**Yoga's Impact on Inflammation, Mood, and Fatigue in Breast Cancer Survivors: A Randomized Controlled Trial**

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Protocol: Yoga's Impact on Inflammation, Mood, and Fatigue in Breast Cancer Survivors:
A Randomized Controlled Trial

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## A. SPECIFIC AIMS

Breast cancer survivors confront a number of post-treatment problems including fatigue (1, 2), decreased physical function (3), fears of recurrence (4), and treatment-related sequelae (5, 6). Fatigue is the most common problem, affecting a third or more of long-term survivors (7); it is also the symptom that interferes the most with daily life (8, 9). Depressive symptoms and impairments in physical performance are reliable correlates of cancer-related fatigue (10). Although the origins of fatigue are multifactorial (11), there is growing evidence that persistent fatigue in cancer survivors may be related in part to overactivation of the inflammatory network (1, 2). Chemotherapy and radiation can dysregulate inflammatory processes (2, 12, 13). Furthermore, cancer treatments are often stressful, and stress, depression and anxiety enhance the production of proinflammatory cytokines (14-20). Indeed, psychological stress and depression promote transcription factor nuclear factor kappa B (NF-κB) activation (21-23), a prime pathway for upregulating proinflammatory cytokine production (21, 22, 24, 25); for example, depressed men showed a larger NF-κB and IL-6 response than nondepressed men to a lab stressor (23). Heightened inflammation can in turn alert the central nervous system to induce "sickness behaviors," including fatigue (2, 26). Thus, stress and depression can promote inflammation, perpetuating a maladaptive feedback loop, and interventions that break the cycle would be very beneficial.

Physical activity interventions that simultaneously enhance physical performance and reduce depressive symptoms can also reduce fatigue-related symptoms (10, 27) as well as inflammation (28). However, fatigue and pain often limit cancer survivors' physical activity, both during and after cancer treatment (5). Yoga offers both psychological and physical benefits for cancer survivors (29), providing graded exercise that can be tailored for individuals who have been sedentary; the postures can be modified easily so that they are appropriate for individuals who have functional limitations (29, 30). There is some evidence that yoga practice benefits mood, distress, and quality of life in cancer survivors (29-31), as well as relevant health behaviors, including sleep quality (32). However, the studies have used small samples and do not address the mechanisms through which yoga influences symptom presentation in cancer survivors.

This project provides the opportunity to examine mechanistic connections among fatigue, stressors, depressive symptoms, and proinflammatory cytokines both cross-sectionally and longitudinally in a randomized clinical trial (RCT), building on our preliminary studies that have demonstrated anti-inflammatory changes associated with yoga. A total of 200 stage 0, I, II, and IIIa breast cancer survivors will be recruited, ages 21 and older; the women will have completed cancer treatment within the past three years (except for tamoxifen/aromatase inhibitors), and will be at least two months post surgery or adjuvant therapy or radiation, whichever occurred last. Data from several studies suggest that proinflammatory cytokines for the average woman have returned to baseline levels by that time for the standard chemotherapies and radiotherapy (12, 13, 33). Using a block-randomized design, participants will be assigned to either a 12-week (twice-weekly) hatha yoga intervention or a delayed intervention arm that receives the yoga intervention after a six-month observation period. Differences between the two arms will be assessed at three months (at the conclusion of the 12-week intervention), and at six months (three months after the formal intervention), controlling for any baseline (pre-randomization) measures.

Our primary endpoints will be proinflammatory cytokines, fatigue, and depressive symptoms. Secondary endpoints will provide data on the mechanisms underlying the intervention's efficacy from four key domains: psychological (quality of life, perceived stress, and stress responsiveness), behavioral (health behaviors), physical functioning (physical symptoms, pain, flexibility, and functional status), and physiological stress responses.

**Specific aims:** (1) Our primary aim is to determine if the yoga intervention will decrease inflammation, fatigue, and depressive symptoms relative to the wait-list controls. Additional aims are (2) to ascertain the extent to which the yoga intervention modulates psychological, behavioral, and physical functioning; (3) to evaluate the relationship between depressive symptoms and the magnitude of the physiological responses elicited by a laboratory stressor, as well as the relationship of both to fatigue; and (4) to assess the extent to which the yoga intervention will decrease physiological stress responses.

**Hypotheses:** (1) Participants assigned to the yoga intervention will demonstrate decreases in inflammatory markers, fatigue, and depressive symptoms, while wait-list controls will not change significantly. (2) Relative to wait-list controls, yoga intervention participants will show improvements in psychological, behavioral, and physical functioning. (3) Higher levels of depressive symptoms will effectively prime the inflammatory response, promoting larger proinflammatory responses to laboratory stressors. Both larger proinflammatory responses to lab stressors and higher levels of depressive symptoms will be associated with greater fatigue. (4) Women assigned to the yoga intervention will demonstrate lower physiological stress responses at three months relative to wait-list controls. This study would fill several significant gaps in the literature by addressing the impact of a yoga intervention on inflammation, fatigue, and depressive symptoms, while also providing important mechanistic information on the ways in which stress and depressive symptoms interact to influence proinflammatory cytokine and fatigue.

## B. BACKGROUND AND SIGNIFICANCE

### B.1. Cancer Survivors' Risk for Disability

Epidemiological data suggest that cancer survivors have twice the likelihood of poor health and disability as individuals who do not have a cancer history (34); moreover, when a cancer survivor has another chronic illness, the likelihood of poor health and disability is 5 to 10 times higher (34). Disability among survivors is most notable in physical functioning, with almost a quarter reporting an inability to work (16.8%) or notable limitations in their ability to work (7.4%) (34).

Importantly, physical performance limitations were present years after a cancer diagnosis, even among younger survivors, e.g., ages 40-49 (35). In fact, recent survivors (<5 years survival) who were 40-49 had a much higher proportion of physical performance limitations (52.3%) than their age-mates with no cancer history (14.8%) or long-term survivors (14.7%), including limitations in stooping, crouching, or kneeling, difficulty reaching overhead, and difficulty getting out of bed; breast cancer survivors comprised the largest subgroup of these younger recent survivors (35).

Related to their risks for disability, cancer survivors have a greater risk for secondary cancers as well as a number of chronic diseases, including cardiovascular disease, diabetes, and osteoporosis (3, 36). The increased risks may be related to genetics, the sequelae of cancer treatment, and health-related behaviors, particularly diet and a sedentary lifestyle (3). Indeed, a spectrum of chronic diseases including cardiovascular disease, diabetes, and osteoporosis have been related to overproduction of proinflammatory cytokines in noncancer populations, and a sedentary lifestyle is also associated with greater inflammation as well (37-42).

Exercise improves physical function in cancer survivors (3) and reduces cancer-related fatigue (43); successful interventions have included a wide variety of interventions including lab-based cardiovascular activity, strength training, and combined interventions (cardiovascular and flexibility exercises), although the majority have emphasized cardiovascular training as the primary intervention (43-49). The broad rationale for activity interventions is based on the evidence that the late effects of cancer and its treatment as well as the deconditioning related to reduced physical activity during treatment lead to a decrease in the capacity for physical performance (50). With deconditioning, normal activities become more fatiguing, leading to a downward spiral resulting in greater fatigue and lessened functional capacity over time (50). In this framework, the enhanced production of proinflammatory cytokines serves to promote the downward spiral (50); as discussed below, physical activity has benefits for physical function, fatigue, mood, and proinflammatory cytokine production.

### B.2. Fatigue in Cancer Survivors

Fatigue is the most common and most distressing symptom reported by cancer survivors, as well as the one that interferes most with daily life (8, 9). Fatigue adversely affects overall quality of life, as well as many daily activities including mood, the sleep-wake cycle, and personal relationships (1, 2, 8, 51).

Depressive symptoms are the strongest predictor of fatigue, although fatigue is not explained by depression (52). For example, in a prospective study of breast cancer patients undergoing radiation, pretreatment fatigue, depressed mood, and anxiety scores were solid predictors of fatigue 2.5 years after treatment (53). Similarly, among a large sample of survivors (N=1,957), women with higher levels of depressive symptoms in the five years after diagnosis were at greater risk for long-term fatigue, even after controlling for initial fatigue (7). Other correlates of fatigue include pain, sleep disturbance, comorbid medical problems, and age (52, 54).

One mechanism underlying fatigue could be the activation of the inflammatory cytokine network (55). The immune activation that is secondary to the tissue destruction and associated inflammation from many

cancer therapies may leave cancer patients especially vulnerable to the behavioral consequences of proinflammatory cytokines, including fatigue (56). Heightened inflammation can alert the central nervous system to induce "sickness behaviors," including fatigue (2, 26).

However, while there are good reasons to believe that fatigue would be related to inflammation, results have been mixed in cytokine studies with cancer patients. For example, 20 fatigued breast cancer survivors had higher levels of interleukin 1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor II (sTNF-RII), neopterin, and depressive symptoms than 20 nonfatigued survivors (1). In contrast, another study with 71 patients with hematological malignancies also found that fatigue was related to depression, but not to a battery of cytokines and inflammatory markers including IL-1α, IL-1 soluble receptor (sIL-1r), IL-6, CRP, or neopterin (10). However, IL-6, IL-1RA, and TNF-α were all related to fatigue among patients with acute myelogenous leukemia or myelodyspalastic syndrome (57). In patients undergoing chemotherapy, relationships between changes various inflammatory markers and fatigue have been mixed, related in part to differences in both the type of chemotherapy and the schedule (12, 13).

**B.3. Stress-Associated Dysregulation of Proinflammatory Cytokine Production: Health Implications**

Depression and anxiety enhance the production of proinflammatory cytokines (14-20). Moreover, both physical and psychological stressors can provoke transient increases in proinflammatory cytokines (58-62). Additionally, stress and depression also contribute to greater risk for infection, prolonged infectious episodes, and delayed wound healing (63-67), all processes that can fuel sustained proinflammatory cytokine production. Furthermore, stress and depression may effectively prime the inflammatory response, promoting larger cytokine increases in response to stressors and/or minor infectious challenges (18, 68-71).

Stress-related changes are important because inflammation has been linked to a spectrum of conditions associated with aging, particularly cardiovascular disease (42), the leading cause of morbidity and mortality. In addition, inflammation has been linked to osteoporosis, arthritis, type 2 diabetes, about 15% of cancers, Alzheimer's disease, and periodontal disease (42, 72, 73). In fact, more globally, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and, ultimately, death (37-41).

IL-6 levels predicted future disability in older adults, a finding that may reflect the effects of the cytokine on muscle atrophy, and/or to the pathophysiologic role played by the cytokine in particular diseases (74). Proinflammatory cytokines including IL-6 may slow muscle repair following injury and accelerate muscle wasting (75); indeed, IL-6 and CRP also play a pathogenic role in a range of diseases associated with disability among the elderly (osteoporosis, arthritis, and congestive heart failure, among others) (74). Thus, sustained and/or amplified inflammatory responses associated with stress and/or depressive symptoms could accelerate progression of a range of age-related diseases (18, 76).

**B.4. NF-κB Activation and Inflammation**

NF-κB regulates the activity of immune cells that produce proinflammatory cytokines (77). NF-κB activation was significantly enhanced following a laboratory stressor (22); indeed, NF-κB activity rose by 341% within 10 minutes, with changes evident in 17 of the 19 participants. Similarly, NF-κB activity was also substantially enhanced among women who were made anxious by the experience of a breast biopsy (21). Stress-related increases in norepinephrine provoke activation of NF-κB both *in vitro* and *in vivo*, linking endocrine alterations to changes in the immune response (22).

Patients who met criteria for major depression produced larger increases in both NF-κB and IL-6 in response to a laboratory speech stressor than non-depressed controls (23). Importantly, the depressed and nondepressed did not differ in this small sample at baseline, prior to the stressor, but showed clear differences in response to stress.

NF-κB appears to be major bridge for stress-induced increases in proinflammatory cytokines and the genes that control their expression, providing an obvious mechanism for translating psychological stress into PBMC activation (22). Indeed, inhibition of NF-κB transcriptional activity could shut off a number of cytokine genes (77).

**B.5. Exercise, Inflammation, and Immune Function**

Higher levels of physical activity clear benefit health, with positive consequences for the cellular immune response, as well as regulation of proinflammatory cytokines (78-80). Both IL-6 and CRP levels are higher in individuals who report less physical activity than in those who are more active, as well as higher in those with a higher body mass index (37, 74, 78-80). Regular physical activity is associated with lower levels of IL-6 and other proinflammatory cytokines (40); intervention studies with moderate cardiovascular training have produced benefits in immunologically-mediated outcomes including influenza vaccine responses (81) and

wound healing (82); as discussed above, prolonged infectious episodes and impaired wound healing can fuel sustained proinflammatory cytokine production (63-67). In addition to its physiological benefits, intervention studies have demonstrated that regular exercise also reduces psychological distress (83-85), which may also serve as an indirect pathway to reduced inflammation. While much of the literature has focused on cardiovascular training, positive effects are also found with a variety of other activity interventions; for example, the flexibility/strength training control group in one study also showed a significant decrease in TNF-α (86), while a tai chi chih intervention produced positive alterations in varicella-virus specific immunity (87).

**B.6. Exercise Interventions in Cancer Patients and Survivors: Rationale and Evidence**

Exercise interventions in cancer patients clearly produce both psychological and physiological benefits (43-49). The majority of the studies have used cardiovascular training as the primary intervention (45). Positive changes include improvements in fatigue, quality of life, cancer-related distress, psychological well-being, aerobic capacity, and muscle strength. Moreover, results of RCTs with noncancer populations also suggest that exercise can also attenuate stress responses among middle-aged and older adults (88-90); a recent meta-analysis suggested that fitness may be associated with slightly greater reactivity, but, importantly, enhanced recovery from stressors (91).

Only a handful of exercise intervention studies with cancer survivors have included immunological measures (92). The sample sizes for randomized and controlled clinical trials addressing immune function ranged from 6-70 patients, with the majority assessing an average of 20 patients, 10 of whom were assigned to the intervention (92). Most were heterogeneous with regard to age, gender, and/or cancer site (92). The studies typically reported favorable immunological changes following the exercise intervention, including enhanced natural killer cell (NK) cytotoxity (93-95).

The most comprehensive immunological study used 53 breast cancer survivors ages 50-69 who were randomized to a cardiopulmonary fitness protocol (3 times/week for 15 week) or a control group (93, 96, 97). Compared to controls, NK cytotoxicity increased significantly in the exercise group, while CRP decreased; there were not significant differences in proliferative responses to PHA, or in the PHA-stimulated production by leukocytes of IL-1α, TNF-α, IL-6, IL-4, IL-10, or TGF-β.

**B.7. Yoga: Rationale and Evidence**

Data from a 1998 national survey showed that an estimated 15 million adults in the USA had tried yoga at least once, and 7.4 million had done so in the past year (98). In 2002 yoga classes were offered in 74% of health clubs, nearly double the percentage reported in 1995 (99).

Yoga has been used in the treatment of a variety of health problems including chronic low back pain, smoking, asthma, rheumatoid arthritis, chronic poststroke hemiparesis, diabetes mellitus, irritable bowel syndrome, and depression (100-114). A number of studies have reported that hatha yoga sessions decrease negative mood ratings in non-depressed individuals (113-116). Several studies that have found promising immunological and endocrinological changes associated with Kabat-Zinn's mindfulness meditation protocol which includes yoga as one component (31, 117, 118).

In the largest, best-controlled study of yoga in older adults to date, the 6-month trial with weekly 90-min sessions produced significant improvement in QOL, as well as flexibility (119). Indeed, the findings likely underestimate the magnitude of the effects that would be expected with a cancer survivor population, as their older adult subjects were healthy and well-functioning, limiting the degree of improvement that was possible (119).

A recent review of yoga for cancer patients and survivors described a number of positive outcomes including sleep quality, improved mood, less reported stress and cancer-related distress, and improvement in quality of life (52); however, the studies were small, many had no control groups, and most did not address the mechanisms of action. Despite these problems, the data, although limited, suggest that yoga could have direct beneficial effects on the immune response, as well as indirect effects through health behaviors.

Disrupted sleep is a common problem affecting between 30-50% of cancer patients; as in other populations, sleep disturbances are associated with anxiety and depressive symptoms (120, 121). Disrupted sleep is also associated with immune dysregulation, including alterations in proinflammatory cytokines (122-125). Thus it is notable that lymphoma patients' sleep quality was enhanced following a 7-session Tibetan yoga RCT (32). Similarly, yoga practice is associated with attenuated weight gain among healthy middle-aged women (126), another potential benefit because physical inactivity appears to be an important contributor to weight gain following breast cancer diagnosis and treatment (127, 128).

**B.8. Biobehavioral Model**

In our biobehavioral model that guides our research (129), one of the key tenets is the premise that

stressors can modulate immune function directly, as well as indirectly, through health behaviors and compliance. There is evidence that greater stress or distress in cancer patients is associated with greater immune dysregulation (56, 130-135), consistent with data from noncancer populations (136). Similarly, resources like social support that moderate distress have also been associated with better immune function in both cancer and noncancer populations (135, 137, 138).

Negative health behaviors can clearly potentiate the effects of stress; however, positive health behaviors may block or ameliorate some adverse effects, and in this regard exercise is a key health behavior for cancer patients. Most cancer patients reduce physical activity after diagnosis and treatment, and do not return to their prediagnosis levels (139). However, as reviewed earlier, in addition to direct positive effects on immune function, exercise interventions can enhance positive moods, decrease fatigue, and improve other health behaviors like sleep. Indeed, the biobehavioral model as originally specified (129) primarily addressed cancer as the relevant health outcome; with this proposed study of cancer survivors, our focus is on the women's lives after breast cancer, and the ways to enhance post-treatment physical functioning, immune function, mood, and, ultimately, health.

## C. METHODS

### C.1. Subjects and Design

A total of 200 stage 0, I, II, and IIIa breast cancer survivors (ages 21 and older) will be recruited. They will have completed cancer treatment within the past three years (except for tamoxifen/aromatase inhibitors), and will be at least two months post- surgery or adjuvant therapy or radiation, whichever occurred last. Using a block-randomized design, we will stratify participants by stage of cancer (stage 0 vs. 1 vs. 2 and 3a) as well as radiation therapy received or not, and then block randomize to either the yoga or the waiting-list control condition within strata. The design will be a randomized clinical trial (RCT) with 3 assessments over a 6-month period.

We are deliberately recruiting a heterogeneous sample with respect to age, stage of cancer, and treatment modalities with the goal of having intervention efficacy data that will be broadly generalizable. In particular, age is likely to be an important moderator of effects, but very few of the exercise intervention trials with cancer patients have been large enough to examine age-related outcomes (49). Rather than setting an arbitrary upper age limit, we will use functional limitations as described below under screening to exclude women for whom the intervention would be inappropriate.

Cancer-related distress and the associated motivation for change decline over time, and thus earlier interventions are likely to be much more successful in changing behavior (3). We considered waiting longer after treatment completion for recruitment related to possible immunological recovery; however, the data from several studies suggest that proinflammatory cytokines for the average woman have returned to baseline levels by the end of a chemotherapy cycle of paclitaxel (regardless of whether it was weekly or every 3 weeks; IL-6, TNF-α, IL-1β) (13), within two months of ending radiotherapy (IL-6, TNF-α, IL-1β) (33), or were no different from baseline at the beginning of the fourth cycle of anthracycline-based chemotherapy (IL-6) (12). We anticipate that more persistent cytokine elevations following treatment will be related to both depressive symptoms and fatigue (56).

### C.2. Subject Recruitment

We will recruit a significant number of research participants directly from the OSU Clinics/ James Cancer Center in collaboration with Dr. Charles Shapiro. For patients recruited through the Comprehensive Breast Services Program/ James Cancer Center in collaboration with Dr. Charles Shapiro, a co-PI, research nurse(s) assigned to the protocol will inform appropriate patients about the study, provide study materials, and/or ask if our research staff can contact them to provide further details. Our project staff will then send a letter to participants who agree to be contacted, describing our study in detail; a prepaid envelope will be included with the letter, as well as a card on which they will be asked to indicate if they would be willing to be contacted by the study team or not. They will be told that if we do not hear from them within two weeks, we will attempt to contact them to determine their interest.

For participants who are recruited from a source other than the OSUCCC (e.g. through general advertisement or through their primary care physician), we will collect all screening information via the phone/web based screening process. Eligible participants will then be scheduled for the first GCRC visit, where we will obtain written consent for access to copies of their medical records related to their breast cancer diagnosis and treatment.

Additionally, we will post information about our study on a National Volunteer Recruitment Registry called ResearchMatch.org to recruit potential participants. Individuals self-register as volunteers, and

ResearchMatch's security features ensure that personal information is protected until volunteers authorize its release to a specific study that may interest them. Volunteers are notified electronically that they are a possible match for a given study and then make the decision regarding the release of their contact information.

To bolster recruitment efforts, we will also use the OSU Cancer Registry as a tool to identify eligible subjects for our study that we may not know about otherwise. We first want to ascertain if we are missing substantial numbers of potential patients by looking at the record and identifying the treating OSU physician(s); if we find we are indeed missing a particular subset, we will then ask that physician's permission to contact their patient using a recruitment letter and informational flyer.

The Cancer Registry will also be used to collect medical information in a more efficient manner. Fortunately, their database has information about cancer stage, tumor size, treatment information, etc. in one place, as they have spent considerable time distilling the treatment history. We will use the Registry to collect or confirm cancer-related information on previously consented subjects.

**C.2.a. <u>Exclusion Criteria</u>** Several exclusion criteria are related to the women's ability to fully participate in the yoga intervention (e.g., breathing problems that require use of oxygen, problems in walking without the assistance of a cane or walker, etc.). Women who cannot comfortably get up and down from the floor 2-3 times in a session will be excluded. Women who have had knee or hip replacement may be excluded if they have limited movement in the joint. Women who cannot comfortably lie on their belly will be excluded (a potential problem for those who are very overweight). We will exclude individuals with notable serious cardiovascular histories, e.g., those who have had life-threatening abnormal heart rhythms.

Other exclusions will include: a prior history of breast or any other cancer except basal or squamous cell, inflammatory breast cancer, diabetes, chronic obstructive pulmonary disease, uncontrolled hypertension, evidence of liver or kidney failure, symptomatic ischemic heart disease, significant visual or auditory problems, mental disorder, cognitive impairment, other medical conditions involving the immune system such as autoimmune and/or inflammatory diseases including rheumatoid arthritis and ulcerative colitis, alcohol or drug abuse, or regular use of medications with major immunological consequences, e.g., steroids.

Although at least one study suggests that successful treatment of depression with antidepressants lowers proinflammatory cytokines (140), some epidemiological studies have not found that individuals taking antidepressants have significantly lower levels on key markers than individuals who are not taking antidepressants (141). Moreover, antidepressants improve mood, but do not reliably reduce fatigue (10, 26), and exclusion of individuals on antidepressants could eliminate some of the most fatigued women. Furthermore, a number of breast cancer survivors who cannot take hormone therapy are taking antidepressants for menopausal symptoms. Thus, antidepressant use will not be an exclusion criteria. We will carefully assess medications prior to study entry and confirm current medications at each blood draw, and carefully monitor relative frequencies between the intervention and control groups.

To determine the efficacy of yoga, women will be recruited who are not currently practicing yoga, meditation, tai chi, or related activities and who had not had classes in yoga or tai chi within the last six months (119), and who had never practiced yoga for more than three months. Moreover, we will exclude women who report that they typically engage in a total of 5 or more hours of vigorous physical activity per week.

Anemia is relatively frequent during and shortly after cancer treatment (10), but the evidence linking low hemoglobin and fatigue has been mixed (33). Each participant will be screened for anemia at the screening session. Women will only be eligible for the study if they have a hemoglobin level≥ 10 g/dl. If a woman is found to be anemic at the screening session, she will be asked to see her physician. She will have the option of being retested for anemia in 6 weeks. If she is no longer anemic, she would be eligible for participation. If a participant is not anemic at the screening session, it is highly unlikely that she will develop anemia as a result of these blood draws. However, as an added precaution, we will assess hemoglobin at each subsequent visit (Baseline, Visit 1, and Visit 2). Results of these hemoglobin tests will be available the afternoon of each session. If a woman is found to have hemoglobin levels below 10g/dl, we will inform her of her hemoglobin level and contact her oncologist or primary care physician. The woman would be ineligible to participate further in any blood draws for the study until her anemia has been treated. (She would be allowed to continue her participation in yoga sessions, if applicable). The woman would be allowed to resume her participation in the study if she provided a letter from her physician indicating that she is no longer anemic, or if we conducted a follow-up anemia test at the CRC that demonstrated that her hemoglobin levels were ≥ 10 g/dl.

Finally, participants who are initially determined to be eligible may be removed from the study at a later date if the yoga instructors or research staff have reason to believe that the yoga sessions or other parts of the study could be unsafe for the participant in some way.

**C. 3. Study Components**

Fasting blood samples to monitor changes in immune function and psychological data will be collected at baseline (time 0), and 3 months, and 6 months after entry into the study, providing data on change during the intervention, as well as maintenance of change. Additionally, subjects' responses to a laboratory stressor will be assessed at baseline.

**C.3.a. Screening Session.** Women who have none of the disqualifying conditions listed above will be scheduled for a screening session in which nurses will draw a blood sample to assess hemoglobin. Nurses will also assess any potential phlebotomy problems, assess height and weight, and complete the central adiposity measurements.

Prior to the screening session, participants will be sent pictures of a person performing each of the positions included in the sequence. They will then be asked if they have any reservations (including anxieties or physical limitations) about their ability to perform the poses. Questions that potential participants have about the different poses will be answered and demonstrated by an instructor. To confirm that the women will be able to fully and safely participate in the yoga intervention, they will also be asked to perform several key poses under close supervision after they are demonstrated by a qualified instructor: Pavana Muktasana, Jathara Parivartanasana, Balasana, Supta Baddha Konasana, and Adho Mukha Svanasana. By demonstrating the poses and then asking the potential participants to perform the poses, we provide a very brief introduction to yoga that will help the women decide if they are interested and want to continue to the baseline session prior to randomization.

Obesity is associated with higher levels of proinflammatory cytokines (142), and abdominal obesity is associated with increased cytokine levels, above and beyond the effects of overall obesity; adipose tissue in the abdomen may secrete up to three times as much IL-6 as other subcutaneous fat tissues (142). Accordingly, we will assess the role of **central adiposity** in cytokine production. Although the measurement of waist and hip circumferences is the most common technique for assessing central adiposity (143), the accuracy can be limited by technical skill of the practitioner and the amount of fat in the abdomen. However, **sagittal abdominal diameter (SAD)** identifies a bony marking which does not change with adiposity, and thus more investigators have begun to use it. Importantly, SAD has been validated with computerized tomography (CT) (144), and thus will be used in this study as well as waist-hip measurements.

**C.3.b. All Sessions.** For each visit including the screening session, subjects will be instructed to fast overnight; breakfast will be provided in the GCRC as soon as they have had blood drawn by a nurse. All fasting samples will be collected between 7:00 and 9:00 AM to control for diurnal variation. For each blood draw after the screening session, subjects will have a catheter (indwelling needle) inserted on arrival at the GCRC. They will then be asked to sit quietly for at least 30 minutes before blood is drawn, to provide enough time to minimize the typical stress-related increases in catecholamines associated with needle insertions (22). We will begin regular blood pressure and heart rate assessments through the use of an automated system, the Dinamap/Critikon 1846SX/P, and/or through use of a Polar heart rate monitor and/or Actiheart monitor. Recent health-related behaviors, assessed at each interview, will include medications, recent alcohol intake, and sleep efficiency.

**C.4. Randomization and Masking**.

On completion of the baseline session, women will be randomly assigned to a treatment group using a block randomization sequence prepared and maintained by a project biostatistician, who will have no subject contact. Participants will be told not to mention their group assignment to any of study personnel during the GCRC assessments, and the research associates who work with subjects in the GCRC will not have access to their group assignment, and will be told to avoid viewing the flexibility tests. The laboratory personnel who analyze blood samples will be blind to all of the participants' data, including group assignment. The GCRC personnel who draw blood and perform the flexibility assessments will be blinded. The three- and six-month assessments will be carefully monitored to maintain blindness. Most of the outcome measures are not subject to experimenter bias, e.g., the battery of computer-scored self-report measures.

**C.5. Subject Retention.**

The extensive nature of the study protocol will be emphasized prior to enrollment so that subjects are aware of the time commitments. Subjects will be offered an opportunity for excellent basic yoga training either immediately (intervention group) or in six months (controls), free parking for all visits, and compensation for their time for the evaluation components ($10 for participation in the screening session, $90 for participation in the first GCRC session, $75 for the three-month follow-up, and $75 for the six-month follow-up, for a total of $250/person).

Demark-Wahnfried argues that cancer patients are motivated for change because the self-reflection that often follows diagnosis provides a “teachable moment” when patients may be particularly receptive to health-related interventions (145). We will build on this idea, offering women an opportunity to learn a new and useful skill.

**C.6. Adherence and Assessment of Adherence**

A review of adherence rates among healthy adults who were 55 and older reported that subjects completed an average of 78% of sessions across 21 trials; adherence tended to be higher for strength and flexibility (87%) than for aerobic exercise (75%) (146). Older adults tend to be more adherent than younger individuals in general (146). Adherence typically decays over the course of a study, with higher rates during the first 3 months of a study compared to the last 3 months (147). Exercise adherence rates in cancer survivors are comparable to those reported in RCTs of older adults without cancer, typically 60-85% for both home-based and supervised RCTs (148). In a six-month study using older adults, weekly yoga classes were attended 77.6% (SD=19.7) (119); a recent review of yoga for cancer patients and survivors reported generally good adherence across a range of cancer types and stages (52). Based on these studies, we would expect good adherence.

We will employ several strategies to maximize compliance. We will provide videos/DVDs to provide help with home practice. We will call any participant who misses a session to discuss the content of the session, to ask about any barriers to participation, and to encourage use of the video/DVD for the time period.

Participants' willingness to accept their random assignment is one of the obvious problems for any RCT. By promising participants the yoga intervention in six months if they are assigned to the wait-list control, we hope to minimize dropouts and contamination after assignment. Participants assigned to the wait-list control will be encouraged to continuing performing their usual activities, but will asked to refrain from beginning any yoga practice or other related activities, and we will get their self-reported activity at each GCRC assessment.

At the six-month assessment, we will ask participants what helped or hindered their practice after completion of the class; we will also ask what was most meaningful for them and use their responses to help guide our future efforts within the broad confines of the protocol. Using these multiple approaches, we hope to achieve at least 80% adherence, that is at least 80% of the women attending at least 80% of the time, or practicing at home with the DVD/video if they are unable to attend.

**C.7. Yoga Intervention**

Hatha yoga combines body postures or *asanas* and breath control techniques (*pranayama*). The yoga sequences were designed to provide therapeutic benefits particularly for depression, fatigue, upper body mobility and strength, and immune function. The repetition across the two weekly sessions is designed to assure that participants understand and can perform the new additions, building on skills through practice and repetition. Each of the two weekly sessions will last 1.5 hours, providing a total of 3 hours per week of supervised yoga practice; in addition, participants will be strongly encouraged to practice at home using the DVD/videos, and data on home practice will be collected at each session. By way of comparison, a tai chi chih intervention that produced alterations in varicella-virus specific immunity had three 45-min sessions per week for 15 weeks, or a total of 2025 minutes (87), compared to 2160 minutes over 12 weeks for our yoga intervention.

To evaluate and limit protocol drift, sessions will be audiotaped, and at least 20% will be randomly checked, using both sessions for the week in the overall evaluation. The checklist to be used by the observer to evaluate protocol drift will assess whether there were any omissions or additions from the predetermined poses (Table 1, attached to protocol).

Throughout all the sessions there are several issues that will be emphasized. First, the importance of home practice and use of the ancillary DVD/video will be encouraged. Also, gradual learning and working at one’s own level are key constructs to help participants feel comfortable.

Restorative poses, which are typically performed lying down and using props for support, are especially effective in combating fatigue, and these are a key thrust throughout all weeks. These poses can be maintained for relatively long periods of time (5-15 minutes), offering the body deep rest and rejuvenation. Moreover, an extended focus on the breath can be attained, approaching a meditative state.
of bodily awareness.

Poses that encourage openness in the chest and/or extension of the spine are especially effective for symptoms of depression; these postures are in opposition to a closed, rounded upper body that may encourage low mood and a sense of withdrawal (149). Breathing exercises affect depressive symptoms by

promoting deep relaxation and mental focus. In addition, a non-judgmental awareness of the body will be encouraged throughout the sequence.

Poses focusing on increased upper body strength and/or mobility will be introduced gradually, with difficulty adjusted based on individual ability and comfort. Upper body movements are also intended to benefit circulation and lymph gland function, particularly in the armpits, upper chest and neck. This may provide benefits for symptoms of lymphedema.

Several poses are believed to benefit immune function. Importantly, the overall emphasis on focused awareness of the breath and purposeful relaxation of the body throughout the sequence calms the sympathetic nervous system and thus would provide broad benefits.

Fatigue and pain can adversely influence physical activity, both during and after cancer treatment (5). Moreover, prolonged inactivity can lead to enhanced fatigue following even very mild exercise (150). Accordingly, we will ask participants to rate fatigue and pain at the beginning and end of each the yoga classes, and we will relate the changes within each session to changes in fatigue and pain across the intervention.

**C.8. Laboratory Stressor**

**NOTE: We had originally proposed to include the laboratory stressor at baseline and at 3 months; however,a 25% funding cut made it impossible, so it was only included at baseline**

**The Trier Social Stress Test (TSST)** will provide data on acute stress-related changes and rate of recovery at baseline. The TSST provides a widely-used, well-validated laboratory stressor that reliably enhances cortisol and catecholamine production (151-154). The TSST includes making a free speech as well as performing mental arithmetic in front of an "audience" panel of 2-3; the TSST takes 15 minutes, including introduction to the speech and 3 minutes of preparation time. For the speech, the participant will be told to imagine that she has applied for a position and was invited to an interview by the selection committee; the participant will be told that she will be given 10 minutes to prepare a speech about why she would be best for the job, and five minutes to talk with the committee, followed by a second experimental task. Both the nature of the speech as well as the particular serial subtraction series can be changed minimally to maintain maximal novelty; for our purposes we will counterbalance the scripts and arithmetic used at baseline. Across a number of studies the TSST has been used to provoke significant changes in cardiovascular function, stress hormones, and self-reported stress (151, 153, 154).

**C.9. Health and Health-Related Behaviors**

When the participant is seen at baseline, 3 and 6 months, we will ask about current medications and any changes in medications. Participants' height and weight will be assessed at baseline, and weight will be reassessed at 3 and 6 months. At each of these visits, women will be evaluated for diet, appetite, and physical activity. Participants will provide information on reproductive health to evaluate the menopausal transition across the study. In the proposed study we will similarly evaluate health behaviors carefully to make sure that they do not account for the relationships among the intervention, depressive symptoms, and immune function.

**Flexibility assessments** will allow us to objectively characterize our two groups of subjects in terms of flexibility at baseline, 3 months, and 6 months. The **sit and reach (SR) test** will provide information on hamstring and low back flexibility (155). Commonly used in fitness assessments, extensive normative data are available, as well as evidence supporting its reliability and validity (155-160). Performed using a sit-and-reach box, it assesses limitation in torso forward flexion (lower back, hamstring and calf flexibility).

The **Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaire,** will assess the weekly frequency and duration of various physical activities. Excellent for middle-aged and older populations, it has a solid history of validation and testing, and it is sensitive to relatively small changes in physical activity (161-164), and it has been used with cancer populations (3). We will assess activity at baseline, 3 months, and 6 months.

The Women's Health Initiative Food Frequency Questionnaire (FFQ) will provide data on the type, frequency, and quantity of foods and beverages consumed in the past 90 days.(165) The USDA Nutrient Database for Standard Reference was used for development of the nutrient database. Use at two time points will allow us to compare groups across time to be sure that there are not systematic differences either at baseline or over time.

The Pittsburgh Sleep Quality Index (166), a self-rated questionnaire, assesses sleep quality and disturbances over a one-month interval; it has good diagnostic sensitivity and specificity (a cut score of 6 or greater yielded a diagnostic sensitivity of 89.6% and specificity of 86.5%) in distinguishing good and poor sleepers. The scale yields a total score as well as 7 sub-scales which include subjective sleep quality, sleep

latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. We will use the full scale at baseline, 3 months, and 6 months to provide data on changes in sleep (124).

Questions from the **OARS Multidimensional Functional Assessment Questionnaire** will be used at screening and at follow-up to assess problems with lungs, kidneys, liver, digestive system, heart, high blood pressure, migraines, hormonal conditions, thyroid, cancer, cataracts, teeth, hernia, gout, hardening of the arteries, circulatory system, prostate, ovarian or uterine, and muscle-related disorders, as well as any medication used for each condition (167). The format is similar to those used in epidemiological studies (168, 169), and provides a simple way to look at frequency of chronic conditions and medications. We will also use the **revised Breast Cancer Prevention Trial (BCPT) symptoms checklist** to provide information about symptoms (170, 171). Pain will be assessed using a visual analogue 0-10 pain thermometer.

The **SF-36** (172) will provide a non-disease specific measure of functioning and well-being with excellent normative data. Developed for the Medical Outcomes Study (172), it taps eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. The energy/fatigue scale has been used in related work (2, 7) and thus will provide a useful benchmark for our findings; moreover, the excellent normative data provide a way to evaluate fatigue in our sample compared with other cancer and noncancer populations (27). Administered at baseline, 3 months, and 6 months.

We will also use 30-item **Multidimensional Fatigue Inventory-Short Form (MFSI-SF) to** provide data about behavioral, cognitive, physical, and affective expressions of fatigue (173, 174).

**C.10. Mood, Stress, and Support Data**

The **Center for Epidemiological Studies Depression Scale** (CES-D) has been used extensively as a brief measure of depressive symptomatology (175, 176). Studies have shown acceptable test-retest reliability and excellent construct validity (176). As the CES-D has also distinguished depressed from non-depressed participants in community and clinical samples, discriminative validity appears acceptable as well (176). Population norms provide cutoffs for varying levels of depression (176), and it has been widely used in cancer studies (3). Administered at baseline, 3 months, and 6 month to follow changes over time.

The **Structured Clinical Interview for DSM-IV, nonpatient version (SCID)** is designed to enable a clinically-trained interviewer to make relatively rapid and valid DSM-IV diagnoses (177, 178); we will use the depression and anxiety modules; we are interested in lifetime prevalence, as well as changes at each follow-up (179). Interrater reliability for SCID-NP diagnoses will be calculated using randomly selected audiotapes for 20% of the subjects.

The **Perceived Stress Scale (PSS)** (180) was designed to measure the degree to which individuals appraise situations in their life as stressful and includes items that assess perceptions of daily life as unpredictable, uncontrollable, and overloading. Correlations between the PSS and symptomatology are statistically significant even after partialing out depressive symptomatology; in fact, PSS scores were better predictors of psychiatric symptoms, physical symptoms, and health services utilization than were life event scores (181). In addition, there are norms for a variety of age groups, including older adults.

The 15-item **Impact of Events Scale (IES)** taps two distinct factors: avoidant and intrusive thoughts following a stressful experience (182). The avoidance items (Cronbach's alpha= .82) assess attempts to suppress thoughts about the experience of their recent life events, while the intrusion items (Cronbach's alpha= .79) assess the unintended thoughts. We will administer the IES with the reworded instructions used in other cancer studies that focus on cancer-related thoughts and behaviors (183, 184). Cancer researchers have found that higher scores, particularly intrusive thoughts, are related to depressive symptoms, while non-cancer studies have reported links among intrusive thoughts, elevated stress hormones, and poorer immune function (185-187).

The **Interpersonal Support Evaluation List (ISEL)** will be used to assess four types of social support: self-esteem, appraisal, tangible, and belonging (188). Items are rated on a four-point scale.

**C.11. Cytokines Produced by PBMCs stimulated with LPS**. Histopaque 1077 gradients will be used to separate PBMCs from whole blood samples. The PBMC cultures, $2x10^6$ cells/ml, will be incubated for 72 hours in 10cc polyproplylene tubes with 3 mls RPMI 1640 media supplemented with 10% human male serum, or medium containing LPS, 5ug/ml.

After 72 hours the tubes will be centrifuge at 1700 rpm for 10 minutes and the supernatants removed and aliquoted into cryovials and stored at -86C until assayed for IL-1b, IL-6, and TNF-α using BD OptEIA kits.

The stored supernatant samples for each subject will be assayed for all the cytokine markers as one run, thus using the same controls for all time points for each person.

**C.12. Interpretation of Results and Potential Problems**

We are experienced PNI researchers who have studied the influences of behavior on endocrine and immune function with a focus on health consequences, and we propose to harness this expertise in the context of the intervention study proposed here. We will keep the following important issues in mind as we conduct the proposed experiments and attempt to interpret results.

We considered using a three-group design, with a structured educational-support group as the third arm to provide a control for social contact, or another form of exercise. However, the educational-support group would have required 1.5 hours of meaningful content twice per week, or a total of 36 hours of equivalent meeting time, which seemed like it would ultimately not be a good control condition. Moreover, while providing interesting data, the costs for the study would have been substantially higher, and the risk of having subjects drop out who were not assigned to their group of choice is substantial. Using a wait-list control provides a control for spontaneous recovery and other potential confounders (189). For the breast cancer patients we propose to recruit, offering the delayed intervention to the wait-list group helps to minimize the drop-out rate in the control group (189).

On a related note, we wanted a follow-up assessment after the our end-of-intervention assessment to examine the durability and persistence of effects. Our choice of six months allowed sufficient time to see differences three months after the end of the intervention, but seemed short enough to minimize subject loss in the wait-list control group.

We debated about whether we should include exercise stress tests at baseline and three months, but decided against them. While it would have been helpful to have the "gold standard" of fitness information for our participants, $VO_2$max is not a primary outcome, and we are not testing physical fitness as a putative change mechanism.

We considered whether we should include genotyping as a facet of this research project. Genetic studies have addressed differences in proinflammatory cytokine production among individuals who have high vs low producer genotypes (190). However, the numbers needed to have sufficient power are very large, and clinical significance has not been demonstrated. Accordingly we have not proposed genotyping for this study because the evidence to date did not seem sufficiently compelling, given the expense and effort.

Finally, what if we find no significant results? For some hypotheses, this appears to be a very unlikely outcome; the associations between stress and proinflammatory cytokine production are well-established, as reviewed earlier (15, 76). Moreover, the absence of significant relationships between cytokines and fatigue in a sample of this size with repeated assessments would be an important null finding. For the yoga intervention, we have carefully designed our studies, and we have sufficient statistical power to detect any clinically meaningful effect sizes. Thus, we believe that negative data, while disappointing, would nonetheless be very useful for the field. Therefore, while we believe that our hypotheses are fundamentally sound, we also appreciate the potential importance of negative data.

**C.13. Sample Size and Power**

We determined that a total of 200 subjects, 100 per group, would enable us to detect small yet meaningful differences in primary and secondary endpoints with 80% power. For cross-sectional hypotheses such as hypothesis 3, the full sample will be available. For post-randomization measures, an attrition rate of approximately 15% is expected. The resulting 85 per group was used to calculate detectable effect sizes for the repeated-measures hypotheses. Examples of detectable differences in group means with 85 subjects per group, 80% power, and type I error rate alpha = 0.05 are 0.46 pg/mL for IL-6, 0.063 pg/mL for TNF-α, 2198 pg/mL for sIL-6r, and 0.7 on the CES-D depressive symptoms scale. Estimated effect sizes were based on studies by Collado-Hidalgo et al. (2) and Bower et al. (7), and also data we collected from an older adult study.

**D.14. Statistical Methods**

The table below gives a representation of the experimental design. Letters in bold indicate the structure of variables that will be used to test the hypotheses on each endpoint. Letters E, F, K, and L are calculated from the pre-stressor and post-stressor measurements; the remainder of the letters represents direct measurements.

Hypotheses 1 and 2 are based on the overall response at the pre-stressor endpoints. For hypothesis 1, the yoga group is expected to exhibit decreases in the primary endpoints, i.e. **H** + **N** < **G** + **M** (controlling for **B** and **A**, respectively). Hypothesis 2 is the same except the sign is reversed since the yoga group is expected to exhibit increases in these psychological, behavioral, and physical functioning endpoints. Hypotheses 3 and 4

address the response to the laboratory stressor. Analysis of hypothesis 3 will be based on the relationship of the stress-related increases in proinflammatory cytokines (**E**, **F**, **K**, and **L**) with depressive symptoms and fatigue. Hypothesis 4 will also be addressed with the stress-related increase variables. The expectation is that the yoga group will have a lower stress-induced physiological increase, i.e. **L** < **K** (controlling for **B** and **A**, respectively).

The primary method of evaluating these hypotheses will be repeated-measures analysis of covariance models. These models will be used to test for differences between the two treatment groups. Proinflammatory cytokines, fatigue, and depressive symptoms, as well as the secondary endpoints, will be the dependent variables; treatment group will be the independent variable. Covariates will include the baseline value of the dependent variable; the stratification variables breast cancer stage (I versus other) and radiation treatment (yes versus no); and race. Models will also be adjusted for other covariates that are significantly associated with the dependent variable at alpha = 0.05. Available data include measures of depression, anxiety, perceived stress, fatigue, pain, quality of life, major life events, and the IES. Other potential covariates are chemotherapy regimen; age; gender; hormone blocker treatment; axillary dissection; sagittal abdominal diameter (SAD); time since last treatment session; time since diagnosis; sleep; amount of physical activity outside of the yoga sessions; and comorbid medical conditions. For hypotheses regarding stress-induced increases, use of beta blockers will be included as a covariate since beta blockers are known to limit the physiological stress response. Summary statistics for each potential covariate will be examined to assess differences in the treatment groups. Subject-specific random effects will be considered in each model. We will use transformations of the dependent variable to correct for skewness when necessary. The models will account for correlation between post-randomized repeated measures from the same subject (i.e. months 3 and 6). Analysis of all endpoints will be on an intent-to-treat basis.

**Table 2.**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Group II Begins Yoga | | | | | | |
| | Baseline | | | 3 Months Post-Treatment | | | 6 Months |
| | Pre-Stressor | Post-Stressor | Stress-Related Increase | Pre-Stressor | Post-Stressor | Stress-Related Increase | No Stressor at month 6 |
| Group I (control) | **A** | **C** | **E** = C - A | **G** | **I** | **K** = I - G | **M** |
| Group II (yoga) | **B** | **D** | **F** = D - B | **H** | **J** | **L** = J - H | **N** |

For hypothesis 1 repeated-measures analysis of covariance models will be fit separately to each inflammatory marker, fatigue, and depressive symptom outcome at months 3 and 6. Only the pre-stressor measures will be used for the month 3 and baseline covariate measures. The overall difference in treatment group means will be the primary contrast in evaluating this hypothesis. The interaction between time and treatment group will also be evaluated.

Hypothesis 2 will also be assessed using repeated-measures analysis of covariance models fit separately to each psychological, behavioral, and physical functioning endpoint (all secondary endpoints). The same contrasts as in hypothesis 1 will be tested, with the difference being that the yoga group is expected to increase relative to the control group for the hypothesis 2 endpoints.

For hypothesis 3 linear regression models will be fit separately to the stress-related increase in each proinflammatory cytokine. The stress-related increase will be defined as the post-stressor minus the pre-stressor measures observed at month 3. The stress-related increase will be the dependent variable;

depressive symptoms and fatigue at month 3 pre-stressor will be the independent variables. The pre-randomization stress-related increase (month 0) will be the baseline covariate. An indicator for women currently taking beta blockers will also be included as a covariate, as beta blockers are known to limit the responsiveness of the sympathetic nervous system. The primary assessment for this hypothesis is whether depressive symptoms and/or fatigue are significantly associated with the stress-related increases. The interaction of depressive symptoms and fatigue will also be included to evaluate whether the levels of fatigue and depression modify the association each has with the stress-related increases.

A second model for hypothesis 3 will evaluate the association between fatigue and depressive symptoms. We will use a repeated-measures linear model for this purpose. Depressive symptoms will be the dependent variable and fatigue will be the independent variable. Pre-stressor measures from months 0, 3, and 6 will be used in the model, taking account of correlation across the three measurements from the same subject. Baseline stratification variables will be included as covariates.

Hypothesis 4 will be analyzed by fitting analysis of covariance models separately to the stress-related increase at month 3 for each physiological measure. The difference in mean stress-related increase between treatment groups will be assessed by each of these models. *We left this analysis in the protocol although we did not have funds to conduct the second stress-related assessment session, with the hopes that we would obtain additional funds that would make it possible.*

Further secondary analyses will examine the efficacy of the intervention using data from only those subjects in the yoga group. Associations between inflammatory markers, depressive symptoms, fatigue, and selected secondary endpoints will be assessed using models described above. In addition, the frequency of yoga practice will be included as a covariate in order to evaluate whether the efficacy of the intervention differed according to frequency of practice.

Any missing data will be investigated to be certain that data sets are as complete as possible. Since each of the proposed models can be fit to unbalanced data, we will be able to use all data that is collected even if there is missing data for some of the repeated measures. We will investigate patterns of missing data, but we do not expect the missing data that arise to be correlated with outcomes of interest.

The analyses described above involve a number of tests of hypotheses. We recognize the importance in conducting such tests to have adequate statistical power for detection of effects, and also to control to the extent possible the frequency of Type I decision errors. As discussed previously, considerable effort has been made to assure that sample sizes are sufficient to provide adequate power to detect meaningful differences. Several approaches will be used to control Type I error and minimize their impact on conclusions. The set of tests involving the primary endpoints (proinflammatory cytokines, fatigue, and depressive symptoms) will be adjusted using Holm's procedure. In addition, emphasis will be given to estimates of effect size so that effects that are statistically significant but of little practical relevance will not receive great attention.

Statistical analyses will be performed using SAS Version 9.1 (SAS Institute, Cary, NC, 2003).

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