Heart-Brain Project

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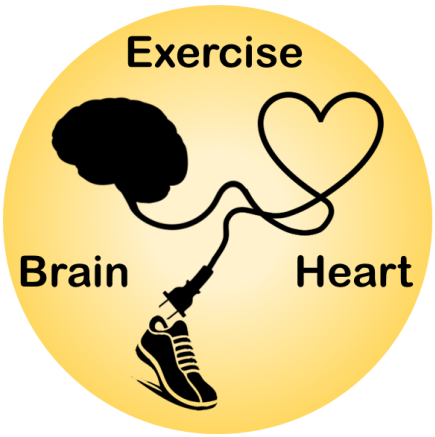
Study Protocol



University of Granada, Spain
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2. Trial summary

Official Title: Effects of Exercise on Brain Health in Patients with Coronary Heart Disease: the Heart-Brain Randomized Controlled Trial

Brief title: Exercise and Brain in Coronary Heart Disease (**Heart-Brain**)

ClinicalTrials.gov ID: NCT06214624

Study ID: 1776-N21

Brief Summary:
The Heart-Brain project is a randomized controlled trial designed to examine the effects of two different exercise programs of 12-week duration: 1) aerobic high intensity interval training (HIIT), and 2) aerobic HIIT plus resistance training, on brain health and other outcomes in coronary heart disease patients.

Keywords: Coronary heart disease, coronary artery disease, ischemic heart disease, exercise, HIIT, resistance training, brain, cognition, magnetic resonance imaging, cerebral blood flow.

Detailed summary:
Introduction: Patients with coronary heart disease (CHD) have higher risk of developing dementia, cognitive impairment, and mental disorders. There is, therefore, a need to identify effective and sustainable initiatives to improve their brain health, and in this context, physical exercise can play a major role. The overall goal of the Heart-Brain project is to investigate the effects of exercise on brain health outcomes in CHD patients.

Methods: This three-arm, single-blinded, randomized controlled trial will include 90 adults with CHD, aged 50-75 years old. Participants will be randomized into: 1) wait-list control group (n=30), participants in this group will be treated as usual outpatient Phase III, including periodic medical revisions and medication control, 2) high intensity interval training (HIIT) exercise program (n=30), and 3) HIIT plus resistance exercise program (n=30). All study outcomes will be assessed at baseline and at 12 weeks, after completing the intervention. The primary outcome of the study is to determine changes on cerebral blood flow assessed by magnetic resonance imaging (MRI), while secondary outcomes include different brain and cardiovascular health markers (i.e., brain structure and function with MRI, hemodynamics and cardiac function through echography, cognitive function, mental health, quality of life, cardiovascular risk factors, physical health, and blood, oral and gut biological markers).

Expected conclusions: The Heart-Brain project will shed light on how exercise can impact brain health in CHD patients, as well as the mechanisms linking exercise to heart and brain, such as changes in cerebral blood flow. The results of the Heart-Brain project will have important clinical implications helping to establish effective preventive strategies based on exercise for delaying cognitive decline in this high-risk population. Furthermore, it will pave the way for future targeted pharmaceutical therapies that mimic exercise effects

3. Scientific background - Trial rationale

Recent studies have shown that the incidence of cognitive impairment in patients with cardiovascular disease is markedly higher than that observed in age-matched healthy controls, supporting a nexus between the heart and the brain (1). Likewise, the prevalence of depression in cardiac patients is 4 times higher (20%) than in the general population (5%)(2). The most common types of cardiovascular diseases include CHD, heart failure, atrial fibrillation, peripheral artery disease, and cerebrovascular diseases such as stroke, and others less prevalent. Since stroke (death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain) is a cardiovascular disease that, by definition, directly damages the brain, the link between stroke and cognition is obvious and better understood. Therefore, focusing on non-stroke patients offers potential for high impact breakthroughs. Among the non-stroke cardiovascular diseases, we decided to focus on CHD, also named coronary artery disease or ischemic heart disease, since it is the most prevalent type of cardiovascular disease accounting for roughly 45% of cardiovascular disease cases and is a leading cause of not only mortality, but also of morbidity (condition of being diseased) and economic burden worldwide (3, 4). CHD consists in a narrowing or blockage of the coronary arteries (usually caused by atherosclerosis). Millions of people live nowadays with CHD and they are at a higher risk not only of cognitive impairment and dementia, as previously mentioned (1), but also of mental disorders such as depression or anxiety (2, 5). In this context, there is a need of identifying effective and sustainable initiatives able to attenuate the cognitive and mental health declines that have been observed to occur more pronouncedly in CHD patients. In this context, it is reasonable to think on exercise as a potential effective treatment. Mounting evidence supports that exercise has systemic and multi-organ positive effects in humans (6). In fact, exercise has been named as the *"Polypill"* due to its multiple health benefits (7, 8). Based on these foundations and on the extensive experience of our group on exercise in relation to cardiovascular and brain health, we have designed the Hearty-Brain project, a randomized controlled trial to investigate the effects of exercise on brain health outcomes in CHD patients.

A key physiological mechanism in the heart-brain interplay and the role of exercise:

Animal models have provided the first steps toward the understanding of the heart-brain connection by proposing potential mechanisms and opening new venues for research in humans(9-12). Compared to animal models, testing some of the proposed mechanisms in humans is more challenging; however, technological developments provide today new opportunities. After a comprehensive review of the existing evidence, we have selected **reduced cerebral blood flow** as a key mechanism explaining how CHD can accelerate cognitive decline and increase the risk of dementia and mental disorders, and how exercise could play an important role in increasing cerebral blood flow. In short, chronic cerebral hypoperfusion, **reduced cerebral blood flow**, limits the oxygen and nutrients delivered to the brain (10, 13, 14). The advances in neuroimaging techniques (particularly in magnetic resonance imaging – MRI) have recently proposed a method to simultaneously assess *in vivo* cerebral blood flow using the Arterial Spin Labelled (ALS-MRI) method and **cerebral vascularization** using magnetic resonance angiography (MRA)(15), which will provide unique and novel information about the connection of these two mechanisms with cognition

and mental health. The blood flow to the brain will be considered the main study variable (i.e. primary outcome) of this proposal since it is believed to be modifiable, and it is highly connected to the other key mechanisms listed below. It has been reported that exercise can increase cerebral blood flow(16) and brain vascularization/angiogenesis (i.e., growth of capillaries)(17), however, these findings are derived from observational evidence and animal studies mainly. These hypotheses need to be tested in randomized controlled trials in humans.

The role of cardiorespiratory fitness in heart-brain interplay:

Closely related to exercise is physical fitness, and it is of utmost importance to investigate the role of physical fitness, and particularly of **cardiorespiratory fitness** (the capacity of performing endurance exercise)(6) as a potential mediator of the effects of exercise on the heart-brain outcomes. A higher cardiorespiratory fitness has shown to be one of the most powerful predictors of survival(18), and has been proposed by the American Heart Association as a "clinical vital sign"(19). The principal investigator of this project, Dr. Ortega, has experience in this field and has made major contributions, as shown by his publications as first or last author in the top journals in the field of Cardiology, such as European Heart Journal (2019-JCR IF=22.7)(20, 21) or Circulation Research (2019-JCR IF =14.5)(22) and invited Editorials/Commentary in Nature Reviews Endocrinology (2019-JCR IF=28.8) and The Lancet Diabetes & Endocrinology (2019-JCR IF=25.3)(23, 24). The group has also experience concerning brain health outcomes. Dr. Ortega has recently led studies as principal investigator showing structural differences in the brain according to cardiorespiratory fitness levels (published in Neuroimage, No. 1 field of Neuroimaging)(25, 26). Concerning mental health, we have led a study showing that having a low cardiorespiratory fitness is associated with 4 times higher risk of having a severe and chronic psychiatric disease (Annals of Internal Medicine, 2019-JCR IF=21.3)(27). Collectively, all this evidence strongly supports that cardiorespiratory fitness, which can be effectively modified with exercise, can play a key role in the heart-brain mechanisms, and we plan therefore to investigate its role in this project.

4. Objectives

The overall objective is to investigate the effects of exercise on brain health outcomes in CHD patients. The primary objective is to examine the effect of high intensity interval training (HIIT) combined with resistance training (R) and HIIT compared to usual care on global and regional cerebral blood flow.

Secondary aims are to:

i. Examine the effect of HIIT+R and HIIT compared to usual care on cerebral vascularization.
ii. Examine the effect of HIIT+R and HIIT compared to usual care on executive function and general cognition.
iii. Examine the effect of HIIT+R and HIIT compared to usual care on cardiorespiratory fitness (treadmill time-to-exhaustion and VO_2peak).

5. Trial Design

A total of 90 adults with coronary heart disease (CHD), between 50-75 years old from Granada (Spain) will be enrolled in the RCT. Participants with CHD will be recruited from two public hospitals in Granada, Spain: the "Hospital Universitario Virgen de las Nieves" and the "Hospital Universitario San Cecilio". Recruitment started in May 2022, and it may extend until March 2024. Participants will be randomized into three groups, one control group and two different exercise intervention groups: 1) Wait-list control group (n=30), participants in this group will be treated as usual outpatient Phase III, which includes periodic medical revisions and medication control (this group will receive the supervised exercise program after the completion of the post assessments), 2) HIIT exercise program (n=30), and 3) HIIT plus resistance exercise program (n=30). These two exercise groups will undertake a 12-week supervised exercise program with the aim of evaluating the effects on cerebral blood flow (primary outcome), and different brain and cardiovascular health outcomes as secondary outcomes (i.e. brain structure and function with magnetic resonance imaging, hemodynamic and cardiac function through echography, cognitive function, mental health, quality of life, cardiovascular risk factors, physical and cardiorespiratory fitness, body composition, physical activity levels, and blood, oral and gut biological markers).
Eligible participants will receive written information and provide informed consent before participation. Randomization will occur on a rolling basis and only after the completion of all baseline assessments, through the REDCap Software (28). The trial protocol is in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #1776-N-21 on December 21st, 2021)

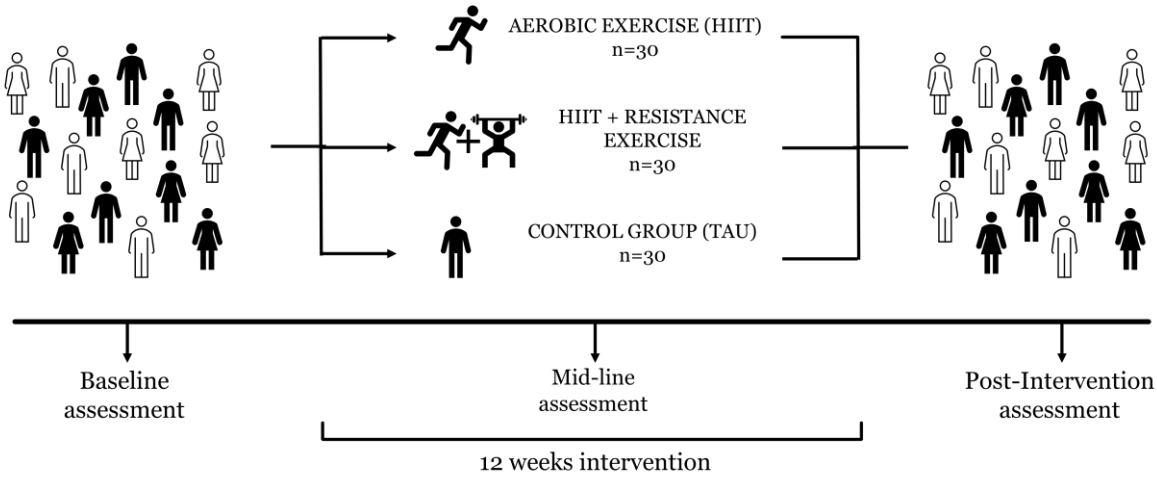

Figure 1. Overview of the Hearty-Brain Study.

6. Disease condition and selection of patients

This randomized controlled trial focuses on the impact of physical exercise on brain health of **coronary heart disease** (CHD) patients. CHD, also named coronary artery disease or ischemic

heart disease, consists in a narrowing or blockage of the coronary arteries (usually caused by atherosclerosis). CHD is the most prevalent type of cardiovascular disease and one of the leading causes of mortality and morbidity worldwide. Recent studies have shown that the incidence of cognitive impairment and dementia in these patients is markedly higher than that observed in age-matched healthy controls.

We plan to enroll 90 patients with CHD meeting the following eligibility criteria:

INCLUSION CRITERIA:

1. Men and women aged between 50 and 75 years old, both inclusive (*Contingency plan: increase the range to 40-75 if we have difficulties to get the study sample)
2. Must have stable coronary heart disease (phase III), proven by invasive coronary angiography or CT with at least one coronary lesion > 50%.
3. Able to speak and read fluent Spanish.
4. Live in Granada city or surrounding areas (able to come to evaluations and exercise program)
5. Living in community during the study (i.e. independent home, non-assisted living facilities)
6. Ejection fraction ≥ 45%.
7. Functional grade I-II according to the New York Heart Association (NYHA) scale.
8. Sinus rhythm.
9. Stable optimal medical treatment (3 or more drugs at the determined by a cardiologist).
10. Physically inactive, considering: 1) not meeting the WHO recommendations in both the aerobic and strength part, and 2) not to be participating in a planned and structured exercise program at least 3 days per week and for more than 3 months. Both conditions must be met to be included. Note: going for a walk will not be considered an exclusion reason.
11. Classified as cognitively normal according to Stics-m

EXCLUSION CRITERIA:

1. Used of assisted walking devices.
2. Acute coronary syndrome in the last year, coronary surgery, or percutaneous intervention in the last 6 months.
3. Treatment for any type of cancer in the last 2 years.
4. Severe hospitalization in the intensive care unit in the last 6 months.
5. Current psychiatric diagnosis (visit to psychiatrist and drug treatment prescription in the last year), including major depression and history of psychiatric illness (schizophrenia, bipolar disorder, hallucinations).
6. Grade III obesity.
7. Diagnosis of neurological or cerebrovascular disorder (e.g. stroke).
8. Medical contraindication for inclusion in an exercise program.
9. Diabetes with uncontrolled glycemia.
10. Resting blood pressure > 180/110.
11. Chest pain with exertion or changes in the ST segment suggestive of severe ischemia during ergometry
12. Severe inducible ischemia
13. Functional capacity in ergometry (<5 METS).

14. Obstructive left main artery disease (significant disease > 50%)
15. Unstable angina
16. Uncontrolled cardiac arrhythmia
17. Presence of metal implants (e.g., pacemaker or implantable cardioverter-defibrillator-ICD) not compatible with MRI (reported during the phone screening)
18. Paroxysmal or persistent atrial fibrillation with episodes in the last 6 months.
19. Moderate to severe pulmonary hypertension.
20. Acute endocarditis, myocarditis, or pericarditis.
21. Moderate to severe valve disease (grade 3-4)
22. Acute pulmonary embolism, or deep vein thrombosis.
23. Aortic dissection
24. High-grade heart block or complete left bundle branch block or altered basal electrocardiogram with difficulties to interpret in exercise testing.
25. Hypertrophic obstructive cardiomyopathy.
26. Retinopathy.
27. Severe autonomic or peripheral neuropathy.
28. Acute systemic illness or fever.
29. Acute or chronic renal failure (estimated glomerular filtration rate < 30 mL/min)
30. Pulmonary fibrosis or interstitial disease (respiratory failure or severe COPD confirmed by pneumological study).
31. Recent treatment for alcohol or substance abuse.
32. Claustrophobia.
33. Any surgery or medical intervention planned during the study period.
34. Plans to participate or current participation in other studies that might interferes with this study.
35. Current pregnancy or intention to get pregnant during the study period.

7. Screening and recruitment

Screening will be based on patients that are defined as eligible by the clinical and research team.
Screening is performed in three phases:

1) Screening based on the eligibility criteria by the clinicians of the research team.
2) Screening based on phone call by the research team.
3) Screening during the baseline assessments using the cardiopulmonary exercise test and cardiac ultrasound.

Participants meeting the eligibility criteria will be recruited from two public hospitals in Granada, Spain: the “Hospital Universitario Virgen de las Nieves” and the “Hospital Universitario San Cecilio”. Recruitment started in May 2022, and it may extend until March 2024. Information necessary for the CONSORT flow diagram will be collected. For the enrollment phase, we will note the number of patients that were assessed for eligibility by the research team, the number of excluded patients (plus reason for exclusion), and the number of randomized participants. For the allocation, the number of participants allocated to the

intervention, and the number of participants who received or did not receive the intervention (plus reasons) will be noted. For follow-up, the number of participants who were lost to follow-up and the number who discontinued the intervention (plus reasons) were counted. Finally, the number of participants that were included in the analyses using the intention-to-treat and per-protocol databases will be described together with the reasons for exclusion.

8. Outcome Measures

Primary Outcome Measures:

1. Primary Outcome: Change in cerebral blood flow (Baseline and 12 weeks)
The main outcome is the change in cerebral blood flow from baseline to 12 weeks. Cerebral blood flow (mL/100 g/min) will be measured using the magnetic resonance imaging technique of TGSE-pCASL (turbo gradient spin echo-pseudo continuous arterial spin labeling). We will analyze both the global cerebral blood flow and the regional cerebral blood flow, as determined by voxel-wise analysis to measure local perfusion.

Secondary Outcome Measures:

2. Change cerebral vascularization (Baseline and 12 weeks)
Cerebral vascularization will be measured using the magnetic resonance angiography TOF (Time-of-flight angiography)

3. Change in executive function and general cognition (Baseline and 12 weeks)
A comprehensive neuropsychological battery will assess several domains of executive function: working memory, cognitive flexibility and inhibitory control, and an executive function score will be computed and used as main behavioral outcome. Additionally, the general cognition will be assessed by the MOCA (Montreal Cognitive Assessment) test.

4. Change in cardiorespiratory fitness (Baseline and 12 weeks). Cardiorespiratory fitness will be assessed by a cardiorespiratory exercise test in a treadmill measuring gas exchange (treadmill time-to-exhaustion and VO2peak)

Other Outcome Measures:

5. Change in blood brain barrier (BBB) permeability (Baseline and 12 weeks)
BBB permeability will be operationally measured by using a recently developed neuroimaging technique that measures water exchange across the BBB using 3D diffusion-prepared arterial spin labelled perfusion MRI.

6. Change in brain morphology (Baseline and 12 weeks)
MRI (magnetic resonance imaging) will measure brain morphology including volume, area, cortical thickness, and shapes by a T1-weighted MPRAGE structural sequence.

7. Change in white matter structure (Baseline and 12 weeks)

MRI (magnetic resonance imaging) will measure white matter structure and lesions by diffusion weighted acquisition sequence.

8. Change in brain function (Baseline and 12 weeks)
MRI (magnetic resonance imaging) will measure brain function during resting state. Measures of brain activity and brain connectivity will be calculated.

9. Change in blood-based neurology biomarkers (Baseline and 12 weeks)
Blood samples will be used to determine plasmatic concentration of peripheral neurology biomarkers including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and cathepsin B (CTSB), as well as novel neurodegenerative biomarkers based on new evidence up to the time of the analysis.

10. Change in saliva-based neurology biomarkers (Baseline and 12 weeks)
Saliva samples will be used to determine concentration of peripheral neurology biomarkers including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and cathepsin B (CTSB), as well as novel neurodegenerative biomarkers based on new evidence up to the time of the analysis.

11. Hemodynamic vascular changes (Baseline and 12 weeks)
Hemodynamic vascular parameters will be measured using ultrasound echography (i.e. carotid intima–media thickness).

12. Hemodynamic cardiac changes (Baseline and 12 weeks)
Cardiac parameters will be measured using ultrasound echography (i.e. ejection fraction, cardiac volumes, and cardiac output)

13. Hemodynamic transcranial changes (Baseline and 12 weeks)
Hemodynamic transcranial parameters will be measured using ultrasound echography (i.e. Doppler diastolic-systolic velocity).

14. Change in general muscular strength (Baseline and 12 weeks)
The maximum isometric strength of the hand and forearm muscles measured with the handgrip test (Kg) will be used to determine general muscular strength.

15. Change in lower body muscular strength (Baseline and 12 weeks)
Muscular strength in lower body will be assessed using the chair stand test (number of repetitions).

16. Change in upper body muscular strength (Baseline and 12 weeks)
Muscular strength in upper body will be assessed using the arm curl test (number of repetitions).

17. Change in physical function (Baseline and 12 weeks)

Senior Fitness Test (including the 6-min walking test) will assess overall physical functioning and z-scores will be calculated.

18. Change in depression (Baseline and 12 weeks)
Depressive symptoms will be assessed using the Global Deterioration Scale, the Health Survey Short Form (SF-36) and the Hospital Anxiety and Depression Scale.

19. Change in anxiety (Baseline and 12 weeks)
Anxiety will be assessed using the Health Survey Short Form (SF-36) and the Hospital Anxiety and Depression Scale.

20. Change in stress outcomes (Baseline and 12 weeks)
Stress outcomes will be assessed using the Perceived Stress Scale.

21. Change in loneliness (Baseline and 12 weeks)
Loneliness will be assessed using the UCLA Loneliness Scale.

22. Change in self-esteem outcomes (Baseline and 12 weeks)
Self-esteem will be assessed using the Rosenberg Self-Esteem Scale.

23. Change in social support outcomes (Baseline and 12 weeks)
Social support will be assessed using the Social Provisions Scale.

24. Change in health-related quality of life (Baseline and 12 weeks)
Global, physical, and mental health-related quality of life will be self-reported using the Health Survey Short Form (SF-36), in which higher scores means a better health-related quality of life.

25. Change in physical activity (Baseline, 6 and 12 weeks)
Physical activity will be measured using the accelerometer Axivity AX, and a self-reported questionnaire based on the Global Physical Activity Questionnaire.

26. Change in sedentary behaviors (Baseline, 6 and 12 weeks)
Sedentary behaviors will be measured using the accelerometer Axivity AX, and a self-reported questionnaire based on the Global Physical Activity Questionnaire.

27. Change in sleep quality (Baseline, 6 and 12 weeks)
Sleep quality will be measured using the accelerometer Axivity AX, and using and using a self-reported questionnaire.
28. Change in diet behaviors (Baseline, 6 and 12 weeks)
Diet behaviors will be self-reported using the 14-item Questionnaire of Mediterranean Diet Adherence (PREDIMED-14), and a self-reported question for supplements intake.

29. Change in body mass index and body composition (Baseline and 12 weeks)

Body mass index (BMI, kg/m^2) will be computed from height and weight measured by SECA instruments, and body composition will be assessed using a dual-energy x-ray absorptiometer (DXA) and a TANITA's Bioelectrical Impedance Analysis.

30. Change in lean mass (Baseline and 12 weeks)
Lean mass (kg) will be assessed using a dual-energy x-ray absorptiometer (DXA) and a TANITA's Bioelectrical Impedance Analysis.

31. Change in fat mass (Baseline and 12 weeks)
Fat mass (kg) will be assessed using a dual-energy x-ray absorptiometer (DXA) and a TANITA's Bioelectrical Impedance Analysis.

32. Change in bone mineral content and density (Baseline and 12 weeks)
Bone mineral content and density (z-score) will be assessed using a dual-energy x-ray absorptiometer (DXA).

33. Change in blood pressure (Baseline and 12 weeks)
Systolic and diastolic blood pressure will be assessed by a blood pressure monitor. Central blood pressure will be also analyzed using the SphygmoCor XCEL

34. Change in arterial stiffness (Baseline and 12 weeks)
Arterial stiffness will be assessed using the pulse wave analysis and pulse wave velocity determined by the SphygmoCor XCEL

35. Change in blood-based inflammatory biomarkers (Baseline and 12 weeks)
Blood samples will be used to determine plasmatic concentrations of inflammatory peripheral biomarkers including tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1beta), glucose, insulin, HDL and LDL cholesterol.

36. Change in saliva-based inflammatory biomarkers (Baseline and 12 weeks)
Saliva samples will be used to determine saliva concentrations of inflammatory peripheral biomarkers including tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1beta)

37. Change in blood-based cardiovascular biomarkers (Baseline and 12 weeks)
Blood samples will be used to determine plasmatic concentrations of cardiovascular peripheral biomarkers including glucose, insulin, HDL and LDL cholesterol.

38. Change in saliva-based cardiovascular biomarkers (Baseline and 12 weeks)
Saliva samples will be used to determine plasmatic concentrations of cardiovascular peripheral biomarkers including glucose, insulin, HDL and LDL cholesterol.

39. Change in epigenetics (Baseline and 12 weeks)
Blood samples will be stored for epigenetic analyses.

40. Change in gene expression (Baseline and 12 weeks)
Blood samples will be stored for genetic analyses, including APOE and BDNF genotypes.

41. Change in oral and gut microbiota (Baseline and 12 weeks)
Saliva and fecal samples will be used to determine oral and gut microbiota including the most representative phyla (i.e., firmicutes, bacteroidetes, and proteobacteria)

9. Sample calculations and statistical analysis

INCLUDE HERE THE SAMPLE CALCULATION

Shortly, the intervention effects will be tested using constrained baseline mixed models (i.e. adjusting for baseline of the outcome studied) for the study outcomes using an intention-to-treat approach as primary analysis. Per-protocol analyses with those participants attending 70% or more of the exercise sessions offered will also be reported. A detailed Statistical Analysis Plan has been developed in a separate document that will be available https://clinicaltrials.gov/study/NCT06214624.

10. Treatments / Interventions

- Aerobic High Intensity Interval Training (HIIT). 12-week duration, 3 times/week. This consists of a 4x4 HIIT (preferably in treadmill), 4 intervals of 4 min at high intensity (85-95% HRmax) and 3 intervals of 3 min of active resting at ~70% HRmax in between. All sessions including 10 min of warming-up and 10 min of cooling down, resulting in 45 min sessions. The first 2 weeks will progress from moderate-intensity training to HIIT for a better adaptation and acceptability of the program.

- Aerobic High Intensity Interval Training plus resistance training (HIIT + R). 12-week duration, 3 times/week. The aerobic part consists of a 3x4 HIIT (preferably in treadmill), 3 intervals of 4 min at high intensity (85-95% HRmax) and 2 intervals of 3 min of active resting (~70% HRmax) in between. The resistance part consists of 2 series of an 8-exercise circuit (combination of upper and lower body exercises using elastic bands and body weight) with a ratio of 20 sec of effort - 40 sec of resting. Sessions will have 5 min of warming up in the treadmill and 5 min of cooling down walking in the gym, comprising a total of 45 min sessions.

- Usual Care / Wait-list control group. The control group (as well as the 2 intervention groups) will be treated as usual in outpatient Phase III, which in Spain includes periodic medical revisions and medication control. In addition, for the control group, we will apply the wait-list strategy providing the supervised exercise program once all data collection for pre- and post-intervention assessment points have been finished.

The HIIT program and the HIIT part of the combined program have been designed based on the guidelines for the delivery and monitoring of HIIT in clinical populations (29) and meet the recommendations of the WHO guidelines in the aerobic part, as it surpasses the minimum of 75 minutes of vigorous intensity or 150 minutes of moderate intensity per week or a combination of them (30). The combined HIIT+resistance program meets the WHO

recommendations on both, the aerobic and the strength part, as it has three sessions of strengthen per week when WHO guidelines recommend at least two. Both exercise programs, has been formulated to provide an isocaloric workload (same energy expenditure) in terms of intensity and duration (See METs estimation per session).

Both training programs are individually tailored. Exercise prescription, monitoring and decisions for progression will be based on the percentage of the peak heart rate (HRpeak) and the rate of perceived exertion (RPE). Furthermore, blood pressure and symptoms will be monitored before, during and after the sessions. HRpeak will be determined in a cardiopulmonary exercise test with ECG and gas exchange analyzer, performed before the intervention, which will also serve as initial clinical assessment and as a cardiorespiratory fitness indicator. Participants who are taking beta-blocker medications are expected to show lower HR ranges (29). Thus, while the HRpeak will be used as a reference for exercise intensity prescription, participants will be encouraged to learn and use RPE (31-33), for cases of discordance between HR and RPE targets (29). In addition to HR and RPE, the judge of the trainers will be last criteria for intensity adaptations, particularly in the strength training, where RPE might be more difficult to identify by unexperienced participants.

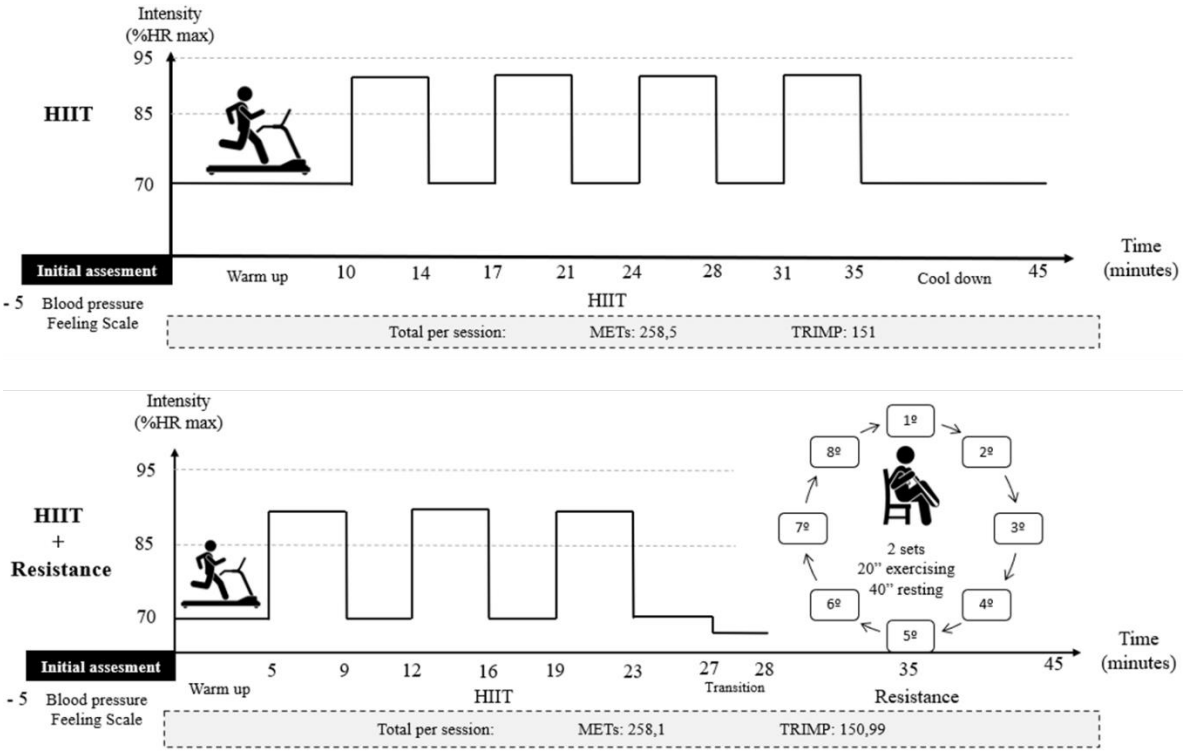

Figure 2. Details of the session structure of the HIIT-based (above) and the HIIT + Resistance-based (below) exercise programs.

11. Adherence, attendance, and compliance

Since the term adherence has been used with different meanings in the literature, in our study protocol and statistical plan, we will refer to two concepts more unequivocally used, attendance and compliance. Attendance will be defined as % of sessions attended by the participant (recorded by the trainers) divided by the actual number of exercise sessions offered (12 weeks x 3 sessions / week = 36, yet there will be slight variation among the study waves due to

holidays or logistic reasons). Compliance is the % of sessions in which the amount of time (HIIT+R 4.5 min; HIIT 6.5 min) in the target heart rate intensity is reached divided by the number of exercise sessions with valid data (e.g. sessions with technical issues of the heart rate bands are not considered) and excluding the familiarization phase (i.e. first two weeks of the exercise intervention). The amount of time (HIIT+R 4.5 min; HIIT 6.5 min) in the target heart rate intensity is based on the exercise protocol and the Guidelines for HIIT Prescription and Monitoring in clinical populations (29): for the first high intensity interval, allow the entire 4-minute period to reach the HR target zone. For subsequent high intensity intervals (i.e. 2nd, 3rd, and/or 4th), allow 2-minutes (halfway) to reach the HR target zone.

All protocol deviations made to the protocol (e.g. change in pre-defined inclusion/exclusion criteria, baseline and post assessments, data cleaning/processing) will be reported and described.

12. Safety and adverse events

Despite HIIT has been shown to be low risk in patients with CHD (34, 35) the safety of the participants is one of the priorities of the study:
The center is located in the Hospital area next to the emergency's unit (200 meters) and the ambulances unit (600 meters). A trained allied health professional (nurse or physician) will be always present in the center during the training sessions to guarantee the safety in case of an adverse event. The center has a full equipped trolley with first aids kit and automatic defibrillator and has get the Andalusian Certification of "Cardioprotected Center" (Decreto 22/2012 of February 14th). Furthermore, all the project team will receive specific training courses in cardiopulmonary resuscitation and use of defibrillation.
As mentioned above a cardiopulmonary exercise test, as well as a cardiac and vascular echography, are performed before the intervention and will serve as clinical assessment to confirm the participants do not have any risk to perform the exercise interventions. Once enrolled, participants will receive regular medical monitoring by the specialized cardiologists involved in the project.
In case of adverse event, we will follow the protocol recommended by the Spanish Council of cardiopulmonary resuscitation (CERCP).
The number and reasons of adverse events (e.g. falls, injuries, musculoskeletal problems, major cardiovascular disease events, and any other events potentially related to the implementation of the trial protocol) at each time point will be collected, reported, and described separately for each study arm. No formal statistical testing will be undertaken. For each adverse event that occurs, it will be clinically ascertained whether the event was due to exercise in the corresponding study arm. A cardiologist from the project team (Eduardo Moreno) with experience in previous clinical trials in adverse event algorithms (e.g. Liverpool Causality Assessment Tool) will be in charge of recording the adverse event (using the Common Terminology Criteria for Adverse Events (CTCAE)) after discussion and consensus with the rest of cardiologist involved in the project.

13. Ethics and legal issues

The trial protocol is in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #1776-N-21 on December 21st, 2021).
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