR max	Nonlinear	(7)(18)(20)(21)
Hornsby et al. [32] (2013)	RCT. Single-center	IIB—III	10	10	T: 51 ± 6 C: 46 ± 11	AC, neoadjuvant chemotherapy	**Aerobic exercise modality:** Continuous & Interval. **Time:**1st w: 15–20 min/ sessions. 2nd -4th w: 30min/ sessions.5th -6th w: 30—45min/sessions. 7th -9th w: 20min/ sessions. 10th -12th w: 20min / sessions. **Frequency:** 3 sessions /w. **Duration:** 12w. **Intensity:** 1st – 4th w: 60% VO_2max. 5th-6th w: 60%-65% VO_2max; 7th -9th w: 60%-70% VO_2max; 10th -12th w: 60%-70%VO_2max & 100%VO_2max	Nonlinear	(5)(22)
Dieli-Conwright et al. [33] (2018)	RCT. Single-center	I—III	48	45	T: 52.8 ± 10.6 C: 53.6 ± 10.1	Chemotherapy, radiotherapy	**Aerobic exercise modality:** Continuous. **Time:** 5 min every 3–4 weeks resulting in a total of 45 min per session by week 16. **Frequency:** 3 sessions /w. **Duration:** 16w. **Intensity: 65%-80%** HR max	Nonlinear	(6)(8)(10)(11)(12)(13)(14)
Dieli-Conwright et al. [34] (2018)	RCT. Single-center	I—III	48	45	T: 52.8 ± 10.6 C: 53.6 ± 10.1	Chemotherapy, radiotherapy	**Aerobic exercise modality:** Continuous. **Time:** 5 min every 3–4 weeks resulting in a total of 45 min per session by week 16. **Frequency:** 3 sessions /w. **Duration:** 16w. **Intensity: 65%-80%** HR max	Nonlinear	(5)
Lee et al. [35] (2019)	RCT. Single-center	I—III	48	45	T: 52.8 ± 10.6 C: 53.6 ± 10.1	Chemotherapy, radiotherapy	**Aerobic exercise modality:** Continuous. **Time:** 5 min every 3–4 weeks resulting in a total of 45 min per session by week 16. **Frequency:** 3 sessions /w. **Duration:** 16w. **Intensity: 65%-80%** HR max	Nonlinear	(9)(19)
Cornette et al. [36] (2016)	RCT. Single-center	I—IIIB	20	22	T: 49 C: 52	3 FEC100, 3	**Aerobic exercise modality:** Continuous. **Time:** Start with 20 min, increase by 5 min per 6 weeks. **Frequency:** 3 sessions /w. **Duration:** 27w. **Intensity:** 18 ± 2 maximum rated perceived exertion	Nonlinear	(5)

Table 1 (continued)

Study	Study design	Stage	Sample size		Age (years)	Cancer Treatment	Aerobic exercise protocol in Intervention Group	Principles of exercise	Outcomes
			T	C					
Ochi et al. [37] (2022)	RCT. Single-center	early-stage	21	23		Hormone therapy	**Aerobic exercise modality:** High Intensity Aerobic Interval. **Time:** NA. **Frequency:** 3 sessions /w. **Duration:** 12w. **Intensity:** Maximum rated perceived exertion 18 ± 2	Linear	(5)
Courneya et al. [38] (2003)	RCT. Single-center	I—IIIA	24	28	T: 59 ± 5 C: 58 ± 6	_	**Aerobic exercise modality:** Continuous. **Time:** Start with 15 min and increase by 5 min every 3 weeks. **Frequency:** 3 sessions /w. **Duration:** 15w. **Intensity:** 70%—75% VO_2max	Nonlinear	(5)(6) (10)
Scott et al. [39] (a) (2020)	RCT. Single-center	I—III	58	57	T: 59 ± 9 C: 58 ± 9	Surgery, chemotherapy, radiotherapy, endocrine therapy	**Aerobic exercise modality:** Continuous. **Time:**1st-4th w:30–40 min; 5th -16th w: 40. **Frequency:** 1st – 3rd w: 3 sessions /w; 4th -16th w: 4 sessions /w. **Duration:** 16w. **Intensity:** 1st – 3rd w: 55%-60% VO_2max, 4th -16th w: 60%—70% VO_2max	Linear	(5)
Scott et al. [39] (b) (2020)	RCT. Single-center	I—III	59	57	T: 58 ± 9 C: 58 ± 9	Surgery, chemotherapy, radiotherapy, endocrine therapy	**Aerobic exercise modality:** Interval. **Time:** 120 min/week. **Duration:** 16w. **Intensity:** alternated between five different dose intensities (55%, 65%, 75%, 80%, and > 95%) of VO_2max	Nonlinear	(5)
Vincent et al. [40] (2020)	RCT. Single-center	I—III	55	26	-	FEC & TZB & TAX	**Aerobic exercise modality:** Continuous. **Time:** 30 min/week. **Frequency:** 2 sessions /w. **Duration:** 6m. **Intensity:** 60%—70% VO_{2peak}	Linear	(5)(6)(11)
Hojan et al. [41] (2020)	RCT. Single-center	IB—IIIA	26	21	T: 54.44 ± 6.29 C: 54.64 ± 5.26	TZB	**Aerobic exercise modality:** Continuous. **Time:** 45–50 min/week. **Frequency:** 5 sessions /w. **Duration:** 9w. **Intensity:** 80% HR max	Linear	(21)(22)
Murtezani et al. [42] (2014)	RCT. Single-center	I—IIIA	30	32	T: 53 ± 11 C: 51 ± 11	Surgery	**Aerobic exercise modality:** Continuous. **Time:** Start with 15 min, increase by 2 min per week. **Frequency:** 3 sessions /w. **Duration:** 10 w. **Intensity:** 50% -75%HRR	Nonlinear	(6)(10)
Lee et al. [35] (2019)	RCT. Single-center	I—III	15	15	T: 47.1 ± 7.9 C: 44.7 ± 11.2	AC	**Aerobic exercise modality:** High Intensity Aerobic Interval. **Time: 20** min. **Frequency:** 3 sessions /w. **Duration:** 8 w. **Intensity:** 7 times of a 1- min interval performed at 90% PPO; followed by a 2 – min interval performed at 10% PPO	Linear	(5)

Table 1 (continued)

Study	Study design	Stage	Sample size		Age (years)	Cancer Treatment	Aerobic exercise protocol in Intervention Group	Principles of exercise	Outcomes
			T	C					
Courneya et al. [43] (2007)	RCT. Single-center	I—IIIA	71	73	T: 49 C: 49	AC & TAX & FEC100C, CE120F	**Aerobic exercise modality:** Continuous. **Time:** Start with 15 min and increase by 5 min every 3 weeks. **Frequency:** 3 sessions /w. **Duration:** 8 w. **Intensity:** 60% -80% VO_2max	Nonlinear	(5)(10)(11) (12) (13)
Jones et al. [44] (2013)	RCT. Single-center	IIB—IIIC	10	10	T: 51 ± 6 C: 46 ± 11	AC	**Aerobic exercise modality:** Continuous & Interva. **Time:** 1st w: 15–20 min/ sessions. 2nd -4th w: 30min/ sessions. 5th -6th w: 30-45min/ sessions. 7th -9th w: 20min/ sessions. 10th -12th w: 20min / sessions. **Frequency:** 3 sessions /w. **Duration:** 12 w. **Intensity:** 1st – 4th w: 60% VO_2max. 5th-6th w: 60%-65%VO_2max. 7th -9th w: 60%-70%VO_2amx. 10th -12th w: 60%-70%VO_2max & 100%VO_2max	Nonlinear	(5)
Irwin et al. [45] (2009)	RCT. Single-center	I—IIIA	37	38	T: 56.5 ± 9.5 C: 55.1 ± 7.7	Radiation and chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 15–30 min/ sessions. **Frequency:** 3 sessions /w. **Duration:** 6m. **Intensity:** 50% increased to 60%-80% HRmax	Nonlinear	(6)(10)(12)(13) (14)(15)
Northey et al. [46] (a) (2019)	RCT. Single-center	I—III	5	6	T: 67.8 ± 7.0 C: 61.5 ± 7.8	Surgery, chemotherapy, radiation. Aromatase inhibitor	**Aerobic exercise modality:** Continuous. **Time:** 20 min/ sessions. **Frequency:** 3 sessions /w. **Duration:** 12w. **Intensity:** 55—65%VO_2max	Linear	(5)
Northey et al. [46] (b) (2019)	RCT. Single-center	I—III	6	6	T: 60.3 ± 8.1 C: 61.5 ± 7.8	Surgery. Radiation. Aromatase inhibitor	**Aerobic exercise modality:** High Intensity Aerobic Interval. **Time:** 20 min/ sessions. **Frequency:** 3 sessions /w. **Duration:** 12w. **Intensity:** 4 intervals in 1st w, increased by one each week until the target of 7 intervals was achieved in 4th w 50—90% VO_2max	Nonlinear	(5)
Fairey et al. [47] (2005)	RCT. Single-center	I—IIIA	24	28	T: 59 ± 5 C: 58 ± 6	Surgery, radiation, chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 15min for weeks 1 through 3, and then systematically increased by 5min every three weeks thereafter to 35 min for weeks 13 through 15. **Frequency:** 3 sessions /w. **Duration:** 15w. **Intensity:** 70—75% VO_2max	Nonlinear	(17)(18)(19)(20) (21)
Irwin et al. [48] (2015)	RCT. Single-center	0—III	45	38	T: 62 ± 7.0 C: 60.5 ± 7.0	Radiation, chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 150 min/w. **Frequency:** 2 sessions /w. **Duration:** 12m **Intensity:** started at 50% of HRmax and increased over the 1st month to 60% to 80% of HRmax	Linear	(5)

Table 1 (continued)

Study	Study design	Stage	Sample size		Age (years)	Cancer Treatment	Aerobic exercise protocol in Intervention Group	Principles of exercise	Outcomes
			T	C					
de Paulo et al. [49] (2018)	RCT. Single-center	I—III	18	18	T: 63.2 ± 7.1 C: 66.6 ± 9.6	Aromatase inhibitor therapy	**Aerobic exercise modality:** Continuous. **Time:** 1-2nd week: 20min. 3-36th week: 30min. **Frequency:** 3 sessions /w. **Duration:** 36w. **Intensity:** 1-2nd w: 50–60% HRmax. 3-10th w: 60–65% HRmax. 11-18th w: 65–70% HRmax. 19-28th w: 70–75% HRmax. 20-36th w: 75–80% HRmax	Linear	(10)(11)(12)(13)(17)(19)(20)(21)
Møller et al. [50] (a) (2015)	RCT. Single-center	I—III	9	10	T:57.17 ± 10.51 C: 46.95 ± 9.19	AC & TAX & CYC	**Aerobic exercise modality:** Continuous & Interval. **Time:** 60–90 min/ sessions. **Frequency:** 3 sessions /w. **Duration:** 12w. **Intensity:** 95–95% HRmax	Nonlinear	(5)(6)(11)(12)(13)
Møller et al. [50] (b) (2015)	RCT. Single-center	I—III	10	10	T: 48.49 ± 8.41 C:46.95 ± 9.19	AC & TAX & CYC	**Aerobic exercise modality:** Continuous. **Time:** 30 min/ sessions. **Frequency:** 5 sessions /w. **Duration:** 12w. **Intensity:** 70–75% HRmax	Linear	(5)(6)(11)(12)(13)
Ma et al. [51] (2018)	RCT. Single-center	-	31	33	T: 44 ± 6 C: 44 ± 6	AC	**Aerobic exercise modality:** Interval. **Time:** 50 min/ sessions. **Frequency:** 3 sessions/w. **Duration:** 16w. **Intensity:** Work: 90 -95% HRmax. Rest: 50 –70% HRmax	Linear	(5)(22)
Al-Majid et al. [52] (2015)	RCT. Single-center	I—II	6	7	T: 52.7 ± 10.7 C: 47.9 ± 10.4	Adjuvant chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 20–40 min/ sessions. **Frequency:** 1st w: 2 sessions, 2nd-12th w: 3 sessions/w. **Duration:** 12w. **Intensity:** 1st w: 40%—50% HRR. 2nd-3rd w: 50%—70% HRR. 4th -12thw: 70%—80% HRR	Nonlinear	(5)
Jones et al. [53] (2013)	RCT. Single-center	0 to IIIA	36	31	T: 56.4 ± 9.6 C: 55.4 ± 7.6	Adjuvant chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 15min for week 1, and then gradually increased minutes of exercise per week to 30 min for weeks 5 through 12. **Frequency:** 5 sessions/w. **Duration:** 6m. **Intensity:** started at 50% HRmax to 60%—80% HRmax	Nonlinear	(21)
Rogers et al. [54] (2009)	RCT. Single-center	I, II, or IIIA	20	19	T: 52 ± 15 C: 54 ± 8	Aromatase inhibitors or selective estrogen receptor modulators	**Aerobic exercise modality:** Continuous. **Time:** 40 – 45 min / sessions. **Frequency:** 1st -2nd week: 3 sessions/w. 3rd-6th week: 4 sessions/w. 7th -12th week: 5 sessions/w. **Duration:** 12w. **Intensity:** moderate intensity	Nonlinear	(6)(12)(16)
Dieli-Conwright et al. [55] (a) (2021)	RCT. Single-center	I—III; Hispanic ethnicity	28	24	T: 46.9 ± 10.2 C: 46.7 ± 10	Surgery, radiation, chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 5 min every 3–4 weeks resulting in a total of 45 min of aerobic exercise per session by 16th w. **Frequency:** 3 sessions/w. **Duration:** 16w. **Intensity: 65%-80%** HR max	Nonlinear	(5)
Dieli-Conwright et al. [55] (b) (2021)	RCT. Single-center	I—III; Non-Hispanic ethnicity	19	22	T: 55.6 ± 10.5 C: 55.9 ± 10.3	Surgery, radiation, chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 5 min every 3–4 weeks resulting in a total of 45 min of aerobic exercise per session by 16th w. **Frequency:** 3 sessions/w. **Duration:** 16w. **Intensity: 65%-80%** HR max	Nonlinear	(5)

Table 1 (continued)

Study	Study design	Stage	Sample size		Age (years)	Cancer Treatment	Aerobic exercise protocol in Intervention Group	Principles of exercise	Outcomes
			T	C					
Nuri et al. [56] (2012)	RCT. Single-center	I to IIIB	14	15	T: 58.27 ± 6.31 C: 58.27 ± 6.31	Hormone therapy	**Aerobic exercise modality:** Continuous. **Time:** Start with 25 min and increase by 10 min every 5 weeks. **Frequency:** 2 sessions/w. **Duration:** 15w. **Intensity:** **45%-65%** HR max	Nonlinear	(5)(6)(10)(14)(15)(16)(17)(20)
Lahart et al. [57] (2018)	RCT. Single-center	I—III	16	16	T: 52.5 ± 10.7 C: 52 ± 8.6	_	**Aerobic exercise modality:** Continuous. **Time:** 1st -3rd month: 30 min/sessions. 4th-6th month: > 30 min/sessions. **Frequency:** 1st -3rd m: 3–5 sessions /w. 4th-6th m: 5–7 sessions /w. **Duration:** 24w. **Intensity:** Moderate -vigorous	Nonlinear	(5)
Rogers et al. [58] (2013)	RCT. Single-center	I, II or IIIA	11	9	T: 58 ± 6.1 C: 53.7 ± 13.9	_	**Aerobic exercise modality:** Continuous. **Time:** 150 min/w. **Duration:** 12w. **Intensity:** Moderate intensity	Linear	(5)(6)(12) (16)
Guinan et al. [59] (2013)	RCT. Single-center	I—III	16	10	T: 50.05 ± 8.27 C: 45.05 ± 9.04	Adjuvant hormone therapy and anti-Her2 directed therapy	**Aerobic exercise modality:** Continuous. **Time:** 21-42min /sessions. **Frequency:** 21-42min /sessions. **Duration:** 8w. **Intensity:** 30%—75% HRR	Nonlinear	(15)(17)(18)(19)(20)
Herrero et al. [60] (2011)	RCT. Single-center	I—II	8	8	T: 50.05 ± 8.27 C:45.05 ± 9.04	CFM	**Aerobic exercise modality:** Continuous. **Time:** Gradually increased from 20 to 30min per session. **Frequency:** 2 sessions /w. **Duration:** 8w. **Intensity:** Gradually increased from 30 to 75% HRR	Nonlinear	(5)(10)(11)(12)
Ligibel et al. [61] (2008)	RCT. Single-center	I—III	42	40	T: 52 ± 9 C:53 ± 9	chemotherapy and/or radiation therapy	**Aerobic exercise modality:** Continuous. **Time:** 90 min / sessions. **Frequency:** 2 sessions /w. **Duration:** 16w. **Intensity:** Moderate intensity	Linear	(6)(10)(12)(14)(15)(16)
Lahart et al. [62] (2016)	RCT. Single-center	I—III	40	40	T: 52.4 ± 10.3 C: 54.7 ± 8.3	Radiation therapy and/or chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 30 min / sessions. **Frequency:** 5 sessions /w. **Duration:** 12w. **Intensity:** Moderate intensity	Linear	(6)(10)(12)(17)(18)(19)(20)
DeNysschen et al. [63] (2010)	RCT. Single-center	I—III	36	30	T: 48.7 ± 8.4 C: 49.5 ± 9.5	Chemotherapy	**Aerobic exercise modality:** Continuous. **Time:** 20–30 min / sessions. **Frequency:** 3–5 sessions /w. **Duration:** 4-6m. **Intensity:** 60–80% VO_2peak	Nonlinear	(10)(12)(13)
Kim et al. [27] (a) (2021)	Cohort trial. Single-center	-	11,154	7410	T: 50.9 ± 9.6 C: 53.1 ± 10.1	Radiotherapy, cardiotoxic chemotherapy, aromatase inhibitor, Tamoxifen	**Aerobic exercise modality:** Continuous. **Time:** 1–499 MET-mins/week. **Duration:** 5 year. **Intensity:** Low	Linear	(1)(2)(3)
Kim et al. [27] (b) (2021)			11,110	7410	T: 50.9 ± 9.4 C: 53.1 ± 10.1		**Aerobic exercise modality:** Continuous. **Time:** 1–499 MET-mins/week. **Duration:** 5 year. **Intensity:** Medium	Linear	(1)(2)(3)
Kim et al. [27] (c) (2021)			10,101	7410	T: 50.6 ± 8.4 C: 53.1 ± 10.1		**Aerobic exercise modality:** Continuous. **Time:** 1–499 MET-mins/week. **Duration:** 5 year. **Intensity:** High	Linear	(1)(2)(3)

Table 1 (continued)

Study	Study design	Stage	Sample size		Age (years)	Cancer Treatment	Aerobic exercise protocol in Intervention Group	Principles of exercise	Outcomes
			T	C					
Jones et al. [28] (a) (2016)	Cohort trial. Single-center	I—III	747	741	T: 56.6 ± 10.5 C: 58.7 ± 10.4	Surgery, chemotherapy, radiotherapy, tamoxifen or aromatase inhibitor	**Aerobic exercise modality:** Continuous. **Duration:** 5 year. **Intensity-Time:** 5.4 MET-h/week	Linear	(1)(2)(4)
Jones et al. [28] (b) (2016)			741	741	T: 57.2 ± 10.3 C: 58.7 ± 10.4		**Aerobic exercise modality:** Continuous. **Duration:** 5 year. **Intensity-Time:** 16.3 MET-h/week	Linear	(1)(2)(4)
Jones et al. [28] (c) (2016)			744	741	T: 55.4 ± 10.5 C: 58.7 ± 10.4		**Aerobic exercise modality:** Continuous. **Duration:** 5 year. **Intensity-Time:** 40 MET-h/week	Linear	(1)(2)(4)

(1) Cardiovascular disease events

(2) Coronary artery disease

(3) Stroke

(4) Heart failure

(5) VO_2max

(6) BMI

(7) the Reynolds risk score

(8) the metabolic syndrome z-score

(9) the Framingham Risk Scor

(10) Weight

(11) Fat mass

(12) BF%

(13) Lean mass

(14) Hip circumference

(15) Waist circumference

(16) Waist-to-hip ratio

(17) Triglyceride

(18) Total Cholesterol

(19) LDL–C

(20) HDL–C

(21) CRP

(22) LVEF(%)

W week, *M* months, *HRmax*: maximal heart rate

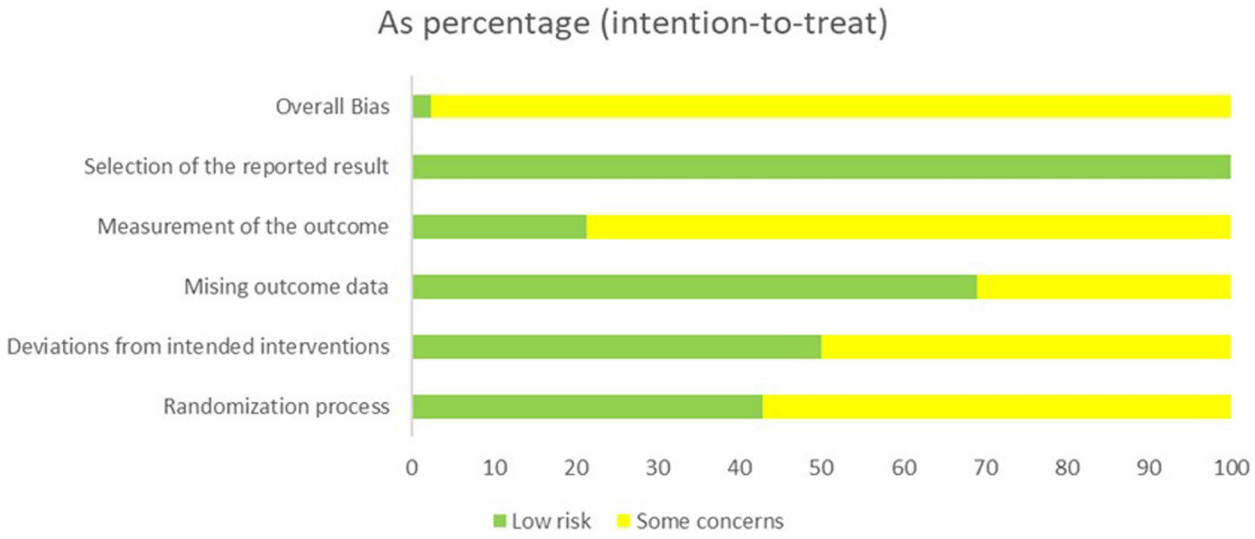

Fig. 2 Risk of bias of included RCTs

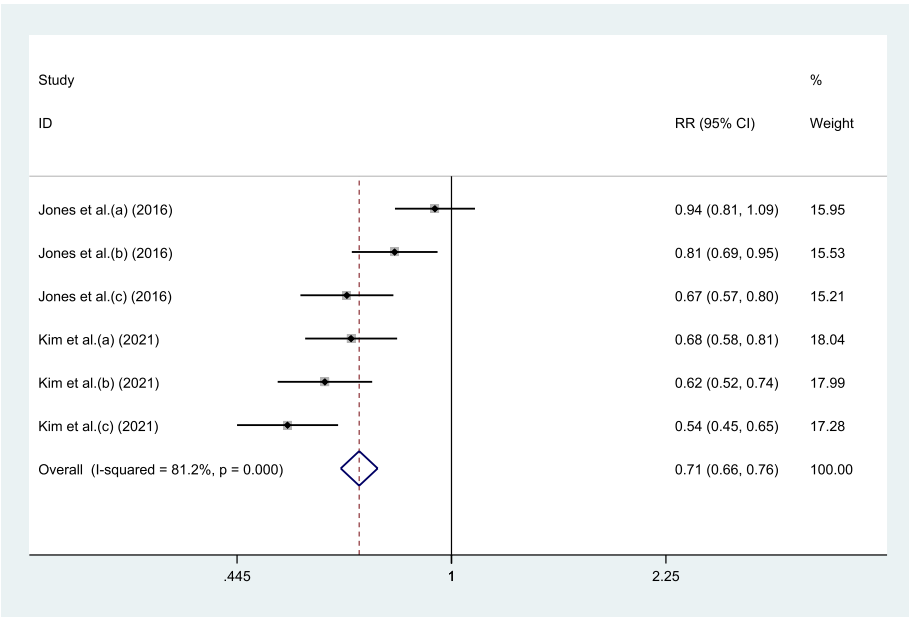

Fig. 3 Forest plot of cardiovascular disease (CVD) events in breast cancer (BC)

Effect of AE on body composition

Twelve RCTs [33, 38, 40, 42, 45, 50, 54, 56, 58, 61, 62] showed a consistent effect of AE on BMI, while the fixed-effect analysis showed no statistically significance. Eleven RCTs [33, 38, 42, 43, 45, 50, 56, 60–63] reported the effect of AE intervention on body weight in women with BC, and meta-analysis showed that AE significantly reduced body weight by 1.966 kg [95% CI (-3.839, -0.094), $p=0.040$] compared with the control group. Four RCTs [33, 45, 61, 64] reported the effect of AE intervention on the HC in women with BC, and meta-analysis showed that AE reduced HC by 2.742 cm [95% CI (-4.278, -1.206), $p=0.000$] compared with the control group. Four RCTs [45, 49, 59, 64] reported WC, four RCTs [54, 56, 58, 61] reported waist-to-hip ratio, and we performed a meta-analysis using a fixed-effects model, while the results showed the effect of AE intervention on the WC and waist-to-hip ratio was not statistically significant in BC patients. Seven RCTs [33, 40, 49, 50, 60, 65] reported the effect of AE intervention on fat mass, thirteen RCTs

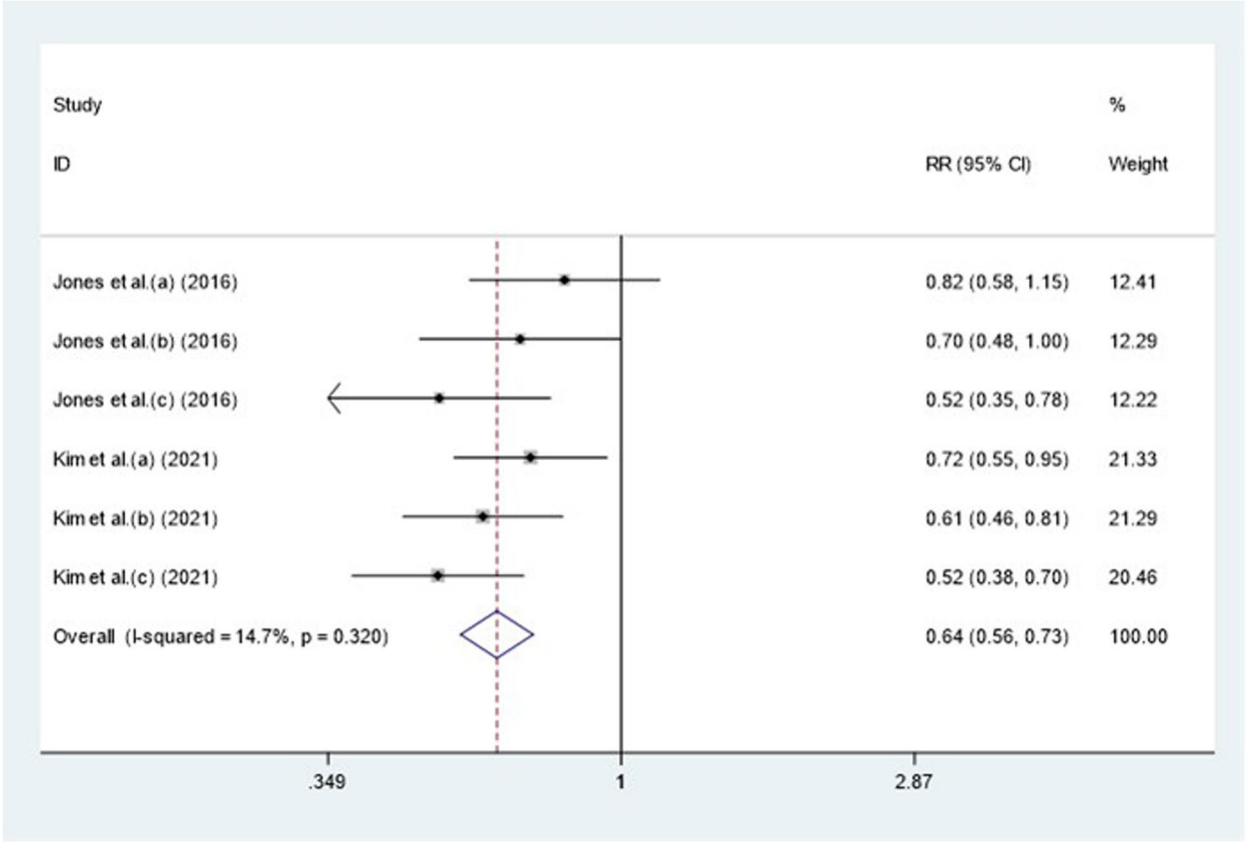

Fig. 4 Forest plot of coronary artery disease (CAD) events in breast cancer (BC)

[30, 33, 43, 45, 49, 50, 54, 58, 60–63] reported BF%, and seven RCTs [33, 43, 45, 49, 50, 63] reported lean mass. Because of the high heterogeneity of the meta-analysis, we performed subgroup analyses based on exercise training principles (linear exercise or nonlinear exercise). The meta-analysis results showed that nonlinear AE significantly reduced fat mass by 4.256 kg [95% CI (-3.839, -0.094), $p=0.04$], while the remaining results were not statistically significant. The results were shown in Supplementary Material 5.

Effect of AE on lipid profile

Five RCTs [47, 49, 56, 59, 62] reported the effect of AE intervention on triglyceride, and our meta-analysis using the fixed effect model showed no statistically significant results. Four RCTs [31, 47, 59, 62] reported the effect of AE on TC, and six RCTs reported HDL-C [31, 47, 49, 56, 59, 62]. Because of the high heterogeneity of their evidence, subgroup analyses based on principles of exercise training showed no statistical significance. Five RCTs reported LDL-C, two [49, 62] of which followed the linear design, and three [35, 47, 59] of which followed the nonlinear design. The results of the subgroup analysis we performed showed no statistically significant effect of nonlinear AE, while linear AE could reduce significantly the LDL-C by 8.534 mg/dL [95% CI (-15.511, -1.557), $p=0.017$]. The results were shown in Supplementary Material 5.

Effect of AE on LVEF

Four RCTs [29, 32, 41, 51] reported the effect of AE intervention on LVEF, three in the linear [29, 41, 51] AE design, and one [32] in the nonlinear AE design. The meta-analysis showed that compared to the control group, AE significantly increased LVEF by 7.081, [95% CI (1.891, 12.272), $p=0.007$]. The result was shown in Supplementary Material 5.

Effect of AE on C-reactive protein

Five [31, 41, 44, 47, 49] RCTs reported the effect of AE intervention on C-reactive protein, including two linear

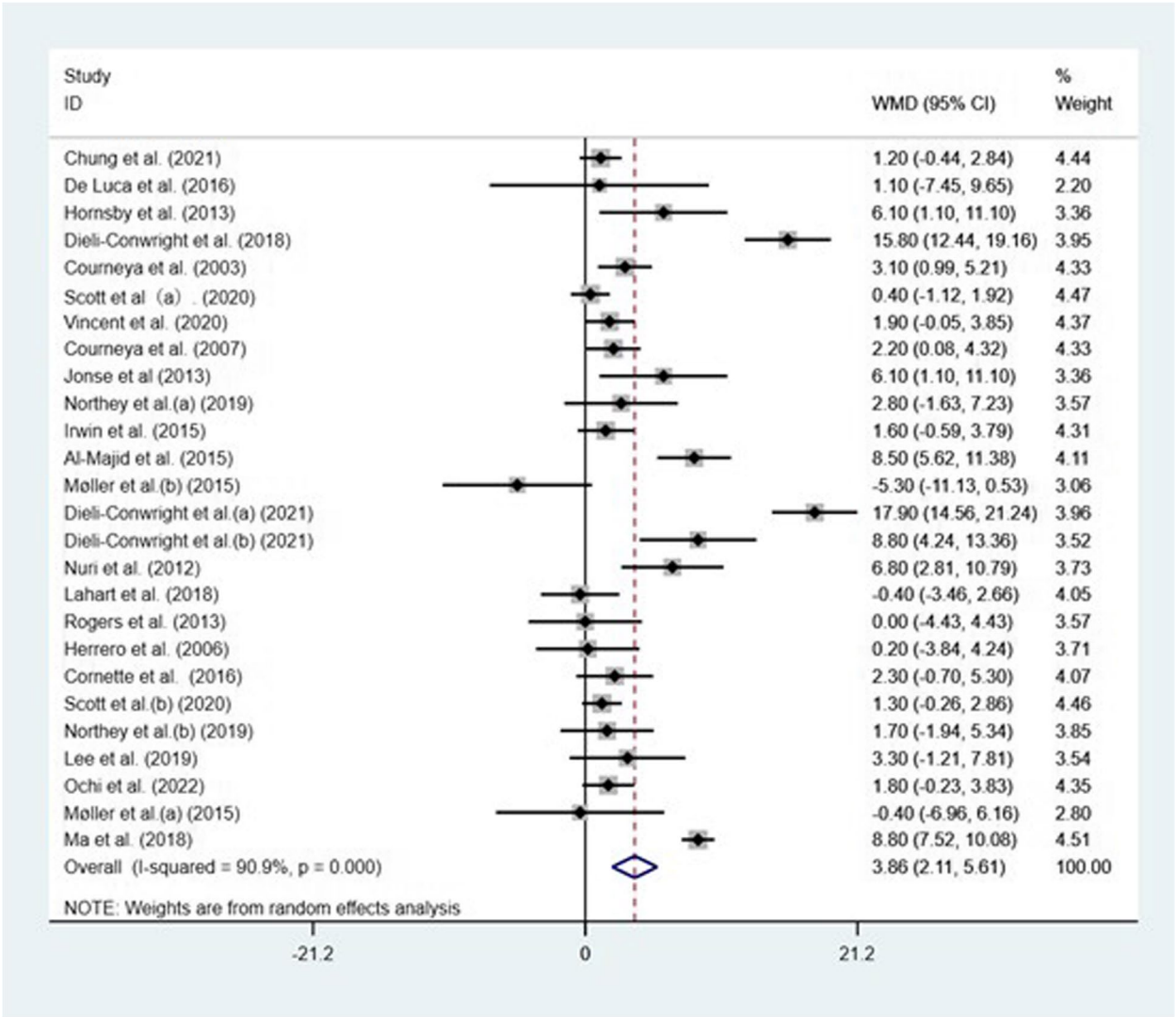

Fig. 5 Forest plot of maximum oxygen uptake (VO_2max) in breast cancer (BC)

exercise design trials and four nonlinear exercise design trials. We performed subgroup analysis and found that the effect of either linear AE design or nonlinear AE design on c-reactive protein in women with BC was not statistically significant. The result was shown in Supplementary Material 5.

Publication *bias*

We assessed the publication bias with funnel plots and Egger's test. The asymmetry of the funnel plots and Egger's test suggest that VO_2max ($P=0.848$) and weight ($P=0.14$) had no significant risk of publication bias, while the BMI ($P=0.028$) and BF% ($P=0.032$) may have moderate publication bias. The funnel plots were shown in Supplementary Material 6.

We performed the meta-trim-fill analysis of the outcomes with publication bias. The combined effect value of BMI before the meta-trim-fill was -0.09 [95% CI (-0.249, 0.069)], and after the meta-trim-fill was -0.215 [95% CI (-0.36, -0.069)]. There was some difference in the combined effect value before and after the meta-trim-fill, suggesting that the BMI outcome may be subject to publication bias and that the result was less stable. The combined effect value of BF% before the meta-trim-fill was -0.146 [95% CI (-0.458, 0.166)], and after the meta-trim-fill was -0.264 [95% CI (-0.554, 0.026)]. The difference between the results before and after the meta-trim-fill was small, suggesting that the effect of publication bias on BF% was small. The two meta-trim-fill plots were shown in Supplementary Material 6.

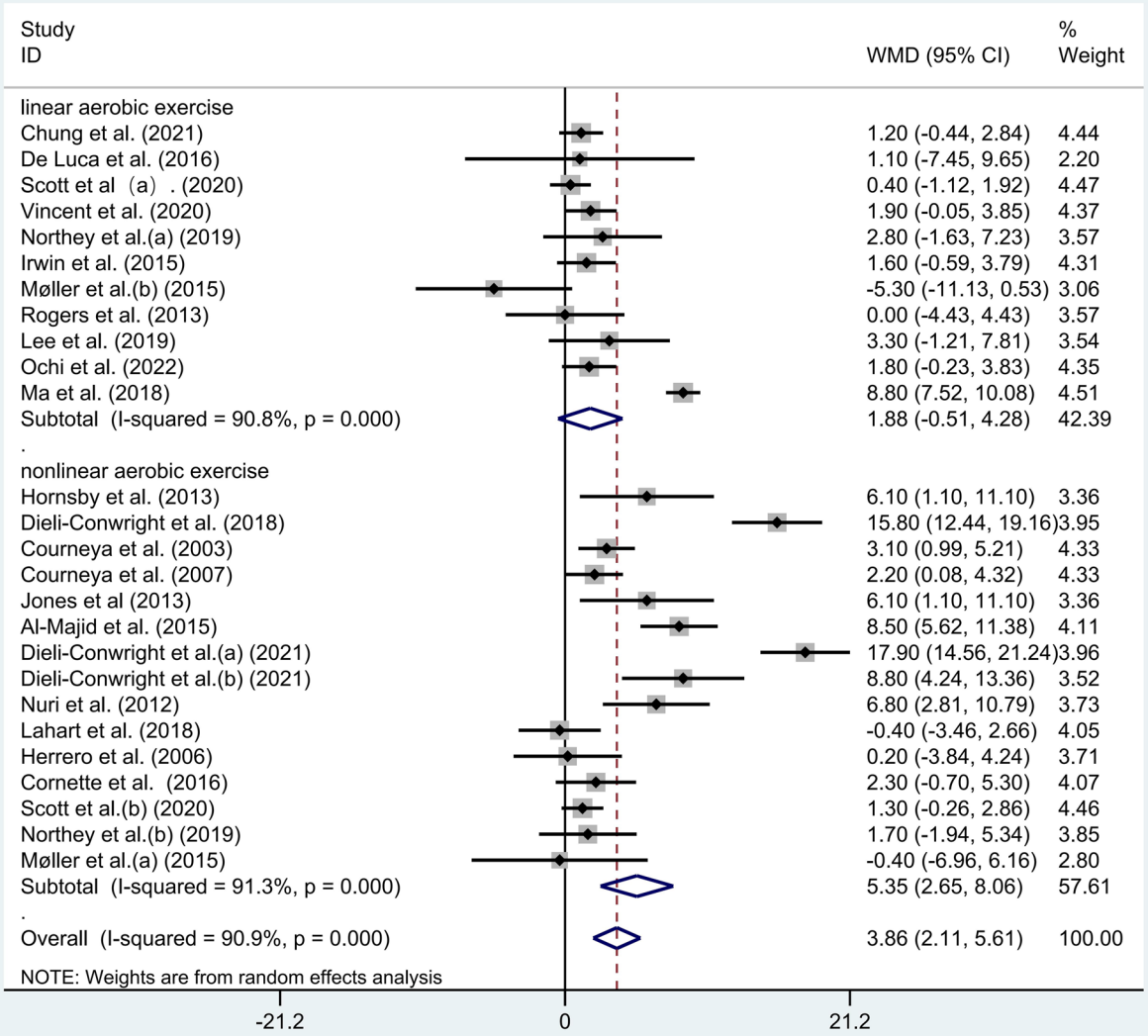

Fig. 6 Forest plot of maximum oxygen uptake (VO_2max) subgroup analysis in breast cancer (BC)

Sensitivity analysis

To determine the impact of each trial on the effect index in highly heterogeneous outcomes, we used a sensitivity analysis in our meta-analyses. Finally, we did not observe the significant effects of any individual trial, as shown in Supplementary Material 7.

Certainty of evidence

We assessed 24 synthesized pieces of evidence with GRADE. A total of 10 of these outcomes were assessed as low certainty, and fourteen were very low certainty. The main reasons to downgrade the quality of evidence are the unsatisfactory risk of bias, the limited sample size of included trials, and high statistical heterogeneity. The summary of findings is shown in Table 2.

Discussion

Meta-analysis of trial results

In this study, we retrieved as many RCTs as possible and performed the meta-analyses to assess the effect of AE on cardiovascular risk factors in female BC and divided them into linear AE and nonlinear AE for subgroup analyses based on exercise training principles. AE reduced the risk of CAD events in female BC. In terms of body composition, AE reduced body weight

Table 2 Evidence profile

Outcome No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		The control	Aerobic Exercise	Difference	
The occurrence of CVD events No. of participants: 59,050 (6 cohort trials)	RR 0.706 (0.659 to 0.757)	3.63%	6.23%	1.6% fewer (1.9 fewer to 1.3 fewer)	Low
The occurrence of CAD events No. of participants: 59,050 (6 cohort trials)	RR 0.640 (0.561 to 0.729)	2.0%	1.1%	0.7% fewer (0.9 fewer to 0.5 fewer)	Low
VO_2max of linear exercise training No. of participants: 517 (11 RCTs)	-	Mean: 22.706 ml·kg·min^{-1}	-	MD 1.884 ml·kg·min^{-1} more (0.514 fewer to 4.283 more)	Very low[a,c]
VO_2max of nonlinear exercise training No. of participants: 699 (15 RCTs)	-	Mean: 27.047 ml·kg·min^{-1}	-	MD 5.354 ml·kg·min^{-1} more (2.645 more to 8.062 more)	Very low[a,c]
BMI No. of participants: 650 (12 RCTs)	-	Mean: 28.502 kg·min^{-2}	-	MD 0.603 kg·min^{-2} fewer (1.366 fewer to 0.160 more)	Very low[a,d,e]
Weight No. of participants: 733 (11 RCTs)	-	Mean: 72.872 kg	-	MD 1.966 kg fewer (3.839 fewer to 0.094 fewer)	Low[a,e]
Fat mass of linear exercise training No. of participants: 137 (3 RCTs)	-	Mean: 25.076 kg	-	MD 1.043 kg fewer (4.808 fewer to 2.722 more)	Low[a,b]
Fat mass of nonlinear exercise training No. of participants: 272 (4 RCTs)	-	Mean: 25.426 kg	-	MD 4.256 kg fewer (7.826 fewer to 0.685 fewer)	Very low[a,b,c]
BF% of linear exercise training No. of participants: 258 (6 RCTs)	-	Mean: 39.908	-	MD 0.380 more (1.274 fewer to 2.035 more)	Low[a,b]
BF% of nonlinear exercise training No. of participants: 452 (7 RCTs)	-	Mean: 36.801	-	MD 1.748 fewer (4.751 fewer to 1.256 more)	Very low[a,b,c]
Lean mass of linear exercise training No. of participants: 56 (2 RCTs)	-	Mean: 36.636 kg	-	MD 1.774 kg fewer (4.011 fewer to 0.464 more)	Very low[a,b]
Lean mass of nonlinear exercise training No. of participants: 397 (5 RCTs)	-	Mean: 44.762 kg	-	MD 0.901 kg more (2.293 fewer to 4.095 more) kg	Very low[a,b,c]
Hip circumference No. of participants: 279 (4 RCTs)	-	Mean: 85.386 cm	-	MD 2.742 cm fewer (4.278 fewer to 1.206 fewer)	Low[a,b]
Waist circumference No. of participants: 212 (4 RCTs)	-	Mean: 89.783 cm	-	MD 1.170 cm fewer (4.838 fewer to 2.498 more)	Low[a,b]
Waist-to-hip ratio No. of participants: 170 (4 RCTs)	-	Mean: 0.827	-	MD 0.011 fewer (0.035 fewer to 0.013 more)	Low[a,b]
Triglyceride No. of participants: 223 (5 RCTs)	-	Mean: 64.367 mg/dL	-	MD 0.315 mg/dL fewer (3.909 fewer to 3.278 more)	Low[a,b]
Total Cholesterol of nonlinear exercise training No. of participants: 171 (5 RCTs)	-	Mean: 131.384 mg/dL	-	MD 9.577 mg/dL fewer, (42.059 fewer to 22.906 more)	Very low[a,b,c]
LDL-C of linear exercise training No. of participants: 116 (2 RCTs)	-	Mean: 78.579 mg/dL	-	MD 8.534 mg/dL fewer (15.511 fewer to 1.557 fewer)	Low[a,b]
LDL-C of nonlinear exercise training No. of participants: 171 (3 RCTs)	-	Mean: 92.744 mg/dL	-	MD 12.895 mg/dL fewer (59.432 fewer to 33.641 more)	Very low[a,b,c]
HDL-C of linear exercise training No. of participants: 116 (2 RCTs)	-	Mean: 35.938 mg/dL	-	MD 0.156 mg/dL more (2.138 fewer to 2.449 more)	Very low[a,b]
HDL-C of nonlinear exercise training No. of participants: 200 (4 RCTs)	-	Mean: 48.654 mg/dL	-	MD 6.997 mg/dL more (8.341 fewer to 22.335 more)	Very low[a,b,c]
CRP of linear exercise training No. of participants: 83 (2 RCTs)	-	Mean: 3.705 mg/dL	-	MD 0.502 mg/dL fewer (2.651 fewer to 1.646 more)	Very low[a,b]
CRP of nonlinear exercise training No. of participants: 212 (3 RCTs)	-	Mean: 2.661 mg/dL	-	MD 0.879 mg/dL fewer (2.388 fewer to 0.629 more)	Very low[a,b,c]

Table 2 (continued)

Outcome No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		The control	Aerobic Exercise	Difference	
LVEF(%) No. of participants: 227 (4 RCTs)	-	Mean: 63.697	-	MD 7.081 more (1.891 more to 12.272 more)	Very low[a,b,c]

CI confidence interval, *MD* mean difference, *RCTs* randomized controlled trials

[a] All studies were assessed as having 'Some concerns' risk of bias

[b] Small study sample size

[c] Statistical heterogeneity exists, $I^2 > 50\%$

[d] Publication bias

[e] Clinical heterogeneity exists

The bold was generated in the original form of the SoF table in the GRADE system

and HC, whereas nonlinear AE reduced fat mass, but had no significant effect on other body components (BMI, lean mass, BF%, waist-to-hip ratio, and WC). The development or maintenance of lean mass (through AE) is an important component of weight management, can help prevent an age-associated decline in metabolic rate and gains in fat mass [63]. The reason for non-significant differences in percent body fat and could be attributed to factors such as dietary intake. As participants progressed through cancer treatment and during post treatment, the exercise may have caused an increase in appetite and subsequent increase in calorie intake. Therefore limiting nutritional intake (i.e. total calories) during exercise is essential for body composition management in BC patients. Other reasons for the lack of significant changes in body fat composition, waist circumference and waist-to-hip ratio may be attributed to the fact that weekly exercise time may not have been sufficient in the intervention group. The total minutes of exercise per week in the AE groups ranged from 90 to 180. This falls short of the report guidelines published in the America [66] of 180 to 300 min per week of beneficial body composition changes.

AE can improve cardiorespiratory fitness by increasing VO_2max, especially for nonlinear AE. AE had no significant effect on CRP and lipid profile (TC, TG, and HDL-C), but linear AE reduced LDL-C. A study directly comparing linear and nonlinear AE in cancer patients found that nonlinear AE resulted in more significant improvements in cardiorespiratory and physical function and a greater reduction than a linear exercise in nausea, vomiting, pain, and severity of adverse effects such as physical fatigue, which supports our findings [20]. We found that AE training significantly increased LVEF compared with controls, which is consistent with a previous systematic review of exercise interventions [67]. The four clinical trials involved included three linear AE training (two for continuous AE and one for intermittent AE) and only one clinical trial of nonlinear AE, and the effects of different exercise types on LVEF still need to be studied in large-scale clinical trials.

Strength and limitations

This is the first systematic evaluation and meta-analysis exploring the effects of AE intervention, particularly exercise design principles, on cardiovascular risk factors in female BC. Previous studies [16, 18, 68] have demonstrated the feasibility, safety, and overall effectiveness of aerobic training for patients with BC; however, there is no consensus regarding the most appropriate training mode to optimize training-induced adaptations. Most studies involving BC patients have prescribed aerobic training based on guidelines from the Clinical Society of Oncology of Australia (COSA) [69], the American College of Sport Medicine (ACSM) [66], and the American Cancer Society (ACS) [70]. Although it has been shown that AE can significantly improve patients' cardiorespiratory endurance, there are more training modes involving linear AE and fewer training modes involving nonlinear AE.

The present meta-analysis has some limitations. There is a high degree of heterogeneity in some results in this article and we believe that the sources of heterogeneity are as follows. According to our classification, one source of bias in the analysis was the method of assessment of cardiorespiratory fitness. Four studies [32, 34, 46, 51] indirectly assessed VO_2max, so there was a small probability of bias regarding the prescribed training intensity and the training-induced increase in VO_2max. This is because some of the trials included in some studies had small sample sizes and there was some risk of bias in several trials. Second, the number of long-term trials conducted is very limited and larger, longer-duration trials are needed to explore the effects of AE on long-term cardiovascular disease risk management. In addition, the risk of bias in

the included trials needs to be considered, which seems to be mainly related to the difficulty of measuring the outcomes. Therefore, it is important to note that the bias assessment of these projects does not reflect the low quality of the study design, but rather expresses the unavoidable bias introduced by the lack of blinding of outcome assessors. Therefore, larger and better-blinded controlled trials should be conducted to properly address this issue.

Perspectives for future research

It is difficult to draw definitive conclusions because the quality of the pooled studies was not high. Nevertheless, our study suggests that AE reduces the risk of CVD and CAD events in female BC and has a positive effect in reducing body weight and HC and improving cardiorespiratory endurance. In terms of exercise design principles, nonlinear AE had a positive effect in reducing fat mass and improving cardiorespiratory endurance, but linear AE showed a positive effect in reducing LDL-C. AE may be an active strategy to effectively reduce cardiovascular risk factors in BC patients and provide options for the development of exercise rehabilitation programs for BC patients. In future, clinical trials (randomized, controlled, blank-controlled), the design and implementation process should take full account of the AE protocol design principles.

Conclusion

In summary, our findings indicated that AE increases the VO_2max in women with BC improving LVEF, and body composition (weight, HC). But there may be no difference regarding the lipid profile (TG, TC, HDL-C), and CRP. We also showed that nonlinear AE training is effective at increasing the VO_2max and reducing the fat mass in female BC. Therefore, high-quality and long-term RCTs are needed to provide data on the persistence of the effect and to strengthen the certainty of the evidence.

Abbreviations

BC	Breast cancer
CS	Cohort studies
AE	Aerobic exercise
US	Usual care
RCTs	Randomized controlled trials
CVD	Cardiovascular disease
CRF	Cardiopulmonary fitness
HC	Hip circumference
WC	Waist circumference
VO_2max	Maximal oxygen consumption
LVEF	Left ventricular ejection fraction
BMI	Body mass index
BF%	Body fat percentage
TC	Total cholesterol
TG	Triglyceride
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
CRP	C reactive protein
NOS	Newcastle-Ottawa Scale
SoF	Summary of findings

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20592-9.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.

Acknowledgements

Not applicable.

Authors' contributions

In this paper, Qian Jiao and Bowen Xu have contributed equally to this study. Jiang Li, Min Yang and Haixia Li designed this study; Qian Jiao registered the protocol; Shanshan Li, Fan Xu, Jiayi Zhong ran the search strategy; Qian Jiao and Bowen Xu performed the screen, inclusion, and quality assessment of the included trials. Qian Jiao, Bowen Xu and Chao Meng conducted the meta-analysis. Qian Jiao and Bowen Xu drafted the first version of this manuscript; Jiang Li and Bowen Xu provided critical revisions and edited the manuscript. Haixia Li revised the manuscript. All authors have approved the final article.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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