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Effect of yoga on musculoskeletal complaints in women during endocrine treatment for breast cancer: protocol of the randomised controlled COBRA trial

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ABSTRACT

Introduction Approximately 40% of women stop endocrine therapy for hormone-receptor-positive breast cancer within the first 5 years of prescribed treatment because of side effects. Musculoskeletal complaints are among the most frequently reported side effects. The Cancer Of the BReast Asanas (COBRA) study examines the effect of an 18-week yoga programme on endocrine therapy-associated musculoskeletal complaints in women with breast cancer.

Methods and analysis In total, 140 women will be randomised in a 1:1 ratio to the intervention or waitlist control group. The intervention programme consists of two times a week 1-hour supervised Hatha or (easy) Vinyasa yoga classes at a yoga or sports centre for 18 weeks and once per week a half-hour at home using videos. The waitlist control group is asked to maintain their habitual lifestyle during the first 18 weeks and will participate in a similar yoga programme to the intervention group for the following 18 weeks. The control group yoga programme is offered live-remote. The primary outcome (musculoskeletal complaints) is assessed with the Brief Pain Inventory questionnaire at baseline and 18 weeks (primary comparison) and additionally at 36 weeks. Secondary outcomes include lower and upper extremity joint complaints, menopausal symptoms, fatigue, sleep, quality of life, anxiety and depression, cognitive complaints and habitual physical activity (all patient-reported), vital signs and anthropometrics, physical fitness, blood biomarkers, medication use, safety data and patient and teacher experiences. At baseline and 18 weeks, cognitive complaints are also assessed with an online neuropsychological test battery.

Ethics and dissemination The COBRA study was approved by the Medical Ethical Committee of the University Medical Center Utrecht. The study started on 8 October 2024, and 65 participants have been included (20 January 2026). Results will be submitted to an international peer-reviewed journal.

Trial registration number NCT06480513.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A methodological strength of this study is that all participants will follow a yoga programme, either on-site (intervention group) or live-remote (waiting list control), to minimise contamination and drop-out after randomisation.
⇒ Another methodological strength is that it reflects a real-world setting, as we select a yoga centre near each participant's home.
⇒ Another methodological strength is that we only include participants with endocrine therapy-associated musculoskeletal complaints, which reduces floor effects and enhances the ability to detect a meaningful treatment effect.
⇒ A limitation of the on-site yoga programme is the expected variation in yoga practice because participants attend classes at various yoga centres, reflecting the pragmatic study design.
⇒ A limitation of the waiting list control group yoga programme is that it is difficult to monitor whether participants are performing the postures correctly and to correct them if necessary, due to the programme's live-remote nature.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women globally, accounting for approximately one in four female cancer cases in 2022.[1] Of these cancers, 85% are hormone-receptor positive, meaning that their growth is driven by hormones. This type of cancer is treated with (neo)adjuvant endocrine therapy, a treatment that blocks or reduces hormone uptake, and typically continued for 5–10 years, depending on tumour stage and recurrence risk.[2 3] The most common types of endocrine therapy are tamoxifen and aromatase inhibitors.

Unfortunately, endocrine therapy can cause several side effects. One of the most common side effects is musculoskeletal complaints, such as pain and stiffness.[4] These complaints may lead to a considerable burden, with approximately 40% of women discontinuing adjuvant endocrine therapy within the recommended minimum of five consecutive years.[5 6] However, extending endocrine therapy for an additional 5 years has been shown to further reduce recurrence rates.[7] Therefore, effective management of these side effects is crucial to improve adherence, ultimately leading to a better prognosis.

Musculoskeletal complaints are commonly treated with analgesics. However, analgesics demonstrate limited efficacy, have their own side effects (eg, gastrointestinal, renal and cardiovascular effects), pose risks of interactions with other medications and are generally not a preferred approach by patients to treat the side effects of endocrine therapy.[8] Therefore, non-pharmaceutical treatments addressing endocrine therapy-associated musculoskeletal complaints might be a preferred option.[9] A randomised controlled study included 141 breast cancer survivors and reported beneficial effects of a 12-month strength and aerobic exercise programme two times a week on joint pain as compared with usual care.[10] However, other randomised controlled trials (RCTs) investigating the effect of exercise therapies on aromatase inhibitor-induced musculoskeletal symptoms demonstrated little benefit.[11]

Another promising option is yoga. Compared with an exercise programme, yoga has both a physical and mental component.[12] The physical component may increase patients' strength, coordination and flexibility. For instance, an 8-month yoga intervention significantly improved leg strength in premenopausal women when compared with usual care.[13] Also, a meta-analysis in older adults showed significant improvements in several physical function outcomes such as balance, lower body flexibility and lower limb strength.[14] Improving strength, coordination and flexibility consequently decreases joint load, thereby possibly decreasing pain. The mental component (breathing and meditation exercises), on the other hand, may activate the parasympathetic nervous system, potentially interfering with the chronic pain cycle and stress response. In addition, yoga has been shown to reduce inflammation, which might also be an underlying mechanism in the development of endocrine therapy-associated musculoskeletal pain.[12 15] Along with the possible positive effect of yoga on musculoskeletal pain, yoga could also be beneficial for individuals with elevated levels of anxiety,[16] depression,[17] persistent fatigue[18] or impaired sleep quality,[19] which might also be (indirect) side effects of endocrine treatment. The synergistic impact on both physical and mental health by yoga may provide a greater health benefit than each component individually.

Feasibility studies indicated that yoga might alleviate musculoskeletal pain in breast cancer survivors.[20–23] For example, participation in a pilot RCT with an 8-week yoga programme significantly reduced joint pain in women diagnosed with stage I or II breast cancer (n=37).[21] Another RCT in which breast cancer survivors followed a 6-week yoga programme two times a week also showed significantly reduced endocrine therapy-associated knee joint pain (n=60).[22] While these findings are promising, the small sample sizes and short intervention periods limit the strength of evidence, highlighting the need for larger, well-designed trials to confirm these effects.

To date, no large-scale RCTs have investigated whether yoga can alleviate endocrine therapy-associated musculoskeletal complaints in women with breast cancer. The Cancer Of the BReast Asanas (COBRA) study will assess the impact of yoga on such complaints in women with stage I–III breast cancer.

METHODS AND ANALYSIS

Design

The COBRA study is a superiority RCT with two parallel study arms. Patients are included at the University Medical Center (UMC) Utrecht, the Netherlands, and recruited from multiple hospitals nationwide. The intervention group participates in an 18-week yoga programme conducted two times a week at a yoga or sports centre near home, and once per week at home using videos. The waitlist control group adheres to their habitual lifestyle during this period. After the intervention period, the waitlist control group will also receive an 18-week yoga intervention, which will be provided live-remote (see figure 1 for an overview). The study started on 8 October 2024, and recruitment is planned to be completed mid-2027.

Participants

In total, 140 women with breast cancer will be enrolled in the COBRA study. Women are eligible if they are diagnosed with stage I–III hormone-receptor-positive breast cancer and have completed all initial treatments (surgery, chemotherapy and radiotherapy) for at least 12 weeks. They should be treated with endocrine therapy (tamoxifen or aromatase inhibitors) for a minimum of 4 months, with the intention to continue for at least eight more months with the same endocrine medication. Women must experience musculoskeletal complaints, as determined by a score of ≥3 on the fifth question of the Brief Pain Inventory (BPI): 'Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours' on a scale of one to ten.[24] Moreover, they should be stabilised on menopausal symptom medication or antidepressants for at least 3 months and 3 weeks, respectively, if applicable, and they should have sufficient understanding of the Dutch or English language. Women will be excluded if any of the following apply: too physically active (ie, >150 min of moderate-to-vigorous physical activity per week), currently practising yoga, having a body mass index (BMI) of >35, participation in a psychological intervention during the study intervention period or previous participation in the intervention group of an exercise study during the breast cancer treatment.

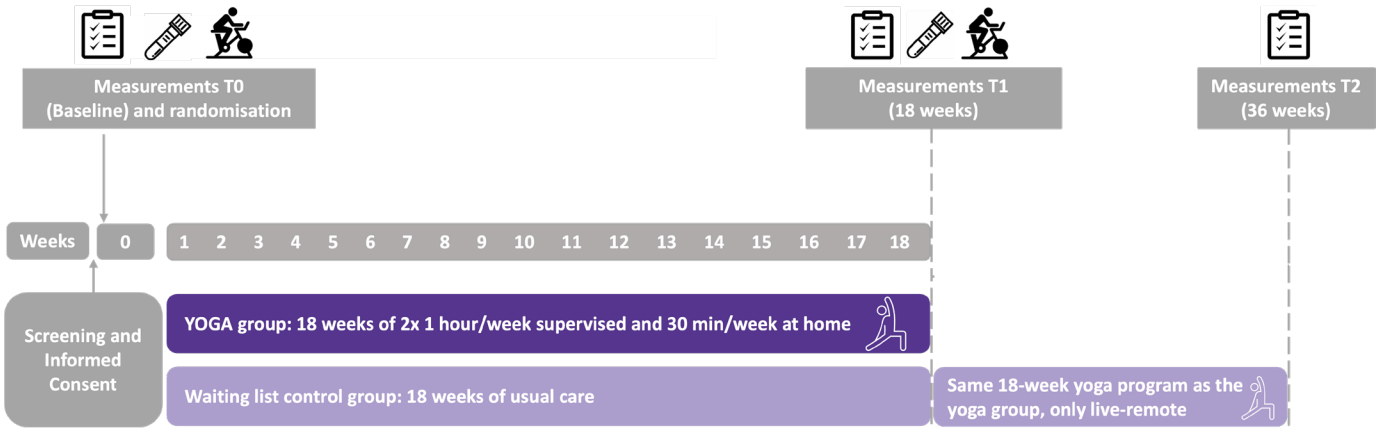

Figure 1 Design of the COBRA study. COBRA, Cancer Of the BReast Asanas.

We also exclude women in any circumstances that would impede their ability to give informed consent or adherence to study requirements, as determined by the study team, and who know beforehand to be absent for three or more consecutive weeks during the intervention period.

Recruitment and randomisation

Treating physicians or oncology nurses inform women during routine follow-up visits about the study and provide them with an information leaflet that contains the study team's contact details. Women may contact the study team directly or give consent for the physician to send their contact details to the study team. Additionally, recruitment is done by sharing study information via (social) media such as LinkedIn, Facebook, patient organisation websites or community newspapers. Interested women can contact the study team directly via email, phone or text message.

After receiving the contact details, the study team contacts the potential participant by phone to explain the study and to assess eligibility. Eligible women who agree to participate sign an informed consent form electronically via ValidSign (see online supplemental file 1). Participants with limited digital competencies can provide written consent by postal mail. Participants receive a digital copy of the signed informed consent form. After providing informed consent, women complete the BPI as part of the screening process. This questionnaire is sent through Castor electronic data capture (EDC), a secure data management system. If the predefined threshold on the BPI is exceeded, women are invited by a member of the study team for a baseline visit at the UMC Utrecht.

Participants receive the baseline questionnaires via Castor 3 days before their baseline visit to complete at home. If preferred, participants are allowed to fill out the questionnaires at the UMC Utrecht as well. During the baseline visit, bodyweight and height, and hip and waist circumference are measured. Blood (20 mL) is drawn, and participants perform physical fitness and performance tests. All results of the baseline visit are recorded on a case report form and subsequently transferred to Castor.

At the end of the baseline visit, participants are randomly assigned in a 1:1 ratio via a computer-generated sequence within Castor EDC, to either the intervention or waitlist control group. The randomisation was installed by an independent researcher of the Julius Centre, with a variable block size unknown to the COBRA study team members who enrol participants, to ensure allocation concealment and prevent predictability. No stratification factors were used. Women are enrolled at randomisation.

Yoga programme of the intervention group

Participants in the intervention group follow an 18-week yoga programme consisting of two supervised 1-hour sessions per week and one unsupervised 30 min yoga session of Hatha or (easy) Vinyasa yoga per week at home using videos. Participants will attend easy Vinyasa yoga classes if these are available at the yoga or sports centre; otherwise, they will attend a regular Hatha yoga class. A member of the study team will identify a suitable yoga or sports centre close to the participant's home. Here, the team member will first participate (in person or online) in the yoga class. If the class is deemed suitable for the study, the team member will provide standardised protocol training to the yoga instructor. This training provides detailed information on the COBRA study, breast cancer and alternative yoga poses for the women in the study. The yoga instructors receive the information on paper as well.

Yoga instructors will monitor the attendance and progress of the participant and provide motivation if needed. If, despite individual adaptations, the yoga classes are too challenging for the participant, they may in consultation with the yoga instructor and the study team switch to less demanding classes (eg, yin yoga).

The supervised yoga classes usually start with meditation exercises, followed by a warm-up, a sequence of postures (in flow, in case of easy Vinyasa), breathing exercises and a deep relaxation. To optimise individual attention, class sizes will be limited to a maximum of 15 participants. Instructors need to have at least 2.5 years of teaching experience or a 500-hour yoga teaching certificate. Also, instructors are asked to monitor attendance

and to motivate the participants if necessary. The once-weekly unsupervised yoga session consists of a selection of 30 min videos, part of these are specifically developed for the COBRA study by experienced yoga teachers, from which participants can choose. This session can be completed at any time during the week. To monitor adherence, participants need to log each session in a study diary.

Yoga programme of the waitlist control group

Participants in the waitlist control group are requested to maintain their current lifestyle during the first 18 weeks of the study programme, and to fill out a diary about their medication use (endocrine treatment medication, pain medication and supplements). After the 18-week primary endpoint measurement, they start with a live-remote yoga programme that follows the programme of the intervention group; that is, a supervised 18-week yoga intervention of two times a week 1-hour sessions of Hatha yoga and once a week an unsupervised 30 min session at home using videos. Moreover, women in the control group join the same (live-remote) class, whereas women in the intervention group participate in regular yoga classes of a yoga or sports centre near their home.

Study endpoints

At baseline and 18 weeks follow-up, participants visit the UMC Utrecht for the measurements. At 36 weeks follow-up, both groups receive the questionnaires again to fill out from home (table 1).

Baseline and follow-up measurements

Primary outcome

The primary outcome is musculoskeletal complaints, assessed by the short form of the BPI at 18 weeks. The BPI is a commonly used, reliable and valid measure to assess pain in cancer patients.[24] Similar to the study of Irwin *et al*,[10] the BPI will be modified to specifically capture joint pain and stiffness by adding the term 'joint pain/stiffness' rather than just the word 'pain' throughout the questionnaire.

The BPI consists of single items, for example, worst pain, that form two domain scores: pain severity and pain interference, each scored on a 0–10 scale. The primary outcome is a hierarchically defined endpoint where we will sequentially test worst pain, pain severity and pain interference to preserve an alpha of 0.05. The order of the sequential testing is: (1) worst pain/stiffness, (2) pain/stiffness severity and (3) pain/stiffness interference.

Worst pain/stiffness is analysed as a single item and categorised as mild (score of 3–4), moderate (score of 5–7) or severe (score of 8–10). Pain severity is a composite score of pain at its worst, least, average and now. Pain interference is a composite score of pain interference with seven daily activities (general activity, walking, work, mood, enjoyment of life, relations with others and sleep).

Secondary outcomes

Patient-reported outcome measures (PROMs)

Upper extremity musculoskeletal symptoms are assessed by the Disabilities of the Arm, Shoulder and Hand questionnaire. This is a 30-item questionnaire that assesses physical functioning and symptoms of musculoskeletal disorders of the upper extremities in patients.[25]

Lower extremity joint symptoms are assessed by the Western Ontario and McMaster Universities Osteoarthritis index, a questionnaire that assesses the pain of the hip and knee joints during the past 7 days in three domains: pain, stiffness and physical functioning.[26]

Health-related quality of life (HRQoL) is assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core questionnaire (QLQ-C30) and by the Breast Cancer module (QLQ-BR45). The EORTC QLQ-C30 is a 30-item questionnaire that assesses quality of life over five functional scales (physical, emotional, role, cognitive and social functioning), one global quality of life scale and three symptom scales (pain, fatigue, nausea and vomiting) as well as single items for specific symptoms. In addition, a composite score can be calculated to represent overall HRQoL. The EORTC QLQ-BR45 is a supplementary questionnaire to the EORTC QLQ-C30, specifically designed for breast cancer patients. It contains nine multi-item scales to assess body image, sexual functioning, breast satisfaction, systemic therapy side effects, arm symptoms, breast symptoms, endocrine therapy symptoms, skin mucosal symptoms and sexual symptoms of breast cancer patients. Also, single items on sexual enjoyment, future perspective and being upset by hair loss are added.[27 28]

Symptoms associated with endocrine treatment are assessed by the Functional Assessment of Cancer Therapy—Endocrine Symptoms questionnaire. This questionnaire assesses the symptoms presented during endocrine treatment within five subscales: physical well-being, social/family well-being, emotional well-being, functional well-being and the endocrine symptom subscale.[29]

Fatigue is assessed by the 20-item Multidimensional Fatigue Inventory, assessing fatigue on five dimensions: general, physical and mental fatigue, reduced activity and reduced motivation.[30]

Anxiety and depression are assessed by the Hospital Anxiety and Depression Scale questionnaire. This questionnaire consists of 14 items: seven items on anxiety and seven items on depression.[31]

Sleep is assessed by the Pittsburgh Sleep Quality Index. This questionnaire assesses sleep quality and disturbances during the past month. It includes seven dimensions: subjective sleep quality, latency and duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction.[32]

Physical activity is assessed by the short questionnaire to assess health-enhancing physical activity. This questionnaire assesses physical activity during commuting, leisure-time, sports activities, household activities and activities at work.[33]

Table 1 Overview of the study parameters and assessment methods used in the COBRA study

Parameter	Assessment method	Baseline	18 weeks	36 weeks
Sociodemographic factors and breast cancer risk factors				
Age, education, marital status, menopausal status, age at menopause, alcohol intake and smoking status	Self-designed questionnaire	X		
Primary patient-reported outcome				
Musculoskeletal complaints	Modified BPI 1. Worst joint pain/stiffness 2. Joint pain/stiffness severity 3. Joint pain/stiffness interference	X	X	X
Secondary patient-reported outcomes				
Lower extremity joint complaints	WOMAC	X	X	X
Upper extremity joint complaints	DASH	X	X	X
Menopausal symptoms	FACT-ES	X	X	X
Fatigue	MFI	X	X	X
Sleep	PSQI	X	X	X
Quality of Life	EORTC QLQ-C30/QLQ-BR45	X	X	X
Anxiety and depression	HADS	X	X	X
Cognitive complaints	FACT-COG	X	X	X
Habitual physical activity	SQUASH	X	X	X
Cognitive functioning				
Online neuropsychologic test battery	Amsterdam cognition scan	X	X	
Biomarkers				
Interleukin-6, tumour necrosis factor alpha, interleukin-1β and high-sensitive C reactive protein*	Blood sampling (serum, plasma, platelets)	X	X	
Vital signs and anthropometrics				
Weight, height, waist and hip circumference	According to SOP	X	X	
Resting heart rate/blood pressure	According to SOP	X	X	
Physical fitness/performance/activity				
Maximal short exercise capacity	Steep ramp test	X	X	
Muscle strength (lower body)	Leg press (hypothetical 1-RM test)	X	X	
Handgrip strength	Handgrip dynamometer	X	X	
Balance	Short-Form Fullerton Advanced Balance (FAB) scale	X	X	
Core strength	Plank position holding time test	X	X	
Clinical data				
Cancer characteristics and treatment history	Medical records	X		
Medical history and concomitant diseases	Log-form	X	X	

Continued

Table 1 Continued

Parameter	Assessment method	Baseline	18 weeks	36 weeks
Pain medication	Patient diary during study			
Compliance endocrine treatment	Patient diary during study			
Safety				
(Serious) adverse events	Active surveillance during study			
Qualitative outcomes				
Patient and teacher experiences	In-depth-interviews after study ends			

*A literature review will be conducted at the end of the study to investigate possible emerging biomarkers.
BPI, Brief Pain Inventory; COBRA, Cancer Of the BReast Asanas; DASH, Disabilities of the Arm, Shoulder and Hand; EORTC, European Organisation for Research and Treatment of Cancer; FACT-COG, Functional Assessment of Cancer Therapy—Cognitive Function; FACT-ES, Functional Assessment of Cancer Therapy—Endocrine Symptoms; HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; PSQI, Pittsburgh Sleep Quality Index; QLQ-BR45, Quality of Life by the Breast Cancer module; QLQ-C30, Quality of Life Core 30-item questionnaire; RM, Repetition Maximum; SOP, Standard Operating Procedure; SQUASH, short questionnaire to assess health-enhancing physical activity; WOMAC, Western Ontario and McMaster Universities Osteoarthritis.

Age, marital status, education level, menopausal status, smoking status and alcohol use are assessed by a self-developed questionnaire.

Cognitive functioning

Cognitive complaints are assessed by the Functional Assessment of Cancer Therapy—Cognitive Function (FACT-COG) questionnaire and by the Amsterdam Cognition Scan.[34 35] The FACT-COG questionnaire includes four subscales: perceived cognitive impairments, perceived cognitive abilities, impact of perceived cognitive impairment on quality of life and comments from others on cognitive functioning.

The Amsterdam Cognition Scan (ACS) is a neuropsychological test battery that includes seven tests with eleven outcome measures in the following domains: learning and memory, attention and working memory, processing speed, executive functioning and motor functioning. Participants complete the ACS at home within 1 week after the baseline and 18-week visits, which takes approximately an hour. The ACS is proven to be a reliable self-administered tool for measuring cognitive functioning.[36]

Vital signs and anthropometry

Vital signs (resting heart rate and blood pressure) will be measured two times and averaged, after a seated 5 min resting period with a 30 s rest period in between. These are measured on the left arm, unless the participant has lymphedema or a Peripherally Inserted Central Catheter line on the left arm, then the right arm is used. If the systolic blood pressure is ≥120 mm Hg and/or the diastolic blood pressure is ≥80 mm Hg, the measurement will be repeated after a 1 min rest period, and the mean value of all measurements will be recorded.

Anthropometrics (height, weight, waist and hip circumference) are measured in light clothing and without shoes during the baseline and 18-week visit. The participants' height is measured using a stadiometer, and weight is measured with a digital weighing scale. Waist circumference is measured at the midway point between the lowest rib and the iliac crest. Hip circumference is measured at the widest part of the hips, with the participant standing with the feet together. Both circumferences are measured two times (with a soft measuring tape) for consistency, and a third time if the first two attempts differ by more than 2 cm. The two closest circumference measurements are averaged.

Physical fitness and performance

Balance is measured with the Short-Form Fullerton Advanced Balance scale. This scale consists of four items: stepping up onto and over a 6-inch bench, a tandem walk, standing on one leg and standing on foam with the eyes closed. The items are rated from 0 (unable to complete the task) to 4 (completed the task perfectly), and the scores are summed up to a total score (0–16). Muscle strength is assessed with three tests: the hand grip strength test, the leg press and the plank position holding test. Hand grip strength is assessed using a handgrip dynamometer (hydraulic Jamar). The participant is asked to squeeze the dynamometer as hard as possible with each hand. The best of three attempts is recorded. Leg strength is assessed using a leg-press hypothetical 1-RM test, according to a standardised protocol. Core strength is assessed with the plank position holding time test. The participant needs to hold the plank position for as long as possible.

The level of fitness is assessed by the Steep Ramp Test using a cycle ergometer.[37] The test begins after 3 min of unloaded cycling at 25 W and increases by 25 W every 10 s. Participants are instructed to cycle at 70–90 revolutions per minute (RPM) and keep on cycling until their maximum capacity. The test ends if the RPM drops below 60 RPM. This is a (short) maximal test, but due to its steep increments, the limiting factor is peripheral muscle

strength and not cardiovascular capacity. Outcomes are the highest achieved output in W (the Maximum Short Exercise Capacity). Also, RPE at termination, total cycling time, heart rates at test completion and 1 min and 2 min thereafter are reported.

Blood markers

Blood samples will be collected to assess inflammatory markers, including interleukin-6, tumour necrosis factor alpha, interleukin-1β and high-sensitivity C reactive protein. Blood sampling will be performed by vein puncture at rest. Plasma, serum and cell pellets will be collected (20 mL). Participants are instructed not to exercise vigorously or drink alcohol in the 24 hours before the visit. Also, during the last 2 hours before the visit, participants are instructed not to smoke, eat or drink (except water).

After collection, the samples will be centrifuged, transferred to cryotubes and stored at ≤−70 °C at the biobank of the UMC Utrecht. Also, a literature review will be conducted to identify the most promising biomarkers. This will offer the opportunity to assess potentially emerging new biomarkers.

Medication use and compliance

The use of pain medication at baseline is assessed via the BPI and questioned during the first visit at the UMC Utrecht. The usage of pain medication during the study and compliance with endocrine therapy are measured via a self-developed diary. For the first 18 weeks, participants record daily all medications taken—date, type, dosage and frequency—including endocrine treatments, pain medications and supplements. Participants are instructed during the first visit at the UMC Utrecht to report only pain medication if it is used to alleviate their musculoskeletal complaints.

Patient and teacher experiences

Experiences and satisfaction with the yoga programme will be explored through semi-structured, in-depth interviews with a purposive sample of participants from the intervention group and yoga instructors. A purposive sampling strategy will be applied to ensure diversity in demographic characteristics among participants. Recruitment will continue until thematic saturation is reached, with an anticipated sample size of at least 12 participants, as we expect saturation to occur after approximately 12–15 interviews. The same qualitative approach will be used for yoga instructors.

Medical data

Medical data (date of diagnosis, tumour type, disease stage, treatment information and endocrine therapy use) is retrieved via the Dutch Cancer registry or the treating physician, with the electronic health records as the source.

Adverse events

Participants and/or yoga instructors are instructed to record any (serious) adverse events (S)AEs that occurred or worsened during or after a yoga session, related to the yoga class or not. (S)AEs are reported until a week after the participant finished the yoga programme. At the follow-up visits, the study team inquires about any (S)AEs according to the Exercise Harms Reporting Method.[38] This method allows for a systematic and standardised manner of asking about any (S)AEs. If any occurred, they are reviewed by the study physician. Also, an adverse event panel, consisting of independent yoga/exercise professionals and clinicians, will review all (S)AE forms and confirm whether the (S)AEs are potentially causally related to the yoga programme or not. Eventually, the (S)AEs are reported in the electronic case report file of Castor. SAEs will also be reported to the ethical committee that approved the study protocol (Medical Ethical Committee (METC), UMC Utrecht) within 7 days.

Sample size

The sample size was calculated based on the first component of the hierarchically defined primary outcome (ie, see also paragraph 2.7.1). Based on the study of Irwin *et al*,[10] a minimal difference of 1.0 on worst pain is considered relevant and realistic, with an assumed SD of 2.5. To detect this difference with 80% power and an alpha of 5%, we need 63 women per group. Considering a drop-out of approximately 15%, the sample size is 70 women per group. As we calculated the sample size using a two-sample t-test, while we will analyse the primary outcome with an analysis of covariance (ANCOVA) approach, this is a conservative estimation, and the power will be even higher.

Data analysis

Baseline demographics and characteristics will be reported by study group, descriptively. Means and SDs will be presented for continuous and normally distributed variables, and medians with IQRs for non-normally distributed variables. Categorical variables will be presented by frequencies per group (absolute numbers and percentages).

The primary intention-to-treat intervention effect of the yoga programme on the primary outcome measure will be analysed using ANCOVA, adjusting for the score at baseline and the following potential prognostic factors at baseline: age, BMI and pain medication use. We additionally calculate standardised effect sizes: Cohen's d. Missing data will be imputed by applying multiple imputation techniques (using the package MICE, in R).

We will analyse all continuous secondary outcome measures (eg, PROMs, cognitive complaints, fitness measures and blood markers) via the same approach as the primary analysis.

In the intervention group, additional within-group analyses will be performed to evaluate whether improvements are sustained at follow-up (36 weeks). The effect of the live-remote yoga programme in the control group will be analysed with a longitudinal data analysis method, where we will compare outcomes at baseline, at 18 weeks

and at 36 weeks (within-group analyses). Exploratory, we will also compare the effects of live-remote yoga with those of in-person yoga. For this comparison, we will use ANCOVA. As the control group receives the live-remote intervention after the primary intervention period, we will align the time-points by using the control group's 18-week and 36-week outcomes as the equivalents of the intervention group's baseline and post-intervention outcomes, respectively.

As per protocol analyses, we will repeat the analyses for the participants with a minimal adherence of 80%. Adherence to the yoga programme will be defined as a percentage (the number of attended sessions divided by the number of sessions offered).

Patient and public involvement

Two patient advocates were involved in the development of the study and provided regular feedback on the protocol, the feasibility of the study (including the burden of the intervention), and were present during study group meetings. Also, they remain involved during recruitment by sharing messages about the study on social media platforms to enhance recruitment. At the end of the study, they will help to determine the most effective way to communicate the results to the study participants and relevant wider patient communities.

ETHICS AND DISSEMINATION

The COBRA study was approved by the METC NedMec on 20 June 2024 (NL86325.041.24, 24-054/G). Substantial amendments will only be implemented after approval by the METC. The study is classified as a low-risk trial; therefore, a low-risk monitoring plan is implemented, including three on-site visits by an academic CRO (Julius Clinical), and no data safety monitoring committee is involved. This study is registered at www.clinicaltrials.gov, number NCT06480513. COBRA study team members ask all participants to provide informed consent before participation, digitally via a secure platform for electronic signatures. Since this trial is classified as low risk, the METC has granted an exemption for clinical trial subject insurance.

Collected data is saved on a secure drive of the UMC Utrecht and retained for at least 15 years, in accordance with the regulation for Clinical Trials and Data Management Plan. Participants' anonymity will be safeguarded by storing data using identification codes rather than names. A separate confidential enrolment log is kept that links names to identification codes.

De-identified data is shared after publication of the main study results on reasonable request. On completion of the study, results will be submitted to an international peer-reviewed journal, presented during scientific and patient conferences, and communicated to the participants and wider patient communities via social media, our website and email.

DISCUSSION

Approximately 40% of women treated with adjuvant endocrine therapy for hormone-receptor-positive breast cancer discontinue treatment prematurely due to side effects.[6] One of the most frequently reported and burdensome side effects is musculoskeletal complaints. Currently, these complaints are mostly treated with analgesics. However, the effectiveness of analgesics is often insufficient, they are not the preferred option for many patients and are accompanied by other side effects. Hence, a non-medicinal solution is preferred. In this study, we examine whether yoga might be an effective intervention to alleviate these musculoskeletal complaints. By doing so, we aim to increase quality of life and potentially support endocrine treatment adherence, which may in turn contribute to improved prognosis.

Feasibility studies have shown that yoga might alleviate musculoskeletal complaints in breast cancer survivors.[20–23] However, to date, no randomised studies investigating the effect of yoga on endocrine therapy-associated musculoskeletal complaints have been performed. Yoga might be a good treatment strategy for several reasons. First, practicing yoga increases physical function outcomes such as balance, lower body flexibility and lower limb strength.[14] Second, yoga stimulates the parasympathetic nervous system, leading to reduced feelings of stress, pain, depression and anxiety.[12 14 16 39] Also, complementary therapies like yoga are increasing in popularity among women with breast cancer.[40 41] Lastly, yoga is considered a safe and easy intervention to implement in daily life. However, we acknowledge that (Hatha/easy Vinyasa) yoga may be too physically or mentally demanding for some participants. Therefore, adaptations to postures and classes will be made if required (ie, in case of a decreased range of motion due to scar tissue or predefined osteoarthritis).

In the COBRA study, women in the intervention group follow in-person classes at yoga or sports centres near their home. We decided on this pragmatic design, as we aim to replicate real-world conditions as closely as possible. As such, participants attend classes that include individuals with and without cancer, which may have advantages (eg, normalisation, broader social interaction) and disadvantages (eg, less peer support, feeling ashamed of own physical appearance). In-person classes allow for intensive surveillance and guidance by the yoga instructors. However, there are also limitations, as there will likely be variation between the classes and instructors. To tackle this variation a study team member assesses beforehand the suitability of the class by participating in a class. Furthermore, teachers will be trained on the (standardised) protocol, breast cancer and the side effects of the treatments.

Women in the waitlist control group follow live-remote yoga classes. Strengths of this delivery method are that all women participate in the same classes, thereby increasing peer support through shared experience, and no travel time is needed, as classes can be followed from home. A limitation is the reduced ability to monitor whether the

participants perform the postures correctly. In addition, it may reduce the sense of connection between the teacher and participants. However, multiple studies have shown that a virtual exercise or yoga intervention in women with breast cancer is feasible.[42 43] For example, one supervised virtual exercise programme study in women using endocrine treatment for breast cancer reported significant improvements in all physical and psychological measures (physical function, energy/fatigue, emotional well-being and pain).[42] Additionally, a study involving older adults found that participants preferred live-remote yoga over in-studio classes due to greater accessibility and convenience, decreased self-consciousness regarding physical appearance and reduced perceived peer competition.[43] Including both delivery methods allows us to explore their feasibility and acceptability, which may help in deciding on the best future implementation of yoga in clinical practice.

In conclusion, in the COBRA study, we primarily investigate the effect of yoga on musculoskeletal complaints in women with hormone-receptor-positive stage I–III breast cancer. Subsequently, we investigate the effect of yoga on a range of patient-reported outcome measures, cognitive complaints, physical fitness, vital signs and anthropometrics, blood markers and safety measures. By alleviating these musculoskeletal complaints, we aim to improve quality of life and potentially promote adherence to endocrine therapy.

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REFERENCES

1 Bray F, Laversanne M, Sung H, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229–63.
2 Goss PE, Ingle JN, Pritchard KI, *et al*. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016;375:209–19.
3 Davies C, Pan H, Godwin J, *et al*. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805–16.
4 Stearns V, Chapman J-AW, Ma CX, *et al*. Treatment-associated musculoskeletal and vasomotor symptoms and relapse-free survival in the NCIC CTG MA.27 adjuvant breast cancer aromatase inhibitor trial. *J Clin Oncol* 2015;33:265–71.
5 Henry NL, Azzouz F, Desta Z, *et al*. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol* 2012;30:936–42.
6 Lemij AA, de Glas NA, Derks MGM, *et al*. Discontinuation of adjuvant endocrine therapy and impact on quality of life and functional status in older patients with breast cancer. *Breast Cancer Res Treat* 2022;193:567–77.
7 Braybrooke J, Bradley R, Hills RK, *et al*. Extending the duration of endocrine treatment for early breast cancer: patient-level meta-analysis of 12 randomised trials of aromatase inhibitors in 22 031 postmenopausal women already treated with at least 5 years of endocrine therapy. *The Lancet* 2025;406:603–14.
8 Condorelli R, Vaz-Luis I. Managing side effects in adjuvant endocrine therapy for breast cancer. *Expert Rev Anticancer Ther* 2018;18:1101–12.
9 Roberts K, Rickett K, Greer R, *et al*. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2017;111:66–80.
10 Irwin ML, Cartmel B, Gross CP, *et al*. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol* 2015;33:1104–11.
11 Roberts KE, Rickett K, Feng S, *et al*. Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal

symptoms in early breast cancer. *Cochrane Database Syst Rev* 2020;1.
12 Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. *J Altern Complement Med* 2010;16:3–12.
13 Kim S, Bemben MG, Bemben DA. Effects of an 8-month yoga intervention on arterial compliance and muscle strength in premenopausal women. *J Sports Sci Med* 2012;11:322–30.
14 Sivaramakrishnan D, Fitzsimons C, Kelly P, *et al*. The effects of yoga compared to active and inactive controls on physical function and health related quality of life in older adults- systematic review and meta-analysis of randomised controlled trials. *Int J Behav Nutr Phys Act* 2019;16.
15 Kiecolt-Glaser JK, Bennett JM, Andridge R, *et al*. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *J Clin Oncol* 2014;32:1040–9.
16 Cramer H, Lauche R, Anheyer D, *et al*. Yoga for anxiety: a systematic review and meta-analysis of randomized controlled trials. *Depress Anxiety* 2018;35:830–43.
17 Cramer H, Lauche R, Langhorst J, *et al*. Yoga for depression: a systematic review and meta-analysis. *Depress Anxiety* 2013;30:1068–83.
18 Bower JE, Garet D, Sternlieb B, *et al*. Yoga for persistent fatigue in breast cancer survivors: a randomized controlled trial. *Cancer* 2012;118:3766–75.
19 Mustian KM, Sprod LK, Janelsins M, *et al*. Multicenter, randomized controlled trial of yoga for sleep quality among cancer survivors. *J Clin Oncol* 2013;31:3233–41.
20 Galantino ML, Desai K, Greene L, *et al*. Impact of yoga on functional outcomes in breast cancer survivors with aromatase inhibitor-associated arthralgias. *Integr Cancer Ther* 2012;11:313–20.
21 Carson JW, Carson KM, Porter LS, *et al*. Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. *Support Care Cancer* 2009;17:1301–9.
22 Tsai C-L, Liu L-C, Liao C-Y, *et al*. Yoga versus massage in the treatment of aromatase inhibitor-associated knee joint pain in breast cancer survivors: a randomized controlled trial. *Sci Rep* 2021;11.
23 Peppone LJ, Janelsins MC, Kamen C, *et al*. The effect of YOCAS©® yoga for musculoskeletal symptoms among breast cancer survivors on hormonal therapy. *Breast Cancer Res Treat* 2015;150:597–604.
24 Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap* 1994;23:129–38.
25 Kennedy CA, Beaton DE, Smith P, *et al*. Measurement properties of the QuickDASH (disabilities of the arm, shoulder and hand) outcome measure and cross-cultural adaptations of the QuickDASH: a systematic review. *Qual Life Res* 2013;22:2509–47.
26 Bellamy N, Buchanan WW, Goldsmith CH, *et al*. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833–40.
27 Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
28 Bjelic-Radisic V, Cardoso F, Cameron D, *et al*. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. *Ann Oncol* 2020;31:283–8.
29 Fallowfield LJ, Leaity SK, Howell A, *et al*. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. *Breast Cancer Res Treat* 1999;55:189–99.
30 Smets EM, Garssen B, Bonke B, *et al*. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315–25.
31 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
32 Buysse DJ, Reynolds CF III, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
33 Wendel-Vos GCW, Schuit AJ, Saris WHM, *et al*. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003;56:1163–9.
34 Wagner LI, Sweet J, Butt Z, *et al*. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J Support Oncol* 2009;7:W32–9.
35 Feenstra HE, Vermeulen IE, Murre JM, *et al*. Online self-administered cognitive testing using the amsterdam cognition scan: establishing psychometric properties and normative data. *J Med Internet Res* 2018;20.
36 Feenstra HEM, Murre JMJ, Vermeulen IE, *et al*. Reliability and validity of a self-administered tool for online neuropsychological testing: the Amsterdam Cognition Scan. *J Clin Exp Neuropsychol* 2018;40:253–73.
37 De Backer IC, Schep G, Hoogeveen A, *et al*. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil* 2007;88:610–6.
38 Spence RR, Sandler CX, Jones TL, *et al*. Practical suggestions for harms reporting in exercise oncology: the Exercise Harms Reporting Method (ExHaRM). *BMJ Open* 2022;12.
39 Posadzki P, Ernst E, Terry R, *et al*. Is yoga effective for pain? A systematic review of randomized clinical trials. *Complement Ther Med* 2011;19:281–7.
40 Voiß P, Höxtermann MD, Dobos G, *et al*. Mind-body medicine use by women diagnosed with breast cancer: results of a nationally representative survey. *Support Care Cancer* 2020;28:1077–82.
41 Boon HS, Olatunde F, Zick SM. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. *BMC Womens Health* 2007;7:4.
42 Myers SA, Weller S, Schwartz S, *et al*. Feasibility of a supervised virtual exercise program for women on hormone therapy for breast cancer. *Transl J ACSM* 2022;7.
43 Haynes A, Gilchrist H, Oliveira JS, *et al*. "I wouldn't have joined if it wasn't online": understanding older people's engagement with teleyoga classes for fall prevention. *BMC Complement Med Ther* 2022;22.