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Study Title: Reducing the **E**xperience of menopausal **S**ymptoms through **T**emperature (REST)

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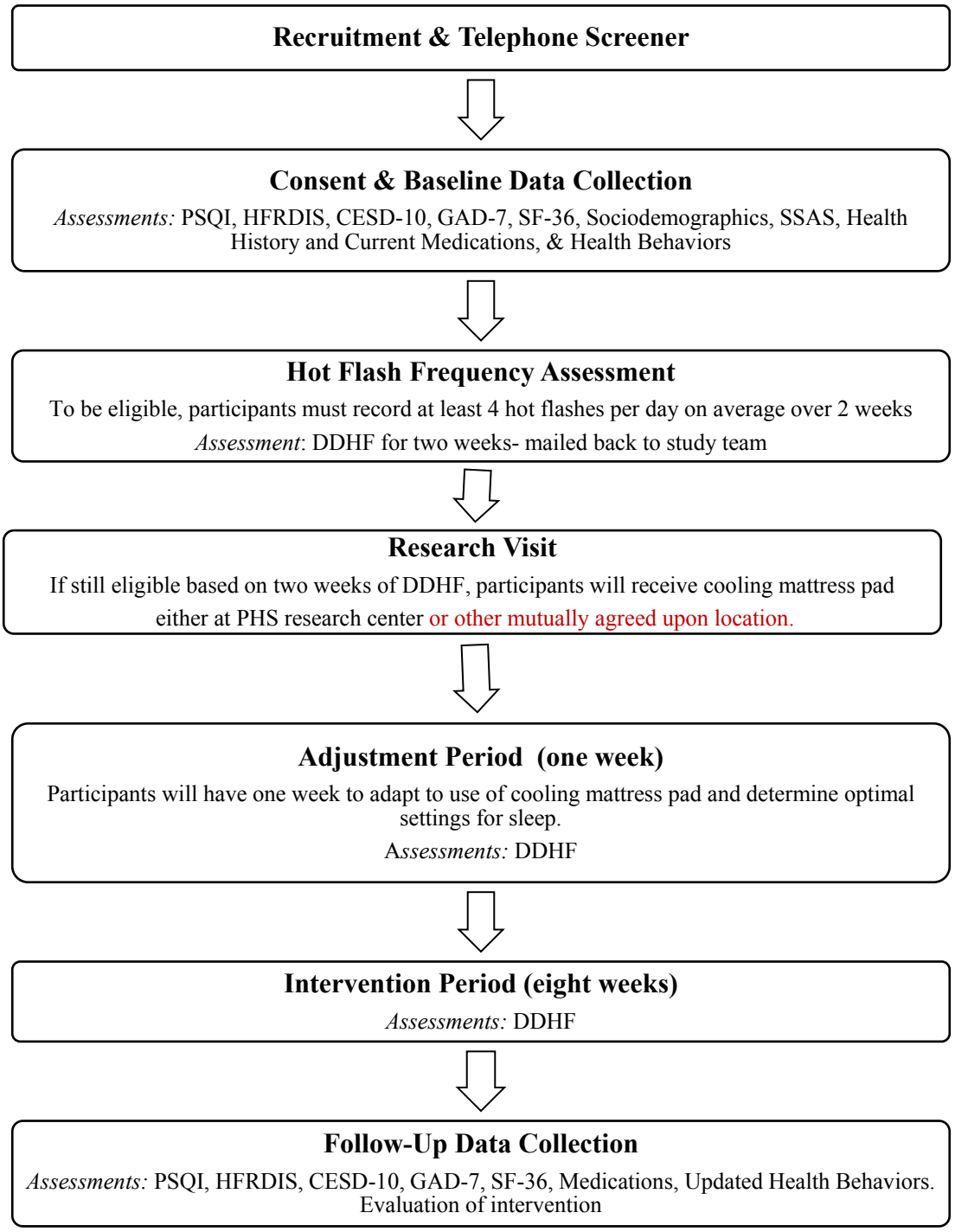
Study Schema



Background, Rationale and Context

Menopause, or the irreversible cessation of menses, occurs with the depletion of ovarian follicles and an associated decline in estrogen secretion. The full extent of the neuroendocrine events surrounding the menopause is not completely understood, but hot flashes and/or night sweats as distinct manifestations of such events are commonly experienced by 64% to 87% of women undergoing natural menopause and almost all women who undergo surgical menopause.[1-4] Hot flashes are "transient episodes of flushing, sweating, and a sensation of heat, often accompanied by palpitations and a feeling of anxiety, and sometimes followed by chills."[5] They are prevalent in women in their 40s and 50s [3] and frequently begin in the early perimenopausal period and peak just prior to a woman's last menstrual period.[6,7] About 1/3 of women experience more than 10 hot flashes per day, usually lasting 1 to 5 minutes with a small percentage continuing for more than 6 minutes.[3]

While some women report experiencing the menopausal transition without any hot flashes[1], for other women, these symptoms can be frequent and severe enough to become debilitating and interfere with daily activities and quality of life.[8-16] Avis et al.[8] found that women reporting hot flashes or night sweats were significantly more likely to experience depressive symptoms (O.R. = 1.83), even controlling for sleep problems and estradiol levels. Hot flashes are one of the chief menopausal complaints for which women in Western societies seek medical treatment[5,17] and are the primary reason that women begin hormone therapy (HT).[18-21]

Estrogen therapy, alone or in combination with progesterone, is currently the gold standard for treatment of vasomotor symptoms. A Cochrane Database systematic review of 21 double-blind, placebo controlled trials showed a mean reduction from HT of approximately 17 hot flashes per week (equivalent to a mean reduction of 2.4 hot flashes per day or 75%) with HT compared to placebo.[22] HT, however, is associated with a number of risks and is often contraindicated for women at high risk for breast cancer.[23-25] Some of the risks of HT include thromboembolic events and breast cancer, as well as troublesome side effects, like breast tenderness and irregular bleeding. The Women's Health Initiative (WHI) trial and the HERS study have demonstrated increased coronary heart disease events and stroke in HT users[26-28] and a doubling of risk of dementia in the WHI combination HT group when compared to the placebo group.[29] A clear increase of breast cancer risk was present after 4 years of HT use.[26] Following publication of the WHI results, many women stopped HT. One study found that among women who had discontinued HT, 25% ultimately resumed therapy because of symptoms. This finding suggests that there are some women for whom symptoms are so severe that they are willing to take HT despite the risk of long-term health consequences.[30]

Given the risks and side effects associated with HT, many women either cannot or choose not to take HT [3,10,25,31], and many women have sought alternatives to HT.[5,32-34] A telephone survey of 886 women aged 45-65 found that 22% used alternatives to HT to manage menopausal symptoms.[35] These alternatives include other pharmaceutical agents, herbal or dietary remedies, and behavioral therapies. Many of the pharmaceutical agents are ineffective or have a high incidence of side effects. Clonidine, an alpha-2 adrenergic agonist, is of limited efficacy and can cause hypotension as an adverse effect.[36,37] Fluoxetine and venlafaxine, two antidepressants may cause disturbing side effects such as dry mouth, anorexia, nausea, constipation, anxiety, sweating, insomnia, and decreased libido.[38] Veralipride is a dopamine antagonist which is

indicated for the treatment of hot flashes, but can have central nervous system, endocrine or respiratory side effects.[39] Bellargal® is not very effective in reducing hot flashes and has side effects including sedation and constipation.

With many of the prescription medications having limited efficacy and multiple side effects, women have turned to over the counter "natural" products to treat menopausal symptoms.[32,33,40] These products include St. John's wort, vitamin E, black cohosh, dong quai, ginseng, evening primrose oil, motherwort, licorice, wild yam, red clover, and soy derivatives.[41] Black cohosh has been found to have a modest effect on hot flashes in trials lasting six months or less. Although few adverse events have been reported, the long-term safety (mainly estrogenic stimulation of the breast or endometrium) is unknown and not enough data exist to support a recommendation for its use in this country.[42] Soy is a popular alternative for relieving hot flashes, but the evidence for its effectiveness is mixed.[43-45] A 12-week double-blind cross-over design clinical trial found no evidence that soy was more effective than placebo.[45] Burke et al.[44] also did not find beneficial effects of soy. Although soy markedly diminished moderate to severe hot flashes in a double-blind, placebo-controlled trial of 104 postmenopausal women, side effects such as gastrointestinal problems, food intolerance, and constipation were experienced by a significant number of participants.[46] Two reviews of randomized controlled clinical trials of complementary and alternative medicine (CAM) therapies for hot flashes did not find evidence that other herbs and nutritional supplements evidence were beneficial.[41,47] Many of these alternative therapies have not been shown to be effective and are not regulated by the Food and Drug Administration. A further problem is that the identity of the compounds and the mechanism of action are unknown.[41]

We have previously conducted three trials of nonpharmacological treatments for hot flashes. Two of these trials were of acupuncture[48,49] and one trial was of yoga.[50] Although all three studies found a significant reduction in hot flashes, women continue to seek other nonpharmacological interventions for their night sweats and hot flashes. A cooling mattress pad system provides a promising device for reducing hot flashes. The devise consists of a mattress pad that is placed between a person's mattress and fitted sheet. Small tubes are embedded in the pad that are connected to a cube that is filled with water and kept next to the bed. Participants can regulate the temperature of the cooling mattress pad by regulating the temperature of the water that flows from the cube to the mattress pad. This is a totally non-invasive device that provides a cooling temperature for sleeping. We hypothesize that the cooling mattress pad will help women sleep and reduce their number of night sweats. It's possible that it may also reduce the number of daytime hot flashes.

Objectives

Objective 1: To obtain preliminary evidence on the efficacy of a cooling mattress pad in reducing subjective hot flashes for peri and postmenopausal women experiencing menopausal hot flashes.

Objective 2: To obtain preliminary evidence on the efficacy of a cooling mattress pad for improving sleep for peri and postmenopausal women experiencing menopausal hot flashes.

Participant Selection

Recruitment

Women will be recruited from the community through flyers (Appendix A). They will call into a study phone line or respond through Be Involved at which time they will be screened for their initial eligibility using a telephone screener (Appendix B). Women who are eligible and willing to participate, will come to the PHS Research Center in Piedmont Plaza 1 or the Center for Integrative Medicine in Piedmont Plaza II to be consented and complete baseline questionnaires or sent materials via mail or email to complete. They will be sent home or givena hot flash diary to complete for two weeks in order to confirm a sufficient number of hot flashes for study eligibility. After two weeks, women will mail back their diaries and continue to record their daily hot flashes until they are notified by study staff of their eligibility, within a week of receiving the diary.

Inclusion Criteria

- Women aged 45-60
- Peri or postmenopausal women (No periods for at least 3 months)
- Experiencing at least 4 hot flashes per day on average per week

Exclusion Criteria

- Initiated CAM or non-CAM treatments for hot flashes in the last 4 weeks.
- Changed dose of a CAM or non-CAM treatments for hot flashes in the last 4 weeks.
- Initiated antidepressants in the last 3 months.
- Changed their dose of an antidepressant in the last 3 months.
- Women who describe their health as fair or poor.

Study Outcomes and Measures

Study Outcomes

- **Primary Outcome Measure**: change in frequency of daytime and nighttime hot flashes based on a daily diary completed every day.
- **Secondary Outcome Measure**: Improved sleep quality, as measured by the Pittsburgh Sleep questionnaire.

Primary Measure

- **Hot Flash Diaries:** All women will complete daily hot flash diaries from the time of their baseline visit through follow up. They will record the number and severity of their hot flashes on the daily hot flash calendar (Appendix C).

Secondary Measure

- **Pittsburgh Sleep Quality Index (PSQI):** Sleep will be assessed using the PSQI, a well validated commonly used self-report sleep measure. The PSQI includes 19 questions on sleep quality in the last month. It provides an overall sleep quality score and sub-scores for subjective quality, latency, duration, efficiency,

disturbances, use of sleep medications, and daytime dysfunction due to sleepiness. The global score ranges 0 to 16, with score >5 indicating poor sleep quality and high sleep disturbance (Appendix D).

Tertiary Measures

- **The Hot Flash Related Daily Interference Scale (HFRDIS):** Hot flash interference will be assess using HFRDIS, a 10-item psychometrically sound measure for assessing the impact of vasomotor symptoms on daily activities and overall quality of life. This validated tool assesses the impact of hot flashes on overall quality of life and 9 specific domains within the past week (work, social activities, leisure activities, sleep, mood, concentration, relation with others, sexuality, and enjoyment of life) (Appendix E).
- **Center for Epidemiologic Studies Depression (CESD-10):** Depressive symptoms will be assessed using the CESD-10, a 10-item scale asking about depressive symptoms in the last week. The CESD is a commonly used measure with established reliability and validity (Appendix F).
- **General Anxiety Disorder (GAD-7):** Anxiety symptoms will be measured with the GAD-7, which consists of 7 items, each describing a common symptom of anxiety. The respondent rates how much he or she has been bothered by each symptom over the past two weeks on a 4-point scale ranging from 0 to 3. Higher scores indicate more anxiety (Appendix G).
- **Health-Related Quality of Life (HRQL)**: HRQL will be measured with the Medical Outcomes Survey Short-Form. This is an extensively used and validated 36-item general HRQL scale. Its 8 subscales include physical function, social function, role limitations due to physical health, role limitations due to emotional problems, bodily pain, vitality, mental health and general health perceptions (Appendix H).
- **Somatosensory Amplification Scale (SSAS):** SSAS is a 10-item questionnaire that assesses sensitivity to a range of uncomfortable bodily sensations and physiologic states which are not typically symptoms of disease. (Appendix J)
- **Health Behaviors:** include standard questions on smoking and physical activity. Active smoking will be ascertained from the American Thoracic Society questions, Physical activity will be measured using 3 items (Appendix L). Change in health behaviors will be measured at the follow-up visit (Appendix N).
- **Evaluation of Intervention:** This investigator developed questionnaire will assess acceptability of intervention (Appendix M)

Measures Timeline

Variable	Measure	Appendix	Baseline	Daily for 11 weeks	Follow-up
Hot Flash Diary	DDHF	C	X	X	
Sleep	PSQI	D	X		X
Hot Flash Interference	HFRDIS	E	X		X
Depression	CESD-10	F	X		X
Anxiety	GAD-7	G	X		X
Health-related quality of life	SF-36	H	X		X
Sociodemographics	Investigator developed	I	X		
Symptom sensitivity	Somatosensory Amplification Scale (SSAS)	J	X		
Health History and Current Medications	Investigator developed	K	X		
Health Behaviors	Investigator developed	L	X		
Evaluation of Intervention	Investigator developed	M			X
Change in Health Behaviors		N			X
Medications Updated		O			X

Study Plan

Design

We will conduct a non-randomized study of 24 peri or postmenopausal women aged 45-60 experiencing at least 4 hot flashes/night sweats/day on average to evaluate their hot flashes/night sweats while using the cooling mattress pad for 8 weeks. The device consists of a mattress pad that is placed between a person's mattress and fitted sheet that is connected to a cube that is filled with water and kept next to the bed. Participants can regulate the temperature of the cooling mattress pad by adjusting the temperature of the water that flows from the cube to the mattress pad. This is a totally non-invasive device.

Women will be recruited from the community through advertisements and initially screened over the telephone. They will be screened for age, menopause status, and average number of hot flashes per day. Those women who are eligible based on the telephone screen, will be invited to come to the Public Health Sciences (PHS) Research Center in Piedmont Plaza 1 or the Center for Integrative Medicine in Piedmont Plaza II for a baseline interview. At that time they will provide informed consent to participate in the study, complete several

questionnaires, and sent home with a 2-week diary to confirm their eligibility with respect to number of hot flashes/night sweats. If it is not possible for the participant to come to one of these locations, the baseline questionnaire and consent will be sent to the participant to be completed at home and mailed back. Two copies of the consent form will be sent to the participant. After received, a study team member will speak with the participant to present the elements of consent, the content of the study, and answer any questions. At the end of the discussion, the participant will be advised to sign and date one form and return it. The second form should be kept by the participant for documentation. Upon receipt of the signed form, the study team member will sign and date with the current date, and add a note detailing the date discrepancy.

.We will ask participants to keep a record of their hot flashes throughout the day by either using a counter app on their phone or maintaining a paper log. After two weeks, women will mail in their diaries and continue to record their daily hot flashes until they are notified by study staff of their eligibility, within a week of receiving the diary.

If still eligible based on the 2-week diary, participants will return to the PHS Research Center to receive a cooling mattress pad and container of distilled water (used to fill cooling mattress pad) to take home and use for the next 9 weeks. If it is not possible for the participant to return to the Research Center, the Chilipad will be delivered to the participant at a mutually agreed upon location. We will allow one week for women to determine the optimal temperature of the cooling mattress pad and the next 8 weeks for the data collection of hot flashes/night sweats while using the cooling mattress pad. Some participants may be away from home and unable to use the cooling mattress pad while participating in the study. We will ask that participants indicate on the Hot Flash Diary whether or not they used the cooling mattress pad the prior night and continue tracking their hot flashes/night sweats even if they did not use the mattress pad.
Participants will mail in their completed Hot Flash Diary every two weeks in a pre-stamped and pre-addressed envelope to ensure that data is being consistently recorded.

At the end of the 9 weeks, women will return to the Research Center or Center for Integrative Medicine, complete additional questionnaires and receive compensation for participating in the study. Participants may also complete the follow-up questionnaires by telephone or mail. Analyses will assess frequency of hot flashes/night sweats experienced by women before and after using the cooling mattress pad. We will use an historical control group to compare results from this study to a control group from a previous study.

Cooling Mattress Pad

The ChiliPad™ cooling and warming system allows adjustments to be made to your bedding surface. The ChiliPad is placed on top of the mattress and an elastic strap is used to hold it in place. The fitted sheet is placed over the ChiliPad. The ChiliPad is connected to the ChiliPad Cube through the tail pipe, which can be placed either at the head or foot of the bed.

Before the first use, the ChiliPad reservoir must be filled with distilled water. Once it is full, you must turn the Cube on so that water begins circulating through the mattress pad. As the water is circulating through the ChiliPad, you must continue to fill the reservoir.

The Cube cools or warms water to your set temperature and circulates it through the pad, generally achieving temperatures to a cool 55 F (13 C) and to a very warm 110 F (43 C). The temperature can be set either on the Cube or through the remote.

The ChiliPad is not an FDA approved device. It does not pose the potential for serious risk to health, safety or welfare of study participants. For the purposes of this study, the device is being used to assess its impact on frequency of daytime and nighttime hot flashes and quality of sleep.

Setting

Women will be recruited from the community through flyers and advertisements and initially screened over the telephone. They will be screened for age, menopause status, and average number of hot flashes per day. Those women who are eligible based on the telephone screen, will be invited to come to the PHS research center located on the first floor of PPI or the Center for Integrative Medicine on the 5th floor of PP II for a baseline interview. If it is not possible for the participant to come to one of these locations, the baseline questionnaire and consent will be sent to the participant to be completed at home and mailed back.

Participant Payments

Study participants will each receive a $25.00 gift card at the end of the study and will be allowed to keep the mattress pad upon completion of the study.

Informed Consent

Study staff will obtain signed informed consent from each study participant at baseline visit. A study investigator will explain the study and allow patients to ask questions.

Risks

This study involves minimal risk to participants. During the time the participant is using the cooling device, their hot flashes may stay the same, decrease, or increase. Participant's sleep, mood and quality of life may improve, worsen, or stay the same. Participants may feel anxious about answering questions about their well-being, sleep, or menopausal symptoms.

The only risks associated with the cooling device are the following: 1) the possibility of disrupted sleep until you find the temperature that works best for you and the noise of the small fan, 2) the possibility of tripping if you do not place the cube properly, and 3) the possibility of risk of mold or mildew on the mattress pad if unwashed after several months.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data.

The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

All participants will be given an ID number that will be used on all forms. Names and telephone numbers associated with the IDs will be separate from all questionnaires and kept in a locked file.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. All team investigators have completed their institution's courses for Protection of Human Research Subjects and will maintain up to date certification throughout the study period.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any adverse events, deviations, or protocol changes will be reported to the IRB by the principal investigator or designated member of the research team. In addition any unanticipated problems, serious and unexpected adverse events, will be reported by the principal investigator or designated member of the research team to the IRB and FDA.

Statistical Considerations

Analytical Plan

Our primary outcomes of interest will be change in number of daily hot flashes (total, daytime, and nighttime) over the eight week period. We will model our outcome in both absolute terms (average number of daily hot flashes each week) as well as in terms of percentage change in average daily hot flashes measured from baseline. We will first conduct a simple t-test on the difference in average number of daily hot flashes at baseline and eight weeks to see if this average difference is significantly different from the null value of zero. We will also conduct repeated measures models with time included as ordinal week (0-9) and the dependent variable pertaining to average daily number of hot flashes for each week or percent change in average daily number of hot flashes for each week. In the simplest repeated measures models we will examine whether the parameter estimate for week is significantly different from zero. We will also examine the effects of covariates such as age and menopause status to determine which are significantly associated with the outcomes, and to estimate an adjusted (least squares mean) outcome measure that will serve as an accurate comparison to our historical control (see below).

Secondarily, we will model the continuous outcome of the total PSQI sleep score, as well as the subscores, using a similar repeated measures approach to that described above

In addition to examining, within our sample of cooling mattress pad users, the question of whether symptoms (hot flashes, sleep disturbance) improve over time, we will also compare any observed improvements with those found in our control group from the Acupuncture in Menopause (AIM) Study[49] to see if cooling mattress pad users experienced significantly different levels of change over time compared to an historical control. (We note that in our AIM control group, there was on average an approximately -3.3% decline in average number of daily hot flashes from baseline to week 8, and there was an increase of .49 in total score on the PSQI over the same period.)

Sample Size

This is a single site, single arm pilot study designed to obtain preliminary evidence that the cooling mattress pad can help reduce hot flashes and night sweats. We will compare results to historical controls from a previous study. Based on this previous study,[49] we estimate that women recruited to our sample will be experiencing, on average, approximately 10 hot flashes at baseline. The average decline in number of daily hot flashes over an 8 week period in the control arm of this study was 0.36 (standard deviation 2.85). In comparison to the 0.36 fewer hot flashes on average in the absence of intervention (i.e., null hypothesis), we will be able to detect in our sample of 24 a decline of 2.1 in absolute number of average daily hot flashes from baseline to week 9, with 80% power and a two-tailed alpha of 0.05. We note that the 'detectable' anticipated decline of 2.1 in number of hot flashes (or just over 20% decline from baseline) is a conservative estimate; in our previously-sited study,[49] a 35% decline in number of hot flashes over 8 weeks has been observed.

Covariates

In addition to sociodemographics (Appendix I) (age, education, marital status, employment status), the following covariates will be assessed:

- **Symptom Sensitivity** is a measure of symptom sensitivity or amplification. The Somatosensory Amplification Scale (SSAS) is a 10-item questionnaire that assesses sensitivity to a range of uncomfortable bodily sensations and physiologic states which are not typically symptoms of disease. The SSAS has been shown to prospectively predict persistence of hypochondriacal symptomatology in transient hypochondriacal patients. This measure has been shown to be a strong predictor of vasomotor symptom reporting. It is included as a covariate because it is highly related to symptom reporting and symptom sensitivity may be an important variable related to treatment efficacy (Appendix J).
- **Health history and current medications.** At the baseline visit, participants will be asked to bring in all medications, vitamins, and herbal supplements they are currently taking so that these can be recorded (Appendix K). Medications will again be assessed at follow-up (Appendix O).
- **Health behaviors** will include standard questions on smoking and physical activity. Active *smoking* will be ascertained from the American Thoracic Society questions, *Physical activity* will be measured using 3 items we have used in previous studies (Appendix L). Change in health behaviors will be assessed (Appendix N)

Appendices

Appendix A	Study Flyer
Appendix B	Telephone Screener
Appendix C	Hot Flash Diaries
Appendix D	Pittsburgh Sleep Quality Index (PSQI):
Appendix E	The Hot Flash Related Daily Interference Scale (HFRDIS)
Appendix F	Center for Epidemiologic Studies Depression (CESD-10)
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Appendix I	Sociodemographics
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Appendix K	Health History and Current Medications
Appendix L	Health Behaviors
Appendix M	Evaluation of Intervention
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