Study Protocol

Official Title:

Effect of Reducing Sedentary Behavior on Blood Pressure

ClinicalTrials.gov ID (NCT number):

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Scientific Background

Hypertension is the most common modifiable risk factor for cardiovascular disease (CVD) [1]. According to the 2017 Blood Pressure Guidelines [2], nearly half of American adults have prevalent hypertension defined as systolic blood pressure (BP) ≥130 mmHg, diastolic BP ≥80 mmHg, or use of antihypertensive medications. An additional 12% have elevated BP defined as non-medicated systolic BP 120–129 mmHg with diastolic BP <80 mmHg [3]. For elevated BP and some patients with a new diagnosis of hypertension and low CVD risk, lifestyle treatment is recommended prior to prescription of antihypertensive medications [2].

Sedentary behavior (SB), defined as low intensity behavior while awake in a seated, reclining, or lying posture [4], has gained attention as a highly prevalent behavior, distinct from moderate-to-vigorous intensity physical activity (MVPA) [5]. Accumulating epidemiological evidence suggests that higher levels of SB are associated with higher BP [6–9], arterial stiffness [10–12], CVD [13], and mortality [14,15]. The 2018 Physical Activity Guidelines Advisory Committee graded the evidence that SB was associated with mortality and CVD as 'strong' [16] and added a nonquantitative recommendation to 'sit less and move more' to the 2018 federal Physical Activity Guidelines [17]. In 2020, Canada released 24-h Movement Guidelines recommending that adults break up and limit SB to <8 h per day [18]. Importantly, the adverse effects of SB appear to be more deleterious in populations who do not achieve recommended levels of MVPA [19]. These data, coupled with Americans spending 57% of the waking day in SB [20], suggest that SB reduction – particularly among inactive adults – could be an additional lifestyle treatment target for high BP.

Yet, there is a dearth of sufficiently-powered, randomized clinical trials (RCT) examining whether SB reduction leads to health benefits, including reduced BP [21–25]. Laboratory crossover studies have shown that interrupting or replacing SB with light-intensity physical activity (i. e., standing or walking) acutely reduces BP [26–30]. Mechanistic studies have begun to explore how prolonged sitting impairs cardiovascular function including hemodynamic, hormonal and sympathetic effects [28,30–32]. However, chronic effects of sustained SB reduction on BP remain unclear. In addition, whether SB reduction improves other markers of CVD risk, such as 24-h ambulatory BP and carotid-femoral pulse wave velocity [cfPWV], is unknown [33–36].

Thus, the Effect of **Re**ducing **Se**den**t**ary Behavior on **B**lood **P**ressure (RESET BP) study, funded by the National Heart, Lung, and Blood Institute (R01HL134809), seeks to examine whether reducing SB can lower BP and improve cardiovascular health. RESET BP is a 3-month randomized clinical trial with a proposed sample of 300 inactive desk workers with non-medicated, elevated BP or hypertension that randomizes participants to either a multicomponent SB reduction intervention or a passive control group. The 3-month intervention, including behavioral counseling every 2 weeks, a sit-stand desk attachment, a wrist-worn activity prompter, and text messages, intends to reduce prolonged SB through standing and light intensity movement breaks. The primary outcome is resting systolic BP. Secondary outcomes include diastolic BP, 24-h ambulatory BP, and cfPWV. The renin-angiotensin-aldosterone system (RAAS) will be evaluated as a potential mediating mechanism. Objective monitoring of SB,

standing, and movement will allow for examination of dose-response associations with outcomes.

Study Objectives

The RESET BP study specific aims are to:

(1) evaluate the efficacy of the intervention targeting decreased SB over 3 months on systolic BP (primary), diastolic BP, 24-h ambulatory BP, and cfPWV;

(2) explore whether RAAS activation (plasma renin activity (PRA) and aldosterone) partially mediates changes in BP elicited by SB reduction;

(3) examine associations between achieved reductions in SB, increases in standing and light physical activity, and BP reduction; and;

(4) evaluate the effect of the SB reduction intervention on other cardiometabolic risk factors that may improve and are related to BP including body weight, glucose, and insulin in an exploratory manner.

Study Design & Methods

Study design overview

Given the current scientific equipoise regarding the effect of reducing SB on BP, a 2-arm, 3-month randomized clinical trial was chosen as the most robust design to establish initial efficacy. Assessments occur at 0 and 3 months and are conducted by blinded assessors. Because the intervention follow-up period is only 3 months, specific time windows were defined for assessment of eligibility criteria (≤30 days before randomization), time to intervention initiation (≤ 2 weeks after randomization), and to complete follow-up assessments (91–101 days after randomization). While intervention participants begin the protocol within 2 weeks of randomization; control participants do not receive any intervention during the 3-month follow-up interval. As remuneration, intervention participants are given the choice to keep their sit-stand desk attachment or return it and receive $200 after completing all follow-up assessments. Control participants are given the choice to receive a delayed intervention (sit-stand desk attachment + behavioral lessons) or receive $200 after completing all follow-up assessments. All participants are given a wrist-worn activity prompter to keep either during (intervention) or following (controls) completion of study follow-up assessments. RESET BP is registered on clinicaltrials.gov (NCT03307343).

Recruitment and screening

Recruitment methods We target recruitment of a representative sample of participants working in the Greater Pittsburgh area, within an approximately 25- mile radius of the main campus of the University of Pittsburgh. We use a variety of referral sources to meet enrollment targets. Flyers are posted in public spaces (such as university buildings, hospitals, coffee shops, and libraries), on public transit (e.g., buses and trolleys), on electronic message boards (such as LinkedIn, Facebook, and Craig's list), and in magazines and newspapers. We also use the University of Pittsburgh Clinical Translational Science Institute's Pitt+Me recruitment registry, send electronic flyers through the University of Pittsburgh's Read Green e-mail system, and the University of Pittsburgh Medical Center's (UPMC) online newsletter. We send postcards or paper/electronic recruitment letters to members of other affiliated research registries, to local businesses and organizations willing to advertise our study to their employees, and to the general public within a 25-mile range of the university campus using a directed mailing strategy that targets households with members in the eligible age strata. We attend events such as health fairs and give lay research presentations for local businesses or groups in the Pittsburgh area to identify eligible candidates. In addition, we partner with individual UPMC primary care physician practices to recruit appropriate patients for our study. Following agreement of the practice physicians to partner with our study, patients can learn about participating in the study by i) seeing posted advertisements in the waiting room or exam room areas; ii) having their doctor directly refer them to the study; or iii) receiving a descriptive letter about the study, cosigned by the primary care practice. To facilitate the "letter" process, we additionally collaborate with the University of Pittsburgh Health Records Research Request (R3) to identify appropriate primary care patients who meet certain eligibility criteria (age, recent BP measurement in range, and not currently using antihypertensive and/or glucose lowering medications). Lastly, we encourage enrolled participants or even individuals that are ineligible during screening to share our study by providing electronic or paper flyers to distribute. Advertisement materials provide a phone number, e-mail, and link to our study-specific website (www.sit-less.pitt.edu). Referral inquiries are then received via e-mail, phone calls, from a Qualtrics online survey available through our website, or via the Pitt+Me Research Registry.

Screening and orientation

Initial study eligibility is determined by trained research staff after a referred candidate has completed a screening survey, either online or by phone. The screening survey includes a detailed summary description of the study, a request for consent to complete the screening survey, and specific questions about the candidate's current medications, medical history, exercise habits, work environment, demographics, and contact information. Self-reported responses to eligibility questions are reviewed by study staff and in consultation with the study investigators, as needed. If a candidate reports information that deems them ineligible, they are told the reason at that time.

Candidates who are determined to be initially eligible by research staff during the self-report screening process are invited to attend an in-person orientation, including an informed consent process, review of self-reported eligibility criteria, and assessment of additional eligibility

criteria (i.e., BP as described below). The average of two baseline BPs determines the participant's final eligibility.

Assessment visits

Assessments occur at baseline and 3 months and are conducted by trained, blinded study personnel.

Resting BP is measured at baseline and 3-month follow-up using a protocol based on published recommendations for accurate BP measurement [38–40]. At each assessment timepoint, BP is measured twice (≥ 1 day apart) on each of two occasions (four total readings), as follows: following verbally-confirmed 8-h abstention from food, caffeine, and nicotine and 24-h abstention from MVPA and alcohol; between 6:00–11:00 AM; using a validated oscillometric device (HEM-907 XL Omron Healthcare, Lake Forest, IL) [41]; following a 10- min quiet rest [42] with arm supported at chest level and feet supported; and using an appropriately sized cuff where the bladder encircles 80% of the arm circumference (as recommended by the American Heart Association) [38,39]. Initially, BP is taken on both arms and the arm with the higher systolic BP is used thereafter for the remainder of the trial [40]. Two measures are taken, with a 1-min rest between, and averaged. If systolic BP differs by ≥10 mmHg or diastolic BP by ≥6 mmHg, a third measurement is taken and included in the average. Staff completed training, undergo regular quality assurance, and follow guided assessment checklists to facilitate per protocol measurements.

24-h ambulatory BP is measured using the Oscar 2 24-h BP monitor (Suntech Medical, Morrisville, NC) on the non-dominant arm with appropriate cuff size based on arm circumference. Participants are provided general instructions to wear the monitor continuously for 25 h, including while sleeping [43]. Using each participant's report of their anticipated bedtime and awakening, the monitor is programed to record a BP every 30 min while awake and every 60 min at night. Data editing follows notable error codes (e.g., "artifact/erratic oscillotertic signal") for physiologic BP readings. Using daytime/awake and nocturnal/asleep periods from the participant diary, daytime and nocturnal BP are determined. Because objectively-measured activity from the 15 min prior and ambulatory BP are directly related [44], concurrently-measured posture (activPAL) and activity (GT3X) in the 15 min prior to ambulatory BP will be used to further classify daytime ambulatory BP for analysis. These include i) seated ambulatory BP (prior 15 min all sitting with <100 cpm) or ii) non-non-seated BP (any standing, stepping, or ≥ 100 cpm in the 15 min prior).

cfPWV is measured following the same pre-visit instruction for measurement of BP. Pulse pressure waveforms are captured from the right carotid and femoral arteries using tonometry after 10 min of supine rest. Sensor output is processed by the Complior AnalyseAnalyze®(ALAM Medical, France) based on current recommendations [45]. Three runs capturing 10 waveforms each are averaged. Using our protocol, our laboratory has excellent inter- and intra-technician ICCs of 0.91 and 0.94–0.98, respectively.

Fasting blood sample collection occurs following an 8-h fast and after participants complete ≥30 min of seated assessments (e.g., BP, questionnaires) to limit the influence of posture on

plasma renin activity and aldosterone. One tube of plasma and serum are collected, processed in a centrifuge, and pipetted into 2 ml cryovials for storage in a -80 ◦C freezer until future analysis for plasma renin activity, aldosterone, glucose, and insulin. Samples are stored to be run simultaneously to reduce inter-batch variability. Plasma and serum are also stored for potential future analyses.

SB and physical activity are self-reported using the Paffenbarger Physical Activity Questionnaire [46] and the Sedentary Behavior Questionnaire [47].

Objective SB and MVPA are measured by two monitors, the activPAL3 micro (PAL Technologies, LTD, Glasgow, Scotland) and the Actigraph GT3X accelerometer (Actigraph, LLC, Pensacola, FL). Both are necessary as these devices are, respectively, best practice methodology for assessing SB (activPAL3) and MVPA (GT3X) [48,49]. Participants are instructed to wear both monitors for 9 days on the thigh (activPAL3, 24- h wear protocol) and hip (GT3X, waking wear protocol). The first two days of monitoring are used in conjunction with the ambulatory BP data to account for concurrent posture and activity during waking 24-h BP monitoring. Days 3–9 (7-day period after the ambulatory BP monitoring is completed) are used to measure usual SB and physical activity. During the wear period, participants complete a diary to report work, non-work, sleep, and non-wear periods that are used in data processing described below. SB and activity data are considered valid if ≥4 days with ≥10 h of waking wear time are captured [50,51].

For activPAL3, 24-h event data are downloaded, exported, and cleaned (removing non-wear and sleep) using established methods for quantifying time spent in SB, standing, or stepping, as well as steps per day, sit-stand transitions, and periods of prolonged sitting (e.g., ≥30 min) [52,53]. These outcomes are averaged across valid days [51], both overall and during reported working hours.

GT3X data are reintegrated into 60-s epochs using ActiLife software. Periods of nonwear are removed using the Choi algorithm [54], after which MVPA is quantified using Freedson vector magnitude cut points [55]. In addition, daily minutes of bouted MVPA (≥10 min with allowance for 2 min below the cut point) will be quantified [50]. Daily estimates of total and bouted MVPA are then averaged across valid days [51].

Anthropometry:

Height is measured at baseline only by stadiometer as the average of two measures within 0.5 cm. Weight is assessed at baseline and follow-up using a calibrated, Tanita digital scale as the average of two measures within 0.1 kg.

Medical history and medication use are assessed at baseline during screening using a standardized form. At the 3-month follow-up, an interval medical history form captures any changes to medical history or medication (start, stop, or change in dosage) that have occurred since the time of randomization.

Diet is measured as a covariate, as no dietary intervention is provided by the study. Dietary habits are assessed using the Diet Screener Questionnaire (DSQ) [56].

Adverse events are captured prospectively as well as systematically at 3-month follow-up during the interval medical history (see above). These two methods are used because the increased contact frequency with intervention participants could result in increased reporting in that group. Any new or worsening medical conditions reported by the participant trigger the completion of an adverse event form. Details of the adverse event are collected and then the adverse event is classified with respect to severity and relationship to the intervention by blinded study personnel.

Contamination is measured in all participants during the follow-up assessment. Control participants are asked not to begin using a sit-stand desk or wrist prompter during the study, and these components are offered as remuneration at the end of the follow-up to discourage use by participants in the control group. The contamination questionnaire assesses whether participants are exposed to each component of the intervention, externally from the RESET BP research (e.g., co-worker or spouse participating in the study, purchase or receipt of an activity-prompting wearable device).

Intervention

Several considerations informed our intervention design. First, at the time we began, quantitative guidelines for reducing SB were not available. We synthesized the available evidence that greater SB, and in particular prolonged SB, was associated with adverse cardiovascular health [10–12,16,26–29] with an expert statement recommending that desk-based workers should avoid prolonged postures (either sitting or standing) and replace 2–4 h of SB per day with standing and activity [37]. Combining these, we set behavioral targets to i) replace 2–4 h of SB per day with standing and light-intensity activity, and ii) reduce periods of prolonged SB (i.e., >60 min).

To achieve this large reduction in SB, a behavior that is ubiquitous, habitual, and often environmentally-determined [57], we use an evidence-based, multi-component intervention strategy across two levels of the socioecological model. The approach includes behavioral strategies (self-monitoring, goal setting, problem solving) [58], environment modification (sit-stand desk attachment) [59], and proximal (fitbit Flex 2) and distal (text messages) external prompts [60]. The overall behavioral target of reducing SB is separated into replacement of SB with standing (2–4 h per day) and the addition of light-intensity movement breaks to interrupt periods of prolonged SB (4–8 per day). Participants are encouraged to accumulate these targets across the day so as to be consistent with ergonomic recommendations to alter posture frequently and to reduce prolonged SB [37].

Facilitated by the interventionist, participants set initial goals at the baseline visit (e.g., stand for 1–2 h per day and take 2–3 additional movement breaks per day). Goals are advanced every other week at intervention contacts to reach the study targets. Fidelity of the intervention is assessed at each intervention contact by measuring delivery (provision of intervention components), receipt (self-report of components working properly and goal setting), and enactment (self-report of self-monitoring and goal achievement) [61].

Randomization

Participants are randomized in a 1:1 ratio to intervention and control groups using random block sizes chosen from small even numbers. The exact block sizes and probability for each block size will be revealed at study completion. The randomization scheme is stratified by participant gender and BP stage (elevated/stage 1/stage 2) to ensure a balance between the two arms of these crucial factors by design rather than chance.

Eligibility Criteria

Inclusion/exclusion criteria

We recruited individuals with elevated or high BP who would be recommended for treatment with lifestyle as first-line therapy [2]. Participants are required to obtain medical clearance from their primary care provider or physician to join the study during screening; the purpose of this clearance is to inform the physician of the participant's screening BP readings and ensure appropriateness for their patient to spend the next three months without antihypertensive medication use. Co-investigator study physicians deemed the three-month follow-up as a reasonable amount of time to try lifestyle-only treatment without initiating pharmacotherapy in this low-risk population, based on clinical treatment guidelines and typical clinical follow-up intervals for elevated or stage 1 BP [2]. Any use of BP or diabetes medication is exclusionary due to the potential influence on study outcomes. Certain criteria were selected to provide a participant group with structured sedentary time that our intervention could effectively modify and for which preliminary recommendations on dose of SB reduction were available [37]. These include desk job with stable employment, supervisor consent to participate, no physical limitation to reducing SB, not already using a sit-stand workstation or activity prompter, and limited planned absences from work during the study period. Finally, we only include inactive participants with self-reported MVPA below current recommendations since the epidemiologic evidence suggests that the deleterious effects of SB are more apparent among inactive adults [16,19].

Eligibility criteria for study participation.

Inclusion criteria

Age: 21–65 years
Elevated or high BP: Resting systolic 120–159 mmHg or diastolic 80–99 mmHg
Inactive lifestyle: Engages in less than 150 min per week of moderate +2× vigorous intensity physical activity by self-report
Desk worker: Currently perform deskwork for ≥20 h per week Office location
Employment within an approximate 25-mile radius
Stable employment: ≥ 3 months in current job, plan to be in current job for the next 3 months
Supervisor approval: Supervisor permission to join the intervention on provided consent form
Cell phone: Possession of a cellular phone able to receive text messages

Exclusion criteria

BP indicating need for medication: Resting systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg
Medications: Antihypertensive or glucose-controlling medications
Comorbid conditions: Conditions that would limit ability to reduce SB (e.g., musculoskeletal condition, current chemotherapy)
Cardiovascular disease: History of ischemic heart disease, chronic heart failure, stroke, or chronic kidney disease
No medical provider clearance: Unable to provide written consent from primary care provider or physician to participate

Other exclusions

Current use of sit-stand or standing desk, SB prompting device, enrollment in a weight loss or exercise study program, recent (< 1 year) or planned bariatric surgery
Pregnancy status: Currently pregnant or pregnant in the last 6 months; breastfeeding currently or in the last 3 months
Inadequate availability: Plans to be away from desk for an extended period (>1 week) during the study period (e.g., for a prolonged vacation or planned surgery)

Innovative adaptations during the COVID-19 pandemic

RESET BP was among the many ongoing clinical trials that were forced to demonstrate 'creativity and persistence' to continue amid government and institutional pandemic restrictions to reduce the spread of the COVID-19 [77]. The University of Pittsburgh suspended non-life-sustaining, in-person research beginning in March of 2020, and allowed research to restart during the summer months using a multilevel approval process that included consultation with institutional administration, human subjects protection, and environmental health safety officers.

Modifications to the intervention

During the initial suspension of in-person research, our first priority was to sustain the intervention for active participants. A major strategy by which our intervention reduces SB is via replacement with standing at a study-provided sit-stand desk attachment in the workplace. The majority of our participants moved their place of work from in-office to their home, which introduced challenges as some participants were unable to relocate their desk attachment and/or had no formal workstation at home. For these participants, we provided additional or different height-adjustable workstations to be used in the home that research staff dropped off on doorsteps. Staff also supported correct assembly and installation remotely. At the same time, we carefully collected data about changes in work environments so that we will be able to consider these changes in post hoc sensitivity analyses. Lastly, though our initial intervention protocol had 3 in-person behavioral lessons, mode of delivery was modified to remote video or phone conference. At the time of this submission, we continue to deliver the intervention remotely by videoconference as the pandemic is still active in our community.

Remote assessments of BP and other outcomes

A second priority during the suspension of in-person research was to modify our assessment protocol to allow for a 'remote exit' of enrolled participants that had finished the 3-month trial. Certain outcomes could not be ascertained using remote-only procedures (i.e., blood sampling and PWV assessment). However, using doorstep drop-off of equipment by staff, conversion of all self-administered questionnaires to online surveys, and videoconferencing, we were able to continue to collect the majority of outcomes *including our primary outcome* using remoteprocedures including two measures of BP on separate days, ambulatory BP, 9-day activity monitoring, and all questionnaires. For remote measurement of resting BP, we purchased additional HEM 907-XL automated devices and developed a protocol that could be completed by the participant during a videoconference with study personnel. This included: i) verbal confirmation of pre-measurement abstentions; ii) self-measurement of arm circumference using a flexible measuring tape that was secured to the arm using study-provided medical tape; iii) self-placement of the appropriate cuff with visual inspection for correct cuff and body positioning via videoconferencing; iv) video observation of the 10-min seated rest; and v) automated measurement with the oscillometric BP monitor screen facing the video camera and non-visible to the participant during measurements (to reduce reactivity). We also added collection of BP measurement location (i.e., clinic, home, or other), again for future consideration in post hoc sensitivity analyses. Through the remarkable dedication and flexibility of the RESET BP staff and participants, we were able to complete remote follow-up assessments on all but one participant (who withdrew from the study) during the in-person research suspension.

Study protocols during re-initiation of in-person research

When designing our research restart plan, we prioritized maintenance of exposure-limiting, remote procedures where study integrity was not compromised. At the current time, this includes our study orientation and informed consent procedures (videoconferncing), self-administered questionnaires (REDCap), and all behavioral intervention contacts (videoconferencing). For our primary outcome of BP, we initially continued at-home assessments since we had developed an acceptable remote method. However, with approval by our institution for this low-contact measurement, we have reinitiated in-clinic BP for the following reasons. Firstly, for the scientific reason that home BP is well known to be lower than clinic BP [78]. Secondly, for the practical reasons that that remote BP measurement took considerably more participant time and created difficult logistics for delivering and retrieving our BP monitors. During the transition back to clinic BP assessments, we took care to match baseline and follow-up assessment locations when possible (i.e., home or clinic) to maximize the internal validity of outcome assessments. Thus, our modified protocol currently includes only necessary in-person assessments due to the currently active pandemic. Our laboratory continues to practice stringent safety procedures aligned with CDC and University of Pittsburgh guidelines including: pre-visit screening with questions and temperature checks, social distancing, limited personnel and time spent in the same room (e.g., research personnel leave the room during resting periods), personal protective equipment including participant and research personnel masks, cleaning all surfaces before and after participant visits, and observing all government and institutional regulations for quarantine and travel restrictions.

Statistical Considerations

Analysis plan Overview:

We will perform main analyses with an intention-to-treat basis. Participants who initiate antihypertensive medication after randomization will be treated as drop-outs for the assessments that take place after medication initiation. We believe this is a conservative approach based on the plausibility that, if any, the greater number of such participants would likely be in the control group. If we were to include their BP outcomes without medication, the intervention effects would even be larger than that observed under this strategy. We will compare the baseline measures between arms using independent samples *t*-, Wilcoxon rank sum, chi-square or Fisher's exact tests, as appropriate. Any found to be different will be used as additional covariates in sensitivity analyses. We will use multiple imputation to account for missing data, including those treated as missing due to medication initiation [62,63].

Aim 1: Hypotheses are about intervention efficacy, aimed at demonstrating greater 3-month improvements in the intervention group compared to the controls. We will fit a series of analysis of covariance models with baseline to 3-month change in each continuous outcome measured once per assessment (resting BP, cfPWV) as the dependent variable, intervention arm as the only factor of interest, and baseline value of the outcome as a covariate. For continuous outcomes measured multiple times per assessment (nocturnal and seated ambulatory BP), we will fit a series of linear mixed models with each 3-month measurement as dependent variable, intervention arm as the fixed effect of interest, average baseline measurement and time of day [63] as fixed effect covariates, and a banded correlation structure. Non-seated ambulatory BP will analyzed similarly, but will include measures of posture, physical activity [64], and proximity to activity as additional fixed effect covariates. Statistical significance of the between-arm comparisons at $\alpha = 0.05$ will serve as the formal tests of the Aim 1 hypotheses.

Aim 2: We will perform an exploratory mediation analysis beginning with simpler crude approaches, employing increasingly complex approaches and basing findings on a model a sufficiently complex model to explain the phenomenon. We will add the change in RAAS measures as additional fixed effects in the Aim 1 statistical models, and note the absolute and relative reductions in the intervention effect to quantify the role that RAAS plays using the naïve causal steps approach. We will employ the Preacher and Hayes multiple mediation approach to more formally examine the said role as well as individual relative contributions of PRA and aldosterone to the mediating role [65]. For a more nuanced exploration incorporating covariates, interaction effects among covariates, treatment and mediators, and potential nonlinearities, we will employ VanderWeele's counterfactual framework but with PRA and aldosterone individually as simple mediators [66]. While exposure-outcome confounding is mitigated due to randomization, any unbalanced covariates will be incorporated. We will be able to appropriately partition the total intervention effect to controlled/natural direct/indirect effects via each measure of RAAS activation, and any differences in mediating role based on assigned intervention. Mediator-outcome covariates are likely not known and/or measured and will be a limitation.

Aim 3: To examine how changes in sedentary behavior and physical activity measures are associated with changes in outcomes, we will compute correlation coefficients between 3-month

changes in those measures and changes in outcome variables measured once per time point. For those measured multiple times per time point (e.g., ambulatory BP), we will consider both averaging by time point before computing correlations and linear mixed modeling strategies similar to those in Aim 1, which can take into account both the correlation among multiple measurements and dependence on time of day, posture, physical activity and/or proximity to physical activity prior to measurement. We will analyze both with and without stratification by arm.

Aim 4: Exploratory continuous outcomes (i.e., adiposity and HOMA) will be analyzed similarly using the methods described for Aim 1 and 3.

Sensitivity analyses will involve adjusting for additional baseline covariates significantly different between groups, repeating analyses excluding participants reporting contamination, and including those initiating antihypertensive medication (if any).

Sample size justification

We based our sample size on prior pilot data from our RiSE [67] and RiSE@Work studies and other sources [68], and published statistical methods [69–72] implemented in commercially available statistical software (PASS 2012®, Number Cruncher Statistical Systems, LLC, Kaysville, UT). We estimated that baseline and change in the primary outcome systolic BP will have standard deviations of 10 and 11 mmHg, respectively. With 300 participants randomized in equal proportions, and with anticipated 240 completers based on an allowance for up to a 20% attrition rate over 3 months, we are able to detect statistical significance of a between-arm difference as small as 4 mmHg in systolic BP change with 80% statistical power in a two-tailed test at $\alpha = 0.05$. At approximately 60% recruitment, our current attrition rate is <2%. We chose 4 mmHg as the most conservative estimate from our prior pilot data, which ranged from 4 to 6 mmHg. We also note this is a clinically meaningful change in systolic BP, corresponding to a Cohen's $d = 0.40$ (small-moderate effect size), that studies of aerobic exercise training have observed similar effects [73,74], and that lifestyle intervention trials achieving similar reductions in systolic BP among samples with elevated-to-stage 1 hypertension have reduced the incidence of progression to stage 2 hypertension by up to 50% [75]. Thus, the sample size affords adequate statistical sensitivity for the primary hypothesis and also will be able to detect similar small-to-moderate effect sizes for secondary outcomes. Among intervention participants, we will be able to detect a correlation as small as 0.25 between changes in activity measures and change in outcomes.

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