

The impact of lifestyle interventions on therapy associated side effects in postmenopausal breast cancer survivors: systematic reviews and meta-analysis

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Abstract

Background: Medically Supervised Exercise (MSE) are advisable for the prevention and treatment related side effects among breast cancer survivors. Aerobic and resistance either exercise, separately or in combination, have been shown to improve physical functioning and manage some symptoms in breast cancer patients. However, the level of evidence on the effects of lifestyle interventions on therapy related adverse events and the required dose responses of exercises are not yet systematically reviewed. This review was conducted to assess the efficacy of medically supervised exercises(MSE) coupled with diet in preventing/managing aromatase inhibitors induced adverse events and improving range of motion(ROM) and health related quality of life (HRQOL) in postmenopausal breast cancer patients following treatment.

Methods: Two independent authors extracted data using PRISMA guidelines of published clinical trials. We searched the Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, EMBASE, as well as clinical practice guidelines. We included only randomized controlled trials that examined exercise interventions coupled with diet interventions in postmenopausal breast cancer women. Health related quality of life (HRQOL) and range of motion were assessed as the main outcomes.

Results: Random effects meta-analysis was conducted for pooling of the effect size. The age of patients varied from 50 to 60 years. The results illustrate that the mean difference (MD) in improving ROM in the MSE group versus no supervised exercises was 1.35% (95% CI: 0.63 to 2.07%, $P = 0.0002$; heterogeneity: $\text{Tau}^2 = 0.71$; $\text{Chi}^2 = 112.14$, $\text{df} = 5$ ($P < 0.00001$); $I^2 = 96\%$). A summary of the data shows that supervised exercises significantly improved ROM and HRQOL in postmenopausal BCS on endocrine therapy compared to no supervised exercises 3.02 (95% CI: 2.59 to 3.45, $P < 0.00001$). These outcomes show that lifestyle interventions (MSE +diet) have positive effects on AI-associated adverse events and likely improve ROM and HRQOL in postmenopausal BC patients.

Conclusion: The evidence was based on a body of research with moderate study quality. Moreover, further studies are recommended to assess the effect of lifestyle interventions on markers of inflammation as the predictors of treatment non-response and associated comorbidities.

Background

Breast cancer (BC) is a major public health challenge globally with the greatest ramifications in low and middle-income countries [1]. GLOBACAN 2012 data indicate that 25% of women were diagnosed with BC worldwide (an estimated 1.7 million cases), and 521,900 related deaths [2]. With this devastating statistics, BC remains an ongoing clinical challenging. BC treatment is multidisciplinary, including surgery, radiation therapy, endocrine therapy and chemotherapy [1]. The two widely used endocrine therapies are aromatase inhibitors (AIs) and tamoxifen, depending to anatomical pathological classification and menopausal status. AIs are the more effective standards of care for long-term estrogen suppression and reduction of risk recurrence in postmenopausal women as compared to premenopausal women [3]. Adherences to endocrine therapy among BC patients ranges from 79.6% at 1 year to 68.3% at 5 years.

Non-adherence to endocrine therapy among BC patients is well acknowledged and associated with both morbidity and mortality [4]. However, estrogen deprivation therapy accompanies various adverse events which are associated with late complications associated with poor prognosis in BCS following a number of treatment strategies [5].

A meta-analysis conducted by Dent et al., (2011) revealed that AIs increase disease free survival (DFS) and overall survivorship (OS) when sequentially administered for 2–3 years following 2–3 years of tamoxifen therapy [6]. Similarly, their use after 5 years of tamoxifen treatment also produces an increase in DFS. As for OS, a clinical and statistical difference may be obtained only when AIs are administered after 2–3 years of tamoxifen treatment. In comparison with tamoxifen, AIs reduce the incidence of thromboembolic and gynaecologic side effects, however, increases body mineral density (BMD) adverse events [6]. Although the impact of adjuvant endocrine therapy related side effects are documented to be associated with both BC recurrence and cardiovascular diseases (CVD) risk [7], medically supervised exercises (MSE) programs have been suggested to be beneficial among postmenopausal BC patients on different BC treatment strategies [8]. While multiple adjuvant therapies are used to manage endocrine related adverse events, current treatment is focused on interventions in patients who already developed symptoms (tertiary prevention) rather than primary prevention.

Diverse risk factors have an impact on Health Related Quality of Life (HRQOL) due to significant functional, psychosocial and metabolic disturbances. Obesity as one of risk factors may require interventions (healthy diet intake and MSE) programs as one of treatment strategies to improve HRQOL in postmenopausal BCS [9, 10]. These exercises aim to restore upper limb function, range of motion (ROM) and muscle strength, and reduce comorbidities associated with BC surgery, radiation therapy and AIs [9]. Current clinical practice for exercises recommended by the American Cancer Society (ACS) [9] and American College of Sports Medicine (ACSM) [10], suggest that aerobic exercises of 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity or an equivalent combination should be initiated for each BCS upon physician fitness examination. For muscle strength, at least moderate intensity resistance exercises (2 days/week) should be performed for each major muscle group. A review revealed that exercise may be beneficial in reducing treatment-related adverse outcomes among cancer patients [9]. Moreover, cancer type-specific exercises, clinical heterogeneity, lack of blinding in many trials, frequency and exercise mode, unknown level of evidence, and timing of exercise regimen are not yet evaluated for evidence based clinical recommendations. Understanding the role of exercise in side effect prevention in postmenopausal BC patients will assist in developing more effective therapy guidelines.

The relationship between lifestyle risk factors and BC recurrence has not been specifically studied in postmenopausal BCS using adjuvant endocrine therapy such as AIs. Given that BMI > 30 kg/m² is a consistent risk factor associated with various side effects among this population. The lifestyle modifications which aim at preventing disease recurrence, typically defined as a relapse event at a local, regional, or distal site, have consisted of a healthy diet, nutritional supplements, regular exercise, or some combination of these components [10]. Therefore, this systematic review and meta-analysis were conducted to assess the efficacy of current recommended lifestyle interventions (MSE + diet) in

preventing Als-induced adverse events in postmenopausal BCS subjected to different BC treatment strategies.

Methods

Ethics proclamations

No Ethics clearance is required to conduct a systematic review and meta-analysis. The primary studies included in this review were approved by the respective national Ethics Committees. The first author performed this verification.

Search strategy and selection criteria

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [11]. We conducted a review of the literature in PubMed/Medline, Embase and the Cochrane Breast cancer registry. The study included only randomised controlled trials (RCTs) investigating the efficacy of MSE programs describing mode of exercises, frequency, length of follow up, and HRQOL scores were computed for meta-analysis. Only English and French published RCTs on the effects of MSE based on ACS and ACSM for cancer survivors were included in the present study. We used the search term: (Breast cancer treatment side effects [MESH] OR BC [MESH]) AND (supervised exercise program OR mentored exercise program) AND (quality of life [tw] OR QOL [tw] endocrine therapy [tw]).

Eligibility criteria were established using the participants, interventions, comparator and outcomes (PICO) framework:

Participants: All randomised controlled trials (RCTs) conducted to assess the effects of lifestyles interventions, which include diet and MSE based on ACSM or ACS guidelines including postmenopausal BCS. The most common adverse events associated with endocrine therapy, surgery, radiation therapy and the study authors of each primary study defined chemotherapies. We excluded animal and in vitro studies.

Interventions: RCT studies involving postmenopausal BC following different BC management strategies with a detailed MSE program (frequency, duration, ROM, types of exercises) coupled with diet or other BC management strategies including endocrine therapies (Als, tamoxifen (TAM)). Studies in which mean difference (MD), relative risk, risk ratio, odd ratios and HRQOL tools used to measure the level of disability were extracted and compared between intervention and control groups without years and settings restriction.

Comparators: Studies involving standard exercises initiated to mitigate Als side effects reported in the literature without medical supervision or other conventional recommended unstructured rehabilitative strategies in postmenopausal BCS or self-reported QOL questionnaires.

Outcome measures

Primary outcomes: Prevention and management of symptoms of Als-associated adverse events/ TAM commonly reported in the literature; such as limited ROM, inflammation and grip-strength.

Secondary outcomes included improved in HRQOL measured with a validated and standardized HRQOL questionnaire which including three dimensions: physical function, psychosocial wellbeing and emotional factors. These may include international classification of functionality (ICF) questionnaire.

Exclusion criteria

Studies including premenopausal women, men, pharmacological interventions, and traditional medicines. Individual studies, non-randomized studies, case controls, duplicated studies, narrative reviews, grey literature, no defined exercise interventions, studies without control groups, case studies, case reports, cross-sectionals and qualitative studies.

Screening and data abstraction

Two medical reviewers (JPM, JM) independently selected the study abstracts and full articles, and risk of bias was performed using standard tools. A third reviewer was consulted if there were disagreements, and such disagreements were resolved by commitment. Clinical heterogeneity was assessed by comparing the study designs, settings, sample sizes, countries of publication, methods used for diagnosis and measurement of outcomes. Random effects meta-analysis was conducted for pooling of the effect size. Statistical heterogeneity was evaluated, using chi-square test of homogeneity and I^2 statistical tests were conducted on quantitative data. Subgroup analysis was conducted for different tools used to measure the side effects associated with both postmenopausal status and Als. Articles were classified as potentially eligible if the titles indicated an RCT on the prevention of side effects associated with BC treatment. If no judgment could be made about the eligibility of a study based on the title, the judgment was based on its title and abstract. Any disagreements about eligibility were resolved at consensus meetings. The same procedure was applied for references included in this systematic review. Review articles identified in the search were screened for relevance and reference lists were checked to identify additional potentially eligible studies. Final decisions about inclusion of all articles judged potentially eligible was based on the full texts of the published articles.

Quality assessment and personal study quality

Two reviewers independently assessed the quality of ten eligible studies (Table 1). Risk of bias was conducted, using the Cochrane risk of bias tool for the appraisal of RCTs, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [12]. The tool contains six domains and each domain was assigned a judgement related to the risk of bias (Table 2 and Figure 1). The judgement could be 'low risk', 'high risk', or 'unclear risk'. The latter judgement was assigned if the risk of bias of a characteristic in an included study was judged to be unclear, or if there was insufficient information on

which to base the judgement. We compared excel datasets between two data extractors and a third reviewer was consulted to resolve discrepancy. A summary of the risk of bias is reported in (Table 2). All analyses were performed using Review Manager Software. Figure 2 shows PRISMA guideline for reporting systematic reviews.

Results

The search strategy identified 4 422 reports. After screening the articles based on inclusion criteria. A total of 109 were assessed for final screening. From these, 68 duplicates and without pre and post measurements, 5 did not describe the exercise programs, 7 did not report control groups. Fourteen were reported in narrative synthesis because of high degree of heterogeneity and 10 were considered for meta-analysis. No adverse events were reported in the included studies. Resistance and aerobic exercises were common among the selected studies. The authors described the mode and frequency of each component of exercises regimen as recommend by ACSM.

NARRATIVE SYNTHESIS

Effects of MSE on arthralgia and bone mineral density in postmenopausal BCS on Als-associated adverse events

Arem *et al.*, (2016) conducted a study to assess the effects of MSE (150 minutes/week of moderate-intensity aerobic exercise and twice-weekly MSE) on arthralgia, or joint pain in postmenopausal BCS taking Als. Authors concluded that the patients are able to initiate and maintain a yearlong MSE exercise program, regardless of other factors that influence activity levels. This is because MSE have shown to improve Al-associated arthralgia [13]. Nyrop *et al.*, (2017) confirmed the similar results [14]. According to Fields *et al.*, (2016) nordic walking as a structured exercise program should be used to reduce pain associated with Als-induced arthralgia in postmenopausal BCS in Als [15]. Knobf *et al.*, (2016) evaluated the effects of a 12-month MSE program (3 times/week) compared to a home-based physical activity group on BMD and biomarkers of bone turnover in postmenopausal BCS taking Als coupled with vitamin D and calcium [16]. No significant difference in BMD was observed for MSE group vs home-based group. However, patients on TAM or no endocrine therapy did not significantly lose BMD, with the exception of the femoral neck [16]. In contrast, patients on Als had significant BMD loss at different levels. The majority of BCS had sufficient serum level of Vitamin D (>20 ng/mL) but there was significantly less bone loss in BCS in the 20-29 ng/mL range at the LS ($p = 0.01$), hip ($p = 0.03$), and GT ($p = 0.008$) compared to lower or higher levels [16].

In a study conducted by Peppone *et.al* (2015) demonstrated that among BCS on endocrine ([Als] or tamoxifen [TAM] on yoga exercises that there are greater reductions in musculoskeletal symptoms such as general pain, muscle aches and total physical discomfort from pre- to post-intervention than the control group (all $p \leq 0.05$). The severity of musculoskeletal symptoms was higher for Al users compared to TAM users. The authors concluded that the community-based yoga program significantly reduced general pain, muscle aches, and HRQO [17]. DeNysschen et al. (2014) who assessed the effects of MSE

program in reducing joint pain and improving HRQOL identified similar results. In addition, MSE reduced joints pain, depressive symptoms, and upper limb mobility and improved in HRQOL among BCS on Als. However, no significant difference changes in cardiovascular endurance or in anthropometric measures were not observed between two groups [18].

Thomas *et al*, (2017) identified that MSE group relative to the usual care group had a significant increase in lean body mass (0.32 vs. -0.88 kg, $p = 0.04$), a decrease in percent body fat (-1.4% vs. 0.48%, $p = 0.03$), and a decrease in BMI (-0.73 vs. 0.17 kg/m², $p = 0.03$). Change in BMI was not different between two groups (0.001 vs. -0.006 g/cm², $p = 0.38$) [8]. Winters-Stone *et al*. (2011) identified that the survivors on MSE program preserved BMD at the lumbar spine (0.48 vs. -2.14%; $p = 0.002$) comparing to usual care ($p = 0.01$) [19]. Lifestyle interventions, which include exercises and healthy diet intake, reduced risk factors for osteoporosis (obesity, BMD) among postmenopausal BCS and may be particularly beneficial for BCS on Als because of the effects of MSE on muscle mass that may reduce CVD risk factors and joint pain [19]. The above results were also confirmed in four other trials [20 - 23].

Effects of diet and MSE on Als-induced obesity in postmenopausal BCS.

Goodwin *et al.*, (2014) evaluated the effects of lifestyles interventions (telephone based dietary education) to reduce obesity-induced Als adverse event. The authors found that MSE coupled with dietary interventions significantly reduced weight gain ($p < .001$) greater in intervention group versus the usual care (4.3 v 0.6 kg or 5.3% v 0.7% at 6 months and 3.1 v 0.3 kg or 3.6% v 0.4% at 24 months) and occurred consistently across strata (BMI 24 to < 30 v ≥ 30 kg/m (2); prior v no prior adjuvant chemotherapy). The authors concluded that telephone-based lifestyle interventions were effective in reducing weight loss, HRQOL in postmenopausal BCS on Als [24]. In addition, Zanardi *et al.*, (2012) found that lipid profile was significantly improved by AP vs. diet: 1.8% decrease in total cholesterol on diet and a further 15.3% decrease with AP vs. diet ($P < 0.001$); a 3.1% decrease in LDL cholesterol after diet and an 18.9% decrease after AP treatment vs diet alone ($P < 0.01$) [25]. A 1year follow-up study on postmenopausal BCS taking endocrine therapy have shown that both home diet based on food naturally high in proteins, calcium, probiotics and prebiotics (D), or this diet and 4' isometric exercises (D+MSE) significantly reduced BMI and fat loss. D patients lost 3.3 kg, 3.2% BF and 1% visceral fat. D+MSE patients lost 6.5 kg, 3.3% body fat 2%, visceral fat. The authors therefore concluded dietary and MSE interventions are effective for ER+/PR±/HER2- BCS on antiestrogenic therapies. Adjunctive MSE program also can be used for anti-drug side effects prevention to counteract sarcopenic obesity [26].

Effects of exercises on treatment induced side effects among postmenopausal BCS with metabolic syndrome

Two RCTs evaluated the effects of exercises on treatment-induced side effects among postmenopausal BCS with CVD related risk factors. The first study after 15 weeks follow up revealed exercise programs may improve metabolic syndrome profiles in postmenopausal women treated with that adjuvant endocrine therapy improved metabolic profiles(peak oxygen uptake (Vo₂peak), rest heart rate (RHR),

systolic blood pressure (SBP), BMI and WHR, waist to hip ratio (WHR), SBP, fasting insulin and glucose, HDL-C and TG) between experimental and control groups [27]. Additionally, Dieli-Conwright *et al* (2018) identified that metabolic syndrome z-score was significantly improved in MSE versus no MSE (MD -4.5; 95% CI: - 5.8 to - 2.8; $p < 0.0010$). Clinical phenotypes of obesity (appendicular bone mass index, $p = 0.001$; BMI, $P = 0.001$) and markers of inflammation, insulin ($p = 0.001$), insulin-like growth factor-1 (IGF-1) ($P = 0.001$), leptin ($P = 0.001$), and adiposity ($P = 0.001$), were statically significant in MSE group compared to non MSE. The authors concluded that MSE should be incorporated into BC treatment and survivorship care plan because of its benefits in attenuating metabolic syndrome and risk factors for CVD [28].

Meta-analysis of the impact of MSE on ROM and HRQOL in postmenopausal BCS

About nine studies were included in meta-analysis [29-37]. The ROM and degree of inflammation were measured using bioimpedance spectrometry and the standardized European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 questionnaire [38], as well as Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire was used to measure the ROM and HRQOL respectively.

Heterogeneity assessment

Our screening revealed that the methods using the RCTs were rigorous. The six domains of risk bias assessed revealed that biases were reduced in the most of included studies.

This meta-analysis included ten RCTs for which the ages of patients ranged from 50 to 60 years. The mean difference (MD) in age between supervised exercises and no supervised exercises groups was -0.34 (95% CI: -1.23 to 0.56) as presented in the forest plot in Figure 3. The difference was not statistically significant, with p-value of 0.46. The pooled on the effects of MSE versus no supervised exercises on ROM (Figure 3). The MD between intervention group versus control group was 1.35 (95% CI: 0.63 to 2.07; $P = 0.002$); heterogeneity: $\text{Tau}^2 = 0.71$; $\text{Chi}^2 = 112.14$, $\text{df} = 5$ ($P < 0.00001$); $I^2 = 96\%$. These results have shown that ROM was improved (SMD =35%) in MSE program compared to no supervised exercises (Statistically significant with $P = 0.0002$) forest plot Figure 4. However, the statistical heterogeneity between RCTs was high. The pooled summary of data on the efficacy of MSE in improving HRQOL has shown moderate evidence that MSE Improved HRQOL compared to no supervised exercises by up to 3.02 (95% CI: 2.59 to 3.45, $P < 0.00001$), as illustrated by the forest plot in Figure 4. The results were statistically significant. Heterogeneities were assessed in three forest plots (Figures 2-4). The overall clinical heterogeneity was high in all meta-analysis. Bias assessment revealed that the random allocation of patients in all RCTs was adequate. Confounding was minimized. Other risk of bias was likely and the final report was graded as moderate.

Discussion

This review summarized the current level of evidence on the effects of lifestyle interventions on Als-associated adverse events and the HRQOL in postmenopausal BCS survivors. The gaps identified in literature are discussed for further investigations. The review identified that Als-associated adverse events such as arthralgias, osteoporosis, obesity, metabolic syndrome, CVD risk factors, joint pain and fatigue were significantly reduced by implementing lifestyle interventions (healthy diet + MSE) in postmenopausal BCS following different treatment strategies. Improvements in potential side effects with MSE were seen across the board regardless of age, disease stages, molecular subtypes of cancer treatment (chemotherapy, radiation, surgery, TAM), and duration of Als therapy. Dose-response effects were also observed, with subjects who participated at least 81% of the MSE regimens having about 24% reduced in worst pain scores, whereas BCS who attended less than 81% of the MSE regimens having about 14% decrease [21]. In addition, cardio-respiratory fitness was correlated with pain scores, BMI, body fat reduction. The findings from our meta-analysis revealed that MSE, combined with usual care, are more effective in improving ROM (MD: 1.35; 95% CI: 0.63 to 2.07, $P = 0.002$; heterogeneity: $\text{Tau}^2 = 0.71$; $\text{Chi}^2 = 112.14$, $\text{df} = 5$, $P < 0.00001$, $I^2 = 96\%$) than no supervised exercises or usual care alone. The pooled MD of HRQOL scores in intervention group compared to the control group was 3.02 (95% CI: 2.59 to 3.45, $P < 0.00001$). Subgroup analysis for exercises mode, types, and intensity was not conducted for regimen heterogeneity throughout the studies. The mean intervention duration was between 3 and 6 months. Studies evaluating the effect of supervised exercises versus no supervised exercises on treatment adverse events postmenopausal BCS, based on our inclusion criteria, are scarce. Further systematic reviews and meta-regressions/regressions can be conducted to identify biomedical pathways that may be influencing the effects of MSE on Al-associated adverse effects, such as Als-associated obesity, mediators of inflammation, genetic risk factors, muscular strength, as well as the time of onset of pain improvement with MSE programs.

Obesity is a known shared risk factor between postmenopausal BC status and NCDs, such as CVD. Inflammation is considered as a major unifying risk factor in sharing the same biological pathways of both CVD and BC [39]. Evidence revealed that lifestyle strategies that target weight loss may decrease perilymphatic inflammatory markers (cells), improve lymphatic function, and reverse pathological mechanisms in gene expression in lymphatic endothelial cells [40]. A Cochrane review conducted by McNeely et al. (2010) confirmed that exercise programs in the postoperative period significantly improved HRQOL as defined by short term physical, psychosocial, and emotional wellbeing. No evidence based result was found on the relationship between obesity induced by lymphatic dysfunction and exercise intervention [41]. This discrepancy related to the effects of exercises on HRQOL observed in our review should be explained by the fact that, our meta-analysis included only postmenopausal BCS who were subjected to ACSM and ACS guidelines for lifestyle interventions. In addition, MSE programs play an important role in the effects of exercise interventions in chronically ill patients. The value of supervision has been attributed to improvements in adherence and exercise intensity, perhaps because of greater encouragement or confidence to exercise when the help of a healthcare provider is at hand. A sports physician or therapist may also help to individualise the exercise regimen to the specific condition of the person, such as the complex sequelae of cancers and its treatment. These MSE effects are evidence

based, and the findings from our review and meta-analysis are statistically significant compared to other exercise strategies. Moreover, the studies included in our meta-analysis were only those with a specified medically supervised programs, for which the components included exercise types, frequency, mode, HR, 1-RM, duration of follow-up, and tailored based on patient comorbidities. This may be one of the reasons that our findings were more significant than other reviews included all types of exercises without considering evidence based guidelines for exercise prescription [10, 42].

Review by Zaidi et al ., (2017) classified BC treatment side effects based on types treatment strategies, molecular subtypes, metabolic profiles/comorbidities and environmental factors[43]. The most known side effects related to surgery and radiation therapy are upper limb edema/inflammation and pain with an incidence rate of about 40% within 5 years following treatment, depending on types of therapy within 5 years following treatment [44]. Given that postmenopausal BC status shares the same risk factors with metabolic syndromes, such as CVD, dyslipidaemia and diabetics, tailored exercise interventions are suggested to reduce BP, and psychosocial and neurological adverse events associated with adjuvant therapy [39]. The present meta-analysis confirmed with moderate evidence that all types of exercises are effective in improving metabolic function, homeostatic, lymphatic systems function and likely to improve BCS survivorship.

Limitations

Outcomes on the correlation of the effects of exercises with BC subtypes, and subgroup based analysis focused on tools used to measure the efficacy of exercises across intervention and control arms were not reported. The meta-analyses of the above limitations were not conducted because of significant heterogeneity within the studies, and these results were reported narratively. Additionally, the results did not consider exercises in patients on other types of unestablished conservative therapies for BC such as yoga, acupuncture, Chinese medicine, and African traditional medicine. Moreover, the findings of this meta-analysis should be considered in light of small sample sizes and few studies evaluating MSE versus no supervised exercises in preventing side effects associated with BC treatment. About half of the studies included in this review were graded low quality of evidence for primary outcomes and moderate quality for secondary outcomes. The exercise modes, frequencies, and duration varied according to setting and author's flexibility, suggesting threat to internal validity. Study samples included females with initially stable conditions who were fit for physical activity. Since many subjects were used to routine standardized exercises, the adherence should be maximized by the fact that safety and feasibility were generally compromised before participating into the trials. As such, the effectiveness, relevance, adherence, side effects, and safety of exercises among those patients with severe comorbidities could not be assessed in this study, and work of this nature could be considered for further assessment. Other bias should be introduced by the lack blinding of patients and assessors of outcomes in many studies. While blinding is not always possible in exercise intervention studies; potential bias may be introduced by objective assessment of ROM for primary outcome. Publication bias was not addressed with a funnel plot because the number of studies was less than ten, and the review included only peer-reviewed articles. It is likely that the omission of unpublished studies and other well conducted observational studies

resulted in publication bias. This is because studies with negative results are less likely to be published and the inclusion of these types of studies may reduce the threats to internal validity. However, to mitigate this potential selection bias, the authors performed risk of bias independently using the Cochrane risk of bias tool. This approach assesses the quality of selected studies, and is a reliable and valid measure of methodological quality of RCTs (<http://training.cochrane.org/handbook>). The generalizability of these findings to other populations with severe stage of BC associated comorbidities should be established with a sufficient level of evidence. Finally, further meta-analysis with high-quality RCTs should also explore the correlation between the ACSM and ACS exercise regimens in assessing the dose-response relationship between different types of exercises and survival outcomes stratified by BC subtypes.

Further perspective

A review on the effects of exercises on cancer related fatigue suggested that exercises may be used in the rehabilitation of cancer and associated comorbidities to reduce inflammatory markers and fatigue [45]. Evidence from rigorous high-quality studies to recommend the impact of different types of exercises, exercise intensity, and weight loss on inflammatory markers is still lacking in the literature. A narrative synthesis evaluating the effects of exercises on markers of inflammation among BCS and a healthy population revealed that the effects were similar in reducing inflammatory markers in both populations. However, research gaps were identified in literature; good understanding of the relationship between exercises and inflammation, as well as, the underlying biological mechanisms that are responsible for these changes in postmenopausal breast cancer patients on endocrine therapy needs further investigations as recommended in previous review [46]. Our review briefly outlined the effects on lifestyle interventions on common adverse associated with endocrine therapy; specifically, with AIs and optimal exercise protocols developed to mitigate these comorbidities. Consequently, we emphasised on the level of evidence and the role of exercise in post-primary treatment in BCS in improving HRQOL. The intent is to encourage healthcare providers and BCS to implement lifestyle interventions as part of the path to prolong survivorship. To remedy physical and psychosocial compromises of these patients, personalized patient-oriented lifestyle programs that embrace the needs, strength and specialized healthcare providers should design preferences of BCS.

Conclusion

The findings from the review suggest that lifestyle interventions have positive effects on AIs-associated adverse events in postmenopausal BCS on improving ROM and HRQOL in postmenopausal BC patients. Further studies are recommended to assess the effect of lifestyle interventions on markers of inflammation as the predictors of treatment non-response and associated comorbidities.

List Of Abbreviations

AIs Aromatase inhibitors

BMI:	Body mass index
BC	Breast cancer
BCS	Breast cancer survivors
MSE	Medically supervised exercise
RCT	Randomized controlled trial

Declarations

- Ethics approval and consent to participate: N/A
- Consent to publish: N/A, all authors read the manuscript and approved for the submission, No individual data are applicable in this study
- Availability of data and materials: N/A
- Competing interests: no conflict of interest declared
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- **Author's contributions**

1. JPM contributed in designing, search strategy, registering of review, protocol writing, data extraction, risk of bias assessment and data analysis.
2. MJ assisted in developing of conceptual framework of the project, critical appraisal and quality improvement, edition of the manuscript.
3. RT Erasmus assisted in critical appraisal, search strategy, edition, co supervising, and quality assessment.
4. JM supervised the process and management of the manuscript, assessment of bias, data analysis, interpretation of final report and literature search for consistency.

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- **Author's information: N/A**

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Tables

Table 1: List of included studies in meta-analysis

Authors/years Country	Mean age/samples	Interventions/ control	Outcomes
Suragadda et al., (2015) India, [39]	N=60(n=30, n=30) MSD = 56.3(3.5)	MSE, mixed AR, 50 min/d or 3-5times/wk,5x weeks/12 weeks versus conventional no SE.	ROM,QOL
Melam et al., (2016) India, [40]	N= 60 (n=30, n=30) MSD = 56.3(3.5)	MSE, mixed AR, 50 min/d or 3-5times/wk,5x weeks/12 weeks versus conventional no SE.	EORTC QLQ C30 and EORTC QLQ-BR23
Mayes et al. 2009, [41]. Australia	N=32(n=16, n=16) MSD=60(10)	MSE versus no, AE, 30-5/3 times daily/12weeks, versus no SE	ROM
McClure et al. 2010, [42] Australia	N=32(n=16, n=16), MSD= (59.7 ± 2.1)	MSE: 60 min/d, twice weekly, /17 weeks (N= 16, N=16) each group. versus no SE	ROM, QRQOL
Mushan et al. (2016), [43] Australia	N=41(n=21, n=20) MSD=58.5 (95%CI:54.2-62.8)	MSE: AE, 150 weekly, 3-5times/12 weeks. versus no SE	ROM, HRQOL
Kim et al. (2010) [44] Korea	N=40(n=20, n=20) MSD = 50.50(10.58)	MSE: Resistance, 15min/d, 5 days, 8 weeks. versus no SE	ROM, HRQOL
Ardehshel et al. (2007) [45] Turkey	N=19(n=9, n=20) MSD=51.6(8.8)	MSE: AR,3 to 6 months, 3 times daily, versus no SE	ROM, QOL
Schmitz <i>et al.</i> (2009),	N=142(n=71, n=70)	MSE: 90 min twice weekly, 12 weeks. versus no SE	ROM,QRQOL

46]SA	MSD=(58±10)		
ener et al. 017, [47] 'urkey	N=60(n=30, n=30) MSD= 53.2±7.7	MSE: 5-8 persons 3 times a week/8 weeks. versus no SE	ROM, HRQOL

Legends: AE= aerobic and resistance, n= sample by group allocation, RCTs= randomised controlled trials, MSE: medically supervised exercises, HRQOL= Health related quality of life, MSD= mean standard deviation, N= sample,

Table 2: Risk of bias assessment

Patient or population: Postmenopausal BCS on adjuvant endocrine therapy

Settings: Australia, USA, Turkey

Intervention: Lifestyle interventions (medically supervised programs+ diet)

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No Participants (studies)	of Quality the evidence (GRADE)	of Comments
	Assumed risk				
	Corresponding risk				
	Control				
Improved ROM	The mean ULV reduction in the intervention groups was 1.35 higher (0.63 to 2.07 higher)		371 (6 studies)	⊕⊕⊕⊕ low ^{1,2}	
Improved HRQOL	The mean improved QOL in the intervention groups was 3.02 higher (2.59 to 3.45 higher)		201 (4 studies)	⊕⊕⊕⊕ moderate ³	
Mean age of BCS	The mean age of BCS in the intervention groups was 0.34 lower (1.23 lower to 0.56 higher)		483 (10 studies)	⊕⊕⊕⊕ moderate ³	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Other bias were more than 75%

² Heterogeneity was more than 75%

Figures

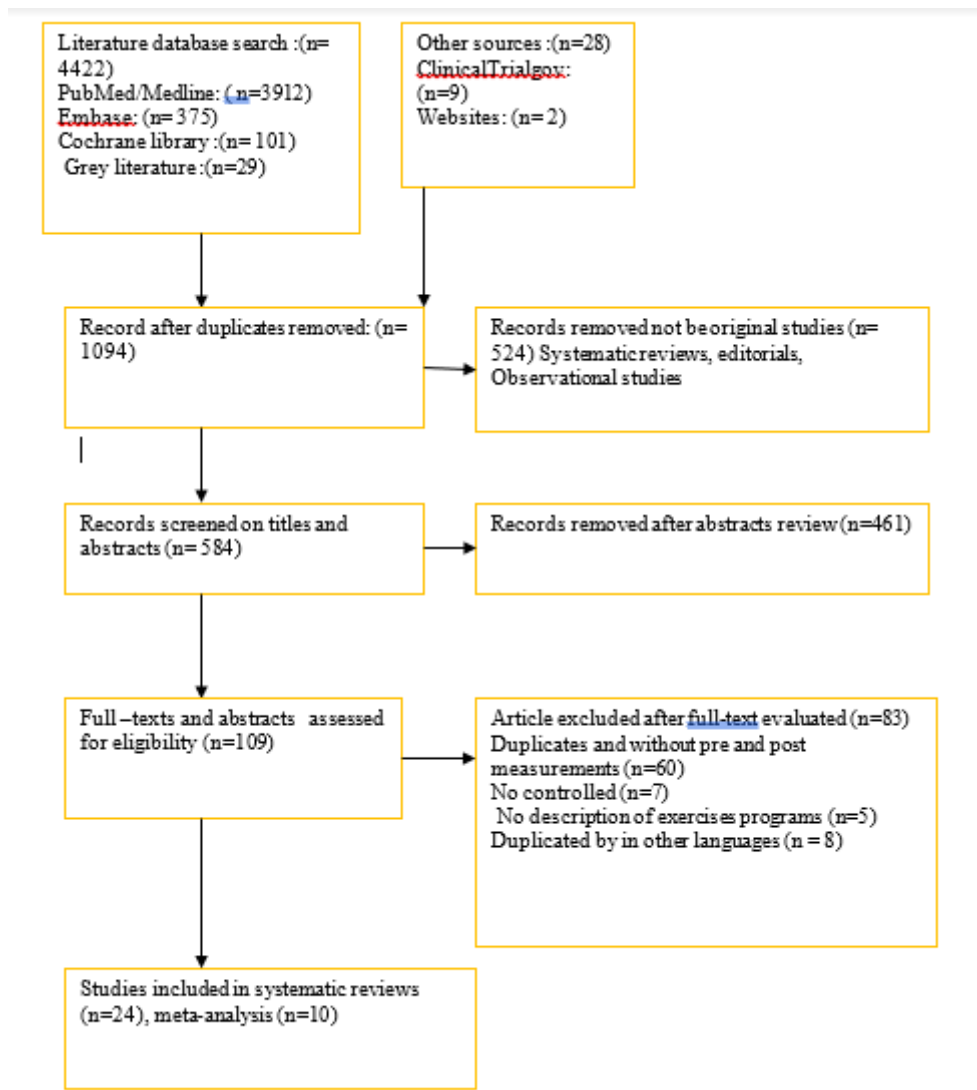


Figure 1

PRISMA diagram

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Buragadda 2015	+	-	-	+	+	+	-
Bushan 2016	+	+	-	-	+	+	+
Hayes 2009,	+	?	-	+	+	+	-
Irdelsel 2007	+	-	+	+	?	+	-
Kim 2010	+	-	-	-	+	+	-
McClure 2010	+	+	?	+	+	+	-
Melan 2016	+	-	-	+	+	+	-
Schmitz 2009	+	+	+	+	+	-	-
Sener 2017	+	+	?	?	+	+	+

Figure 2

Risk of bias assessment

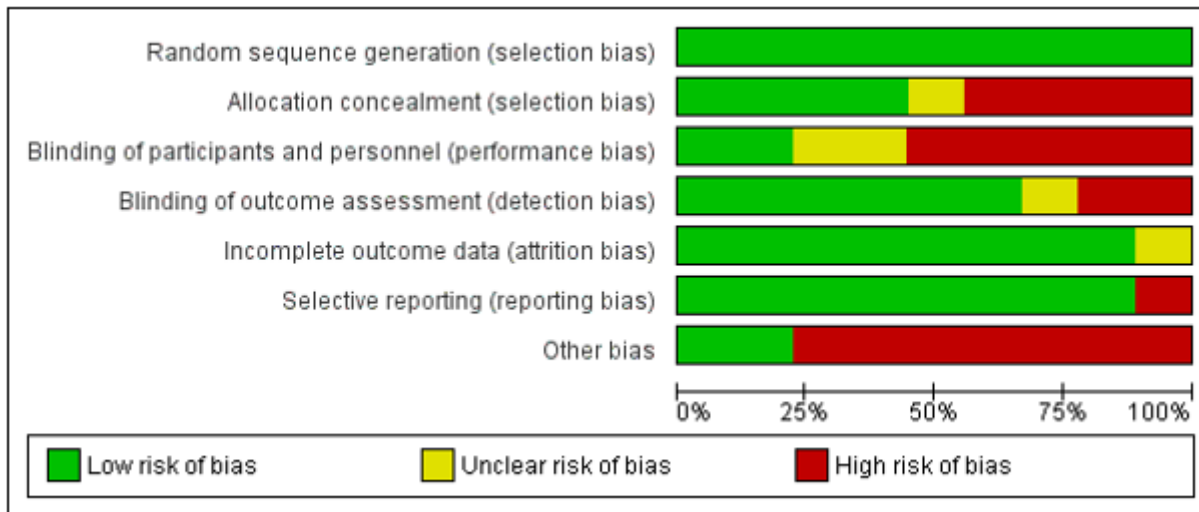


Figure 3

forest plots of the effects of exercises

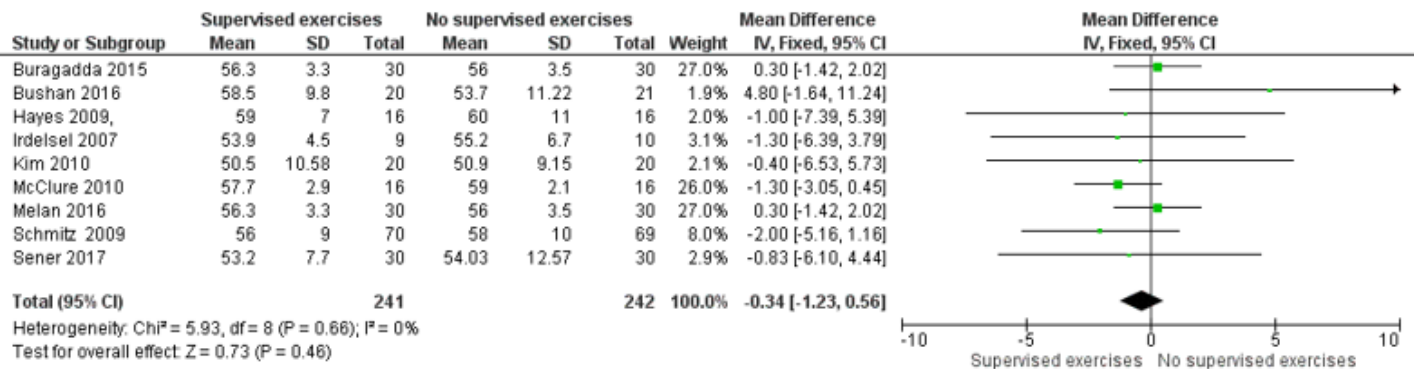


Figure 4

Forest plot of comparison: Supervised exercises vs No supervised exercises; Parameter: Age

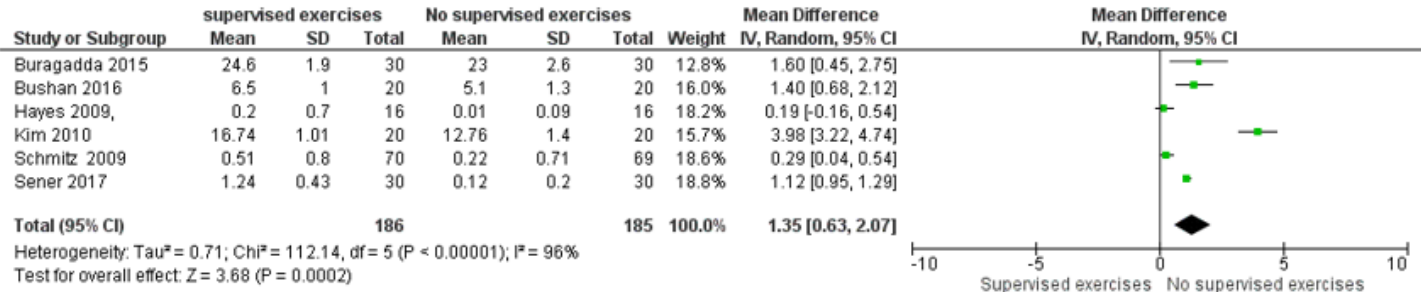


Figure 5

Forest plot of comparison: Supervised exercises vs No supervised exercises; Outcome: improved ROM