Study Protocol and Statistical Analysis Plan (SAP)

Official Title: Smartphone-based Mindfulness Training for Health Following Early Life Adversity

(Brief Title: Remote Mindfulness Training Following Early Life Adversity)

ClinicalTrials.gov ID (NCT number): NCT05516108

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Study Purpose

Early life adversity (ELA) confers potential lifelong health complications, and interventions are needed to mitigate risk. Mindfulness-based interventions (MBIs) have shown promise for improving mental health outcomes among adults exposed to childhood trauma, but whether MBIs can offset physical health risk is unknown. This two-arm, parallel-group, randomized trial aims to investigate the feasibility and acceptability of remote mindfulness and coping interventions among emerging adults who recall a history of childhood trauma with the goal to inform an efficacy trial examining stress-related health outcomes.

Overview

Adults with a history of ELA will be recruited (n=80). Participants will one week of baseline ambulatory stress ratings (5x daily), continuous mobile sensor data (e.g., heart rate, activity, and location from wearable devices and smartphones), and blood samples to assess inflammatory biomarkers (e.g., IL-6, CRP, TNF-a, IL-8, IL-10). Participants will then be randomly assigned to a 14-lesson smartphone-based (a) mindfulness intervention or (b) structurally matched active control intervention that trains common coping skills, both boosted with practice prompts randomly delivered throughout the day to permit retrospective evaluation of JIT prompts. Ambulatory and sensor data will again be collected during the intervention and for one week at post-intervention and one-month follow-up, and inflammatory biomarkers will be assessed at post-intervention and follow-up. Participants will be surveyed about the acceptability of mobile data collection and intervention delivery.

Study Objectives

This trial aims to evaluate the feasibility, acceptability, and preliminary effects of smartphone-based mindfulness and control interventions among emerging and young adults with a history of ELA. Two primary hypotheses will be tested:

- The interventions and assessments will meet feasibility and acceptability benchmarks in this sample, including recruitment targets, safe implementation, and intervention/assessment adherence and fatigue.
- Mindfulness training is expected to reduce daily life stress, normalize stress biology, and reduce markers of inflammation from pre-intervention to post-intervention and one-month follow-up.

Exploratory aims involve (1) developing machine learning models to estimate daily life stress from passive sensor data and (2) using these models to inform future JIT intervention.

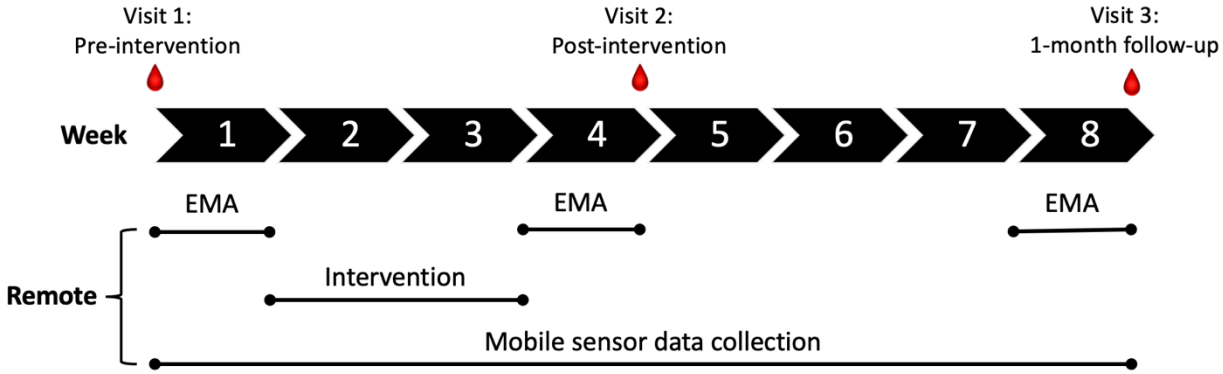
Methods

Participants:
80 participants will be recruited. English-speaking adults (ages 18-29 years) who report moderate-to-severe physical, emotional, or sexual abuse in childhood (based on Childhood

Trauma Questionnaire thresholds) and own data-enabled Android or iOS smartphones will be recruited in Pittsburgh. Those with severe mental health diagnoses (e.g., psychosis) will be excluded for safety. The sample is expected to be 65% white, 30% black, 5% other race; 5% Hispanic; and 50% female.

Recruitment:
Participants will be recruited for a study testing smartphone stress reduction programs, primarily through The University of Pittsburgh Pitt+Me research registry has nearly 30,000 potential participants ages 18-29. Interested participants will be pre-screened online for preliminary eligibility, then invited for an in-person baseline eligibility screening and visit.

Procedures:
Data will be collected across an 8-week study period as follows:



Lab visits include blood draw and questionnaire assessments. Ecological Momentary Assessment (EMA) includes surveys delivered at four random times daily and end-of-day diary assessments. Mobile sensor data collection includes AWARE phone sensor and Fitbit data.

T1: Baseline. Participants will attend a study visit to confirm eligibility, provide informed consent, complete psychosocial assessments, and prepare for the at-home assessments and intervention. Dried blood spot (DBS) samples will be collected to assess inflammatory biomarkers. During a one-week ambulatory stress assessment, participants will provide four ecological momentary assessments (EMA) and one evening diary survey daily assessing stress and resilience; stress physiology (HR) and activity (e.g., steps, sleep) via wearable device; and smartphone sensor data.

T2: Two-week intervention. Following baseline assessments, participants will be randomly assigned to the mindfulness intervention or coping control intervention condition. Participants will complete one 20-minute audio-guided lesson each day, plus receive 3 brief text-based practice prompts daily at random times. The interventions were developed by Shinzen Young and Emily Lindsay and are matched on attentional demand, lesson length and structure, and voice. Interventions will be delivered via smartphone app that securely tracks participant activity, including timestamps at lesson and practice prompt start/completion and daily survey responses (stress assessments pre- and post-lesson, pre- and post-practice prompt, and each evening; practice prompt receptivity). This data will be integrated with phone sensor and wearable data to inform future JIT intervention tailoring. Staff will check in with participants on intervention days 3, 9, and 14 to provide support and monitor for adverse events.

Mindfulness intervention: Based on Young's Unified Mindfulness system, lessons train meditation techniques for 3 mindfulness skills: (1) concentration, a stable attention on present-moment body experiences; (2) sensory clarity, the detection and discrimination of sensory experiences; and (3) equanimity, an attitude of acceptance and receptivity toward present-moment experiences. Practice prompts build on the skills trained in each lesson, encouraging participants to practice brief moments of mindful awareness, mindfulness while doing daily tasks, or formal meditation for 5-10 minutes.

Coping control intervention: To parallel the structure of the mindfulness intervention without training present-moment attention or acceptance skills, participants are instructed to: (1) reflect and mind wander; (2) reappraise past and future events; and (3) analyze and solve personal problems. Practice prompts encourage participants to take brief mind-wandering breaks, apply reappraisal or problem-solving skills, or reflect for 5-10 minutes. This program controls for nonspecific effects (e.g., goals, daily practice, and treatment expectancies). Here, an active control program will inform the feasibility of the RCT design for future trials and will preempt differential dropout issues that are commonly seen in studies using no-treatment control groups.

T3: Post-intervention. Immediately following the intervention, participants will complete a one-week ambulatory stress assessment, including mobile sensor data collection, a psychosocial assessment in the lab, including qualitative program evaluations, and a blood draw to assess inflammatory biomarkers as at T1.

T4: Continued mobile sensor monitoring. Continuous sensor data and weekly self-reported intervention practice will be collected during a post-intervention three-week monitoring period.

T5: One-month follow-up. As at T1 and T3, participants will complete a one-week ambulatory stress assessment and return to the lab for a psychosocial assessment and blood draw. Participants will be debriefed and offered access to the interventions. Outcome assessors will be blind to condition during the trial.

Measures:

Participants will complete the following questionnaires in-person at pre-intervention (Visit 1), post-intervention (Visit 2), and one-month follow-up (Visit 3):

1. Demographics and health status data (e.g., age, sex, race, ethnicity, BMI, health status) (Visit 1 only)
2. Early Life Adversity, including Childhood Trauma Questionnaire, childhood emotional neglect, SES (via parent education and food insecurity), and domestic violence (Visit 1 only)
3. Treatment Expectancy-Credibility Questionnaire
4. Pittsburgh Sleep Quality Index
5. Perceived Stress Scale
6. Five Facet Mindfulness Questionnaire
7. Acceptance and Action Questionnaire – II

8. PROMIS Anxiety
9. PROMIS Depression
10. PROMIS Positive Affect
11. PROMIS Social Isolation
12. PROMIS General Self Efficacy
13. PROMIS General Life Satisfaction
14. Distress Tolerance Scale
15. Post Traumatic Stress Disorder Checklist
16. Cambridge Depersonalization Scale
17. Self Compassion Scale
18. Everyday Discrimination Scale (Visit 1 only)
19. Adverse Effects Survey (Visit 2, Visit 3 only)
20. Study Burden (Visit 3 only)

The following outcomes will also be collected:

1. *Ambulatory Stress Assessments*, delivered to participants' smartphones at T1, T3, and T5, will assess (1) EMA stress (state stress perceptions, stress events) and resilience (state positive/negative affect, social interactions) four times daily during between 8am and 8pm, and (2) average daily life stress via diary (stress perceptions, stress events), resilience (positive/negative emotions, social interactions), and intervention practice (T3, T5 only). At T2, participants will complete stress surveys before and after each intervention lesson, before and after each JIT prompt, and each evening, which will inform adherence and JIT prompt timing.
2. *Ambulatory Physiology*, tracked and stored via Fitbit wearable device throughout T1-T5, will include continuous HR data (via photoplethysmography) to pair with EMA stress surveys. Physiological data and continuous physical activity (via pedometer) and sleep (via actigraphy) data will be integrated daily into the AWARE database and will be used in machine learning analyses with passive sensor data to evaluate predictive models of state stress in daily life.
3. *Smartphone Passive Sensor Data* will be collected throughout T1-T5. The open-source AWARE application will be installed on participants' Android or iOS smartphones to continuously and unobtrusively collect data characterizing behavioral and contextual features. Sensor data will include device usage, location, movement, activity, noise, conversation, and communication; these features will be used to predict stress.
4. *Inflammatory biomarkers* will be quantified in batch from DBS samples collected at T1, T3, and T5. Pro-inflammatory cytokine IL-6 will be assessed using R&D's Ella Automated Immunoassay System. A larger panel of pro- and anti-inflammatory markers (e.g., TNF, CRP, IL-8, IL-10) will be assessed via multiplex with additional funding.

Eligibility Criteria:

Inclusion Criteria:

1. Emerging adults between 18 and 29 years old
2. English speaking
3. History of adverse childhood experiences (specifically, moderate-to-severe physical, emotional, or sexual abuse in childhood: scoring >9, >12, or >7 on respective

Childhood Trauma Questionnaire subscales 1)
4. Data-enabled Android or iOS smartphone
5. Able to meet study requirements

Exclusion Criteria:

1. Self-reported diagnosis of chronic physical disease (e.g., cancer, HIV, heart disease, diabetes, bleeding disorder)
2. Self-reported diagnosis of chronic mental disorder (e.g., schizophrenia, personality disorder, or psychotic illness) major neurological disorder, or suicidal thoughts or wishes at baseline
3. Medication use that interferes with HPA-axis activity (e.g., corticosteroids) or autonomic activity (e.g., antihypertensive medication)
4. Current antibiotic, antiviral, or antimicrobial treatment
5. Shift workers
6. Pregnancy or breastfeeding
7. Excessive alcohol use
8. Frequent illicit drug use
9. Regular systematic mind-body practice (>2 times per week)

Statistical Analysis Plan (SAP)

Power:
Sample size balances rules of thumb for pilot trial sample size (which range from 25-35 participants per treatment arm estimating a small between-group effect size, with larger pilot trials more accurately estimating variance and allowing for smaller sample sizes in efficacy trials) with calculations to detect medium within-group effects of mindfulness on EMA stress (d=.40). Therefore, we plan to enroll 80 participants (40 per condition).

Statistical Analysis Plan:
This study will evaluate two primary aims and one exploratory aim:

Aim 1 evaluates the feasibility and acceptability of the interventions and assessments, with the prediction that interventions and assessments will meet feasibility and acceptability benchmarks in this ELA sample, and mindfulness and control groups will show equivalence on these measures.

- Planned analysis: Feasibility and acceptability will be evaluated by comparing screening and enrollment numbers, participant retention, adherence to intervention and assessment protocols, treatment expectancies, intervention fatigue, and prompt timing to proposed benchmarks for success. Specifically, minimum feasibility benchmark ranges are as follows: 10% of those screened will be eligible; 60-70% of eligible participants will enroll; <10% of participants will show increases in daily stress, a measure of safe implementation; 80-90% of enrolled participants will be retained through the intervention period and 75-85% through the follow-up assessment period; participants will complete 85-95% of the intervention lessons, 60-70% of practice prompts, 75-90% of ambulatory assessments, and provide mobile sensor data on >75% of days. ANOVAs will test for equivalence of mindfulness vs. control groups on

feasibility and acceptability outcomes.

Aim 2 tests for mindfulness intervention changes to establish effect sizes for a future RCT, with the prediction that mindfulness training will reduce daily life stress, normalize stress biology, and reduce markers of inflammation from pre-intervention to post-intervention and one-month follow-up.

- Planned analysis: MLMs will be used to test for mindfulness intervention changes in daily life subjective stress events and perceptions, stress-related HR in daily life (HR during high stress surveys relative to average person-centered HR), and markers of inflammation from pre-intervention to post-intervention and one-month follow-up. Secondary MLM analyses will test for mindfulness intervention changes in daily life resilience (positive/negative affect; social factors) and daily life HRV. Tertiary MLM analyses will test for between-group differences (mindfulness vs. coping intervention) on all outcomes.

Exploratory aims involve developing machine learning models to estimate daily life stress from passive sensor data and lay the groundwork for future JIT intervention. First, machine learning models developed to estimate daily life stress from passive sensor data aim to have at least 80% accuracy and 70% recall. We will use the open-source RAPIDS pipeline to extract aggregated behavioral features. We will approach stress detection as a binary classification problem where each interval prior to a random EMA is assigned a value of 0 (low stress) or 1 (high stress) based on perceived stress rating and sensor features from that interval are used to predict class membership. We will use the RAPIDS pipeline to evaluate different cross-validation approaches (e.g., leave-one-out) as well as different machine learning algorithms (e.g., random forests, extreme gradient boosting machines). Methods will be evaluated in an iterative and exploratory manner to determine which yields the best performance with regard to accuracy and interpretability. We will examine overall accuracy, precision (i.e., positive predictive value), recall (i.e., sensitivity), and area under the receiver operating characteristic curve (AUROC) in evaluating model performance. Second, MLMs will test whether mindfulness practice prompts delivered at high stress times (operationalized as being ≥ 1 SD above the person-centered stress mean) reduce state stress and end-of-day stress each day during the intervention. These exploratory analyses will inform the design and implementation of a tailored JIT intervention in a future trial.

Finally, analyses will be run separately by sex to examine potential patterns hidden in pooled analyses.