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Cardiovascular and functional adaptations, health-related outcomes and safety of different intensities of community-based exercise in older women under socioeconomic vulnerability: The COmmunity-Based EXercise in OLD age (COBEX-OLD) randomized clinical trial protocol

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Method Article

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ABSTRACT

Background: Older women under socioeconomic vulnerability are at high risk of several poor health-related outcomes, including cardiovascular diseases and frailty. Physical exercise is a well-established tool to counteract numerous age-related disorders, and community-based exercise programs (CBEP) may be an effective strategy to reduce some barriers to exercise in people experiencing socioeconomic vulnerability. However, most studies on CBEP have lacked adequate methodological designs, and have assessed only a few risk factors and/or physical fitness parameters.

Purpose: To investigate the effects of CBEP and its intensity on cardiovascular health, cardiovascular and physical functional adaptations, underlying physiological mechanisms and safety of the exercise program in older women under socioeconomic vulnerability.

Methods: One hundred and forty-one older women will undergo assessments of cardiovascular health, arterial and venous hemodynamic function, physiological parameters underlying cardiovascular health, physical functional capacity, quality of life and mental health markers. Participants will then be randomized to high-intensity interval training associated with resistance training (HIIT+RT, n=47), moderate-intensity continuous training associated with RT (MICT+RT, n=47) or control (n=47) groups and will be reevaluated after six and 12 months of follow-up. The safety of CBEPs will be assessed throughout the follow-up. CBEPs will consist of two weekly sessions that will include 5 min of warm-up, 20 to 50 min (progressive volume throughout the session) of specific training (HIIT+RT or MICT+RT) and a 5 min cool-down.

Discussion: The findings of the present study may help optimize the exercise prescription to improve cardiovascular health and functional capacity in older women under socioeconomic vulnerability.

Clinical trial registration: RBR-7n2srw8

Keywords: aging; arterial stiffness; cardiometabolic health; high-intensity interval training; venous insufficiency; women's health

INTRODUCTION

Population aging is a global reality. There were nearly 1.1 billion older adults worldwide in 2022 (13.7% of the population) [1], and projections indicate that the number of older adults will double by 2050 (2.1 billion, 21.6% of the population) and triple by 2100 (3.1 billion, 29.8% of the population) [2]. This demographic shift poses significant public health challenges, because the age-related physiological and behavioral changes result in increased risk of non-communicable chronic diseases, and impairments on physical functional performance and quality of life [3–5]. Socioeconomic status also affects numerous health-related outcomes across all age groups [6]. For example, the incidence of cardiovascular disease (CVD), the leading cause of death worldwide, was 68% higher in individuals with low socioeconomic status [7]. In the same study, the risk of all-cause and CVD mortality during five years of follow-up was 123% and 436% higher, respectively, in individuals with low socioeconomic status [7]. Thus, strategies to mitigate or reverse age-related physiological, functional, and psychosocial changes are crucial for promoting health in older adults, particularly those under socioeconomic vulnerability.

Regular physical exercise is a well-established tool to counteract numerous age-related disorders, [3,8] and is inversely associated with CVD incidence and mortality [5], as well as its risk factors [3,8]. However, adherence to exercise programs is very low, particularly among older adults, women, individuals with low socioeconomic status, and those with CVD risk factors [9,10]. Community-based exercise programs (CBEP) are structured group exercise programs designed to promote regular physical activity in the community [11]. The lower need for financial, human, and material resources, compared to individualized exercise programs, makes CBEP a potential strategy to reduce barriers to exercise for individuals with low socioeconomic status [11]. Additionally, a large number of individuals can simultaneously attend a CBEP session [11]. Furthermore, older adults' adherence to CBEP appears to be higher than to individualized exercise programs (~69% *vs*. ~50%) [12].

Positive effects of CBEP in older adults include improvements on physical fitness, [11,13,14] CVD risk factors [11,14,15], balance and fall risk [16]. However, most previous studies had short follow-up periods [11,15], or only investigated the effects of moderate-intensity multicomponent exercise programs [13,14,16]. Moreover, the benefits of exercise for older adults may be modulated by intensity [11,17] and modality [11,18]. For example, exercise programs that include high-intensity interval training (HIIT) appear to be more

effective for some CVD outcomes than programs that only include moderate-intensity continuous training (MICT) [11,17,19]. Accordingly, a previous study by our group assessed the effect of CBEP intensity and modality in older women with low socioeconomic status and showed that HIIT combined with resistance training (HIIT+RT) was superior to MICT combined with RT (MICT+RT) and RT alone for improving cardiovascular parameters [19]. Indeed, HIIT+RT was also superior for maintaining cardiovascular and functional improvements after three months of CBEP cessation [19].

However, the cardiovascular variables investigated in our previous study were limited to blood pressure (BP) and arterial stiffness [19]. Although both variables are recognized as independent risk factors for CVD events and mortality [20,21], the concept of cardiovascular health is much broader, including BP and seven other metrics of cardiovascular health [22]. These eight metrics, when at optimal levels, are associated with greater CVD-free survival, total longevity, and quality of life [22], including in older women [23]. On the other hand, to our knowledge, the effect of CBEP on cardiovascular health in older women under socioeconomic vulnerability is unknown. Studies in this area are of utmost importance, given that the association between socioeconomic vulnerability and worse cardiovascular health is stronger in women than in men [24]. Moreover, cardiovascular health has shown a bimodal distribution, with some population segments showing modest improvements, while groups under socioeconomic vulnerability show worsening trends [22,25]. In this context, if the previous superior benefit of HIIT+RT is confirmed and extended to other cardiovascular health parameters, it could have a significant impact on the health of this high-risk population. It could also reduce the burden on public health, given the low-cost potential of this CBEP [19].

It is worth noting that the cardiovascular benefits of CBEP may not be limited to improvements in traditional CVD risk factors associated with arterial diseases (e.g., coronary artery disease, cerebrovascular disease, peripheral artery disease, hypertension, etc.). For example, lower-limb chronic venous insufficiency is a highly prevalent disorder in older adults that is associated not only with negative impacts on health and quality of life but also with economic burdens on public health [26]. Strategies for the prevention, management, and treatment of lower-limb chronic venous insufficiency are particularly welcome for older women under socioeconomic vulnerability, given that older age, female sex, and

socioeconomic vulnerability are well-established risk factors for its development [27–29]. Indeed, socioeconomic vulnerability is one of the main predictors of its severity [28,29].

Regular exercise is a recommended intervention for individuals with chronic venous insufficiency, particularly those with venous ulcers [26,30]. However, the quality of evidence is low, and the benefits are generally related to ulcers (e.g., wound area, recurrence, and healing time) or quality of life [26,30]. Therefore, it has been recommended to carry out studies on the effect of different exercise programs on standardized venous insufficiency outcomes in both individuals with and without venous insufficiency. [26] Such investigation is particularly welcome in older women under socioeconomic vulnerability, given their higher risk for the development and worsening of venous insufficiency [27–29]. Mainly if comparing the effects of exercise programs of different intensities, as endothelial function and vascular remodeling are important mechanisms underlying the development and treatment of venous insufficiency [31], which are modulated by exercise and its intensity [32].

Finally, previous studies on CBEP or HIIT lack adequate methodological designs (e.g., sample size, follow-up duration, appropriate control groups, intention-to-treat analysis, etc.), [33] safety/tolerance analysis [34], and investigation of their effects on physiological mechanisms underlying cardiovascular health or venous insufficiency (e.g., cardiac autonomic activity, endothelial function, redox status, etc.) [32,35,36]. In this context, studies investigating the long-term effects of different CBEP on cardiovascular health and risk factors in older adults under socioeconomic vulnerability are required, given that CVDs are the leading cause of morbidity and mortality in older adults [5], with even higher prevalence in those with low socioeconomic status [7]. Such studies could aid in the development of more effective guidelines for promoting cardiovascular health in this population.

Thus, our purpose is to investigate, in older women under socioeconomic vulnerability, the effect of 12 months of community-based HIIT+RT *vs*. MICT+RT on: (i) cardiovascular health, (ii) arterial and venous hemodynamic function; (iii) physiological mechanisms underlying cardiovascular health and hemodynamic function; (iv) physical functional performance, quality of life, and mental health markers; and (v) adverse events associated with exercise sessions. Our hypotheses are: (i) HIIT+RT will be more effective than MICT+RT for improving cardiovascular health, arterial and venous hemodynamic parameters, and the mechanisms involved in their control; (ii) both CBEP will be similarly effective for

improving physical functional performance, quality of life, and mental health markers; and (iii) the occurrence of exercise-related adverse events will be minimal and similar between the programs.

METHODS

Population and study design

The present research will be a prospective, randomized, single-blind study evaluating the effect of one year of community-based HIIT+RT *vs*. MICT+RT in older women under socioeconomic vulnerability (Brazilian Registry of Clinical Trials Identifier: RBR-7n2srw8). This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations [37], and the study findings will be reported in line with CONSORT guidance [38]. The participants will be older women enrolled in the Service of Coexistence and Strengthening of Bonds for Older Adults, linked to the Municipal Department of Social Welfare of the Municipality of Bauru [39]. To be eligible for this service, older women must be registered in the government Single Registry for Social Programs (CadÚnico) and referred by the reference team of the Comprehensive Family Care Service at one of the Social Assistance Reference Centers in the municipality. [39] Inclusion criteria for participation in the study will include: (i) age ≥ 60 years; (ii) no participation in structured exercise programs during the three months prior to the study enrollment; (iii) absence of uncontrolled CVD or metabolic diseases; (iv) absence of musculoskeletal, neurological, or pulmonary disorders that impair safe exercise participation; and (v) absence of active venous ulcers. The last three inclusion criteria will be assessed following the recommendations of Brazilian Society of Exercise and Sports Medicine and Brazilian Society of Cardiology [40].

At least 141 volunteers meeting the inclusion criteria will be included in the study. They will undergo assessments of cardiovascular health, arterial and venous hemodynamic function, physiological parameters related to cardiovascular health, physical functional performance, health-related quality of life (HRQL), and mental health markers. Participants will then be randomized into HIIT+RT (n = 47), MICT+RT (n = 47), or control (n = 47) groups. Randomization will be in clusters, with at least two clusters per group. After randomization, participants will undergo CBEP (HIIT+RT or MICT+RT) or control follow-up and will be reassessed after six and 12 months (Figure 1). All assessments will be conducted in

the morning by an experienced evaluator blinded to the participant's group allocation, in a temperature-controlled environment between 21 and 24 °C (except for the six-minute walk test (6MWT), which will be conducted at room temperature). The safety of the exercise programs will also be assessed using a structured questionnaire on the occurrence of acute and late adverse events, which will be administered throughout the follow-up period. Participants will be informed about all the procedures and objectives of the research, and will sign the informed consent form prior to their inclusion in the study.

The primary outcomes will be cardiovascular health, and arterial and venous hemodynamic function. Secondary outcomes will be physiological mechanisms underlying cardiovascular health and hemodynamic function, physical functional performance, HRQL, mental health markers, and adverse events associated with exercise sessions. The sample size was estimated following recommendations for sample size calculation in randomized clinical trials [41]. Given the absence of previous clinical studies evaluating the effect of exercise interventions on the cardiovascular health index investigated, the primary outcomes carotid-femoral pulse wave velocity (cfPWV) endothelial function (flow-mediated dilation (FMD)) and heart rate variability (HRV) were used for a priori estimation of the sample size. The sample size of 141 participants (47 in each group) was estimated based on previous studies [19,42,43], using the GPower® software (a priori power analysis for two-way repeated measures analysis of variance (ANOVA)), for a type I error of 0.05, power of 0.95, correlation between repeated measures of 0.5 and unassumed sphericity ($\epsilon = 0.5$). For cfPWV, the sample size was estimated considering the net effect between groups (HIIT+RT – MICT+RT), based on the reference study that reported η^2 0.126 (f=0.38) [19], resulting in 34 participants per group. For HRV, the effect size between groups in changes (Δ) in the high-frequency (HF) band was derived from Table 3 of the study by Sant'Ana et al. [42], which described paired effects of 0.50 (TC) and 1.53 (TI) after 32 sessions. Converting this contrast to a net effect between groups resulted in f=0.365 for the group × time interaction, estimating 36 participants per group. For FMD (%), we used as a reference the study by He et al. and colleagues [43], conducted in postmenopausal women, which observed a significant time × group interaction ($F_{2,32}$=4.421; p=0.02), with η^2=0.216, corresponding to an f=0.526, resulting in 18 participants per group. Considering an estimated sample loss of 30% during follow-up, the total sample size was adjusted to 47 participants per group (141 participants in total), in order to ensure statistical power in all three outcomes.

To ensure the study maintains adequate statistical power and addresses potential attrition or variability in outcomes, we will perform a pre-specified sample size adjustment plan. An interim analysis will be conducted after 50% of participants have completed the six-month follow-up to assess key parameters (i.e., effect size, variability, and dropout rates). If the observed effect size is smaller than initially assumed, or if variability or dropout rate are higher than expected, the sample size will be recalculated using the updated parameters (maintaining type I error, power and sphericity). The interim analysis will be performed by an independent statistician blinded to group allocation, and adjustments will be approved by the data monitoring committee.

Clinical and anthropometric assessment

Participants will undergo clinical evaluation and anamnesis, following the recommendations of the Brazilian Society of Exercise and Sports Medicine and the Brazilian Society of Cardiology, [40] to assess eligibility for participation in the study, general health status and medication use. Participants will be asked about sociodemographic characteristics, personal and family history of chronic diseases (diabetes, hypertension, dyslipidemia, cardiac conditions, and neoplasms), medication use, substance and dietary supplement consumption, previous adverse health events related to physical activity/exercise (fainting, chest pain, dizziness, nausea, and vomiting), and musculoskeletal/osteoarticular complaints and limitations. Body mass, height, body mass index (BMI), and waist circumference will be measured on a separate day from the clinical evaluation, in the morning between 8:00 and 9:00 AM. Body mass (kg) will be measured (to the nearest of 0.1 kg) by a digital scale (Ramuza® digital scale; Ramuza *Indústria e Comércio de Balanças* Ltda., Santana do Parnaíba, SP, Brazil), with minimum of clothes and no shoes. Height (m) will be measured without shoes, using a standard stadiometer attached to the scale, to the nearest of 0.1 m. BMI will be calculated as body mass divided by height squared (kg/m^2), and waist circumference will be measured at the midpoint between the last rib and iliac crest (to the nearest of 0.1 cm), using a flexible and inextensible tape (Sanny TR4010™ anthropometric tape, American Medical do Brasil Ltda., São Bernardo do Campo, Brazil).

Cardiovascular health

The Life's Essential 8 Cardiovascular Health Index will be used to assess cardiovascular health. [22] This index includes metrics of cardiovascular health, divided into two domains: health behaviors (diet, physical activity, nicotine exposure, and sleep quality) and health factors (BMI, blood lipids, blood glucose, and BP). Each metric will be scored individually from 0 to 100 points, and the average score of the eight metrics will be the cardiovascular health score, as previously recommended. [22] Health behavior metrics will be assessed through anamnesis, conducted after the evaluation of lower limb venous function, using validated instruments for diet assessment, [44] physical activity, [45] and sleep quality. [46] Except for smoking exposure, which will be assessed with the following questions:

1. Are you a smoker? ( ) Yes ( ) No
   1.a. If yes, what? ( ) cigarette ( ) cigar ( ) pipe ( ) vaporizer
   ( ) other – describe: _____
   Quantity (per day or week): _____
   1.b. If no, have you ever been a smoker? ( ) Yes ( ) No
   If yes, When did you quit? _____
2. Do you live with a smoker? ( ) Yes ( ) No
   2.a. If yes, does the person smoke indoors? ( ) Yes ( ) No

BMI and BP will be measured as described in anthropometric and hemodynamic assessments subsections, respectively. For the assessment of blood lipid and glucose metrics, a blood sample (nearly 3.5 ml) will be collected from the antecubital vein (on a separate day from other evaluations), in the morning (between 7:00 am to 08:30 am), and after 10 hours of fasting (at least 48 hours after the last exercise session to avoid acute exercise effects). Samples will be collected into vacutainer dry tubes, immediately placed in ice, and centrifuged at 1.700 × g for 5 min at -4 °C for serum separation. Serum total cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides, blood glucose, and HbA1c (only in participants with diabetes) will be analyzed by the spectrophotometry method using a biochemical analyzer with specific reagents (A-15®, BioSystems S.A., Barcelona, Spain).

Arterial hemodynamic function and cardiovascular autonomic control

Resting HR, BP, HRV, cfPWV, central pressures, and endothelial function (FMD) will be measured after anthropometric measurements. Participants will be instructed to have breakfast two hours before the start of the evaluations, to avoid physical activity for the previous 24 hours, to avoid caffeine, alcohol, and stimulants consumption for the previous 12 hours, and to have an empty bladder. Participants will also be instructed to take their regular medications at their usual time. Resting HR and BP (non-dominant arm) will be measured in the seated position, after a 10-min seated rest, in triplicate (2-min interval between each measurement), and using a digital telemetry system (Polar H10™, Polar Electro Inc, Kempele, Finland) and an automatic monitor (Omron HEM 7200™, Omron Healthcare Inc., Dalian, China), respectively. The average of the 3 BP and HR measurements will be used for intra- and inter-group analyses. HRV measurements, an index of cardiovascular autonomic control, will be performed after HR and BP measurements, with participants quietly in the supine position, awake, and breathing spontaneously. The HR signals will be acquired and recorded beat-to-beat for 10 min, using a digital telemetry system with a sampling frequency of 1,000 Hz (Polar H10™, Polar Electro Inc, Kempele, Finland). Data will be transmitted to a computer as text files and the Fast Fourier Transform to a sequence of 256 stable R–R intervals (iRR) will be used to calculate frequency (low-frequency band (LF: 0.04–0.15 Hz), high-frequency (HF: 0.15–0.4 Hz), and LF/HF ratio) and time (iRR mean and variance) domain indexes (Software Kubios HRV™ version 2.0, University of Kuopio, Finland), as previously described. [47]

cfPWV, augmentation index (Aix), and central pressures will be measured after HRV assessment, using a non-invasive automated device (Complior Analyze™ PWV and Central Pressure Analysis™; AlamMedical, Saint-Quentin-Fallavier, France), as previously recommended. [48] The measurements will be performed with the participants in the supine position, and common carotid and femoral arteries pressure waveforms will be measured using a pressure-sensitive transducer. Supine BP (measured once with an automatic device – Omron HEM 7200™, Omron Healthcare Inc., Dalian, China) and the distance between the measuring sites (D, measured in a straight line with a sliding anthropometric caliper) will be recorded and inserted into equipment's software before waveforms measurements. Pressure-sensitive transducers will then be positioned at recording sites, pressure waveforms will be measured during 10 to

15 cardiac cycles, and average cfPWV (cfPWV = D/t, where t means pulse transit time), Aix (ratio of augmentation pressure expressed as the difference between the second and first pressure peaks in the pulse wave), and central pressures (assessed directly from the carotid pressure waveform, using mean and diastolic pressures to calibrate the carotid signal) will be automatically calculated. Measurements will be performed twice, and the mean between measurements will be considered for analysis. If the two measures differ by more than 0.5 m/s, a third measurement will be performed, and the median will be considered for analysis. [48]

Subsequently, endothelium-dependent function will be assessed by the noninvasive and standardized method of brachial artery FMD. All measurements will be performed with participants in the supine position, at the right arm (fixed nearly 80º from the torso at a foam supporting cradle), by an experienced operator with more than 100 scans/y, and following the recommendations for technique execution and data acquisition. [49] A BP cuff will be positioned at participants' forearm (2 to 3 cm below the elbow), and an ultrasound device (SonoSite M-Turbo™; Fujifilm Inc., Bothell, Washington, USA) with a 6–13 MHz linear transducer will continuously scan and record brachial artery diameter and blood flow velocity for 9 min. The 9 min scan will consist of 1 min pre-cuff inflation (baseline), 5 min of cuff-inflation to 50 mmHg above resting systolic BP, and 3 min of post-cuff release during (hyperemia). The ultrasound transducer will be positioned in the longitudinal plane on the distal third of participants' arm, and the scan will be recorded with an external video card attached to a laptop microcomputer. Doppler blood flow and B-mode artery diameter video images will be analyzed using a semiautomatic edge-detection and wall tracking software (Cardiovascular Suite™, Quipu srl, Pisa, Italy). FMD will be determined by the following formula: FMD (%) = (peak diameter – baseline diameter)/baseline diameter × 100. [49] Baseline diameter will be the average vessel diameter measured during the 1-min baseline recording, and peak diameter will be the largest diameter observed during hyperemia. Shear rate will be calculated by the following formula: shear rate = 8 × mean blood velocity/internal diameter. [49] The relevant shear rate stimulus for the FMD response will be calculated as the area under the curve of the shear rate up to the peak diameter, which will be used to normalize FMD response.

Common carotid artery intima-media thickness (cIMT) will be measured following FMD evaluation using an ultrasound device (SonoSite M-Turbo™; Fujifilm Inc., Bothell, Washington, USA)

with a 6–13 MHz linear transducer. Measurements will be performed by the same trained examiner on both sides (right and left), and with participants at supine position with the head rotated at ~45° away from the measured artery. The cIMT scan will begin above the clavicle, and the transducer directed longitudinally along the carotid artery until the carotid bifurcation is reached. Ultrasound parameters will be adjusted to optimize the appearance of the intima border along the vessel (e.g., gain, depth, and focal zone). Three measurements will then be performed on the artery posterior wall, in the segment 1-2 cm below carotid bifurcation. The presence of plaques or cIMT will be measured, [50] and the average of the three measurements will be used for analysis. [51] Subclinical atherosclerotic disease will be defined as the presence of atheromatous plaques (cIMT greater than or equal to 1.5 mm or protrusions into the vessel lumen) without hemodynamic repercussion and/or cIMT greater than 1.0 mm, which are cutoff values that have been shown to be predictive of cardiovascular events. [52,53] If plaques with hemodynamic repercussion (stenosis > 50%) are found, peak systolic velocity (PSV) and the morphological percentage of stenosis will be measured.

Venous hemodynamic function of lower extremities

The evaluation of lower extremities venous hemodynamic function will consist of clinical, perimeter, and ultrasound assessments, and will occur following the clinical and anthropometric assessment. The clinical evaluation will be performed after the anthropometric measurements, with participants in the standing position, in a properly lit environment, allowing visualization of the lower limbs and any venous pathways. For this evaluation, the Clinical manifestations, Etiologic factors, Anatomic distribution of disease, and Pathophysiologic findings (CEAP) classification will be used (Table 1). [54,55] Each clinical class will be further characterized by subtype for the presence (S, symptomatic) or absence (A, asymptomatic) of symptoms (e.g., C2A, C5S...). Symptoms will include pain, tightness, itching, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction. [54] After the clinical evaluation, standardized measurements of ankle and calf diameter will be taken with an anthropometric tape (Sanny TR4010™, American Medical do Brasil Ltda., São Bernardo do Campo, Brazil). The ankle diameter will be measured 3 cm above the medial malleolus, and the calf diameter will be measured 10 cm below the tibial tuberosity (largest diameter). Subsequently, venous doppler

ultrasound will be performed by a qualified examiner, using an ultrasound device (SonoSite M-Turbo™; Fujifilm Inc., Bothell, Washington, USA) with a 6–13 MHz linear transducer. The presence and magnitude of venous valve reflux and general characteristics of the venous wall in B-mode will be assessed according to the criteria previously defined. [56] Venous diameters will also be recorded at 4 predefined points, with 3 points on the Great Saphenous Vein and 1 point on the Small Saphenous Vein. The deep venous system of the Great Saphenous Vein (thigh and leg) and the middle third of the Small Saphenous Vein will also be assessed. [57] The points analyzed during the exam for reflux and venous diameter recording are shown in Figure 2. Venous reflux will be assessed by peak velocity (PVR – cm/s) and time (TR – ms).

RedOx State Parameters

Lipid peroxidation, carbonylated proteins, plasma antioxidant capacity, advanced oxidation protein products (AOPPs), and plasma antioxidant enzymes activity will be measured to assess cellular signaling and modulation of important CVD and vascular function control pathways. For this, a blood sample (nearly 10 ml) will be collected from the antecubital vein (at the same time of blood collection for lipids and glucose analysis) into vacutainer tubes with ethylenediaminetetraacetic acid (EDTA). Immediately after collection, the tubes will be gently inverted 8-10 times to ensure proper mixing of the blood with the anticoagulant, placed in ice, and centrifuged at 1.500 × g for 15 min at -4 °C. The supernatant (plasma) will be aspirated using a clean transfer pipette, aliquoted into sterile pre-labeled cryovials, and immediately frozen at -80°C until analysis.

Lipid peroxidation will be measured by the concentration of malondialdehyde (MDA). Plasma samples (nearly 200µl) will be homogenized (ULTRA-TURRAX™ T25 basic, IKA™ Werke, Staufen, Germany) with 1.0mL of cold phosphate-buffered saline (PBS) pH 7.4, and centrifuged at 800g at 4ºC for 10 min. Nearly 100µL of the supernatant will then be mixed with 700µL of 1% orthophosphoric acid and 200µL of thiobarbituric acid (42mM). After that, the samples will be kept at 100ºC for 60 min in a water bath and immediately cooled on ice. In a 2mL tube, 200µL will be mixed with 200µL of sodium hydroxide/methanol (1:12 v/v). After vortexing, the samples will be centrifuged for 3 min at 13.000 g. 200µL of the supernatant will be transferred to a glass vial and 50µL will be injected into the column. It

will be used an HPLC system (Shimadzu LC-10AD™ system, Shimadzu, Kyoto, Japan) with a C18 Luna column (5µm, 150 × 4.60mm, Phenomenex Inc., Torrance, CA, USA), a Shimadzu RF-535 fluorescence detector (excitation 525nm, emission 551nm) and a phosphate buffer flow of 0.5mL/min (KH2PO4 1mM, pH 6.8) 2525. MDA levels will be determined by the peak area in the chromatograms relative to the standard curve of known concentrations. [58]

Plasma carbonylated proteins will be measured by a spectrophotometric method. [59,60] For this, plasma samples will be incubated with 2,4-dinitrophenylhydrazine (DNPH) for 1 hour for derivatization of carbonylated proteins. Immediately after, the samples will be deproteinized with trichloroacetic acid and centrifuged. The supernatant will be discarded, and the sediment will be washed three times with ethanol/ethyl acetate solution to remove excess DNPH, avoiding the quantification of chromophores not bound to carbonylated protein. Finally, 6M guanidine hydrochloride will be added to the washed sediment, and the reading will be performed at a wavelength of 370nm. Total protein concentrations in the samples will be quantified using commercial tests to adjust the values of carbonylated proteins. Carbonylated protein concentrations will be expressed in µg/g of protein.

Plasma antioxidant capacity will be determined by the total antioxidant performance assay. [61] This assay uses 100uL of plasma that will be initially incubated with the fluorescent indicator BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene), for 10 mins at 37ºC. The free radical generator AAPH (2,2`Azobis (2-amidino-propane)-dihydrochloride) will then be added to the samples. The prepared samples will be applied in triplicate (200uL in each well) in specific plates (Perkin-Elmer, Boston, USA). Phosphatidylcholine will be used as a hydrophilic matrix reference. The fluorescence reader (Wallac Vitor 2X™, Perkin-Elmer, Boston, USA) will be programmed to perform readings every 5 min for 3 hours and 30 min. During this time, as the antioxidant protection is depleted, the probe (BODIPY) begins to be oxidized by the generated free radicals, providing fluorescence to the medium. Thus, it will be possible to observe the fluorescence curve and determine the antioxidant percentage relative to the hydrophilic matrix.

Advanced oxidation protein products (AOPPs) will be measured by spectrophotometric detection, as previously described. [62] Plasma samples (200µL) will be diluted 1:5 with PBS. It will be used 200µL of chloramine T (0-100µmol/L) for the calibration curve, and the blank will be only PBS (200µL). All

samples will be placed on a microtiter plate and mixed with 10µL of 1.16 M KI and 20µL of acetic acid. Absorbance will be measured immediately at 340nm (Multiskan Ascent spectrophotometer, Labsystems, Vantaa, Finland). The final concentration of AOPPs will be expressed in chloramine units (µmol/L).

For plasma antioxidant enzymes activity, 200µl (1:10v/v) in KH2PO4 (10 mmol/L)/KCl (120 mmol/L), pH 7.4 and centrifuged at 2,000g for 20min will be used. The activity of superoxide dismutase (SOD) will be measured based on the inhibition of a superoxide radical reaction with pyrogallol, and absorbance values will be measured at 420nm. [63] Catalase activity will be evaluated by monitoring the decrease in hydrogen peroxide levels at 240nm. [64] The activity will be expressed as pmol of H2O2 reduced/min/mg of protein. The results will be expressed as µmol hydroperoxide-reduced/min/mg of protein. Protein will be quantified using bovine serum albumin as a standard, as previously described. [65] Absorbance values for all analyses will be measured on a UV/VIS spectrophotometer (Pharmacia Biotech, Houston, USA), and the values will be expressed in units per milligram of protein.

Physical functional performance

Physical functional performance will be assessed after FMD measurement, through measures of flexibility, handgrip strength, lower extremity muscle strength/power, mobility, and aerobic performance, as previously described. [11,19] Posterior thigh and lower back flexibility will be measured by the sit and reach test, using a portable sit and reach test equipment (Instant Pro Sanny™, American Medical do Brasil Ltda., São Bernardo do Campo, Brazil). The measurements will be performed with the participants without shoes and seated on the floor with their legs fully extended and feet flat against the sit-and-reach equipment. The participants will be then instructed to place one hand on top of the other, with the fingertips aligned, and to exhale and slowly reach forward as far as possible with both hands along the sliding measuring scale, keeping the knees fully extended, and holding the position for 2 seconds at the farthest point (bouncing or jerking movements will not be allowed). The distance reached by the fingertips will be recorded in centimeters. The test will be performed three times, and the best score will be considered for analysis.

Handgrip strength will be measured after sit and reach test, using a hydraulic dynamometer (JamarTM™ hydraulic hand dynamometer, Sammons Preston, Bolingbrook, USA). To perform the measurement, the patient will be at seated position, with the elbow flexed at 90^{o} and a neutral wrist (between 0^{o} and 30^{o} of extension and between 0^{o} and 15^{o} of ulnar deviation). Participants will receive a brief demonstration of the handgrip test and will be allowed to perform one to two practice trials with each hand to familiarize themselves with the procedure. Participants will be then instructed to squeeze the dynamometer with maximal effort for 3 to 5 seconds, and verbal encouragement ("Go! Squeeze as hard as you can!") will be provided to ensure maximal effort. Three measures will be performed with each hand, with a 30-second rest period between trials. The mean of each hand will be calculated, and the highest mean will be used for analysis.

Lower extremity muscle strength/power will be measured after handgrip strength test by the five-time sit-to-stand (FTSTS) test. The test will be performed using a standard armless chair (seat height of 46 cm) placed against a wall to prevent its movement during the test. Participants will be seated at the chair with their back straight, feet flat on the floor and positioned shoulder-width apart, knees flexed at nearly 90^{o}, and arms crossed over their chest. A brief demonstration of the FTSTS will be given, and it will be allowed one practice trial to ensure understanding of the procedure. Participants will be instructed to stand up fully and sit down as quickly as possible five times without using their arms for support. The test began with the verbal cue "Ready, go!". The stopwatch will be started and stopped as soon as the participant initiated (to project the shoulders forward) the first stand and the participant's torso touch the chair after the fifth stand, respectively. The researcher will be stood nearby to provide physical support if the participant lost balance or was at risk of falling. Two trials will be performed with a 1-min rest period between trials. The trials will be measured in seconds (to the nearest of 0.01) and the fastest of the two trials will be used for analysis.

Mobility will be measured after the FTST by the timed-up and go (TUG) test, which will be performed in a clear, flat and unobstructed area (to allow for safe movement during the test). A standard armless chair (seat height of 46 cm) will be placed against a wall (to prevent its movement during the test), and a cone will be placed on the floor at a 3 m distance from (in front) the chair. Participants will be seated at the chair with their back resting against the chair back, feet flat on the floor, and arms resting

beside the trunk. A brief demonstration of the TUG will be given, and it will be allowed one practice trial to ensure understanding of the procedure. Participants will be instructed to stand up from the chair, walk at their normal pace to the cone placed 3 meters away, turn around the cone, walk back to the chair, and sit down. The test will begin with the verbal cue "Ready, go!". The stopwatch will be started and stopped as soon as the participant initiated (to project the shoulders forward) the first stand and the participant's torso touch the chair after sitting down, respectively. The researcher will be stood nearby to provide physical support if the participant lost balance or was at risk of falling. Two trials will be performed with a 1-min rest period between trials. The trials will be measured in seconds (to the nearest of 0.01) and the fastest of the two trials will be used for analysis.

Aerobic performance will be measured after the TUG by the six-minute walking test (6MWT). The test will be performed on a 30 m length flat surface, using cones and measure tape to mark the ground, and following the recommendations of the European Respiratory Society/American Thoracic Society. [66] Briefly, participants will be asked to wear comfortable clothing and footwear suitable for walking, will be familiarized with the 0 to 10 rate of perceived exertion scale, [67] and will be instructed to walk as far as possible during the 6 minutes. They will be also instructed that they may slow down, stop, and rest if necessary, but resume walking as soon as he/she is able. Participants will stand at the starting line, and the test will begin with the verbal cue "Ready, go!". Standardized encouragement will be provided at minutes 1, 3 and 5 (e.g., "You're doing well; Keep up the good work!"), but there will be no specific advice on pacing. If a participant needs to stop and rest, the timer will continue, and they will be instructed to resume walking as soon as possible. The total distance walked will be recorded in meters, and its absolute (total distance walked) and relative (percentage of predicted distance) [68] levels will be used to assess walking performance. HR (Polar™ H10 heart rate sensor; Polar Electro Inc, Kempele, Finland), pulse oxygen saturation (SpO_2; G-Tech™ Led finger oximeter, Accumed Produtos Médico Hospitalares Ltda., Duque de Caxias, Brazil), RPE will be measured before, every 2 min of exercise (at the end of 2^{nd}, 4^{th} and 6^{th} min of exercise), and after at the end of 1^{st}, 3^{rd} and 6^{th} min of recovery. BP (Omron HEM 7200™, Omron Healthcare Inc., Dalian, China) will be measured before, immediately after, and at the 6^{th} min of recovery. The average of HR and SpO2 measured every 2 min of exercise will be considered exercise HR and exercise SpO2, respectively. Absolute (total distance walked during test) and relative

(percentage of predicted distance) [68] distances will be used to assess walking performance. The partial oxygen desaturation during the exercise phase will be defined as a reduction of ≤ 4% in SpO2 during any moment of walking when compared to pre-exercise levels.

Health-related quality of life and mental health markers

HRQL and mental health markers will be assessed by validated questionnaires, which will be answered after cIMT evaluation. The validated versions to Brazilian population of the World Health Organization Quality of Life abbreviated (WHOQOL-BREF) [69] and older adults (WHOQOL-OLD) [70] questionnaires will be used to assess HRQL. The validated versions to Brazilian population of the Brunel Mood Scale (BRUMS) [71] and Beck Depression Inventory (BDI-II) [72] will be used assess mental health markers.

Adverse events related to exercise sessions

The safety of the CBEPs will be assessed through a structured questionnaire on the occurrence of potential acute (during the exercise session) and late (between sessions) adverse events. [34] For acute adverse events, the following questionnaire will be administered at the end of each exercise session:

- During the exercise session, did you experience or have:

  (1) muscle/joint pain? ( ) yes / ( ) no – if yes, where? _____;

  (2) dizziness or lightheadedness? ( ) yes / ( ) no;

  (3) nausea? ( ) yes / ( ) no;

  (4) vomiting? ( ) yes / ( ) no;

  (5) mental confusion? ( ) yes / ( ) no;

  (6) shortness of breath? ( ) yes / ( ) no;

  (7) pain or discomfort? ( ) yes / ( ) no;

  (8) any other discomfort? ( ) yes / ( ) no – if yes, what/where? _____.

For late adverse events, the following questionnaire will be administered at the beginning of each training session (starting from the second session), only for participants who attended the previous session:

- In the period between the last session and today, did you experience or have:

  (1) muscle/joint pain? ( ) yes / ( ) no – if yes, where? _____;

  (2) dizziness or lightheadedness? ( ) yes / ( ) no;

  (3) nausea? ( ) yes / ( ) no;

  (4) vomiting? ( ) yes / ( ) no;

  (5) mental confusion? ( ) yes / ( ) no;

  (6) shortness of breath? ( ) yes / ( ) no;

  (7) pain or discomfort? ( ) yes / ( ) no;

  (8) any other discomfort? ( ) yes / ( ) no – if yes, what/where? _____.

Community-based exercise programs and control follow-up

All participants will receive educational guidance before the beginning of follow-up, which will consist of two lectures about the importance of physical activity for their health promotion, the physical activity recommendations, and practical daily life tips to meet the recommendations [4]. Participants from control will receive no other intervention and will be only contacted to return to follow-up assessments. Participants from exercise groups will also be familiarized with the 6 to 20 RPE scale during the lectures, [67] which will be used to prescribe/control the intensity of exercise sessions.

CBEPs will consist of two weekly sessions, with at least one day between them, held in the morning (between 08:00 and 09:00) or afternoon (between 14:00 and 15:00), according to the availability of times provided by the Service of Coexistence and Strengthening of Bonds for Older Adults. All exercise sessions will be conducted in groups, at the same time for participants in the same cluster, but on different days of the week between different clusters. These sessions will be supervised by an experienced exercise professional, who will be assisted by undergraduate students for participant guidance/supervision. The sessions will consist of 5 minutes of warm-up, 20 to 50 minutes (progressive volume over the follow-up) of specific training (HIIT+RT or MICT+RT) and 5 minutes of cool-down, totaling 30 to 60 minutes per session, as previously described. [11,19]

In summary, HIIT+RT sessions will consist of warm-up (4 min of walking at level 9 on the RPE scale), HIIT exercise (1 min of brisk walking or running [according to the participant's fitness level] at

level 15 to 17 on the RPE scale, alternated with 2 min of walking at level 9 to 11 on the RPE scale), and six RT exercises (bodyweight squat, wall or counter push-up, deadlift with elastic band or stick, bent-over or seated row with elastic band, floor or chair crunch, and shoulder press or lateral raise with elastic band). The relative intensity (RPE level) of the exercise will be maintained throughout the 12-month follow-up, and the external load will be adjusted according to the participants' fitness improvement (e.g., increasing walking/running speed, increasing the speed of execution/contraction time of strength exercises, etc...). The HIIT+RT volume will start (weeks 1 and 2) with 3 HIIT intervals (9 min) and 1 set of 15 to 20 reps, and will progressively increase to: 4 HIIT intervals (12 min) and 2 sets of 10 to 15 reps (weeks 3 to 5); 5 HIIT intervals (15 min) and 2 sets of 15 to 20 reps (weeks 6 to 8); 6 HIIT intervals (18 min) and 3 sets of 10 to 15 reps (weeks 9 to 12); and 7 HIIT intervals (21 min) and 3 sets of 15 reps (week 13 onwards).

MICT+RT sessions will consist of warm-up (4 min of walking at level 9 on the RPE scale), MICT exercise (walking or brisk walking [according to the participant's fitness level] at level 11 to 13 on the RPE scale), and the same six RT exercises performed by the HIIT+RT group. The relative intensity (RPE level) of the exercise will be maintained throughout the 12-month follow-up, and the external load will be adjusted according to the participants' fitness improvement (e.g., increasing walking speed, increasing the speed of execution/contraction time of strength exercises, etc...). The MICT+RT volume will start (weeks 1 and 2) with 12 min and 1 set of 10 to 15 reps, and will progressively increase to: 15 min and 2 sets of 10 to 15 reps (weeks 3 to 5); 19 min and 2 sets of 15 to 20 reps (weeks 6 to 8); 22 min and 3 sets of 10 to 15 reps (weeks 9 to 12); and 26 min and 3 sets of 15 reps (week 13 onwards). The HIIT+RT and MICT+RT programs were based on a previous study that showed that the estimated energy expenditure is not different between HIIT and MICT sessions with the present volume and intensity. [73]

The RT exercises described above may be replaced by others that work the same muscle groups to motivate participants throughout the follow-up (e.g., variations of squats/lunges; variations of push-ups/bench press with elastic band; variations of deadlifts with elastic band/adapted hand weights; variations of rows [seated, bent-over...] with elastic band/adapted hand weights; variations of shoulder press/lateral raise/front raise with elastic band/adapted hand weights; and different variations of crunches). Additionally, to maintain the prescribed relative intensity of effort for each participant, the external load will be constantly adjusted by increasing walking/jogging speed, increasing the resistance of elastic bands,

adapting hand weights, increasing the speed of execution, and/or increasing the time under tension. The frequency of each participant in the exercise sessions will be recorded throughout the follow-up.

Statistical Analysis

Data will be analyzed using the Statistical Package for Social Sciences™ for Windows™ (SPSS™ version 21.0, IBM Corp., New York, USA). Categorical variables will be described in absolute and relative frequency. For quantitative variables, the normality, homoscedasticity, and sphericity of the data will be verified by the Shapiro-Wilk, Levene, and Mauchly tests, respectively. Data with parametric distribution will be described as mean ± standard deviation or mean (95% confidence interval). Data with non-parametric distribution will be described as median (interquartile range 25-75%) or median (minimum – maximum). Pearson or Spearman correlation coefficients, and regression analyses will be used to verify the relationship between clinical characteristics, cardiovascular health, arterial and venous hemodynamic function parameters, functional physical performance, quality of life, and mental health in the pre-intervention period. The initial difference between groups in clinical and demographic variables will be analyzed by Chi-square tests (categorical variables), one-way ANOVA (parametric data), or Kruskal-Wallis (non-parametric data). Bonferroni or Mann-Whitney U (with Bonferroni correction) will be used to identify significant differences indicated by ANOVA or Kruskal-Wallis, respectively. The evaluation of the effect of interventions will be performed by intention-to-treat analysis (all participants will be analyzed in the group to which they were originally assigned, regardless of compliance with the intervention). The amount and reason (e.g., measure error, participant refusal, etc.) of missing data will be noted. Little's MCAR test will be used to analyze missing values. Multiple imputation will be used for data missing completely at random (MCAR) or at random (MAR). The assumption of MAR will be tested by running sensitive analyses under missing not at random (MNAR) assumptions. Two-way ANOVA with repeated measures will be used to indicate significant differences intergroup, intragroup, and interaction of parametric variables. If there are significant baseline differences between groups in any relevant variable (e.g., age, body mass index, comorbidities…), ANCOVA will be used and the variable(s) will be included as a covariate in the analysis model. Greenhouse-Geisser or Huynh-Feldt will be used for sphericity correction if necessary. Bonferroni *post hoc* analysis will be used to identify significant

differences identified by ANOVA or ANCOVA. For nonparametric variables, Kruskal-Wallis and Friedman tests will be used to identify significant intragroup and intergroup differences, respectively. Mann-Whitney U and Wilcoxon Signed-Rank (with Bonferroni correction) will be used to identify significant differences indicated by Kruskal-Wallis or Friedman, respectively. The impact of CBEPs' compliance on primary and secondary outcomes will be explored by: (i) repeating the main analyses only with participants who achieved high adherence (at least 50% or 70% of participation in proposed exercise sessions) and comparing these results with the results of the intention-to-treat analysis; and (ii) using linear or logistic regression to assess the relationship between compliance (i.e., number of exercise sessions completed) and changes (absolute and relative) in primary and secondary outcomes. Finally, linear or logistic regression will be used to identify potential predictors of adherence (e.g., age, comorbidities, distance to the exercise location, among others). The level of significance will be set at $P < 0.05$.

DISCUSSION

The COBEX-OLD study may provide a significant contribution to the current understanding of CBEPs effects on cardiovascular health, functional capacity, and overall well-being in older women under socioeconomic vulnerability. This population is often at higher risk for CVD due to a combination of age-related physiological changes and socioeconomic factors. [3,5–7] By focusing on this demographic group, the present study will address a critical gap in the literature and will provide valuable insights into how CBEPs interventions can improve health in this often neglected and vulnerable population. The comparison of long-term HIIT+RT and MICT+RT will also address a literature gap, because previous research has largely focused on short-term interventions or moderate-intensity exercise. [11,13–16] In addition, the present study will also explore underlying physiological mechanisms, functional performance, and safety, which provide a comprehensive understanding of how exercise can be optimized for this high-risk group.

One of the key potential contributions of the present study is its comprehensive assessment of cardiovascular health using the Life's Essential 8 Cardiovascular Health Index, a metric that encompasses both traditional risk factors and broader health behaviors. [22] While previous studies have primarily examined isolated cardiovascular risk factors, [11,14,15,19] the COBEX-OLD study provides a more nuanced

evaluation of cardiovascular health. This is particularly relevant for older women under socioeconomic vulnerability, who often face a higher burden of cardiovascular disease (CVD) and related risk factors. [5–7] If the potential superiority of HIIT+RT over MICT+RT in improving cardiovascular health metrics is confirmed, the study could inform more effective exercise prescriptions to this population. This potential finding is crucial for developing or improving evidence-based guidelines that can be implemented in community settings to promote cardiovascular health and reduce the burden of disease.

Additionally, the study's focus on arterial and venous hemodynamic function, as well as on physiological mechanisms underlying cardiovascular health, provides new insights and a deeper understanding into how different exercise intensities affect vascular health. This is particularly important due to the high prevalence and understudied condition of chronic venous insufficiency in older women under socioeconomic vulnerability, [6,26,28,29] which could lead to more effective prevention and management strategies for venous insufficiency, thereby improving quality of life and reducing healthcare costs for this high-risk population. Furthermore, the study provides valuable data on the feasibility and tolerability of HIIT+RT and MICT+RT in older women by systematically monitoring adverse events and dropout rates. The concerns about the safety, tolerance and adherence of HIIT in older and clinical populations make this study's assessment relevant, because it could challenge existing perceptions and encourage the adoption of HIIT programs in community settings. Indeed, the evaluation of CBEPs in a socioeconomically vulnerable population highlights the potential of low-cost, scalable interventions to reduce health disparities and improve quality of life in underserved populations.

Finally, the rigorous methodological design, including a randomized controlled trial with a long follow-up addressing potential biases and robust data collection, ensures the reliability and validity of the COBEX-OLD study's findings. The present study could support the development of targeted interventions that address the specific needs of socioeconomically vulnerable populations, ultimately reducing the burden of CVD and improving functional independence in older women. The COBEX-OLD study may underscore the importance of community-based approaches in promoting healthy aging and reducing health inequities. In this context, future research should build on these findings to explore the long-term sustainability of such interventions and their impact on broader health outcomes, including mortality and healthcare utilization.

Statement of Ethics

This study is being conducted in accordance with the Declaration of Helsinki. This human study was approved by the Research Ethics Committee of the School of Sciences, São Paulo State University - approval: 6.753.356. The study is registered with the Brazilian Registry of Clinical Trials under registration number RBR-7n2srw8. All participants will provide written informed consent prior to participating in this study.

Conflict of Interest Statement

The authors have no competing interests to declare.

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Author Contributions

EGC, LBG, AJTF, CA, MLS, RMA and RGJ participated in the study conception and design. EGC, AJTF, VTdA, BF and RMA participated in funding acquisition. EGC participated in project administration. All authors participated in methodology and supervision. The first draft of the manuscript was prepared by EGC. All authors contributed to manuscript draft improvement – review and editing. All authors read and approved the final version of the manuscript.

Data Availability Statement

The data will be shared with the academic community or the general public through presentations at events, technical reports, and scientific articles. The raw data will be made available to other researchers and may be used provided the source (study name, REBEC registration, and dataset DOI) is cited. Participants' names will remain confidential, and the study will be available in the University's database (in .pdf format) with acknowledgments to any potential funding agencies.

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TABLES

Table 1. CEAP classification. [54]

Classification	Description of clinical signs
C0	No visible or palpable signs of venous disease
C1	Presence of telangiectasias (microvarices) or reticular veins
C2	Presence of varicose veins, distinct from reticular veins, with a diameter of at least 3 mm
C3	Edema
C4	Skin or subcutaneous tissue changes secondary to chronic venous disease, divided into 2 subclasses for better definition of disease severity
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or white atrophy
C5	Healed venous ulcer
C6	Active venous ulcer

FIGURE LEGENDS.

Figure 1. Study design flowchart. * Adverse events will be quantified throughout follow-up.

Figure 2. Representation of the sites for venous diameter measurement and valve reflux assessment. Point 1: 5 cm above point J, medial region (Great Saphenous Vein – thigh); Point 2: 5 cm below Point J, medial region (Great Saphenous Vein – proximal leg); Point 3: 3 cm above the medial malleolus, anteromedial region (Great Saphenous Vein – distal leg); Point 4: 3 cm above the lateral malleolus, posterolateral region (Small Saphenous Vein).

Figures

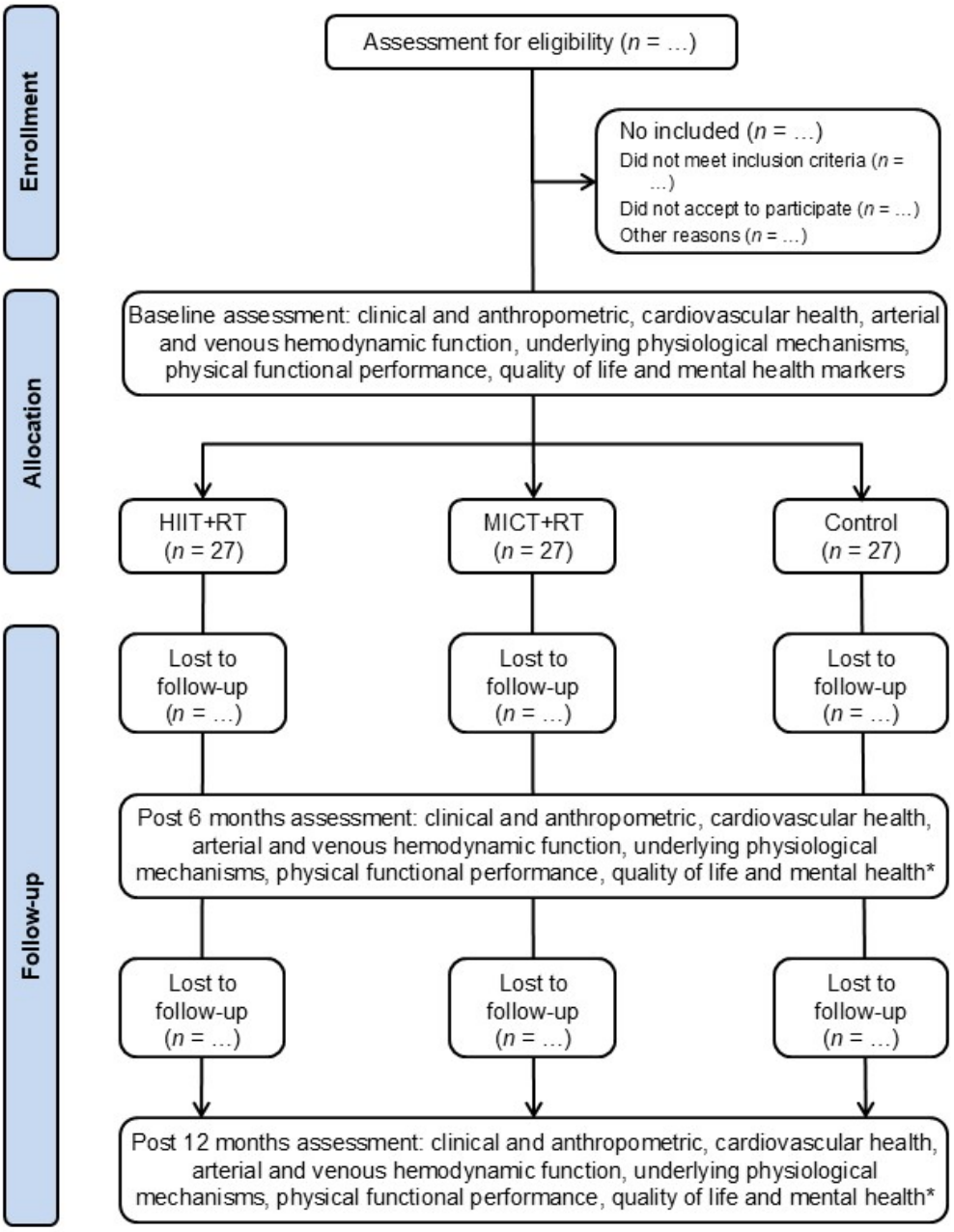


Figure 1

Study design flowchart. * Adverse events will be quantified throughout follow-up.

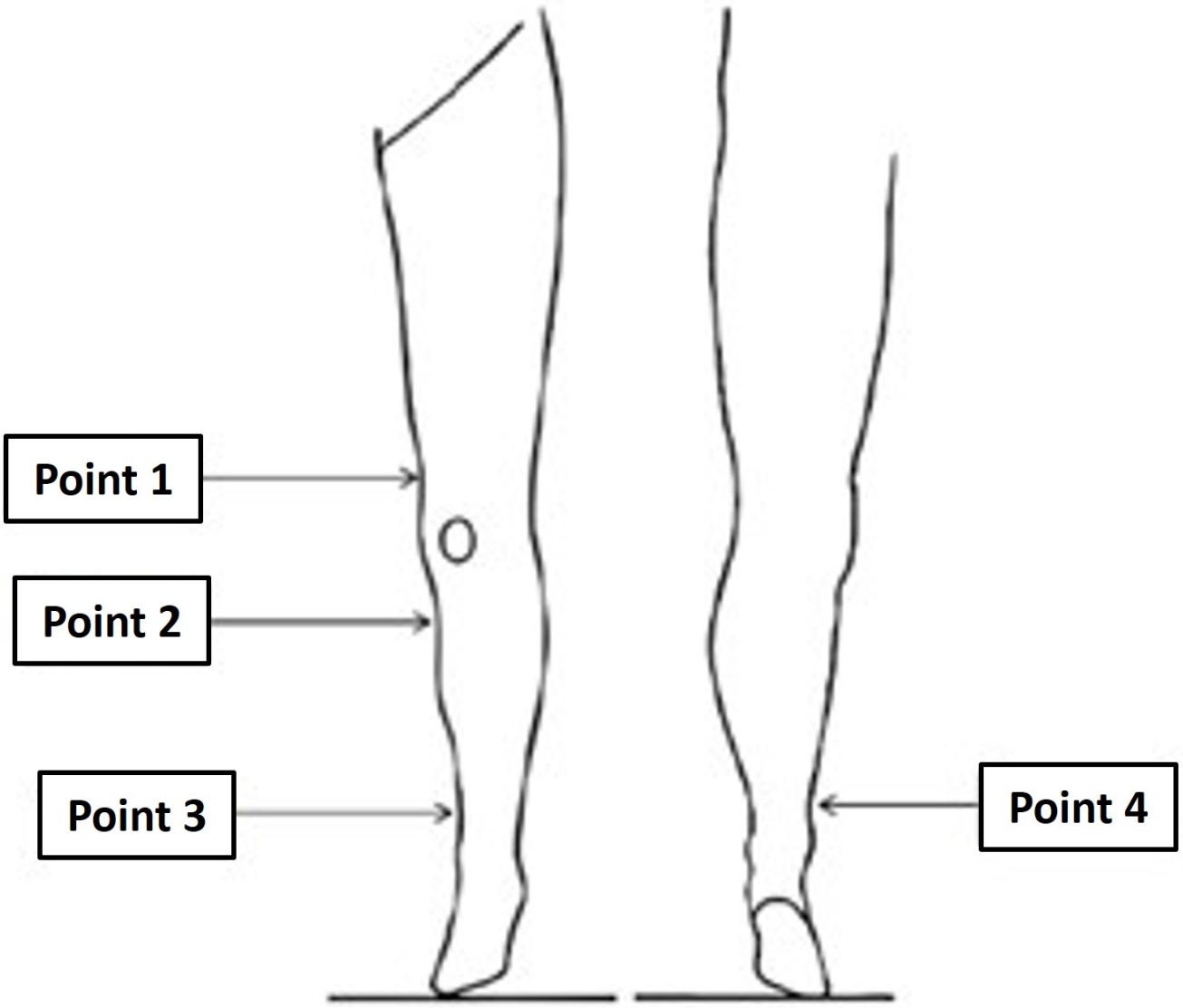


Figure 2

Representation of the sites for venous diameter measurement and valve reflux assessment. Point 1: 5 cm above point J, medial region (Great Saphenous Vein – thigh); Point 2: 5 cm below Point J, medial region (Great Saphenous Vein – proximal leg); Point 3: 3 cm above the medial malleolus, anteromedial region (Great Saphenous Vein – distal leg); Point 4: 3 cm above the lateral malleolus, posterolateral region (Small Saphenous Vein).