




BMJ Open Effects of a laboratory-based aerobic exercise intervention on brain volume and cardiovascular health markers: protocol for a randomised clinical trial

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ABSTRACT

Introduction Physical activity (PA) has beneficial effects on brain health and cardiovascular disease (CVD) risk. Yet, we know little about whether PA-induced changes to physiological mediators of CVD risk influence brain health and whether benefits to brain health may also explain PA-induced improvements to CVD risk. This study combines neurobiological and peripheral physiological methods in the context of a randomised clinical trial to better understand the links between exercise, brain health and CVD risk.

Methods and analysis In this 12-month trial, 130 healthy individuals between the ages of 26 and 58 will be randomly assigned to either: (1) moderate-intensity aerobic PA for 150 min/week or (2) a health information control group. Cardiovascular, neuroimaging and PA measurements will occur for both groups before and after the intervention. Primary outcomes include changes in (1) brain structural areas (ie, hippocampal volume); (2) systolic blood pressure (SBP) responses to functional MRI cognitive stressor tasks and (3) heart rate variability. The main secondary outcomes include changes in (1) brain activity, resting state connectivity, cortical thickness and cortical volume; (2) daily life SBP stress reactivity; (3) negative and positive affect; (4) baroreflex sensitivity; (5) pulse wave velocity; (6) endothelial function and (7) daily life positive and negative affect. Our results are expected to have both mechanistic and public health implications regarding brain–body interactions in the context of cardiovascular health.

Ethics and dissemination Ethical approval has been obtained from the University of Pittsburgh Institutional Review Board (IRB ID: 19020218). This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule.

Trial registration number NCT03841669.

INTRODUCTION

Physical *inactivity* is estimated to account for >350 000 deaths per year in the USA alone, with an additional 3.2 million annual

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The high-resolution neuroimaging data in addition to peripheral mediators and subclinical markers of cardiovascular disease (CVD) risk will allow us to test novel mechanistic hypotheses about the relationships between brain and cardiovascular health.
- ⇒ The neurobiological and peripheral physiological assessment methods in the context of a 12-month experimental manipulation of exercise to understand the links between brain health and cardiovascular health will test several hypotheses about how exercise affects both brain and cardiovascular health.
- ⇒ The multivariate nature of the CVD data, neuroimaging data and questionnaires will provide the investigators with an opportunity to examine effect moderation, individual differences in response to the intervention and for modelling key potential mediators for the effects.
- ⇒ A limitation of the study is the assessment of outcomes at only two time points.
- ⇒ The multivariate nature of the data could raise concerns about the dimensionality and multicollinearity for hypothesis testing.

deaths globally.¹ On the other hand, physical *activity* (PA) is critical for reducing risk for many chronic diseases (eg, some cancers, cardiometabolic conditions and atherosclerotic cardiovascular disease (CVD)), and it has beneficial effects on a range of proximal mediators and markers of chronic disease risk—especially CVD risk.^{2–5} These include blood pressure (BP), cardiac autonomic control, inflammation, glucose regulation, adiposity and lipid levels. In patient samples, clinical trials show that PA accelerates recovery from myocardial infarction,⁶ coronary bypass surgery and congestive heart



failure,⁷ improves quality-of-life⁸ and reduces risk for new CVD events and all-cause mortality.⁹ Further, cardiac patients who improve cardiorespiratory fitness show a 20% reduced mortality rate over an 11-year follow-up period.¹⁰ In view of clear scientific evidence on PA and health, many national and international organisations have nearly identical recommendations for people to engage in PA. The most recent was established in 2018 and 2020 by the US Physical Activity Guidelines Committee and WHO, respectively, advising >150 min of moderate intensity exercise, or 75 min of vigorous intensity aerobic exercise per week to improve cardiovascular health and to reduce risks for premature mortality.^{5 11–13}

These benefits translate into brain-based improvements in cognitive, affective, stress-buffering and self-regulatory behaviours.^{14–16} Indeed, human and animal evidence show that the brain exhibits appreciable structural and functional plasticity (ie, change) from PA.^{17–21} As a result of this evidence, many organisations (eg, National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association) have developed campaigns to educate the public and healthcare professionals on the neurocognitive benefits of PA.²² In support of these health campaigns, Barnes and Yaffe²³ reported that >1.1 million Alzheimer's disease cases in the USA are potentially attributable to physical inactivity. Noteworthy here is that Alzheimer's disease and other forms of dementia are highly comorbid with CVD and often predicted by CVD risk factors that are affected by PA (eg, hypertension).^{24–29} Moreover, exercise may exert 'stress-buffering' effects at the level of physiology and behaviour (eg, by reducing aspects of negative affect and depressive symptoms), which may define additional pathways to reduce CVD risk.^{14 15} What is not known, however, is whether the beneficial effects of exercise on the brain extend beyond emergent cognitive, affective and stress-buffering processes to also include beneficial effects on physiological and systemic mediators of CVD risk that are regulated by the brain. If so, such effects may help to more precisely define and refine novel and brain-based targets for intervention and prevention efforts.

Accordingly, the fundamental premise of this study is that PA, in the form of moderate-intensity aerobic exercise, is beneficial for both cardiovascular health and plasticity of neural circuits that regulate peripheral physiological mediators of CVD risk.^{30–32} Yet, despite the well-established associations between exercise and brain plasticity, we have a limited understanding of the mechanisms by which exercise affects brain plasticity or how these changes may relate to CVD risk. Similarly, although converging lines of evidence raise the possibility that aerobic exercise may partly influence CVD risk via its effects on brain plasticity, this possibility has never been tested at multiple levels of analysis in a well-controlled exercise intervention. The Exercise, Brain, and Cardiovascular Health study combines neurobiological and peripheral physiological assessment methods in the context of an experimental manipulation of exercise

to better understand the links between brain health and CVD risk.

Project objectives

The aim of this study is to assess whether a 12-month moderate-intensity PA intervention induces changes in peripheral markers of cardiovascular control and health (eg, cardiorespiratory fitness, peripheral vascular function), and whether those changes are associated with exercise-induced structural and functional plasticity of the hippocampus and related brain circuits. Similarly, we aim to examine whether a 12-month moderate-intensity PA intervention induces changes in visceral control circuits of the brain, and whether those changes are associated with baroreflex sensitivity (BRS), heart rate variability (HRV) and glucocorticoid control.

METHODS AND ANALYSIS

Project period

Study is planned for the period between September 2019 and May 2024.

Setting

The intervention and assessments will take place in Pittsburgh, Pennsylvania, USA.

Study design

This study is a 12-month single-blind, randomised clinical trial (RCT), in which participants will be assigned to either: (1) moderate-intensity aerobic PA for 150 min/week or (2) a health information control group. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials statement.³³ The trial procedures are summarised in [figure 1](#). The current protocol includes modifications to offset disruptions caused by COVID-19 pandemic.

Recruitment

We will randomise 130 healthy participants between 26 and 58 years of age (50% female). Recruitment of racial and ethnic minorities will be in proportion to the demographic representation of the greater Pittsburgh community: 28% black; 1% Hispanic; 2% Asian. Recruitment strategies include advertisements via newspapers, radio and television, direct mail, research registries and online media (eg, Facebook).

Participant selection

Eligibility criteria were crafted to recruit individuals who can safely engage in regular moderate-to-vigorous intensity exercise for 12 months (see [table 1](#)). The goal was to create eligibility criteria that would maintain safety while maximising generalisation of the results to a broad population.

Blinding and randomisation

Participants will be randomised after completion of the baseline sessions and evaluation of data quality assurance

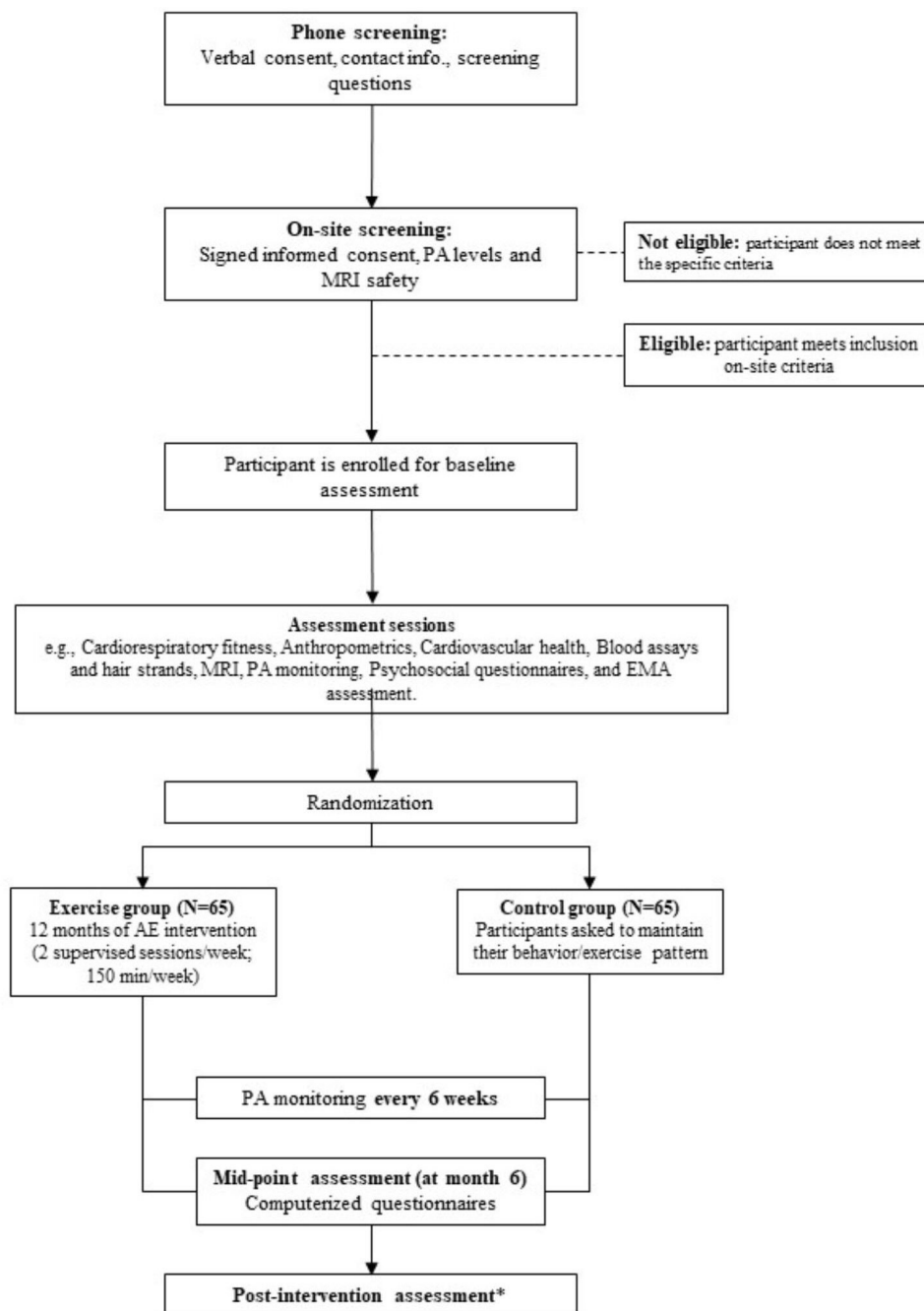


Figure 1 Visual representation of the procedures and participant flow in the Exercise, Brain, and Cardiovascular Health trial. *Postintervention assessment includes the same outcomes that were collected during baseline assessment. EMA, ecological momentary assessment; PA, physical activity.

on a web-based system through the Research Electronic Data Capture (REDCap) randomisation module. The allowable time from signing the informed consent to randomisation is 8 weeks with the goal of having all sessions completed within 30 days. The lead study biostatistician randomises participants using a stratified permuted block randomisation algorithm with equal allocation to one of the two groups: (1) 150 min/week of moderate-intensity exercise (ie, brisk walking) or (2) a health information control group. We also consider stratification by two factors: (1) age at study entry (≤ 40 and > 40

years) and (2) sex (male, female) to ensure equal allocation of participants to each group based on these criteria. Briefly, the stratified permuted block randomisation algorithm allows flexibility in achieving balanced allocation of participants among treatment groups by age and gender to minimise differences across the different conditions by the end of the trial. All investigators and staff involved in data collection and management will be blinded to group assignment. Only staff involved in the implementation of the exercise intervention, scheduling of sessions and study coordination are unblinded to group assignment.

Table 1 Exercise, Brain, and Cardiovascular Health inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Men and women 26–58 years ▶ Ambulatory without pain or the use of assisted walking devices ▶ Able to speak and read English (>10 years) ▶ Engaging in <100 min/week of exercise and <75th percentile of VO₂max ▶ Living in community for duration of the study ▶ Reliable means of transportation ▶ Eligible to undergo MRI 	<ul style="list-style-type: none"> ▶ Self-reported chronic psychotic illness (eg, schizophrenia, bipolar disorder) or neurological disorder or brain injury resulting in ongoing symptoms or cognitive impairment (eg, multiple sclerosis, cerebral palsy, major head injury) ▶ Self-reported prior heart attack, stroke, bypass surgery, angioplasty, congestive heart failure, arrhythmia (cardiac rhythm problems) ▶ Hypertension (SBP/DBP greater than/or equal to 160/100 mm Hg)* ▶ Liver (ie, hepatitis B or C, liver failure or cirrhosis) or kidney disease ▶ Lung disease requiring drug treatment ▶ Type I diabetes, insulin-dependent type 2 diabetes, uncontrolled type 2 diabetes (defined as an HbA1c level >10) ▶ Regular use† of all centrally active or psychotropic medications (SSRIs are permitted) ▶ Current use of prescribed blood pressure medication ▶ Current pregnancy or plans to become pregnant over the next year ▶ Treatment for cancer in the past 12 months—except non-melanoma skin cancer ▶ Not fluent in English ▶ Nightshift work‡ ▶ MRI incompatible ▶ Colour blindness ▶ Suspected alcohol use disorder ▶ Unwillingness to either complete the study requirements or to be assigned or randomised to the two intervention groups

*>140 SBP/90 DBP is allowed, but feedback card and information about elevated levels will be provided to the participant.

†Regular use is defined as taking medications more than seven times in a 2-week period.

‡Defined as a period of work in which half or more of the hours worked are between midnight and 08:00 in the morning and this has occurred more than 12 times during the past year).

DBP, diastolic blood pressure; MCI, mild cognitive impairment; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitors.

The PIs are only unblinded in the case of an adverse or serious adverse event.

Calculation of sample size

We conducted power analysis and sample size estimation for hypothesis testing based on achieving 80% power at the significance level of 0.05. The estimated effect size (Cohen's *d*) based on prior 6 to 12-month PA interventions in different age ranges^{20 21 34 35} is between 0.30 and 0.50. Assuming a conservative effect size ($d=0.30$), 65 participants per group is sufficient to detect differences in brain volume at 80% power even after 20% attrition ($N=52/\text{group}$). Meta-analyses of prior randomised exercise interventions showed moderate-to-large effects on CVD risk markers ($d=0.60$) and cardiorespiratory fitness ($d=0.58$).³⁶ Based on previous studies and meta-analyses, we are sufficiently powered with the planned sample size to test for exercise-induced changes in CVD markers.

Outcomes

Our primary endpoints will be 12-month change scores resulting from three different measurements: (1) hippocampal volume, (2) mean systolic blood pressure (SBP) reactivity averaged from Stroop and Multi-Source Interference Task (MSIT) stressors during functional MRI (fMRI) and (3) HRV. Our secondary outcomes will result from changes in: (1) ecological momentary assessment, (2) BP, (3) negative and positive affect, (4) BRS, (5)

pulse way velocity, (6) vasodilation, (7) brain activity, (8) connectivity, (9) cortical thickness and (10) volume.

See [table 2](#) for a complete schedule of all study assessments.

Primary outcomes

Brain MRI

We will use a Siemens Prisma 3-T scanner with a 64-channel head coil. Screening for safety, a history of claustrophobia, and metal implants or devices will occur during the initial telephone screening.

Sequences will include a high-resolution three-dimensional magnetisation-prepared rapid acquisition with gradient echo (MPRAGE) T1-weighted anatomical scan, a hippocampal focal T2-weighted sequence, a resting state echo planar imaging (EPI) scan and several task-evoked EPI scans (see [table 3](#)).

Three tests will assess task-evoked fMRI brain activity: (1) a modified Stroop task; (2) a modified MSIT and (3) an Affective responding and regulation task.^{37–39} Before scanning, practice on the tasks confirms task comprehension and comfort. In the Stroop task, a series of colour words (ie, red, blue, yellow and green) are displayed on a screen in various colour fonts and the participant is asked to identify the font colour in which each word is printed by pressing a button on an MRI-compatible response system. In the MSIT, a series of four numbers appear on the screen with three of the numbers being identical and

Table 2 Assessment schedule

	Phone screening	Baseline	Every 6 weeks	6 months (mid-point)	12 months (follow-up)
Health history	√				
Stadiometer measurements		√			√
Cardiorespiratory fitness		√			√
Cardiovascular health		√			√
Blood assays		√			√
Hair strands		√			√
MRI		√			√
Physical activity monitoring		√	√		√
Psychological assessment and questionnaires		√		√	√
Ecological momentary assessment		√			√

one being different (eg, 1114). The participant identifies the location of the different numbers by pressing a button. Feedback is provided after each response, and congruent and incongruent conditions are presented in both tasks; also, performance difficulty is titrated upwards over time during incongruent conditions of both the Stroop task and MSIT to increase the psychological challenge, as detailed in Sheu *et al* and Gianaros *et al*.^{37 38} In the Affective task, negative images from the International Affective Picture System database are presented on the screen in two conditions: (1) ‘look’, in which participants are instructed to simply observe the image, or (2) ‘decrease’, in which participants are instructed to think of

something that would make them feel less negative about the image (ie, reappraise the image). Participants indicate how negative they feel after each image, using a scale ranging from 1 to 5 (‘not at all negative’ to ‘very negative’).³⁹ After the MRI, a survey is administered to confirm comprehension of the task, and to collect information about the strategies used to feel less negative and the degree of success associated with strategy employment.

Finally, cardiovascular activity during the MRI scan is monitored via a Siemens SpO₂ monitor on the left index finger, a Siemens respiration belt and a 4-lead Siemens ECG monitor. During the Stroop task and MSIT, BP is taken every 60s (at the onset of each block) using a TeslaM3 BP machine (Siemens, Erlangen, Germany). In addition, three BP readings, 2 min apart, are taken in the practice room while the participant is seated, and three BP readings (2 min apart) are taken during the MPRAGE scan. The second and third readings are averaged and used as baseline measures of BP.

Cardiovascular health

Multiple non-invasive measurements will assess cardiovascular health/function, including the following sections.

Autonomic function and arterial stiffness

These measures will be collected using a dual impedance cardiography (ICG) method that we have previously detailed (eg, first).⁴⁰ We will obtain an ECG concurrently with a basal ICG (Z0) and the first derivative of pulsatile ICG change (dZ/dt) using tetrapolar lead configurations applied to the (1) thorax assessing aortic blood flow onset and (2) calf assessing peripheral pulse transit time in line with standard ICG guidelines.⁴¹ Digitised recordings of interbeat intervals will be collected during a 5 min sitting period of both paced (11 breaths per minute) and unpaced respiration to assess HRV and pulse wave velocity (ie, arterial stiffness). Continuous beat-by-beat BP will also be monitored using cuffs placed around the brachial artery and index/middle fingers, which will assess total peripheral resistance, BRS and blood pressure variability.

Table 3 Selected details of the MRI protocol

Sequence	Parameters
T1-weighted MPRAGE structural	Sagittal, 0.8 mm isotropic resolution, TE/TI/TR=2.31/1060/2400 ms, field of view (FOV) 256 mm, 224 slices
High resolution hippocampus	Resolution: 0.4×0.4×2 mm, TE/TR=78/8830 ms, aligned perpendicular to hippocampus
fMRI Stroop task	Resolution: 2.5×2.5×2.5 mm, TE/TR=40/1000 ms, multiband factor=8, 64 slices, 280 measurements
Resting state EPI	Resolution: 2.5×2.5×2.5 mm, TE/TR=40/1000 ms, multiband factor=8 (CMRR EPI sequence 60–63), 64 slices, 480 measurements
MSIT	Resolution: 2.5×2.5×2.5 mm, TE/TR=40/1000 ms, multiband factor=8, 64 slices, 280 measurements
Emotional reappraisal	Resolution: 2.5×2.5×2.5 mm, TE/TR=40/1000 ms, multiband factor=8, 64 slices, 338 measurements

EPI, echo planar imaging; fMRI, functional MRI; MPRAGE, magnetisation-prepared rapid acquisition with gradient echo; MSIT, Multi-Source Interference Task; TE, echo time; TI, inversion time; TR, repetition time.

Endothelial health

Venous occlusion plethysmography will measure endothelial function.⁴⁰ First, BP occlusion cuffs are placed around the wrist and brachial artery, as well as an indium-gallium strain gauge wrapped around the forearm to measure changes in circumference (ie, volume). During a standardised sequence of inflations/deflations in cuff pressure, forearm blood flow is measured via changes in circumference from the strain gauge. Following 'resting/baseline' readings, the brachial cuff is inflated to 40 mm Hg above SBP for 5 min until the pressure is released and 'max' blood flow readings are recorded. This post-occlusion state is referred to as reactive hyperaemia and provides a reliable index of endothelium dependent vasodilation. Max flow readings are compared with baseline readings to derive a percentage increase, with greater values associated with better endothelial health.

Secondary outcomes

Ecological momentary assessment

Ecological momentary assessment (EMA) will assess ambulatory BP and daily life experiences.⁴² EMA involves data collection in real-time and in the natural environment, usually with the assistance of mobile or wearable devices.⁴³ During each of the 2-week long monitoring periods (pretreatment and post-treatment, 7–10 days in duration), participants will be equipped with a mobile smart phone, an ambulatory blood pressure (ABP) monitor (Oscar 2, Suntech Medical; Morrisville, NC) and a wrist-worn accelerometer (ActiGraph GT9X Link; ActiGraph; Pensacola, FL). The accelerometer will be used for the assessment of sleep and PA. On four of the monitoring days (three weekdays and one weekend day), the ABP monitor will be worn during waking hours. The monitor will be programmed to inflate on an hourly basis throughout each waking day. During the four ABP days, participants will complete hourly questionnaires following each ABP reading. The hourly assessments are designed to assess psychosocial stress and daily life mood or affect. Participants will be trained on how to use each of these ambulatory monitoring devices. If the expected number of interviews and BP readings are insufficient, participants will be asked to complete extra day(s) of monitoring.

Blood assays and hair strands

Fasting blood samples for the assessment of inflammatory and metabolic measures will be collected at baseline and postintervention. A hair sample (50 mg or 100–150 hair strands) will also be collected and banked for the analysis of cortisol levels. Each blood draw collects approximately 50cc of blood. Blood will be transported and processed within 1 hour of the draw. Samples of plasma, serum, whole blood, RNA and isolated mononuclear cells will be stored at -80°C for analysis in batches with both samples collected from each participant assayed together and all samples assayed in duplicate. The main blood analytes to be assessed include glucose¹, insulin¹, triglycerides¹, and

total and HDL cholesterol¹, interleukin (IL)-6², tumour necrosis factor- α ², IL-1ra², IL-10², intercellular adhesion molecule-1², vascular cell adhesion molecule-1², C reactive protein¹ and brain derived neurotrophic factor². Analytes identified by ¹ will be measured by the University of Pittsburgh Medical Center's Central Laboratory Services. Analytes identified by ² will be measured in the Behavioral Immunology Laboratory (Director: Marsland).

Cardiorespiratory fitness testing

Cardiorespiratory fitness will be measured from a graded exercise test (GXT) (TrueOne 2400, ParvoMedics, Salt Lake City, UT) using a modified Balke protocol.⁴⁴ After a brief warm-up session, including a resting BP reading and ECG (NASIFF CardioSuite ECG cart), the participant will walk on a motor-driven treadmill at a constant speed (2.0 to 4.5 mph—based on the ability of the participant in consultation with the exercise physiologist) and increments of an incline. The intensity is increased in 2 min stages with a 2% increase in incline at each stage. Heart rate is continuously monitored via a 12 lead ECG along with BP readings (Tango 2, SunTech Medical) and rating of perceived exertion (RPE),⁴⁵ every 2 min. Cardiac impedance and HRV are also measured (Mind Ware Technologies). Each test will be administered by an exercise physiologist. Following the American College of Sports Medicine (ACSM) criteria,⁴⁶ a maximal test is determined when three of the four criteria are met: (1) plateau in VO_2 between two or more workloads (increase less than 0.15 L/min or 2.0 mL/kg/min during the last minute of corresponding workloads); (2) respiratory exchange ratio ≥ 1.10 ; (3) heart rate within 10 beats of age predicted maximal heart rate ($220 - \text{age}$); (4) rating of RPE ≥ 17 . Using the 9th edition of the ACSM Guidelines for Exercise Testing and Prescription, participants scoring >75 th percentile will be excluded from further continuation in the study.⁴⁷

Stadiometer measurements

Height and weight will be recorded before the GXT. Weight will be measured on a calibrated digital scale to the nearest 0.1 kg, wearing light clothing and without shoes. Height will be assessed using a calibrated stadiometer to the nearest 0.1 cm.

PA monitoring

PA monitoring will be conducted for the measurement of activity patterns throughout the trial, confirming engagement of exercise intensity during any unsupervised sessions, and to determine contamination of systematic changes in activity for the control group or the aerobic exercise group. A triaxial accelerometer (ActiGraph GT9X Link) will be worn around the non-dominant wrist at baseline, postintervention and every 6 weeks during the intervention for both groups. At each measurement point, the device is worn for a minimum of seven consecutive days, including sleep. A wear log will also be collected

during each of these periods. The device can be worn during bathing, showering and swimming.

Psychosocial assessment

A battery of questionnaires will be administered at baseline and 12-month follow-up using REDCap surveys including social, mood and quality of life scales and instruments (~2.5 hours; see table 4). Exercise self-efficacy, social support, mood and anxiety, and personality traits have all been shown to either influence exercise adherence or brain health and might explain, mediate, or moderate some of the effects of exercise on brain or CVD outcomes.

Intervention

Aerobic exercise condition

Supervised exercise will take place two times a week for 60 min and once a week for 30 min at home. Levels of exercise intensity will be prescribed based on maximal responses during the initial GXT. As the participants will be low active at baseline, the prescribed intensity will be 50%–60% of the maximum heart rate reserve for weeks 1–6 and 70%–85% for the remainder of the programme as long as it is deemed safe by the monitoring exercise physiologist and trainer, reaching the prescribed goal of 150 min/week. Participants who feel comfortable increasing the intensity more quickly will be allowed to do so if the exercise trainer agrees that it is safe. A heart rate monitor (Polar A370 or Unite watch, Polar USA, Lake Success, NY) will be worn during all sessions to ensure that exercise is occurring within the target heart rate zone. Certified exercise instructors will monitor attendance, intensity, frequency and safety. Walking, jogging or running on a treadmill will be the encouraged mode of exercise, but other types of aerobic exercise equipment such as treadmill, bike (upright or recumbent), elliptical, stair climber or rower will be allowed. Participants can use up to two different modes at each session. All modes of activity will be recorded. Compliance to home-based exercise will be monitored by exercise diaries, heart rate monitors and actigraphy. All exercise sessions start and end with 5–10 min of stretching for the purpose of warming up and cooling down.

Health information control group

The control group will be instructed to wear an ActiGraph monitor for 7 days every 6 weeks. They will not be asked to change their behaviour or exercise patterns and encouraged to perform activities as they normally would. Any change in sedentary behaviour or PA will be monitored by the ActiGraph device and examined for change at the completion of the trial.

Statistical analysis of outcomes

Before testing the specific aims, we will conduct exploratory data analysis to summarise characteristics of the sample, outcomes distributions and clinical variables. Summary statistics (mean, SD for continuous variables, frequency for categorical variables), graphical representation (boxplots, histograms, spaghetti plots) and

simple pairwise correlations will be used to describe the distribution of the data, missing data and potential multicollinearity among key variables. Furthermore, transformations will be applied as needed for all non-normal data including hepatocellular carcinoma and blood biomarkers prior to analysis.

All outcomes will be tested using an intent-to-treat framework. Sensitivity will be explored using adherence to the intervention (eg, per protocol). Dropout reasons and missing data mechanisms will be reported. We will test for completely random dropouts to examine whether missingness is unrelated to other observed and unobserved measurements (missing completely at random) or to the observed measurements only (missing at random). Additional sensitivity analyses will be conducted to evaluate informative dropouts. We will apply pattern-mixture models by stratifying our data by dropout patterns and fitting separate regression models to strata.

Before testing hypotheses about mediation, we need to test whether the intervention modifies proximal endpoints that will serve as the primary outcomes of the study. To do so, we will use a general linear mixed model (GLMM). The GLMM will include random effects (intercept and slope) for individual participants and a treatment-by-time interaction as a fixed effect. This technique will allow us to model the changes in scores as a function of both time and group while also including other potentially confounding variables in the regression model. Similarly, since we are considering individual changes over time and group, we will be able to test our hypotheses with respect to the response to the intervention (eg, responders vs non-responders to exercise). GLMM modelling is a popular approach to model both individual-specific and average (population-level) changes in longitudinal data by accounting for the within-person correlation among repeated measurements and individual heterogeneity in the change curve. Linear contrasts will be used to test for differences among intervention groups and measurement times via F-test or χ^2 test accordingly.

We will also test whether exercise-induced changes to peripheral physiological pathways statistically mediate the effects of exercise on the brain and whether the effects of exercise on the brain statistically mediate any beneficial effects of exercise on peripheral mediators of CVD risk, using longitudinal mediation models in a structural equation modelling framework. We will test the mediation effect by calculating the indirect path effects. These tests will be conducted at the significance level of 0.01 to reduce the risk of inflation of type 1 error. We will also explore the role of other potential mediators (ie, sleep) and moderators (eg, sex) in the direction and strength of associations.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Table 4** Psychosocial assessment

Barratt Impulsiveness Scale (BIS-11) ⁵¹	30 item self-report instrument designed to assess the personality/behavioural construct of impulsiveness
Barriers Self-Efficacy Scale (BARSE) ⁵²	A 13-item questionnaire that assesses the degree of confidence that one could exercise despite a variety of limitations such as bad weather, while on vacation, etc
Big Five Trait Taxonomy II Questionnaire (BFI-II) ⁵³	A 44-item questionnaire that measures the Big Five personality dimensions including Openness-to-experience, Conscientiousness, Extraversion, Agreeableness and Neuroticism
Brief-COPE Scale ^{54 55}	A 28-item questionnaire to rate by the 4-point Likert scale a broad range of coping responses to stressful events
Brief Fatigue Inventory (BFI) ⁵⁶	A 9-item questionnaire that measures severity of fatigue (three items) and the interference with daily activities (six items) on numeric scales from 0 to 10
Chapman Handedness Questionnaire ⁵⁷	A 13-item questionnaire to determine the extent to which a person is left-handed, right-handed or ambidextrous
Cohen Hoberman Inventory of Physical Symptoms (CHIPS) ⁵⁸	A 33-item questionnaire to determine participant's experiences of everyday physical symptoms
Composite Scale of Morningness (CSM) ⁵⁹	A 13-item measure examining participants' optimum times of day and quality of sleep
Emotion Regulation Inventory (ERQ) ⁶⁰	A 10-item scale designed to measure respondents' tendency to regulate their emotions in two ways: (1) Cognitive Reappraisal and (2) Expressive Suppression on a 7-point Likert-type scale
Exercise Self-Efficacy (EXSE) ⁶¹	An 8-item measure to assess degree of confidence in the ability to continue exercising at a moderate intensity three times per week for at least 40 min per session
Exercise Social Provisions Scale (EXSPS) ⁶²	A 24-item questionnaire about current relationships within the exercise programme, such as I do not think other people in the exercise group respect my skills and abilities. Adapted from its original form to be specific to exercise
Interpersonal Support Evaluation List (ISEL) ⁶³	A 40-item questionnaire to evaluate the impact of perceived availability of social support resources on health and well-being
Lantz' 3-item Financial Strain Scale	Also known as Financial Chronic Stress Scale. ⁶⁴ It focuses on measures that capture the psychosocial distress related to insufficient financial resources (aka financial strain)
Life Events List (LEI) ⁶⁵	A 55-item questionnaire that measures the amount of change, using Life Change Units, a person experienced and adjusted to in the previous 12 months. Only 24 items were included in this study
Life Orientation Test (LOT) ⁶⁶	A 10-item questionnaire that measures optimism vs pessimism. Of the 10 items, 3 items measure optimism, 3 items measure pessimism and 4 items serve as fillers
NCI Dietary Questionnaire (NCI DHQ-II) ⁶⁷⁻⁶⁹	A 24-hour recall questionnaire of food and nutrients intakes. The NCI method estimates the distribution of usual intake, assess the effects of non-dietary covariates on usual consumption and correct bias partially
MESA Community Neighborhood Perception Scale ^{70 71}	A 36-item questionnaire which includes seven neighbourhood dimensions to assess aesthetic quality, walking environment, availability of healthy foods, safety, violence, social cohesion and activities with neighbours
Mindful Attention Awareness Scale (MAAS) ⁷²	15-item scale designed to assess a core characteristic of dispositional mindfulness, namely, open or receptive awareness of and attention to what is taking place in the present
Multidimensional Outcome Expectations for Exercise Scale (MOEES) ⁷³	A 15-item questionnaire to assess participants' beliefs or expectations about the benefits of regular exercise or physical activity
Paffenbarger Physical Activity Questionnaire ⁷⁴	This questionnaire measures leisure time PA. It includes several questions regarding the frequency and intensity of PA and is able to estimate energy expenditure by a PA index
Penn State Worry Questionnaire (PSWQ) ^{75 76}	16-item scale designed to measure the trait of worry in adults. This scale measures the excessiveness, generality and uncontrollable dimensions of worry
Perceived Stress Scale (PSS) ⁷⁷	A 10-items questionnaire measuring the degree of perceived stress regarding certain life events during the past month
Physical Activity Enjoyment Scale (PACES) ^{78 79}	An 18-item questionnaire that assesses enjoyment for physical activity using a 7-point bipolar Likert scale, from 1 (I enjoy it) to 7 (I hate it)
Physical Activity Self-Regulation Scale (PASR-12)	A 12-item scale that measures self-regulation strategies to support physical activity adaptations and adherence

Continued

Table 4 Continued

Physical Self-Perception Profile (PSPP) ⁸⁰	A 24-item questionnaire assessing physical self-esteem
Pittsburgh Sleep Quality Index (PSQI) ⁸¹	A 9-item questionnaire assessing sleep quality
Positive and Negative Social Exchange Scale (PANSE)	This questionnaire assesses the type and frequency of positive and negative social support (emotional, instrumental and informational) that one received from others in the past month
Positive and Negative Affect Schedule (PANAS) ⁸²	Self-reported questionnaire that consists of two 10-item scales to measure positive and negative affect
PROMIS Anger (long form)	It measures self-reported angry mood (irritability, frustration), negative social cognitions (interpersonal sensitivity, envy, disagreeableness) and efforts to control anger
PROMIS Anxiety (short form)	It measures self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness) and somatic symptoms related to arousal (racing heart, dizziness)
PROMIS General Life Satisfaction	It assesses one's evaluation of life experiences and whether one likes his/her life or not
PROMIS Scale for Depression (short form)	It assesses self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness) and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning and purpose)
PROMIS Severity of Substance Use	IT assesses severity of substance use over the past 30 days
Sheldon Cohen's Social Network Index (SNI)	This version of the questionnaire also assesses type and quantity of one's membership in social groups (interaction in person or talked to on the phone on a regular basis, including family, friends, workmates, neighbours)
Rosenberg Self Esteem Scale (RSE) ⁸³	A 10-item scale that measures global self-worth by assessing both positive and negative feelings about the self
Sitting Time Questionnaire ⁸⁴	A 5-item questionnaire that assesses how much time participants spend sitting at work, at home, while watching TV or leisure time, and driving on an average day. The amounts are broken down by weekday and weekends
Social Provisions Scale (SPS)	It assesses the provisions of social relationships which reflect what we receive from relationships with other people
Two-way Social Support Scale (delivering-support items only)	The delivering-support items of this 2-way Social Support scale are made up of two subscales: amount of emotional support given to others and amount of instrumental support given to others
Women's Health History	This health history form asks about reproductive history and health including information about menopause, pregnancies and contraception use

Monitoring

Data management and quality control

All adverse events and serious adverse events will be carefully monitored, recorded and reported to the institutional Human Research and Protections Office and the Data Safety and Monitoring Board (DSMB) as necessary. Our DSMB meets approximately every 6 months to discuss study progress and safety. All adverse events will be reported in future manuscripts according to NHLBI guidelines.

Before the start of the study and data collection, all staff receive ethics training and certification of research training. In addition, to maintain consistency in data collection and intervention procedures over the course of the trial, all staff undergo annual on-site training certification.

There is an 8-week window to complete all baseline measures. Once a participant enrolls, all non-electronic

data are double entered into a REDCap database⁴⁸ in which appropriate permissions are controlled by a data management team. Before randomisation, all data are accounted for, checked for quality control purposes and archived on a secure server.

At postintervention, each assessment session will be repeated. These sessions are collected over a 4-week window opening exactly 2 weeks before their 12-month anniversary and closing 2 weeks after their 12-month anniversary. It is encouraged to complete session 1 and session 2 within 2 weeks of the intervention completion.

COVID-19 adjustments

The current protocol was designed to address actual and expected challenges to conducting interventional research during the COVID-19 pandemic. The principal goal was to preserve the ability to test the primary aims while also minimising data loss and participant attrition;



conserving financial and staff resources; mitigating risks and maximising safe research interactions between staff and participants; and, reducing bottlenecks in testing and enrolment deficits during research operations. The exercise intervention group will be offered the flexibility to engage in exercise either in the laboratory setting with our exercise trainers or to exercise remotely (or a combination depending on exposure, shut-downs, illness, need for reduced capacity in the exercise setting, etc). Remote monitoring of behaviour and exercise compliance will include weekly phone calls between participants and exercise trainers, distribution of videos and routines for participants to use, purchasing and mailing heart rate monitors to monitor exercise intensity, and frequent use (every 6 weeks) of actigraphy monitoring to capture activity patterns. We intend to be as accommodating as possible while carefully recording behaviours, adherence and compliance.

Limitations

Because of subject burden, MRI costs and other complications, we are not able to assess participants at multiple time points over the course of the 12-month interval. We recognise that multiple measurement points would provide a higher resolution for modelling trajectories of change and temporal precedence for determining causality. We also recognise the multivariate nature of the CVD data, neuroimaging data and questionnaires and will follow procedures to reduce the number of dimensions by aggregating variables according to correlated and theoretical constructs. We also recognise that participating in an exercise research study could lead to behavioural changes in the control group condition (eg, changes in the amount of PA), which could contaminate the interpretation of the comparison between the control and exercise groups. To account for possible contamination, we have included PA monitoring, every 6 weeks, using an ActiGraph device during the intervention period to examine whether the results vary as a function of the magnitude of change in PA for the control group. Finally, in developing the inclusion and exclusion criteria, we balanced goals about generalisability to a broad population while maintaining and ensuring safety of the participants. As such, all results should be interpreted in the context of the sample characteristics.

DISCUSSION

Cumulative epidemiological evidence indicates that physical inactivity confers risk for CVD, and, in turn, that PA can reduce CVD morbidity and mortality. The biological and behavioural mechanisms through which PA may reduce these risks, some of which may be regulated by the brain, are still unclear. Here we describe the design of an RCT to test whether aerobic exercise induces changes in brain circuits and to investigate how these changes associate with CVD risk. We will also examine how exercise alters stress physiology and positive and negative affect

and how these relate to both exercise-induced changes in brain circuits and CVD risk.

Recent work has shown the importance of brain circuits in risk for CVD,⁴⁹ but the present study has the unique opportunity to expand this knowledge to better elucidate causal mechanisms using an experimental manipulation. Identifying the biological pathways by which exercise influences the brain and peripheral physiology could lead to new approaches (pharmaceutical and non-pharmaceutical) that target particular pathways involved in disease onset and progression. The outcomes from this study have the potential to transform our understanding of the brain's role in transducing the effects of exercise on cardiovascular health, an effect with relevance to scientists and health professionals alike. In this study, the PA prescription aligns with globally recognised guidelines⁵⁰ so the effects observed are likely to be generalisable to a variety of widely used interventions, broadly informing efforts to improve both brain health and CVD risk.^{2,3} In sum, our trial will allow us to develop a more comprehensive and realistic model of the interrelationships between exercise, peripheral physiology, risk factors for CVD and brain plasticity.

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REFERENCES

- World Health Organization (WHO). n.d. Available: <https://www.who.int/>
- Lee I-M, Shiroma EJ, Lobelo F, *et al*. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *The Lancet* 2012;380:219–29.
- Blair SN, Kohl HW, Barlow CE, *et al*. Changes in physical fitness and all-cause mortality: A prospective study of healthy and unhealthy men. *JAMA* 1995;273:1093–8.
- Steinberg H, Jacovino C, Kitabchi AE. Look inside look AHEAD: why the glass is more than half-full. *Curr Diab Rep* 2014;14:500:1–6..
- Donnelly JE, Blair SN, Jakicic JM, *et al*. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009;41:459–71.
- Huang C-J, Webb HE, Zourdos MC, *et al*. Cardiovascular reactivity, stress, and physical activity. *Front Physiol* 2013;4:314.
- Nedeljković UD, Krstić NM, Varagić-Marković SL, *et al*. Quality of life and functional capacity one year after coronary artery bypass graft surgery. *Acta Chir Iugosl* 2011;58:81–6.
- Marquez DX, Aguiñaga S, Vásquez PM, *et al*. A systematic review of physical activity and quality of life and well-being. *Transl Behav Med* 2020;10:1098–109.
- Cherubini A, Lowenthal DT, Williams LS, *et al*. Physical activity and cardiovascular health in the elderly. *Aging Clin Exp Res* 1998;10:13–25.
- Lee D, Sui X, Artero EG, *et al*. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. *Circulation* 2011;124:2483–90.
- Piercy KL, Troiano RP, Ballard RM, *et al*. The physical activity guidelines for Americans. *JAMA* 2018;320:2020–8.
- Bull FC, Al-Ansari SS, Biddle S, *et al*. World health organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020;54:1451–62.
- Powell KE, King AC, Buchner DM, *et al*. The scientific foundation for the physical activity guidelines for Americans. *J Phys Act Health* 2018;16:1–11.
- Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. *Br J Sports Med* 2009;43:22–4.
- Prakash RS, Voss MW, Erickson KI, *et al*. Physical activity and cognitive vitality. *Annu Rev Psychol* 2015;66:769–97.
- Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiology of Aging* 2014;35:S20–8.
- Erickson KI, Donofry SD, Sewell KR, *et al*. Cognitive aging and the promise of physical activity. *Annu Rev Clin Psychol* 2022;18:417–42.
- Erickson KI, Prakash RS, Voss MW, *et al*. Brain-derived Neurotrophic factor is associated with age-related decline in hippocampal volume. *J Neurosci* 2010;30:5368–75.
- Stillman CM, Jakicic J, Rogers R, *et al*. Changes in cerebral perfusion following a 12-month exercise and diet intervention. *Psychophysiology* 2021;58. 10.1111/psyp.13589 Available: <https://onlinelibrary.wiley.com/doi/10.1111/psyp.13589>
- Erickson KI, Voss MW, Prakash RS, *et al*. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A* 2011;108:3017–22.
- Colcombe SJ, Erickson KI, Scalf PE, *et al*. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* 2006;61:1166–70.
- NHLBI, NIH. Health Topics, Available: <https://www.nhlbi.nih.gov/health>
- Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011;10:819–28.
- Crichton GE, Elias MF, Davey A, *et al*. Cardiovascular health and cognitive function: the Maine-Syracuse longitudinal study. *PLoS ONE* 2014;9:e89317.
- Kuller LH, Lopez OL, Mackey RH, *et al*. Subclinical cardiovascular disease and death, dementia, and coronary heart disease in patients 80+ years. *J Am Coll Cardiol* 2016;67:1013–22.
- Nagai M, Hoshida S, Ishikawa J, *et al*. Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. *J Hypertens* 2008;26:1636–41.
- Okonkwo OC, Schultz SA, Oh JM, *et al*. Physical activity attenuates age-related biomarker alterations in Preclinical AD. *Neurology* 2014;83:1753–60.
- Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev* 2006;30:730–48.
- Rovio S, Kåreholt I, Helkala E-L, *et al*. Leisure-time physical activity at Midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* 2005;4:705–11.
- Gianaros PJ, Wager TD. Brain-body pathways linking psychological stress and physical health. *Curr Dir Psychol Sci* 2015;24:313–21.
- Koban L, Gianaros PJ, Kober H, *et al*. The self in context: brain systems linking mental and physical health. *Nat Rev Neurosci* 2021;22:309–22.
- Kraynak TE, Marsland AL, Wager TD, *et al*. Functional Neuroanatomy of peripheral inflammatory physiology: A meta-analysis of human neuroimaging studies. *Neurosci Biobehav Rev* 2018;94:76–92.
- Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- Stillman CM, Jakicic J, Rogers R, *et al*. Changes in cerebral perfusion following a 12-Month exercise and diet intervention. *Psychophysiology* 2021;58. 10.1111/psyp.13589 Available: <https://onlinelibrary.wiley.com/doi/10.1111/psyp.13589>
- Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. *Psychol Sci* 2007;18:233–9.
- Murtagh EM, Nichols L, Mohammed MA, *et al*. The effect of walking on risk factors for cardiovascular disease: an updated systematic review and meta-analysis of randomised control trials. *Preventive Medicine* 2015;72:34–43.
- Sheu LK, Jennings JR, Gianaros PJ. Test-retest reliability of an fMRI paradigm for studies of cardiovascular reactivity. *Psychophysiol* 2012;49:873–84. 10.1111/j.1469-8986.2012.01382.x Available: <http://doi.wiley.com/10.1111/psyp.2012.49.issue-7>
- Gianaros PJ, Sheu LK, Uyar F, *et al*. A brain phenotype for Stressor-evoked blood pressure reactivity. *JAMA* 2017;6.
- Gianaros PJ, Rasero J, DuPont CM, *et al*. Multivariate brain activity while viewing and Reappraising affective scenes does not predict the multiyear progression of Preclinical Atherosclerosis in otherwise healthy Midlife adults. *Affec Sci* 2022;3:406–24.
- Scudder MR, Jennings JR, DuPont CM, *et al*. Dual impedance Cardiography: an inexpensive and reliable method to assess arterial stiffness. *Psychophysiology* 2021;58. 10.1111/psyp.13772 Available: <https://onlinelibrary.wiley.com/doi/10.1111/psyp.13772>
- Sherwood A, Allen MT, Fahrenberg J, *et al*. Methodological guidelines for impedance Cardiography. *Psychophysiology* 1990;27:1–23.
- Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol* 2008;4:1–32. 10.1146/annurev.clinpsy.3.022806.091415 Available: <https://www.annualreviews.org/toc/clinpsy/4/1>
- Kamarck TW, Schwartz JE, Shiffman S, *et al*. Psychosocial stress and cardiovascular risk: what is the role of daily experience *J Pers* 2005;73:1749–74.
- Balke B, Ware RW. An experimental study of physical fitness of air force personnel. *U S Armed Forces Med J* 1959;10:675–88.
- Borg GAV. Psychophysical bases of perceived exertion. *Med & Sci Sports Exercise* 1982;14:377.
- Edvardsen E, Hem E, Anderssen SA. End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: A cross-sectional study. *PLoS One* 2014;9:e85276.
- American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Lippincott williams & wilkins, 2013.
- Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (Redcap)—A Metadata-driven methodology and Workflow process for providing Translational research Informatics support. *J Biomed Inform* 2009;42:377–81.
- Relation between resting Amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Br Dent J* 2017;222.
- WHO. *Global recommendations on physical activity for health*. Geneva, Switzerland: World Health Organization Publications, 2010.
- Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* 1995;51:768–74. 10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1 Available: [http://doi.wiley.com/10.1002/1097-4679\(199511\)51:6<768::AID-JCLP2270510607>3.0.CO;2-K](http://doi.wiley.com/10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-K)
- McAuley E. The role of efficacy Cognitions in the prediction of exercise behavior in middle-aged adults. *J Behav Med* 1992;15:65–88.

- 53 Caprara GV, Barbaranelli C, Borgogni L, *et al.* "The "big five questionnaire": A new questionnaire to assess the five factor model". *Personality and Individual Differences* 1993;15:281–8.
- 54 Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med* 1997;4:92–100.
- 55 Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. *J Pers Soc Psychol* 1989;56:267–83.
- 56 Mendoza TR, Wang XS, Cleeland CS, *et al.* The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. *Cancer* 1999;85:1186–96.
- 57 Chapman LJ, Chapman JP. The measurement of handedness. *Brain Cogn* 1987;6:175–83.
- 58 Cohen S, Hoberman HM. Positive events and social supports as buffers of life change Stress1. *J Appl Social Psychol* 1983;13:99–125. 10.1111/j.1559-1816.1983.tb02325.x Available: <http://www.blackwell-synergy.com/toc/jasp/13/2>
- 59 Randler C. Validation of the full and reduced composite scale of Morningness. *Biological Rhythm Research* 2009;40:413–23.
- 60 Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Pers Soc Psychol* 2003;85:348–62.
- 61 McAuley E, Lox C, Duncan TE. Long-term maintenance of exercise, self-efficacy, and physiological change in older adults. *J Gerontol* 1993;48:218–24.
- 62 Cutrona C, Russel D. The provisions of social relationships and adaptation to stress. In: Jones W, Perlman D, eds. *Advances in Personal Relationships*. JAI Press, 1983: 37–67.
- 63 Cohen S, Mermelstein R, Kamarck T, *et al.* Measuring the functional components of social support. *Social Support: Theory, Research and Applications* 1985:73–94.
- 64 Lantz PM, House JS, Mero RP, *et al.* Stress, life events, and socioeconomic disparities in health: results from the Americans' changing lives study. *J Health Soc Behav* 2005;46:274–88.
- 65 Cochrane R, Robertson A. The life events inventory: A measure of the relative severity of psycho-social stressors. *J Psychosom Res* 1973;17:135–40.
- 66 Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from Neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the life orientation test. *J Pers Soc Psychol* 1994;67:1063–78.
- 67 Subar AF, Thompson FE, Kipnis V, *et al.* Comparative validation of the block, Willett, and National Cancer Institute food frequency questionnaires the eating at America's table study. *Am J Epidemiol* 2001;154:1089–99.
- 68 Thompson FE, Subar AF, Brown CC, *et al.* Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. *J Am Diet Assoc* 2002;102:212–25.
- 69 EGRP/DCCPS/NCI/NIH. Diet history questionnaire II (DHQ II) for U.S. and Canada. n.d. Available: <https://epi.grants.cancer.gov/dhq2/>
- 70 Mayne SL, Moore KA, Powell-Wiley TM, *et al.* Longitudinal associations of neighborhood crime and perceived safety with blood pressure: the multi-ethnic study of Atherosclerosis (MESA). *Am J Hypertens* 2018;31:1024–32.
- 71 Mujahid MS, Diez Roux AV, Morenoff JD, *et al.* Assessing the measurement properties of neighborhood scales: from Psychometrics to Ecometrics. *Am J Epidemiol* 2007;165:858–67.
- 72 MacKillop J, Anderson EJ. Further Psychometric validation of the mindful attention awareness scale (MAAS). *J Psychopathol Behav Assess* 2007;29:289–93.
- 73 Wójcicki TR, White SM, McAuley E. Assessing outcome expectations in older adults: the multidimensional outcome expectations for exercise scale. *J Gerontol B Psychol Sci Soc Sci* 2009;64:33–40.
- 74 Paffenbarger RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978;108:161–75.
- 75 Gillis MM, Haaga DAF, Ford GT. Normative values for the Beck anxiety inventory, fear questionnaire, Penn state worry questionnaire, and social Phobia and anxiety inventory. *Psychological Assessment* 1995;7:450–5.
- 76 Meyer TJ, Miller ML, Metzger RL, *et al.* Development and validation of the Penn state worry questionnaire. *Behav Res Ther* 1990;28:487–95.
- 77 Cohen S. Perceived stress in a probability sample of the United States. 1988.
- 78 Murrock CJ, Bekhet A, Zauszniewski JA. Psychometric evaluation of the physical activity enjoyment scale in adults with functional limitations. *Issues Ment Health Nurs* 2016;37:164–71.
- 79 Kendzierski D, DeCarlo KJ. Physical activity enjoyment scale: two validation studies. *J Sport Exerc Psychol* 1991;13:50–64.
- 80 Fox KR, Corbin CB. The physical self-perception profile: development and preliminary validation. *J Sport Exerc Psychol* 1989;11:408–30.
- 81 Buysse DJ, Reynolds CF 3rd, Monk TH, *et al.* The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- 82 Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–70.
- 83 Robins RW, Hendin HM, Trzesniewski KH. Measuring global self-esteem: construct validation of a single-item measure and the Rosenberg self-esteem scale. *Pers Soc Psychol Bull* 2001;27:151–61.
- 84 Chau JY, van der Ploeg HP, Dunn S, *et al.* A tool for measuring workers' sitting time by domain: the workforce sitting questionnaire. *Br J Sports Med* 2011;45:1216–22.