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STUDY PROTOCOL

Effects of Blood Flow Restriction Combined with Aerobic Stepping Exercise in Sarcopenia: A Study Protocol for a Randomized Clinical Trial

Hui Zhang[1,2], Mengli Li[3], Zhiyu Mao[2], Tongtong Yin[2], Jiaying Qi[2], Fangfang Wang[2], Li Wang[2]

[1]School of Nursing, Suzhou Vocational Health College, Suzhou, Jiangsu, 215009, People's Republic of China; [2]School of Nursing, Suzhou Medical College of Soochow University, Suzhou, Jiangsu, 215006, People's Republic of China; [3]School of Nursing, The Hong Kong Polytechnic University, Hong Kong, People's Republic of China

Correspondence: Li Wang, School of Nursing, Suzhou Medical College of Soochow University, No. 1 Shizi Street, Suzhou, Jiangsu, 215006, People's Republic of China, Tel +86-512-6522-1499, Fax +86-512-6512-5097, Email li-wang-1@suda.edu.cn

Background: Blood flow restriction training (BFRT) can produce effects similar to high-intensity exercise at lower intensities, making it a potentially more suitable method for older adults with sarcopenia. This study aims to determine the efficacy of the intervention on improving physical fitness in older adults with sarcopenia when blood flow restriction (BFR) and aerobic exercise (AE) are combined (BFR-AE) and to explore the related metabolic and signaling mechanisms.

Methods: This is a three-arm, parallel, randomized controlled trial. A total of 171 participants, aged 60 to 90 years, with sarcopenia will be randomly assigned (1:1:1) into one of three groups: a control group, an AE group, and a BFR-AE group. The participants in the control group will maintain their usual diet and activity habits. Those in the AE and BFR-AE groups will undergo a 12-week program of AE and BFR-AE respectively. The primary outcomes will include two long-term indicators: the 6-minutes walking test and 30-s chair stand test. Secondary outcomes will include additional long-term measures (eg, appendicular skeletal muscle mass index, handgrip strength, five-time chair stand test, lower extremity knee extensor and flexor muscle strength, sleep quality, emotion status, serum metabonomic and signal proteins), as well as instantaneous indicators (eg, blood pressure, heart rate, saturation of pulse oxygen, rating of perceived exertion, pain score and blood lactate concentration), adherence to exercise, and adverse events. Outcomes will be assessed at one of or all the time points of baseline, 12 and 24 weeks.

Discussion: It is expected that, after 12 weeks of intervention, both exercise groups will show improvements in cardiorespiratory and muscular fitness, with the BFR-AE group demonstrating greater benefits than the AE group alone.

Keywords: blood flow restriction, aerobic exercise, sarcopenia, muscular fitness, cardiorespiratory fitness

Background

Sarcopenia, also known as muscle wasting syndrome, is a common chronic disease among the older adults who are above 60 years.[1] The prevalence of sarcopenia increases with aging. It is reported that in individuals over 80 years old the prevalence rate is 1.5 to 2 times higher than in those aged 60 to 80.[2] This is closely related to the significantly declined muscular and cardiorespiratory fitness with advancing age. Muscle strength typically peaks between ages 20 and 30, remains stable until around age 40, and then gradually declines, with a linear decrease of 1% to 2% per year after age 65.[3] Cardiorespiratory fitness also diminishes with age due to structural and functional changes in blood vessels, reduced myocardial contractility, and decreased cardiac output.[4]

On the contrary, sarcopenia can exacerbate the decline in physical fitness, being one of the primary concerns. Insufficient muscular fitness hinders older adults from handling typical exercise loads, increases the risk of fatigue and injuries, and significantly diminishes their overall physical activity capacity. The decline in functional capacity can further exacerbate sarcopenia, causing a vicious circle, resulting in adverse effects such as falls, fractures, disability, increased hospitalization rates, and mortality, thus increasing the burden on society and families. In addition to notably lower muscle fitness, a meta-analysis

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has shown that older adults with sarcopenia also have reduced cardiorespiratory fitness compared to the general population, making them more susceptible to cardiovascular diseases.[5] The decline in cardiorespiratory fitness exacerbates fatigue and reduces exercise efficiency. This means that, at the same intensity, the body requires more energy to complete the same workload, further worsening the decline in muscle fitness and muscle cross-sectional area.[6]

Interventions for sarcopenia include both pharmacological and non-pharmacological approaches. Since there are no drugs specifically treat for sarcopenia,[7] exercise- and nutrition-based non-pharmacological interventions are currently the research focuses and the most effective means for improving multiple components of physical fitness in individuals with sarcopenia. Some studies have found that, in older adults with sarcopenia, exercise interventions alone can produce effects comparable to those achieved by combining exercise with nutritional interventions.[8]

The primary exercise interventions are resistance exercise (RE) and aerobic exercise (AE). RE involves working against resistance to enhance muscle volume and strength.[9] With lower levels of cardiorespiratory fitness, AE is also one of the recommended exercise methods for individuals with sarcopenia. Research suggests that AE not only significantly enhances cardiorespiratory fitness but can also improve muscular fitness by altering muscle fiber-level contractile characteristics.[10] The improvements in muscle volume and strength from AE may not be as substantial as those achieved through RE.[11] However, compared to RE, AE is simpler, induces lower cardiovascular stress, and is generally more easily accepted by older adults. American College of Sports Medicine (ACSM) and American Heart Association (AHA) jointly suggest that older adults can adopt low-intensity AE in the early stages, and increase RE after their physical fitness level reaches a certain level.[12]

The impact of exercise on various components of physical fitness is closely linked to exercise intensity. However, in older adults with sarcopenia, the lower physical fitness level often makes it difficult to participate in higher intensity exercises. Therefore, exploring alternative intervention that can deliver effective results at lower exercise intensities would be highly beneficial, both in terms of effectiveness and adherence.

Blood flow restriction training (BFRT) is one such promising method. Also known as blood flow occlusion training or KAATSU training, BFRT involves applying external pressure to the limbs using pressure devices (typically inflatable or non-inflatable bands) during exercise, restricting arterial blood flow to the working muscles.[13] As a novel training approach, BFRT has been shown to increase muscle cross-sectional area, muscle strength, aerobic performance, and other aspects of fitness at low intensities.[14] In BFRT, the blood flow restriction (BFR) is primarily combined with RE and AE.

When BFR combined with RE (BFR-RE), it can significantly enhance muscle strength, size, and mass of trained limbs in a short period, while also reducing muscle atrophy.[15,16] However, BFR combined with AE (BFR-AE) has also shown potential benefits individuals with sarcopenia[17] or those at high risk, such as older adults with insufficient exercise.[18] BFR combined with low-intensity AE may be more effective in promoting muscle hypertrophy and strength compared to AE alone.[18] Another study suggests that, compared to traditional AE, BFR-AE can significantly improve cardiorespiratory fitness, as measured by the 6-minute walk distance (6MWD), and enhance lower limb strength, as assessed by the 30-s chair stand test, in older adults with sarcopenia.[17] Despite these promising results, the long-term effect of BFR-AE in this population have not yet been explored.

In our study, we aim to develop a BFR-AE intervention program tailored for individuals with sarcopenia and to investigate its rehabilitative effects and underlying mechanisms for enhancing cardiorespiratory and muscular fitness. The exercise adaptation theory[19] serves as the theoretical foundation guiding the program's design and intervention. This theory explains how the human body adapts to training stimuli, resulting in improved physiological performance, adaptability and exercise ability.[20] Based on this framework, we have designed a 12-week progressive intervention of BFR-AE specifically for older adults with sarcopenia to encourage adaptive physiological changes. This approach aims to increase their physiological reserve function, subsequently enhancing physical function, psychological well-being, sleep quality, and other health outcomes. We hypothesize that BFR-AE will produce superior effects compared to traditional AE. The results of this study will provide new insights and approaches for sarcopenia rehabilitation, contributing to more effective improvements in the health status of affected individuals worldwide.

Methods

Study Objectives

The objective of this study is to evaluate the efficacy of the BFR-AE in treating older adults with sarcopenia.

Design

This is a three-arm, parallel-group, randomized clinical trial, in which the participants will be randomly assigned (1:1:1) a control group, an aerobic stepping exercise (AE) group, and a BFR-AE group, accepting a 12-week exercise intervention or no exercise. The assessments are conducted at baseline (t_0), post-intervention at 12-weeks (t_1) and after follow-up with additional 12-weeks (t_2). A research flow chart to explain the whole research scheme is shown in Figure 1. The Standard Protocol Items: Recommendations for Interventional Trials schedule of Enrolment, Interventions and Assessments are presented in Figure 2.

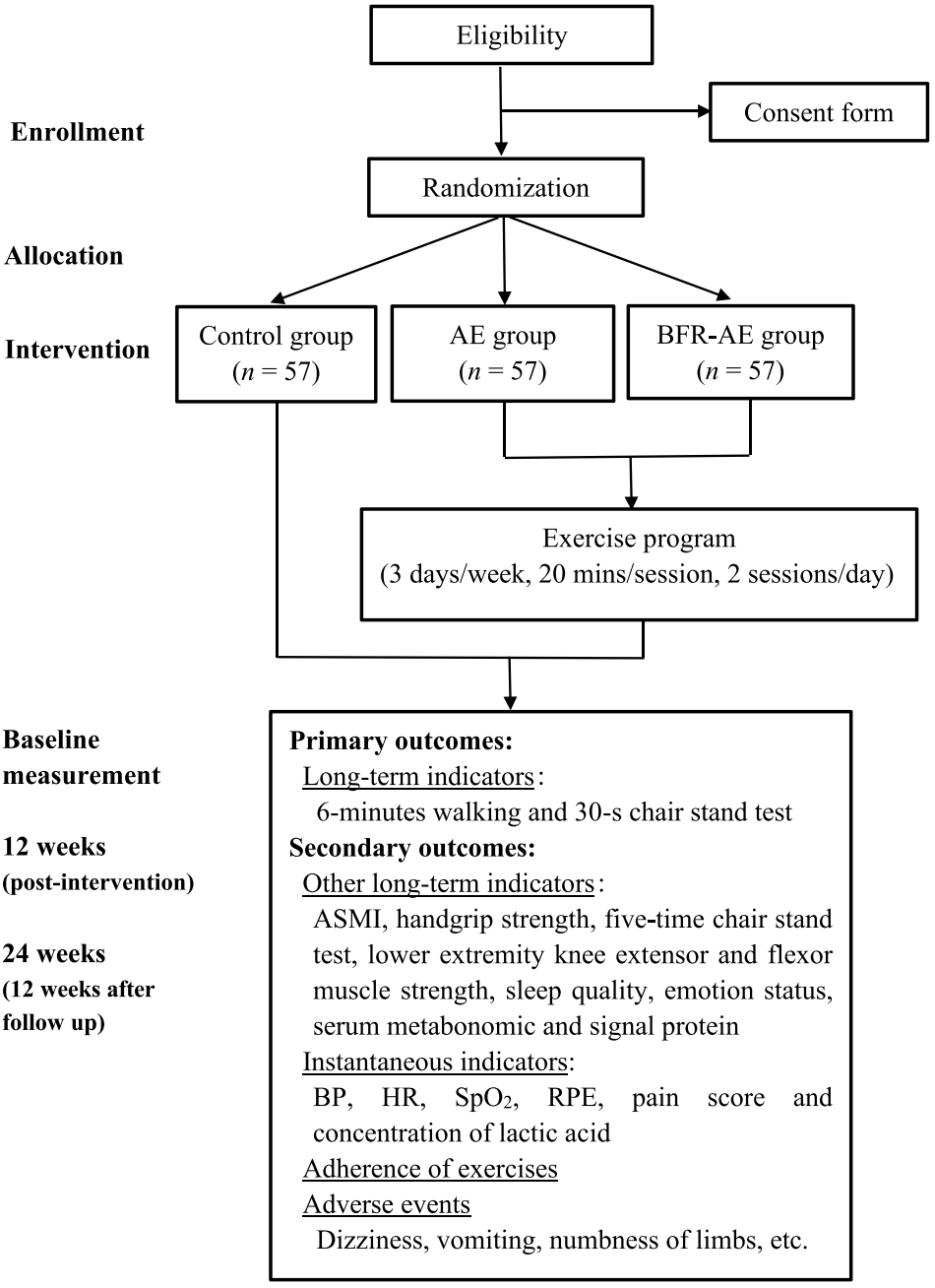

Figure 1 Experimental design.

Abbreviations: AE, aerobic exercise; BFR, blood flow restriction; ASMI, appendicular skeletal muscle mass index; BI, Barthel index; BP, blood pressure; HR, heart rate; SpO_2, saturation of pulse oxygen; RPE, rating of perceived exertion.

	Study Period			
	Screening	**Before intervention**	**Post intervention**	**Follow-up**
Time point (weeks)	$-t_1$	t_0	$t_1(12)$	$t_2(12)$
Enrollment				
Eligibility screen	X			
Informed consent	X			
Sociodemographic date	X			
Randomization		X		
Interventions				
Arm1: Control group				
Arm2: AE group			←	→
Arm3: BFR-AE group			←	→
Assessments				
Primary outcomes				
6-minutes walking test		←	—	→
30-s chair stand test		←	—	→
Secondary outcomes				
Other long-term indicators				
ASMI		←	—	→
Handgrip strength		←	—	→
Five-time chair stand test		←	—	→
Knee extensor muscle strength		←	—	→
knee flexor muscle strength		←	—	→
Pittsburgh Sleep Quality Index		←	—	→
Self-rating Anxiety Scale		←	—	→
Self-rating Depression Scale		←	—	→
Serum metabonomic		←	—	→
Serum signal protein		←	—	→
Instantaneous indicators				
Blood pressure		←	—	→
Heart rate		←	—	→
Saturation of pulse oxygen		←	—	→
Rating of perceived exertion			←	→
Pain score			←	→
Concentration of lactic acid		X	X	
Adherence of exercises			←	→
Adverse events			←	→

Figure 2 Schedule of enrollment, intervention and assessment.
Notes: Time points are: $-t_1$ = 2 weeks prior to allocation; t_0 = allocation and baseline testing; t_1 = after 12 weeks of interventions; t_2 = after 12 weeks of follow-up.
Abbreviations: AE, aerobic exercise; BFR, blood flow restriction; ASMI, appendicular skeletal muscle mass index.

Participants and Setting

One hundred seventy-one older adults (aged 60~90 years) with sarcopenia meet the inclusion and exclusion criteria will be recruited from three nursing homes. All intervention activity will take place in the rehabilitation centers of nursing homes where the participants reside.

The inclusion criteria include ① age between 60 and 90; ② conform to the diagnostic criteria of sarcopenia, possible sarcopenia and low muscle mass (pre-sarcopenia) from Asian Working Group for Sarcopenia (AWGS) in 2019;[21] ③ have independent living ability; ④ able to communicate; ⑤ have no regular exercise habit; ⑥ previously never engaged in BFRT; ⑦ willing to participate in the study.

The exclusion criteria include ① have contraindications of bioelectrical impedance analysis (BIA) test, including heart stents, pacemakers, steel plates or nails in their bodies; history of bone or joint surgery or blood vessel or skin graft surgery of lower limbs within 6 months; ② mobility disorder of dominant arm; ③ history of serious cardiovascular diseases or in the acute stage of diseases (such as acute myocardial infarction, acute heart failure, atrioventricular block); ④ using anticoagulant drugs; ⑤systemic open soft tissue injury and lymphedema; ⑥ hypertension that cannot be controlled by drugs (≥150/100mmHg); ⑦ other exercise contraindications (such as respiratory failure, cardiac function level 2 and above).

Participants who are unable to continue due to personal or objective reasons will be categorized as withdrawals.

Sample Size Determination

Sample size was calculated using PASS 15 software [Means (Multiple comparisons)] based on primary outcomes of 30-s chair stand test (used to assess muscle fitness) and 6MWD (used to assess cardiorespiratory fitness).

According to our prior experiment, the mean values of the 3 groups for 30-s chair stand test were 20.05, 15.96, 14.06, respectively, and the standard deviations were 8.85, 7.09, 5.69 respectively, the sample size of each group was 28. Assuming a dropout rate of 30%, the adjusted sample size for each group was calculated as 28/(1–0.3) = 40. Since there are three measurement points during the intervention, with potential dropouts at two of these points, the baseline sample size for each group was further adjusted to 40/(1–0.3) = 57. Therefore, a total of 171 participants will be included across the three groups.

Similarly, the mean values of 6MWD in the 3 groups were 460.56, 449.22 and 441.32 respectively, and the standard deviations were 80.56, 75.66, 71.60 respectively. Each group has a sample size of 15. Assuming a dropping rate of 30%, the adjusted sample size of each group was 15/(1–0.3) = 21. With potential dropouts at two of these points, the sample size was adjusted as 21/(1–0.3) = 30, and 90 cases will be included in the three groups.

Between the results derived from the two outcome indicators, the larger value is selected. Thus, the final sample size is set at 171, with 57 participants in each group.

Recruitment and Screening

The recruitment will be performed through face to face introduction after the consent of managers of nursing homes and in a cluster convenience sampling way. The older adults whose Barthel index (BI) in healthcare record between 96 and 100 and is willing to accept sarcopenia diagnostic tests will sign informed consent. During the tests, blood pressure (BP), heart rate (HR), saturation of pulse oxygen (SpO_2) and venous ultrasound of lower limbs will also be measured. After these, the eligible participants will be fully informed about the purpose and the risks of the trial, both orally and in writing forms.

Randomization and Allocation Concealment

Randomization will be conducted by a separate researcher who is not involved in screening and intervention. The randomization is completed using random number within a sequence in SPSS 25.0 software. Random grouping and visual box sorting function will be applied to generate a group of random numbers, be assigned to one of the number "0, 1, 2" and evenly divided into 3 groups. The control group is denoted as "0", the AE group as "1", and BFR-AE group as "2". The results will be kept in an opaque envelope and will not be opened until the exercise intervention starts. The researcher responsible for randomization and allocation will not participate in recruitment and intervention.

Blinding

To minimize bias, the researchers who perform the data analysis will be blinded to the group allocation and the exercise intervention.

Interventions

Participants in AE and BFR-AE groups will accept aerobic stepping exercise program and BFR combined with aerobic stepping exercise program respectively. The ones in control group are requested to maintain their usual diet and activity habit unchanged.

AE Program

The prescription of AE program include the following components.

(1) Style: continuous exercise with stepping machine (Jiujian, SCS1, China). The machine consists of 12 levels of pedal resistances and, the higher the level is, the greater the resistance is. The cycling miles are recorded automatically.

(2) Phases and intensity: ① 1~4 weeks (Initiating phase): low to moderate intensity; ② 5~12 weeks (Maintenance phase): moderate intensity; ③ 13~24 weeks (Follow-up phase): moderate intensity.

The exercise intensity will be determined through the heart reserve rate (HRR). Firstly, HRR is calculated out for each participant. According to previous literature, the exercise target heart rate (THR) of low and moderate intensity of AE equals to 30%~39% HRR and 40%~59% HRR plus resting heart rate (HR_{rest}), respectively.[22] The specific calculation method is as follows: HRR = maximal heart rate (HR_{max}) - HR_{rest}; HR_{max} = 207–0.7*age;[23] THR = HRR*expectation degree + HR_{rest}. If the patients' HR during exercise reach moderate intensity of AE or Rating of Perceived Exertion (RPE) between 12 and 13, it means they reach to the standard of exercise intensity.[22]

The HR_{rest} and HRR will be remeasured every two weeks during 1~12 weeks to ensure the suitable intensity. If a participant reaches moderate exercise intensity continuously for three sessions, lactate concentration will be measured using fingertip blood two minutes after the last session ends.

(3) Duration: 20 minutes each session, 2 sessions a day, and 10 minutes rest between 2 sessions.

(4) Frequency: 3 times/week, once every other day.

(5) Cycling speed: 60 rpm is recommended, but could be adjusted based on individual preference.

(6) Time period: exercise sessions will take place at half an hour after meals and not within 2 hours of bedtime. With these guidelines, participants can select exercise times that suit their preferences and habits. Participants will arrive at the intervention room within a fixed time period.

(7) Warm up and cool down exercises: a respective 3 minutes stepping exercise with resistance of the first level (level one).

(8) Indications of exercise cessation: significant hypertensive response, including systolic blood pressure > 250mmHg or diastolic blood pressure > 115mmHg; systolic blood pressure drop > 10mmHg; $SpO_2 \leq 80\%$ or less; occurrence of adverse events; self-requested termination by the participant.

The exercise will be performed in the special intervention room in the nursing homes. The temperature and humidity of the room are kept at 22~27°C and 50%~60%, respectively. Participants wear clothing of similar thickness in each time of exercise.

For safety reason, the intervention room is equipped with first aid kit, electrocardiograph monitoring instrument, temperature and humidity detector, pulse oximeter, stopwatch, omron electronic sphygmomanometer, the wooden chair with armrest, some bread, fruit, candy, snacks, hot water, cups, exercise recording sheet and other necessary materials. Three qualified nursing researchers will provide exercise supervision and safety monitoring for six participants. Additionally, each nursing home will have two or three nurses, doctors, and sports trainers available for emergency assistance if needed.

BFR-AE Program

In the BFR-AE program, the prescription of AE remains the same as in the AE program; however, BFR is applied to the lower limbs during AE sessions.

The BFR is applied using the elastic BFR bands (BStrong, United States; 7.5 cm wide × 105 cm long). The upper edge of the band is positioned as close to the groin as possible without limiting leg movement and the cuff is secured with

velcro to ensure it remains snug and does not slip during exercise. When in place, the uninflated band should have enough space underneath to fit the researcher's index finger. The band remains inflated at 250 mmHg throughout the exercise session and is slowly deflated within 30 seconds after exercise. Lightweight, close-fitting pants are recommended to ensure no wrinkles form beneath the bands. Warm up and cool down exercises follow the same protocol as in the AE program, with the additional BFR during warm up at an inflation pressure of 75 mmHg.

Baseline Character Measurements

A self-designed questionnaire is used to gather demographic information (eg, sex, age), health-related data [eg, resting BP, HR, diagnosed disease, and current medications], and exercise or activity details (eg, participations in physical activities and duration) (Table 1). Participants are instructed to complete the questionnaires uniformly and the

Table 1 General Information of Participants

Indicators	Results
Demographic Data	
Age (years)	Original values
BMI (kg/m^2)	Original values
Sex	Male / Female
Educational level	Primary school and below / Junior high school / Senior high school or technical secondary school / Junior college or undergraduate / Graduate and above
Marital status	Married / Unmarried and others
Occupation	Physical labor / Physical and mental labor / Mental labor
Living in nursing home (months)	Original values
Health-related data	
SBP (mmHg)	Original values
DBP (mmHg)	Original values
Heart of rest (beats/min)	Original values
Hypertension	Yes / No
Diabetes	Yes / No
Stroking	Yes / No
Hyperlipidemia	Yes / No
Bronchitis or asthma	Yes / No
Parkinson	Yes / No
Coronary heart disease	Yes / No
Cancer	Yes / No
Other diseases	Yes / No
Current medication	Yes / No
Take health supplements	Yes / No
Falling history	Yes / No
Assist tool	Yes / No
Self health care level	No / Low / Moderate / High
Joint dysfunction	Yes / No
Surgery of lower limbs	Yes / No
Pain	Yes / No
Exercise or activity	
Physical activity	Yes / No
Physical activity (hours/day)	Original values
Physical activity (days/week)	Original values
Intensity of Physical activity (sweating)	No / Slight / Moderate / Heavy
Sedentary time (hours/day)	Original values
Willing to exercise	No / Weak / Moderate / Strong
Acceptance of knowledge	Yes / No
Sarcopenia diagnosis	Possible sarcopenia / Sarcopenia / Severe sarcopenia / Pre-sarcopenia

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

questionnaires will be collected on-site. Each questionnaire will be checked for errors and omissions, and any issues will be promptly addressed by researchers.

Outcomes

Primary outcomes

The 6MWD and 30-s chair stand test which stand for cardiorespiratory and muscle fitness respectively are considered as primary outcomes.

6MWD

The 6MWD test procedure follows the principles of the American Thoracic Association.[24] The researchers record the walking distance of the participants every minute in time. If the participants are physically intolerant and unable to continue the test, their walking distance and time are recorded and the test is ended ahead of time.

30-s Chair Stand Test

The 30-s chair stand test follows the procedure described in previous literature.[25] The participants will complete the up-and-sit movements as many times as possible within 30 seconds. If the last sit-up is completed more than 50% when the "end" commond is issued, it will be counted.

Secondary Outcomes

Secondary outcomes include additional long-term indicators, instantaneous indicators, exercise adherence and adverse events.

Additional Long-Term Indicators

Additional long-term indicators consist of appendicular skeletal muscle mass index (ASMI), handgrip strength, five-time chair stand test, lower extremity knee extensor and flexor muscle strength, Pittsburgh sleep quality index (PSQI), self-rating anxiety scale (SAS), self-rating depression scale (SDS), serum metabonomic and signal protein.[11, 26–30]

ASMI is measured by BIA with a composition analyzer (INBOBY, S10, Korea). The handgrip strength is measured by a hydraulic dynamometer (Jamar, 563213, USA). The five-time chair stand test will follow AWGS's recommendation.[21] Lower extremity knee extensor and flexor muscle strength is tested with the MicroFET3 portable muscle strength and range of motion tester (Hoggan, 120382, USA). PSQI is used to evaluate the sleep quality of the last month[31] and SAS and SDS are used to test the anxiety and depression status of participants.[28,29] Serum metabonomic is tested based on nuclear magnetic resonance (NMR) technology. Serum signal proteins, including growth hormone (GH) and vascular endothelial growth factor (VEGF), are measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D, USA).

Instantaneous Indicators

Instantaneous indicators include BP, HR, SpO_2 and lactic acid before and after exercises, RPE, and pain score.

BP, P and SpO_2 will be measured with wrist electronic sphygmomanometer (OMRON, 18F052-21, China) and pulse oximeter (Yuyue, YX102, China) respectively in sitting position. The HR is equal to the pulse rate if the participants do not have atrial fibrillation. In this study, the measured pulse rate is used to replace the HR. Lactic acid will be tested through lactic acid tester (LACTATE SCOUT, EKF, Germany). Blood sample from the tip of the left ring finger will be collected before and after exercise when the participants get the moderate intensity of AE. The degree of fatigue will be evaluated by Rating of Perceived Exertion Scale[22] and the pain is assessed by numeric rating scale (NRS).[32]

Adherence of Exercise

It will be expressed as a percentage of the ratio of actual exercise to the prescribed amount of exercise. Exercise adherence = [actual exercise time per day * times per week/target exercise completion time per day (40 min) * exercise times per week (3 times)] * 100%. The result of 80%, 60~80% and a less than 60% stand for good, medium and poor exercise adherence respectively.

Adverse Events

The adverse events of the participants during the test, the time of occurrence and the way of treatment will be recorded and reported. The doctors and nurses are responsible for dealing with the adverse events.

Statistical Analysis

IBM SPSS 23.0 statistical software will be used for data analysis. The principle of intention-to-treat (ITT) analysis will be employed to evaluate efficacy. The ITT sample will include all eligible individuals, including those who withdrew from the study, but will exclude individuals who were not eligible. If the results are not significant, we will conduct a per-protocol (PP) analysis to further clarify the findings. The Shapiro–Wilk test will assess data normality. Numerical variables conforming to a normal distribution will be expressed as mean ± standard deviation (SD); otherwise, they will be expressed as median and interquartile range M (P_{25}, P_{75}). Categorical variable data will be shown as frequency and percentage n (%). Missing data will be imputed using Multiple Imputation (MI). Generalized Estimating Equations (GEE) will compare the same index across different time points before and after intervention. If statistically significant differences are found between the three groups, a paired sample t-test will be conducted for pairwise comparison with appropriate correction on the P values.

Data Management and Monitoring

All personal information, including details like age and disease progression, will be kept strictly confidential. Electronic data will be stored on a protected platform at the university, while paper copies of assessment forms will be stored in locked cabinets located at the university location of the remote study research staff. All data will be double entered for data quality monitoring, with 20% of the entries randomly selected for verification and correction.

Harm

All data will be carefully collected and assessed from participants. Once an adverse event occurs, participants are instructed to quickly contact researchers. All adverse events will be reported together with the other outcomes of this study.

Discussion

Currently, BFR-RE is the primary intervention for older adults with sarcopenia. A meta-analysis examining BFRT to improve muscle fitness in individuals with skeletal muscle-related diseases identified 20 articles. Among these, 13 focused on populations at risk for sarcopenia, including postmenopausal women, individuals with knee dysfunction, and frail older adults, three articles addressed knee anterior cruciate ligament surgery, three discussed knee arthritis, and one involved patients with inclusion body myositis. The study concluded that the effectiveness of BFRT is still inferior to that of traditional high-intensity exercise.[33] However, compared with low-load training, low-load BFR training is more effective, tolerable and therefore a potential clinical rehabilitation tool. It is important to note that this study is not specifically targeting older adults with sarcopenia, and the overall quality of the 20 articles was not very high. Additionally, there is a lack of research on the long-term effects of BFR-AE in this population. Therefore, the objective of this study is to develop an intervention plan that incorporates BFR-AE specifically designed for sarcopenia. This study aims to investigate both the rehabilitative outcomes and the underlying mechanisms that contribute to improvements in cardiorespiratory and muscular fitness.

To the best of the authors' knowledge, this will be the first study to utilize elastic BFR bands combined with AE in older adults with sarcopenia. This study is designed as a three-arm, parallel, randomized controlled trial conducted in three different nursing homes, adhering strictly to the principles of randomization and blinding. Randomization will be performed using a random number sequence generated in SPSS 25.0 software. While the participants and primary researchers will be aware of the group assignments, to minimize bias, the researcher responsible for data analysis will remain blinded to both the group allocations and the exercise interventions. Furthermore, the large sample size may enhance the generalizability of the results to broader populations.

In this study, AE is used as the primary intervention, with cardiorespiratory fitness identified as the primary outcome. Traditional methods for measuring cardiorespiratory fitness include VO_{2max}, heart rate load, and 6MWD.[34] While VO_{2max} is considered the gold standard, the 6MWD is more convenient and has demonstrated reliable predictive validity for VO_{2max}. Therefore, this study will utilize the 6MWD as an indicator of cardiorespiratory fitness in older adults with sarcopenia. A few studies have applied BFR-AE to individuals at high risk for sarcopenia, such as older adults with insufficient physical activity.[18] Results indicate that, compared to AE alone, combined exercise significantly improves cardiopulmonary fitness (as measured by 6MWD) and lower limb strength (assessed through the 30-second chair stand test). For example, Ozaki et al conducted a 10-week intervention involving BFR combined with walking (20 minutes per session, four times a week at 45% HRR) for older adults at risk of sarcopenia.[17] Their findings showed that the combined group had greater improvements in knee extensor muscle strength and muscle cross-sectional area compared to the walking-only group. These studies suggest that BFR-AE may enhance both cardiorespiratory fitness and muscle fitness in older adults with sarcopenia. Consequently, we have selected the 30-second chair stand test as a secondary primary outcome to evaluate muscle fitness.

For the data analysis, we will employ ITT analysis to evaluate efficacy, which minimizes selection bias by including all randomly assigned participants, regardless of whether they completed the study. However, because participants who deviated from the protocol are still included in the analysis, there is a possibility that the exercise effect may be overestimated. Additionally, lower adherence could lead to negative results. In instances where the findings are not significant, we will conduct PP analysis as supplementary results.

We may encounter several challenges during the experiment. First, if we strictly adhere to the diagnostic criteria for sarcopenia, the number of eligible participants may be insufficient, necessitating recruitment from additional nursing homes, which could increase the burden on our resources. In this study, we will use the diagnostic criteria established by AWGS2019,[21] including severe sarcopenia, sarcopenia, and possible sarcopenia. This approach aligns with the recommendations of the 2019 Asian Consensus on the Diagnosis and Treatment of Sarcopenia, emphasizing the importance of early prevention and timely intervention.[21] Second, exercise adherence among older adults may be lower than in healthier populations. To enhance adherence, we will implement exercise reminders on designated exercise days for both the AE and BFR-AE groups, and researchers will be available to address any questions participants may have regarding the intervention. Additionally, we will display an exercise ranking list, updating it monthly with the names of participants who have met their prescribed exercise goals. The top ten participants will be featured on a publicity board in the nursing home to motivate others to maintain their exercise routine.

This study has several limitations. First, while AE can improve muscle fitness, it may not be as effective as RE. In future research, we plan to develop combined AE and RE programs to enhance muscle fitness more effectively. Additionally, for the sake of convenience and feasibility in older adults with sarcopenia, maximal or peak oxygen uptake will not be tested. Instead, we will use the 6MWD to assess cardiorespiratory fitness, and HR and RPE will be utilized to evaluate and adjust exercise intensity.

Conclusion

This study aims to evaluate the effects of BFR-AE on improving physical fitness in older adults with sarcopenia through a randomized controlled trial and to explore the associated metabolic and signaling mechanisms. The findings from this study will offer caregivers and healthcare professionals new approaches for the prevention and management of sarcopenia.

Access to Data

Any third party will have access to the final trial data under reasonable request to the corresponding author.

Dissemination Plan and Authorship

Findings of the study will be published in peer-reviewed journals and at provincial, national and international conferences. In accordance with the International Committee of Medical Journal Editors' standards, authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. No researcher shall include identifiable personal health information in any publication or presentation.

Confidentiality

Only permitted researchers have access to data and research design. The data will be strictly confidential before, during and after the research. We will not share any information with third parties. The relevant members of the Ethics Committee of Soochow University will also strictly abide by the confidentiality regulations and avoid any form of data leakage.

Trial Registration

This study was registered under the access code ChiCTR2200064080 in the Chinese Clinical Trial Registry on 26 September, 2022.

Trial Status

The protocol was started in March 2022, and approval from the ethics committee was obtained in June 2022. Patient recruitment will begin in October 2022 and is expected to be completed in June 2023. The study will be completed in October 2024.

Research Ethics Approvals

The study will be conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Soochow University, China (protocol code SUDA20220723H01 and date of approval 23 July 2022). Protocol modifications will be approved by Ethics Committee prior to implementation of the changes.

Patient and Public Involvement

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

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; had agreed on the journal to which the article had been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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