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# Mindfulness-Based Stress Reduction for Overweight/Obese Women With and Without Polycystic Ovary Syndrome: Design and Methods of a Pilot Randomized Controlled Trial

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## Abstract

Mindfulness-based stress reduction (MBSR) may be beneficial for overweight/obese women, including women with polycystic ovary syndrome (PCOS), as it has been shown to reduce psychological distress and improve quality of life in other patient populations. Preliminary studies suggest that MBSR may also have salutary effects on blood pressure and blood glucose. This paper describes the design and methods of an ongoing pilot randomized controlled trial evaluating the feasibility and effects of MBSR in PCOS and non-PCOS women who are overweight or obese. Eighty six (86) women with body mass index ≥25 kg/m$^2$, including 31 women with PCOS, have been randomized to 8 weeks of MBSR or health education control, and followed for 16 weeks. The primary outcome is mindfulness assessed with the Toronto Mindfulness Scale. Secondary outcomes include measures of blood pressure, blood glucose, quality of life, anxiety and



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depression. Our overall hypothesis is that MBSR will increase mindfulness and ultimately lead to favorable changes in blood pressure, blood glucose, psychological distress and quality of life in PCOS and non-PCOS women. This would support the integration of MBSR with conventional medical treatments to reduce psychological distress, cardiovascular disease and diabetes in PCOS and non-PCOS women who are overweight or obese.

**Keywords**

Glucose; Obesity; Stress

## 1. Introduction

Polycystic ovary syndrome (PCOS), defined as chronic hyperandrogenic anovulation, is a common endocrine disorder that affects 5-10% of reproductive-aged women [1]. Insulin resistance almost always underlies PCOS and increases the risk for impaired glucose tolerance and type 2 diabetes, major risk factors for cardiovascular disease [2-5]. Additional cardiometabolic risk factors associated with PCOS include obesity, hypertension, dyslipidemia, inflammation, endothelial dysfunction, and subclinical atherosclerosis [6-11]. Women with PCOS are also at increased risk for psychological distress, body dissatisfaction and reduced quality of life due to their obesity, hirsutism, acne, irregular menses and infertility [12-14]. In women with PCOS the reported prevalence of emotional distress is 38%, depression 21-46%, and anxiety 34% [15-17]. Structured clinical interviews reveal that among women with PCOS, the lifetime incidence of any major depressive episode is 67%, social phobia 27%, eating disorder 21%, and suicide attempt 14% [18].

As more than two thirds (69%) of adults in the U.S. are overweight or obese, non-PCOS women who are overweight/obese represent a large at-risk group that shares some of the same cardiometabolic risks and psychological stressors seen in PCOS women [19-24]. In both PCOS and non-PCOS women, psychological distress could contribute to increased risk of cardiovascular disease and diabetes by: 1) promoting unhealthy behaviors, 2) impeding adherence to medical treatment, 3) contributing to obesity and insulin resistance by altering the activities of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, 4) increasing chronic inflammation through effects on the immune system [17, 25-28]. Despite this, current treatment strategies emphasize diet and exercise to reduce obesity and insulin resistance, but fail to address the management of psychological distress in these at-risk patient populations.

In both PCOS and non-PCOS women, psychological distress is a potentially modifiable cardiometabolic risk factor that can be targeted with mindfulness-based stress reduction (MBSR), a standardized mindfulness meditation program that is increasingly being offered in medical and health care settings to enhance psychological health and overall well-being [29]. MBSR has been shown to reduce psychological distress and improve quality of life in various patient populations [30-33].

In this paper, we describe the design and methods of an ongoing pilot randomized controlled trial (RCT) evaluating the feasibility and effects of MBSR in PCOS and non-PCOS women

who are overweight or obese. The primary outcome is mindfulness assessed with the Toronto Mindfulness Scale. Secondary outcomes include measures of blood pressure, blood glucose, quality of life, anxiety and depression. Our overall hypothesis is that MBSR will increase mindfulness and ultimately lead to favorable changes in blood pressure, blood glucose, psychological distress and quality of life in PCOS and non-PCOS women. This would support the integration of MBSR with conventional medical treatments to reduce psychological distress, cardiovascular disease and diabetes in PCOS and non-PCOS women who are overweight or obese.

## 2. Materials and Methods

### 2.1. Recruitment, Screening and Consent

**2.1.1. Study Population—**Subjects were recruited through Medicine and Obstetrics and Gynecology clinics at Penn State Hershey Medical Center, as well as through paper, radio and website advertisements, from November 2011 to December 2013 (ClinicalTrials.gov Identifier: NCT01464398). They were eligible if they met the following inclusion and exclusion criteria.

Inclusion criteria:

1. Women, age 18 years or older
2. Body mass index (BMI) ≥ 25 kg/m$^2$ (overweight or obese)

Women who were on metformin, insulin, medications for hypertension, ovarian suppressive therapy etc. were allowed to participate in the study on such medical therapy provided that they have been on a stable medical regimen for at least the previous 6 weeks. Information on use of medications, including those for diabetes and hypertension, were collected to be evaluated as a potential covariate in the analyses.

Exclusion criteria:

1. Current pregnancy
2. Secondary causes of hyperandrogenemia, such as known or suspected androgen secreting tumors, Cushing's syndrome, or hyperprolactinemia (prolactin >30)
3. Untreated hypothyroidism or hyperthyroidism (defined as Thyroid Stimulating Hormone (TSH) <0.2 or >5.5 mIU/mL)
4. Severe active neuropsychological disorder such as psychosis or suicidal ideation
5. Severe untreated depression or anxiety. Women with severe depression or anxiety will be allowed to participate if they are under the care of a mental health specialist as long as they have permission to do so from their mental health specialist and will continue to follow-up with their mental health specialist during the study.
6. History of an inpatient admission for psychiatric disorder within the past two years
7. Active alcohol or drug abuse
8. Inability to read, speak or write English

9. Inability to commit to the intervention and follow-up
10. Current enrollment in a stress reduction program
11. Mindfulness practice within the past 6 months (regular formal practice at least once a week)
12. Current enrollment in other investigative studies
13. Type 1 diabetes

**2.1.2. Screening and Consent Process—**The Institutional Review Board (IRB) of the Pennsylvania State University College of Medicine approved the study. At initial contact, by email or telephone, the research coordinator pre-screened potential subjects with a brief eligibility questionnaire with the major inclusion and exclusion criteria. A phone script and recruitment intake form were used to minimize any bias in the presentation of the study. Subjects who qualified for further screening were then scheduled for a screening visit at the Penn State General Clinical Research Center (GCRC). Prior to the screening visit, subjects were counseled about the purpose of the study, the procedures, the potential risks, and the time commitment. In addition, subjects under the care of a therapist were sent a letter to give to their therapist. This letter described the study and asked the therapist to sign and return the letter if there were no contraindications to the subject participating in the study.

During the screening visit, the research coordinator obtained written informed consent in person from all subjects. Subjects also signed a statement of understanding of the Class Schedule and Homework which listed the dates and times of the classes that they could be assigned to and the requirement of home practice 25 to 30 minutes per day for 6 days per week. Subjects were given a copy of the signed statement to take home with them. They were given another copy at the baseline visit as a reminder.

Subjects presented to the GCRC fasting for 12 hours for the screening visit. Blood work was obtained to identify appropriate study subjects and identify their PCOS status (PCOS or non-PCOS), including total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), TSH and prolactin. If the subject had any of these tests in the past year, their medical records were obtained and accepted in lieu of repeating the test for screening. The medical records of subjects were also reviewed when needed to confirm whether the subject has PCOS. We determined the PCOS status of subjects using the classic National Institutes of Health (NIH) definition of PCOS as chronic hyperandrogenic anovulation [34]. The PCOS status was not needed to determine eligibility but it was important to determine subjects' PCOS status as randomization was stratified by PCOS status so that the effects of MBSR in PCOS could be estimated. A urine pregnancy test was administered to all subjects at the screening visit, and any woman found to be pregnant was excluded from the study. Vital signs were also recorded, including blood pressure and heart rate. The modified Ferriman-Gallwey (F-G) hirsutism score was determined by trained study personnel [35]. If the F-G score was > 8, labs for total and free testosterone were not needed at the time of screening, but they were collected at the subsequent study visits.

At the screening visit, subjects were screened for depression and suicidal thinking using the Patient Health Questionnaire-2 (PHQ-2) [36, 37] and Item #9 of PHQ-9, respectively [38]. These are self-administered questionnaires that were reviewed by blinded study personnel for completeness. If a subject scored 3 or greater on the PHQ-2, the Full PHQ-9 was administered and a clinical interview was performed to determine the presence of a significant depressive disorder. If a subject scored 1 or greater on the 9th item of PHQ-9 ("Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?"), then the Full PHQ-9 and the P4 Screener were administered and a clinical interview was performed to assess suicide risk [39]. Subjects were considered at higher risk if they answered "Somewhat Likely" or "Very Likely" to Item 3 of the P4 Screener ("How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life some time over the next month?"), or if they answered "No" for Item 4 of the P4 Screener ("Is there anything that would prevent or keep you from harming yourself?"). Subjects were considered at lower risk if they answered "YES" to Items 1 or 2 of the P4 Screener. The remaining subjects were considered to be at minimal risk. Subjects with suicidal ideation were referred to one of the following appropriate resources for immediate evaluation: (1) Psychiatric consult, (2) Milton S. Hershey Medical Center Emergency Department, or (3) Suicide Crisis Numbers.

### 2.2. Study Design

Eighty six (86) women with BMI ≥25 kg/$m^2$, including 31 women with PCOS, were randomized to one of two groups for 8 weeks and followed for 16 weeks: (1) MBSR, or (2) health education control. The PCOS and non-PCOS women were in the same intervention classes, and they will be analyzed together in the primary analysis. The primary outcome is the Toronto Mindfulness Scale (TMS) which measures mindfulness and will allow us to demonstrate that the MBSR intervention increases mindfulness in the participants. Major secondary outcomes include hemoglobin A1c (HbA1c) as an integrated measure of glucose, mean arterial pressure (MAP) as an integrated measure of blood pressure, Short Form-36 (SF-36) as a measure of health-related quality of life, and Brief Symptom Inventory 18 (BSI-18) as a measure of overall psychological distress that includes sub scores for anxiety and depression.

### 2.3. Randomization

Randomization to MBSR or the health education control was performed using a random number generator. Personnel in the Penn State Hershey Medical Center Department of Public Health Sciences used Statistical Analysis System software version 9.2 proc plan to create a list based on permuted-blocks randomization scheme with subjects equally allocated to the two arms. Randomization to MBSR or health education control was stratified based on PCOS status (PCOS or non-PCOS) so that there would be an equivalent number of PCOS women in each arm of the study, which would allow the estimation of effect sizes of MBSR in PCOS. Personnel in the Department of Public Health Sciences selected a block size without revealing it to any of the blinded investigators or study personnel.

Randomization to MBSR or the health education control was performed by personnel in the Department of Public Health Sciences, and was not be communicated to research personnel

who are collecting and reviewing outcomes data. Personnel in the Department of Public Health Sciences communicated the randomization scheme to the Class Scheduler who is not involved in the collection or review of outcomes data. The Class Scheduler communicated the study group assignments to the subjects and the instructors. The Class Scheduler, subjects and instructors were asked to keep the assignments concealed from the rest of the study personnel who are blinded. The principal investigator, study coordinator and all study personnel involved in the collection and review of outcomes data are blinded.

### 2.4. Mindfulness-based stress reduction (MBSR)

Those randomized to MBSR received the standard MBSR program developed by Jon Kabat-Zinn at the University of Massachusetts Medical Center [40]. One adaptation to the standard course was the duration of home practice, which was 25 to 30 minutes per day instead of the standard 45 minutes per day. While the reports on adherence to home practice in MBSR programs are relatively small in number, research has shown that adherence to requested home practice, when participants are asked to do 45 minutes of daily home practice, is less than 45 minutes. Reports on adherence indicate that participants' daily home practice of formal meditation ranges from 15 to 35 minutes [41-43]. We chose to ask participants to practice 25 to 30 minutes as we have previously reported positive clinical outcomes and high adherence with this duration of home practice [31, 44, 45]. In addition, research on what makes for a necessary or appropriate dosage of home practice in MBSR has yielded inconclusive findings. There are some reports showing correlations between home practice and health outcomes, and other reports showing no correlations [41, 43, 46].

The instructor who led the MBSR intervention in this study was well qualified having completed professional MBSR training (practicum level) at the University of Massachusetts and with 9 years of experience (since 2005) in training others in mindfulness. The instructor has attended 9 seven-day silent retreats at Insight Meditation Society and has a daily personal mindfulness practice. The study MBSR instructor received weekly supervision for the first 8-week MBSR class, and periodic supervision for subsequent MBSR classes, totaling 24 hours of supervision during the study. The senior MBSR instructor providing the supervision was well suited for the supervisory role given his expertise in teaching MBSR. He is the first author of "Teaching Mindfulness: A Practical Guide for Clinicians and Educators" [47]. Supervision consisted of phone meetings with the senior MBSR instructor to discuss any problems or questions that arose during the MBSR sessions. At the end of each session, the study MBSR instructor completed a Fidelity Report, rating how well specific fidelity items, key components of the MBSR intervention, were covered on a scale of 0 (poor) to 10 (excellent), the overall quality of the presentation on a scale of 0 (poor) to 10 (excellent), and the engagement of the subjects on a scale of 0 (not at all engaged) to 10 (very engaged). To further monitor adherence to the protocol, the instructor audio recorded one to two sessions per 8-week MBSR class. The supervisor reviewed these audio recordings to help ensure fidelity and provide feedback to the study MBSR instructor. The supervisor also completed a Fidelity Report after reviewing each audio recording. The study MBSR instructor was expected to cover >90% of the material in each session. Table 1 gives an overview of the MBSR intervention used in this study, including the themes, pre-specified fidelity items and their weights, and home practice for each session.

### 2.5. Control Group: Health Education Control

Those randomized to the control group received education on the diagnosis, symptoms, complications and treatments for PCOS and obesity, diet, exercise and general stress management. Diet recommendations were based on American Diabetes Association (ADA) guidelines for nutritional management of PCOS [48]. The health education classes were led by a registered dietitian.

### 2.6. Study Visits and Procedures

After the screening visit, there was a baseline visit (before the intervention), 8-week visit (right after the intervention) and 16-week visit (end of study). Figure 1 summarizes the measurements obtained at each study visit, including validated questionnaires, focused physical exam and laboratory assessments. All questionnaires were self-administered questionnaires that were reviewed by blinded study personnel for completeness. All measurements were collected in all subjects regardless of intervention, and the mode of administration of the assessments was consistent. Study personnel collecting measurements were blinded.

**2.6.1. Baseline Visit—**The baseline visit was scheduled within 4 weeks prior to the planned start of the study intervention. Eligible women who consented to participate presented to the GCRC in a 12-hour fasting state for the baseline visit. A single blood draw was obtained from each subject in order to measure baseline HbA1c, glucose, insulin, lipid panel, high sensitive C-reactive protein (hsCRP), DHEAS and total and free testosterone levels. The fasting glucose and insulin will be used to calculate the Homeostatic index of insulin resistance (HOMA-IR). The HbA1c test had to be run immediately, but the remaining blood samples were frozen so that all the subjects' samples could be run together in batch. A urine pregnancy test was also administered to all subjects at the baseline visit.

Subjects were provided with salivary cortisol sampling kits including supplies and written step-by-step Salivary Cortisol Collection Instructions before their baseline study visit. Subjects were asked to pick 2 consecutive weekdays in the week before their baseline study visit to collect the saliva. On each day 3 salivary samples were collected: 1) immediately upon awaking in the morning, defined as "As soon as you are aware of being awake for the day and will not go back to sleep, sit up, remain in bed and collect the first sample of the day," 2) 30 minutes later before brushing teeth, consuming food or beverages, or exercising, and 3) at night just before going to sleep. Subjects were instructed not to eat or drink, brush their teeth, exercise physically, or consume prescription or over-the-counter medications 60 minutes prior to sample collection. Subjects were given a Diary for Salivary Cortisol Collection to record the date and time when each sample was taken, and to answer questions about consumption of food, alcohol, nicotine, caffeine, and prescription and over-the-counter medications, and exercise activities around the time of sampling. The saliva collecting equipment (Salimetrics, State College, PA) consisted of a small cotton swab, housed inside a centrifuge tube, in turn housed in a holding tube. Holding tubes were pre-labeled with the subject number, day (1,2) and sample (S1, S2, S3) number using freeze resistant labels. Subjects were provided with a freezer bag labeled for each day of collection. When collecting a saliva sample, subjects were instructed to place the cotton swab under the

tongue for at least 60 seconds, deposit the cotton swab into the centrifugation tube within the holding tube and store the entire sample in a freezer. Subjects brought their frozen saliva samples to the baseline study visit. The samples were then stored in a secure freezer to be run later in batch.

A brief physical exam was performed on all subjects at baseline. Height, weight and waist and hip circumferences were recorded to the nearest 0.1 cm, 0.1 kg and 1 cm, respectively. Subjects were weighed while dressed in light clothing, without shoes. Waist was measured at the level of the umbilicus and hip circumference was measured at the widest diameter. Blood pressure was determined in the right arm in the sitting position at each visit. A large cuff was used when necessary. To determine mean arterial pressure (MAP), subjects rested in a seated position for at least 5 minutes. Then three separate systolic and diastolic blood pressure measurements were obtained at least 1 minute apart in accordance with American Heart Association (AHA) recommendations [49]. MAP was calculated as 2/3 mean diastolic blood pressure + 1/3 mean systolic blood pressure. Pulse was also recorded. The modified F-G hirsutism score was determined by trained study personnel [35]. An acne assessment was made by trained personnel using a standard acne lesion assessment (count) diagram and definitions. Training including photographic examples of each grade were provided to study personnel. When counting facial acne lesions, it is important that all lesions be counted, both noninflammatory and inflammatory, examining areas of the forehead, cheeks, and chin and avoiding the nose.

Subjects completed the following questionnaires at baseline: Medical History, PCOS Questionnaire (PCOSQ) (PCOS subjects only) [50-52], Brief Symptom Inventory-18 (BSI-18) [53-56], Five Facet Mindfulness Questionnaire (FFMQ) [57-59], Toronto Mindfulness Scale (TMS) [60], SF-36 [61], Female Sexual Distress Scale (FSDS), Positive and Negative Affect Schedule (PANAS) [62], and the Perceived Stress Scale-10 (PSS-10) [63]. The safety questionnaires PHQ-2 and Item #9 of PHQ-9 were also administered at baseline following the same procedures as described above during the screening visit. Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and PROMIS Sleep-Related Impairment surveys were administered at baseline as sleep disturbances are common and sleep may be an important mediator of the effects of MBSR. To determine any potential effects of subjects' expectations on outcomes, the Acupuncture Expectancy Scale was modified to a Stress Reduction Expectancy Scale (SRES) and administered to all subjects at baseline [64]. The PCOSQ was administered only to the PCOS women as it is PCOS-specific and cannot be administered to non-PCOS women. All the remaining questionnaires were administered to all subjects (PCOS and non-PCOS).

Prior to completing the TMS questionnaire (the primary outcome), subjects were instructed to "sit quietly for the next 15 minutes and pay attention to your breathing or anything else that might arise." Afterwards, subjects were asked to describe the degree to which each of the 13 items in the TMS described what they just experienced on a 5-point scale from 0 (not at all) to 4 (very much). The TMS measures an individual's ability to be mindful, a mode of curious, decentered awareness dependent on the development of a composite set of skills.

At the baseline visit all subjects were given menstrual diaries to record menstrual bleeding during the study. Subjects were also given Daily Practice Logs to record the time they spent on home practice. To keep subjects' study group assignments concealed from blinded study personnel, the Daily Practice Logs were collected enclosed in envelopes.

After the baseline visit, subjects were randomized to 8 weeks of MBSR or health education control. Randomization took place in the week prior to the start of the intervention classes. During the study, all subjects continued to receive usual care from their physicians. All subjects had been on a stable medical regimen during the 6 weeks prior to screening and they were advised not to change or discontinue any of their medications during the study unless directed to do so by their physician. During the study, all subjects were encouraged to continue their routine activities and they were asked not to take part in any new, additional health education, exercise or stress reduction program.

**2.6.2. Follow-up 8-week visit and 16-week (end of study) visit—**Subjects presented to the GCRC after a 12 hour fast and the procedures in the baseline visit were repeated as described above. All subjects completed the Follow-up Medical History questionnaire, including any changes in the use of medications. Salivary cortisol and menstrual diaries were collected. At the 8-week visit, subjects completed the following two additional questionnaires: 1) Perceived Outcomes (PO) which asked subjects to rate their efficacy, satisfaction, and confidence [64] with the intervention, and (2) Ratings and Description of Barriers (RDB), if any, that prevented the subject from accepting or adhering to MBSR or health education control. To ensure that the subject's study group assignment remained concealed from the blinded study personnel, these questionnaires were handed out and collected in enclosed envelopes.

## 2.7. Original protocol

The original protocol for this study included only women with PCOS and randomized subjects to 1 of 3 groups: 1) MBSR, 2) health education control, or 3) waitlist control. We randomized 11 PCOS women under the original protocol, in which 2 were randomized to MBSR, 4 to health education control and 5 to waitlist control. The protocol was subsequently modified to the current version based on our experience after running the first set of MBSR and health education classes. The main revisions included dropping the waitlist group to increase the size of the classes, and opening up the study to non-PCOS women with overweight/obesity who could also potentially benefit from MBSR. As the revised protocol and the original protocol are on the same continuum, we expect that these protocol changes will ultimately benefit the project. The total sample size of 86 includes the 6 women randomized to MBSR or health education control under the original protocol as the intervention classes themselves did not change.

## 2.8. Data Analysis

**2.8.1. Sample Size—**It is expected that mindfulness outcomes from baseline to week 8 will show very little to no improvement in the health education control arm. It is hypothesized that mindfulness outcomes from baseline to week 8 will show improvement in the MBSR treatment arm as compared to the health education control arm. Conservative

estimates of effect size and variability for sample size estimation were primarily based on an article by Gayner et al for TMS Total Score, TMS Curiosity Subscale, and TMS Decentering Subscale and assumed a within-subject correlation coefficient of 0.6 [65]. Further, the sample size estimates were based on the intent-to-treat principle and have been inflated to account for the potential of 15% subject dropout or non-compliers.

A sample size of 72 (36/group which includes a 15% dropout factor) will provide 90% power to detect an absolute difference in Toronto Mindfulness Scale (TMS) Total Score change from baseline to week 8 means between the MBSR and health education control groups, assuming change from baseline TMS Total Score group means of 0.3 in health education control and 7.6 in MBSR; a standard deviation of 8.6; and a two-sided test having type I error of 0.05. Even if the variability is 10% larger than expected, i.e., a standard deviation of 9.5, we would still have 83% power to detect these same absolute differences in means between the MBSR and health education control groups. Given the target sample size of 72, we will have 87% power to detect an absolute difference in TMS Curiosity Subscale change from baseline to week 8 means between the MBSR and health education control groups, assuming change from baseline TMS Curiosity Subscale group means of −1.0 in health education control and 2.8 in MBSR; a standard deviation of 4.7; and a two-sided test having type I error of 0.05. Given the target sample size of 72, we will have 81% power to detect an absolute difference in TMS Decentering Subscale change from baseline to week 8 means between the MBSR and health education control groups, assuming change from baseline TMS Decentering Subscale group means of 1.2 in health education control and 4.9 in MBSR; a standard deviation of 5.0; and a two-sided test having type I error of 0.05.

**2.8.2. Statistical analyses—**The primary outcome is the Toronto Mindfulness Scale (TMS) to demonstrate that the MBSR intervention increases mindfulness in the participants. Secondary outcomes include (1) measures of glucose metabolism: HbA1c, fasting glucose, fasting insulin and HOMA-IR, (2) lipid profile, (3) androgenic hormone profile: testosterone and DHEAS, (4) hsCRP as a measure of inflammation, (5) salivary cortisol profile including the cortisol awakening response (CAR), diurnal cortisol slope, waking cortisol and bedtime cortisol, (6) blood pressure including MAP, (7) anthropometrics including weight, (8) F-G hirsutism score, (9) acne, (10) quality of life using the SF-36 in all subjects and the PCOSQ in PCOS subjects only, (11) BSI-18 as a measure of overall psychological distress that includes sub scores for anxiety and depression, (12) FFMQ which explores different aspects of mindfulness, (13) PROMIS Sleep Disturbance and Sleep-Related Impairment, (14) female sexual distress using the FSDS, (15) perceived stress using PSS-10, (16) positive and negative affect using PANAS, and (17) other adherence and feasibility measures including recruitment, retention, class attendance, and home practice.

Data analysis will follow the principle of intent-to-treat (ITT) regardless of subject compliance with the sessions. PCOS and non-PCOS subjects will be analyzed together in the primary analysis (MBSR vs. Health Education). Linear mixed-effects models will be fit and contrasts constructed to assess differences between treatment groups with respect to changes in continuous outcomes over time [66]. The change from baseline in primary (Toronto Mindfulness Scale) and secondary continuous outcomes will be the dependent variables. The independent variables will include treatment group, time of the visit, the

baseline value of the outcome measure, and potentially confounding variables. We will adjust for major covariates using linear mixed models. Given a sample size of 72, we should have adequate power to adjust for some covariates or degrees of freedom [67]. The sample size should be adequate to account for 2 to 4 covariates in addition to group (2 degrees of freedom), visit (2 degrees of freedom), and the interaction of visit with group (1 degree of freedom). We will look at the following variables that may mediate some of the effects of the intervention and use the 2 to 4 that are most important as covariates in the final model: age, BMI, use of diabetes medication, use of medication for high blood pressure, adherence, blood pressure, HbA1c and class size. In this particular setting, analyzing the change from baseline within a linear mixed-effects models framework can be reduced to multiple linear regression; however, linear mixed-effects models provide greater flexibility in case of missing data.

The women with PCOS will be assessed in secondary analyses to provide adequate information to appropriately power a future study of MBSR in women with PCOS. Secondary exploratory analyses to generate hypotheses for future studies include: (1) PCOS:MBSR vs. PCOS:Health Education, (2) PCOS:MBSR vs. non-PCOS:MBSR, (3) PCOS:Health Education vs. non-PCOS:Health Education.

## 3. Results

### 3.1 Trial Registration and Conduct

The trial was registered at clinicaltrials.gov (NCT01464398) prior to the start of enrollment. The study protocol, case report forms, and informed consent forms were reviewed and approved by the IRB of the Pennsylvania State University College of Medicine. Subject accrual (including accrual of PCOS subjects), subject retention, adherence data, and adverse events were monitored regularly as outlined in the Data and Safety Monitoring Plan. Any protocol deviations or violations were reported to the IRB.

### 3.2. Study Governance

The study is led by the Principal Investigator at the Pennsylvania State University College of Medicine. The research team meets regularly and includes experts in PCOS, women's health, endocrinology, MBSR, biostatistics and clinical trials. There is an independent monitoring committee, which met regularly via phone to review the conduct and progress of the trial and make recommendations.

### 3.3 Study Progress

Eighty-six (86) women, including 31 women with PCOS, have been randomized to MBSR or health education control for 8 weeks and followed for 16 weeks. We planned to randomize 72 overweight or obese women, but we actually randomized 86 overweight or obese women in order to achieve our goal of at least 30 women with PCOS while maintaining reasonable class sizes. Table 2 shows the demographic and clinical characteristics of the study participants. Recruitment, intervention and follow-up were completed in June 2014. We are currently running the proposed assays and preparing to analyze the data.

## 4. Discussion

The purpose of this pilot RCT is to determine the feasibility and effects of MBSR in PCOS and non-PCOS women who are overweight or obese. We are aware of only one other study of mindfulness in women with PCOS which showed that a mindfulness-based intervention significantly improved stress, depression, anxiety and quality of life in 38 women with PCOS [68]. In the overweight/obese population, mindfulness-based interventions appear to reduce obesity-related eating behaviors including binge eating and emotional eating [69, 70]. However, the effect on weight loss remains unclear although one study has shown preliminary efficacy for women attempting to lose weight [71, 72]. Previous studies suggest that MBSR may also have beneficial effects on blood glucose, blood pressure and cardiovascular risk factors in patients with type 2 diabetes [44, 73]. The effect on glucose levels remains unclear as studies have shown mixed results when looking at the effects of mindfulness-based interventions on hemoglobin A1c [44, 74-76].

In an MBSR trial it is of great importance that the instructor delivering the intervention is well trained in MBSR. In this study the MBSR instructor was well-trained and also received regular supervision from a senior MBSR instructor during the study. To further ensure fidelity to MBSR, we developed fidelity reports for each session including weighted fidelity items. This allowed us to monitor implementation fidelity throughout the study. The study MBSR instructor was expected to cover >90% of the material. These fidelity reports also tracked the quality of presentation and the responsiveness of participants in each session.

As we recruited overweight or obese women, it was important to make clear to the subjects that the primary focus of the study was stress reduction, not weight reduction. To further minimize the influence of subjects' expectations, all subjects were informed that the study was designed to test the effects of two different types of stress reduction programs, one of which is combined with health education. Subjects were not told that one program was hypothesized to be more effective than the other. This limited any bias that could result from subjects perceiving that they have, or have not, received an effective intervention.

To control for instructor attention and group support, both the MBSR group and the health education control group received 26 hours of instructor-led class time as 2.5 hour sessions once a week for 8 weeks plus a 6 hour retreat session. This session schedule and duration is similar to the standard MBSR format [40, 46]. The instructors recorded attendance at each session. All subjects in the MBSR and health education control groups were instructed to spend 25 to 30 minutes a day (for 6 out of 7 days/week) reviewing the course materials, which included formal and informal mindfulness practices for the MBSR group and review of health education materials for the health education control group. All subjects were instructed to keep time logs (Daily Practice Logs) of these home activities, including comments regarding their experiences with these home activities. All subjects in the MBSR and health education control group were given the same written guidelines on diet and exercise at their first intervention session.

## 5. Conclusions

We have assembled an interdisciplinary team of experts in MBSR, PCOS, women's health, endocrinology, clinical trials and biostatistics to conduct this pilot RCT of MBSR in overweight/obese women with and without PCOS. Our overall hypothesis is that MBSR will increase mindfulness and ultimately lead to favorable changes in blood pressure, blood glucose, psychological distress and quality of life in PCOS and non-PCOS women. This would support the integration of MBSR with conventional medical treatments to reduce psychological distress, cardiovascular disease and diabetes in PCOS and non-PCOS women who are overweight or obese.

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## Abbreviations

| | |
|---|---|
| **BMI** | Body mass index |
| **BSI-18** | Brief Symptom Inventory-18 |
| **DHEAS** | Dehydroepiandrosterone sulfate |
| **FFMQ** | Five Facet Mindfulness Questionnaire |
| **F-G** | Ferriman-Gallwey hirsutism score |
| **FSDS** | Female Sexual Distress Scale |
| **HbA1c** | Hemoglobin A1c |
| **HEC** | Health education control |
| **HOMA-IR** | homeostatic index of insulin resistance |
| **hsCRP** | high sensitive C-reactive protein |
| **MAP** | Mean arterial pressure |
| **MBSR** | Mindfulness-based stress reduction |
| **PANAS** | Positive and Negative Affect Schedule |
| **PCOS** | Polycystic ovary syndrome |
| **PCOSQ** | PCOS Questionnaire |
| **PHQ** | Patient Health Questionnaire |
| **PROMIS** | Patient-Reported Outcomes Measurement Information System |
| **PSS-10** | Perceived Stress Scale-10 |

| | |
|---|---|
| **SF-36** | Short Form-36 |
| **TMS** | Toronto Mindfulness Scale |
| **TSH** | Thyroid stimulating hormone. |

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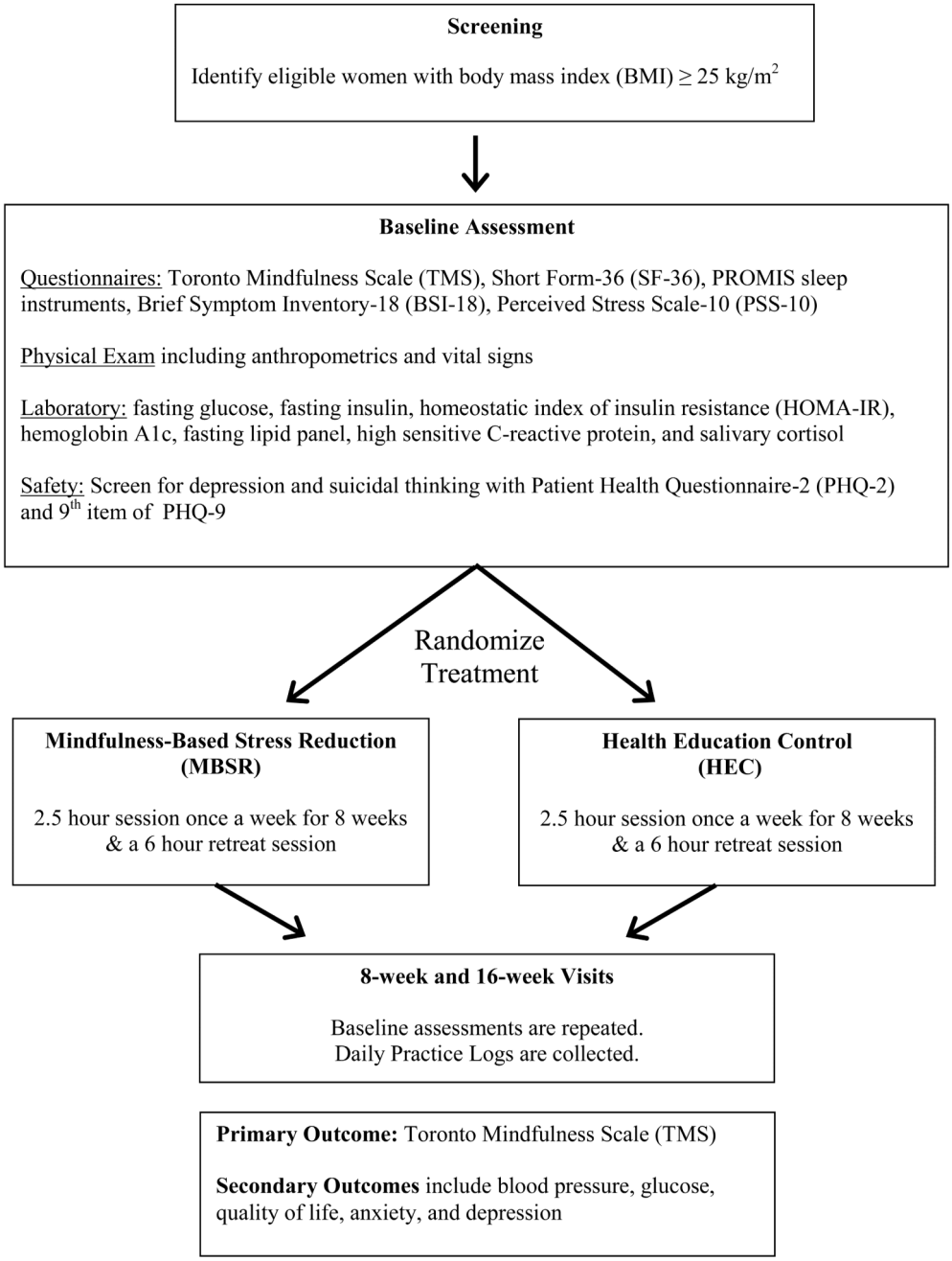


**Figure 1.**
Overview of study design

## Table 1

**Overview of the Mindfulness-based stress reduction (MBSR) intervention in this study, including the themes, pre-specified fidelity items and their weights**

| Session | Theme | Time | Fidelity Items | Weight |
|---|---|---|---|---|
| 1 | Mindfulness as a Pathway to Stress Reduction | 2.5 hrs | Introductions, guidelines and safety<br>Defining mindfulness & examples<br>Raisin-mindful eating<br>Breath awareness & process<br>Body scan with relaxation cues & process<br>Home practice instructions | 25<br>25<br>10<br>30<br>10 |
| 2 | Stress Physiology Perceptions & Creative Responding | 2.5 hrs | Body scan with awareness & Introduce standing yoga & process– emphasizing pure awareness<br>Home practice discussion– success & obstacles; Stress reactivity, perception & creative responding<br>Introduce breath meditation & process<br>Home practice instructions | 30<br>30<br>30<br>10 |
| 3 | Pleasant Events - Awareness of enjoyment to toxicity & Creative Responding | 2.5 hrs | Breath meditation with instructions on posture; Process opening & home practice with emphasis on embodiment & ownership of present experience Introduce floor yoga – themes of gentleness, non-striving, being present, listening to body & process Process Pleasant Events Calendar– tie in foundations of acceptance and letting go<br>Introduce walking (if time)<br>Home practice instructions | 20<br>30<br>30<br>10<br>10 |
| 4 | Unpleasant Events, Awareness of Stress Reactivity Choice in Responding | 2.5 hrs | Standing yoga<br>Introduce meditation with prominent sensations & process<br>Process Unpleasant Events Calendar– triangle of awareness, noticing patterns, link acceptance Stress defined via literature and experience;<br>Creative responding: current science and explore through dialogue/personal experience or teaching stories<br>Home practice instructions | 10<br>30<br>25<br>25<br>10 |
| 5 | Patterns & Possibilities | 2.5 hrs | Floor yoga<br>Introduce expanded awareness meditation & process<br>Process home practice– process being stuck, shutting down, noticing patterns<br>Creative responding– from habit to choices, tying in foundations of letting be, letting go, softening & creating space, allowing for new possibilities<br>Introduce mindful walking & process, if time<br>Home practice instructions | 10<br>30<br>20<br>20<br>10<br>10 |
| 6 | Interpersonal Communications – A Mindful Approach | 2.5 hrs | Yoga<br>Sitting meditation with less instruction, more space, choiceless awareness<br>Discuss Full Day retreat<br>Process home practice– Difficult Communications Calendar<br>Introduce communication styles & process-noticing assumptions<br>Home practice instructions | 10<br>20<br>10<br>20<br>30<br>10 |
| Full Day Retreat | Moment to Moment Presence with Full Range of Experience | 6 hrs | Opening instructions<br>Review of all practices heretofore<br>Introduce mountain and loving-kindness<br>Closing activity, breaking silence | 10<br>50<br>30<br>10 |

| Session | Theme | Time | Fidelity Items | Weight |
|---|---|---|---|---|
| 7 | Mindful Listening and Responding | 2.5 hrs | Yoga<br>Choiceless awareness<br>Process Full Day retreat<br>Process home practices and interpersonal styles<br>Introduce mindful listening & process<br>Closing meditation (choice)<br>Home practice instructions | 10<br>10<br>10<br>20<br>30<br>10<br>10 |
| 8 | Endings & Transitions – Reflections - Continuation | 2.5 hrs | Body scan & process<br>Process home practice– no recordings<br>Yoga<br>Sitting–extended silence & guided reflection over 8 weeks & process<br>Review resources (manual)<br>Group closure<br>End meditation (choice) | 10<br>10<br>10<br>30<br>10<br>20<br>10 |

## Table 2
**Demographic and clinical characteristics of study participants**

| | Overall (N=86) | Mindfulness-Based Stress Reduction (N=42) | Health Education Control (N=44) |
|---|---|---|---|
| | **N (%)** | **N (%)** | **N (%)** |
| Race | | | |
| White | 77 (89.5%) | 37 (88.1%) | 40 (90.9%) |
| Black | 5 (5.8%) | 3 (7.1%) | 2 (4.6%) |
| Other | 4 (4.7%) | 2 (4.8%) | 2 (4.6%) |
| Hispanic Ethnicity | 4 (4.7%) | 1 (2.4%) | 3 (6.8%) |
| | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| Age (yrs) | 44.5 (12.5) | 47.0 (11.5) | 42.2 (13.1) |
| Weight (kg) | 103.2 (24.1) | 104.2 (21.5) | 102.3 (26.6) |
| Body Mass Index ($kg/m^2$) | 38.9 (8.7) | 39.0 (7.7) | 38.8 (9.7) |
| Waist circumference (cm) | 43.8 (7.5) | 44.3 (8.0) | 43.3 (7.0) |
| Average Systolic Blood Pressure (mm Hg) | 124.3 (16.2) | 126.2 (16.7) | 122.4 (15.7) |
| Average Diastolic Blood Pressure (mm Hg) | 77.7 (8.5) | 79.2 (8.6) | 76.2 (8.3) |