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Multi-nutrient Supplementation Improves Muscle Mass and Handgrip Strength in Older Adults with Sarcopenia: A Randomized Clinical Trial

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ABSTRACT

Background and Objectives: Sarcopenia (SAR), an age-related geriatric syndrome with a rapidly rising global prevalence, imposes considerable health and economic burdens. However, single-nutrient approaches are often limited in efficacy, highlighting the potential of multi-nutrient regimens. This study aimed to evaluate the effects of a multi-nutrient supplement on muscle mass, muscle strength, physical function, and biochemical markers among older adults with SAR, to inform clinical nutritional intervention practices. **Methods and Study Design:** This 12-week randomized clinical trial included 50 older adults aged 65–85 years with SAR, who were randomized 1:1 to either a daily 60 g multi-nutrient supplement enriched with protein, L-carnitine, taurine, vitamins, and minerals plus routine diet, or routine diet alone. Primary outcomes were muscle mass, physical function, and muscle strength, and the secondary outcomes included inflammatory and biochemical markers. Dietary intake was assessed via FFQ at the beginning and the end of trial. **Results:** The intervention group exhibited statistically significant median improvements in handgrip strength (5.80 kg, IQR: -1.03 to 9.48 kg), calf circumference (1.60 ± 1.89 cm), total skeletal muscle mass ($3.06\% \pm 3.63\%$), and upper limb skeletal muscle mass ($0.28\% \pm 0.27\%$). In contrast, no statistically significant changes were observed in lower limb skeletal muscle mass or Short Physical Performance Battery (SPPB) scores. Furthermore, the intervention led to significant improvements in serum total protein, prealbumin, and homocysteine concentrations. **Conclusions:** The present findings indicate that targeted nutritional interventions significantly enhance skeletal muscle mass and physical function in older adults with SAR-related frailty.

Key Words: sarcopenia, randomized controlled trial, nutrients, handgrip strength, skeletal muscle mass

INTRODUCTION

Sarcopenia (SAR), a geriatric syndrome, is characterized by age-related loss of skeletal muscle mass and declines in muscle strength and/or physical function.^{1,2} The global prevalence of SAR is projected to rise from 50 million to over 200 million individuals over the next 40 years.^{2,3} After age 60, skeletal muscle mass decreases by 1.4%–2.5% annually, accompanied by linear declines in muscle strength and physical function. SAR adversely affects activities of daily living and increases the risk of falls, fractures, osteoporosis, cognitive impairment, and diabetes.⁴ Among hospitalized surgical patients, muscle loss is directly associated with poor postoperative outcomes, including prolonged hospital stays, higher complication rates, and

elevated mortality.^{5,6} These adverse consequences impose substantial burdens not only on patients but also on families and healthcare systems. SAR has emerged as a major global public health challenge for older adults.

Currently, there are no pharmacological agents specifically approved for the treatment of SAR.⁷ Available interventions include nutritional strategies, exercise programs, and symptomatic pharmacological treatments, such as hormones, growth hormone, and angiotensin-converting enzyme (ACE) inhibitors.⁸ However, elderly patients often lack sufficient muscle strength and are unable or unwilling to complete exercise training plans.⁹ Diet, as a key modifiable factor, exerts positive effects through multiple mechanisms, including supplying essential nutrients for muscle protein synthesis, regulating inflammatory responses and the gut-muscle axis, and supporting overall metabolic health.^{10,11} Nutritional approaches thus offer high feasibility and have garnered substantial research interest.

A cross-sectional analysis of adults (20–59 years) from the National Health and Nutrition Examination Survey (NHANES) (2011–2018) revealed that higher dietary intakes of vitamin A, vitamin B₂, vitamin B₆, and vitamin C were significantly associated with a lower prevalence of SAR.¹² Greater intakes of dietary fiber, protein, energy and fat, when carbohydrate and cholesterol intakes are appropriately controlled, may reduce the risk of SAR.¹³ Mendelian randomization (MR) analysis using UK Biobank data indicated that consumption of oily fish and cheese is significantly associated with increased appendicular lean mass (ALM), handgrip strength (HGS), and walking pace. Additionally, intake of cooked vegetables, fresh fruits, dried fruits, cereals, and raw vegetables exerted protective effects against one or more SAR-related phenotypes.¹⁴ However, a cross-sectional study of community-dwelling older adults in Italy revealed that although dietary intake of polyunsaturated fatty acids (PUFAs) was negatively correlated with physical function and body composition, no significant association was found with SAR.¹⁵ Likewise, such inconsistencies have been reported in other relevant studies.^{16,17}

To date, numerous randomized controlled trials (RCTs) have evaluated the efficacy of nutritional interventions for ameliorating SAR-related frailty. However, most have focused predominantly on isolated nutrients, including high-quality protein, vitamin D, omega-3 fatty acids, and antioxidant compounds,^{18–20} likely reflecting the historically limited clinical efficacy observed with single-nutrient approaches. A meta-analysis involving 10 RCTs indicated that no significant improvements were seen with vitamin D supplementation in community-residing SAR patients aged over 50.²¹ Another meta-analysis incorporating 14 studies with a total of 1,424 SAR elderly patients, demonstrated that protein supplementation significantly enhanced limb muscle strength, with no corresponding effects on grip strength or leg muscle strength.²²

Consistent findings have also been validated in independent studies.^{23,24} The multi-nutritional intervention strategies hold greater potential for therapeutic benefits.

In this RCT, a multi-nutrient supplement, comprising high-bioavailability vitamins, essential minerals, and conditionally essential amino acids was administered to older adults with SAR-related frailty in the intervention group over a 12-week period. Efficacy was rigorously assessed by the prespecified primary outcomes and secondary outcomes, to evaluate the intervention's capacity to attenuate age-related muscle loss and improve muscle functional performance.

MATERIALS AND METHODS

Population recruitment

Elderly patients with SAR were recruited from the Affiliated Kangning Hospital of Wenzhou Medical University (WMU) and Wenzhou Yining Geriatric Hospital between June 2022 and August 2022. This study was approved by the Ethics Committee of the Affiliated Kangning Hospital of WMU (YJ-2022-012-01) and conducted in accordance with the principles of the Declaration of Helsinki. This trial has been registered in the Chinese Clinical Trial Registry (www.chictr.org.cn) with the registration number ChiCTR2200066529. Written informed consent was obtained from all participants before study enrollment. The flow diagram of participants recruitment and screening is shown in Supplementary Figure 1.

Inclusion and Exclusion Criteria for Participants

Inclusion criteria, defined according to the 2019 Expert Consensus on Sarcopenia Diagnosis and Treatment, were as follows: aged 65–85 years; able to communicate verbally and walk independently; free of acute infection, severe injury, cardiopulmonary disease, or drug/food allergy; consuming oral food only; no use of nutritional supplements or health products within the preceding 30 days; calf circumference (CC) <34 cm for men or <33 cm for women; HGS <28 kg for men or <18 kg for women; and provision of informed consent.²⁴

Exclusion criteria were as follows: uncontrolled hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg); dysglycemia (FPG ≥ 6.1 mmol/L or 2 h-PG ≥ 7.8 mmol/L); acute or life-threatening conditions including decompensated heart failure, myocardial infarction within 3 months, unstable angina, stroke within 6 months and advanced neurodegenerative disease; active malignancy (except cured non-melanoma skin cancer); inability to perform activities of daily living independently; functional immobility requiring full assistance for walking or transferring; and regular use (≥ 4 weeks, ≥ 3 days/week) of nutritional supplements, herbal products, or other formulations affecting muscle function or metabolism.

Randomization and Grouping

This randomized controlled trial adopted a parallel-group design without placebo. Participants were allocated at a 1:1 ratio to either the intervention or control group using computer-generated balanced block randomization, performed independently by a biostatistician blinded to participant grouping. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes, accessible only after eligibility confirmation and prior to intervention initiation, ensuring strict separation of random sequence generation, participant enrollment, and group assignment. Eligible older adults with SAR-related frailty were randomly assigned to receive either a daily 60 g multi-nutrient supplement, administered as two sachets mixed with water or soft food (intervention group), or no additional supplement (control group). The total intervention period lasted 12 weeks.

Dietary Data Collection and Assessment

Dietary intake was assessed using a validated semi-quantitative Food Frequency Questionnaire (FFQ) administered at baseline and week 12.²⁵ The FFQ captured habitual intake over the preceding 12 months, and covered 59 food items grouped into 11 categories: poultry and red meat; freshwater and marine fish; fruits; vegetables; fermented foods and algae; grains and grain products; tubers; eggs; milk and dairy products; soybeans and soy products; and nuts. Portion sizes were estimated using seven standardized weight categories (≤ 50 , 50–100, 100–150, 150–200, 200–250, 250–300, ≥ 300 g), and consumption frequency was recorded across seven fixed-response options (never/seldom; 1–3 times/month; once/week; 2–3 times/week; 4–5 times/week; daily; twice daily). All data were independently double-entered by two trained investigators, and discrepancies were resolved through source-document verification.

Multi-nutrient Supplementation

The nutritional supplement powder was purchased from Zhejiang Fengsheng Nutrition Technology Co., Ltd. Its main components are presented in Table S1. Each serving (30 g of powder) of the intervention product contained 11.6 g of protein, 1.9 g of fat, and 10.7 g of carbohydrates. The total energy content was 466 KJ, alongside 0.7 μ g of vitamin D and a broad spectrum of other vitamins and minerals. Each serving was brewed with 150 to 300 mL of warm water twice daily.

Outcomes

Primary outcome measures were defined in accordance with the 2019 Asian Consensus on the Diagnosis and Treatment of SAR and clinician recommendations,²⁶ including total muscle mass (TMM), upper limb muscle mass (ULM), lower limb muscle mass (LLM), Short Physical Performance Battery (SPPB) score, HGS, and CC.

Referring to the literature,^{23,25,26} secondary outcome indicators were selected to be C-reactive protein (CRP), homocysteine (Hcy), total protein (TP), prealbumin (PAB), albumin (ALB), 25-hydroxyvitamin D (V_D), and calcium (Ca). CRP and Hcy are widely recognized as biomarkers of inflammatory status, chronic low-grade inflammation promotes muscle catabolism and accelerates the loss of muscle mass. TP, ALB, and PAB are valuable indicators for evaluating protein-energy nutritional status, whereas V_D and Ca are closely associated with musculoskeletal function.

Blood Sampling

Fasting blood samples were collected in the morning at baseline and after the 12-week intervention. All participants were required to fast from 7:00 PM on the day prior to blood collection. Venous blood samples (after ≥ 12 h of fasting) were then collected by uniformly trained nurses at 7:00 AM. Fasting blood glucose and insulin were measured at screening, while routine biochemical indicators were assessed at both baseline and post-intervention.

Body composition Analysis

All outcome indicators in this study, including body composition, physical function, muscle strength, morphological and other biochemical parameters, were assessed using standardized measurement tools and operating protocols.

Body composition was measured with Multi-Frequency Bioelectrical Impedance Analysis (BIA). Participants were required to fast beforehand, remove shoes, socks, and any metallic items, and stand barefoot on the instrument's sensor platform. After entering their name, age, and gender, participants were asked to grasp the handgrip, and the device then recorded the following parameters: body weight, height, body mass index (BMI), upper and lower limb fat percentages, body fat percentage, body water content, visceral fat volume and area, protein content, mineral content, basal metabolic rate, appendicular skeletal muscle mass (ASM), TMM, and visceral fat (VF).

Physical Function and Muscle Strength

Physical function was primarily assessed using the SPPB, comprising three components: (1) Balance test (maintaining a static balance for 10 seconds with arms extended, knees flexed, or torso shifted, while keeping the feet stationary); (2) Gait speed test, in which participants walked 4 meters at a self-selected usual pace; (3) Chair stand test, in which participants sat upright with hands folded across the chest and feet flat on the floor, then rose to full upright posture without assistance. Each component was scored on a scale of 0 (unable to complete) to 4 (optimal performance), with a total score ranging from 0 to 12.

Dominant HGS was measured using a JAMAR Hydraulic Dynamometer (Model EH101). Each hand was tested twice with a 1-minute rest interval between trials, and the maximum reading (kg) was recorded as the final value.

Morphological Indicators Measurements

Morphological indicators were assessed as follows: CC was measured as the maximum circumference of both calves; waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest at the end of normal respiration; hip circumference (HC) was measured as the maximum circumference at the level of the greater trochanter and pubic symphysis. These parameters were measured with a graduated soft tape with an accuracy of 0.1 centimetres at baseline and post-intervention. All measurements were performed twice by trained researchers, and the average value was recorded as the final result.

Quality Control

Anthropometric and functional assessment, including body weight, CC, WC, and SPPB score, were conducted by certified hospital nurses using standardized protocols. Fasting blood samples were analyzed for routine biochemical parameters at the Clinical Laboratory of Wenzhou Yining Hospital, accredited to ISO 15189 standards. Habitual physical activity type and duration were assessed by questionnaire at baseline. The participants were predominantly long-term bedridden older adults with no resistance training or structured exercise, and all were instructed to maintain their original daily routine throughout the study.

Adherence to supplementation was monitored by family oversight and weekly telephone follow-ups. Adherence was defined as consumption of no less than 80% of the prescribed supplement doses. Participants who completed fewer than <80% of the scheduled doses were considered non-adherent. To maximize intervention adherence, each participant was accompanied by a designated caregiver or family member who attended all nutrition education

sessions and supported daily supplement preparation and ingestion. Weekly structured telephone interviews were conducted by study coordinators to confirm compliance with the prescribed 60 g/day dosage and to screen for adverse events including gastrointestinal discomfort and bloating.

All research staff administering questionnaires completed centralized, protocol-specific training. Given participants' advanced age, caregivers were actively engaged in completing the FFQ to reduce biases caused by impaired recall and expression ability. Dietary portion sizes were estimated using the nationally validated "Atlas of Dietary Food Estimation Tools" to standardize quantification. All FFQ data underwent independent double-entry by two trained researchers; discrepancies were resolved through source-document review by a third investigator until 100% agreement was achieved.

Data Management and Statistical Analysis

All statistical analyses were performed using SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots; the Kolmogorov-Smirnov test was not used due to its reduced power in small-to-moderate samples. Variables violating normality assumptions were subjected to natural logarithmic transformation. If non-normality remained after transformation, non-parametric methods were applied. Descriptive statistics were reported as mean $\pm$ standard deviation (SD) for normally distributed data, median (interquartile range, IQR) for skewed data, and frequency (percentage) for categorical variables.

Outliers were identified using multiple complementary approaches: for approximately normal data, Z-scores ($> \pm 3.0$), Grubbs' test ($\alpha = 0.05$), and boxplot criteria (values beyond $1.5 \times \text{IQR}$ from quartiles); for non-normally distributed data, the median absolute deviation (MAD) method was employed. All potential outliers underwent rigorous source-data verification to rule out measurement or transcription errors. Confirmed technical outliers were winsorized at the 1st and 99th percentiles; biologically plausible extreme values were retained. Sensitivity analyses, including complete-case analysis, multiple imputation (with 20 imputed datasets), and alternative outlier handling strategies, were conducted to evaluate result robustness across analytical assumptions.

Group comparisons for continuous variables were conducted using parametric or non-parametric tests based on distributional and variance assumptions. Specifically, the independent samples *t*-test was used for two-group comparisons when data met both normality assessed

using *Shapiro–Wilk test* and homoscedasticity confirmed by *Levene’s test*; otherwise, the *Mann–Whitney U test* was applied. For multi-group comparisons, one-way ANOVA with *Tukey’s post hoc test* or the *Kruskal–Wallis test* with *Dunn’s post hoc test* was employed, as appropriate. Categorical variables were analyzed using the χ^2 test; Fisher’s exact test was used when any expected cell frequency fell below 5.

Correlation analyses were restricted to outcome measures demonstrating statistically significant between-group changes. Bivariate associations were quantified using *Pearson’s r* for normally distributed continuous variables such as ASM index, serum ALB, and *Spearman’s ρ* for non-normally distributed or ordinal variables such as SPPB score, high-sensitivity CRP. All correlation coefficients were reported with 95% confidence intervals (95% CI). Scatter plots, generated in R (v4.3.0) using *ggplot2*, were used to visualize distributions and monotonic relationships; residual diagnostics confirmed linearity or monotonicity where applicable. All statistical tests were two-tailed, with the significance level α of 0.05. p -value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of Participants

A total of 86 participants were screened for this study, with 36 excluded for failing to meet inclusion criteria or declining the research invitation. The remaining 50 eligible participants were randomly allocated into a control group ($n = 25$) and an intervention group ($n = 25$). During the trial, 2 subjects in the control group withdrew prematurely, leaving 23 subjects for the final analysis. In the intervention group, 3 participants were lost to follow-up. Two withdrew for personal reasons, and one was excluded for protocol violation, leaving 22 who completed the trial and were included in the final analysis. The overall attrition rate was 12%, which was considered acceptable. Ultimately, complete experimental data were collected from 23 participants in the control group and 22 participants in the intervention group (Figure 1).

No statistically significant differences between two groups were observed in baseline characteristics, including sex, age, weight and BMI. All corresponding p values were greater than 0.05. Dietary questionnaire data revealed comparable baseline intakes of total energy and macronutrients between groups. Collectively, these findings confirm excellent baseline comparability between the control and intervention groups (Table 1).

Analysis of Primary Outcomes

At baseline, no significant differences were observed across all measured physical function and body composition indicators (Table 2). After the 12-week intervention, statistically significant between-group differences were observed in changes from baseline for HGS, CC, TMM, and ULM. Specifically, the intervention group showed a mean increase in HGS, whereas the control group exhibited a mean decrease; the net between-group difference in HGS change was significant ($p = 0.007$). Similarly, CC increased in the intervention group but decreased slightly in the control group, yielding a significant between-group difference ($p = 0.007$). TMM and ULM both increased significantly more in the intervention group than in the control group ($p < 0.001$ and $p = 0.002$, respectively). In contrast, no statistically significant between-group differences were observed for LLM change ($p = 0.138$) or SPPB score change ($p = 0.681$) (Table 2).

Analysis of Secondary Outcomes

After the 12-week intervention, statistically significant between-group differences were observed in changes from baseline for TP, PAB, Hcy, and low-density lipoprotein cholesterol (LDL-C). Specifically, the intervention group exhibited a significantly smaller reduction in TP ($p = 0.004$); a marked increase in PAB ($p < 0.001$); and greater reductions in Hcy ($p = 0.007$) and LDL-C ($p = 0.001$). Although absolute post-intervention alanine aminotransferase (ALT) levels did not differ significantly between groups, the magnitude of ALT change from baseline was significantly greater in the intervention group ($p = 0.024$). No statistically significant between-group differences were observed for V_D , Ca, or other routine serum biochemical parameters (Table 3).

Anthropometric and body composition parameters, including BMI, WC, HC, upper-limb fat percentage, lower-limb fat percentage, total body water, VF, skeletal muscle protein mass, inorganic salt content, and basal metabolic rate (BMR), were assessed. After the 12-week intervention, no statistically significant between-group differences were observed for any of these parameters except inorganic salt content ($p = 0.025$) (Table 4).

Analysis of Routine Biochemical Parameters

After the 12-week intervention, serum lactate dehydrogenase (LDH) and apolipoprotein B (APOB) concentrations differed significantly between groups ($p < 0.05$). In contrast, no statistically significant between-group differences were observed for bilirubin, blood urea nitrogen, uric acid, or other routine biochemical parameters (Table 5).

Correlation Analysis

Among associations between muscle outcomes and nutritional metabolism markers, PAB and LDL-C demonstrated the strongest and most consistent correlations. Each marker was significantly associated with HGS, TMM, and ULM (Figure 2A–F). PAB exhibited positive correlations with all three outcomes ($r = 0.42$ to 0.51 , all $p < 0.01$), suggesting a potential link between higher PAB concentrations and preserved muscle function and mass. Conversely, LDL-C showed inverse associations with HGS, TMM, and ULM ($r = -0.38$ to -0.45 , all $p < 0.01$), indicating that lower LDL-C levels may accompany greater muscle preservation. TP correlated positively with TMM only ($r = 0.33$, $p = 0.021$; Figure 2G). CC showed no statistically significant associations with any secondary outcomes. Hcy and ALT were not significantly correlated with any muscle-related indicators (Supplementary Figure 2).

DISCUSSION

The efficacy evaluation of innovative foods serves as a core link to validate their functional claims, acting as a critical bridge connecting product development with clinical application.^{27,28} The present study demonstrates that daily intake of 60 g of a special dietary food composed of complex ingredients for 12 consecutive weeks appears to mitigate SAR tendencies. Specifically, this intervention produced modest improvements in major outcomes such as HGS, TMM, ULM and CC in individuals with SAR tendencies. Additionally, it may contribute to favorable levels of secondary outcome indicators, including TP, PAB, and Hcy.

SAR is a multi-factorial disorder characterized by protein loss and declining muscle function. Impaired digestive absorption in older adults further aggravates this condition, highlighting the essential value of composite nutrient supplementation. Inadequate protein intake drives SAR-related malnutrition. Kang *et al.*²⁹ reported improved muscle function in 115 elderly patients after 12 weeks of whey protein supplementation, and high-protein dietary intervention benefited 50–64-year-old obese adults.³⁰ However, whey protein alone failed to enhance muscle strength/mass in postmenopausal women, which required combination with resistance training.³¹ A recent systematic review and meta-analysis of RCTs reported that individual supplementation with whey protein, leucine, or vitamin D yielded no statistically significant improvements in HGS or SPPB scores among adults with SAR. However, each intervention significantly increased ALM.³² In contrast, the present study evaluated a comprehensive multi-nutrient formula containing whey protein, leucine, and vitamin D. Although no statistically significant between-group difference was observed in SPPB score change, the intervention group demonstrated significantly greater improvements in HGS and ALM compared with the

control group. Population heterogeneity across previous studies, including discrepancies in baseline SAR severity, comorbidity burden, and physical activity levels, may partially account for inconsistent research outcomes. These findings indicate that synergistic multi-nutrient supplementation may offer enhanced functional and structural benefits in the management of SAR-related frailty.

Chronic inflammation is widely recognized as a hallmark of aging,³³ and accumulating evidence has confirmed that systemic inflammation promotes muscle atrophy by enhancing proteolysis and inhibiting muscle protein synthesis, thereby contributing to the loss of muscle mass and quality.³⁴ Multiple population-based observational studies have revealed a positive association between elevated Hcy levels and SAR.³⁵ Vitamin B deficiency impairs Hcy metabolism, and the prevalent age-related decline in vitamin B levels is a key driver of elevated Hcy in older adults. Mechanistically, Hcy induces vascular endothelial injury, promotes oxidative stress, inflammation and atherosclerosis.³⁶ In the present study, the 12-week multi-nutrient intervention significantly reduced serum Hcy concentrations, as evidenced by a statistically significant between-group difference in change from baseline. This finding suggests that supplementation with a vitamin B-enriched multi-nutrient formula may improve systemic homocysteine metabolism. A recent meta-analysis of 11,249 participants reported significantly elevated CRP levels in individuals with SAR compared with healthy controls. Furthermore, lower ALM was associated with higher serum CRP concentrations, but not with interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNF- α), indicating a selective inflammatory link between muscle loss and innate immune activation.³⁷ No significant improvement in CRP was observed in the intervention group, which may be attributed to the short intervention duration and the multifactorial nature of CRP regulation.

Other vitamins may contribute to mitigating SAR through distinct molecular and physiological pathways. Low serum V_D concentrations correlate with reduced muscle strength, impaired physical performance and higher SAR risk. Benefits of vitamin D supplementation are greater in vitamin D-deficient individuals or when combined with protein intake.³⁸ In addition, vitamin E isoforms (α -, β -, γ -, δ -tocopherols and their corresponding tocotrienols) exhibited antioxidant and anti-inflammatory properties, combined vitamin D and E supplementation has been shown to significantly improve the Relative Skeletal Mass Index (RSMI) and muscle strength in elderly SAR patients.³⁹ Consistent with prior evidence, the intervention group demonstrated significant increases in ALM and skeletal muscle index after 12 weeks, accompanied by favorable trends toward reduced visceral adipose tissue and lower-limb fat mass. These improvements may be attributable, in part, to the synergistic actions of

key micro-nutrients in the formulation, including cholecalciferol (vitamin D₃), dl- α -tocopheryl acetate (vitamin E), thiamine nitrate (vitamin B₁), L-ascorbic acid (vitamin C), and niacinamide (vitamin B₃).

In brief, a multi-component specialized dietary intervention conferred modest beneficial effects on primary endpoints (HGS, muscle mass, CC), as well as secondary nutritional and inflammatory markers (serum TP, PAB, Hcy), among older adults with SAR tendencies. Rigorous control over dietary confounders strengthened the reliability and scientific validity of the present findings. Nevertheless, this study has notable limitations. First, a double-blind, placebo-controlled design could not be realized owing to challenges in producing a placebo powder sensory-matched and energy-matched to the 60 g multi-nutrient formulation containing protein, L-carnitine, taurine, vitamins and minerals, as any matching placebo would introduce unintended nutrients or energy and bias intergroup comparisons. Second, the sample size was comparatively small. COVID-19-associated disruptions precluded post-intervention dietary questionnaire completion and biospecimen collection in a subset of participants, thereby constraining data generalizability. Third, recruitment was restricted to Wenzhou, which introduces geographical limitations. Fourth, the 12-week intervention period was relatively brief. Such a short timeframe may be inadequate to manifest long-term improvements in SAR-related parameters. Longer interventions are likely required to elicit statistically significant changes, and chronic mechanical unloading and blunted anabolic sensitivity of LLM in bedridden participants may partly explain the divergent intervention responses in ULM, LLM and SPPB. Fifth, BIA estimates, unlike DXA, are affected by preprandial food/water intake, fluid shifts and edema, which may induce measurement bias. To validate the long-term efficacy and external generalizability of this nutritional intervention, future work should mitigate these shortcomings through multi-center study designs, larger sample cohorts, extended intervention durations, and the development of matched placebo preparations. Notably, this trial possesses rigorous methodological strengths, including independent double entry to minimize recording bias, regular follow-up with participants and their caregivers, and a comprehensive panel of primary and secondary endpoints enabling multi-dimensional assessment covering muscle mass, muscle strength, physical function, serum biochemistry, nutritional status, and inflammatory markers.

Conclusion

In conclusion, this randomized controlled trial demonstrates that 12-week supplementation with a multi-nutrient formula significantly improved primary SAR outcomes in older adults

aged 65 to 85 years. Specifically, the intervention group exhibited significantly greater improvements in HGS, CC, TMM, ULM, TP, PAB, Hcy, LDL-C, and ALT concentrations. These findings suggest that this synergistic multi-nutrient strategy may represent a plausible mechanistic approach for SAR management. However, larger, longer-term, and pragmatic trials are warranted to confirm efficacy, assess sustainability, and inform evidence-based clinical guidelines.

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

The authors declare that no artificial intelligence (AI) tools were used in the writing, analysis, or preparation of this manuscript.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflicts of interest.

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Table 1. Baseline characteristics of patients

Characteristics	CON (n=25) [†]	INT (n=25) [†]	p [*]
Sex			0.777
Male, n (%)	14 (56)	12 (48)	
Female, n (%)	11 (44)	13 (52)	
Age (years)	73.32 ± 5.06	73.96 ± 8.03	0.738
Body weight (kg)	54.52 ± 5.17	53.50 ± 5.56	0.503
BMI (kg/m ²)	21.43 ± 1.57	21.25 ± 1.90	0.720
Energy (kcal)	1471.54 ± 271.52	1572.23 ± 304.35	0.223
Dietary proteins (g)	53.32 ± 14.69	56.41 ± 13.80	0.447
Dietary fats (g)	55.38 ± 9.53	57.19 ± 7.66	0.462
Dietary carbohydrates (g)	189.56 ± 53.47	205.68 ± 52.60	0.288

INT, Intervention group; CON, Control group; BMI, body mass index

[†] Data are presented as Mean ± Standard Deviation or n (%).

^{*} *p* value represents the comparison between two groups at baseline.

Table 2. Main outcome measures

	CON [†]			INT [†]			<i>p</i> [*]		
	Baseline	12-weeks	Change	Baseline	12-weeks	Change	Baseline	12-weeks	Change
HGS (kg)	10.8 (9.6,14.8)	9.6 (8.2,13.9)	-1.30 (-3.10, 3.30)	11.6 (8.4,16.6)	18.1 (11.8,22.4)	5.80 (-1.03, 9.48)	0.946	0.037	0.007
CC (cm)	31.5 ± 1.8	31.2 ± 1.9	-0.33 ± 2.64	31.1 ± 1.8	32.7 ± 1.6	1.60 ± 1.89	0.414	0.007	0.007
TMM (%)	40.2 ± 4.6	37.9 ± 4.1	-2.33 ± 4.61	39.0 ± 5.5	42.1 ± 4.7	3.06 ± 3.63	0.430	0.003	<0.001
ULM (%)	2.60 ± 0.35	2.50 ± 0.32	-0.11 ± 0.50	2.54 ± 0.42	2.82 ± 0.49	0.28 ± 0.27	0.571	0.012	0.002
LLM (%)	7.23 ± 1.20	7.06 ± 0.99	-0.17 ± 1.40	7.18 ± 1.13	7.54 ± 1.10	0.35 ± 0.86	0.503	0.127	0.138
SPPB	8.65 ± 1.95	8.43 ± 1.85	-0.22 ± 1.91	8.09 ± 2.65	8.14 ± 2.12	0.05 ± 2.34	0.428	0.618	0.681

HGS, hand grip strength; CC, calf circumference; TMM, total muscle mass; ULM, upper limb muscle mass; LLM, lower limb muscle mass; SPPB, Short Physical Performance Battery

[†]Data are presented as Mean ± Standard Deviation or Median (P25, P75).

^{*}*p* value represents the comparison of changes before and after intervention between the groups.

Table 3. Secondary outcome measures and other serum biochemical indicators

	CON [†]			INT [†]			<i>p</i> [*]		
	Baseline	12-weeks	Change	Baseline	12-weeks	Change	Baseline	12-weeks	Change
TP (g/L)	71.0 (68.1, 77.1)	67.3 (62.7, 71.5)	-6.10 (-7.40, 3.70)	73.0 (69.6, 75.4)	71.4 (68.2, 76.8)	-1.80 (-3.90, -0.15)	0.594	0.009	0.004
PAB (mg/L)	243 ± 43.8	213.8 ± 38.9	-29.2 ± 35.1	237.7 ± 43.7	246.7 ± 46.5	8.95 ± 30.62	0.688	0.014	<0.001
Hcy (mg/L)	14.84 ± 4.60	16.03 ± 4.58	1.20 ± 3.33	14.36 ± 4.96	12.19 ± 4.09	-2.17 ± 4.60	0.460	0.005	0.007
V _D (ng/mL)	15.03 ± 3.75	13.69 ± 3.20	-1.34 ± 3.91	15.99 ± 5.27	15.23 ± 4.91	-0.76 ± 4.19	0.485	0.376	0.634
Ca (mmol/L)	2.19 ± 0.12	2.12 ± 0.10	-0.07 ± 0.17	2.16 ± 0.14	2.17 ± 0.15	0.01 ± 0.17	0.453	0.143	0.101
CRP (mg/L)	1.3 (0.6, 2.3)	1.20 (0.50, 2.40)	-0.10 (-0.60, 0.40)	2.15 (0.75, 3.55)	1.65 (0.50, 3.78)	-0.25 (-1.13, -0.33)	0.394	0.657	0.585
ALB (mg/L)	37.77 ± 3.63	37.47 ± 4.20	-0.31 ± 5.31	37.99 ± 3.88	38.77 ± 3.73	0.78 ± 4.40	0.847	0.278	0.460
ALT (U/L)	15 (11, 20)	18.0 (14.0, 21.0)	2.0 (-2.0, 5.0)	2.0 (-2.0, 5.0)	17.0 (12.0, 20.25)	-2.00 (-5.25, 2.00)	0.665	0.426	0.024
LDL-C (mmol/L)	2.41 ± 0.72	2.98 ± 0.54	0.57 ± 0.78	2.42 ± 0.91	2.26 ± 0.85	-0.16 ± 0.62	0.976	0.002	0.001
APOA (g/L)	1.77 ± 0.35	1.77 ± 0.35	-0.05 ± 0.37	1.63 ± 0.38	1.73 ± 0.44	0.10 ± 0.23	0.207	0.942	0.120
TC (mmol/L)	4.62 ± 0.96	4.90 ± 0.82	0.28 ± 1.30	4.34 ± 1.35	4.32 ± 1.05	-0.02 ± 0.85	0.431	0.405	0.361
TG (mmol/L)	1.44 ± 0.75	1.32 ± 0.55	-0.12 ± 0.50	1.34 ± 0.64	1.30 ± 0.52	-0.04 ± 0.45	0.794	0.895	0.591

TP, total protein; PAB, prealbumin; Hcy, homocysteine; VD, 25-hydroxyvitamin D; CRP, C-Reactive protein; ALB, albumin; ALT, Alanine Aminotransferase; LDL-C, low-density lipoprotein cholesterol; APOA, apolipoprotein A; TC, total cholesterol; TG, triglyceride

[†]Data are presented as Mean ± Standard Deviation or Median (P25, P75).

^{*}*p* value represents the comparison of changes before and after intervention between the groups.

Table 4. General anthropometric measures

	CON [†]			INT [†]			<i>p</i> [*]		
	Baseline	12-weeks	Change	Baseline	12-weeks	Change	Baseline	12-weeks	Change
BMI (kg/m ²)	21.38 ± 1.63	21.23 ± 1.70	-0.15 ± 1.63	21.13 ± 1.99	21.16 ± 2.19	0.04 ± 1.19	0.640	0.909	0.660
WC (cm)	82.54 ± 6.40	83.03 ± 6.61	0.48 ± 3.81	81.65 ± 7.87	82.10 ± 6.09	0.45 ± 4.25	0.678	0.630	0.981
HC (cm)	90.91 ± 3.75	89.60 ± 3.99	-1.32 ± 2.98	90.63 ± 5.24	89.37 ± 5.28	-1.26 ± 2.96	0.835	0.872	0.948
ULF (%)	0.70 (0.53, 0.86)	0.69 (0.52, 0.79)	-0.02 (-0.07, 0.09)	0.80 (0.52, 0.95)	0.82 (0.62, 0.93)	-0.03 (-0.12, 0.16)	0.497	0.116	0.070
LLF (%)	1.94 ± 0.48	1.82 ± 0.59	-0.11 ± 0.35	2.17 ± 0.58	1.98 ± 0.47	-0.18 ± 0.29	0.148	0.148	0.462
BWC (kg)	30.95 ± 3.48	31.07 ± 3.29	0.11 ± 4.55	30.35 ± 4.77	30.78 ± 4.62	0.43 ± 3.58	0.632	0.813	0.799
VF (kg)	5.90 ± 1.70	5.66 ± 1.73	-0.24 ± 2.12	5.86 ± 1.88	5.59 ± 1.50	-0.27 ± 0.94	0.939	0.879	0.945
PQ (kg)	9.17 ± 0.89	8.77 ± 0.84	-0.40 ± 1.35	8.97 ± 1.46	9.06 ± 1.16	0.09 ± 0.91	0.224	0.625	0.156
IS (kg)	2.60 (2.30, 2.90)	2.80 (2.70, 2.90)	0.30 (-0.2, 0.5)	2.55 (2.38, 3.10)	2.60 (2.38, 2.73)	-0.10 (-0.40, 0.30)	0.819	0.025	0.768
BMR (kcal)	1355.61 ± 130.08	1340.17 ± 91.15	-15.43 ± 168.22	1326.95 ± 132.41	1356.82 ± 164.64	29.86 ± 113.43	0.242	0.725	0.294

BMI, body mass index; WC, waist circumference; HC, hip circumference; ULF, upper limb fat percentage; LLF, lower limb fat percentage; BWC, body water content; VF, visceral fat; PQ, protein quantity; IS, inorganic salts; BMR, basal metabolic rate.

[†]Data are presented as Mean ± Standard Deviation or median (P25, P75).

^{*}*p* value represents the comparison of changes before and after intervention between the groups.

Table 5. Biochemical measures

	CON [†]			INT [†]			<i>p</i> [*]		
	Baseline	12-weeks	Change	Baseline	12-weeks	Change	Baseline	12-weeks	Change
BIL (mol/L)	11.26 ± 3.63	10.93 ± 3.14	-0.33 ± 3.81	11.36 ± 4.35	10.95 ± 3.99	-0.41 ± 3.20	0.938	0.985	0.944
BUN (mmol/L)	5.83 ± 2.22	5.64 ± 1.69	-0.19 ± 2.42	6.33 ± 2.02	5.86 ± 1.52	-0.47 ± 1.86	0.291	0.649	0.670
Cr (μmol/L)	73.0 (62.1, 82.7)	64.4 (54.2, 88.7)	-7.60 (-28.9, 11.0)	70.1 (55.8, 93.6)	60.1 (50.4, 87.2)	-6.80 (-16.2, 1.45)	0.838	0.674	0.570
UA (μmol/L)	335.43 ± 75.82	309.48 ± 79.65	-25.96 ± 95.13	334.59 ± 73.24	309.05 ± 75.63	-25.55 ± 85.59	0.699	0.964	0.988
TBA (μmol/L)	6.08 ± 5.48	5.69 ± 5.90	-0.39 ± 2.35	6.42 ± 4.50	5.98 ± 3.96	-0.44 ± 2.03	0.334	0.173	0.940
LPA (mg/dL)	12.86 ± 7.39	12.69 ± 6.39	-0.17 ± 8.54	10.96 ± 4.82	13.36 ± 7.81	2.40 ± 5.47	0.517	0.964	0.236
LDH (U/L)	194.96 ± 36.41	195.26 ± 32.92	0.30 ± 37.81	179.73 ± 38.85	168.09 ± 30.53	-11.64 ± 28.61	0.109	0.006	0.238
FBG (mmol/L)	4.61 (4.31, 5.09)	5.07 (4.50, 5.34)	0.33 (-0.23, 0.75)	4.58 (4.24, 5.45)	4.78 (4.45, 5.47)	0.11 (-0.14, 0.35)	0.768	0.401	0.137
HDL-C (mmol/L)	1.29 ± 0.32	1.33 ± 0.31	0.04 ± 0.42	1.18 ± 0.41	1.23 ± 0.37	0.05 ± 0.27	0.326	0.364	0.884
APOB (g/L)	1.13 ± 0.25	1.08 ± 0.26	-0.05 ± 0.40	1.05 ± 0.30	0.91 ± 0.29	-0.14 ± 0.40	0.364	0.042	0.432
K (mmol/L)	4.34 ± 0.37	4.40 ± 0.36	0.05 ± 0.47	4.23 ± 0.38	4.23 ± 0.42	0.00 ± 0.50	0.295	0.150	0.713
Na (mmol/L)	138.74 ± 2.24	138.98 ± 2.72	0.24 ± 3.25	139.02 ± 3.23	139.64 ± 2.59	0.62 ± 2.21	0.296	0.408	0.651
P (mmol/L)	1.12 ± 0.14	1.13 ± 0.14	0.01 ± 0.21	1.16 ± 0.20	1.17 ± 0.17	0.01 ± 0.25	0.456	0.467	0.949
Cl (mmol/L)	101.80 ± 2.25	101.17 ± 2.76	-0.63 ± 3.51	101.08 ± 4.21	101.68 ± 4.09	0.60 ± 4.62	0.484	0.627	0.320
Mg (mmol/L)	0.85 ± 0.06	0.83 ± 0.07	-0.02 ± 0.09	0.83 ± 0.06	0.83 ± 0.07	0.00 ± 0.07	0.341	0.994	0.459

BIL, bilirubin; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TBA, total bile acid; LPA, lipoprotein(a); LDH, lactate dehydrogenase; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; APOB, apolipoprotein B.

[†]Data are presented as Mean ± Standard Deviation or Median (P25, P75).

^{*}*p* value represents the comparison of changes before and after intervention between the groups.

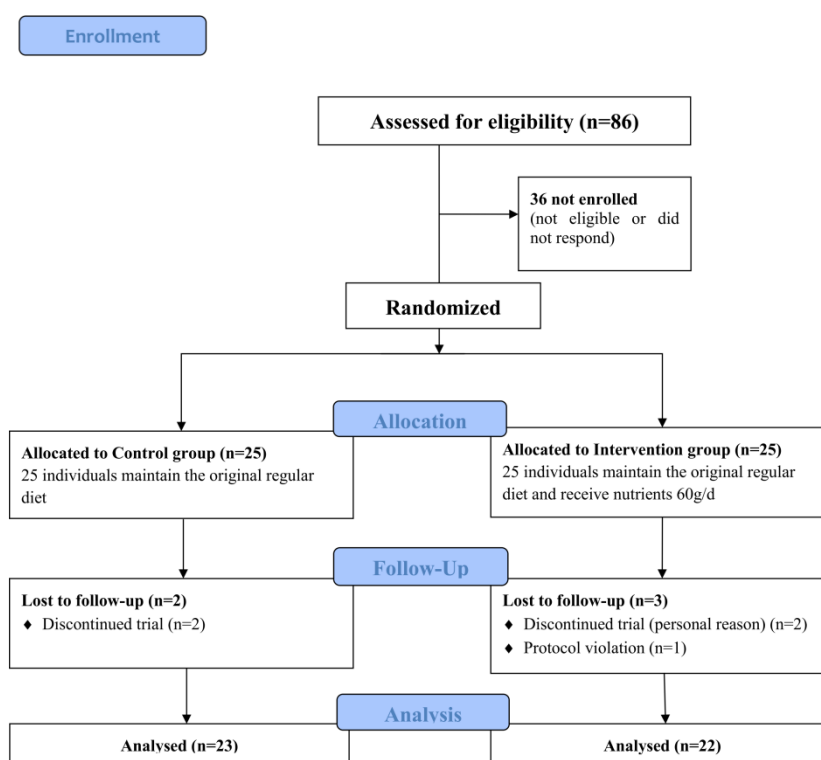


Figure 1. Process Flow Intervention Diagram

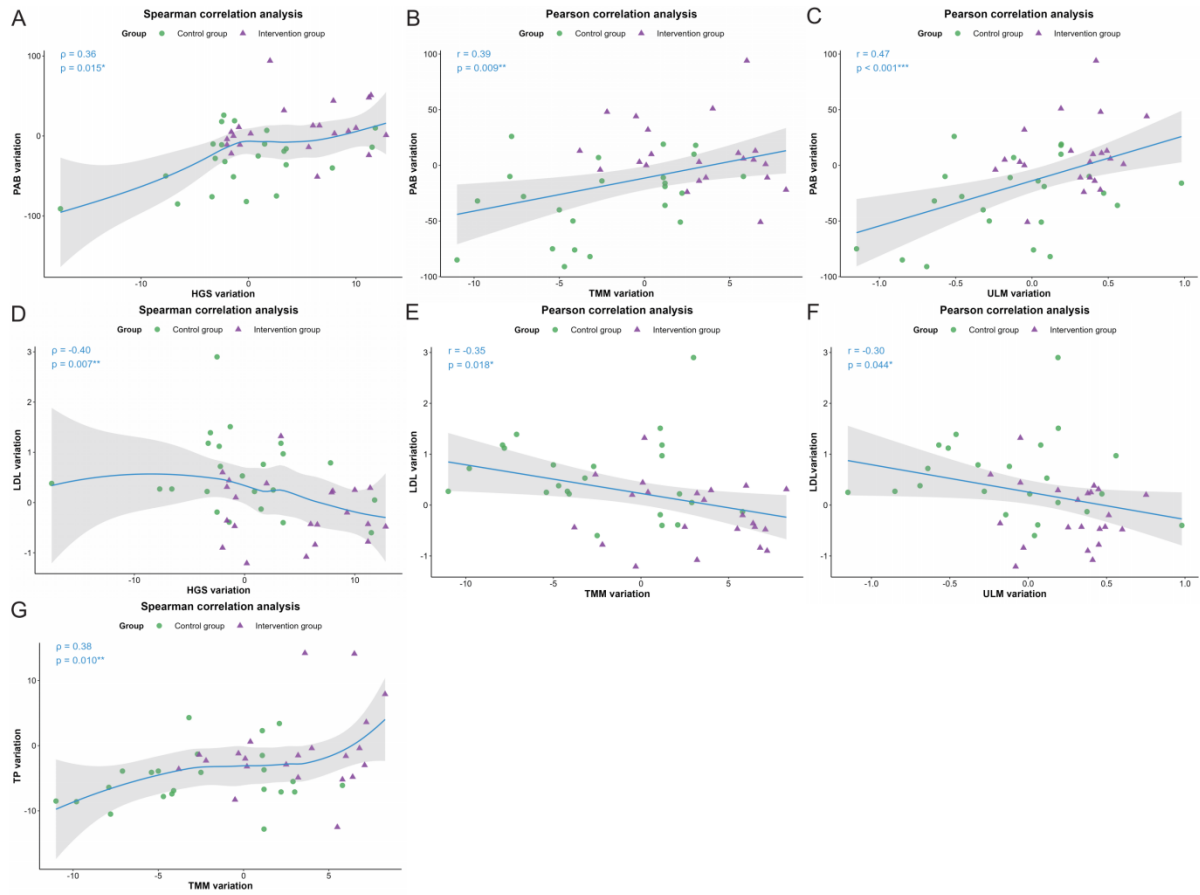
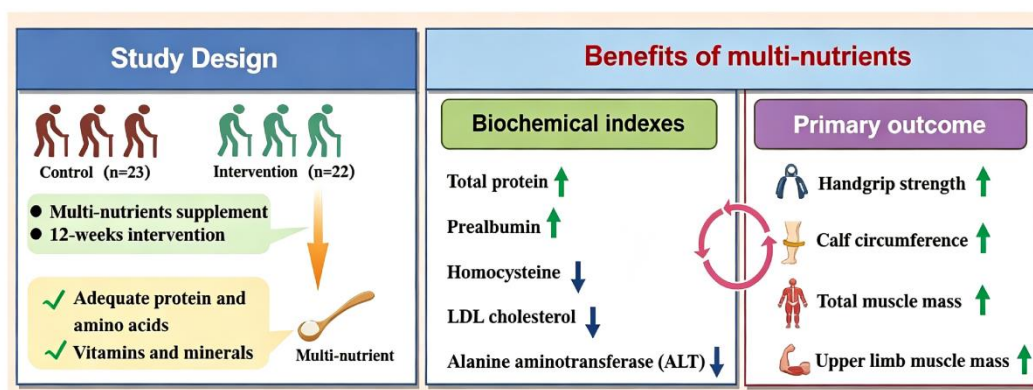


Figure 2. Correlation Analysis of the outcomes and indicators. Green dots represent the control group; purple triangles represent the treatment group. "Spearman" or "Pearson" indicates the correlation analysis method, corresponding to rank correlation and linear correlation, respectively. Correlation coefficients (r or ρ) and p -values are presented. *, **, and *** denote statistical significance at $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively. Fitted lines and confidence bands: Blue straight lines and curves represent fitted lines; gray areas represent 95% confidence interval bands.



Graphical abstract. Multi-nutrient supplementation improves handgrip strength, calf circumference, and total as well as upper-limb muscle mass in older adults with sarcopenia, accompanied by favorable changes in serum biochemical profiles.