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Original Study

Impacts of High-Protein Oral Nutritional Supplements Among Malnourished Men and Women with Sarcopenia: A Multicenter, Randomized, Double-Blinded, Controlled Trial

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A B S T R A C T

Background: Recent evidence suggests that nutritional interventions may improve muscle outcomes in malnutrition and sarcopenia.
Objectives: We evaluated the effects of 2 high-quality oral nutritional supplements (ONS) differing in amount and type of key nutrients in older adult men and women.
Design: A multicenter, randomized, double-blinded, controlled clinical trial.
Participants: Malnourished and sarcopenic men and women, 65 years and older (n = 330).
Intervention: A 24-week intervention period with 2 energy-rich (330 kcal) ONS treatment groups: Control ONS (C_{ONS}, 14 g protein; 147 IU vitamin D_3) versus Experimental ONS (E_{ONS}, 20 g protein; 499 IU vitamin D_3; 1.5 g CaHMB) taken twice daily. Both ONS also contained other vitamins, minerals, and nutrients in varying amounts.
Measurements: Isokinetic peak torque (PT, Nm) leg strength, grip strength (kg), and gait speed ($m \cdot s^{-1}$) were assessed at baseline and 12 and 24 weeks. Left and right leg muscle mass (LMM, kg) were assessed by dual-energy x-ray absorptiometry (DXA). Muscle quality (MQ) was leg strength expressed relative to the tested LMM ($Nm \cdot kg^{-1}$). Subgroup analyses were performed: severe sarcopenia (low skeletal mass index, low grip strength [<30 kg men; <20 kg women], low gait speed [$<0.8\ m \cdot s^{-1}$]) and mild-moderate sarcopenia (low skeletal mass index, normal gait speed, or normal grip strength).
Results: Both ONS groups (E_{ONS} and C_{ONS}) improved PT, MQ, grip strength, and gait speed from baseline with no treatment differences. Those with severe sarcopenia (44%) exhibited lower baseline PT and MQ, with no differences in strength improvements between treatments. However, participants with mild-moderate sarcopenia exhibited higher baseline PT and MQ, with differences in strength improvements at 12 weeks ($E_{ONS} > C_{ONS}$, $P = .032$) in those with normal grip strength. There were no treatment differences based on sarcopenic severity for either grip strength or gait speed.
Conclusion: ONS improved strength outcomes in malnourished older adults with sarcopenia. In those with mild-moderate sarcopenia, but not severe sarcopenia, consumption of the E_{ONS} improved leg muscle strength and quality compared with the standard C_{ONS}.

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Malnutrition and sarcopenia are conditions that are common and overlapping in older adults.[1] Both conditions are strongly influenced by nutrition, where an inadequate nutrient intake is a contributing factor to weight loss and consequently functional impairment. Low lean body mass, a characteristic of sarcopenia, has recently been included in the definition of malnutrition.[2] Another characteristic of sarcopenia, reduced muscle strength, also has been suggested as an indicator of nutritional status.[3] Malnutrition and sarcopenia independently contribute to an increased risk of adverse outcomes, such as falls,[4,5] physical disability,[6] poor quality of life,[7,8] and increased mortality.[9–11] Therefore, interventions for older adults that address both malnutrition and sarcopenia may help reduce these negative outcomes and prolong an older adult's independent lifestyle and improve the quality of life.

The benefits of nutritional interventions for malnutrition-related outcomes are unequivocal.[12] However, the impact of nutrition on sarcopenia is less certain. Most studies report the effects of short-term nutritional interventions on muscle protein synthesis, whereas there are very few high-quality randomized controlled trials.[13] A recent review of the prevalence of sarcopenia and interventions to treat it by the International Sarcopenia Initiative[13] concluded that muscle function impairments in older adults can be improved by exercise interventions, whereas the effects of protein supplementation alone were inconsistent. The authors indicated, however, that calcium β-hydroxy β-methylbutyrate (CaHMB), a metabolite of leucine, showed promise,[13] which was also consistent with a recent meta-analysis examining the benefits of CaHMB on preserving muscle mass in older adults.[14]

The overall expert recommendation was that "Further studies are needed to determine the effect of different nutrition interventions on muscle mass and function using robust, multi-centre and standardised approaches with single or complex nutrition interventions and clinically relevant outcomes (muscle strength, physical performance)."[13]p757

The anabolic signaling of amino acids in skeletal muscle is thought to be primarily triggered by the consumption of essential amino acids, particularly the branched chain amino acid *leucine*.[15,16] It has been shown that higher amounts of protein are needed in older adults compared with young adults to stimulate muscle protein synthesis due to the *anabolic resistance* of aging muscle.[17] Thus, it has been recommended that older adults need at least 1.0 to 1.2 $g \cdot kg^{-1} \cdot d^{-1}$, which is greater than the current US Recommended Dietary Allowance of 0.8 $g \cdot kg^{-1} \cdot d^{-1}$, to maintain muscle function.[18] Because HMB is derived exclusively from leucine in the body,[19] and both leucine and HMB have been shown to stimulate muscle protein synthesis and attenuate muscle protein breakdown,[16] many of the beneficial effects of leucine may be mediated, in part, by HMB.

A recent pilot study[20] demonstrated that the consumption of 3 g CaHMB daily for 24 weeks positively influenced both leg strength and muscle quality (MQ) in healthy older men and women compared with a placebo. These findings suggested that CaHMB may improve clinically relevant strength parameters associated with the loss of functionality and performance. Despite some earlier limited evidence in healthy older adults,[21–23] it remains unclear whether the magnitude of these effects would be similar or greater for older adults with a combination of malnutrition and sarcopenia, who present elevated risks of morbidity and mortality.[5,6,10]

Vitamin D_3 supplementation is widely recognized to improve bone health, postural stability, and prevent falls and fractures leading to disability.[24,25] Supplementation is especially relevant to older men and women, due to a combination of malnutrition, reduced sunlight exposure, and a decrease in synthesis capacity of skin.[24] Current scientific opinion is 800 IU (20 μg) of vitamin D from all sources should be consumed daily to prevent falls in men and women older than 60 years.[25]

Older adults with malnutrition and sarcopenia may not consume sufficient amounts of high-quality protein and/or other nutrients through diet alone. Finding a convenient and compliant nutritional strategy for the attenuation of both malnutrition and sarcopenia would be advantageous. Oral nutritional supplements (ONS) are ideally suited to provide high-quality nutrition when diet alone is insufficient to meet nutritional needs. Furthermore, because of their energy, protein, and vitamin density, supplementing an older adult's diet with an ONS should not reduce the typical dietary intake, but should improve body weight and several functional outcomes, such as hand grip strength.[3,26] To that end, the purpose of this study was to evaluate the effects of 2 high-quality ONS differing in amount and type of key nutrients in older adult men and women with combined malnutrition and sarcopenia.

Methods

Research Design

This was a 24-week, prospective, randomized, double-blinded, controlled, 2-treatment parallel study design. Men and women 65 years and older from 8 countries across Europe and North America with both malnutrition and sarcopenia were enrolled. Malnutrition was defined as a Subjective Global Assessment rating of B or C.[27] Sarcopenia was defined as low grip strength (<20 kg women; <30 kg men) and/or low gait speed (<0.8 $m \cdot s^{-1}$) in conjunction with low skeletal mass index.[28] Enrolled individuals were stratified for gender and age at each study site and randomized into ONS treatment groups: (1) Control ONS (C_{ONS}) and (2) Experimental ONS (E_{ONS}). The protocol was reviewed by local ethics committees or institutional review boards and all participants signed a written informed consent. This study was a registered on ClinicalTrials.gov with the identifier: NCT01191125.

Participants were instructed to drink 2 servings of the ONS daily between regular meals throughout the duration of the study. Participants also were instructed to continue their usual diet, physical activity, and lifestyle habits, with the following exceptions: (1) consumption of study product daily and (2) the recommended ad libitum diet contained a minimum of 0.8 g protein per kg body weight.

Study participants visited the research facility at baseline (week 0) and every 6 weeks (±1 week) thereafter until the end of the 24-week intervention. At each visit, study staff reviewed product intake forms to assess compliance, dietary intake, recorded medication changes, and adverse events. Fasting blood draw, height (measured only at baseline, m), weight (calibrated stadium scale, kg), body composition, leg strength, grip strength, and gait speed tests were conducted at baseline and at 12 and 24 weeks.

To reduce the potential for learning effects, each participant visited the laboratory for 2 familiarization trials before the baseline assessment (separated by at least 1 day within 4 days before baseline) and 1 familiarization trial ≤4 days before both the 12- and 24-week assessments to practice the strength and functionality tests. Finally, all study staff were trained first by webinar and second in person by a single investigator (JTC) on how to perform the body composition, strength, and functionality tests according to standardized testing protocols.

Study Products

Ready-to-drink 220-mL ONSs were packaged indistinguishably except for a 5-digit code to maintain the double-blind study design. Products were isocaloric, providing 330 kcal per serving (Table 1). Each serving of the C_{ONS} (Ensure Plus; Abbott, Zwolle, Netherlands) contained 14 g protein, 11 g fat, 44 g carbohydrate, 147 IU vitamin D_3, and additional vitamins and minerals. Each serving of the E_{ONS} provided 20 g protein, 11 g fat, 36 g carbohydrate, 1.5 g CaHMB, 499 IU vitamin D_3,

Table 1
Approximate Compositions of Control (C_{ONS}) and Experimental (E_{ONS}) Products

Ingredient	Unit	C_{ONS} 220 mL	E_{ONS} 220 mL
Protein	g	14	20
Fat	g	11	11
Carbohydrate	g	44	36
CaHMB	g	0	1.5
Fructooligosaccharide	g	0	1.7
Carnitine	mg	0s	40
Vitamin A (Palmitate)	μg RE	194	132
Vitamin A (Palmitate)	IU	642	440
Vitamin A (B-Carotene)	μg RE	64	132
Vitamin A (B-Carotene)	IU	642	1320
Vitamin D_3	μg	3.7	12
Vitamin D_3	IU	147	499
Vitamin E	mg α TE	5.3	5.5
Vitamin E	IU	7.9	8.1
Vitamin K_1	μg	26	33
Vitamin C	mg	26	35
Folic Acid	μg	73	77
Vitamin B_1	mg	0.44	0.57
Vitamin B_2	mg	0.59	0.75
Vitamin B_6	mg	0.59	0.75
Vitamin B_{12}	μg	1.4	1.3
Niacin equivalent	mg	5.7	6.6
Pantothenic acid	mg	2.4	2.4
Biotin	μg	13	13
Choline	mg	121	154
Sodium	mg	264	242
Potassium	mg	440	616
Chloride	mg	242	139
Calcium	mg	257	352
Phosphorus	mg	202	209
Magnesium	mg	66	55
Iron	mg	4.6	4.6
Zinc	mg	3.5	3.9
Manganese	mg	1.1	1.1
Copper	μg	396	539
Iodine	μg	48	48
Selenium	μg	18	20
Chromium	μg	17	19
Molybdenum	μg	35	33

and other vitamins, minerals, and nutrients in varying amounts (Table 1). Product intake was recorded by participants on daily product intake forms that were reviewed with site staff at each visit.

Leg Strength

Maximal voluntary isokinetic peak torque (PT) for the leg extension exercise was measured at $60^\circ \cdot s^{-1}$. A standardized testing protocol was used as previously described[29] with 2 familiarization trials before the baseline assessment and 1 familiarization trial before the 12- and 24-week assessments. All measurements were performed using calibrated isokinetic dynamometers (site models included Biodex; Biodex Medical Inc, Shirley, NY, Cybex; Cybex International, Inc, Ronkonkoma, NY, KinCom; Chattanooga Group, Hixson, TN, and TechnoGym; TechnoGym SpA, Gambet-Tola, Forli, Italy) that tested the dominant leg determined by kicking preference; however, if the dominant leg was unable to perform the isokinetic strength tests for any reason, the contralateral leg was used. Each participant performed 3 consecutive, maximal, voluntary, isokinetic leg extension muscle actions at $60^\circ \cdot s^{-1}$ ($1.05\ rad \cdot s^{-1}$). The average PT across the 3 repetitions was used as the representative value expressed in Newton-meters (Nm) measured at baseline and 12 and 24 weeks.

Grip Strength

Grip strength was measured with a calibrated dynamometer (Jamar hydraulic hand dynamometer; Patterson Medical, Warrenville, IL) adjusted to the appropriate grip width.[30,31] Participants were asked to squeeze the dynamometer handle as quickly and forcefully as possible with the dominant hand according to previously described procedures.[32,33] Each participant completed 3 trials, and the average of the trials was analyzed as the final grip strength value expressed in kilograms.

Gait Speed

Gait speed (s) was measured by timing the participant's ability to walk 4 m at a normal pace.[34] Each participant performed the gait speed assessment twice, with the faster of the 2 times used as the representative score. A score of $<0.8\ m \cdot s^{-1}$ (≥ 5.0 s during 4 m) was used to identify participants with low gait speed.[28]

To be enrolled in this study, either participants' grip strength values must have been <20 kg for women and <30 kg for men, and/or gait speed scores must have been $<0.8\ m \cdot s^{-1}$ [28] during the screening visit (before the first familiarization visit). Participants were naive to the grip strength and gait speed cutoffs for inclusion at the time of screening. Subsequent grip strength and gait speed scores were measured after the familiarization visits at baseline and 12 and 24 weeks. Incidentally, 11% (n = 37) of the participants' grip strength values and gait speed scores at baseline marginally exceeded the cutoffs that had originally been met at the screening visit. However, all participants fell below the sarcopenia cutoffs at baseline from the initial dual-energy x-ray absorptiometry (DXA) measurements (described in the following section).

Body Composition

DXA was used to measure body composition with whole-body, supine DXA scans (site models included GE Lunar Prodigy Advance; GE Lunar Prodigy Pro or Primo; GE DPX Pro, Bravo, or Duo; General Electric [GE] Healthcare, Madison, WI; or Hologic Discovery A; Hologic, Inc, Bedford, MA). All DXA scans were standardized to a common phantom and sent to an independent laboratory for analysis (Body Composition Analysis Center, Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA). Measurements queried from the independent laboratory at baseline included whole-body fat mass (FM, kg), regional appendicular lean soft tissue (ALST, kg; used only for calculating sarcopenia inclusion criteria), leg muscle mass (LMM, kg) as the sum of both the left and right leg muscle mass values, and tested leg muscle mass (TLMM, kg) representing the leg used for the strength testing.

Baseline DXA scans were used to classify participants with sarcopenia based on the following procedure. First, ALST was considered the sum of lean soft tissue mass from both the right and left arms and legs, which were defined by computer-generated and manually adjusted regions of interest (established by the independent laboratory) separating the appendages from the trunk and head. Second, total body skeletal muscle (kg) was calculated according to the equation validated by Kim et al,[35] in which for sex, men = 1 and women = 0, and age is expressed in years:

$$\text{TBSM} = (1.13 \times \text{ALST}) - (0.02 \times \text{age}) + (0.61 \times \text{sex}) + 0.97$$

Third, the relative skeletal mass index (RSMI, %) was calculated with the equation adapted from Janssen et al,[36] in which body mass is expressed in kilograms:

$$\text{RSMI} = (\text{TBSM} \div \text{body mass}) \times 100$$

Fourth, the absolute skeletal mass index (SMI, $kg \cdot m^{-2}$) was calculated according to the equation of Baumgartner et al,[37] in which height is expressed in meters:

$$\text{SMI} = \text{ALST} \div \left(\text{height}^2\right)$$

Fifth, an adjusted lean mass (ALM, kg) value was calculated according to the equations of Newman et al,[38] in which FM is total body FM expressed in kilograms and height is expressed in meters:

$$\text{ALM for men} = -22.48 + (24.14 \times \text{height}) + (0.21 \times \text{FM})$$

$$\text{ALM for women} = -13.19 + (14.75 \times \text{height}) + (0.23 \times \text{FM})$$

Finally, participants were defined as sarcopenic at baseline if their values fell below any 1 of 4 cutoff models: (1) RSMI $\leq$ 28% for women or $\leq$ 37% for men,[36] (2) SMI $<$ 5.45 kg·m^{-2} for women or $<$ 7.26 kg·m^{-2} for men,[37] (3) SMI $<$ 5.67 kg·m^{-2} for women or $<$ 7.25 kg·m^{-2} for men,[39] or (4) ALM $<$ −1.73 kg for women or $<$ −2.29 for men.[38]

Muscle Quality

MQ (Nm·kg^{-1}) was calculated as PT relative to the TLMM. The equation was PT (Nm) ÷ TLMM (kg). MQ has been used and described previously as an indicator of muscle function.[20,40]

Sarcopenia Severity Classifications

Sarcopenia severity was evaluated in participants with low skeletal mass according to baseline grip strength and gait speed cutoffs as follows[28]: (1) *Severe sarcopenia* included participants with both impaired gait speed ($<$0.8 m·s^{-1}) and impaired grip strength ($<$20 kg [women]; $<$30 kg [men]); and (2) *mild-moderate sarcopenia* (denoted

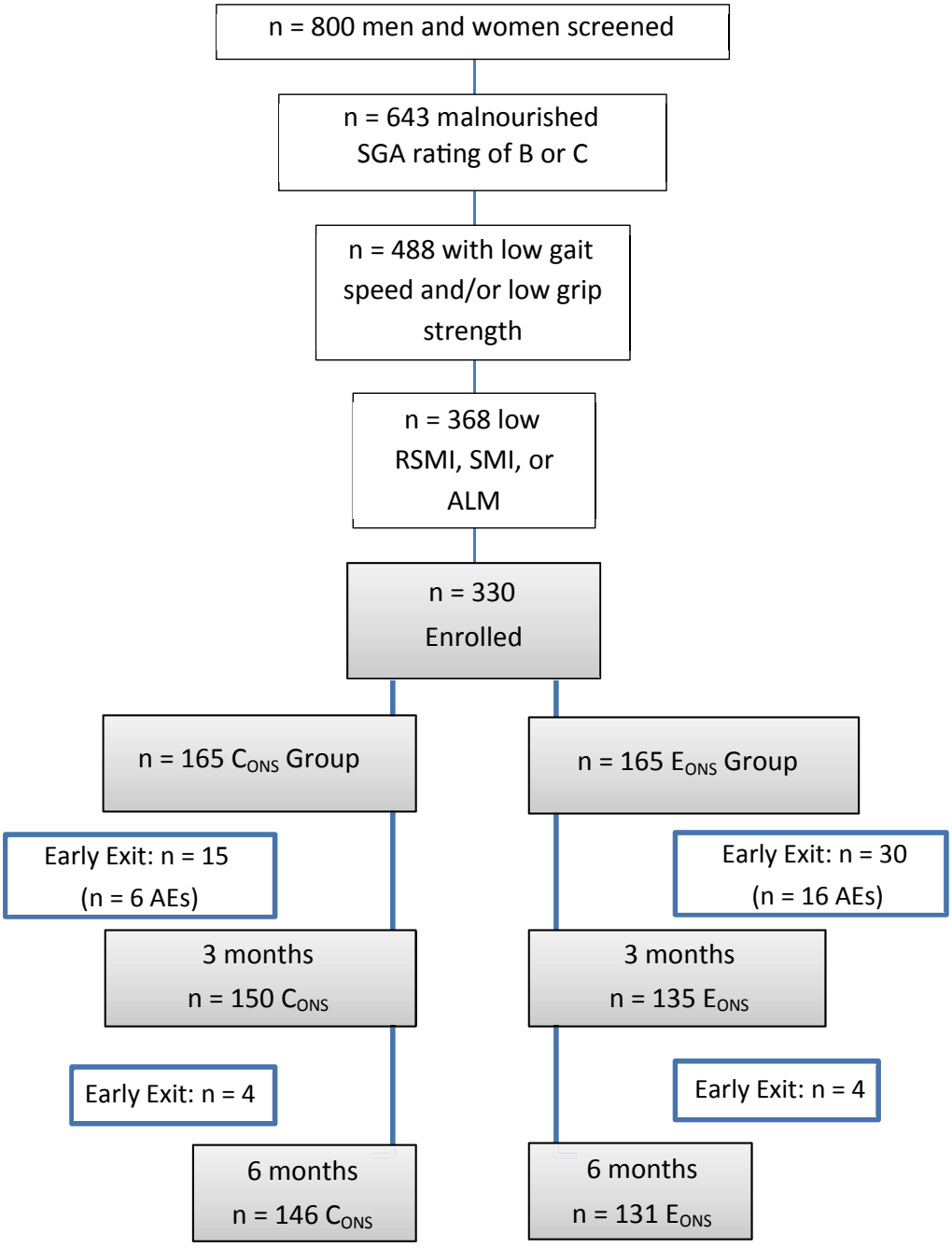

Fig. 1. Participant flow throughout the study.

simply as *sarcopenia* herein) included any participants without severe sarcopenia. Because sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP)[28] as having either impaired gait speed (normal grip) or impaired grip strength (normal gait), these participants were further subcategorized: (3) sarcopenia with normal gait were participants with normal gait speed ($\geq$0.8 $m \cdot s^{-1}$); and (4) sarcopenia with normal grip were participants with normal grip strength ($\geq$20 kg [women]; $\geq$30 kg [men]).

Dietary Instruction and Assessment

Participants were provided dietary education and instruction on methods to increase their habitual protein intake to a minimum of 0.8 g protein per kg body weight per day ($g \cdot kg^{-1} \cdot d^{-1}$). Participants were given 3-day dietary logs to record their food intake. Three-day dietary records were recorded from a sample of 2 weekdays and 1 weekend day. Records were reviewed and entered into food composition analysis programs (such as the US Department of Agriculture's (USDA) SuperTracker, www.supertracker.usda.gov; USDA National Nutrient Database for Standard Reference, http://ndb.nal.usda.gov) used to estimate daily energy intake ($kcal \cdot d^{-1}$) and daily protein intake ($g \cdot kg^{-1} \cdot d^{-1}$) as an average of the 3 days. If protein intake was less than 0.8 $g \cdot kg^{-1} \cdot d^{-1}$, dietary instructions on methods to increase protein intake were given and reinforced.

Vitamin D

Samples of blood drawn from a superficial vein were sent to a commercial laboratory (ICON Central Laboratories, Inc., Farmingdale, NY) for analysis of serum 25-OH vitamin D ($nmol \cdot l^{-1}$) at baseline and 12 and 24 weeks.

Statistical Analyses

This study was powered to detect an effect size of 0.56 for PT based on a difference between groups of 5.65 Nm (SD = 10.11 Nm) as well as to allow for the detection of an effect size of 0.44 for the secondary variable, LMM, based on a difference between groups of 0.19 kg (SD = 0.43 kg). Assuming an alpha level of $P \leq .05$ with a 2-tailed test and power of 0.80, the required sample sizes were n = 52 and n = 82 per group for PT and LMM, respectively. Therefore, the study was designed with a planned enrollment of n = 150 participants per group to allow for up to 45% attrition.

The primary outcome variable in this study was established a priori as change in PT, whereas the secondary outcome variables were weight, LMM, TLMM, grip strength, gait speed, and product compliance. Therefore, change from baseline at 12 and 24 weeks for all variables were analyzed. Baseline and change values were expressed as median ±25th and 75th interquartile ranges (IQR), because many, but not all, variables were non-normally distributed based on the presence of non-normal residual distributions. Consequently, nonparametric analyses were used. The Wilcoxon rank sum test was used for between-group analyses, and the Wilcoxon signed rank test (nonparametric equivalent to the paired *t*-test) was used for the within-group analyses. Data were analyzed and presented as ITT. SAS versions 9.1.3 and 9.2 (SAS, Inc., Cary, NC) were used for all statistical analyses. An alpha level of $P \leq .05$ was considered statistically significant for all comparisons.

Results

Participants

A total of 800 men and women were evaluated for eligibility (Figure 1), and malnutrition was confirmed in 80%. At least 1 measure of strength or physical performance was impaired in 76%. Within this group, sarcopenia was further observed in 75%. A total of 330 of these men and women were enrolled into the study, of which 88% completed the study in the C_{ONS} group and 79% in the E_{ONS} group.

Baseline characteristics are shown in Table 2. There were no differences between groups at baseline. The median age at enrollment was 77 years, and most were women (62%). With one exception, all participants exhibited a Subjective Global Assessment (SGA) rating of "B" (mild to moderate malnourishment); one in the E_{ONS} group had an SGA rating of "C" (severe malnourishment). All participants had a low skeletal muscle mass (ie, low RSMI, SMI, or ALM), which classified them as sarcopenic,[28] whereas the median body mass index (BMI) of 26 $kg \cdot m^{-2}$ indicated that most were not underweight. Subjects in the C_{ONS} and E_{ONS} groups were well-matched in FM and LMM.

Table 2
Baseline Characteristics of Study Subjects

	C_{ONS} Group n = 165	E_{ONS} Group n = 165
Age, y	77 (71, 81)	77 (71, 81)
Gender, % women	62%	62%
Weight, kg	70 (60, 78)	68 (58, 78)
BMI, $kg \cdot m^{-2}$	26 (24, 29)	25 (23, 29)
Leg strength, Nm	57 (37, 77)	56 (37, 73)
Grip strength, kg	19 (15, 26)	19 (15, 27)
Gait speed, $m \cdot s^{-1}$	0.8 (0.7, 0.9)	0.7 (0.6, 0.9)
FM, kg	25 (20, 30)	25 (18, 30)
LMM, kg*	12 (10, 15)	12 (10, 14)
RSMI, %	25 (23, 31)	26 (23, 30)
MQ, $Nm \cdot kg^{-1}$	9.1 (7.0, 12.1)	9.2 (6.7, 12.4)
Daily energy intake, $kcal \cdot d^{-1}$	1620 (1257, 2012)	1627 (1253, 1971)
Daily protein intake, $g \cdot kg^{-1} \cdot d^{-1}$	0.97 (0.73, 1.30)	0.94 (0.70, 1.20)
Serum vitamin D, $nmol \cdot L^{-1}$	60 (40, 78)	65 (45, 85)

Values are percentages or median (25th, 75th IQR). There were no significant differences ($P > .05$) between groups at baseline.
*LMM data represent the sum of left and right LMMs acquired from the DXA.

Table 3
Baseline Leg Strength, Grip Strength, and Gait Speed in Sarcopenia Severity Classifications

	C_{ONS} Group	E_{ONS} Group
Severe sarcopenia	n = 64	n = 80
Leg strength, Nm	50 (31, 64)	48 (31, 62)
Grip strength, kg	16 (12, 19)	17 (14, 20)
Gait speed, $m \cdot s^{-1}$	0.68 (0.59, 0.73)	0.66 (0.58, 0.74)
MQ, $Nm \cdot kg^{-1}$	8.8 (6.0, 11.7)	8.3 (5.6, 11.2)
Sarcopenia*	n = 101	n = 83
Leg strength, Nm	62 (46, 88) $^{.0006}$	64 (45, 81) $^{<.0001}$
Grip strength, kg	23 (18, 30) $^{<.0001}$	23 (18, 33) $^{<.0001}$
Gait speed, $m \cdot s^{-1}$	0.84 (0.79, 0.95) $^{<.001}$	0.87 (0.79, 0.97) $^{<.0001}$
MQ, $Nm \cdot kg^{-1}$	10.0 (7.6, 12.1) $^{ns\ .059}$	10.6 (7.8, 13.2) $^{.0019}$
Sarcopenia, normal gait*,†	n = 75	n = 61
Leg strength, Nm	61 (46, 82) $^{.0051}$	60 (41, 75) $^{.0051}$
Grip strength, kg	20 (17, 26) $^{<.0001}$	19 (15, 28) $^{.0014}$
Gait speed, $m \cdot s^{-1}$	0.91 (0.82, 1.0) $^{<.0001}$	0.93 (0.84, 1.0) $^{<.0001}$
MQ, $Nm \cdot kg^{-1}$	9.6 (7.3, 12.0) ^{ns}	9.1 (7.4, 12.8) $^{.034}$
Sarcopenia, normal grip*,†	n = 46	n = 39
Leg strength, Nm	71 (54, 98) $^{<.0001}$	76 (59, 111) $^{<.0001}$
Grip strength, kg	31 (23, 35) $^{<.0001}$	33 (26, 36) $^{<.0001}$
Gait speed, $m \cdot s^{-1}$	0.78 (0.67, 0.87) $^{<.0001}$	0.76 (0.68, 0.89) $^{<.0001}$
MQ, $Nm \cdot kg^{-1}$	11.2 (8.6, 12.4) $^{.007}$	11.3 (9.1, 13.5) $^{.0002}$

Values are medians (25th, 75th IQR). Superscript *P* values are compared with the severe sarcopenia group. Two participants were missing grip strength or gait speed assessments at baseline.
*Despite meeting inclusion criteria during the screening process, 37 participants recorded both normal grip strength and gait speed at baseline.
†Thirty-seven participants appear in both subgroups.

Leg Strength

There were no differences between groups in PT at baseline (median [25th, 75th IQR] = 57 [37, 77] Nm for C_{ONS}; 56 [37, 73] Nm for E_{ONS}) (Table 2). At 12 weeks, PT increased from baseline in both groups (2 [−3, 9] Nm for C_{ONS}, $P < .001$; 3 [−1, 10] Nm for E_{ONS}, $P < .001$), which was maintained throughout the 24 weeks (2 [−3, 10] Nm for C_{ONS}, $P < .001$; 4 [−4, 8] Nm for E_{ONS}; $P < .001$), with no differences between treatments.

Table 2 shows PT values at baseline, Table 3 shows PT values at baseline separated by sarcopenia severity classification, and Figure 2A shows PT values at 12 and 24 weeks also separated by sarcopenia severity classification. The severe sarcopenia group had the lowest PT at baseline compared with the other sarcopenia groups ($P < .01$, Table 3). The sarcopenia group with normal grip strength exhibited higher PT at baseline compared with the sarcopenia group with normal gait speed; however, both were still greater than ($P < .01$) the severe sarcopenia group (Table 3). Figure 3 shows the treatment differences observed in PT at 12 (Figure 3A) and 24 (Figure 3D) weeks. Participants with sarcopenia and normal grip strength in the E_{ONS} group increased PT from baseline to 12 weeks, which was greater ($P = .032$) than the C_{ONS}

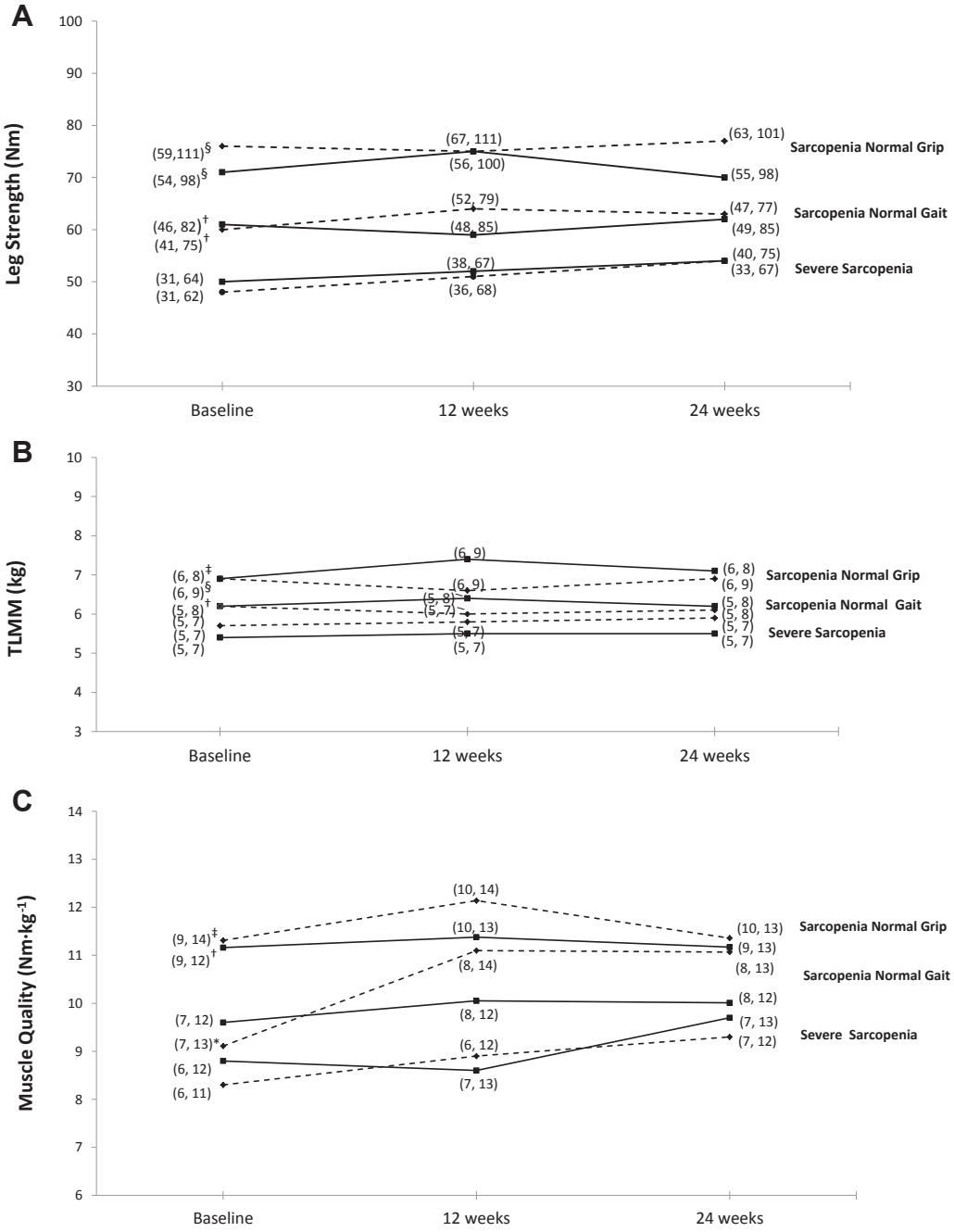

Fig. 2. Median (25%, 75% IQR) for (A) leg strength (Nm), (B) TLMM (kg), and (C) MQ ($Nm \cdot kg^{-1}$) at baseline and 12 and 24 weeks. Solid line = C_{ONS}; dashed line = E_{ONS}. Symbols represent the baseline differences of the sarcopenia subgroups with normal grip strength and normal gait speed compared with the severe sarcopenia group. *$P < .05$, †$P < .01$, ‡$P < .001$, §$P < .0001$.

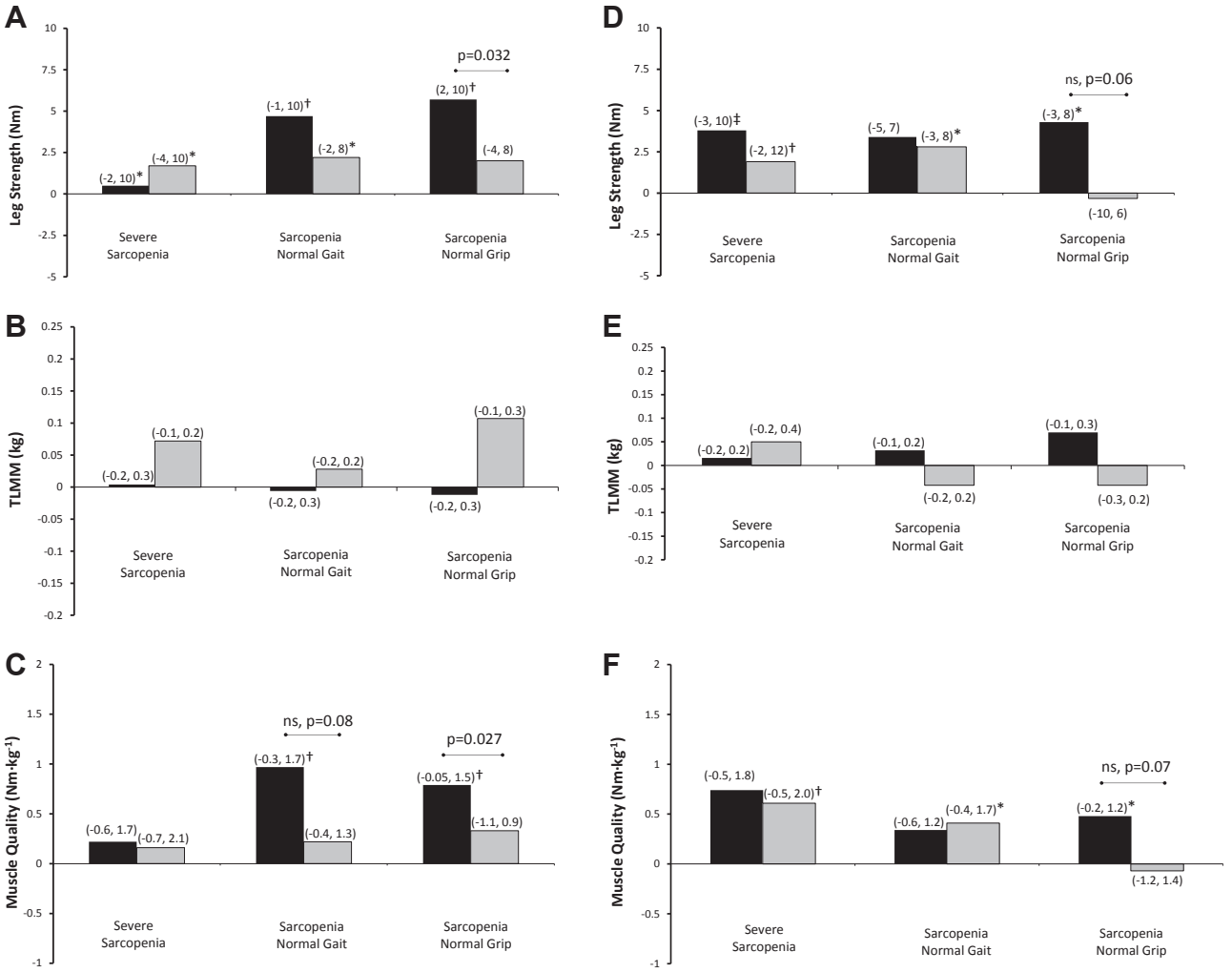

Fig. 3. *Left column*: Change from baseline to 12 weeks expressed as median (25%, 75% IQR) for (A) leg strength (Nm), (B) TLMM (kg), and (C) MQ (Nm·kg^{-1}). *Right column*: Change from baseline to 24 weeks expressed as median (25%, 75% IQR) for (D) leg strength (Nm), (E) TLMM (kg), and (F) MQ (Nm·kg^{-1}). Gray = C_{ONS}; Black = E_{ONS}. Symbols represent significant changes from baseline. *$P < .05$, †$P < .01$, ‡$P < .001$. *P* values represent significant differences between treatment groups.

treatment (Figure 3A). At 24 weeks, the participants with sarcopenia and normal grip strength increased PT from baseline to 24 weeks ($P < .05$), although this increase was not quite statistically greater than the C_{ONS} treatment (Figure 3D, $P = .06$). Interestingly, the increases in PT observed in the E_{ONS} group from baseline to 12 weeks appeared to be maintained in the sarcopenia normal grip strength subgroup at 24 weeks, but not in the C_{ONS} group (Figure 3D). The severe sarcopenia group also showed an improvement from baseline in PT at 24 weeks with the E_{ONS} treatment (Figure 3D).

Grip Strength

Grip strength improved from baseline to 12 weeks, which was maintained through the 24-week period in both treatment groups ($P < .001$). The observed changes across both treatment groups and all sarcopenia severity classifications ranged from 0.50 to 0.83 kg at 12 weeks and 0.25 to 1.33 kg at 24 weeks. Both the severe sarcopenia and sarcopenia with normal gait speed groups increased grip strength at 12 and 24 weeks with no treatment differences observed (Table 4); however, the single exception was in the sarcopenia group with normal gait speed, in which the increase was not statistically significant at 12 weeks in the E_{ONS} treatment group (Table 4).

Gait Speed

Gait speed improved from baseline to 12 weeks and baseline to 24 weeks in both treatment groups. The observed changes across both treatment groups and all sarcopenia severity classifications ranged from 0.01 to 0.05 m·s^{-1} at 12 weeks and 0.03 to 0.08 m·s^{-1} at 24 weeks ($P < .05$). Both the severe sarcopenia and sarcopenia with normal grip strength groups increased gait speed at 12 and 24 weeks with no treatment differences observed (Table 4).

Body Composition

Table 5 summarizes the baseline values, and Table 6 shows the changes from baseline for BMI, body weight, FM, LMM, and TLMM for the sarcopenia severity classifications. BMI, body weight, and FM increased from baseline in all sarcopenia severity classifications at both 12 and 24 weeks (Table 6). There were no differences between treatments (except in the sarcopenia group with normal gait speed, in which the change from baseline to 12 weeks in BMI and body weight were greater for C_{ONS} compared to E_{ONS}). There were no changes in LMM or TLMM across the 24-week study, except LMM at 12 weeks in C_{ONS} participants with severe sarcopenia, but this was not maintained at 24 weeks or was this observed in TLMM. There were no treatment differences for LMM or TLMM.

Table 4
Changes from Baseline in Grip Strength and Gait Speed for Sarcopenia Severity Classifications

Sarcopenia Severity	Visit	C_{ONS} Group	E_{ONS} Group
Severe sarcopenia			
Grip strength, kg	12 wk	0.83 (−0.67, 2.00) $^{.0077}$	0.68 (−0.50, 2.17) $^{.002}$
	24 wk	1.33 (−0.33, 3.0) $^{<.0001}$	0.67 (0.0, 2.8) $^{<.0001}$
Gait speed, $m \cdot s^{-1}$	12 wks	0.04 (−0.02, 0.13) $^{.0006}$	0.03 (−0.01, 0.11) $^{.0022}$
	24 wks	0.06 (0.02, 0.15) $^{<.0001}$	0.04 (−0.01, 0.11) $^{.0003}$
Sarcopenia*			
Grip strength, kg	12 wk	0.67 (−0.67, 2.33) $^{.004}$	0.67 (−0.67, 2.33) $^{.03}$
	24 wk	0.67 (−0.83, 3.00) $^{.02}$	1.33 (0.17, 3.5) $^{.001}$
Gait speed, $m \cdot s^{-1}$	12 wk	0.02 (−0.04, 0.10) $^{.006}$	0.01 (−0.05, 0.08)
	24 wk	0.02 (−0.03, 0.11) $^{.04}$	0.05 (−0.04, 0.15) $^{.002}$
Sarcopenia, normal gait speed*,†			
Grip strength, kg	12 wk	0.83 (−0.67, 2.67) $^{.0057}$	0.50 (−0.67, 2.33)
	24 wk	0.67 (−0.95, 3.33) $^{.0212}$	1.33 (0.33, 3.50) $^{.0084}$
Gait speed, $m \cdot s^{-1}$	12 wk	0.02 (−0.04, 0.09)	−0.01 (−0.08, 0.08)
	24 wk	0.01 (−0.07, 0.10)	0.04 (−0.06, 0.14)
Sarcopenia, normal grip strength*,†			
Grip strength, kg	12 wk	0.50 (−1.13, 2.50)	0.83 (−2.00, 3.00)
	24 wk	0.25 (−1.62, 1.32)	1.18 (−2.17, 2.67)
Gait speed, $m \cdot s^{-1}$	12 wk	0.05 (−0.01, 0.12) $^{.003}$	0.05 (−0.0, 0.10) $^{.032}$
	24 wk	0.06 (−0.02, 0.11) $^{.0017}$	0.07 (0.02, 0.17) $^{.0007}$

Values are median change scores (25th, 75th IQR). Superscript *P* values indicate changes from baseline.

*Despite meeting inclusion criteria during the screening process, 37 participants recorded both normal grip strength and gait speed at baseline.

†Thirty-seven participants appear in both subgroups.

Muscle Quality

Table 2 shows MQ values at baseline, and Table 3 shows baseline MQ values separated by sarcopenia severity classification. Figures 2C, 3C, and 3F show the changes in MQ at 12 and 24 weeks for all the sarcopenia severity classifications. Those with severe sarcopenia had the lowest MQ at baseline compared with the sarcopenia groups with normal gait speed or normal grip strength (Table 3, $P < .05$), except for those with normal gait speed in the C_{ONS} group. Those with sarcopenia and normal grip strength in the E_{ONS} group improved MQ to a greater extent ($P = .027$) than those in the C_{ONS} group from baseline to 12 weeks (Figure 3C), but the treatment difference at 24 weeks did not reach statistical significance (Figure 3F, $P = .07$). A similar finding was observed during the first 12 weeks for those with sarcopenia and normal gait speed in the E_{ONS} group, although the treatment effect did not reach statistical significance (Figure 3C, $P = .08$). Like PT after 24 weeks, the improvements in MQ were largely sustained in the E_{ONS} group, whereas those with sarcopenia and normal grip strength in the C_{ONS} group showed an attenuated ability to maintain the changes in MQ (Figure 3F). At 24 weeks, the severe sarcopenia group appeared to benefit from both interventions.

Table 5
Baseline Body Composition for Sarcopenia Severity Classifications

	C_{ONS} Group	E_{ONS} Group
Severe sarcopenia	n = 64	n = 80
BMI, $kg \cdot m^{-2}$	28 (25, 30)	27 (23, 29)
Body weight, kg	69 (59, 78)	69 (57, 76)
FM, kg	27 (22, 32)	25 (18, 31)
LMM, kg*	11 (9, 13)	11 (10, 14)
TLMM, kg†	5.4 (4.8, 6.6)	5.7 (5.1, 6.9)
Sarcopenia‡	n = 101	n = 83
BMI, $kg \cdot m^{-2}$	26 (23, 28) $^{.003}$	25 (23, 29)
Body weight, kg	70 (62, 77)	68 (60, 80)
FM, kg	24 (18, 28) $^{.026}$	25 (19, 28)
LMM, kg*	13 (11, 16) $^{.0026}$	13 (10, 16) $^{.014}$
TLMM, kg†	6.4 (5.3, 8.1) $^{.002}$	6.3 (5.3, 8.0) $^{.011}$
Sarcopenia, normal gait speed‡,§	n = 75	n = 61
BMI, $kg \cdot m^{-2}$	25 (23, 28) $^{.002}$	24 (23, 28)
Body weight, kg	68 (59, 76)	64 (57, 77)
FM, kg	23 (18, 28) $^{.018}$	24 (18, 28)
LMM, kg*	12 (10, 16) $^{<.01}$	12 (10, 14)
TLMM, kg†	6.2 (5.3, 8.1) $^{.008}$	6.2 (5.2, 7.3)
Sarcopenia, normal grip strength‡,§	n = 46	n = 39
BMI, $kg \cdot m^{-2}$	26 (24, 29)	27 (23, 30)
Body weight, kg	75 (67, 80) $^{.045}$	77 (64, 87) $^{.002}$
FM, kg	25 (18, 30)	26 (21, 32)
LMM, kg*	14 (11, 16) $^{<.001}$	14 (12, 17) $^{<.0001}$
TLMM, kg†	6.9 (5.7, 8.2) $^{<.001}$	6.9 (5.9, 9.0) $^{<.0001}$

Values are medians (25th, 75th IQR). Superscript *P* values are compared with the severe sarcopenia group.

*LMM data represent the sum of left and right legs muscle masses acquired from the DXA.

†TLMM data represent the single LMM acquired from the DXA corresponding to the leg used during the strength testing.

‡Despite meeting inclusion criteria during the screening process, 37 participants recorded both normal grip strength and gait speed at baseline.

§Thirty-seven participants appear in both subgroups.

Compliance and Dietary Intake

Treatment compliance was calculated as a percentage of actual consumption divided by expected consumption over the 24-week period. Compliance in the C_{ONS} group was 88% (median intake 2.0 [1.7, 2.0]) servings$\cdot d^{-1}$ and 86% (1.9 [1.5, 2.0]) servings$\cdot d^{-1}$ in the E_{ONS} group.

Dietary intakes of energy, protein, and serum vitamin D at baseline and 12 and 24 weeks are shown in Figure 4. Baseline energy intake ($kcal \cdot d^{-1}$), protein intake ($g \cdot kg^{-1} \cdot d^{-1}$), and serum vitamin D ($nmol \cdot l^{-1}$) were similar in C_{ONS} and E_{ONS} groups. As expected due to high compliance, both groups increased energy intake and protein intake by 12 weeks, which was maintained through 24 weeks with differences between treatments at both time points for protein intake (Figures 4D and 4E, respectively). Furthermore, as expected due to high compliance, both groups increased serum vitamin D at 12 and 24 weeks from baseline with a treatment difference ($E_{ONS} > C_{ONS}$) at 12 and 24 weeks (Figure 4F).

Adverse Events

The highest percentage of participant-reported adverse events (AEs) and/or serious adverse events (SAEs) was associated with the gastrointestinal system with n = 47 (28.5%) in the E_{ONS} group and n = 53 (32.5%) in the C_{ONS} group. Most of these were assessed as probably or possibly related to study product. There were no statistically significant differences between treatment groups for AEs or SAEs. Two participants in the E_{ONS} group died as a result of SAEs for infections; neither event was related to the study product as determined by the site physicians.

Discussion

The main finding from this study was that in men and women with malnutrition and sarcopenia, supplementation with high-quality ONS improved the primary outcome variable of leg strength assessed as PT. Improvements in PT were observed at both 12 and 24 weeks compared with baseline in both groups with no treatment differences between groups. Compliance was high, as demonstrated by increases in protein intake and vitamin D levels. Based on the EWGSOP suggestion[28] to incorporate the conceptual staging of sarcopenia, post hoc analyses were carried out on *severe* and *mild-moderate* sarcopenia subgroups. These analyses indicated that men and women with severe sarcopenia were more physically and functionally compromised than those with mild-moderate sarcopenia. Therefore, further subgroup analyses were performed to determine if sarcopenia staging[28] may differentially affect leg strength responses to the nutritional interventions.

Table 6
Changes from Baseline in Body Composition for Sarcopenia Severity Classifications

Sarcopenia Severity Classification	Visit	C_{ONS} Group	E_{ONS} Group	*P* Values for Between-Group Treatment Effects
Severe sarcopenia		n = 64	n = 80	
BMI, kg·m^{-2}	12 wk	0.8 (0.3, 1.4) $^{<.0001}$	0.7 (0.3, 1.1) $^{<.0001}$	—
	24 wk	1.0 (0.2, 2.0) $^{<.0001}$	0.8 (0.0, 1.6) $^{<.0001}$	—
Body weight, kg	12 wk	2.0 (0.8, 3.1) $^{<.0001}$	2.0 (0.7, 3.0) $^{<.0001}$	—
	24 wk	2.7 (0.5, 4.5) $^{<.0001}$	2.0 (0.1, 4.1) $^{<.0001}$	—
FM, kg	12 wk	1.7 (0.8, 2.9) $^{<.0001}$	1.5 (0.7, 2.2) $^{<.0001}$	—
	24 wk	2.4 (1.0, 3.4) $^{<.0001}$	1.8 (−0.0, 3.1) $^{<.0001}$	—
LMM, kg*	12 wk	0.14 (−0.10, 0.41) $^{.026}$	0.08 (−0.26, 0.54)	—
	24 wk	0.10 (−0.32, 0.57)	0.10 (−0.31, 0.46)	—
TLMM, kg†	12 wk	0.07 (−0.14, 0.23)	0.00 (−0.24, 0.25)	—
	24 wk	0.05 (−0.18, 0.40)	0.02 (−0.21, 0.20)	—
Sarcopenia‡		n = 101	n = 83	
BMI, kg·m^{-2}	12 wk	0.8 (0.3, 1.2) $^{<.0001}$	0.5 (0.0, 1.1) $^{<.0001}$	—
	24 wk	0.9 (0.2, 1.3) $^{<.0001}$	0.7 (0.1, 1.4) $^{<.0001}$	—
Body weight, kg	12 wk	2.0 (0.9, 3.2) $^{<.0001}$	1.4 (0.0, 2.9) $^{<.0001}$	—
	24 wk	2.5 (0.7, 3.6) $^{<.0001}$	1.9 (0.4, 4.0) $^{<.0001}$	—
FM, kg	12 wk	1.3 (0.3, 2.4) $^{<.0001}$	1.1 (0.4, 2.0) $^{<.0001}$	—
	24 wk	2.2 (0.5, 3.8) $^{<.0001}$	1.9 (0.9, 2.8) $^{<.0001}$	—
LMM, kg*	12 wk	0.05 (−0.36, 0.56)	−0.05 (−0.28, 0.29)	—
	24 wk	−0.08 (−0.39, 0.40)	0.06 (−0.27, 0.39)	—
TLMM, kg†	12 wk	0.10 (−0.16, 0.24)	−0.01 (−0.20, 0.25)	—
	24 wk	−0.05 (−0.25, 0.21)	0.04 (−0.13, 0.21)	—
Sarcopenia, normal gait speed‡,§				
BMI, kg·m^{-2}	12 wk	0.8 (0.3, 1.2) $^{<.0001}$	0.4 (0.0, 1.0) $^{<.0001}$	.042
	24 wk	0.9 (0.2, 1.3) $^{<.0001}$	0.7 (0.2, 1.3) $^{<.0001}$	—
Body weight, kg	12 wk	2.0 (0.9, 3.3) $^{<.0001}$	1.2 (0.0, 2.9) $^{<.0001}$	.032
	24 wk	2.5 (0.5, 3.6) $^{<.0001}$	1.8 (0.5, 4.0) $^{<.0001}$	—
FM, kg	12 wk	1.4 (0.3, 2.5) $^{<.0001}$	1.1 (0.3, 1.9) $^{<.0001}$	—
	24 wk	2.2 (0.5, 3.9) $^{<.0001}$	1.9 (0.9, 2.6) $^{<.0001}$	—
LMM, kg*	12 wk	−0.04 (−0.37, 0.46)	−0.05 (−0.30, 0.36)	—
	24 wk	−0.10 (−0.41, 0.37)	0.02 (−0.30, 0.39)	—
TLMM, kg†	12 wk	0.03 (−0.19, 0.20)	−0.01 (−0.22, 0.26)	—
	24 wk	−0.04 (−0.24, 0.18)	0.03 (−0.12, 0.21)	—
Sarcopenia, normal grip strength‡,§				
BMI, kg·m^{-2}	12 wk	0.8 (0.3, 1.1) $^{<.0001}$	0.7 (0.1, 1.1) $^{<.0001}$	—
	24 wk	0.8 (0.4, 1.2) $^{<.0001}$	1.2 (0.0, 1.6) $^{<.0001}$	—
Body weight, kg	12 wk	2.2 (0.8, 3.1) $^{<.0001}$	2.3 (0.3, 3.2) $^{<.0001}$	—
	24 wk	2.3 (1.3, 3.5) $^{<.0001}$	3.2 (0.1, 4.6) $^{<.0001}$	—
FM, kg	12 wk	1.3 (0.6, 2.3) $^{<.0001}$	1.1 (0.4, 2.6) $^{<.0001}$	—
	24 wk	2.0 (0.2, 3.8) $^{<.0001}$	1.9 (0.9, 3.4) $^{<.0001}$	—
LMM, kg*	12 wk	0.22 (−0.50, 0.64)	−0.07 (−0.28, 0.30)	—
	24 wk	0.01 (−0.24, 0.51)	0.15 (−0.22, 0.46)	—
TLMM, kg†	12 wk	0.11 (−0.14, 0.29)	−0.01 (−0.18, 0.27)	—
	24 wk	−0.04 (−0.26, 0.23)	0.07 (−0.13, 0.27)	—

Values are median change scores (25th, 75th IQR). Superscript *P* values represent changes from baseline. Dashes indicate that the *P*-value for that particular between-group treatment effect was greater than 0.05.

*LMM data represent the sum of left and right legs muscle masses acquired from the DXA.

†TLMM data represent the single leg muscle mass acquired from the DXA corresponding to the leg used during the strength testing.

‡Despite meeting inclusion criteria during the screening process, 37 participants recorded both normal grip strength and gait speed at baseline.

§Thirty-seven participants appear in both subgroups.

Based on previous literature in malnutrition, an improvement in muscle strength in response to ONS was expected.[41–44] Differences in responses to the E_{ONS} between sarcopenia subgroups were notable. Early benefits in leg strength (at 12 weeks) were observed in men and women with mild-moderate sarcopenia who consumed the E_{ONS} compared with those who consumed the C_{ONS}. This was not observed in the severe sarcopenia subgroup. In the mild-moderate sarcopenia subgroups, the increases in PT in response to E_{ONS} were higher than responses to the C_{ONS} group. At 24 weeks, the severe sarcopenia subgroup did demonstrate improvements in leg strength above baseline, which may have reflected a delayed time course in skeletal muscle adaptations[45,46] that may extend with more severe muscle dysfunction. Incidentally, physical and morphological differences between the sarcopenia staging subgroups may explain the differential responses to the ONS intervention. For example, the severe sarcopenia subgroup displayed lower baseline LMM, PT, MQ, grip strength, gait speed, and higher FM than the mild-moderate sarcopenia groups (Figure 2, Tables 2 and 4). This may have been due to a more compromised status, which has been associated with inflammation and metabolic and vascular dysfunction.[47,48] These can negatively affect the responses of muscle to nutritional input and could explain the observed differences among the severe and mild-moderate sarcopenic subgroups to the ONS interventions.

The importance of baseline physical characteristics was further emphasized by the Sarcopenia Project of the Foundation for the National Institutes of Health,[49] which reported a pooled analysis of data from 4 randomized trials of various interventions in older women. The results showed that adaptations in muscle function and strength were dependent on the participants' baseline grip strength. Although the interventions varied, baseline muscle strength was able to differentiate the responses to sarcopenia interventions. Likewise, the results of the present study supported the authors' conclusions[49] that muscle weakness, defined by grip strength, is able to differentiate responses to the ONS intervention, and suggests that sarcopenia staging should

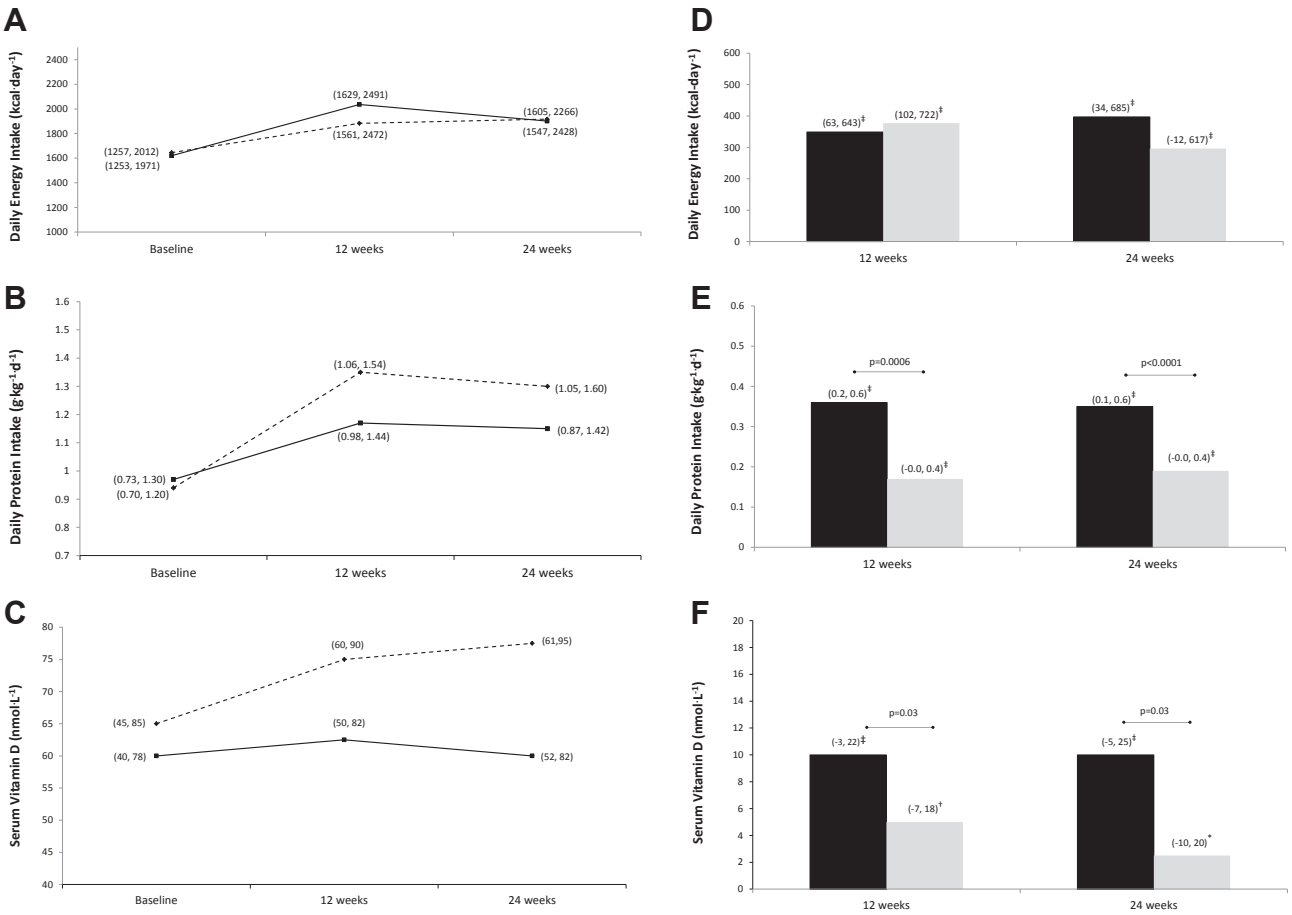

Fig. 4. *Left column*: Median (25%, 75% IQR) for (A) energy intake (kcal·d^{-1}), (B) protein intake (g·kg^{-1}·d^{-1}), and (C) serum vitamin D (nmol·l^{-1}) at baseline and 12 and 24 weeks. *Right column*: Median (25%, 75% IQR) for (C) energy intake (kcal·d^{-1}), (D) protein intake (g·kg^{-1}·d^{-1}), and (E) serum vitamin D (nmol·l^{-1}) change from baseline at 12 and 24 weeks. For (A), (B), and (C), solid line = C_{ONS}; dashed line = E_{ONS}. For (D), (E), and (F), Gray = C_{ONS}; Black = E_{ONS}. Symbols represent significant changes from baseline. *$P < .05$, †$P < .01$, ‡$P < .0001$. *P* values represent significant differences between treatment groups.

be considered in future intervention study designs. Although 44% of participants enrolled in the current study were categorized as having severe sarcopenia, its prevalence using EWGSOP criteria in other groups with malnutrition or chronic disease is unknown. Dam et al.,[50] reevaluated sarcopenia data using EWGSOP criteria from more than 10,000 adults older than 65 years and reported prevalence of sarcopenia was 5.3% and 13.3%, in men and women, respectively, whereas the prevalence of severe sarcopenia was 0.7% in men and 2.9% in women. Cruz-Jentoft et al[13] reported the prevalence of sarcopenia in patients in long-term care ranged from 14% to 33% (2 studies) and was 10% in a single study of hospitalized patients; however, data on severe sarcopenia in the clinical groups were unavailable, as not all groups made the distinction.

Previous studies have demonstrated that older adults may experience *anabolic resistance*[15] due, in part, to impaired blood flow and the subsequent limited amino acid delivery to the muscle.[51–53] Timmerman et al[47] reported that a prior bout of aerobic exercise increased the anabolic effects of nutrient consumption in older adults by improving the nutrient-signaled vasodilation and subsequent nutrient delivery to the muscle. The authors[47] defined the importance of *nutritive flow* by suggesting that muscle blood flow is an important factor for the delivery of nutrients (amino acids) to the muscle in order for the nutrients to have an anabolic effect. In the present study, the subgroup that benefited the most from the E_{ONS} were those who were mild-moderately sarcopenic with normal grip strength (impaired gait). This subgroup also displayed the highest baseline leg strength (Table 3). Normal grip and high leg strength indirectly suggested that blood flow to the large quadriceps femoris muscles governing leg strength may have been more viable for this group, which also may explain why this group experienced the largest improvements in PT and MQ from baseline to 12 weeks while consuming the anabolic nutrient-rich E_{ONS}. Greater nutritive flow to the muscle would, in theory, deliver greater amounts of all nutrients to the muscle, resulting in greater gains in muscle strength. In contrast, the severe sarcopenia group had lower leg strength, which may have indirectly indicated poorer leg muscle blood flow, and in turn, less anabolic response from the E_{ONS} treatment.

Another factor that can contribute to low baseline muscle strength is inflammation within the muscle, as seen in patients with cachexia.[54,55] Although HMB is known to downregulate muscle inflammation,[56–58] the possible decline in transport to the muscle due to diminished nutritive flow could also explain the low response to E_{ONS} intervention in the severe sarcopenia subgroup.

Because this study was a nutrition-only trial without any exercise intervention, no conclusive link can be drawn between the benefits of E_{ONS} and muscle blood flow and/or muscle inflammation. Future studies are needed to investigate the effects of including light resistance and aerobic exercise to enhance nutritive flow on the chronic adaptations to ONS interventions. Additionally, because there were many differences between ONS studied, no conclusions can be drawn regarding benefits of any individual or subgroup of macro- or micronutrients.

Despite the differential responses in leg strength and MQ observed among sarcopenia subgroups, there was an increase in grip strength over time in response to both ONS interventions (except in the subgroup with normal grip strength). Similarly, there was an increase in gait speed over time in all subgroups (except the group with normal gait speed) in response to both ONS interventions. These overall findings indicated that both ONS treatments (E_{ONS} and C_{ONS}) are capable of eliciting clinical benefits in simple field measurements (grip strength and gait speed) of sarcopenia in malnourished older adults.

In conclusion, the strengths of the current study include a well-controlled, adequately powered, large sample, multicentered study with multiple familiarization visits to minimize the learning effects associated with effort-based outcome variables, such as leg strength, grip strength, and gait speed. The present study demonstrated that improvements in clinically relevant measures, such as strength and functionality, can be achieved by daily supplementation with a high-quality ONS. Furthermore, sarcopenia staging seems to affect the leg strength adaptations to the ONS interventions, which supports the incorporation of the EWGSOP conceptual framework of sarcopenia staging into clinical practice. Populations with mild-moderate sarcopenia are more responsive to the E_{ONS} enriched in key nutrients compared with the standard C_{ONS}. Populations with severe sarcopenia may need multimodal interventions (good nutrition and possibly exercise) to achieve similar magnitudes of leg strength improvement as the mild-moderate sarcopenia subgroups, particularly within a limited time course. Therefore, sarcopenia staging should be considered in future intervention study designs.

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