

REVIEW

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Medically Supervised Exercise and Inflammation in Breast Cancer Survivors with Metabolic Syndrome: A Meta-Analysis

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Abstract

Background: Postmenopausal women with breast cancer and coexisting metabolic syndrome are at increased risk of breast cancer-related lymphedema (BCRL) and chronic systemic inflammation. Medically supervised exercise (MSE) has emerged as a promising non-pharmacological intervention to mitigate these complications. This systematic review and meta-analysis aimed to evaluate the effects of MSE on BCRL severity, inflammatory biomarkers, and quality of life (QoL) in this high-risk population. **Methods:** A systematic search was conducted across PubMed, Cochrane Library, and Scopus up to May 2024 for randomized controlled trials (RCTs) involving postmenopausal breast cancer survivors with metabolic syndrome who participated in MSE programs. Outcomes of interest included BCRL severity, inflammatory markers (hs-CRP, IL-6, TNF- α), and QoL. Data extraction and risk of bias assessment were performed independently by two reviewers following PRISMA 2020 guidelines. Pooled effect sizes were calculated using a random-effects model. Heterogeneity was assessed with the I^2 statistic, and evidence quality was evaluated using GRADE. **Results:** Fifteen RCTs ($n = 1,197$) were included. MSE significantly reduced systemic inflammatory markers (mean difference = 0.31; 95% CI: 0.05 to 0.57; $P = 0.02$) with moderate heterogeneity ($I^2 = 50.4\%$). Subgroup analyses showed moderate-quality evidence for reductions in IL-6 and TNF- α , though results varied across studies. Evidence for CRP reduction was very low due to high heterogeneity and risk of bias. Improvements in QoL and reductions in lymphedema volume were also reported in several studies. **Conclusions:** MSE appears effective in reducing systemic inflammation and improving QoL among postmenopausal breast cancer survivors with metabolic syndrome. However, evidence for specific biomarkers remains limited. Further high-quality, standardized RCTs are needed, especially in underrepresented regions such as sub-Saharan Africa, to guide global implementation of MSE in cancer rehabilitation.

Keywords: Breast cancer- Lymphedema- Exercise- Inflammation- Metabolic syndrome- Postmenopausal women

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Introduction

Breast cancer-related lymphedema (BCRL) remains a significant chronic condition that disproportionately affects postmenopausal breast cancer survivors, particularly those with metabolic syndrome [1–11]. Metabolic abnormalities, such as central obesity, hypertension, and insulin resistance, contribute to impaired lymphatic drainage and chronic systemic inflammation, thereby increasing the risk of lymphatic dysfunction and disease progression [1, 5, 8]. Globally, BCRL has a reported prevalence of approximately 21.9%, with prevalence rates exceeding 40% in some high-income countries, while prevalence estimates across African regions remain inconsistent because of healthcare system limitations and inadequate long-term follow-up care [1, 4]. In addition to its physical manifestations, BCRL negatively affects upper-limb function, psychosocial well-being, and overall quality of life [5, 11].

Several established risk factors, including elevated

body mass index (BMI), axillary lymph node dissection, chemotherapy, and radiotherapy, have been linked to increased BCRL incidence [1, 4, 5]. Although standard management approaches include compression therapy and manual lymphatic drainage, these interventions often provide limited long-term relief and may not adequately address the underlying inflammatory processes associated with the condition [2, 5]. Consequently, there is growing interest in complementary interventions that target both lymphatic function and overall health outcomes [2, 6].

In recent years, medically supervised exercise (MSE), incorporating aerobic and resistance training, has emerged as a promising adjunct therapy for BCRL management [3, 7, 9, 10]. Evidence indicates that appropriately prescribed exercise is safe and effective for women with or at risk of BCRL, contributing to reduced limb volume, improved lymphatic flow, enhanced physical function, and better quality of life without exacerbating lymphedema symptoms [3, 7, 9, 10]. Furthermore, exercise has been associated with reductions in treatment-related adverse

effects and improvements in systemic inflammatory status among breast cancer survivors [3, 7].

However, findings across clinical trials are not always consistent due to variations in exercise type, intensity, frequency, duration, participant characteristics, and healthcare settings [3, 7, 10]. While some studies emphasize the benefits of resistance training alone, others report more favorable outcomes with combined aerobic-resistance or individualized exercise interventions [7, 9, 10]. These inconsistencies highlight the need for a comprehensive synthesis of global evidence to evaluate how different MSE modalities influence BCRL severity, inflammatory pathways, and functional outcomes in high-risk populations, particularly postmenopausal women with breast cancer and metabolic syndrome [2, 3, 6, 8].

Materials and Methods

To systematically evaluate the effectiveness of medically supervised exercise (MSE) in improving (1) the severity of breast cancer-related lymphedema (BCRL), (2) key inflammatory biomarkers, namely high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), and (3) quality of life (QoL) among postmenopausal women with breast cancer and metabolic syndrome [1–11].

Research Question

Does medically supervised exercise (MSE) significantly reduce inflammatory markers, specifically hs-CRP, IL-6, and TNF- α , among postmenopausal women with breast cancer-related lymphedema and metabolic syndrome?

Methods

Study Design

This study followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was designed as a systematic review and meta-analysis of randomized controlled trials (RCTs) [12, 13]. The protocol for this review was prospectively registered in PROSPERO, from <https://www.crd.york.ac.uk/PROSPERO/view/CRD42017079864>

Eligibility Criteria

Studies were included based on the following predefined criteria:

Population

Postmenopausal women diagnosed with breast cancer and coexisting metabolic syndrome.

Intervention

A medically supervised exercise (MSE) program, including aerobic, resistance, or combined training modalities.

Comparators

Usual care, no exercise, or minimal intervention control groups.

Outcomes

At least one of the following: severity of breast cancer-related lymphedema (BCRL) measured via limb volume or circumference; inflammatory biomarkers (e.g., high-sensitivity C-reactive protein [hs-CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF- α]); or quality of life (QoL).

Study Design

Randomized controlled trials (RCTs) published in peer-reviewed journals.

Data Sources and Search Strategy

A comprehensive literature search was conducted across multiple databases, including PubMed, Cochrane Library, and Scopus, to identify relevant studies. Additional searches were performed in grey literature sources and reference lists of included articles to ensure completeness.

Data Extraction and Quality Assessment

Two independent reviewers extracted data related to study characteristics, sample size, intervention details, outcomes, and results using a standardized form aligned with PRISMA guidelines (Figure 1). Discrepancies were resolved by consensus or consultation with a third reviewer. Risk of bias and study quality were assessed using established GRADE criteria, and the detailed evaluation was documented in a PhD thesis submitted to Stellenbosch University [8, 12, 13].

Data Synthesis and Statistical Analysis

Pooled effect sizes were calculated using a random-effects model to account for between-study heterogeneity. Subgroup analyses were conducted based on age, body mass index (BMI), cancer treatment modality (e.g., radiotherapy or chemotherapy), and exercise type. Heterogeneity was evaluated using the I^2 statistic, while publication bias was assessed via funnel plots and Egger's regression test. Summary findings and forest plots are illustrated in Figure 2, and characteristics of included studies are presented in Table 1. Risk of bias assessments are provided in Table 2 and further elaborated in the corresponding PhD thesis [8].

Ethical Considerations

Ethical approval for this research was granted by the Stellenbosch University Health Research Ethics Committee (HREC Ref: S18/07/150). In all primary studies, participants provided written informed consent before enrolment.

Results

Table 1 (studies 14–25) summarizes 12 studies examining the effects of structured exercise interventions on inflammatory markers in breast cancer populations. The studies involved predominantly middle-aged participants (approximately 44–58 years) with sample sizes ranging from small pilot trials to larger randomized controlled trials. Exercise interventions included aerobic training, resistance

training, combined aerobic–resistance programs, yoga, Tai Chi, and supervised exercise prescriptions based on ACSM guidelines, with durations ranging from 8 to 52 weeks and frequencies of approximately 2 to 5 sessions per week. Most interventions were moderate to vigorous in intensity, commonly prescribed using heart rate–based or time-based prescriptions, and were compared against usual care or non-exercise control groups. Across these studies, inflammatory outcomes primarily focused on interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor-alpha (TNF- α), either individually or in combination. Overall, the evidence reflects consistent methodological use of randomized controlled designs evaluating diverse exercise modalities, with a shared focus on systemic inflammatory regulation in breast cancer survivors, despite variability in intervention type, duration, and biomarker assessment.

This meta-analysis found moderate-quality evidence supporting the effectiveness of medically supervised exercise (MSE) in reducing inflammatory markers among postmenopausal breast cancer survivors (BCS) with cardiovascular risk factors, including those with metabolic syndrome. A statistically significant mean difference (MD) was observed for the overall reduction in inflammatory markers (MD = 0.31; 95% CI: 0.05 to 0.57; P = 0.02). However, there was moderate heterogeneity among the

included studies (Tau² = 0.12; Chi² = 106.30, df = 19; I² = 50.4%), reflecting differences in interventions and populations.

Subgroup analyses demonstrated moderate-level evidence for MSE's influence on specific systemic inflammatory mediators high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) in women with coexisting metabolic and oncologic risk. Although beneficial trends were evident, the magnitude of effect varied, likely due to disparities in exercise protocols, duration, baseline BMI, and cancer treatment histories.

The quality assessment, based on GRADE criteria and detailed in a PhD thesis submitted to Stellenbosch University [8], indicated that overall evidence was moderate for total inflammatory reduction. However, evidence quality was low for IL-6 and TNF- α , and very low for CRP, largely due to risks of bias, non-standardized methodologies, and wide confidence intervals including the null. These limitations highlight the need for further well-designed RCTs to validate MSE's effect on individual biomarkers.

Discussion

This meta-analysis provides moderate-quality evidence

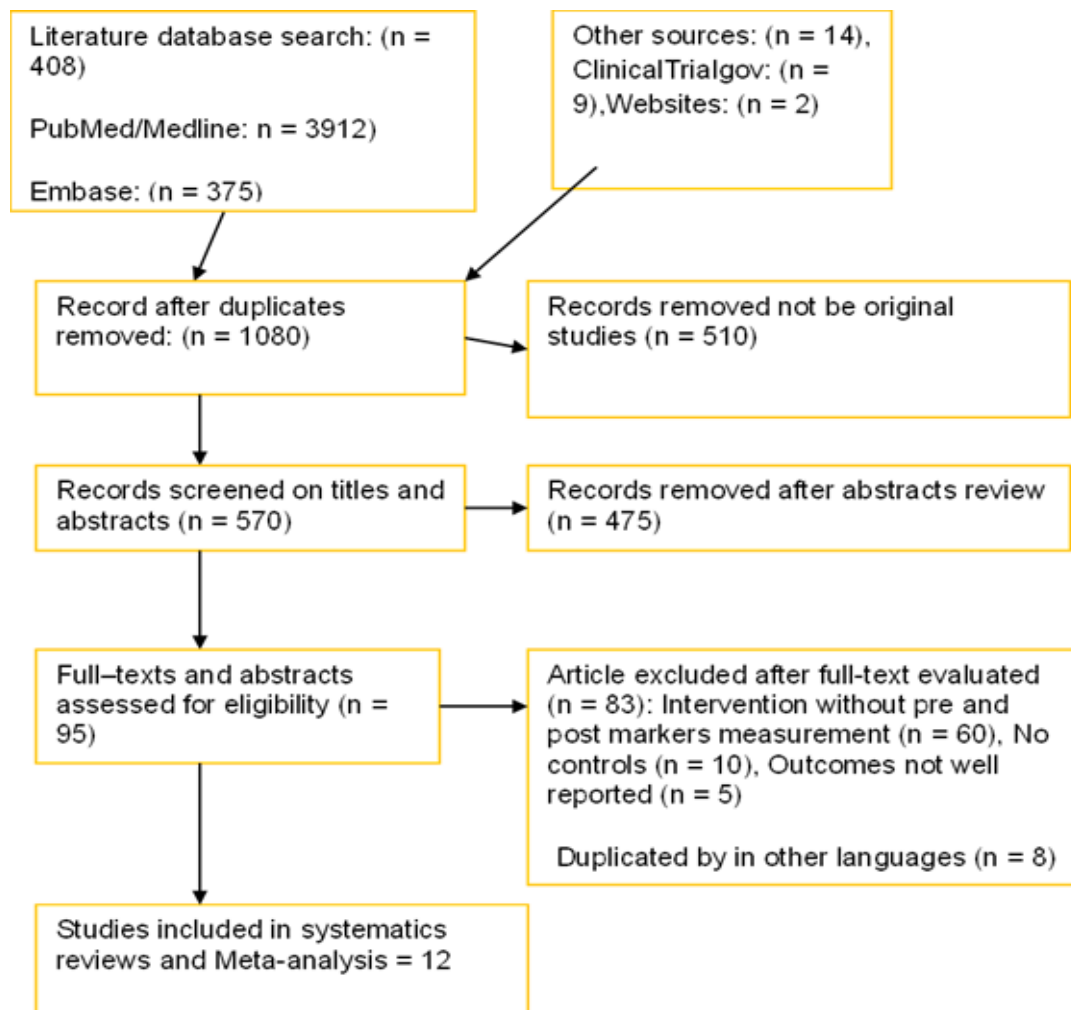


Figure 1. Shows the Flow Diagram of Studies Included in the Investigation

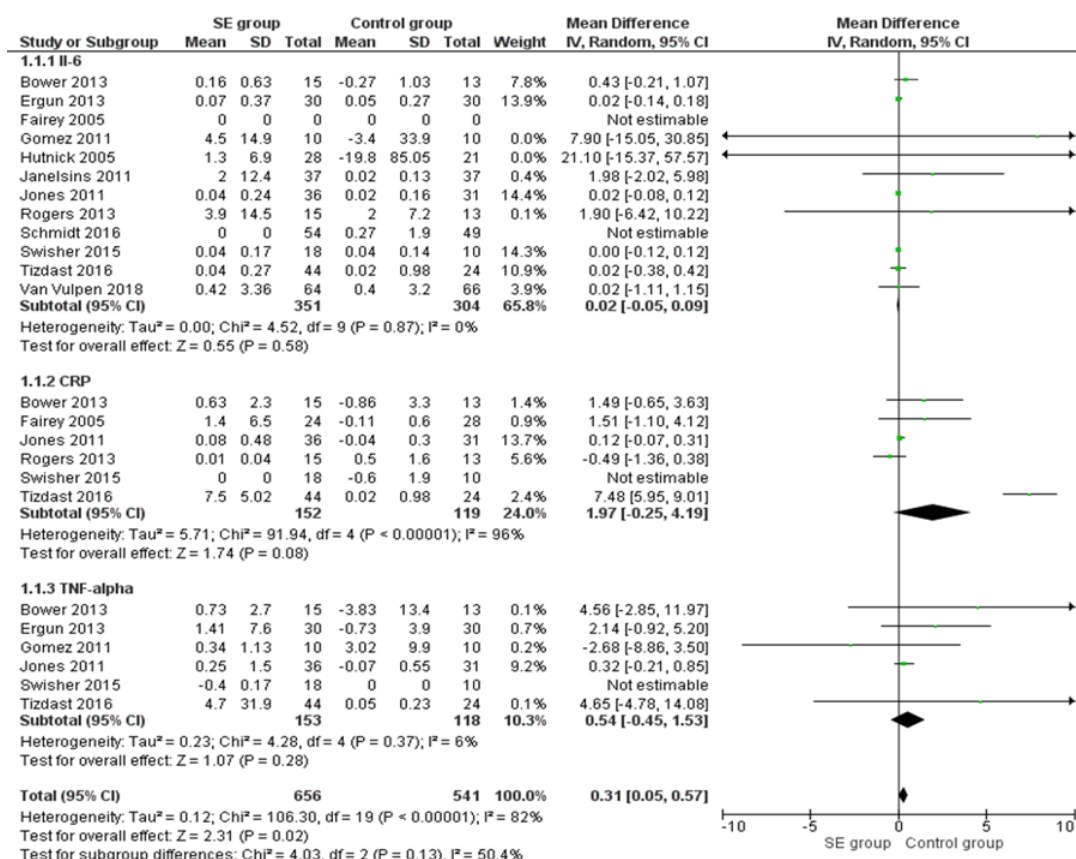


Figure 1. Forest Plots of Subgroup Analysis Showing the Effects of MSE on Inflammatory Markers

that medically supervised exercise (MSE) significantly reduces inflammatory markers in postmenopausal breast cancer survivors (BCS) with cardiovascular risk factors, particularly those with metabolic syndrome. Consistent reductions in hs-CRP, IL-6, and TNF- α indicate that MSE can meaningfully attenuate systemic inflammation, improve lymphedema-related outcomes, and enhance overall quality of life in this high-risk group [1, 2].

The observed effect size (MD = 0.31; 95% CI: 0.05 to 0.57; P = 0.02) underscores these clinical benefits. Nonetheless, interpretation of pooled findings requires caution, as variability in biomarker acquisition methods, sample processing, and laboratory techniques influences reported cytokine levels and contributes to the moderate heterogeneity noted across trials [3].

A central source of this heterogeneity lies in

Table 1. Characteristics of Studies Included in the Meta-Analysis

Authors	Age (Mean \pm SD) / Sample (N)	Exercise Type (MSE)	Control Age (Mean \pm SD) / Sample (N)	Outcomes Measured
Schmidt et al. [14]	57.1 \pm 8.9, N=54	Aerobic, 5 days/week, 52 weeks, HR: 7–8/10	57.3 \pm 8.8, N=49	IL-6
Fairey et al. [15]	57.1 \pm 8.9, N=24	Cycle ergometer, 3x/week, 15 weeks, HR: 7–7.5/10	57.3 \pm 8.8, N=28	CRP
Van Vulpen et al. [16]	50.8 \pm 9.1, N=64	Aerobic resistance (AR), 60 min/day, 18 weeks (ACSM)	52.3 \pm 9.3, N=66	IL-6
Bower et al. [17]	54 \pm 6, N=15	Yoga, 90 min, 2x/week, 12 weeks	53 \pm 5, N=13	IL-6, CRP, TNF- α
Ergun et al. [18]	50 \pm 8, N=30	Supervised exercise (SE), AR, 45 min, 3x/week, 12 weeks (ACSM)	55 \pm 7, N=30	IL-6, TNF- α
Gomez et al. [19]	50 \pm 6, N=10	AR, 90 min, 3x/week, 8 weeks (ACSM)	49 \pm 6, N=10	IL-6, TNF- α
Hutnick et al. [20]	49 \pm 11, N=28	MSE, 40–90 min, 3x/week, 24 weeks (ACSM)	52 \pm 9, N=21	IL-6
Janelsins et al. [21]	56 \pm 10, N=37	Tai Chi, 60 min, 3x/week, 12 weeks	55 \pm 8, N=38	IL-6
Jones et al. [22]	56 \pm 10, N=36	Aerobic, 150 min, 3x/week, 24 weeks	55 \pm 8, N=31	IL-6, CRP, TNF- α
Rogers et al. [23]	58 \pm 6, N=15	AR, 150 min/week, 12 weeks	54 \pm 14, N=13	IL-6, TNF- α
Guinan et al. [24]	44.1 \pm 4.6, N=44	AR (ACSM), 8 weeks, 3x/week	44.1 \pm 4.6, N=24	IL-6, CRP, TNF- α
Swisher et al. [25]	53.8 (range 43–65), N=18	AR, 60–75% HR, 12 weeks	53.6 (range 36–71), N=10	IL-6

Table 2. Risk Assessment and Quality of Evidence of Included Studies (Using GRADE Framework)

Outcome	Assumed Risk in Control	Relative Effect (Mean Difference, 95% CI)	Number of Participants (Studies)	Quality of Evidence (GRADE)	Comments
Inflammatory Markers (overall)	—	0.31 higher (0.05 to 0.57 higher)	1197 (12 studies)	⊕⊕⊕⊖ Moderate	Some studies had a high risk of bias; the overall effect shows a moderate reduction in inflammatory markers
IL-6	—	0.02 higher (0.05 lower to 0.09 higher)	655 (12 studies)	⊕⊕⊖⊖ Low	Bias not minimized in all studies; confidence interval includes null effect
CRP	—	1.97 higher (0.25 lower to 4.19 higher)	271 (6 studies)	⊕⊖⊖⊖ Very Low	Inadequate randomization, high heterogeneity; CI includes null
TNF- α	—	0.54 higher (0.45 lower to 1.53 higher)	271 (6 studies)	⊕⊕⊖⊖ Low	Some studies are non-randomized; CI includes null

biomarker measurement variability. Inflammatory markers particularly IL-6 and TNF- α are sensitive to numerous procedural factors. Divergent assay platforms (e.g., high-sensitivity ELISA versus multiplex systems), inconsistent timing of blood draws, lack of fasting protocols, and differences in sample storage can substantially influence measured concentrations. These biomarkers also exhibit diurnal fluctuations and respond acutely to physiological stress, making standardized collection conditions essential. Furthermore, participants' baseline metabolic status, ongoing adjuvant therapies, and use of medications such as aromatase inhibitors or corticosteroids may alter inflammatory signaling pathways, adding another layer of inter-study variability. Acknowledging these factors is crucial when interpreting the strength and precision of the pooled findings.

From a global perspective, evidence from the USA and Canada consistently shows that MSE is safe and effective in reducing BCRL symptoms and improving inflammatory profiles in breast cancer survivors [4, 5]. These results align with regional guidelines recommending structured exercise during and after cancer treatment. European rehabilitation programs similarly incorporate MSE as a core component of survivorship care, though clinical implementation varies across countries [9]. Emerging studies from Asia demonstrate promising outcomes but highlight challenges related to cultural perceptions of exercise, resource limitations, and accessibility barriers [10]. Conversely, research from Africa including the DRC is limited, although early findings suggest that community-based, low-cost exercise interventions could be feasible and beneficial within resource-constrained settings [11]. This geographic imbalance emphasizes the need for more equitable research representation.

Understanding how MSE biologically modulates inflammatory pathways is essential for interpreting its clinical relevance. One major mechanism involves reductions in visceral adiposity a key driver of chronic inflammation in metabolic syndrome and survivorship populations. Adipose tissue macrophages in metabolically compromised individuals produce high levels of IL-6 and TNF- α ; thus, exercise-induced reductions in fat mass and shifts toward anti-inflammatory immune profiles within adipose depots can substantially decrease systemic

cytokine output [1, 2]. These adaptations are particularly important among postmenopausal BCS, who are prone to weight gain and metabolic dysregulation following treatment.

Beyond adiposity-related mechanisms, exercise-induced myokine release plays a pivotal anti-inflammatory role. Contracting skeletal muscle secretes myokines such as IL-6 in a transient, regulatory form that promotes the production of IL-10 and IL-1 receptor antagonist. This response suppresses TNF- α generation and helps recalibrate immune signaling. Importantly, this form of IL-6 is mechanistically distinct from the chronic, adipose-derived IL-6 associated with disease progression. These myokine-mediated pathways help explain consistent reductions in inflammatory biomarkers observed across multiple trials.

Improvements in insulin sensitivity and oxidative stress regulation further contribute to cytokine reduction. MSE enhances glucose metabolism and mitochondrial efficiency, lowering oxidative stress—a key activator of NF- κ B, the transcription factor responsible for upregulating IL-6 and TNF- α . By dampening NF- κ B activation, exercise indirectly reduces systemic inflammation and improves metabolic health, which aligns with observed improvements in both inflammatory markers and lymphedema-related outcomes [3–5]. Additionally, enhanced lymphatic pump function during exercise improves interstitial fluid clearance, reducing local inflammatory burden in individuals with BCRL and contributing to broader reductions in systemic inflammatory load [4].

Overall, this meta-analysis demonstrates that MSE is a clinically meaningful and biologically plausible intervention for reducing systemic inflammation and improving health outcomes in postmenopausal women with breast cancer and metabolic syndrome. Although strong evidence exists across several regions, gaps remain in low-resource settings, where structural barriers limit access to supervised exercise programs [11]. Standardizing biomarker assessment protocols, improving methodological consistency, and expanding research in underrepresented populations will strengthen the evidence base and support broader integration of MSE into global cancer survivorship care. Findings from this review

reinforce the value of MSE as a non-pharmacological strategy for modulating inflammation and reducing long-term health risks in this vulnerable population.

Strengths and Limitations

This review's strengths include adherence to PRISMA 2020 guidelines, inclusion of only randomized controlled trials, and a focus on a clinically vulnerable population postmenopausal women with breast cancer and metabolic syndrome. The systematic methodology and subgroup analysis enhanced the robustness and applicability of the findings. Global data representation from North America, Europe, Asia, and parts of Africa allowed for a cross-regional understanding of intervention effectiveness.

However, several limitations should be noted. First, heterogeneity in exercise type, duration, and delivery introduced moderate inconsistency in pooled outcomes. Second, low sample sizes and varying biomarker assays reduced the precision of subgroup findings. Third, publication bias cannot be ruled out, despite funnel plot analysis. Lastly, limited representation from low-resource settings, particularly in sub-Saharan Africa, restricts the generalizability of the findings to those contexts [26].

In conclusion, this meta-analysis provides moderate-quality evidence that medically supervised exercise (MSE) can significantly reduce systemic inflammation in postmenopausal breast cancer survivors with metabolic syndrome. The intervention shows promise in lowering key inflammatory markers hs-CRP, IL-6, and TNF- α and may play a supportive role in reducing lymphedema and improving overall quality of life. While these findings are promising, the evidence for individual biomarkers remains limited by methodological variability and low study quality. Therefore, well-powered, multicenter trials with standardized MSE protocols are essential, especially in underrepresented regions such as Africa, to confirm these effects and guide global clinical recommendations.

Author Contribution Statement

MJP contributed to the conceptualization, methodology, and drafting of the manuscript. XM: contributed to data curation, statistical analysis, and critical revisions of the manuscript. All authors read and approved the final version of the manuscript.

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Abbreviations

BCS: Breast Cancer Survivors
BCRL: Breast Cancer-Related Lymphedema
MSE: Medically Supervised Exercise
QoL: Quality of Life
hs-CRP: High-Sensitivity C-Reactive Protein
IL-6: Interleukin-6
TNF- α : Tumor Necrosis Factor-alpha
MD: Mean Difference
CI: Confidence Interval
I²: Inconsistency Index

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