

Strength and Function Response to Clinical Interventions of Older Women Categorized by Weakness and Low Lean Mass Using Classifications From the Foundation for the National Institute of Health Sarcopenia Project

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Background. The Foundation for the National Institutes of Health Sarcopenia Project developed data-driven cut-points for clinically meaningful weakness and low lean body mass. This analysis describes strength and function response to interventions based on these classifications.

Methods. In data from four intervention studies, 378 postmenopausal women with baseline and 6-month data were evaluated for change in grip strength, appendicular lean mass corrected for body mass index, leg strength and power, and short physical performance battery (SPPB). Clinical interventions included hormones, exercise, and nutritional supplementation. Differences in outcomes were evaluated between (i) those with and without weakness and (ii) those with weakness and low lean mass or with one but not the other. We stratified analyses by slowness (walking speed ≤ 0.8 m/s) and by treatment assignment.

Results. The women (72 ± 7 years; body mass index of 26 ± 5 kg/m²) were weak (33%), had low lean mass (14%), or both (6%). Those with weakness increased grip strength, lost less leg power, and gained SPPB score ($p < .05$) compared with nonweak participants. Stratified analyses were similar for grip strength and SPPB. With lean mass in the analysis, individuals with weakness had larger gains in grip strength and SPPB scores regardless of low lean mass ($p < .01$).

Conclusions. Older women with clinically meaningful muscle weakness increased grip strength and SPPB, regardless of the presence of low lean mass following treatment with interventions for frailty. Thus, results suggest that muscle weakness, as defined by the Foundation for the National Institutes of Health Sarcopenia Project, appears to be a treatable symptom.

Key Words: Strength—Function—Sarcopenia—Gait speed—Clinical trials.

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THE age-related loss of muscle mass and strength, termed sarcopenia, represents a significant healthcare burden in the United States, reflecting \$18.5 billion in costs in 2000 (1). Based on these statistics, reducing the incidence of sarcopenia by 10% nationwide would result in a potential saving of \$1.1 billion (1), thus highlighting the importance of

establishing proven interventions. To advance research, consensus on the clinical definition of sarcopenia is required. Currently, estimates of sarcopenia prevalence vary widely due to use of multiple parameters to define the condition (2).

In 1989, Rosenberg and colleagues (3) first coined the term sarcopenia as “a reduction in muscle mass with aging.”

This definition stimulated others to characterize this condition (4,5). In 1998, Baumgartner and colleagues (4) first defined sarcopenia using appendicular skeletal lean mass, measured via dual-energy x-ray absorptiometry, as less than two standard deviations below the mean of a reference group of young persons (4). Yet muscle function and lean mass are not clearly associated, thus recent studies have suggested broader parameters to define sarcopenia (5,6). Weakness is associated with disability and mortality, but the role of muscle mass is less clear (7–9). Several working groups have made recommendations for defining sarcopenia based on review of the literature and expert opinion (5,10). Most recently, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project used data pooled from numerous large epidemiologic studies and clinical trials to develop data-driven criteria for clinically meaningful weakness and low lean mass based on cut-points for grip strength and dual-energy x-ray absorptiometry-based appendicular lean mass (ALM), respectively (6). In the FNIH Sarcopenia Project, individuals classified as weak had a higher risk for incident mobility disability after 3 years of follow-up (11), yet it is unclear whether these proposed cut-points identify individuals who will benefit from interventions to improve mobility. The FNIH Sarcopenia Project specifically included studies of clinical trials to address this question of whether response to interventions was altered by sarcopenia, as defined by the data-driven cut-points.

The current study seeks to determine whether individuals, when categorized by the FNIH parameters for clinically meaningful weakness and low lean mass, respond to interventions for frailty. We used pooled data from four randomized trials of several different frailty interventions to compare the changes in muscle strength and function among groups of older adults defined as weak and having low lean mass according to the FNIH proposed criteria. We hypothesized that participants with weakness, with or without low lean mass, would respond equally well to interventions as those without weakness.

METHODS

Participants

This study included data from four different clinical trials in women conducted at the University of Connecticut, CT. Recruitment and enrollment criteria varied and included (i) 6-month trial with 99 women (mean 77 ± 6 years) with frailty and low dehydroepiandrosterone sulfate (DHEA-S) levels who received 50 mg/d DHEA or placebo and participated in an exercise program (chair aerobics or chair yoga) (12); (ii) 6-month trial with 126 postmenopausal women (mean age 75 ± 7 years) with frailty treated with fish oil or placebo (13); (iii) a 2-year trial with 189 women aged 59–78 years on hormone therapy for a minimum of 2 years testing moderate resistance training (two to three sets of 10–14 repetitions) effects on

femoral bone quality (14); (iv) a 3-year trial with 167 postmenopausal women (75 ± 6 years), community-dwelling but frail, who received 0.25 mg 17-beta estradiol (15). All participants regardless of intervention or control group assignment were provided with calcium citrate and vitamin D supplements; the calcium dose ranged from 630 to 1300 mg of calcium to meet a combined nutritional/supplement goal of 1500 mg/d and the vitamin D dose ranged from 400 to 1000 IU/d. Study durations ranged from 6 to 36 months; however, data presented are on interventions from baseline to 6 months. Data on body composition and/or physical performance from the randomization visits were available in 378 women.

The Institutional Review Board at the University of Connecticut Health Center approved all studies and all women provided written informed consent. Eligibility information has been previously reported.

Measures

Short physical performance battery.—The short physical performance battery (SPPB) includes three elements (gait, transfers, and balance), all components important in maintaining independence; it predicts mortality, nursing home admission (16), subsequent disability, and loss of independent ambulation. The SPPB which includes ability to rise from a chair, static balance, and the 8 foot walk (16) was assessed using the published protocol. Gait speed was defined as the length of the walking course divided by the time it took participants to walk the course at their usual pace. If more than one walking test was administered, the average gait speed (m/s) was used. Participants were asked to rise once from a standard chair without using their arms. If able to rise once successfully, participants were then asked to complete five chair stands and the time to complete the chair stands was recorded in seconds.

Lower extremity strength.—Maximum lower extremity strength (Newtons) and power (Watts) was measured on a Keiser seated leg press (14).

Upper extremity strength.—Grip strength was measured by a handheld Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL), and the maximum value from either hand was analyzed.

Body composition.—Total body fat mass and total bone-free lean mass (kg) were acquired from total body scans using a fan-beam dual energy x-ray absorptiometer (Lunar, Madison, WI). Standard image analysis protocols were followed. The ALM was defined as the sum of lean mass from both arms and legs. Participants with invalid lean mass measurements for an arm or leg were excluded; this was usually due to metallic joint replacement. The validity and reproducibility of dual-energy x-ray absorptiometry have been reported previously (4).

Definitions of clinically meaningful weakness and low lean mass.—The FNIIH cut-points were used to determine weakness and low lean mass (grip strength <16 kg, ALM/BMI < 0.512, respectively); these cut-points found to be predictive of future mobility impairment (11). We compared those with weakness to those without weakness. In addition, we compared those with weakness and low lean mass, those with weakness without low lean mass, and those without weakness.

Outcome measures.—Grip strength, low lean mass (ALM_{BMI}), leg strength (LS), leg power (LP), and SPPB were evaluated at baseline and follow-up (6 months). Scores for absolute change were calculated as follows: [6 month measure – baseline measure].

Covariates.—Height (cm) was measured on Harpenden stadiometers and weight (kg) was measured on standard balance beam using standard protocols. Body mass index was calculated as weight divided by height² (kg/m²). Chronic diseases including diabetes, congestive heart failure, chronic obstructive pulmonary disease, cancer were collected where possible, definitions were study specific and dichotomized as present or absent.

Statistical Analysis

The baseline characteristics were compared between treatment groups using chi-square tests for categorical data or one-way analysis of variance for continuous data. One-way analysis of variance was used to compare the absolute changes in grip strength, LS, LP, walking speed, SPPB, and ALM between those classified as weak to those who

were not weak, and among groups defined as weak with low lean mass, weak with normal lean mass, and not weak. The studies were combined to provide enough participants to address the question of differential response to treatment in those with FNIIH-defined sarcopenia. We felt this appropriate as all interventions (even the control of calcium and vitamin D) have been used in studies for the treatment of frailty, sarcopenia, or falls. In addition to analyzing all participants combined, analyses were conducted stratified by treatment assignment (active vs. control) and mobility status (gait speed < 0.8 m/s, yes/no). Expert opinion has estimated gait speed less than 0.8 m/s as a cut-point predictive of shorter life expectancy, poor health, and decreased function (17). We did further subanalyses base on exercise (any exercise vs no exercise and resistance exercise vs no resistance exercise). Statistical analyses were performed using SPSS version 19.0 (Chicago, IL).

RESULTS

Data were collected from 378 postmenopausal women ages 71.9 ± 7 years with a body mass index of 26.0 ± 4.8 at baseline and 6-months follow-up. Table 1 outlines baseline characteristics for study participants. The majority of participants had walking speeds > 0.8 m/s ($n = 355$); 33% of participants had weakness, 14% had low lean mass, and 6% of participants had both.

In analysis of the entire group, those with weakness increased SPPB scores compared with those without weakness. Similar results were seen when stratified by slowness and treatment assignment though not always reaching statistical significance due to sample size

Table 1. Baseline Age, Physical Performance, and Body Composition Characteristics of Study Populations

	Total ($n = 377$)	Control ($n = 168$)	Active ($n = 209$)	p Value
Age (y)	71.7 ± 6.8	71.9 ± 6.8	71.6 ± 6.8	.734
BMI (kg/m ²)	25.9 ± 4.9	25.9 ± 5.0	25.9 ± 4.8	.954
SPPB score	10.5 ± 1.7	10.6 ± 1.6	10.5 ± 1.7	.629
Baseline GS (kg)	19.9 ± 6.4	20.1 ± 6.8	19.7 ± 6.1	.570
Baseline GS/BMI (kg/kg/m ²)	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	.623
Baseline ALM (kg)	15.6 ± 2.3	15.5 ± 2.4	15.7 ± 2.2	.452
Baseline ALM/BMI (kg/kg/m ²)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	.315
Baseline leg power (Watts)	217 ± 76	209 ± 72	225 ± 79	.110
Baseline gait speed (m/s)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	.163
Absolute change in				
SPPB	0.3 ± 1.7	0.2 ± 1.9	0.4 ± 1.5	.187
Grip strength (kg)	-0.2 ± 4.2	-0.2 ± 4.1	-0.3 ± 4.3	.849
GS/BMI (kg/kg/m ²)	-0.1 ± 0.2	-0.1 ± 0.2	-0.1 ± 0.2	.885
ALM (kg)	-0.0 ± 0.6	-0.1 ± 0.6	0.0 ± 0.7	.075
ALM/BMI (kg/kg/m ²)	0.0 ± 0.2	0.0 ± 0.3	-0.0 ± 0.1	.187
Leg power (Watts)	-20.1 ± 49.5	-17.1 ± 47.6	-22.9 ± 51.3	.364
Gait speed (m/s)	-0.0 ± 0.1	-0.0 ± 0.1	-0.0 ± 0.2	.149

Notes: Mean \pm SD; ALM = appendicular lean mass; BMI = body mass index; GS = grip strength; SPPB score = short physical performance battery score. Categories are distinguished by weakness at baseline (defined by GS < 16 kg) and low ALM < 15.02 kg, and low lean mass by $ALM_{BMI} < 0.512$. p value indicates differences between active treatment and placebo groups. Active group included the following interventions: 50mg dehydroepiandrosterone (DHEA) + chair aerobics/chair yoga; 1.2g fish oil; lower extremity progressive resistance training; 0.25 mg 17-beta estradiol. Control groups received the following interventions: placebo for DHEA + chair aerobics/chair yoga, 1.2g olive oil, upper extremity nonprogressive resistance exercise, and placebo for estradiol. All participants (active and control) received calcium and vitamin D supplementation.

Table 2. Absolute Change in Muscle Quality Variables for Normal and Low Grip Strength Groups

Variables	All Participants		Slowness Present?				Treatment Assignment			
			No		Yes		Active		Control	
	Not Weak (N = 252)	Weak (N = 124)	Not Weak (N = 246)	Weak (N = 106)	Not Weak (N = 6)	Weak (N = 17)	Not Weak (N = 133)	Weak (N = 65)	Not Weak (N = 113)	Weak (N = 41)
Grip strength	-0.97*	1.21*	-0.97*	1.01*	-1.00	2.53	-0.78*	0.68*	-1.19*	1.51*
Leg strength (GS)	-9.84	-31.30	-9.00	-21.38	-64.33	-112.70	-0.46	2.94	-17.90*	-55.71*
Leg power	-23.65*	-5.50*	-24.33*	-5.92*	20.33	-2.10	-30.36*	6.67*	-18.05	-23.68
Walking speed	-0.02	-0.03	-0.02	-0.04	0.05	0.03	-0.02	-0.02	-0.03	-0.07
SPPB	0.02*	0.84*	0.00*	0.68*	0.83	1.53	0.16	0.52	-0.18*	0.93*
ALM _{BMI}	0.01	-0.01	0.01	-0.01	0.01	-0.00	-0.00	-0.02	0.03	0.00

Notes: ALM_{BMI} = appendicular lean mass standardized to body mass index; GS = grip strength; SPPB = short physical performance battery. Categories are distinguished by weakness at baseline (defined by GS < 16 kg).

*Significance between those with normal and low GS within the grouping (ie, whole group).

SPPB Absolute Changes

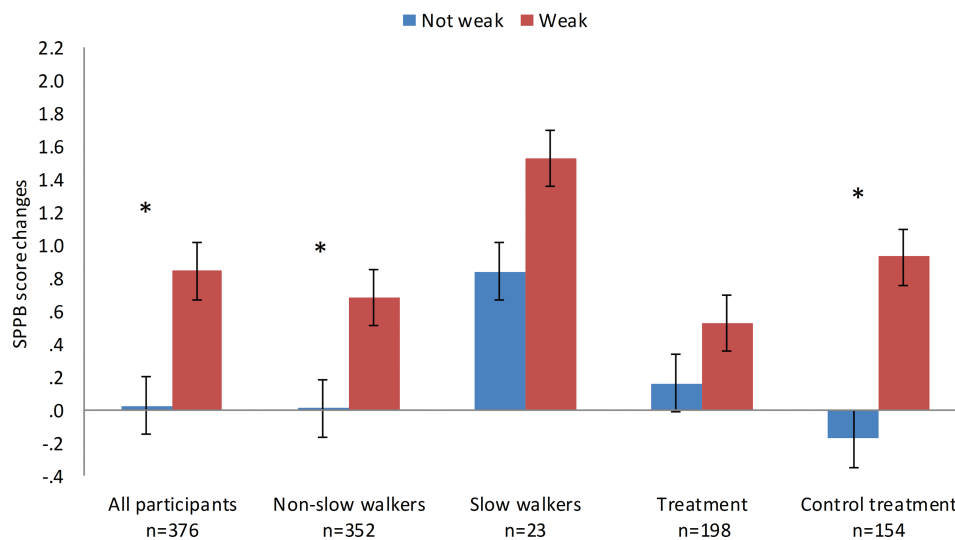


Figure 1. Measured change in short physical performance battery after 6 months in all participants, nonslow (>0.8 m/s) and slow walkers (≤0.8 m/s), active or placebo treatment (various interventions). Categories are distinguished by weakness at baseline (defined by grip strength < 16 kg). *Significant at $p < .05$.

(Table 2, Figure 1). Those without weakness at baseline demonstrated loss of grip strength, whereas those with weakness improved. The results were similar in all subgroup analyses with the exception of those with slow walk speed, most likely due to the small sample size (Table 2, Supplementary Figure 3a). The LP declined regardless of weakness classification, although less in those with weakness. Results were similar when stratified by slowness or treatment assignment. Table 2, Supplementary Figure 3b). Subgroup analyses were also completed by comparing exercise (upper/lower extremity resistance, yoga, aerobics vs. nonexercise (estrogen, fish oil) and resistance training (upper/lower extremity resistance) against other (yoga, aerobic, estrogen, fish oil) in the same classifications as other analyses to address impact of exercise against other interventions. The results are of similar magnitude but may lose significance due to smaller sample sizes (data not shown).

Participants were further classified into three groups (not weak [$n = 251$], weak with low lean mass [$n = 24$], weak without low lean mass [$n = 100$]; Table 3, Figure 2). SPPB, grip strength, and LP had significant absolute changes, whereas LS, walking speed and ALM_{BMI} did not (Table 3) for each of the three groups. The SPPB increased in both weak groups compared with not weak grip strength (Figure 2). Similar results were seen in those stratified by with slowness and treatment (control and active) (Figure 2). Grip strength increased in those with weakness, regardless of the presence of low lean mass at baseline, and this change was significant only in the weak without low lean mass group. (Table 3, Supplementary Figure 4a). Similar results were seen when stratified for slowness and treatment group (control) (Supplementary Figure 4a). Overall, those with normal grip strength lost more LP than the weak groups, although the differences did not always reach significance (Supplementary Figure 4b).

Table 3. Absolute Change in Muscle Function Variables for Not Weak; Weak, Low Lean; and Weak, Not Low Lean Groups

	Slowness Present												Treatment Assignment										
	All Participants						Yes						Active			Control							
	No		Weak		Not Weak		Not		Weak		Weak Not		Not Weak		Weak		Weak Not		Not Weak		Weak		Weak Not
	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean	Weak	Low Lean
	(N = 251)	(N = 24)	(N = 100)	(N = 245)	(N = 21)	(N = 85)	(N = 6)	(N = 3)	(N = 14)	(N = 133)	(N = 11)	(N = 54)	(N = 112)	(N = 10)	(N = 31)								
Grip strength (GS)	-0.98*	0.94*	1.28**†	-0.98*	0.88*	1.05**†	-1.00	1.33	2.79	-0.78	1.75	0.48	-1.22*	0.09*	2.00**†								
Leg strength	-9.84	-43.00	-27.18	-9.00	-43.00	-12.43	-64.33	NA	-112.70	-0.46	-28.08	13.28	-17.90	-57.92	-54.50								
Leg power	-23.65	-4.08	-6.00	-24.33	-4.08	-6.67	20.33	NA	-2.10	-30.36*	-2.17*	9.61**†	-18.05	-6.00	-33.32								
Walking speed	-0.02	-0.06	-0.03	-0.02	-0.08	-0.03	0.06	0.06	0.02	-0.02	-0.08	-0.01	-0.03	-0.07	-0.07								
SPPB	0.02*	1.21*	0.75**†	0.00*	1.29*	0.53**†	0.83	0.67	1.71	0.16*	1.82*	0.26*	-0.18*	0.70*	1.00**†								
ALM _{BMI}	0.01	0.01	-0.01	0.01	0.01	-0.02	0.01	0.00	-0.00	-0.00	0.02	-0.02	0.03	0.00	-0.00								

Notes: ALM_{BMI} = appendicular lean mass standardized to body mass index; SPPB = short physical performance battery. Categories are distinguished by weakness at baseline (defined by GS < 16 kg) and low lean mass (defined by ALM_{BMI} < 0.512).

*Significance within grouping.

†Post hoc analysis: Not weak is significantly different from weak, not low lean $p < .001$.

**Post hoc analysis: Not weak is significantly different from both weak low lean and weak, not low lean $p < .01$.

DISCUSSION

Compared with those without weakness at baseline, those with weakness demonstrated better response to interventions aimed at improving strength and physical function. This work is consistent with prior work demonstrating the ability of weak individuals to improve strength and function (18–20). Whether observed increases from frailty interventions are clinically meaningful are yet to be determined. However, recent work from the FNIH Sarcopenia Project revealed that muscle weakness, defined as grip strength < 16 kg in women, increased the likelihood of mobility impairment, regardless of lean mass (11). Thus, if achieved increases in strength bring weak individuals above the previously established thresholds for clinically meaningful weakness (21), strength improvements may be considered clinically meaningful.

Although all weak individuals improved their grip strength more than those who were not weak, those without low lean mass had the greatest response. These results suggest that the preservation of lean mass was beneficial in the response to interventions to improve frailty. We are uncertain if this has been demonstrated before. Fiatarone demonstrated improved muscle strength in very frail, old nursing home participants with resistance training (18), whereas others have failed to demonstrate gains in frail adults (20,22). In our analyses of SPPB score, those with weakness had similar improvements regardless of the low lean mass category; those with weakness also had greater improvements compared with individuals without weakness. The differences between gains in strength against gain in function may be due to adiposity, although our definition of lean mass corrects for body mass and should mitigate some of this effect. Functional gains may be more difficult in those with increase adiposity (23) and those with increased adiposity are more likely to have normal lean mass (24).

In the present study those without weakness declined in strength or function even with interventions. The biological process of aging is associated with declines in muscle mass, strength, and function (3). A 12-year study found a significant decrease in skeletal muscle strength with an annual decline ranging from 1.4% to 2.5% (25), reductions in LS (2.5 N-m/y [in men] and 1.8 N-m/y [in women]) and quality of ~10% per decade (26) and decline in walking speed (27). Mechanisms to explain the decline include inflammation, oxidative stress, mitochondrial dysfunction, and alterations in fiber types with age (28,29). The reason for the lack of response is not clear, although may be explained by regression to the mean (30). Previous studies have demonstrated changes in muscle strength in healthy adults (not limited to frail adults) with progressive resistance training (25,31,32) and in those with frailty (18,19). None of the interventions were progressive resistance training, so that the effects may have been unsuccessful in those with preserved function as they did not have a muscular challenge sufficient to change

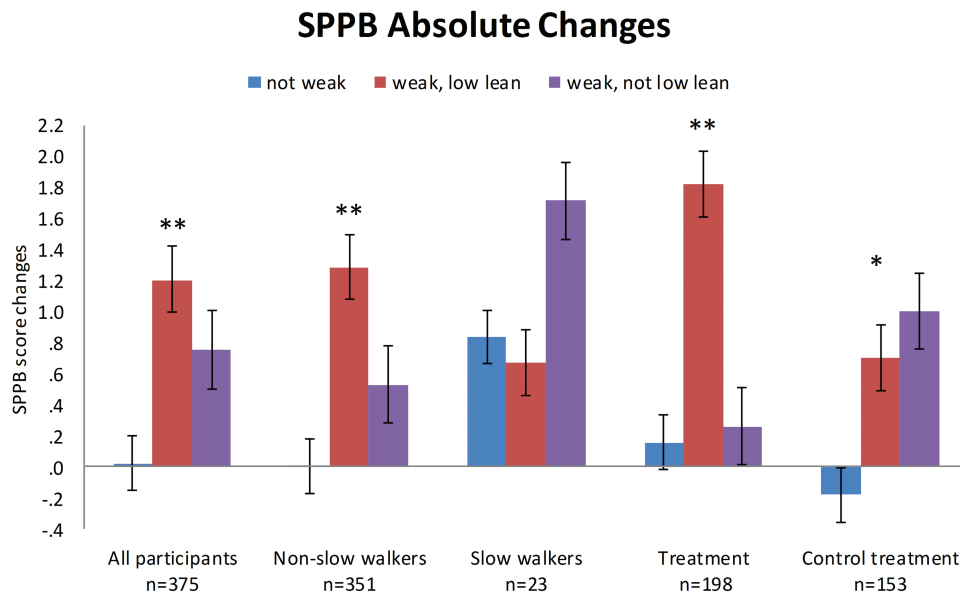


Figure 2. Measured change in short physical performance battery after 6 months in all participants, nonslow (>0.8 m/s) and slow walkers (≤ 0.8 m/s), active or placebo treatment (various interventions). Categories are distinguished by weakness at baseline (defined by grip strength < 16 kg and low lean mass by $ALM_{BMI} < 0.512$). ALM_{BMI} = appendicular lean mass corrected for body mass index. Post hoc statistical analysis: *not weak is significantly different from weak, not low lean $p < .001$; **not weak is significantly different than both weak low lean and weak, not low lean $p < .01$.

strength or function. According to the overload principle, exercise should be performed at intensity higher than the usual load to increase the metabolic demand and facilitate a training response (33).

In contrast to changes in grip strength, LS and power declined regardless of weakness, slowness, or treatment classification. It is unclear why lower extremity strength and power changes differed from observed changes in grip strength. However, muscles in the upper body may be more adaptable to interventions in older adults, as Sousa and colleagues (34) similarly found greater changes in upper body than lower body measures in older adults in response to an intervention. The reason for this anatomical difference is unknown, but may be related to the greater age-related longitudinal declines in lower body than upper body strength in women (7,35). The clinical relevance of changes in lower extremity measures are more difficult to interpret as unlike grip strength, no consensus thresholds based on large pooled analyses have been established for lower extremity measures. As earlier studies have reported stronger associations between strength and function when strength is assessed on the corresponding muscle group (36–39), further research is warranted on the clinical relevance of lower extremity strength and power measures.

The individuals in these randomized studies were selected for some level of frailty and if selected for a component not related to strength/sarcopenia, physiologic factors other than sarcopenia could have had more impact in strength and function. Fried and colleagues (39) established cut points to identify malfunctioning physiologic systems associated with frailty and demonstrated that three or more abnormal systems

are 26 times more likely to result in a frailty diagnosis. The physiologic systems include hematologic, inflammatory, endocrine, adiposity, neuromuscular, and micronutrient, so that the affected system may or may not result in a significant impact on muscle (39). Furthermore, both frailty and sarcopenia are complex systems so that adjusting for one system may not be enough to correct frailty or sarcopenia (28,39). The interventions evaluated in the current analysis included anabolic (exercise and DHEA), hormonal (estrogen), and micronutrient (calcium and vitamin D) interventions; however, in frail and sarcopenic individuals, inflammation or hematologic systems are also frequently involved (40,41). Neglecting to include interventions for anemia and inflammation may have prevented improvements in some sarcopenic and frail patients.

Anabolic agents may be most beneficial to those with low strength. DHEA supplementation demonstrated no benefit in muscle strength or body composition in a trial of healthy, nonfrail older men and women (42). Studies that found improvement in physical strength or function with DHEA combined supplementation with exercise in older, frailer adults (43,44). The control group most likely benefited from calcium and vitamin D supplementation. Numerous studies demonstrate corrective effects of vitamin D on muscle strength and function in older adults (45–48), although not all (49). A 6-month study of calcium and vitamin D supplementation in 46 elderly institutionalized participants demonstrated improved hip flexor and knee extensor strength by 16.4% and 24.6% in those receiving calcium plus vitamin D group and no improvements in the calcium plus placebo group (48). Community dwelling elderly women in the

lowest tertile of strength and mobility improved after 1 year of vitamin D supplementation (47). Vitamin D increased gait speed and decreased body sway whereas resistance training improved strength in a study of elderly participants with vitamin D levels ≤ 16 ng/mL (45).

The study has several limitations. The sample size is small and would benefit from a larger population; we may have missed differences on some measures. The data is pooled from diverse studies with different interventions. The different inclusion criteria specific to each study may have altered the ability to combine the studies. Furthermore, the interventions were varied [exercise, hormones, and nutrition] which also may limit the ability to combine the data. Although the individuals in the population were selected for frailty, those with the most severe frailty were not well represented and studies in a more frail population will need to be done to confirm results. Finally, the role of the FINH cut-points in men will also need further exploration.

In summary, the definitions of clinically meaningful muscle weakness proposed by FINH were able to differentiate response to interventions targeting frailty in older, frail postmenopausal women. The response was consistent when we evaluated all participants or when stratified by slowness or treatment assignment. Thus, muscle weakness appears to be a treatable symptom in sarcopenia diagnosis. The differentiation of whether lean mass preservation allows for more improvement in strength and whether those with low lean mass have more dramatic improvements in function with interventions will require further study and larger sample sizes.

SUPPLEMENTARY MATERIAL

Supplementary material can be found at: <http://biomedgerontology.oxfordjournals.org/>

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