The Combined Intervention of Exercise, Fruit, and Vitamin Supplementation on Frailty in Community-Dwelling Older Adults: A Pragmatic Cluster Randomized Controlled Trial

Protocol

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Nanjing Medical University

Protocol version history

Version Date	Protocol Version	Details of Changes
August 3, 2023	1.0	-
September 5, 2023	2.0	Adding detail description of the intervention
January 18, 2024	3.0	Adding information on trial registration and ethical approvals

1 Introduction

Frailty, a complex clinical condition, is characterized by the progressive loss of physiological capacity and increased vulnerability to stress [1] [2] [3]. With a rapidly expanding aging population, frailty is highly prevalent, varying from 4% to 59% depending on measurement tools or setting [4]. Frailty is associated with adverse outcomes, such as falls and fractures, hospitalization, disabilities, lower quality of life, dementia, and early mortality [5] [6] [7].

Remarkably, frailty is a dynamic entity and transitions between different states (robust, pre-frail, and frail) occur frequently over time [8]. Hence, preventing or slowing the progression of frailty before it precipitates significant functional decline is crucial for both clinical practice and public health. Current interventions for frailty show limited efficacy, primarily due to their initiation after the onset of pre-frailty or frailty, missing critical early windows for action[9-16]. Additionally, frailty manifests heterogeneously across physical, cognitive, and social domains, requiring personalised management strategies[17].

The WHO recommends identifying vulnerable older adults and supporting them maintain and enhance their intrinsic capacity to prevent or reverse functional decline [18]. Preserving functional capacity, particularly muscle strength, is crucial for healthy aging and could delay frailty progression. Grip strength, a key marker of muscle strength, typically begins to decline around age 50, with men experiencing an average reduction of 5 kg per decade and women 3 kg, with further acceleration during hospitalization [19,20]. Decreased grip strength is generally recognized as an indispensable clinical manifestation of frailty [21] [3]

Optimising outcomes may benefit from a focus on modifiable risk factors, emphasizing early intervention and precise population targeting. Evidence shows that a link between inadequate physical activity and low fruit consumption with frailty [22] [23] [24]. Inadequate fruit intake is associated with increased frailty risk, likely due to the protective effects of vitamins on physiological resilience and cellular aging[25]. However, combined interventions incorporating exercise, fruit intake, and vitamin

supplementation to preserve muscle strength for slowing frailty progression in at-risk older adults remain underexplored.

Moreover, there are few studies exploring interventions that are suitable for long-term implementation in community settings. Thus, the prospective cluster-randomized, controlled, two-armed study assesses the effect of the combined intervention of exercise, fruit, and vitamin supplementation on frailty among older adults aged 65-80 years with low levels of physical activity and fruit intake. 14 villages are randomized in a 1:1 ratio to either the intervention or control arm. Participants in the intervention groups receive the combined intervention at both individual and group levels, whereas those in the control groups receive routine health education only. It is hypothesized that participants submitted to the combined intervention will present better muscle strength. If effective, this trial has the potential for implementation through other community-based effective organizing.

2 Setting

The evaluation is conducted at community activity centers or daycare centers in Wuzhong District, Suzhou. As a major economic hub in China's Yangtze River Delta region, Suzhou is situated in the eastern part of Jiangsu Province and features a well-developed infrastructure. Wuzhong District, located in the central part of Suzhou, contains numerous community activity centers that offer adequate public spaces for the evaluation. A complete list of the study sites can be found on the trial's official government website (https://www.suzhou.gov.cn/).

3 Participant eligibility

Participants are included in the study if they meet the following criteria: (1) are permanent residents aged 65 – 80 years; (2) are able to walk independently both indoors and outdoors; (3) have total physical activity less than 1400 metabolic equivalent task (MET)-min/week; (4) have daily fruit intake less than 50 g; (5) have not taken vitamin B or vitamin C supplements in the preceding 3 months; (6) have sufficient Chinese proficiency to provide informed consent.

The exclusion criteria are as follows: (1) participants who are not present at their residences during the survey; (2) participants who refuse to engage or fail to complete the questionnaire.

4 Interventions

Intervention Level: The intervention is implemented at both individual and group levels.

Intervention Methods:

(1) Individual-level: includes structured exercises (fitness aerobics, Baduanjin, hand grip ball exercises, and simple repetitive movements), fruit consumption, and vitamin supplementation (vitamin C and B complex);

(2) Group-level: includes communication and discussion sessions, as well as health education activities.

Frequency of Intervention:

(1) Individual-level: exercise sessions and fruit consumption are administered three times per week for two months (specifically during the 1st and 6th months). Each session lasts at least 30 minutes and involves the consumption of a minimum of 50 grams of fruit. Additionally, one tablet of vitamin B complex and one tablet of vitamin C are administered daily throughout the entire intervention period;

(2) Group-level: a 15-minute communication and discussion session is conducted after each individual-level intervention. A 45-minute health education session is conducted during the final session of each month.

At the individual level, the intervention is conducted 3 times weekly for 2 months (the 1st and 6th months). To guarantee uniformity in the intervention delivery, it is administered at 14:00 across all groups, unless otherwise specified in particular circumstances. Participants gather at the nearest community activity centre. Community workers project fitness aerobics videos and act as trainers, calling on participants to stand up and join the exercises. Investigators record the start time, and each session lasts approximately 20 minutes. To accommodate participants' physical conditions and preferences, the principle is to encourage rather than enforce participation. If participants decline fitness aerobics, community workers distribute

hand grip balls as an alternative. Participants are instructed to grip the ball with maximum strength (hold for 2 seconds, relax for 2 seconds). Finally, community workers guide participants to do a series of simple repetitive movements, including clenching fists, rubbing hands, sitting leg lift, shoulder shrug, sitting leg lift palm clap, and leg cross clap arm.

The duration of exercise lasts longer than 30 minutes. The investigators supervise the entire process, ensuring participants' adherence to the exercise routine. They actively remind and encourage participants to continue exercising if they pause or discontinue during the session. Exercise time and any discomfort symptoms during exercise are recorded in detail. The investigators immediately terminate the exercise session if a participant experiences any discomfort.

The fruit is divided into 50-gram portions. Various types of fruit, with priority given to varieties exhibiting high antioxidant capacity and locally cultivated fruits, including cherry tomatoes, bananas, oranges, and others, are prepared to accommodate the needs of different participants. For each intervention, two types of fruit are selected. Participants are required to consume the fruit on-site (they may consume more than 50 grams), and the actual amount consumed is recorded. In addition, information is collected on the participants' average daily fruit intake at home between interventions.

During the intervention, the participants take one tablet of vitamin B complex daily, which contains vitamin B1 (3 mg), vitamin B2 (1.5 mg), vitamin B6 (0.2 mg), niacinamide (10 mg), and calcium pantothenate (1 mg), along with one separate tablet of vitamin C containing 100 mg daily. All supplements are manufactured by Huazhong Pharmaceutical Co., Ltd. Medication compliance is monitored.

In the group-level intervention, a 15-minute communication and discussion session is conducted. Community health workers provide brief health education on preventing frailty in the local dialect and encourage participants to continue exercising and eating fruits at home. Furthermore, a health education session is held in the last session of each month, with a minimum duration of 45 minutes. The purpose of this session is to reinforce participants' theoretical understanding, thereby

consolidating the intervention's effects and fostering long-term adherence to healthy habits.

A standardized on-site intervention protocol is developed to ensure the consistency and standardization of procedures across all intervention sites (Table 1). Adequate staffing and clear task allocation are essential for the orderly on-site implementation of the intervention. Each site is staffed with a minimum of five personnel, who can be flexibly assigned to different roles based on operational needs (Table 2).

Table 1. Standardized on-site intervention procedures

Step	Workflow	Precautions
Check-in	(1) Upon arrival at the intervention session, participants are registered by a staff member, who documents their name and time of attendance on a session-specific sheet. (2) Before the intervention session begins, participants are seated and encouraged to engage in social interaction through casual conversation.	If no staff member is familiar with the participants, consider distributing name tags to facilitate monitoring and recording during the intervention.
Vitamin Supplementation	(1) A staff member distributes vitamin tablets and water to each participant sequentially, explains the procedure, and instructs them to take the supplement. (2) The investigator documents each participant's vitamin consumption.	-
Fruit Intake	(1) It is recommended that two fruit types be prepared for each session. (2) Pre-weighed fruit portions are distributed to each participant with instructions for immediate consumption. The actual intake is then observed and recorded. (3) For participants who prefer to avoid cold foods, fruit may be gently warmed using hot water prior to consumption. (4) Participants are required to consume all fruit on-site and may not take any away.	Diabetic participants are advised to select from fruits with a low glycemic index.
Exercise	(1) After all participants complete the friut and vitamin intervention, two staff members subsequently organize the group for physical	-

	exercise. (2) A supervised session of group aerobics is initiated, with the start time recorded. Participants are provided a stress ball as needed if they are unwilling or unable to complete the aerobics. This combined session lasts 15-20 minutes. A 10-minute session of repeated limb movements is conducted. For specific exercise details, please refer to the "2.3 Interventions" section. (3) Record the activity details and end time.	
Distribution of next-day vitamins	The vitamin tablets for the following day are distributed. Participants are instructed to consume them the next day. Adherence is assessed during the subsequent intervention session.	-
Information archiving	Following all daily intervention activities, each participant's intervention record form is photographed. The images are compiled and submitted to the project team for verification, data entry, and archiving.	-

Table 2. Staffing and responsibilities at each intervention site

Task	Number of Personnel	Responsibilities
Leader	1 from community hospital 1 from project team	Coordinate and manage on-site activities
Registration	1 from community hospital	Register participants and distribute name tags; Document at-home fruit intake and vitamin supplementation
Distributes materials and records intervention data	2 from community hospital 1 from project team	Distribute exercise equipment, fruit, and vitamins; Document fruit and vitamin intervention data
Exercise instructor	1-2 from community service center/day care center.	Lead group exercises
Exercise session monitor	1 from community hospital 1 from project team	Supervise, guide, and motivate participants; Promptly provide stress balls as an alternative activity to those unwilling to exercise.

5 Outcomes

5.1 Primary outcome

The primary outcome of the trial is the change in handgrip strength at 12 months from baseline. Handgrip strength is measured using a hand-held grip dynamometer. Participants are instructed to grip the dynamometer with their left and right hands respectively while standing, keeping their arms close to their bodies and straight down, exerting maximum force. This test is conducted 3 times, and the values are recorded in kilograms.

5.2 Secondary outcome

1) The change in handgrip strength at 6 months from baseline. The definition and measurement method are the same as the primary outcome.

2) The change in frailty score at 6 months and 12 months from baseline. The outcome is defined as the change in the score of modifiable variables in the frailty index from baseline. The frailty index consists of more than 20 variables, covering age, physical measurements, sleep quality, history of surgery, falls, fractures, medical history, oral hygiene, respiratory function, and self-assessed physical function. The frailty index is a continuous variable, with a higher value indicating a frailer status.

3) A composite of all-cause death, myocardial infarction, angina, and stroke within 12 and 24 months after enrollment. Angina is defined as receiving treatment for any of the following ICD codes: I20. Myocardial infarction is defined as receiving treatment for any of the following ICD codes: I21 or I22. Stroke is defined as receiving treatment for any of the following ICD codes: I60-I64.

4) All-cause death within 12 and 24 months after enrollment.

5) Myocardial infarction within 12 and 24 months after enrollment.

6) Angina within 12 and 24 months after enrollment.

7) Stroke within 12 and 24 months after enrollment.

8) All-cause hospitalization within 12 and 24 months after enrollment. It is defined as any hospital admission event, irrespective of cause.

9) The change in lipid parameters at 12 months and 24 months from baseline. Lipid parameters include total cholesterol (TC) and triglycerides (TG).

10) The change in fasting blood glucose at 12 months and 24 months from baseline. It is measured by the Glucose Oxidase (GOD) method.

11) Incremental cost-effectiveness ratio (ICER). It is calculated by dividing the difference in costs between the two interventions by the difference in their effects.

6 Adherence to the intervention

Completion of a single intervention is defined as engaging in at least 30 minutes of physical activity and consuming at least 50 grams of fruit supplementation. If the participants do not meet the criteria, the values will be recorded truthfully. Theoretically, participants in the intervention group are expected to attend 12 on-site interventions each month of the intervention period. Good compliance among participants is defined as completing 9 or more.

If the study participant is absent more than 3 times in each intervention month, the expected intervention deadline should be postponed to complete the established number of interventions. If participants reject the plan, the reasons for their refusal will be recorded.

7 Participant timeline

Please see Figure 1.

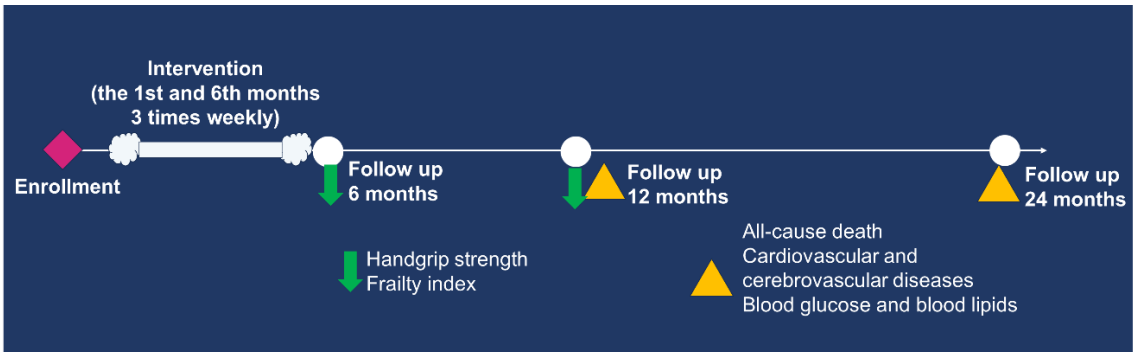

Figure 1. Participant flow from enrollment to the end of follow-up.

8 Sample size

Sample size was estimated using PASS (Power Analysis and Sample Size) software (version 15.0.5) based on data from previous studies. Previous studies showed that the Cohens' d value was between 0.25~1.25 [26-30]. With the exception of one study that enrolled frail individuals with a 12-week intervention and a 4-month follow-up, which reported a Cohen's d of 1.25, all other studies reported Cohen's d

values below 0.7. Based on this information, we assumed a medium effect size of Cohen’s d = 0.45 [31], considering probabilities of 5% for type I error, 20% for type II error, and 0.05 for intraclass correlation coefficient (ICC). We randomized all 14 clusters (villages) into two arms with 1:1 ratio, and the total sample size was calculated to be 700 (50 participates per cluster). Estimating a conservative 25% loss to follow-up or drop-out, a total of 934 participants will be required.

9 Recruitment

Study recruitment begins in February 2024. To enhance recruitment efficiency and population representativeness, 14 villages/communities are selected from the existing Suzhou Older Adults Cohort (SOAC) using a random cluster sampling method.

Potential participants are identified and their eligibility is verified by the investigators. All eligible participants are informed of the study objectives. Recruitment efforts are then conducted via telephone and door-to-door approaches, after which written informed consent is obtained.

10 Randomization and masking

To prevent contamination, individual randomization is not considered [32]. The randomization units are villages, and the SAS PROC PLAN process generates a random sequence to assign 14 clusters (villages/communities) to the intervention and control arms in a 1:1 allocation ratio. The random allocation sequence is generated by an independent statistician, the clusters are enrolled by separate personnel, and an independent investigator assigns the clusters to interventions.

The randomization assignments remain concealed until the recruitment and collection of baseline data are completed. Due to the cluster design and the nature of the intervention, neither the participants nor the community health-care providers and research staff are blinded. However, the clinical outcome assessments are conducted in a blinded manner.

11 Data collection and management

All data collectors are trained in questionnaire content and electronic device operation. The anthropometric measurements are trained prior to the formal

investigation. In addition to blood pressure, height, blood oxygen, and heart rate variables, the remaining variables are recorded with precision up to two decimal places. Data are collected using electronic devices, and a paper copy is provided as a backup in case of electronic failure. Data quality checks are built into the e-questionnaire, for example, limiting ranges of responses/measurements to the credible range, setting questions as ‘required’ to avoid missing questions, and checking for consistency between questions. Participants who do not complete the intervention are still followed up and assessed for outcome measures.

12 Statistical analysis

Primary analyses will be conducted based on the intention-to-treat (ITT) principle, with no imputation for missing endpoint data. The primary outcome will be the change in handgrip strength from baseline to 12 months. A generalized linear mixed model (GLMM) will be employed. The model will include treatment, time, and the treatment-by-time interaction as fixed effects. Random effects will account for subject, hand nested within subject, and community (cluster).

Given the potential for type I error due to multiple comparisons, all analyses of secondary outcomes will be interpreted as exploratory. Changes in handgrip strength (from baseline to 6 months) and the frailty index (from baseline to 6 and 12 months) will be analyzed following the same method as the primary outcome. The effect of the intervention on a composite endpoint, comprising all-cause mortality, myocardial infarction, angina, and stroke, as well as on all-cause hospitalizations, will be evaluated using GLMM with a Poisson distribution. Each individual component of the composite outcome will be analyzed using the same method. Additionally, changes in total cholesterol, triglycerides, and fasting blood glucose from baseline to 12 months will be evaluated using a GLMM, which will include treatment as a fixed effect and incorporate community as a random effect to account for clustering.

Several sensitivity analyses and subgroup analyses will assess the robustness of the primary outcome findings. Statistical significance will be defined as two-tailed $P < 0.05$. All analyses will be performed using R version 4.4.1.

13 Ethics and dissemination

All participants enrolled in this trial are provided with insurance. This RCT is carried out in accordance with the principles from the Helsinki Declaration. This trial has been approved by the Institutional Review Board of Nanjing Medical University (ID:2023588). The trial is registered at www.clinicaltrials.gov (ID: NCT06225271).

14 Publication policy

The study results will be published in an appropriate international peer-reviewed scientific journal. All authors must fulfil the criteria for authorship according to the ICMJE group. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall data set, consider all reasonable requests to make the data set available in whole or part for secondary analyses and scientific publication.

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