Supplementary Online Content

Bhasin S, Apovian CM, Travison TG, et al. Effect of protein intake on lean body mass in functionally limited older men: a randomized clinical trial. *JAMA Intern Med*. Published online March 12, 2018. doi:10.1001/jamainternmed.2018.0008

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Energy and Protein Distribution in 0.8-g/kg/d and 1.3-g/kg/d Groups

	Pre-packaged Meals		**Discretionary Foods**		**Daily supplements**			
Group	Protein	Energy*	Protein	Energy*	Protein	Energy*	CHO	Vitamins/minerals
0.8-g/kg/d	0.7 g/kg/d	78%	0.1 g/kg/d	15%	0 g/kg/d	7%	0.5 g/kg/d	Multivitamin, 1260 mg calcium, 1,000 IU vitamin D3
1.3-g/kg/d	0.7 g/kg/d	78%	0.1 g/kg/d	15%	0.5 g/kg/d	7%	0 g/kg/d	Multivitamin, 1260 mg calcium, 1,000 IU vitamin D3

* Percent of daily requirements; CHO, carbohydrate

eTable 2. Dietary Adherence With Packaged Meals and Supplements During Months 1 to 3 and Months 4 to 6

Variable	0.8 g/kg/d protein plus Placebo	1.3 g/kg/d protein plus Placebo	0.8 g/kg/d protein plus Testosterone	1.3 g/kg/d protein plus Testosterone
	Months 1-3			
	N=22	N=23	N=17	N=19
Food (%)	80.6 ± 14.8 84.0	80.5 ± 12.9 79.0	85.6 ± 13.8 89.2	86.1 ± 11.4 88.8
Supplements (%)	93.0 ± 10.1 95.5	90.3 ± 15.2 93.8	94.3 ± 8.8 95.8	94.3 ± 6.8 96.7
	Months 4-6			
	N=21	N=21	N=17	N=19
Food (%)	74.5 ± 23.2 79.5	77.1 ± 13.8 82.8	82.2 ± 14.1 83.8	85.2 ± 15.3 90.9
Supplements (%)	92.6 ± 11.0 98.2	91.2 ± 12.4 96.0	94.0 ± 8.4 97.3	96.6 ± 6.2 99.2

Legend: Compliance with packaged meals and supplements was derived from Dietary Compliance Checklists. Values are expressed as mean ± standard deviation and median.

eTable 3. Estimated Protein and Energy Intake From 24-Hour Food Recalls				
Variable	**0.8 g/kg/d protein plus Placebo**	**1.3 g/kg/d protein plus Placebo**	**0.8 g/kg/d protein plus Testosterone**	**1.3 g/kg/d protein plus Testosterone**
	Months 1-3			
	N=22	N=23	N=17	N=19
Protein, g/kg/d	0.84 ± 0.07 0.85	1.18 ± 0.15 1.19	0.85 ± 0.08 0.87	1.22 ± 0.08 1.23
Energy, kcal	2522 ± 269 2477	2387 ± 454 2397	2479 ± 387 2389	2414 ± 331 2397
	Months 4-6			
	N=21	N=21	N=17	N=19
Protein, g/kg/d	0.81 ± 0.10 0.80	1.17 ± 0.13 1.17	0.83 ± 0.10 0.83	1.20 ± 0.15 1.20
Energy, kcal	2423 ± 361 2355	2369 ± 477 2280	2441 ± 427 2363	2406 ± 352 2427

Legend: Protein intake from 24-hour recalls. The values are expressed as mean ± standard deviation and median.

eTable 4. Model-Based Estimates of Mean Change in Laboratory Variables by Intervention Groups, With Estimated Differences Attributable to the 2 Interventions. Point and 95% confidence intervals estimates are shown.

	[a]Comparison between Protein Groups				[a]Comparison between Testosterone Groups			
	Protein 0.8g	**Protein 1.3g**	**Difference**	**P-value**	**Placebo**	**Testosterone**	**Difference**	**P-value**
Total protein, g/dL	-0.05 (-0.14, 0.04)	-0.03 (-0.12, 0.06)	0.02 (-0.10, 0.15)	0.725	0.01 (-0.06, 0.08)	-0.06 (-0.14, 0.02)	-0.07 (-0.18, 0.03)	0.176
Albumin, g/dL	-0.10 (-0.16, -0.04)	-0.10 (-0.16, -0.05)	0.0001 (-0.08, 0.08)	0.998	-0.05 (-0.09, -0.003)	-0.10 (-0.15, -0.05)	-0.05 (-0.12, 0.02)	0.165
BUN, mg/dL	-0.01 (-1.30, 1.27)	4.41 (3.19, 5.64)	4.43 (2.64, 6.21)	<0.001	2.32 (1.21, 3.43)	1.82 (0.59, 3.06)	-0.50 (-2.14, 1.15)	0.549
Creatinine, mg/dL	0.06 (0.03, 0.09)	0.05 (0.02, 0.08)	-0.01 (-0.05, 0.03)	0.540	0.03 (0.01, 0.05)	0.07 (0.05, 0.10)	0.04 (0.01, 0.08)	0.017
Urinary urea nitrogen excretion, g/24h	0.27 (-0.88, 1.43)	2.18 (0.99, 3.37)	1.91 (0.23, 3.58)	0.026	1.84 (0.92, 2.75)	1.01 (-0.02, 2.03)	-0.83 (-2.21, 0.55)	0.235
Serum calcium, mg/dL	-0.02 (-0.12, 0.09)	0.09 (-0.01, 0.18)	0.10 (-0.04, 0.24)	0.158	0.13 (0.05, 0.20)	-0.06 (-0.14, 0.02)	-0.18 (-0.29, -0.08)	0.001
24 hour urinary calcium, mg/24h	43.58 (21.43, 65.74)	39.19 (17.94, 60.45)	-4.39 (-35.18, 26.40)	0.777	58.23 (39.41, 77.06)	31.26 (10.29, 52.23)	-26.97 (-54.88, 0.94)	0.058
Total cholesterol, mg/dL	0.08 (-6.19, 6.35)	-4.37 (-10.34, 1.60)	-4.45 (-13.10, 4.19)	0.308	2.78 (-2.48, 8.05)	-9.40 (-15.27, -3.53)	-12.18 (-20.05, -4.32)	0.003
HDL cholesterol, mg/dL	-1.41 (-3.30, 0.48)	0.54 (-1.26, 2.34)	1.95 (-0.67, 4.56)	0.142	1.57 (-0.13, 3.26)	-2.45 (-4.33, -0.57)	-4.01 (-6.50, -1.52)	0.002
LDL cholesterol, mg/dL	0.60 (-4.73, 5.93)	-2.11 (-7.12, 2.91)	-2.71 (-10.03, 4.61)	0.463	1.72 (-2.88, 6.31)	-4.41 (-9.47, 0.66)	-6.12 (-12.94, 0.70)	0.078
Triglycerides, mg/dL	4.30 (-10.26, 18.86)	-15.33 (-29.16, -1.49)	-19.62 (-39.71, 0.47)	0.055	-2.36 (-12.95, 8.22)	-13.56 (-25.39, -1.73)	-11.20 (-27.23, 4.84)	0.168
AST, U/L	2.22 (0.22, 4.23)	2.36 (0.45, 4.28)	0.14 (-2.63, 2.92)	0.920	1.11 (-0.16, 2.39)	2.50 (1.09, 3.91)	1.39 (-0.44, 3.22)	0.133
ALT, U/L	2.86 (0.47, 5.26)	1.67 (-0.61, 3.95)	-1.19 (-4.49, 2.11)	0.476	2.07 (0.29, 3.85)	1.58 (-0.41, 3.57)	-0.49 (-3.15, 2.17)	0.713
Hematocrit, %	2.32 (1.59, 3.05)	2.26 (1.56, 2.97)	-0.05 (-1.07, 0.96)	0.915	-0.12 (-0.72, 0.48)	4.32 (3.65, 4.99)	4.44 (3.55, 5.34)	<0.001
PSA, ng/mL	0.18 (0.02, 0.35)	0.24 (0.08, 0.39)	0.06 (-0.17, 0.28)	0.619	0.02 (-0.11, 0.16)	0.36 (0.21, 0.51)	0.34 (0.14, 0.54)	0.001

[a] Estimates are derived from a mixed effects regression model of mid-treatment and end-of-treatment outcomes, with control for baseline values, as described in Methods. Prespecified group comparisons are made as follows: for protein groups, model-based estimates of change from baseline to end of treatment are shown. These comparisons control for randomization to testosterone or placebo injection, along with other

covariates, as described in Methods. For testosterone groups, changes from baseline are assumed to be the consistent at the mid-treatment and end of treatment timepoints. Estimates shown here are therefore interpretable as both mid-treatment and end-of-treatment mean effects of testosterone intervention changes from baseline. These control for assignment to protein group as well as other covariates. P-values are taken from F-tests of the hypotheses that protein and testosterone interventions have no effect on outcomes, controlling for covariates, and subject to the parameterization described above. Please see Methods for detail.

eTable 5. Model-Based Estimates of Mean Change in Outcomes by Intervention Groups, With Estimated Differences Attributable to the 2 Interventions. Point estimates and 95% confidence intervals are shown.

Variables	[a]Comparison between Protein Groups				[a]Comparison between Testosterone Groups			
	Protein 0.8 g/kg/d	Protein 1.3 g/kg/d	Difference	P-value	Placebo	Testosterone	Difference	P-value
Total Body Mass, kg	2.44 (1.62, 3.26)	1.66 (0.87, 2.46)	-0.78 (-1.92, 0.37)	0.18	1.19 (0.56, 1.82)	2.43 (1.72, 3.13)	1.23 (0.30, 2.16)	0.01
Total Lean Mass, kg	2.23 (1.68, 2.78)	2.54 (2.01, 3.08)	0.31 (-0.46, 1.08)	0.43	0.37 (-0.06, 0.81)	3.91 (3.43, 4.40)	3.54 (2.88, 4.20)	<0.001
Total Fat Mass, kg	0.19 (-0.46, 0.85)	-0.93 (-1.57, -0.30)	-1.12 (-2.04, -0.21)	0.02	0.66 (0.18, 1.13)	-1.35 (-1.88, -0.82)	-2.01 (-2.69, -1.33)	<0.001
Appendicular Lean Mass, kg	1.11 (0.74, 1.48)	1.15 (0.79, 1.50)	0.04 (-0.48, 0.55)	0.89	0.14 (-0.12, 0.40)	2.00 (1.71, 2.28)	1.86 (1.48, 2.23)	<0.001
Appendicular Fat Mass, kg	-0.10 (-0.35, 0.16)	-0.49 (-0.74, -0.25)	-0.40 (-0.75, -0.05)	0.03	0.21 (0.03, 0.40)	-0.74 (-0.94, -0.53)	-0.95 (-1.22, -0.68)	<0.001
Trunk Lean Mass, kg	1.16 (0.86, 1.45)	1.40 (1.12, 1.69)	0.24 (-0.17, 0.66)	0.24	0.23 (-0.01, 0.47)	1.93 (1.67, 2.20)	1.70 (1.34, 2.06)	<0.001
Trunk Fat Mass, kg	0.24 (-0.22, 0.70)	-0.44 (-0.89, 0.005)	-0.69 (-1.33, -0.04)	0.04	0.47 (0.14, 0.80)	-0.67 (-1.04, -0.31)	-1.15 (-1.62, -0.67)	<0.001
Percent Lean Mass, %	0.91 (0.36, 1.46)	1.72 (1.19, 2.25)	0.81 (0.05, 1.58)	0.04	-0.32 (-0.73, 0.09)	2.62 (2.17, 3.08)	2.95 (2.34, 3.55)	<0.001
Leg Press Strength, Newton	155 (94.9, 215)	156 (92.6, 219)	0.89 (-86.9, 88.7)	0.98	90.4 (38.4, 142)	175 (120, 229)	84.1 (7.5, 161)	0.03
Chest Press Strength, Newton	50.1 (36.1, 64.1)	38.3 (24.5, 52.0)	-11.8 (-31.6, 7.9)	0.24	20.8 (8.3, 33.3)	57.8 (44.9, 70.7)	37.0 (18.8, 55.1)	<0.001
Leg Press Power, watts	42.0 (17.1, 66.8)	68.4 (41.3, 95.6)	26.4 (-10.5, 63.4)	0.16	22.1 (-0.3, 44.4)	60.2 (36.7, 83.7)	38.2 (5.3, 71.1)	0.03
6-minute walking distance, meters	38.2 (15.7, 60.7)	37.3 (15.6, 59.0)	-0.89 (-32.1, 30.4)	0.96	42.8 (23.8, 61.9)	29.5 (9.3, 49.7)	-13.3 (-40.5, 13.8)	0.33
Stair climbing power, watts	53.3 (31.2, 75.4)	25.0 (3.2, 46.8)	-28.3 (-59.8, 3.2)	0.08	42.4 (22.0, 62.8)	20.3 (-0.89, 41.4)	-22.1 (-51.5, 7.3)	0.14
Loaded stair climbing power, watts	60.6 (36.1, 85.1)	49.1 (24.8, 73.4)	-11.5 (-46.5, 23.5)	0.52	66.9 (46.0, 87.8)	32.3 (10.7, 53.9)	-34.7 (-64.5, -4.8)	0.02
Loaded walk speed, m/s	0.11 (0.05, 0.17)	0.10 (0.04, 0.16)	-0.01 (-0.10, 0.07)	0.81	0.10 (0.05, 0.15)	0.09 (0.04, 0.14)	-0.01 (-0.08, 0.07)	0.88
SF-36 Composite Score	0.54 (-2.95, 4.02)	-1.58 (-4.98, 1.82)	-2.12 (-6.99, 2.75)	0.39	0.32 (-2.08, 2.72)	-0.49 (-3.10, 2.13)	-0.80 (-4.07, 2.46)	0.63
SF-36 Physical Function Domain	-0.97 (-6.05, 4.11)	-2.95 (-7.89, 2.00)	-1.98 (-9.11, 5.15)	0.58	-3.99 (-7.93, -0.05)	0.44 (-3.87, 4.76)	4.44 (-1.34, 10.2)	0.13
PGWBI Composite Score	-0.35 (-2.82, 2.12)	1.42 (-0.99, 3.82)	1.77 (-1.68, 5.21)	0.31	0.19 (-1.96, 2.34)	0.77 (-1.60, 3.14)	0.58 (-2.63, 3.79)	0.72
DABS Composite Score	-1.68 (-4.84, 1.48)	0.92 (-2.16, 4.00)	2.60 (-1.85, 7.05)	0.25	-1.60 (-4.14, 0.95)	1.18 (-1.62, 3.97)	2.77 (-1.07, 6.61)	0.15
DABS Negative Affect Score	-1.87 (-4.65, 0.83)	-2.17 (-4.81, 0.48)	-0.30 (-4.10, 3.50)	0.88	-1.79 (-4.13, 0.55)	-1.49 (-4.03, 1.05)	0.30 (-3.20, 3.80)	0.87
DABS Positive Affect Score	0.82 (-1.62, 3.26)	2.00 (-0.40, 4.39)	1.18 (-2.25, 4.60)	0.50	1.15 (-0.84, 3.13)	1.50 (-0.69, 3.69)	0.35 (-2.59, 3.29)	0.81
FACIT Composite Score	-0.42 (-2.42, 1.59)	0.12 (-1.83, 2.08)	0.54 (-2.26, 3.34)	0.70	0.19 (-1.39, 1.78)	0.26 (-1.49, 2.00)	0.06 (-2.27, 2.40)	0.96

[a] Estimates are derived from a mixed effects regression model of mid-treatment and end-of-treatment outcomes, with control for baseline values, as described in Methods. Prespecified group comparisons are made as follows: for protein groups, model-based

estimates of change from baseline to end of treatment are shown. These comparisons control for randomization to testosterone or placebo injection, along with other covariates, as described in Methods. For testosterone groups, changes from baseline are assumed to be the consistent at the mid-treatment and end of treatment timepoints. Estimates shown here are therefore interpretable as both mid-treatment and end-of-treatment mean effects of testosterone intervention changes from baseline. These control for assignment to protein group as well as other covariates. P-values are taken from F-tests of the hypotheses that protein and testosterone interventions have no effect on outcomes, controlling for covariates, and subject to the parameterization described above. Please see Methods for detail. SF-36, MOS 36-item Short Form Survey Instrument; PGWBI, Psychological General Well-being Index; DABS, Derogatis Affective Balance Scale; FACIT, The Functional Assessment of Chronic Illness Therapy.

eTable 6. Adverse Event and Serious Adverse Event Profile by Randomized Group and Physiologic System

	0.8g protein and Placebo Injection (N = 24)		1.3g protein and Placebo Injection (N = 24)		0.8g protein and Testosterone Injection (N=22)		1.3g protein and Testosterone Injection (N = 22)		[c]p-value	
Physiologic System	[a]Total AEs	[b]Participants	[a]Total AEs	[b]Participants	[a]Total AEs	[b]Participants	[a]Total AEs	[b]Participants	[d]Protein Groups	[e]Testosterone Groups
Cardiovascular	5	3	2	1	1	1	5	4	0.96	0.50
Respiratory	8	8	9	9	4	3	9	6	0.64	0.22
Gastrointestinal	7	5	4	4	4	4	13	6	0.96	0.41
Genital/Urinary	9	7	8	7	6	6	9	6	0.70	0.83
Endocrine/Metabolic	2	2	2	2	0	0	7	5	0.16	0.50
Musculoskeletal	32	14	14	10	18	11	28	11	0.12	0.48
Hematologic/Lymphatic	1	1	0	0	1	1	1	1	0.60	0.58
Neurologic	4	4	2	2	0	0	9	4	0.74	>0.99
Dermatologic	7	4	4	4	5	5	8	6	>0.99	0.18
Psychiatric	2	2	0	0	0	0	1	1	0.60	>0.99
Infectious Disease	14	10	10	7	8	7	2	2	0.022	0.22
Other	18	11	16	10	8	6	9	4	0.26	0.08
SAEs	2	2	3	2	0	0	1	1	>0.99	0.38

AEs, adverse events; SAEs, serious adverse events. A total of 336 adverse events were reported by 81 participants and 6 serious adverse events reported by 5 participants. [a] Total number of AEs reported. [b] Number and percent of participants reporting at least one event. Chi-square or Fisher's Exact test. [d] Comparison, across protein groups, of proportion of individuals experiencing one or

more events. [e] Comparison, across testosterone groups, of proportion of individuals experiencing one or more adverse events.

eMethods. Supplemental Methods

METHODS FOR OUTCOMES ASSESSMENT

Muscle strength

Maximal voluntary strength of the lower and upper extremities was assessed using the one repetition maximum (1-RM) method (1) for the seated leg press and chest press exercises that employed pneumatic resistance (Keiser Sport, Fresno, CA). Details of the procedures have been previously described (2-3). Briefly, subjects were tested with standardized seat, foot, and hand placements, familiarized with the exercises, practiced the technique, and completed a 5-minute warm-up before testing. Full range of motion repetitions was assured with the use of a limit bar set at each subjects' full extension in both exercises during unloaded repetitions. The 1-RM procedure consisted of a warm up set with 5 to 8 repetitions at a resistance set to about 50% of the participant's estimated 1-RM followed by 1-minute rest. The test progressed with sets of increasing loads and fewer repetitions interspersed with standardized rest periods until the subject was able to perform only one full range of motion repetition. Maximal force was expressed in Newtons.

Leg Press Power

Peak leg press power (watts) was measured using the same leg press instrument and positioning used for the 1-RM assessment (2). The leg press machine was instrumented with an electronics package (A420, Keiser Sport) that enabled the measurement of force and velocity and hence, power. Subjects performed five repetitions with 15 seconds rest between repetitions at 60% of their baseline 1-RM. Peak power was identified as the value across the five repetitions. The same absolute load that was used at baseline was used at subsequent time points.

Six-Minute Walk Test

The 6-minute walking test was performed at a self-selected walking pace on a 30-m indoor course using standard procedures (3). Subjects were asked to choose a pace that would allow them to walk as far as safely possible without running. Total distance walked and gait speed over 6 minutes was calculated.

Unloaded and loaded stair climbing power

Two stair climb tests were administered in which subjects climbed a flight of 12 steps as rapidly as possible without running (unloaded stair climb) while the second test required subjects to carry a load equivalent to 20% of their baseline body weight evenly distributed in two canvas tote bags (loaded stair climb) (2). Two trials of the unloaded and loaded stair climb tests were given with 1.5 minutes rest between trials. The unloaded trials were always given first. The same absolute load carried at baseline was used at the end of the study. Time to ascend the stairs was precisely measured with an electronic digital timer and switch mats (Lafayette Instruments, Lafayette, IN) placed at the base of the steps and on the 12^{th} step. Stair climb power (watts) was calculated from the product of the total rise of the 12 steps, body weight plus load carried, and acceleration of gravity all divided by time.

Unloaded and loaded 50-m gait speed

Subjects performed two trials of each walk test in an indoor corridor without (unloaded) and with (loaded) carrying a load equivalent to 20% of their baseline body weight. Trials were separated by 1.5 minutes rest and subjects were asked to complete each trial as fast as possible without running. Walking speed (m/s) over 50-m was precisely measured with a wireless timing system using infrared sensors (Trac Tronix, Lenexa, KS).

Health-Related Quality of Life and Self-Reported Physical Function

We utilized the physical function domain score of the MOS SF36 instrument to evaluate self-reported physical function. The MOS SF-36 is one of the most well-known quality-of-life

instruments and has been widely used in prior clinical trials (1). The 36 questions of MOS-SF36 questionnaire cover 8 subscales of mental and physical health: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems, and mental health. The physical function domain includes questions related to limitations in activities of daily living such as walking and stair climbing. Responses to each of the SF-36 items are scored and expressed as a standardized score on a 0–100 scale; higher scores represent better self-perceived health (5).

Psychological General Well Being Schedule

Wellbeing was assessed by using the Psychological General Well-Being Index (PGWBS), a validated 22-item, questionnaire that has been used to assess wellbeing, and shown to be androgen responsive (6). The PWBI has scores for positive wellbeing, general health, depressed mood, vitality, self-control, and anxiety and a composite score. The raw scores are then standardized to a 0 to 100 scale, higher scores representing better wellbeing.

Fatigue

The fatigue was assessed by using the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale scale, a validated 13-item instrument that has been used to characterize fatigue in chronic illnesses (7). The FACIT Fatigue Scale measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point Likert scale (4 = not at all fatigued to 0 = very much fatigued) (3). Thus lower scores indicate higher level of fatigue.

Affects Balance

We used the Derogatis Affects Balance Scale (DABS), a 40-item multidimensional mood and affects inventory that measures affectivity and affects balance in terms of eight primary affects dimensions (four positive-joy, contentment, vigor, affection, and four negative- anxiety depression, guilt, hostility), and five global scores (4). It requires only 5 to 7 minutes to complete, and has been validated (8). The responses are entered on a 5-point Likert scale.

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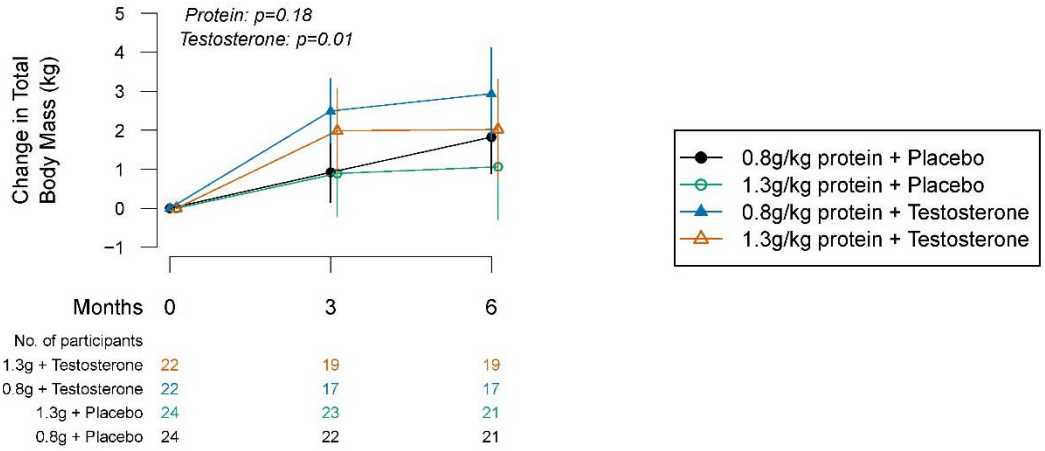
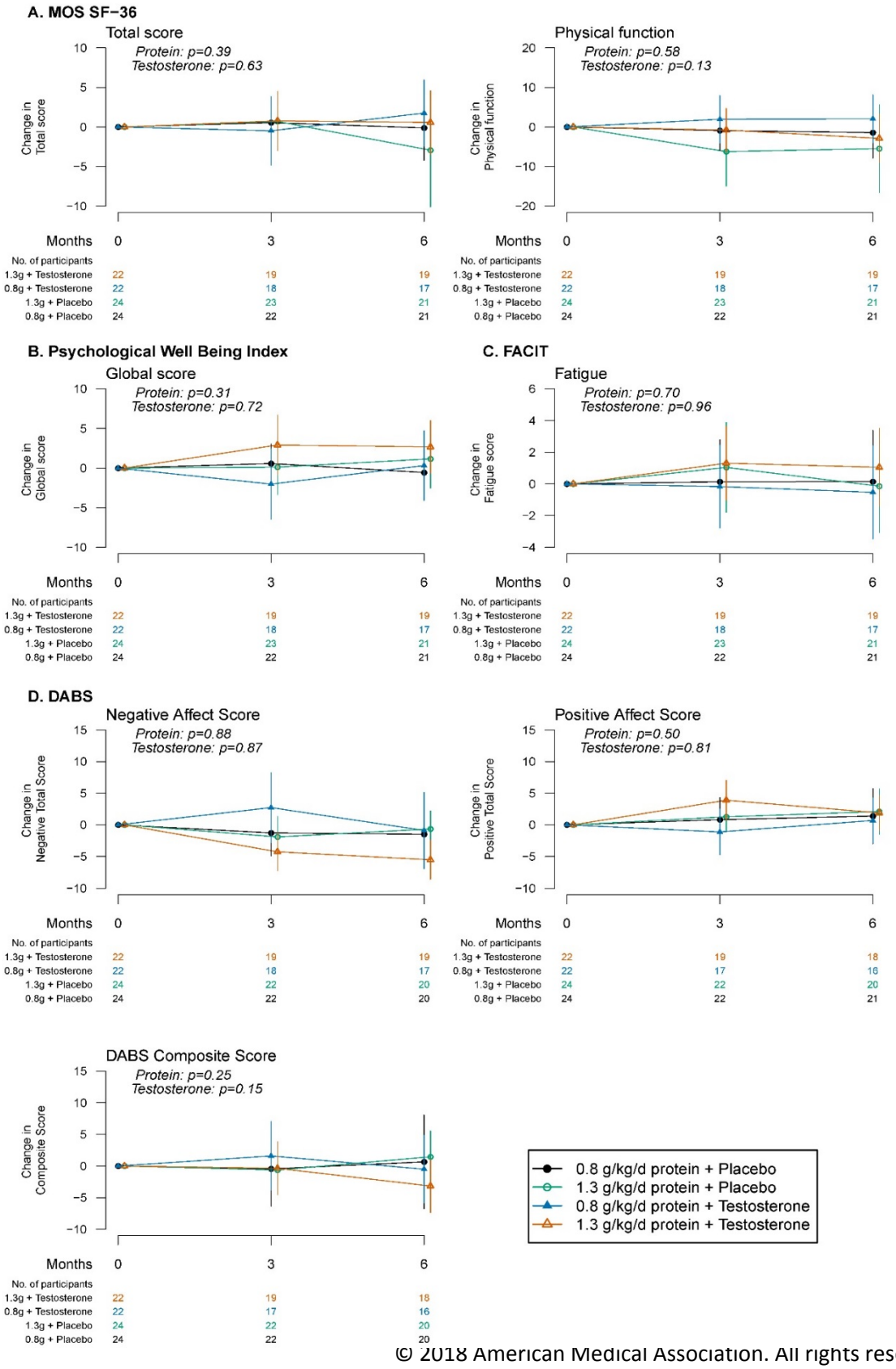
eFigure 1. Total Body Mass



Months	0	3	6
No. of participants			
1.3g + Testosterone	22	19	19
0.8g + Testosterone	22	17	17
1.3g + Placebo	24	23	21
0.8g + Placebo	24	22	21

eFigure 2. Patient−reported Outcomes



eFigure Legends

eFigure 1. Changes in Whole Body Mass

The change in whole body mass in kilograms from baseline assessed using dual energy X-ray absorptiometry are shown as mean and 95% confidence intervals. The number of randomized participants in each of the four intervention groups who contributed the data at each time point is shown at the bottom. The P-values, derived using the mixed model framework, for the protein level effect (0.8-g/kg/day vs 1.3-g/kg/day) and testosterone effect (testosterone vs placebo) are also shown. The months represent the time points (0, 3 and 6 months) at which the measurements were performed.

eFigure 2. Changes in Patient-reported Outcomes

Health-related quality of life was assessed using Medical Outcomes Study – Short Form-36 questionnaire; psychological wellbeing using the Psychological General Wellbeing Index; positive and negative affect using the DABS Affectivity Balance Scale; and fatigue using the FACIT-1 questionnaire. The number of randomized participants in each of the four intervention groups who contributed the data at each time point is shown at the bottom. The P-values, derived from the mixed model framework, for the protein level effect (0.8-g/kg/day vs 1.3-g/kg/day) and testosterone effect (testosterone vs placebo) are also shown. The months represent the time points (0, 3 and 6 months) at which the measurements were performed.