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Original Study

Effects of a Vitamin D and Leucine-Enriched Whey Protein Nutritional Supplement on Measures of Sarcopenia in Older Adults, the PROVIDE Study: A Randomized, Double-Blind, Placebo-Controlled Trial

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A B S T R A C T

Background: Age-related losses of muscle mass, strength, and function (sarcopenia) pose significant threats to physical performance, independence, and quality of life. Nutritional supplementation could positively influence aspects of sarcopenia and thereby prevent mobility disability.
Objective: To test the hypothesis that a specific oral nutritional supplement can result in improvements in measures of sarcopenia.

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Design: A multicenter, randomized, controlled, double-blind, 2 parallel-group trial among 380 sarcopenic primarily independent-living older adults with Short Physical Performance Battery (SPPB; 0–12) scores between 4 and 9, and a low skeletal muscle mass index. The active group (n = 184) received a vitamin D and leucine-enriched whey protein nutritional supplement to consume twice daily for 13 weeks. The control group (n = 196) received an iso-caloric control product to consume twice daily for 13 weeks. Primary outcomes of handgrip strength and SPPB score, and secondary outcomes of chair-stand test, gait speed, balance score, and appendicular muscle mass (by DXA) were measured at baseline, week 7, and week 13 of the intervention.

Results: Handgrip strength and SPPB improved in both groups without significant between-group differences. The active group improved more in the chair-stand test compared with the control group, between-group effect (95% confidence interval): −1.01 seconds (−1.77 to −0.19), $P = .018$. The active group gained more appendicular muscle mass than the control group, between-group effect: 0.17 kg (0.004–0.338), $P = .045$.

Conclusions: This 13-week intervention of a vitamin D and leucine-enriched whey protein oral nutritional supplement resulted in improvements in muscle mass and lower-extremity function among sarcopenic older adults. This study shows proof-of-principle that specific nutritional supplementation alone might benefit geriatric patients, especially relevant for those who are unable to exercise. These results warrant further investigations into the role of a specific nutritional supplement as part of a multimodal approach to prevent adverse outcomes among older adults at risk for disability.

Preserving physical mobility, function, and ultimately independent living is of utmost importance for frail older adults.[1] Sarcopenia, the age-related loss of muscle mass, strength, and function[2,3] makes up a large component of physical frailty.[4] It is a strong risk factor for reduced mobility, events like falls and fractures,[5] and is directly related to rates of hospital and long-term care admissions,[6] increased disability,[7] reduced independence, quality of life, and ultimately resulting in death.[8] The onset and progression of sarcopenia is multidimensional involving physical inactivity, altered metabolism, neuromuscular deterioration, and marginal nutrient intakes and absorption.[2] The component of marginal nutrient intakes is of foremost interest here, because it is a modifiable risk factor of sarcopenia. Particularly protein, essential amino acids, leucine, and vitamin D intake are identified as important factors in the management of sarcopenia.[9] Inadequate protein intake [ie, below the recommended dietary allowance of 0.8 g/kg body weight (BW)/day] as well as vitamin D status (ie, 25-hydroxyvitamin D < 50 nmol/L) are often cited as being strongly correlated with lower muscle mass,[10,11] physical performance and muscle strength,[12,13] and a risk for falls and fractures.[14] Even in the presence of total per-day adequate protein intake, older adults' muscle is less sensitive to anabolic stimuli,[15] such as resistance exercise[16] and mixed meals,[17,18] compared with younger adults, a condition known as "anabolic resistance."[19]

Recent recommendations focus on daily protein intakes that should be at least 1.0 to 1.2 g/kg BW/day for healthy older people, and 1.2 to 1.5 g/kg BW/day for geriatric patients with acute and chronic diseases.[17,20] Further, given the blunted sensitivity of older muscles to low doses of amino acids, there are indications that dietary protein should be appropriately distributed to at least 25 to 30 g of high-quality protein per meal containing approximately 2.5 to 2.8 g of leucine, to stimulate muscle protein synthesis.[17] These concepts of intake timing, as well as protein quality, are subjects of several recent studies.[21,22] In a recent study, a bolus intake of a leucine-enriched, whey protein nutritional supplement stimulated acute postprandial muscle protein synthesis in both healthy and sarcopenic elderly.[23]

Therefore, we hypothesized that providing a targeted nutritional supplement containing whey protein, enriched with leucine and vitamin D in a timely bolus amount, would result in the accretion of muscle protein and improvements of muscle strength and function independent of physical exercise among nonmalnourished sarcopenic older adults at high risk for disability. We explored the efficacy and safety of this concept compared with an iso-caloric control supplement for improving measures of sarcopenia: lower-extremity function (Short Physical Performance Battery [SPPB] and its individual components), muscle strength (handgrip strength), and muscle mass [appendicular muscle mass by dual X-ray absorptiometry (DXA)].

Methods

Design and Participants

This was a 13-week, multicenter, randomized, controlled, double-blind, 2 parallel-group study among non–protein-energy malnourished older participants with mobility limitations. The study protocol was approved by institutional review boards at each location and registered under the Dutch trials register with the identifier: NTR2329 (http://www.trialregister.nl/trialreg). Study procedures were performed in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects.

Participants were recruited from 18 study centers in 6 European countries: Belgium, Germany, Ireland, Italy, Sweden, and the United Kingdom. Older adults (≥65 years) were screened for mild to moderate limitations in physical function (SPPB score 4–9), and for low skeletal muscle mass index [SMI; (skeletal muscle mass/BW * 100) ≤37% in men and ≤28% in women] using bioelectric impedance analysis (BIA 101; Akern, Florence, Italy)[24] because of its feasibility for an extensive screening process at multiple research sites. Further, participants were then eligible to participate if they had a body mass index (BMI) between 20 and 30 kg/m,[2] no major cognitive impairment (Mini Mental State Examination score ≥ 25), and were able and willing to provide informed consent. Potential participants were excluded if they had comorbidities such as kidney or liver failure, malignancies over the past 5 years, anemia, or acute inflammation (C-reactive protein concentration >10 mg/L), or presented with contraindications for calcium/vitamin D supplementation and/or were using medication interfering with the nutritional intervention.

Intervention

Participants were randomized to receive either the active or an iso-caloric control product. The active product contained, per serving, 20 g whey protein, 3 g total leucine, 9 g carbohydrates, 3 g fat, 800 IU vitamin D, and a mixture of vitamins, minerals, and fibers, whereas the iso-caloric control product did not contain any protein or micronutrients, and only carbohydrates, fat, and some trace elements

(Supplemental Table 1). Both were delivered as 40 g powder to be reconstituted with 100 to 150 mL water and consumed twice daily before breakfast and lunch to provide an adequate bolus of protein in addition to the meals.

Stratification and Randomization

Permuted block randomization (block size 4) to the active or control group was stratified for SPPB categories 4 to 6 and 7 to 9 and study center. The randomization sequence was computer-generated by a blinded statistician not involved in data collection or analysis. All investigators, study staff, and participants were blinded to group allocations, and the randomization code was not broken until statistical modeling of the primary and secondary outcomes was complete.

Outcome Measures

Blinded research staff assessed the outcomes during designated visits at week 7 and 13.

One of the 2 primary outcome measures, handgrip strength, was measured using a hydraulic hand dynamometer (Jamar; Preston, Jackson, MO). Two consecutive measures of grip strength in both hands were recorded to the nearest kilogram with the participant in an upright position and the arm of the measured hand parallel to the body. Maximum grip strength was calculated by taking the average of the highest measurement from both hands.

The other primary outcome measure, SPPB, consisted of the 3 components: gait speed (4-meter walk at a usual pace), chair stand test (time required to rise 5 consecutive times from a chair without arm rests), and balance (3 different standing balance tests) according to the method outlined in Guralnik et al.[6] Each component was scored from 0 (not possible) to 4 (best performance) and summed in a total score ranging from 0 to 12. The individual outcomes related to physical function: chair rise test, gait speed, and balance score, were predefined as separate secondary outcomes.

Other secondary outcomes were appendicular muscle mass (by DXA) and questionnaires of self-reported physical activity, activities of daily living, and health-related quality of life. DXA (different models from Hologic, Bedford, MA, and Lunar, Fairfield, CT) was used to measure appendicular muscle mass at baseline and week 13. Central blinded analysis of raw DXA data from all sites was performed at Vrije Universiteit Brussel, to ensure uniformity in the analysis.

Self-reported amount of physical activity was measured using the European version of the Physical Activity Scale for the Elderly (PASE).[25] The Barthel index[26] measured the level of independence in activities of daily living with possible scores between 0 and 100 (highest scores best). Health-related quality of life was measured using the EQ-5D,[27] both as an index and as a visual analogue scale (VAS) between 0 and 100.

Product compliance was measured using self-completed intake diaries. Adequate compliance was defined as having consumed 10 of the possible 14 servings per week. Dietary assessment was done at baseline and week 13 using 3-day prospective diet records for 2 week-days and 1 weekend day. Additional energy and protein intakes from both supplements were added to the habitual 3-day intakes (ie, nonsupplementary intake) to assess total intakes.

Fasting glucose and insulin were measured at screening, serum 25-hydroxy-vitamin D and insulinlike growth factor 1 (IGF-1) at baseline, week 7, and week 13. Safety assessments included the examination of participant medical history, recording of medication use, nutritional supplements, and adverse events via telephone calls throughout the intervention and at each of the visits. Additional safety assessments were done at the designated visits. These included monitoring vital signs, gastrointestinal tolerance, evaluating laboratory parameters related to liver and renal function, and inflammatory status.

Statistical Analyses

This study was powered to detect an effect size of 1.9 kg for handgrip strength[28,29] and a 0.5-point difference in SPPB.[30] Assuming an α-value of 0.025, a 2-sided effect, and using the Hochberg principle for 2 primary outcomes, a sample size of 300 gave 80% power to observe an effect. Eighty additional participants were randomized under the guidance of the data monitoring committee following the blinded interim analysis.

Analyses were performed as intention-to-treat, defined as all participants randomized, regardless of whether they finished the full study protocol. Baseline unadjusted means and SDs and week 7 and week 13 unadjusted mean changes from baseline [medians and interquartile ranges (IQRs) for non-normal data] are presented. A mixed model for repeated measures (MMRM) was performed including the baseline value in the outcome vector and fixed factors for treatment and time (continuous). In this model, the treatment by time interaction coefficient estimates the potentially differential change in outcomes over time between active and control group. No adjustments were made for multiple testing for secondary outcomes due to the exploratory nature of the study. Continuous variables that were positively skewed were log-transformed before analysis in the MMRM. The MMRM for all outcomes included the predefined covariates baseline protein intake, age, and sex. For 16 participants, imputation was performed for missing baseline protein intake using the overall group mean intake. Missing values in outcome variables were not imputed because mixed models can handle missing data by maximum likelihood.[31] The Mann-Whitney *U* test was used for categorical variables that could not be used in the MMRM model.

All statistical analyses were done using SAS software (version 9.4; SAS, Inc, Cary, NC) according to the predefined statistical analysis plan. The statistical analyses were repeated by independent statisticians (Julius Centre, Utrecht University), who confirmed the findings.

Results

Between June 30, 2010, and May 30, 2013, 1240 older adults were screened for participation, 380 of whom were randomized to the intervention or control groups (Figure 1). After the 13-week intervention, 302 participants completed all 3 study visits (79% completion rate). Baseline background characteristics were similar in both groups (Table 1). The mean age of the population at enrolment was 77.7 years, most of whom were women (65%), and living independently (87%). All participants had low muscle mass, a mean SPPB score of 7.5 (Table 2), a mean BMI of 26.1 kg/m^2, and were nonmalnourished based on the Mini Nutritional Assessment Short-Form (99.5%). Intervention compliance was high (median: 93%) from baseline to follow-up, and did not differ between groups.

There was no significant difference in handgrip strength changes over time between the control and active groups. Handgrip strength improved significantly over time in the intervention group ($P = .005$), whereas there was likely no time effect in the control group ($P = .06$). SPPB scores increased significantly over time in both active and control groups ($P < .001$), but with no significant treatment $\times$ time effect (Table 2).

Chair-stand time improved significantly in both groups over time ($P < .001$), with a significantly greater improvement in the active group compared with control ($P = .018$). Both groups improved significantly over time in gait speed ($P < .001$), but the

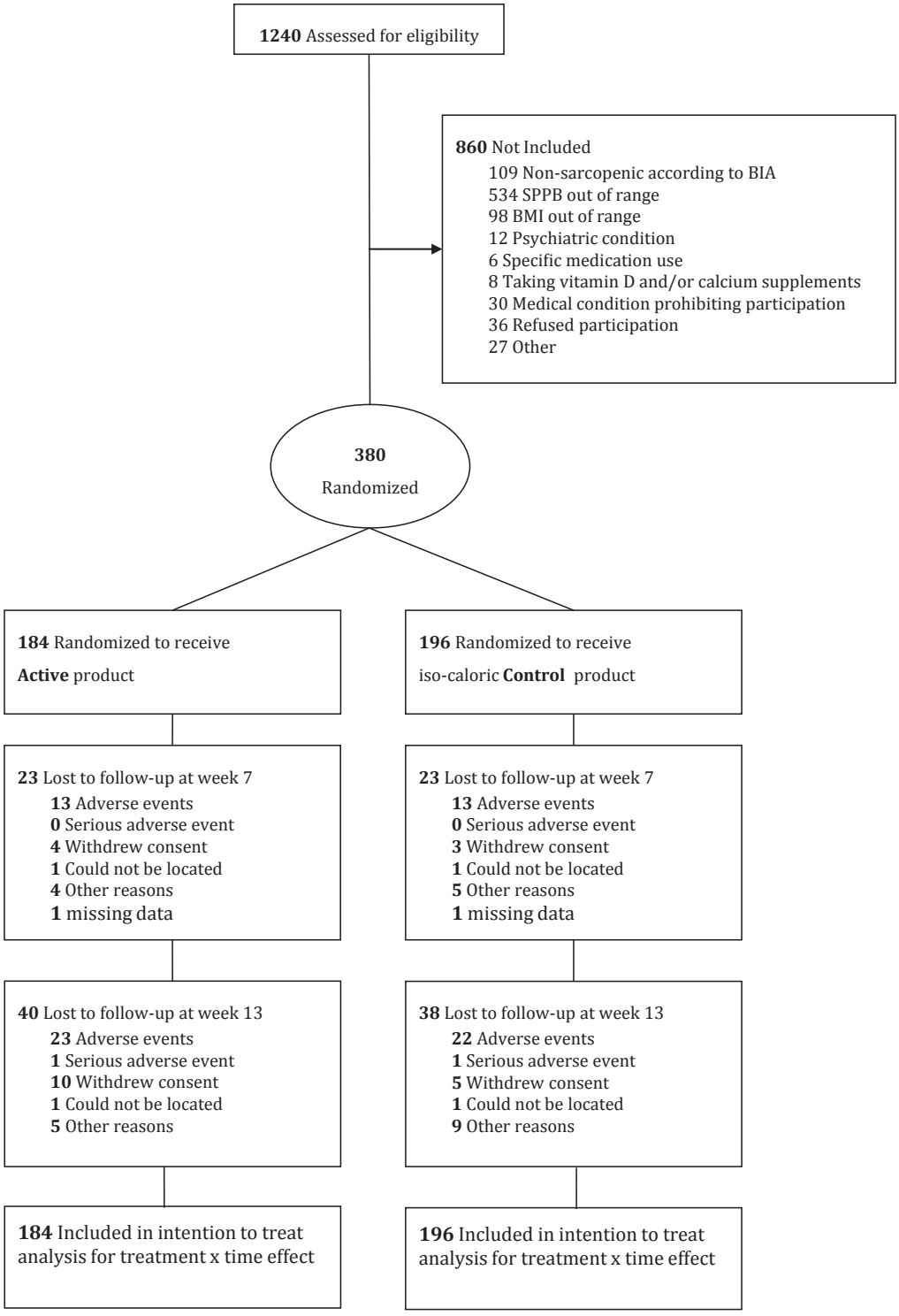

Fig. 1. Participant screening, randomization and follow-up.

treatment × time effect was not significant. Balance scores remained unchanged both over time and by treatment (Table 2).

The increase in appendicular muscle mass was significantly greater in the active group than the control group, leading to a mean estimated difference of 0.17 kg (95% confidence interval [CI] 0.004–0.338) ($P = .045$) (Figure 2). There was a significant gain over time in appendicular muscle mass in the active group alone ($P < .001$).

No treatment × time effects were observed in the PASE questionnaire, Barthel index, or quality of life as measured with the EQ-5D index. There was a significant time effect observed in the active group in the quality of life EQ-5D VAS score, leading to a trend for a mean treatment × time effect of 2.5 mm (95% CI −0.17–5.16; $P = .07$).

Habitual dietary energy intakes, without supplements, decreased significantly over time in both groups, whereas supplementation in

Table 1
Baseline Demographic and Clinical Characteristics

	Active n = 184	Control n = 196
Age, mean (SD), y	77.3 (6.7)	78.1 (7.0)
Sex, female n (%)	120 (65.2)	129 (65.8)
Living situation, n (%)		
Institutionalized	18 (9.8)	19 (9.7)
Home care	4 (2.2)	10 (5.1)
Living independently	162 (88.0)	167 (85.2)
Mini Mental State Examination, median (IQR)	29.0 (27.0–30.0)	29.0 (28.0–30.0)
Hemoglobin concentration, median (IQR), mmol/L	8.4 (7.9–8.9)	8.5 (8.0–8.9)
BMI, mean (SD), kg/m^2	26.0 (2.5)	26.2 (2.8)
Mini Nutritional Assessment Short-Form (MNA-SF), n (%)		
Malnutrition	1 (0.5)	1 (0.5)
Risk of malnutrition	15 (8.2)	19 (9.7)
No malnutrition	168 (91.3)	176 (89.8)
Protein intake, median (IQR), g/kg body weight/day	1.0 (0.9–1.2)	1.0 (0.8–1.2)
Fasting glucose concentration, median (IQR), mmol/L	5.2 (4.9–5.8)	5.2 (4.9–5.7)
Fasting insulin concentration, median (IQR), mU/L	9.0 (5.0–13.0)	9.0 (6.0–14.0)
Handgrip strength male, median (IQR), kg	26.8 (22.0–30.8)	27.1 (22.0–32.1)
<30 kg, n (%)	45 (70.3)	45 (69.2)
Handgrip strength female, median (IQR), kg	16.5 (13.5–21.5)	16.8 (14.2–20.5)
<20 kg n, (%)	80 (69.6)	94 (74.0)
Gait speed n (%), <0.8 m/s	101 (54.9)	109 (55.6)
SMI (BIA), n (%)		
Normal SMI	0 (0)	0 (0)
Class I sarcopenia*	154 (84)	164 (84)
Class II sarcopenia†	30 (16)	32 (16)
Appendicular muscle mass (DXA), mean (SD), kg	17.9 (4.1)	17.5 (3.8)

BIA, bioelectric impedance analysis; SMI, skeletal muscle mass index; DXA, dual energy x-ray absorptiometry.

*Class I sarcopenia (skeletal muscle mass, kg/body mass, kg * 100), men: 31%–37%, women: 22%–28%.

†Class II sarcopenia (skeletal muscle mass, kg/body mass, kg * 100), men: <31%, women: <22%.

both groups led to a significant increase in total energy intakes at week 13 ($P < .001$).

Habitual protein intakes were not different between groups at baseline and did not change significantly from baseline to week 13, nor did it differ between groups. Participants in the active group alone showed an increased total protein intake at week 13 ($P < .001$) (Table 3).

At baseline, 25-hydroxyvitamin D concentrations were 50 nmol/L or lower in 51% and 53% of the participants in the control and active group, respectively. In the active group, 25-hydroxyvitamin D concentrations improved significantly ($P < .001$) at week 13 (Table 3). At follow-up, 1 participant in the control group (<1%) and 4 participants in the active group (3%) showed 25- hydroxyvitamin D concentrations of 125 nmol/L or higher. There was a significant time × treatment effect in IGF-1, with an effect size of: 12.6 μg/L (95% CI 7.4–18.1; $P < .001$).

Based on (serious) adverse events, gastrointestinal tolerance, and laboratory parameters, both study products seem safe and the data do not give rise to any concern. There were no statistically significant differences in incidence of (serious) adverse events between the groups (Figure 1).

Discussion

This 13-week specific nutrition intervention among non–protein-energy malnourished older adults with mobility limitations did not lead to significant differences in SPPB or handgrip strength. There were, however, significant gains in muscle mass and improvements in chair stand ability in the active group versus control. This suggests that a vitamin D and leucine-enriched whey protein nutritional supplement, which stimulated muscle protein synthesis in an acute setting,[32,33] could improve measures of sarcopenia over a 3-month intervention.

Exercise should be considered as the standard treatment for increasing muscle strength and improving physical performance among adults with sarcopenia.[34–36] In this robust trial, however, we aimed to investigate the isolated effect of a targeted nutritional intervention. This area has mostly focused on the acute effects on muscle protein synthesis. Very few longer-term nutritional intervention studies have been performed to assess changes in muscle mass, strength, and function among older adults at risk for mobility disability.[37] Fiatarone and colleagues[38] did not show any effect of a nutritional supplement alone given for 10 weeks to 100 frail nursing home residents. In a more recent study in prefrail and frail older adults (n = 65), Tieland and colleagues[39] demonstrated that nutritional supplementation led to improvements in SPPB, but did not result in differences in muscle mass or strength.

In this study, we selected sarcopenic older adults characterized by both low muscle mass and function, using a nutritional supplement specifically targeted for aging muscle. To our knowledge, this is the only study using nutritional supplementation alone to result in an increased muscle mass among this population. Adults older than 70 years lose on average 5% to 10% of their muscle mass per decade.[40–42] The approximate gain of 1% total appendicular muscle mass that we observed after 13 weeks of intervention would translate, therefore, into saving 1 to 2 years of muscle mass decline.

High habitual protein intake could be correlated with appendicular muscle mass retention.[10] At baseline, habitual protein intakes in both groups were above the recommended dietary allowance of 0.8 g/kg per day for adults.[43] The active group alone achieved a higher total protein intake of 1.5 g/kg per day, which is in line with recent PROT-AGE and European Society for Clinical Nutrition and Metabolism recommendations for geriatric patients (1.2–1.5 g/kg per day).[17,20] Beyond protein quantity, quality and timing of the protein supplementation are also considered crucial determinants for retention of muscle mass and function.[15,17,20] In short-term studies, bolus intake of whey protein and leucine provided sufficient levels of essential amino acids, particularly leucine, required to elicit an appropriate acute muscle protein synthesis response.[32,33,44] The leucine-enriched whey protein blend seems to be an appropriate approach to preserve muscle mass and function in older sarcopenic adults, possibly through the timely stimulation of muscle protein synthesis and the anabolic environment, as suggested by the IGF-1 increase we observed.[45]

Additionally, serum 25-hydroxyvitamin D concentrations between 60 and 75 nmol/L are suggested to be optimal for lower-extremity strength, and falls and fracture prevention.[46] During the 3-month supplementation of at least 800 IU daily vitamin D in the active group, baseline serum 25-hydroxyvitamin D concentrations of median 48 (IQR 34–66) nmol/L (<50 nmol/L is considered insufficient) increased by median 25 (IQR 14–39) nmol/L, which resulted in concentrations within the optimal range.[46] Reversing the vitamin D inadequacies, in combination with leucine and amino acids, could have contributed to the favorable effect we observed on muscle parameters.[47]

This study is not without limitations. Our primary outcome measurement, handgrip strength, is a well-validated proxy measurement for lower-body strength,[48] but is less sensitive to intervention changes than other measures of strength. A study showed that although handgrip and leg-press strength are well-correlated with each other and with muscle mass, leg strength showed an intervention effect, whereas handgrip strength did not.[49]

Table 2
Muscle Strength and Function Outcomes

	Mean (SD)	Change From Baseline, Mean (SD)		Estimated Between-Group DifferenceMean (95% CI)Active − Control	*P**
	Baseline	Week 7	Week 13		
Handgrip strength, kg					
Active†	20.9 (7.9)	0.20 (3.2)	0.79 (3.6)‡	0.30§ (−0.46–1.05)	.44
Control‖	20.6 (7.5)	0.34 (2.8)	0.54 (3.2)		
SPPB					
Active¶	7.5 (1.9)	0.50 (1.26)	0.86 (1.38)**	0.11§ (−0.21–0.42)	.51
Control††	7.5 (2.0)	0.51 (1.21)	0.77 (1.45)**		
Chair-stand time, s‡‡					
Active§§	17.1 (15.2, 21.2)	−1.4 (−3.3–0.4)	−2.5 (−4.2 to −0.6)**	−1.01§ (−1.77 to −0.19)	.018
Control‖‖	17.6 (14.6, 20.6)	−1.0 (−3.0–1.1)	−1.2 (−3.3–0.8)**		
Balance test¶¶					
Active¶	3.0 (2.0, 4.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	N.A.	.89
Control††	3.0 (2.0, 4.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)		
Gait speed, m/s					
Active¶	0.8 (0.2)	0.03 (0.11)	0.07 (0.12)**	0.01§ (−0.02–0.04)	.46
Control***	0.8 (0.2)	0.03 (0.10)	0.05 (0.12)**		

N.A., not applicable; SPPB, Short Physical Performance Battery.
*The *P* value represents the time × treatment interaction derived from a mixed model (MMRM) adjusting for age, sex, and baseline protein intake.
†Baseline: n = 179, week 7: n = 155, week 13: n = 139.
‡*P* value <.01 derived from MMRM assessing the within-group change from baseline (time effect).
§MMRM: active: n = 144, control: 158.
‖Baseline: n = 192, week 7: n = 169, week 13: n = 154.
¶Baseline: n = 184, week 7: n = 159, week 13: n = 143.
**P value < .001 derived from MMRM assessing the within-group change from baseline (time effect).
††Baseline: n = 196, week 7: n = 173, week 13: n = 158.
‡‡Median and interquartile range (IQR) presented since data had non-normal distributions. Data were log-transformed to enable a MMRM analysis.
§§Baseline: n = 162, week 7: n = 141, week 13: n = 126.
‖‖Baseline: n = 170, week 7: n = 152, week 13: n = 138.
¶¶Median and IQR presented because data were categorical, *P* value derived from Mann-Whitney test for nonparametric means. The within-group effect of time was not assessed because the MMRM could not be performed on these categorical data.
***Baseline: n = 196, week 7: n = 172, week 13: n = 158.

In the other primary outcome measurement, SPPB, we also did not observe an intervention effect. This is likely explained by the unexpected positive and significant time effect both in the intervention and control groups. Furthermore, the SPPB is by nature a categorical score, and is less sensitive to changes than a continuous numerical scale. Although the significant changes in the chair-stand test did not result in significant differences in the overall SPPB score, the improvement we observed could be clinically meaningful. The chair-stand test is a robust measure of lower-extremity function because it requires lower-body strength, power, and good balance and coordination.[50] Poor chair-stand performance is an independent risk factor for physical disability, hospitalization, and mortality.[51]

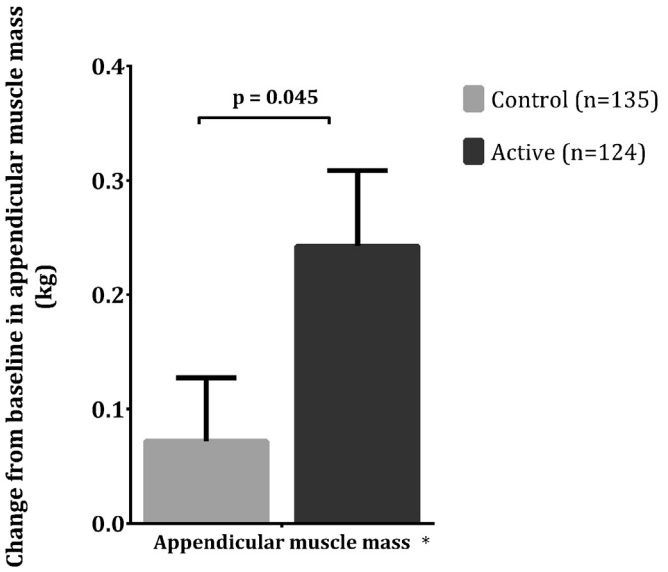

Fig. 2. Change (kg) in appendicular muscle mass from baseline to week 13 follow-up. *The raw mean change from baseline to week 13 and SE. The *P* value represents the time × treatment interaction derived from a mixed model (MMRM) adjusting for age, sex, and baseline protein intake.

As such, the sarcopenic screening measures of handgrip strength and SPPB may not be appropriate outcomes for measuring effects of sarcopenia interventions. We urge future researchers to carefully select sensitive and specific outcomes for sarcopenia, such as lower-extremity strength and function.

Although this study was performed among a robust sample of independently living older adults with mobility limitations, we could not include the full spectrum of older adults in the population at large. Groups such as those recovering from hospitalization and immobilization might benefit from nutritional supplementation, even while potentially unable to exercise. Although structured physical activity programs are not always practical or feasible, and maintaining good compliance is often problematic,[52] ideally, this nutrition intervention would be combined with exercise. A recent study demonstrated a reduction in major mobility impairment after a long-term structured physical activity program.[36] These interventions, taken together, address 2 major mediating and reversible factors of sarcopenia and physical frailty, and have the potential to prolong mobility, independence, and quality of life.

Conclusion

We present here a 13-week intervention of a vitamin D and leucine-enriched whey protein oral nutritional supplement that resulted in improvements in muscle mass and lower-extremity function among sarcopenic older adults. This study shows proof-of-principle that specific nutritional supplementation alone might benefit geriatric patients, especially relevant for those who are unable to

Table 3
Nutritional and Biochemical Outcomes

	Median (IQR)	Change From Baseline Median (IQR)	Estimated Between-Group Difference Mean (95% CI) Active − Control	P*
	Baseline	13 weeks		
Serum 25-hydroxyvitamin D (nmol/L)†				
Active‡	48.0 (34.0–66.0)	25.0 (14.0–39.0)§	34.2 (29.2–39.6)¶	<.001
Control‖	49.0 (34.0–65.0)	−6.0 (−11.0–0.00)§		
Serum IGF-1 (μg/L)†				
Active**	113.0 (80.0–145.0)	9.0 (−2.0–23.0)§	12.6 (7.4–18.1)¶	<.001
Control‖	114.0 (90.0–139.0)	−1.5 (−12.0–14.0)		
Non-supplementary dietary energy intake (kcal/day)†,††				
Active‡‡	1698 (1423–2028)	−124 (−395–161)§§	31.7 (−52.6–122.5)¶	.41
Control‖‖	1612 (1407–1918)	−127 (−372–160)§		
Non-supplementary dietary protein intake (g/kg BW/day)†,††				
Active‡‡	1.0 (0.9–1.2)	−0.1 (−0.2–0.1)	0.02 (−0.05–0.09)¶	.56
Control‖‖	1.0 (0.8–1.2)	−0.1 (−0.2–0.1)§§		
Total dietary energy intake including supplement (kcal/day)††,¶¶				
Active‡‡	1698 (1423–2028)	166 (−95–458)	N.A.	.92
Control‖‖	1612 (1407–1918)	165 (−122–463)		
Total dietary protein intake including supplement (g/kg BW/day)††,¶¶				
Active‡‡	1.0 (0.9–1.2)	0.5 (0.3–0.6)	N.A.	<.001
Control‖‖	1.0 (0.8–1.2)	−0.1 (−0.2–0.1)		

N.A., not applicable.
*The *P* value represents the time × treatment interaction derived from a mixed model (MMRM) adjusting for age, sex, and baseline protein intake.
†Median and IQR presented since data had non-normal distributions. Data were log-transformed to enable a MMRM analysis.
‡Baseline: n = 180, week 13: n = 143.
§*P* value <.001 derived from MMRM assessing the within-group change from baseline (time effect).
‖Baseline: n = 191, week 13: n = 157.
¶MMRM: active: n = 144, control:158.
**Baseline: n = 182, week 13: n = 143.
††Data calculated based on 3-day dietary intake records, including 1 week day and 1 weekend day on the week of baseline and 13-week follow-up. Energy and nutrient contributions by the supplement were estimated on an individual level by average reported compliance completed during the week of dietary assessment. This proportion was multiplied by the nutrient composition of both the active and control supplements and added to the total habitual intakes.
‡‡Baseline: n = 176, week 13: n = 138.
§§*P* value <.05 derived from MMRM assessing the within-group change from baseline (time effect).
‖‖Baseline: n = 188, week 13: n = 152.
¶¶Median and IQR presented because data had non-normal distributions. *P* value derived from Mann-Whitney test for nonparametric means. Within-group effect of time was not assessed because the MMRM was not performed on these data.

exercise. These results warrant further investigations into the role of a specific nutritional supplement as part of a multimodal approach to prevent adverse outcomes among older adults at risk for disability.

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Supplementary Data

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