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

Statistical Analysis Plan

The data management and statistical analysis plan is directed to support the aims of the study

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SAP version history

Version Date	SAP Version	Details of Changes
August 3, 2023	1.0	-
May 6, 2025	2.0	Adding detail description of GLMM estimation
July 6, 2025	3.0	Adding effect size description
September 14, 2025	4.0	Add Graphical/Tabledisplays

Introduction

Frailty is an age-related syndrome characterised by diminished physiological reserve and reduced resilience to minor stressors, leading to adverse health outcomes and posing a growing public health challenge. It progresses dynamically from robustness to pre-frailty and frailty, highlighting the potential for intervention to reverse it [1].

The WHO recommends identifying vulnerable older adults and supporting them maintain and enhance their intrinsic capacity to prevent or reverse functional decline [2]. 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 [3, 4].

Physical activity demonstrates strong potential for mitigating frailty progression [5]. Inadequate fruit intake is associated with increased frailty risk, likely due to the protective effects of vitamins on physiological resilience and cellular aging [6]. This prospective cluster-randomised, controlled, two-armed study is designed to assess the effect of the combined intervention of exercise, fruit, and vitamin supplementation on mitigating frailty progression in at-risk older adults.

1 Study objective and outcomes

1.1 Study objective

This study is a prospective, cluster-randomised, controlled trial with two arms, aimed at evaluating the effectiveness of a combined intervention involving exercise, fruit consumption, and vitamin supplementation on muscle strength preservation in older adults aged 65-80 years who have low levels of physical activity and fruit intake.

2.2 Outcomes

2.2.1 Primary outcome

The primary outcome of the trial is the change in handgrip strength at 12 months from

baseline.

Time Frame: baseline, 12th month after initiation of intervention

Type: repeated measured continuous variable

2.2.2. Secondary outcomes

(1) The change in handgrip strength at 6 months from baseline.

Time Frame: baseline, 6th month after initiation of intervention

Type: repeated measured continuous variable

(2) The change in frailty score at 6 months and 12 months from baseline.

Time Frame: baseline, 6th month, 12th month after initiation of intervention

Type: repeated measured continuous variable

(3) A composite of all-cause death, myocardial infarction, angina, and stroke within 12 and 24 months after enrollment.

Time Frame: 12th month, and 24th month after initiation of intervention

Type: time-to-event (survival data)

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

Time Frame: 12th month, and 24th month after initiation of intervention

Type: time-to-event (survival data)

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

Time Frame: 12th month, and 24th month after initiation of intervention

Type: time-to-event (survival data)

(6) Angina within 12 and 24 months after enrollment.

Time Frame: 12th month, and 24th month after initiation of intervention

Type: time-to-event (survival data)

(7) Stroke within 12 and 24 months after enrollment.

Time Frame: 12th month, and 24th month after initiation of intervention

Type: time-to-event (survival data)

(8) All-cause hospitalization within 12 and 24 months after enrollment.

Time Frame: 12th month, and 24th month after initiation of intervention

Type: time-to-event (survival data)

(9) The change in total cholesterol at 12 months and 24 months from baseline.

Time Frame: baseline, 12th month, and 24th month after initiation of intervention

Type: repeated measured continuous variable

(10) The change in triglycerides at 12 months and 24 months from baseline.

Time Frame: baseline, 12th month, and 24th month after initiation of intervention

Type: repeated measured continuous variable

(11) The change in fasting blood glucose at 12 months and 24 months from baseline.

Time Frame: baseline, 12th month, and 24th month after initiation of intervention

Type: repeated measured continuous variable

(12) Incremental cost-effectiveness ratio (ICER).

Time Frame: 12th month after initiation of intervention

3 Study design

3.1 Design

This prospective cluster-randomised, controlled, two-armed study is designed to assess the effect of the combined intervention of exercise, fruit, and vitamin supplementation on mitigating frailty progression among older adults aged 65-80 years with low levels of physical activity and fruit intake. 14 villages were randomized in a 1:1 ratio to either the intervention or control arm. Participants in the experimental group receive the combined intervention at both individual and population levels, whereas those in the control groups receive routine health education only.

3.2 Trial sites

Community activity centres or day care centres in Wuzhong District, Suzhou.

3.3 Interventions

3.3.1 Experimental group

Intervention level:

Individual-level intervention

Intervention methods:

(1) Exercise: including fitness aerobics; Baduanjin; hand grip ball exercises; finger exercises; simple repetitive movements (clenching fists, rubbing hands, sitting leg lift, shoulder shrug, sitting leg lift palm clap, and leg cross clap arm).

(2) Fruit consumption: on-site consumption required, two types of fruit available for selection at each session.

(3) Vitamin supplementation: including vitamin C and B complex vitamins.

Frequency of intervention:

(1) Exercises: 3 times weekly for 2 months (during the 1st and 6th months). Each session lasts more than 30 minutes.

(2) Fruit consumption: 3 times weekly for 2 months (during the 1st and 6th months). Each session involves more than 50 grams of fruit.

(3) Vitamin supplementation: during the intervention period, the participants took one tablet of vitamin B complex and one tablet of vitamin C daily.

Intervention level:

Group-level intervention

Intervention methods:

(1) Communication and discussion sessions;

(2) Health education activities.

Frequency of intervention:

(1) A 15-minute discussion session after each individual-level intervention;

(2) A 45-minute health education session conducted monthly.

3.3.2 Control group

Participants in the control group receive routine health education and do not receive the active intervention.

3.4 Randomisation

To prevent contamination, individual randomisation was not considered [7]. Moreover, a cluster-randomised controlled design allowed for the assessment of interventions at

multiple levels [8]. The randomisation units were villages. A simple random sampling approach was used, with the SAS PROC PLAN procedure generating a random sequence to assign 14 clusters (villages) to the intervention and control arms in a 1:1 allocation ratio.

3.5 Blinding

The randomisation assignments will 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 can be blinded. However, the clinical outcome assessments will be conducted in a blinded manner.

3.6 Sample size

The sample size was estimated using PASS (Power Analysis and Sample Size) software (version 15.0.5) based on data from previous studies. These studies reported Cohen's d values ranging from 0.25 to 1.25 [9, 10, 11, 12, 13]. 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 estimated effect size of Cohen' d = 0.45, considering probabilities of 5% for type I error, 20% for type II error, and 0.05 for intraclass correlation coefficient (ICC). A total of 14 clusters (villages) were randomised into two arms in a 1:1 ratio. With 50 participants per cluster, the total calculated sample size was 700. Estimating a conservative 25% loss to follow-up or drop-out, a total of 934 participants will be required.

4 Analysis consideration

4.1 Trial hypothesis

The hypothesis H0: "No difference in the change of handgrip strength at 12th month between two groups." will be tested against the alternative" H1: "The change of handgrip strength at 12th month is different between two groups."

4.2 Study population data sets

Two study populations will be considered in the analysis as follows:

-Intent-to-Treat population

Intent-to-treat (ITT) population will be defined at the moment the randomisation is performed. This will be the primary analysis for the trial.

-Per-protocol population

For the per-protocol analysis, the experimental group will be defined as those participants who actually received the treatment. Participants will be excluded from the per-protocol population if they complete fewer than 9 intervention sessions per month (with 12 sessions required monthly) or fail to complete the 12-month surveys. This population will be used for the supportive analyses.

4.3 Study close date

The data collection close date is the date on which the last participants completed follow-up to achieve outcomes (complete 24 months follow-up).

4.4 Data cleaning

The data will then be checked to ensure that there are no erroneous entries and that all missing data is properly coded.

4.5 Data check-up

Once all data have been inputted and checked, the database will be locked. The data will be exported to R for statistical analysis.

5 Statistical analyses

5.1 Primary outcome analysis

5.1.1 ITT analysis of the primary outcome - the primary analysis

For the primary analysis of the ITT population, the between-group difference in the primary outcome (change in handgrip strength from baseline to 12 months) will be estimated using a generalized linear mixed model (GLMM), assuming a Gaussian distribution. Fixed effects will include group, time, the interaction between group and

time, and baseline handgrip strength. The random effects structure will account for multiple sources of variation: subject-specific random intercepts and slopes for time, random intercepts for the left and right handgrip measurements within subjects, and random intercepts for communities (clusters). An exchangeable residual covariance structure will be applied to account for within-subject correlations over time. Adjusted mean differences and 95% confidence intervals (CIs) between groups will be estimated from the fixed effects of the model.

5.1.2 Sensitivity analysis

5.1.2.1 Per-protocol analyses

The primary analysis model will be repeated in the Per-Protocol (PP) population.

5.1.2.2 Covariate adjusted analysis

The primary analysis model will be repeated in the ITT population with adjustment for age (continuous), sex (binary), education level (categorical), alcohol status (categorical), smoking status (categorical), BMI (continuous), and medical history including stroke (binary), cardiovascular disease (binary), tumour (binary), and COPD (binary).

If the above GLMM model does not converge, GLMM model will be performed with less covariates until convergence.

5.1.2.3 Generalized estimating equation (GEE) analysis

The change in handgrip strength from baseline between groups will be estimated using generalized estimating equations (GEE) that will account for within-cluster correlation, with an exchangeable working correlation structure. This analysis will be applied to the ITT population based on available data. The model will include group, time, the interaction between group and time, and baseline handgrip strength. The results will be reported as the adjusted mean difference between the study groups, with corresponding 95% confidence intervals.

5.1.3 Subgroup analyses

The primary analysis model will be repeated in prespecified subgroups, provided each contains a sufficient number of subjects after stratification. Stratification will be

conducted by the following factors: age (65-70 years, >70 years), sex (male, female), education status (illiterate, literate), marital status (married, living alone), smoking status (never smoker, former/current smoker), alcohol consumption (never drinker, former/current drinker), multimorbidity status (yes, no), household economic status (poor/moderate, good), baseline frailty status (robust, pre-frail), baseline physical activity level (≥600 MET-min/week, <600 MET-min/week), and body mass index (normal/underweight, overweight/obese).

Multimorbidity is defined as the presence of two or more of the following chronic conditions: diabetes mellitus, hypertension, tumour, coronary heart disease, stroke, and chronic obstructive pulmonary disease.

5.2 Secondary outcome analysis

For continuous variables with repeated measurements, changes in handgrip strength (from baseline to 6 months) and changes in the frailty index (from baseline to 6 and 12 months) will be analyzed using GLMM, consistent with the primary analysis. In the frailty index analysis, the random effect structure will not include the "hand nested within subject" term.

The effect of the intervention on the composite endpoint, which includes all-cause mortality, myocardial infarction, angina, and stroke, and on all-cause hospitalizations, will be assessed using a GLMM with a Poisson distribution. These models will include treatment as a fixed effect. The random effects will include community (cluster). Each individual component of the composite outcome will be analyzed using the same method.

For non-repeated measurements, changes in total cholesterol, triglycerides, and fasting blood glucose from baseline to 12 months will be evaluated using a GLMM. These models will include treatment as a fixed effect. The random effects will include community (cluster).

Given the potential for type I error due to multiple comparisons, all analyses of secondary outcomes will be interpreted as exploratory. Secondary outcome analyses will be based on the ITT population.

5.3 Handling of missing data

No imputation of missing data will be conducted. The GLMM accommodates missing data directly, and the GEE model utilizes the available data without imputation.

6 General considerations for data analyses

R will serve as the primary software for all data analyses and the generation of statistical graphs and data displays. Statistical significance was defined as a two-sided p-value of less than 0.05, and no adjustment was made for multiple comparisons.

6.1 Other data summaries

Continuous variables will be summarized based on the number of subjects with non-missing data (n), mean, standard deviation (SD), median, and interquartile range (IQR). Confidence intervals will be reported for continuous effectiveness variables. Categorical variables will be summarized by the absolute frequency and percentage of subjects (%) within each category level. The denominator for percentages will be the number of subjects in the treatment arm with available data, unless otherwise specified.

6.2 Graphical/table displays

Mean values for some continuous outcomes will be plotted. Additional tables would be generated if more analysis were conducted.

Table 1. Characteristics of the study participants.

	Statistics	Control group	Experimental group
Age	Mean(SD)		
Women	n (%)		
Education			
High school or higher	n (%)		
Junior high school	n (%)		
Primary school	n (%)		
Illiterate	n (%)		
Marital status			
Singlehood	n (%)		
Married	n (%)		
Widowed	n (%)		
Divorced	n (%)		
Unspecified			
Smoking status			

Never	n (%)
Former	n (%)
Current	n (%)
Drinking status	
Never	n (%)
Former	n (%)
Current	n (%)
Medical conditions	
Hypertension	n (%)
Dyslipidemia	n (%)
Diabetes	n (%)
CHD	n (%)
Stroke	n (%)
Tumor	n (%)
Frail index	
Robust	n (%)
Prefrail	n (%)
Total physical activity volume	
< 600 MET-min/week	n (%)
≥600 MET-min/week	n (%)
Fruit intake, g/day	Mean(SD)
BMI, kg/m^2	Mean(SD)
Handgrip strength	
Left handgrip strength, kg	Mean(SD)
Right handgrip strength, kg	Mean(SD)
Fasting blood glucose, mmol/L	Mean(SD)
Total cholesterol, mmol/L	Mean(SD)
Triglycerides, mmol/L	Mean(SD)

Table 2. Intervention effects on handgrip strength

		Control group (N=595)	Experimental group (N=475)	Change from baseline (95% CI)		Group difference (95% CI)	*P* value
				Within-Control group	Within- Experimental group		
Baseline	Left						
	Right						
6 months	Left						
	Right						
12 months*	Left						
	Right						
Sensitivity analysis							
PP analysis							
GEE analysis	Left						
	Right						
Covariate adjusted analysis							

Table 3. Intervention effects on secondary outcomes

Outcome	Control group N=595	Experimental group N=475	Change from baseline (95% CI) Within-Control group	Change from baseline (95% CI) Within- Experimental group	Group difference (95% CI)	*P* value
Frailty index						
Baseline						
6 months						
12 months						
Total cholesterol						
Baseline						
12 months						
Total triglycerides						
Baseline						
12 months						
Fasting blood glucose						
Baseline						
12 months						
All-cause death, myocardial infarction, angina, or stroke						
12 mouths						
— no. of events (rate)						
All-cause death						
— no. of events (rate)						
Myocardial infarction						
— no. of events (rate)						
Angina						
— no. of events (rate)						
Stroke						
— no. of events (rate)						
All-cause hospitalizations						
— no. of events (rate)						

7 Study variable list

Variable	Type
name	categorical
IdentityID	categorical
intervention_group	categorical
Survey_community	categorical
age	continuous
education_level	categorical
marital_status	categorical
smoking_status	continuous
date_data	date
Frequency_of_drinking	categorical
gender	continuous
Have_you_taken_vitamin	categorical
How_many_days_of_vigorous_exerci	categorical
Time_spent_in_a_day_of_vigorous_	categorical
How_many_days_of_moderate_exerci	categorical
Time_spent_in_a_day_of_moderate_	categorical
How_many_days_of_walk	categorical
Time_spent_in_a_day_of_walk	categorical
Frequency_unit_selection_spring_	categorical
Fruit_Consumption_Times_spring_o	categorical
Weight_per_serving__spring_or_su	categorical
daily_consumption_spring_and_sum	categorical
Frequency_unit_selection_autumn_	categorical
Fruit_Consumptio_Times_autumn_wi	categorical
Weight_per_serving_autumn_winter	categorical
daily_consumption_autumn_and_win	categorical
Calf_Circumference	continuous
Blood_oxygen	continuous
CHD_PREVIOUS	continuous
COPD_PREVIOUS	continuous
DM_PREVIOUS	categorical
ST_PREVIOUS	continuous
TUMOUR_PREVIOUS	categorical
HBP_PREVIOUS	categorical
dyslipidemia_PREVIOUS	categorical
Night_sleep_time_hours	continuous
have_trouble_falling_asleep_more	categorical
History_of_surgery	continuous
Difficulty_swallowing_food	continuous
appetite_for_the_past_month	categorical
Unusual_sounds_in_the_chest_whil	categorical
Whether_you_have_coughed_frequen	categorical
Sadness_or_depression_for_more_t	continuous
Walk_500_meters_without_others_h	continuous
Climb_one_floor_without_others_h	continuous
Feeling_tired	continuous

Weight_loss_of_more_than_2500g	continuous
Whether_feel_short_of_breath	categorical
selfcare_ability	categorical
Daily_activities	categorical
heart_rate	continuous
fasting_glucose	continuous
total_cholesterol	continuous
triglycerides	continuous
Left_Hand_grip_1	categorical
Left_hand_grip_2	categorical
Left_hand_grip_3	continuous
Right_hand_grip_1	categorical
Right_hand_grip_2	categorical
Right_hand_grip_3	continuous
Whether_interim_body_completed	continuous
Whether_interim_questionaire_com	continuous
interim_Calf_Circumference	continuous
interim_heart_rate	categorical
interim_Blood_oxygen	continuous
interim_Left_Hand_grip_1	categorical
interim_Left_hand_grip_2	categorical
interim_Left_hand_grip_3	continuous
interim_Right_hand_grip_1	categorical
interim_Right_hand_grip_2	categorical
interim_Right_hand_grip_3	continuous
zq_Whether_change_exercise_habit	categorical
zq_Whether_vigorous	categorical
zq_How_many_days_of_vigorous_exe	categorical
zq_Whether_know_vigorous_time	categorical
zq_Time_spent_in_a_day_of_vigoro	categorical
zq_Whether_moderate	categorical
zq_How_many_days_of_moderate_exe	categorical
zq_Whether_know_moderate_time	categorical
zq_Time_spent_in_a_day_of_modera	categorical
zq_Whether_walk	categorical
zq_How_many_days_of_walk_ifT	categorical
zq_Whether_know_walk_time	categorical
zq_Time_spent_in_a_day_of_walk	categorical
zq_sitting_time_a_week_hours	categorical
zq_Whether_change_fruit_habits_s	categorical
zq_Frequency_of_fruit_consumptio	categorical
zq_Frequency_of_fruit_consumpti1	categorical
zq_Weight_per_serving	categorical
zq_Night_sleep_time_hours	categorical
zq_have_trouble_falling_asleep_m	categorical
zq_Difficulty_swallowing_food	categorical
zq_appetite_for_the_past_month	categorical
zq_Unusual_sounds_in_the_chest_w	categorical
zq_Whether_you_have_coughed_freq	categorical

zq_Sadness_or_depression_for_mor	categorical
zq_Feeling_tired	categorical
zq_Whether_feel_short_of_breath	categorical
zq_selfcare_ability	categorical
zq_Daily_activities	categorical
first_times	continuous
second_times	categorical
zq_tice_if	continuous
zq_question_if	continuous
first9	continuous
second9	continuous
neither9	continuous
all9	continuous
all0	continuous
final_Whether_complete_bodytest	continuous
final_Calf_Circumference	continuous
final_heart_rate	continuous
final_Blood_oxygen	continuous
final_Left_Hand_grip_1	categorical
final_Left_hand_grip_2	categorical
final_Right_hand_grip_1	categorical
final_Right_hand_grip_2	categorical
final_completion_questionnaire	continuous
final_Whether_change_exercise_ha	categorical
final_Whether_vigorous	categorical
final_How_many_days_of_vigorous_	categorical
final_Whether_know_vigorous_time	categorical
final_Time_spent_in_a_day_of_vig	categorical
final_Whether_moderate	categorical
final_How_many_days_of_moderate_	categorical
final_Whether_know_moderate_time	categorical
final_Time_spent_in_a_day_of_mod	categorical
final_Whether_walk	categorical
final_How_many_days_of_walk_ifT	categorical
final_Whether_know_walk_time	categorical
final_Time_spent_in_a_day_of_wal	categorical
final_sitting_time_a_week_hours	continuous
final_Whether_change_fruit_habit	categorical
final_Frequency_of_fruit_consump	categorical
final_Frequency_of_fruit_consum1	categorical
final_Weight_per_serving	categorical
final_Night_sleep_time_hours	continuous
final_have_trouble_falling_aslee	categorical
final_Difficulty_swallowing_food	continuous
final_appetite_for_the_past_mont	categorical
final_Unusual_sounds_in_the_ches	categorical
final_Whether_you_have_coughed_f	categorical
final_Sadness_or_depression_for_	continuous
final_Walk_500_meters_without_ot	continuous

final_Climb_one_floor_without_ot	continuous
final_Feeling_tired	continuous
final_Weight_loss_of_more_than_2	continuous
final_Whether_feel_short_of_brea	categorical
final_selfcare_ability	categorical
final_Daily_activities	categorical
final_total_cholesterol	continuous
final_triglycerides	continuous
final_LDL_C	continuous
final_HDL_C	continuous
final_survey_date	date
CVD_and_death_condition	continuous
CVDadeath_followup_duration	continuous
admission_followup_duration	continuous
admission_condition	continuous

8 Reference

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