



The Effect of Yoga Interventions on Cancer-Related Fatigue and Quality of Life for Women with Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Women with breast cancer (BC) are living longer with debilitating side effects such as cancer-related fatigue (CRF) that affect overall well-being. Yoga promotes health, well-being and may be beneficial in reducing CRF. Although there have been previous systematic reviews and meta-analyses, the effects of yoga on CRF and quality of life (QOL) remain unclear, particularly in comparison with other types of physical activity (PA). Our objective is to carry out a systematic review and meta-analysis of the effects of yoga on CRF and QOL in women with BC. **Methods:** Electronic databases were searched (MEDLINE, Embase Classic+Embase and EMB Reviews, Cochrane Central CT) from inception to May 2018. Randomized controlled trials were included if they were full text, in English, included a yoga intervention, a comparator (including non-PA usual care or alternate PA intervention), and reported on CRF or QOL. Effects of yoga were pooled using standardized mean difference (SMD) via a random effects model. **Results:** Of the 2468 records retrieved, 24 trials were included; 18 studies compared yoga to a non-PA comparator and 6 to a PA comparator. Yoga demonstrated statistically significant improvements in CRF over non-PA (SMD -0.30 [-0.51 ; -0.08]) but not PA (SMD -0.17 [-0.50 ; 0.17]) comparators. Additionally, yoga demonstrated statistically significant improvements in QOL over non-PA (SMD -0.27 [-0.46 ; -0.07]) but not PA (SMD 0.04 [-0.22 ; $+0.31$]) comparators. **Discussion:** This meta-analysis found that yoga provides small to medium improvements in CRF and QOL compared to non-PA, but not in comparison to other PA interventions.

Keywords

breast cancer, yoga, meta-analysis, physical activity, cancer-related fatigue, quality of life, systematic review

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Background

Breast cancer (BC) is 1 of the most common cancers diagnosed in women worldwide.¹ With advancements in screening and treatment for BC, the mortality rate has decreased by 48% since 1986 in Canada,² however, in over 100 countries BC remains the leading cause of death.¹ Consequently, a greater number of women are living longer following a diagnosis of BC and managing the side effects and symptoms (such as fatigue, pain, cardiovascular disease, or depression)³ from the disease and its treatment, which can cause a reduction in quality of life (QOL).

Cancer-related fatigue (CRF) is a debilitating side effect that is experienced by 42% to 100% of women with BC.⁴⁻⁷ CRF varies by disease stage and treatment and is the most prevalent, long-lasting and distressing symptom

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experienced by people with cancer.^{4,5,8} CRF is a multi-dimensional symptom that affects an individual's physical, emotional, and mental state.⁹⁻¹¹ Rest has been previously suggested to alleviate CRF for anyone diagnosed with cancer⁴; however, increasing sedentary behavior can lead to muscle atrophy and decreased cardiovascular functioning, leading to an overall decrease in physical functioning and exacerbation of fatigue.^{4,10,12,13} Conversely, physical activity (PA), specifically moderate to vigorous PA (MVPA), has been shown to have a positive effect on CRF in multiple trials in women with BC.^{14,15} However, a majority of women with BC do not meet the recommended levels of MVPA for various reasons; physical, psychosocial, environmental and organizational factors.¹⁶⁻¹⁸ Many people with cancer, including BC, experiencing CRF have reported fatigue as a barrier^{19,20} to exercise participation, as well as preferences for mild intensity physical activity including yoga.²⁰ Furthermore, physical activity guidelines for people with cancer recommend that the volume and intensity of exercise may need to be reduced for those experiencing severe CRF (based on specific cutpoints on individual fatigue measures).^{7,21} It is therefore essential to understand how alternative, less intense PA may affect CRF.

Yoga, a form of exercise, is grounded in Eastern traditional practice where there are often 8 aspects to the practice,^{22,23} while in Western society yoga consists of the 2 main aspects of postures and breath control.²⁴ Yoga is practiced to improve health and well-being, and is purported to affect multiple dimensions of health (physical, mental, emotional, and spiritual).^{22,23} In a narrative review comparing the benefits of yoga and exercise on a variety of health outcomes among healthy and diseased adults including those with cancer, Ross and Thomas found yoga had similar benefits as conventional exercise for balance, menopausal symptoms, pain, mood, stress, quality of life (QOL), and CRF. However, in a variety of healthy and chronically ill (non-cancer) populations yoga showed smaller benefits for physical fitness (eg, VO₂ max, and energy expenditure)²³; this may hold true for individuals diagnosed with cancer. The incorporation of multiple dimensions within the practice of yoga may explain its role in positively effecting CRF.^{23,24} There are a variety of types of yoga such as Hatha, Bikram, and Iyengar, which include different aspects of physical poses, breath control and meditation.²⁵ Furthermore, yoga can be adapted specifically for individuals with cancer; yoga postures can help with strength and flexibility, breath control assists with relaxation and focus, while meditation can help to calm the mind.²⁵

To date, 5 systematic or comparator reviews^{16,25-28} and 8 meta-analyses have evaluated the effects of yoga on CRF and/or QOL; of these, 3 meta-analyses evaluated the role of yoga interventions on fatigue in multiple populations including BC and 2 on QOL.^{27,29,30} 4 meta-analyses included yoga interventions within a broader analysis of the

relationship of all exercise on CRF only in individuals with cancer (including BC),^{5,14,31,32} and 1 meta-analysis included mindfulness stress reduction therapy as a yoga comparator in women with BC on CRF and QOL.³³ The previous systematic reviews and meta-analyses were limited in their elucidation of the role of yoga exclusively to improve CRF and QOL in BC population, as yoga and/or BC were not the only focus of the reviews. Thus, it is still unclear what the effect of yoga interventions is on CRF or QOL for women with BC, and whether yoga is superior to other forms of PA. With this new evidence-based knowledge, healthcare practitioners and exercise specialists would be more equipped to provide exercise prescriptions and education to assist women with BC in reducing their CRF and improving QOL. Thus, the PICO(T) for this present study was a population of adult women diagnosed with BC, various forms of yoga as the intervention type, with both active and non-active comparators, the outcome evaluated was both CRF and QOL, and type of studies included were randomized controlled trials. The objective of this systematic review and meta-analysis is to determine the role of yoga interventions in improving CRF and QOL in women with BC compared to non-active and active comparators.

Methods

This meta-analysis followed the PRISMA guidelines³⁴ (see Figure 1 for the PRISMA diagram). An electronic search was completed by an academic librarian (RF) of 3 databases (MEDLINE, Embase Classic+Embase and EMB Reviews, Cochrane Central Register of Controlled Trials databases) from database inception until September 2016, with an updated search performed in May 2018. Additional screening of bibliographies from a previous systematic review¹⁴ was completed to identify any missed articles from the database search; no additional articles were identified.

Eligibility criteria for this systematic review and meta-analysis were randomized controlled trials that included full text articles published in English. Our population of interest was women, diagnosed with BC (at any stage), receiving any type of treatment, age 18 years or older. Studies included some form of yoga intervention, which could include a variety of different types of yoga (eg, Hatha, Iyengar, Restorative). Interventions could be compared to waitlist control, standard or usual care, control group, health education, supportive therapy, or another form of exercise. Studies were included irrespective of intervention length. Studies needed to measure CRF or QOL as a primary or secondary outcome using a validated scale.

Independent reviewers (MO, DS, CL) evaluated the title and abstract of all articles obtained through the electronic search to determine if a study met inclusion and exclusion criteria. Two reviewers evaluated each citation. All citations that met the inclusion criteria based on initial title and

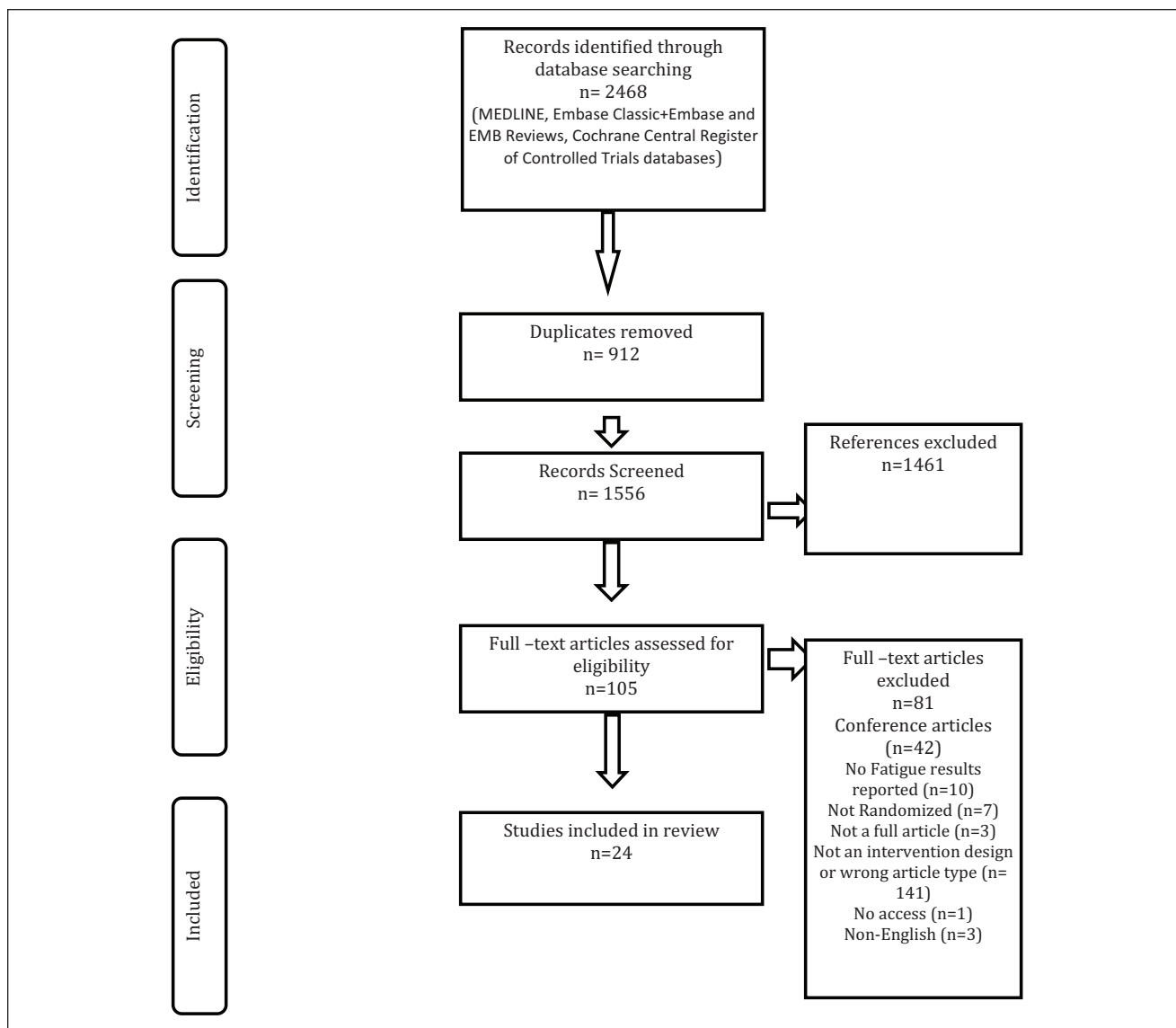


Figure 1. PRISMA diagram.

abstract review were read in full to confirm eligibility. Consensus was achieved through discussion. A standardized data extraction form was used by 3 independent reviewers (MO, DS, CL) to extract the data from eligible studies (See Supplemental Table 1). Data from each study was extracted by 2 reviewers. All disagreements were resolved by an additional reviewer (SMHA).

Reviewers extracted relevant information such as study characteristics, intervention design and outcome measures. Meta-analysis comparators were classified as non-active or active comparators. Non-active comparators consisted of control group, waitlist, usual care, health education, and supportive therapy. Active comparators consisted of physically active interventions such as aerobic training or resistance training.

Primary authors were contacted to attempt to rectify missing data from the included articles. Reference lists of previous systematic reviews and meta-analyses were reviewed. If no further data were forthcoming, missing within-group standard deviations (SD) were computed in this priority sequence: (1) from 95% confidence intervals or standard errors, when they were reported; (2) from the same group's SD at a different time in the study; (3) from the SD in the other group in the same study; (4) by dividing the interquartile range by 1.35.³⁵ Within-group medians were used to replace missing within-group means.³⁵ The pooled effects of yoga on CRF and QOL, compared to a non-physically active control, were calculated using random effects models; the standardized mean difference³⁵ was the effect measure, as studies varied in the instruments used to

measure outcomes. Additionally we analyzed the effects of yoga on CRF and QOL against physical activity-based comparators in the same fashion as non-active comparators. These analyses used outcomes measured at the assessment point directly following the intervention period. Heterogeneity was assessed with the I-squared test. Subgroup analysis was completed to explore differences in treatment effects across subgroups formed by cancer treatment, frequency of yoga sessions per week, length of intervention, use of relaxation within intervention, geographical region of study, fatigue measure used, and risk of bias level. Study bias was evaluated by authors MO, SMHA, and GT with the Cochrane risk of bias tool³⁶ and publication bias was assessed visually using funnel plots. Analyses were conducted using the metafor packages in the R statistical software (Version 3.5.0).³⁷

Results

We identified 2468 records through the electronic search through May 2018. Following the removal of duplicates (n=912), 1556 citations were initially screened, and 105 full-text studies were assessed for eligibility. From the full text screening, 80 studies were excluded and 24 were included^{22,38-58} (see Supplemental Table 2 for exclusion reasons). Authors were contacted twice by email to obtain any missing data.

Eighteen studies compared yoga to a non-active comparator, and 4 compared yoga to an active comparator for CRF, whereas ten and 2 compared yoga to a non-active comparator and active comparator for QOL, respectively (see Supplemental Table 3 for breakdown). The 24 articles were published between 2006 and 2018 and were conducted in the United States (n=13), as well as India (n=2), Turkey (n=2), Germany (n=2), Australia (n=1), Poland (n=1), Canada (n=1), Belgium (n=1) and Taiwan (n=1). The studies included a total of 1394 women diagnosed with BC, and mean ages ranged from 45 to 69 years old. Studies predominantly assessed women who had completed BC treatment (n=11), compared to those currently on treatment (n=9), or a combination of current and completed treatment (n=4). The mean intervention length across the 24 studies was 9.5 weeks, with a range of 6 to 26 weeks. Yoga sessions ranged from 30 to 90 minutes with an average session of 72 minutes. The intensity level of the yoga intervention was not clearly defined within the included studies; however, 14 studies described the yoga programs as gentle, low, or modified to participants' abilities (see Table 1 for study descriptions). Hatha was the most common form of yoga intervention assessed (n=16)^{22,39,40,43,45-48,50,53-59}; additionally, Vivekananda Yoga Anusandhana Samsthana (VYASA) (n=2),^{41,42} Satyanada (n=1),⁴⁹ Baba Joga (n=1)³⁸ and general or unspecified (n=4)^{44,51,52,59} interventions were evaluated. Yoga interventions were supervised in most of the

studies, only 2 studies^{53,57} used non-supervised interventions. Waitlist control was used in eleven studies, and 1 of those studies had a third comparison group consisting of stretching. Control or usual care comparators consisted of supportive therapy (n=2), health/wellness education (n=1), oncologist recommendations for exercise (n=1) stretching exercises (n=1), self-hypnosis (n=1), and cognitive behavior therapy (n=1). The active comparators comprised of physical exercise (n=2), "rapid easy strength training" (n=1) and aerobic training (n=1). Data extracted from each study included can be seen in Supplementary Table 1.

Of the 24 articles, 22 provided data on CRF and 12 on QOL. Fatigue was measured with multiple scales, the most common scales were Functional Assessment of Cancer Therapy (FACT)—Fatigue (FACT-F) subscale (n=5) and Brief Fatigue Inventory (BFI, n=5), followed by the Eastern Co-operative Oncology Group Quality of Life Questionnaire—C30 (EORTC QLQ-C30) Fatigue subscale (n=4), Fatigue Symptom Inventory (FSI, n=2) and Visual Analog Scale (n=2). QOL was also measured with multiple scales, the most common being the EORTC QLQ C30 (n=5 studies) and FACT-Breast (n=5 studies), followed by Medical Outcomes Short Form 36 (n=3), FACT-General (n=2) and Lymphedema Quality of Life Questionnaire (n=1).

Overall, the studies contained low-moderate scores for risk of bias (Figure 2 and Supplemental Figure 4). The most common methodological weaknesses were not indicating how the participants were randomized (n=12 studies), and no indication of allocation concealment (n=8 studies). Only 1 study indicated that participants were blinded to the study hypothesis, and 2 studies indicated some or all of the outcome assessors were blinded to group allocation. As these interventional studies required participants to actively participate in the yoga intervention, blinding participants to their intervention allocation would not be possible. Although attrition occurred within all studies, 3 studies did not provide reasons for study attrition therefore had high risk of bias; the remaining studies providing some description as to why and how it affected the outcome. Most studies had low risk for other potential sources of bias.

Cancer-Related Fatigue

Compared to non-active comparators (n=18 studies), reduction of CRF with yoga had a small to moderate pooled SMD of -0.30 (95% CI -0.51, -0.08) (Figure 3A). Comparing yoga intervention to active comparators (n=6), there was a small SMD of -0.17 (95% CI -0.50, 0.17) (Figure 3B). There was substantial heterogeneity in both analyses (vs. non-active comparators: $I^2=62%$; vs. active comparators: $I^2=55%$). Heterogeneity for both the control and active comparator meta-analysis was explored through subgroup analyses (see below).

Table 1. Study Description.

Study	Type of yoga	Total participants	Intervention	Comparator
Andysz et al ³⁸	Baba Joga yoga	28 (Yoga <i>n</i> = 12, Control <i>n</i> = 16)	Once per week for 10 weeks	Control group
Banasik et al ⁶⁰	Iyengar yoga	18 (Yoga <i>n</i> = 7, Control <i>n</i> = 7)	Twice per week for 8 weeks	Control group
Bower et al ⁴⁰	Iyengar yoga	31 (Yoga <i>n</i> = 16, active comparator <i>n</i> = 15)	Twice per week for 12 weeks	Health education
Chandwani et al ⁴²	Vivekanada Yoga Anusandhana Samsthana (VYASA)	61 (yoga <i>n</i> = 27, control <i>n</i> = 31)	Up to 2 times per week in center and 1 time at home for 6 weeks	Control group
Chandwani et al ⁴¹	Vivekanada Yoga Anusandhana Samsthana (VYASA)	163 (yoga <i>n</i> = 53, control <i>n</i> = 54, active comparator <i>n</i> = 56)	Up to 3 times per week for 6	Stretch group
Cramer et al ⁴³	Hatha yoga	40 (yoga <i>n</i> = 19, control <i>n</i> = 19)	Once per week for 12 weeks with certified hatha yoga instructor	Control group
Culos-Reed et al ⁴⁴	Type not specified	38 (yoga <i>n</i> = 20, control <i>n</i> = 18)	7-week intervention, frequency of classes not indicated	Control group
Danhauer et al ⁴⁵	Restorative yoga	44 (yoga <i>n</i> = 22, control <i>n</i> = 22)	Once per week for 10 weeks with instructor	Control group
Gregorie et al ⁴⁶	Hatha yoga	138 (yoga <i>n</i> = 21, control <i>n</i> = 24, active comparators <i>n</i> = 68)	Once per week for 6 weeks	Self-hypnosis and cognitive behaviour therapy
Kiecolt-Glaser et al ⁴⁷	Hatha yoga	200 (yoga <i>n</i> = 10, control <i>n</i> = 100)	Twice per week for 12 weeks	Control group
Littman et al ²²	Viniyoga	63 (yoga <i>n</i> = 32, control <i>n</i> = 31)	At least once per week for 26 weeks	Control group
Lotzke et al ⁴⁸	Iyengar yoga	92 (yoga <i>n</i> = 45, active comparator <i>n</i> = 47)	At least 3 times per week for 12 weeks	Physical Exercise
Loudon et al ⁴⁹	Satyananda yoga	59, 28 randomized (yoga <i>n</i> = 15, control <i>n</i> = 13)	At least once in center session and daily home practice for 8 weeks	Control group
Moadel et al ⁵⁰	Hatha yoga	128 (yoga <i>n</i> = 84, control <i>n</i> = 44)	Once per week for 12 weeks	Control group
Pruthi et al ⁵¹	Type not specified	30 (yoga <i>n</i> = 15, control <i>n</i> = 15)	Once per week for 8 weeks	Control group
Siedentopf et al ⁵²	Type not specified	75 (yoga <i>n</i> = 49, control <i>n</i> = 44)	Twice per week for 5 weeks	Control group
Stan et al ⁵³	Hatha yoga	34 (yoga <i>n</i> = 18, active comparator <i>n</i> = 16)	3–5 times per week for 12 weeks	Rapid easy strength training
Taso et al ⁵⁴	Anusara Yoga	60 (yoga <i>n</i> = 30, control <i>n</i> = 30)	Twice per week for 8 weeks	Control group
Taylor et al ⁵⁵	Restorative/Pranayama Yoga	33 (yoga <i>n</i> = 14, control <i>n</i> = 12)	Once per week for 8 weeks	Control group
Vadiraja et al ⁶¹	Type not specified	88 (yoga <i>n</i> = 42, active comparator <i>n</i> = 33)	Between 3–4 times per week (in center and home practice) for 6 weeks	Supportive therapy
Vadiraja et al ⁵⁹	Asanas, breathing, mediation, yogic relaxation techniques	91 (yoga <i>n</i> = 42, control <i>n</i> = 33)	Twice per week for 12 weeks	Control group
Winters-Stone et al ⁵⁷	Restorative yoga DVD	95 (yoga <i>n</i> = 47, control <i>n</i> = 43)	Up to three times per week for 8 weeks	Control group
Vardar Yağlı et al ⁵⁶	Yogasana	52 (Yoga <i>n</i> = 24, active comparator <i>n</i> = 28)	Three times per week for 6 weeks	Aerobic training
Vardar Yağlı and Ulger ⁵⁸	Asanas	20 (yoga <i>n</i> = 10, active comparator <i>n</i> = 10)	Once per week for 8 weeks	Physical exercise

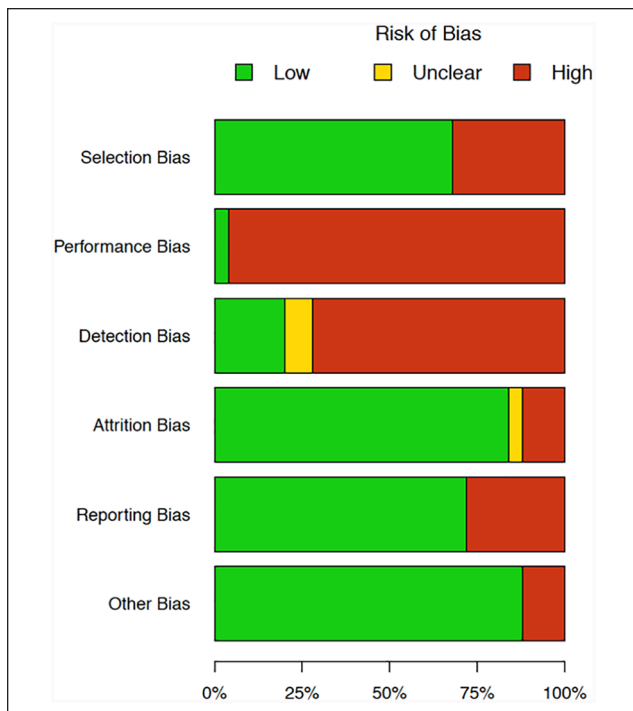


Figure 2. Overview of risk of bias (n = 24 studies).

Quality of Life

Compared to non-active comparators (n = 10 studies), yoga had a small to moderate beneficial effect on QOL (SMD 0.27, 95% CI 0.46, 0.07) (Figure 4A). There was low heterogeneity ($I^2=21\%$). Compared to active comparators, yoga had a negligible pooled effect, with a SMD of -0.04 (95% CI 0.22, -0.31) (Figure 4B). There was no heterogeneity ($I^2=0\%$).

Subgroup Analyses and Heterogeneity

For the CRF outcome, only the subgroups examining specific fatigue measures identified differential effects of yoga ($P<.01$). The FSI (n=2), showed a larger effect size (-1.25; 95% CI -1.71, -0.8) than the EORTC QLQ-C30 fatigue item (n=3; -0.63; 95% CI -0.96, -0.31), the BFI (n=5, 0.00; 95% CI -0.24, +0.24), and FACT-F (n=4; -0.12; 95% CI -0.47, +0.24) (test for between-group effect $P<.001$) (see supplementary Figure 1a-g). No differential effect by subgroup was found for CRF related to cancer treatment phase ($P=.19$), number of yoga sessions per week ($P=.11$), length of intervention ($P=0.97$), use of relaxation within intervention ($P=.85$), geographical location of study ($P=0.43$) or risk of bias level of the study ($P=.22$).

For the QOL outcome, only 1 subgroup analysis indicated a differential effect of yoga (test for between-group effect $P=0.02$): the number of sessions completed per

week. Specifically, yoga completed once per week resulted in a moderate effect size (0.42; 95% CI 0.20, 0.64) whereas 2 or more sessions per week had a negligible effect (0.02; 95% CI -0.24, 0.28) (See supplemental Figure 2a-e).

Discussion

This study provides a rigorous updated examination of the role of yoga on CRF and QOL for women with BC. Based on 24 trials, the meta-analysis suggests a small to moderate beneficial effect of yoga on CRF compared to a non-active group, but no benefit was found compared to an active group. Similarly, when comparing yoga to both a non-active and active group for QOL, there was a small to moderate-sized beneficial effect for QOL for yoga compared to the non-active group, but not for the active group. From the studies that described adherence to their interventions, the data suggest that participants were moderately to highly adherent with yoga and PA interventions.

There is substantial heterogeneity between these studies for the CRF outcome, however low to no heterogeneity for QOL. In the CRF subgroup analysis, it appeared that for studies examining the effect of yoga, 1 fatigue outcome measure (the FSI) may be more sensitive to change than several others, as we found substantial heterogeneity ($I^2=69\%$) in that subgroup analysis. This may be due in part to the FSI evaluating both physical and mental aspects of fatigue, compared to the EORTC QLQ-C30, BFI and FACT-F, which predominantly evaluate the physical aspect of fatigue.⁶²

Our findings confirm and extend previous systematic reviews and meta-analyses. A review by Sadja et al in 2014²⁵ found that yoga may be beneficial in reducing CRF for women with BC, when compared to non-active comparator (control group). Three previous meta-analyses^{29,30,63} compared yoga to a range of non-active comparators (control, wait-list, supportive therapy). Boehm et al⁶³ included 19 studies and found similar results to ours (SMD=0.27 [0.23;0.31]), as well as Buffart et al²⁹ (n=15) (SMD=-0.51 [-0.79;-0.220]), compared to Lin et al³⁰ (n=4) who did not find statistically significant results (SMD=-0.15 [-0.29;0.09]),^{29,30,63} this may be due to the smaller sample size. When comparing our findings to meta-analyses that evaluated overall exercise interventions (including yoga)^{5,32} and exercise (with no yoga intervention)^{11,15} for CRF benefit, our findings also demonstrate similar results. However, none of the previous reviews evaluated yoga versus an active comparator as we have. Our findings suggest that yoga provides benefits on CRF compared to non-active comparators, similar to the literature. However, our findings additionally suggest that yoga may have similar benefits on CRF as physical activity, however yoga is better than no activity at all. This is an important finding that can be used in clinical practice to incorporate a yoga program into

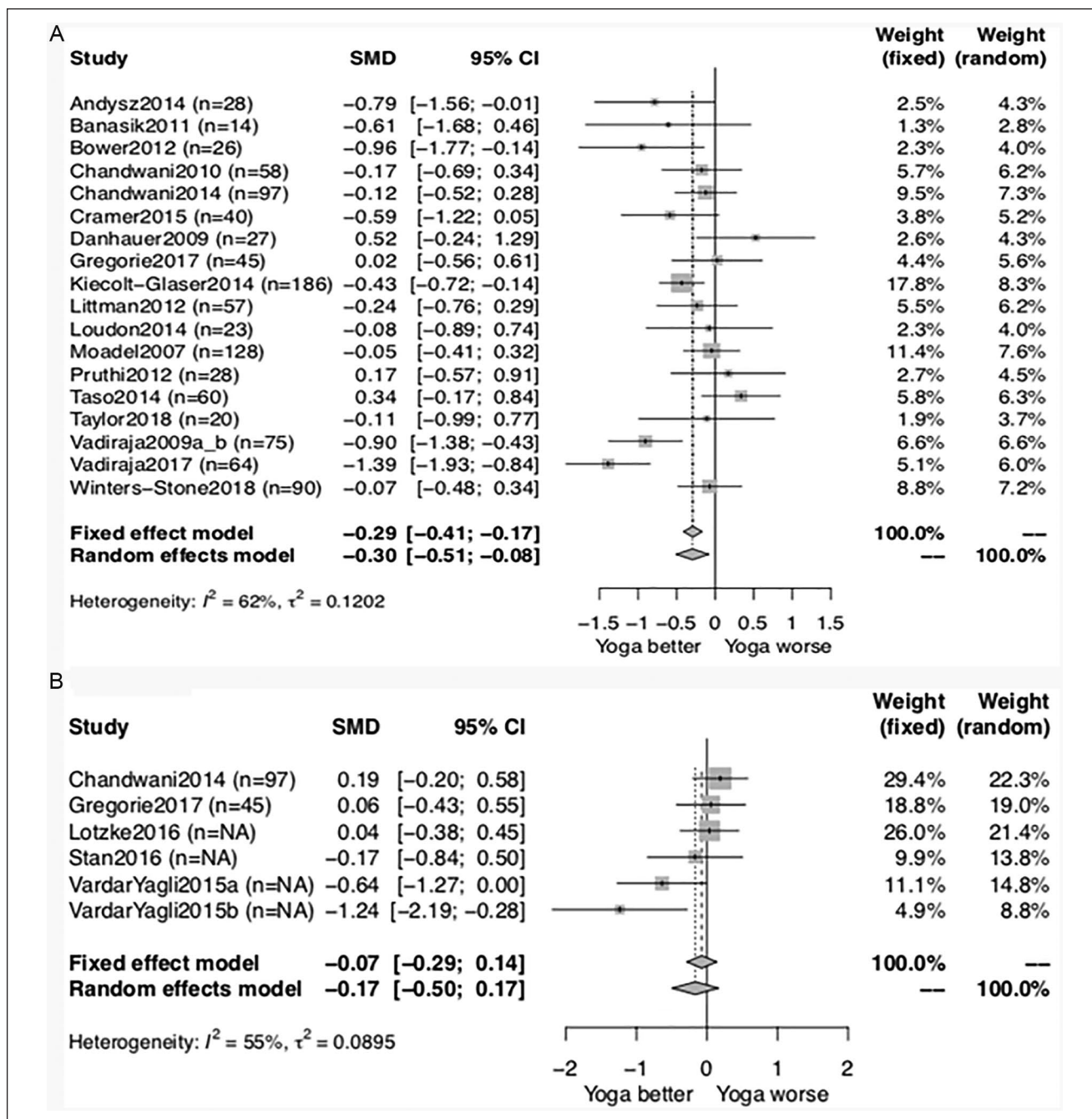


Figure 3. Forest plot for CRF using comparisons of post-values with. (A) Non-active comparators. (B) Active comparators.

an expanded set of prescription options to assist women with BC in managing their CRF.

Strengths of this review include a rigorous literature search, screening and data extraction, follow-up with authors on insufficient data, and completing a study quality assessment. There are also limitations to our study, as we excluded non-English, non-randomized, non-full text publications and focused on breast cancer only studies. We used post values rather than change score values for the

meta-analysis as this provided the review with more robust data for inclusion in meta-analyses. Additional limitations relate to the evidence, which require our analyses to be interpreted with caution. Such limitations included the following: multiple studies (CRF only [n=1],⁵² QOL only [n=12]^{39,40,46,47,51,54-59,61}) were excluded from the meta-analysis due to insufficient data. We also recognize the need to be cautious in interpreting subgroup analyses because of the risk of false-positives. Any such findings would require

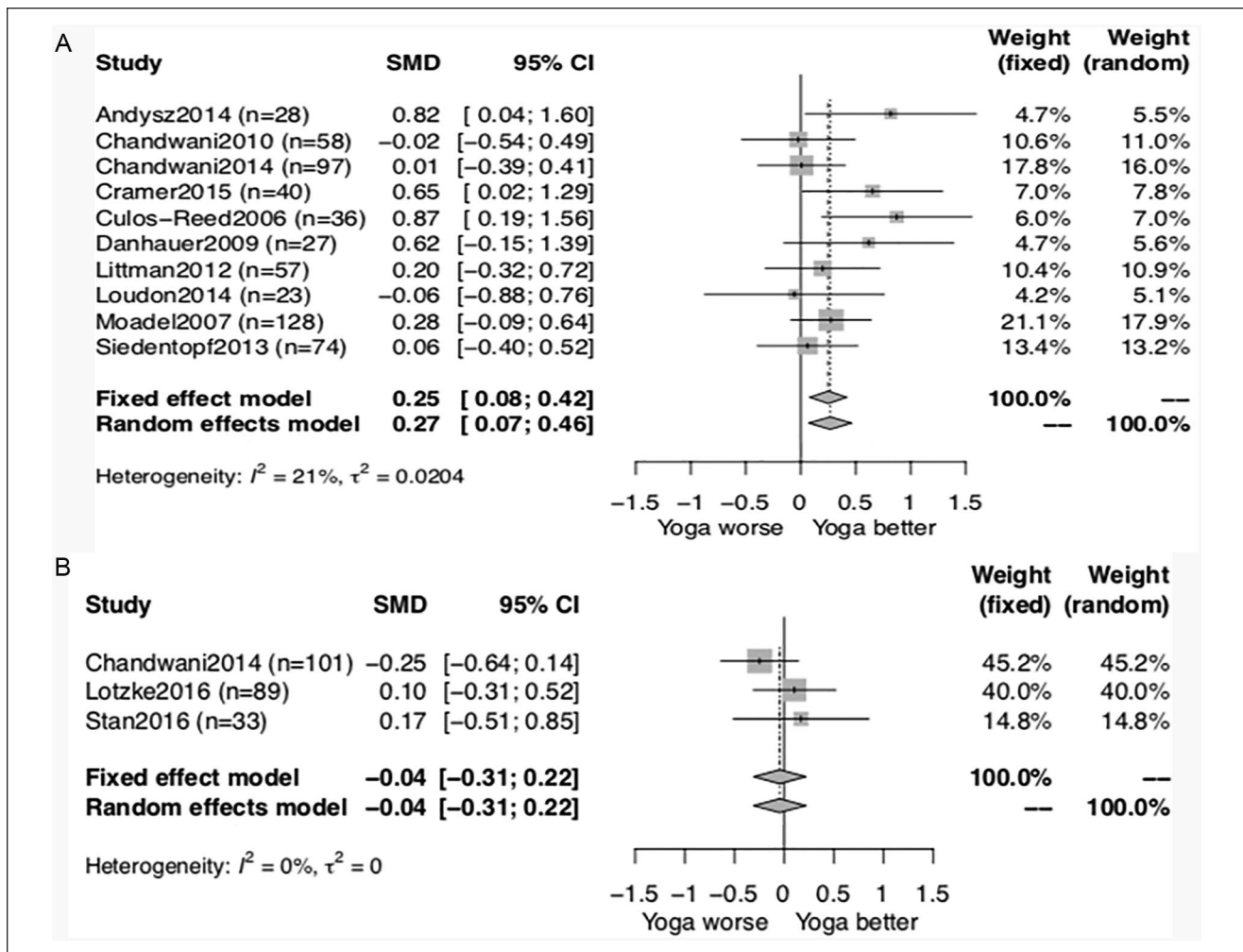


Figure 4. Forest plot for QOL using comparisons of post-values with. (A) Non-active comparators. (B) Active comparators.

validation in future trials. Data extraction was limited by the ways in which studies reported their results, which varied widely and included baseline and post-intervention mean and standard deviation, mean change and standard deviation, to median and interquartile range, standard error, and other variations. Additionally, many of the studies evaluated had high risk of bias in the participant and outcome assessor blinding categories/items and the number of active comparator studies was relatively small. Future research should focus on conducting phase III RCTs to help build evidence on the effects of yoga on CRF (eg, optimal “dose” and treatment duration, key elements).

This systematic review and meta-analysis will assist clinicians and researchers by providing a summary of current evidence on the effects of yoga on CRF and QOL. This meta-analysis demonstrates that yoga is beneficial in improving CRF and QOL for women with BC and that these benefits are comparable to the active comparators such as aerobic, resistance or combination of aerobic and

resistance exercise. The findings from this review should encourage the recommendation of yoga as a prescription to reduce CRF. Of note, many women with BC may find yoga easier to adopt than other physical activity interventions for various reasons, such as providing benefits to managing CRF through lower intensity physical activity, and our findings confirm it to be equally efficacious for CRF and QOL outcomes. Future research should focus on studying the sensitivity of different CRF scales and understanding the barriers to implementation of yoga in the real world.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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