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Protocol for a randomized controlled trial comparing phone-based prenatal mindfulness training to usual care for pregnant people at risk for hypertensive disorders of pregnancy

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Abstract

Hypertensive disorders of pregnancy (HDP) are the most common medical conditions in pregnancy and a leading cause of maternal morbidity and mortality in the United States. There are few interventions available to prevent HDP, and those currently available do not target underlying mechanisms of disease. Mindfulness training (MT) is effective at reducing blood pressure in non-pregnant patients with pre-hypertension and hypertension and has proven more effective at blood pressure reduction than other stress management interventions. MT thus holds great

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Declaration of interests

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promise as a mind-body intervention to prevent HDP. This randomized trial will harness subjective and objective ecological momentary assessment methodology combined with wearable biosensor technology to capture psychological, physiological, and interpersonal processes through which MT may lead to improved maternal cardiovascular parameters. Pregnant women at risk for HDP will be randomized to an 8-week phone-delivered MT intervention or usual care. Through these methods, we will evaluate psychological, physiological, and interpersonal responses to daily experiences linking MT to cardiovascular parameters among women at risk for HDP.

Keywords

Pregnancy; mindfulness; mechanisms; hypertensive disorders of pregancy

Introduction

Hypertensive disorders of pregnancy (HDP) affect 16% of all pregnancies in the United States and are a leading cause of perinatal morbidity and mortality with 6.3% of maternal deaths in the US attributable to HDP.[1,2]. There are significant racial and ethnic disparities in HDP prevalence as well as cardiovascular complications, and these are more likely to cause maternal deaths in Black compared to White women.[3,4] There is emerging evidence that exposure to HDP increases lifetime cardiovascular disease risk by 2–4 times and is considered an independent, sex-specific risk factor by the American Heart Association.[5–7] This extends the impact of these pregnancy-related disparities across the life course.[8–10]

Options for prevention of HDP are currently limited to low-dose aspirin, which when initiated early in pregnancy among people at risk for HDP, reduces the incidence by 18%.[11,12] Trials of non-pharmacological interventions to prevent HDP, including exercise, vitamin intake, calcium supplementation, fish oil, and salt restriction have not shown significant effects on HDP risk reduction,[13,14] with the exception of dietary interventions for women with comorbid gestational diabetes.[15] As pregnant people may be reluctant to take medications during pregnancy,[16] effective non-pharmacological interventions to prevent HDP are sorely needed.

Mindfulness training (MT) is a novel preventive strategy for HDP. According to the ‘Mindfulness Stress Buffering Theory’,[17] MT teaches participants to observe stressors with acceptance and equanimity, leading to reduced emotional reactivity and improved health. A recent systematic review and meta-analysis of studies conducted in non-pregnant adults found a significant benefit of mindfulness-based interventions on blood pressure.[18,19] These interventions were more effective at reducing blood pressure in patients with pre-hypertension[20] and hypertension[21] than other stress management interventions including yoga and progressive muscle relaxation.

MT has not been tested as an intervention to prevent or treat HDP. Preliminary results from our pilot randomized controlled trial of prenatal MT for pregnant women at risk for HDP indicated that MT resulted in lower blood pressure and lower rates of HDP.[22] Theory and available evidence indicate that MT elicits relaxation, decreases autonomic activation and stress biomarkers, and decreases loneliness. These dynamic processes may serve as

mechanistic pathways to improved cardiovascular parameters in women at risk for HDP. However, these have not been studied in pregnancy, and the mechanism(s) driving the cardiovascular effects seen in our pilot trial are unknown. Knowledge of how MT may affect cardiovascular parameters in pregnancy is necessary in order to target key pathways to HDP.

Unfortunately, most trials of mindfulness-based interventions have been conducted in higher-SES non-Hispanic White samples.[23] In a qualitative study, Black women identified barriers to MT participation, including stigma, caregiver burden, and excessive time commitment.[24] Thus, interventions to curb rates of maternal HDP in the US must be acceptable across racial groups. In our previous pilot randomized controlled trials (RCT) assessing phone-base MT in pregnancy[22,25], samples were socioeconomically diverse, suggesting that phone-delivered MT is feasible and acceptable among pregnant women who might not participate in traditional mindfulness-based interventions.

There is, therefore, an urgent need to test the efficacy and potential mechanisms of prenatal MT for prevention of HDP in a diverse population. In this protocol document, we will describe the study methods, statistical analysis plans, ethical approval, and dissemination plan of an ongoing RCT that will provide new data on the mechanisms through which prenatal MT might impact HDP and other cardiovascular parameters in a diverse population of pregnant women at risk of HDP.

Our primary aim is to evaluate a psychological mechanism, where we will measure the impact of phone-based MT on negative affective responses to everyday stress. We hypothesize that participants in the MT group will display decreased negative affective responses to everyday experiences, which will mitigate cardiovascular parameters of risk among pregnant women at risk for HDP. Our secondary aim will be to examine a potential physiologic mechanism. We hypothesize that MT will be associated with lower heartrate variability, which will mitigate cardiovascular parameters of risk among pregnant women at risk for HDP. Lastly, we will evaluate an interpersonal mechanism. We hypothesize that MT will be associated with higher degrees of subjective and objective measures of social support, which will mitigate cardiovascular parameters of risk among pregnant women at risk for HDP.

Methods and Analysis

Objectives:

The primary objective of this trial is to evaluate potential mechanisms through which phone-based prenatal MT might lower rates of cardiovascular parameters of risk among pregnant women at risk for HDP. We will assess three different potential mechanistic pathways: (1) psychological responses, (2) physiological responses, and (3) interpersonal responses to daily experiences linking MT to cardiovascular parameters among pregnant women at risk for HDP.

Study Design:

This study is a randomized controlled trial to evaluate mechanisms through which prenatal MT is linked to cardiovascular parameters. The trial aims to recruit 150 pregnant women

at risk for HDP ("moderate" or "high" risk as defined by the American College of Obstetricians and Gynecologists (ACOG) risk stratification paradigm)[26] at <20 weeks' gestation. Participants complete a baseline 2-week 'burst' of daily ecological momentary assessments (EMA), electronically activated recorder (EAR) and biometric assessments including 24-hour ambulatory blood pressure and uterine artery doppler via ultrasound (Figure 1). Following this baseline 'burst', participants are randomized to 8 weeks of weekly phone-based MT sessions versus usual care. Following this intervention period, participants from both care conditions complete an additional follow-up 'burst' of daily EMA and EAR, and biometric assessments.

Study settings and participants:

Partipants are recruited from ambulatory sites providing prenatal care and ultrasound services. These sites are affiliated with a large regional referral center in New England, performing over 8,500 deliveries annually. Cumulatively these ambulatory sites care for >5,000 patients per year, and serve a population that is racially, ethnically, and socioeconomically diverse.

Eligibility Criteria:

Participants are randomized only if they fulfill all inclusion criteria and none of the exclusion criteria (Table 1). Utilization of broad inclusion criteria increases the generalizability of our results.

Study Design:

Pregnant women at risk for HDP are randomly assigned to either 8 weeks of phone-based MT delivered weekly plus usual care, or to usual care alone.

1. **Phone-based MT**: Each intervention session will last approximately 30 minutes (4 hours of total intervention). Mindfulness training sessions occur once per week and are led by an experienced MT instructor. Participants have the same instructor throughout the intervention. They are provided with recordings or audio files of mindfulness exercises and asked to practice mindfulness activities daily in between sessions and record the date and duration of their practice. The intervention was originally developed by our study team for patients with cardiovascular disease[27–29] and has previously been demonstrated to be feasible and acceptable in a perinatal population.[22,25,30] The intervention is based upon the curriculum of the Mindfulness-Based Stress Reduction program, and includes practices such as awareness of breath, awareness of sensations, awareness of sounds, emotions, and thoughts, open awareness, as well as cultivating mindfulness throughout daily activities. Intervention sessions are manualized, and treatment fidelity checklists developed following Treatment Fidelity Workgroup guidelines to ensure standardized administration.[31] Participants randomized to the mindfulness condition continue to receive care as usual (see below) in addition to the mindfulness training intervention.

2. **Usual care**: Participants randomized to usual care continue to receive their regularly scheduled prenatal care, which may include interventions to prevent or treat hypertension during pregnancy (such as low-dose aspirin).

Screening and enrollment of participants:

We employ recruitment techniques that have been successful in previous randomized clinical trials in the same setting. We use electronic medical charts to generate reports of potentially eligible patients by site. Potentially eligible pregnant people are approached at prenatal care or ultrasound appointments to determine interest in participation. They are then screened for additional eligibility criteria in person or via the phone. Those who are eligible and interested complete a phone-based informed consent visit.

Randomization, allocation concealment, and blinding:

Once participants have completed the baseline 'burst' of EMA, EAR and biometric data collection, they are randomly assigned in a 1:1 ratio using a computer-generated stratified randomization sequence. A web-based randomization sequence was prepared using R,[32] stratified by maternal age at enrollment.

A subject's group assignment will be generated only after the patient has agreed to participate in the study, informed consent is completed, and all baseline assessments are completed. The randomization scheme was implemented in Research Electronic Data Capture (REDCap), a secure internet-based data management system.[33,34] To assign a participant to either study condition, the study staff clicks a button in REDCap after confirming participant eligibility.

The PI, co-investigators, and prenatal care provider are blinded to the participant's group assignment. The participants are not blinded to intervention arm. Trained research staff at each site abstract outcome data from the medical record without reference to participant study group. Once all data are collected at both sites, the database will be locked and ready for unblinding and analyses.

Study assessments:

Ecological momentary assessments (EMA): EMA assessments occur during the two-week 'burst' periods at 4 semi-random intervals between 9am and 9pm via a web-based encrypted data collection platform (ilumivu) delivered by smartphone. Data is uploaded to the cloud in real-time, enabling RAs to regularly check (and promote) compliance. EMA surveys query for pregnancy experiences (adapted from Daily Dose-Response Hypothesis of Mindfulness),[35] mood states (adapted from the validated Positive and Negative Affect Schedule Scale),[36] and social context (using the National Institutes of Health toolbox of adult social relationships).[37] Each survey takes less than 3 minutes to complete.

Electronically Activated Recorder (EAR): The EAR, an ambient audio capture method that is deployed on a smartphone, permits objective assessment of social context.[38–42] In this study, the EAR is programmed to intermittently record ambient sound for 30 sec every 12 minutes between 9:00 pm and 9:00am, totaling 12 minutes per day. Participants wear

the EAR app, which is loaded onto a dedicated research smartphone, on them while going about their daily lives. The participants are aware that they are intermittently recorded but are unaware exactly when it is on and the ambient sound recording is occurring. After participants have completed the study, sound files are downloaded and coded for participant behavior and social context. Sound files are coded using a modified version of the validated Social Environment Coding of Sound Inventory.[43] Specifically, the coding structure has been modified for the prenatal participant population, and files will be coded for interpersonal behavior in response to social context (.e.g, "Participant is RECEIVING physical help/support from another person. Examples of physical help/support can include medically necessary help (e.g., assistance standing up, bringing a glass of water) or other physical behaviors (e.g., help with moving a heavy object, picking up a child from daycare)"), activities (e.g., "Participant is socializing or hanging out with peers/friends/ romantic partner"), and context (e.g., "Participant is with MORE THAN ONE other person, and they are engaged in a conversation, interaction, or joint activity of some kind")). EAR methods will provide objective evidence on prenatal behavior and social context and will be the first, to our knowledge, to objectively measure prenatal social context in vivo. The voluntary nature of participation and importance of protecting their privacy is emphasized. If desired, participants can request to delete the recordings prior to coding by indicating this verbally to the research staff.

Biometric sensor data: During both of the 2-week 'bursts', participants are provided with a wearable biosensor device (Garmin Vivosmart Series activity monitors) that will continually monitor heart rate (HR) and inter-beat-interval (used to calculate heart rate variability (HRV)) throughout the period of EMA collection. HRV data will also be integrated using the ilumivu platform, and available 24–48 hours after the period of collection. This enables assessment and promotion of compliance. HRV is calculated using raw HR data collected in the 5 minutes prior to EMA prompt by computing the root mean squares of successive differences (RMSSD). The RMSSD is less affected by respiratory rate, HR, or recording duration than other HRV calculations.[44,45] Raw data is checked for outliers (+/− 3SD, biologically implausible values); missing data is estimated using full-information maximum likelihood estimation.[46]

24-hour ambulatory blood pressure measurement (ABPM): Ambulatory blood pressure is assessed every 30 minutes over 24-hours using Microlife WatchBP03, validated for use in pregnancy.[47] ABPM will be measured at baseline and following the intervention period before EMA/EAR 'bursts'. ABPM software automatically calculates average daytime and nighttime SBP and DBP, and nocturnal blood pressure dipping. Upper arm circumference is measured before monitoring to ensure proper cuff size. Participants are instructed to adhere to usual activities with minimal restrictions over the 24-hours. Consistent with ABPM guidelines,[48] ABPM is considered invalid if >30% or >2h of measurements are missing; participants with invalid tests are asked to repeat 24-hour monitoring.

Research ultrasound: Uterine artery Doppler ultrasound parameters (blood velocities and parameters of vascular impedance) are measured by Doppler ultrasound techniques

before and after the intervention.[49] Fetal biometric measurements will be collected to assess growth parameters. The sonographer and physician reviewing ultrasound images are blinded to study group allocation.

Outcomes: The primary outcome evaluates negative affect as a *psychological mechanism* linking MT to HDP (Table 2). Metrics considered include 1) EMA responses to perceived stress assessed during the pre and post-intervention 'bursts'. Group-related changes in negative affect between pre- and post-intervention will also be correlated with cardiovascular parameters of risk for HDP (24-hour systolic blood pressure, uterine artery doppler pulsatility index). The same protocol will be performed for the two secondary outcomes. To evaluate a *physiological mechanism*, heart rate variability assessed during the pre- and post-intervention 'bursts' will be compared by mindfulness arm and will be correlated with cardiovascular parameters of risk for HDP (24-hour systolic blood pressure, uterine artery doppler pulsatility index). Lastly, to evaluate an *interpersonal mechanism*, we will examine interpersonal behavior using both the coded EAR recordings and EMA. EAR coded data provide observed indicators of interpersonal behaviors and EMA permits assessment of subjective internal interpersonal perception. Additional covariates will be collected via questionnaires at the baseline and follow-up periods. Table 3 contains a full outline of study measures and measurement timeline.

Power considerations and sample size: Based on results from our pilot randomized trial, we expect medium to large effect sizes (d=.62-.80). To minimize assumptions about gains in power afforded by the latent analytic framework, we examined power to detect a range of effects with G*Power using a repeated measures framework, assuming two groups and two observed assessment occasions. We ultimately decided on a total sample size of 150 (N=120 for final analyses, conservatively estimating 20% attrition) after evaluating larger and smaller samples given the tradeoff of sample and power as a function of effect size.

Statistical Analysis Plan

Analyses will be performed according to the intention-to-treat principle, with participants retained consistent with initial treatment assignment. Baseline characteristics (e.g. age, BMI, gestational age, sociodemographic characteristics) will be compared between groups to ensure that the randomization scheme has been successful in creating balanced groups.

In order to test our hypothesis that women randomized to mindfulness (relative to those randomized to usual care) will evidence decreased negative affective responses to everyday experiences, we will utilize a latent difference score (LDS) approach.[50–52] The use of latent constructs, as compared with data reduction approaches, has the benefit of permitting estimation of unequal weights across indicators, can allow for partial measurement invariance whereby indicators can function differently over time, smaller standard errors, and increased power.

Autonomic responses will be defined as HRV across each EMA sampling period. We will test our hypothesis that, relative to women randomized to usual care, women randomized to mindfulness training will exhibit decreased physiological responses to everyday experiences at follow-up. Again, analyses will test for the expected impact of treatment group on LDS of

physiological responses (indicated by parameters throughout each 2-week sampling period). This model will then be expanded to examine the expected association of the physiological responses to cardiovascular parameters observed at follow-up.

Lastly, interpersonal behavior will be defined as number of positive and negative interpersonal responses to everyday experiences as measured by EMA or EAR. This will also be evaluated using LDS, using latent constructs indicated by EMA or EAR. We hypothesized that the treatment group will evidence greater post-interventions prosocial language and reduced emotional and behavioral reactivity to social interactions relative to the comparison group, with these effects observed to be associated with improved cardiovascular parameters at follow-up.

Safety: MT is a behavioral, low-risk intervention. However, there is a small risk of emotional discomfort associated with MT. When emotional discomfort arises during MT it is typically mild and self-limited in duration. At each session, the mindfulness instructor queries whether the participant has any psychological discomfort or if any distress has arisen during the prior week's individual practice. If a participant demonstrates signs of severe emotional discomfort, they are excused from participation in the MT session. The instructor notifies the PI who advises on next steps. If at any point during the study a participant reports significant psychological distress, screens positive for perinatal depression, or reports suicidal ideation, study staff immediately contacts the PI who evaluates the patients over the phone and instructs study staff on next steps (e.g. refer to participant to the ED).

Data Safety and Monitoring Board (DSMB): An independent DSMB is monitoring trial safety and data integrity on a regular basis. The DSMB is composed of international experts in clinical psychology, mindfulness, obstetric medicine and maternal-fetal medicine. The DSMB meets every 6 months throughout the trial, and reviews aggregate data related to the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered. Study specific adverse events that are monitored include elevated blood pressure (>140/90) detected on 24-hour ambulatory blood pressure assessment, symptoms of pre-eclampsia reported at study visits (including persistent headache, visual changes, epigastric or right upper quadrant tenderness, acute onset swelling), embarrassment from questionnaire items, fetal abnormalities detected on research ultrasound, and/or positive screening for suicidal ideation or domestic violence.

Data management

Data Collection: Data is collected and managed with REDCap, an established, secure, web-based data capture and management tool developed at Vanderbilt University and supported by the institutional bioinformatics team. Detailed antepartum, intrapartum, and postpartum information from study participants is collected by trained research assistants. 5% of data is double abstracted to ensure fidelity of the data abstraction procedures. Phone sessions of mindfulness are audiotaped to enable assessment of treatment fidelity. An unblinded investigator is responsible for monitoring treatment fidelity of the mindfulness sessions and will review a total of 10% of tapes across the study. Treatment fidelity

checklists for each mindfulness session are used to monitor reliability, validity, and fidelity of the mindfulness intervention.

Loss to follow-up and missing data: Strategies used in prior studies are employed to achieve excellent follow-up and minimize missing data. Written authorization is obtained to access delivery records if participants end up delivering at a facility not participating in the study. Active data management occurs at each site, including monthly data review for rates and patterns of missing data. Remedial measures including data re-abstraction and staff retraining will be used as needed to minimize missing data. Despite these efforts, data may still be missing. If significant deficiency is noted it will be addressed analytically.

Ethics and Dissemination

Ethical approval has been granted by an institutional review board (#020120). Informed written consent will be obtained from each participant before conducting any study-related procedures. The protocol is registered on Clinical Trials Registry (NCT04626245).

Discussion:

HDP is a common condition during pregnancy and is associated with short- and long-term maternal morbidity and adverse offspring outcomes. Preventative approaches are limited, and the only ones that have been proven efficacious are pharmacological, which many pregnant people are reluctant to initiate. MT has been shown to lower systolic blood pressure in adult populations[18–21] and has demonstrated promise in preventing HDP. However, the potential psychological, physiological and interpersonal mechanisms that underpin MT effects on blood pressure remain unknown. This rigorous randomized controlled trial will provide the high-quality data needed to evaluate the efficacy and underlying mechanisms for utilization of MT for prevention of HDP among at-risk pregnant women. This new knowledge will facilitate development and refinement of future MT interventions that target the specific mechanism or mechanisms that most significantly impact risk for HDP.

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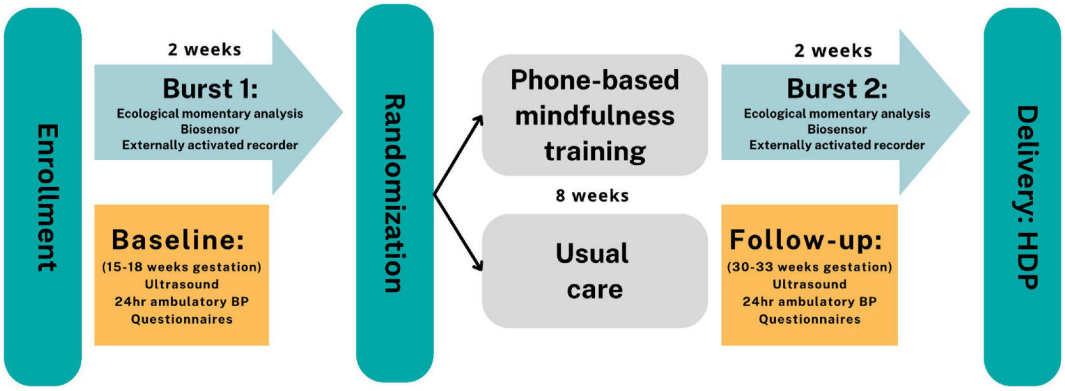

Figure 1: Summary of Study Procedures:

N=150 will be enrolled and randomized to Mindfulness Training or Usual Care. 2 weeks of EMA before and after the intervention will assess psychological, physiological, and interpersonal responses to daily experiences using ecological momentary analysis, biosensor data and externally activated recordings. Maternal cardiovascular parameters of risk for HDP including uterine artery doppler and 24-hr ambulatory blood pressure measurement will also be measured before and after the intervention at baseline and follow-up.

Table 1:

Study eligibility criteria

Inclusion criteria
Pregnant women ≥ age 18
Singleton gestation
English-speaking
<20 weeks gestation
Normal blood pressures at enrollment
'Moderate' to 'high' risk for preeclampsia based on ACOG guidelines
Exclusion criteria
Multifetal gestation
History of chronic hypertension
Active suicidality or psychosis
Ongoing mind-body practice (e.g., yoga, meditation, mindfulness ≥ once a week)

Table 2:

Primary and secondary outcomes

PRIMARY OUTCOME			
Outcome Measure	**Definition**	**Assessment Method**	**Assessment Timecourse**
Psychological mechanism: Negative affective responses to momentary stress	Reported mood associated with daily stressors	EMA surveys	Pre- and post- intervention 'burst'
SECONDARY OUTCOMES			
Outcome Measure	**Definition/Assessment**	**Assessment Method**	**Assessment Timecourse**
Physiological mechanism: Heart rate response to momentary stress	Heart rate variability	Biosensor	Pre- and post- intervention 'burst' in 5 - minute epochs prior to each EMA survey prompt
Interpersonal mechanism: Interpersonal behavior	Number of positive and negative interpersonal responses to everyday experiences	EMA, EAR	Pre- and post- intervention during EMA/EAR 'burst'

Abbreviations: ecological momentary assessment (EMA), electronically activated recorder (EAR)

Table 3:

Lists the study instruments and the time in pregnancy during which they will be administered.

	Baseline	EMA/EAR/ biosensor 'burst'	MT	EMA/EAR/ biosensor 'burst'	Follow-up
Gestational age at completion	< 20 w	20–22w	22–30w	30–32w	32w
Interview Measures					
Health Behaviors	X				X
Psychosis Screen	X				
Preeclampsia screen	X		X		X
Self-Report Measures					
Edinburgh Postnatal Depression Scale (EPDS)	X				X
Perceived Stress Scale	X				X
Five Facets of Mindfulness Scale	X				X
Multidimensional Assessment of Interoceptive Awareness (MAIA)	X				X
Pittsburgh Sleep Quality Index	X				X
Adverse childhood experiences (ACE)	X				
Quality of Life Measure	X				X
PTSD Checklist for DSM-5	X				X
Big Five Extra Short Personality Measure	X				
Life Orientation Test-Revised	X				X
Difficulties in Pregnancy (NuPDQ)	X				X
Persistent and Intrusive Negative Thoughts Scale (PINTS)	X				X
Prenatal Social Support Instrument (PSSI)	X				X
Prolonged Activation Race- Related Stress scale	X				X
Race-Related Vigilance questionnaire	X				X
Religion & Spirituality	X				X
EMA Measures					
Perceived Stress		X		X	
Daily Hassles		X		X	
Positive and Negative Affect Scale		X		X	
Pregnancy-specific anxiety		X		X	
Social Relationships		X		X	
Mindful Responding		X		X	
EAR Measures					
Interpersonal behavior		X		X	
Physical Heal h Assessments					
24-hour blood pressure	X				X
Heart rate/Heart rate variability		X		X	
Research Ultrasound	X				X

“w” = weeks’ gestation. “h” = hour. “EMA” = ecological momenary assessment. “EAR” = electronally activated recorder. “MT” = mindfulness training.