Special Article

Criteria for Clinically Relevant Weakness and Low Lean Mass and Their Longitudinal Association With Incident Mobility Impairment and Mortality: The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project

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Background. This analysis sought to determine the associations of the Foundation for the National Institutes of Health Sarcopenia Project criteria for weakness and low lean mass with likelihood for mobility impairment (gait speed ≤ 0.8 m/s) and mortality. Providing validity for these criteria is essential for research and clinical evaluation.

Methods. Among 4,411 men and 1,869 women pooled from 6 cohort studies, 3-year likelihood for incident mobility impairment and mortality over 10 years were determined for individuals with weakness, low lean mass, and for those having both. Weakness was defined as low grip strength (<26kg men and <16kg women) and low grip strength-to-body mass index (BMI; kg/m^2) ratio (<1.00 men and <0.56 women). Low lean mass (dual-energy x-ray absorptiometry) was categorized as low appendicular lean mass (ALM; <19.75kg men and <15.02kg women) and low ALM-to-BMI ratio (<0.789 men and <0.512 women).

Results. Low grip strength (men: odds ratio [OR] = 2.31, 95% confidence interval [CI] = 1.34–3.99; women: OR = 1.99, 95% CI 1.23–3.21), low grip strength-to-BMI ratio (men: OR = 3.28, 95% CI 1.92–5.59; women: OR = 2.54, 95% CI 1.10–5.83) and low ALM-to-BMI ratio (men: OR = 1.58, 95% CI 1.12–2.25; women: OR = 1.81, 95% CI 1.14–2.87), but not low ALM, were associated with increased likelihood for incident mobility impairment. Weakness increased likelihood of mobility impairment regardless of low lean mass. Mortality risk patterns were inconsistent.

Conclusions. These findings support our cut-points for low grip strength and low ALM-to-BMI ratio as candidate criteria for clinically relevant weakness and low lean mass. Further validation in other populations and for alternate relevant outcomes is needed.

Key Words: Muscle—Sarcopenia—Mobility—Impairment.

ROSENBERG [1] first highlighted the functional significance of the ubiquitous age-related loss of muscle mass by naming it "sarcopenia," and a surge of investigations into the functional consequences of low lean mass soon followed [2,3]. It has become clear, however, that low lean mass, by itself, is a poor predictor of functional outcomes compared with low strength [4,5]. Operational definitions of sarcopenia have evolved to include measures of strength and function, and several recommendations for clinical criteria have been published [6–9], yet there are currently no data-driven consensus criteria validated for their ability to predict relevant clinical outcomes. The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project aimed to address this gap in knowledge, and in the first two phases of the project, we determined preliminary, evidence-based cut-points for both grip strength and grip strength standardized to body size as candidate indicators of clinically relevant weakness [10], and cut-points for both appendicular lean mass (ALM) and ALM standardized to body size as candidate criteria for clinically relevant low lean mass [11].

In the third phase, presented here, we sought to validate our candidate criteria by determining whether they predict future mobility impairment, defined as usual gait speed ≤0.8 m/s [12], over a 3-year follow-up among those without current mobility impairment. Testing this hypothesis is important to provide further evidence about whether to adopt these proposed criteria for research and clinical evaluation. In supplemental analyses, we examined all-cause mortality as a secondary clinically relevant outcome.

METHODS

Participants

Recruitment criteria and description of the studies participating in the FNIH Sarcopenia Project have been previously described [10,11]. Eligible participants for the current analyses included those from cohorts with concurrent information on gait speed, grip strength, and ALM at a single time point (baseline), baseline age ≥65 years, baseline gait speed >0.8 m/s, a follow-up gait speed measurement approximately 3 years after baseline, and follow-up information on survival. Of the 26,625 participants in the pooled data, 8,371 were ineligible because they were from studies without follow-up data; 10,052 did not have dual-energy x-ray absorptiometry scans or follow-up data; 960 were eligible but missing gait speed, grip strength, or ALM; and an additional 962 were missing follow-up data, yielding a final sample size of 6,280 (4,411 men and 1,869 women). Follow-up gait speed data were missing from 665 participants, leaving 5,615 (4,034 men and 1,581 women) eligible for analyses of incident mobility impairment. The final sample included participants from the Study of Osteoporotic Fractures original (study visit 6) [13] and African American cohorts (study visit 1; [14]), the Osteoporotic Fractures in Men Study Sleep Study ancillary study [15–17], the Health, Aging and Body Composition study (year-6 clinic visit; [18]), the Framingham Study Offspring cohort (exam cycles 6 and 7, 1996–2001; [19]), and men from the Invecchiare in Chianti study (year-3 visit; [20]).

Grip Strength

Maximum grip strength (kilograms) was measured using a handheld dynamometer using similar protocols across studies. Most studies used a Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL; [21]). Grip strength less than 26 kg for men and less than 16 kg for women was considered weak [10]. A secondary criteria for weakness based on grip strength-to-body mass index (BMI) ratio ($weak_{BMI}$) was also determined, with weakness defined as $weak_{BMI}$ less than 1.00 in men and less than 0.56 in women [10].

Lean Mass

Whole-body dual-energy x-ray absorptiometry scans were obtained with either a Lunar or Hologic densitometer using similar protocols across studies. Our low lean mass criteria was defined as ALM less than 19.75 kg for men and less than 15.02 kg for women [11]. A secondary criteria for low lean mass based on ALM-to-BMI ratio (ALM_{BMI}) was identified, with low ALM_{BMI} defined as less than 0.789 in men and less than 0.512 in women [11].

Gait Speed

Gait speed (meters per second) was assessed at baseline and after approximately 3 years of follow-up as speed over a 4-m course at the usual pace. For cohorts using a 6-m course, gait speed was converted to 4-m speeds using a published formula [22]. Mobility impairment was defined as a gait speed ≤0.8 m/s [12].

Mortality

Date of death (any cause) for participants was ascertained according to protocols for each cohort. Survival time was calculated as the number of days from the baseline visit until death or up to 10 years of follow-up.

Other Variables

Information on baseline age (years) and BMI (weight in kilograms divided by height in meters squared, kg/m^2) was available in all participants.

Statistical Analyses

To evaluate potential differences between participants included and excluded from the mobility impairment analysis, we compared baseline characteristics between those who did and did not have follow-up mobility impairment information up using analysis of variance or the Kruskal–Wallis test for continuous variables, and the chi-square test for categorical variables.

We planned a priori to pool data across all cohorts to evaluate the predictive validity of our candidate criteria for incident mobility impairment and mortality. For both outcomes, we calculated cohort-specific effect estimates (SAS version 9.2, SAS Institute Inc. Cary, NC), which were then combined to calculate pooled effect estimates using random-effects meta-analysis (23) using the Metafor package for R. The presence and extent of heterogeneity among studies were evaluated using the Q test ($p < .10$) and I^2 statistic.

Logistic regression was used to calculate the age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for incident mobility impairment for our weakness (weak and weak$_{BMI}$) and low lean mass (ALM and ALM$_{BMI}$) criteria, separately for men and women. To determine whether combinations of weakness and low lean mass criteria predict incident mobility impairment, participants were further categorized into four groups: (a) not weak with normal lean mass, (b) not weak with low lean mass, (c) weak with normal lean mass, and (d) weak with low lean mass. ORs for incident mobility impairment were calculated for each group with the "not weak with normal lean mass" group as the referent. Analysis was done separately for each of the four different combinations of our weakness and low lean mass criteria: (a) weak + ALM; (b) weak + ALM$_{BMI}$; (c) weak$_{BMI}$ + ALM and (d) weak$_{BMI}$ + ALM$_{BMI}$.

For mortality, we used Cox proportional hazards regression to calculate the sex-specific age-adjusted mortality rate ratios and 95% CIs for the weakness and low lean mass criteria, and for their combinations. No violations of the proportional hazards assumption were detected ($p < .05$ for interactions of independent variables with time).

RESULTS

Among the 6,280 participants eligible for mobility impairment and mortality analyses, more women had low ALM compared to men (38% vs 9%), but the prevalence of low ALM$_{BMI}$ (15% vs 18%) was similar (Table 1). Weakness defined by weak and weak$_{BMI}$ was prevalent in 3% and 6% of men, respectively, and 11% of women for both definitions. The proportion of men and women with combined weakness and low lean mass was very low (≤7%) regardless of definition used. Baseline characteristics by participating cohort are listed in Supplementary Tables 1 and 2.

Incident Mobility Impairment

The 377 men (8.5%) excluded from the incident mobility impairment analysis due to missing follow-up mobility data were older, slower, weaker, and had lower BMI and lean mass than men who were included (Supplementary Table 3). The 288 (15%) excluded women were older, slower, and had lower lean mass. For the 5,615 participants

Table 1. Baseline Characteristics* of FNIH Sarcopenia Project Participants Included in Longitudinal Analyses Including Pre-specified Categorizations of Baseline Weakness and Low Lean Mass

	Women	Men
N	1,869	4,411
Age (y)	76.5 ± 4.5	74.0 ± 5.5
BMI (kg/m²)	27.3 ± 5.1	27.3 ± 3.7
<25 (%)	34	27
25 to <30 (%)	38	53
≥30 (%)	26	20
Gait speed (m/s)	1.1 ± 0.2	1.3 ± 0.2
Grip strength (kg)	22.1 ± 5.8	41.3 ± 8.5
Grip strength/BMI	0.83 ± 0.24	1.54 ± 0.36
ALM (kg)	16.2 ± 2.9	24.1 ± 3.4
ALM/BMI	0.60 ± 0.09	0.89 ± 0.11
Weak† (%)	11	3
Weak$_{BMI}$‡ (%)	11	6
Low ALM§ (%)	38	9
Low ALM$_{BMI}$‖ (%)	15	18
Weak + ALM		
Not weak, normal lean mass (%)	58	89
Not weak, low lean mass (%)	31	8
Weak, normal lean mass (%)	4	2
Weak, low lean mass (%)	7	1
Weak + ALM$_{BMI}$		
Not weak, normal lean mass (%)	77	81
Not weak, low lean mass (%)	12	17
Weak, normal lean mass (%)	9	1
Weak, low lean mass (%)	2	1
Weak$_{BMI}$ + ALM		
Not weak, normal lean mass (%)	55	86
Not weak, low lean mass (%)	34	8
Weak, normal lean mass (%)	7	5
Weak, low lean mass (%)	4	1
Weak$_{BMI}$ + ALM$_{BMI}$		
Not weak, normal lean mass (%)	79	80
Not weak, low lean mass (%)	10	14
Weak, normal lean mass (%)	7	2
Weak, low lean mass (%)	4	4
Died over follow-up (%)	18	19
Mean follow-up time (y)	7.4	8.4

Notes: ALM = appendicular lean mass; BMI = body mass index.
*Mean (±*SD*) unless otherwise noted.
†Weak: grip strength <26 men; <16 women.
‡Weak$_{BMI}$: ratio of grip strength-to-body mass index <1.00 men; <0.56 women.
§ALM: appendicular lean mass <19.75 men; <15.02 women.
‖ALM$_{BMI}$: ratio of appendicular lean mass to body mass index <0.789 men; <0.512 women.

included, 7% of men and 23% of women developed incident mobility impairment (Supplementary Table 4).

Weak (Figure 1) was associated with a twofold higher odds of mobility impairment for men (OR = 2.31, 95% CI 1.34–3.99) and women (OR = 1.99, 95% CI 1.23–3.21). Weak$_{BMI}$ (Figure 2) was more strongly associated with incident mobility impairment in both men (OR = 3.28, 95% CI 1.92–5.59) and women (OR = 2.54, 95% CI 1.10–5.83), though there was evidence of heterogeneity among women (Q test: $p < .01$; $I^2 = 80\%$).

Low lean mass defined by ALM$_{BMI}$ (Figure 3) was associated with higher odds of incident mobility impairment for both
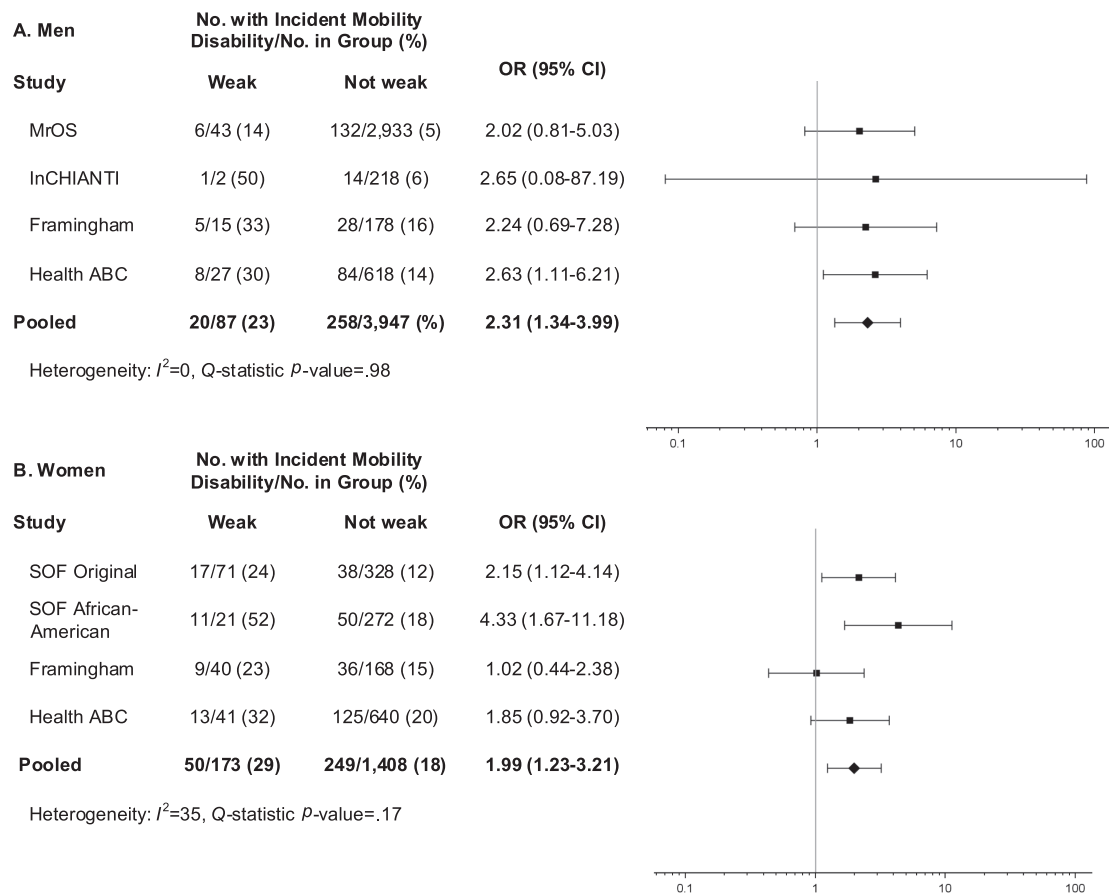
Figure 1. Age-adjusted odds ratios (OR) for incident mobility impairment (gait speed ≤ 0.8 m/s) after approximately 3 years of follow-up for proposed low grip strength criteria (weak) among men (**A**) and women (**B**) in the FNIH Sarcopenia Project.

men (OR = 1.58, 95% CI = 1.12–2.22) and women (OR = 1.81, 95% CI 1.14–2.87), yet the ALM criterion was not (Figure 4).

Men who were weak with normal lean mass had two to nearly five times the odds of incident mobility impairment than those who were not weak with normal lean mass (Supplementary Figures 1–4). This group also tended to have greater odds of mobility impairment than weak men with low lean mass, with the exception of the weak + ALM_{BMI} combination (Supplementary Figure 2), where weak men with low lean mass had the greatest odds of mobility impairment, though there was some evidence of heterogeneity across cohorts for the not weak with low lean mass group (Q test: $p = .08$, $I^2 = 51\%$). Among men who were not weak, low lean mass defined by either criterion was not associated with incident mobility impairment. When weakness and low lean mass criteria were combined in women, there was significant heterogeneity among cohorts for the combinations of weak +ALM, $weak_{BMI}$ + ALM, and $weak_{BMI}$ + ALM_{BMI} (Q test: all $p < .10$, all $I^2 > 52\%$). For the weak + ALM_{BMI} combination (Supplementary Figure 2), there were higher odds in all three risk groups relative to the not weak with "normal lean mass group," with the highest odds in the "weak with low lean mass" group.

Mortality

Over 10 years of follow-up, 18% of women and 19% of men died (Supplementary Table 1). Weak and $weak_{BMI}$ criteria were associated with 63%–74% higher mortality rates among men, whereas in women, only weak was associated with a 48% higher rate (Supplementary Figures 5–6). Among men, ALM was associated with 37% greater morality rate, while ALM_{BMI} was not associated with mortality (Supplementary Figures 7–8), though there was significant heterogeneity for this criterion (Q test: $p = .02$, $I^2 = 75\%$). Neither ALM nor ALM_{BMI} were associated with mortality among women. For all combinations of weakness and low lean mass criteria among men, mortality rates were consistently highest among those with weakness, though estimates were statistically significant only for men with normal lean mass (Supplementary Figures 9–12). Among men who were not weak, ALM was associated with 33%–41% higher mortality rate compared to normal lean mass, yet there was evidence of significant heterogeneity for ALM_{BMI}. For combinations of weakness and low lean mass among women, those who were weak tended to have increased mortality rates, though mortality rate ratio CIs exclude the null value only for those who were

A. Men	No. with Incident Mobility Disability/No. in Group (%)		
Study	Weak	Not weak	OR (95% CI)
MrOS	21/124 (17)	117/2,850 (4)	4.33 (2.58-7.27)
InCHIANTI	3/7 (43)	12/213 (6)	7.59 (1.35-42.73)
Framingham	6/27 (22)	27/166 (16)	1.23 (0.44-3.43)
Health ABC	17/52 (33)	75/593 (13)	3.35 (1.78-6.28)
Pooled	**47/210 (22)**	**231/3,822 (6)**	**3.28 (1.92-5.59)**

Heterogeneity: I^2=41, Q-statistic P-value=.14

B. Women	No. with Incident Mobility Disability/No. in Group (%)		
Study	Weak	Not weak	OR (95% CI)
SOF Original	12/44 (27)	42/351 (12)	2.68 (1.27-5.64)
SOF African-American	18/39 (46)	43/250 (17)	4.47 (2.12-9.41)
Framingham	6/38 (16)	39/170 (23)	0.65 (0.25-1.69)
Health ABC	25/50 (50)	113/631 (18)	4.35 (2.39-7.92)
Pooled	**61/171 (36)**	**237/1,402 (18)**	**2.54 (1.10-5.83)**

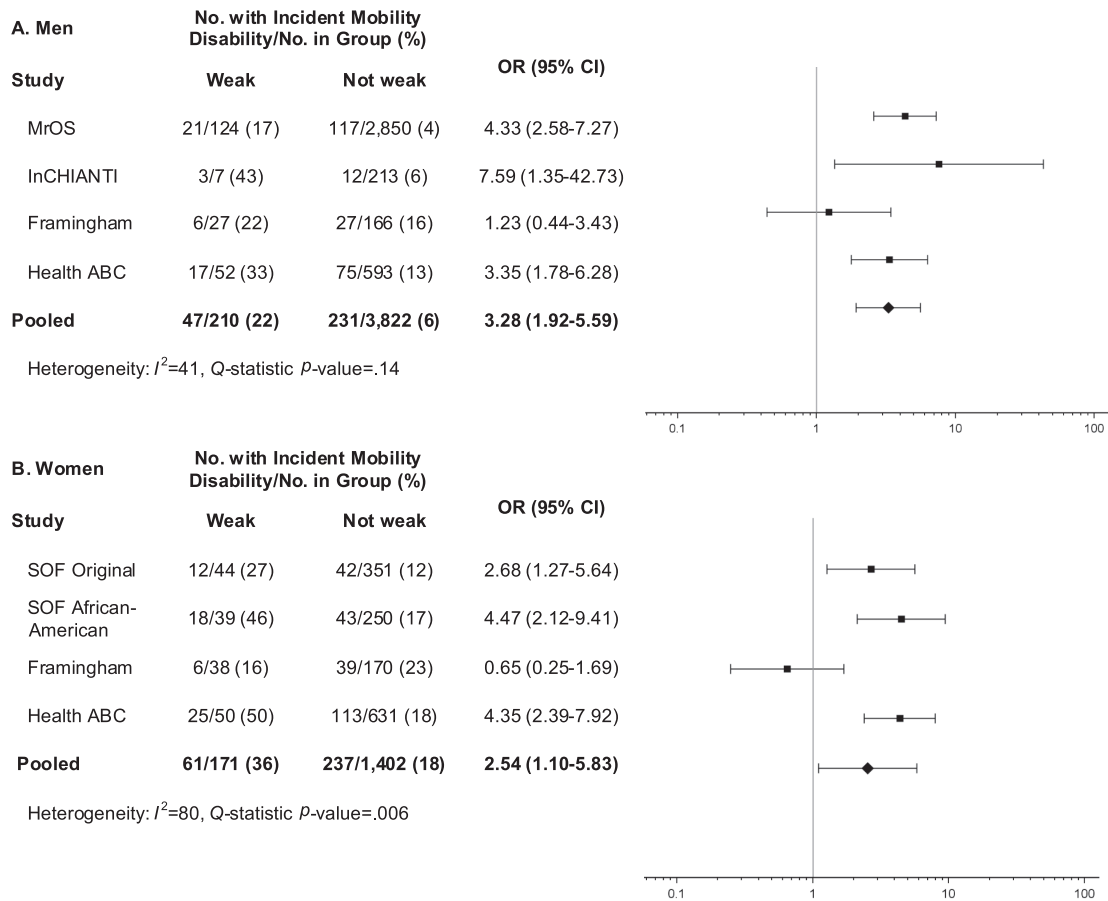Heterogeneity: I^2=80, Q-statistic P-value=.006

Figure 2. Age-adjusted odds ratios (OR) for incident mobility impairment (gait speed ≤ 0.8 m/s) after approximately 3 years of follow-up for proposed low grip strength-to-BMI ratio criteria (weak$_{BMI}$) among men (**A**) and women (**B**) in the FNIH Sarcopenia Project.

weak with low lean mass for the weak + ALM combination (Supplementary Figure 9), and those who were weak with normal lean mass for the weak + ALM$_{BMI}$ combination (Supplementary Figures 10).

DISCUSSION

Our results suggest that our criteria for low-absolute grip strength (weak) and low BMI-standardized grip strength (weak$_{BMI}$) both strongly predict incident mobility impairment after 3 years among nonimpaired older men and women, although in women there was evidence of heterogeneity among cohorts for the association with weak$_{BMI}$. Low BMI-standardized ALM (ALM$_{BMI}$) was not as strongly associated with incident mobility as weakness, but it did significantly predict incident mobility impairment. When we explored whether the likelihood for mobility impairment varied across groups defined by combinations of our weakness and low lean mass criteria, there was no clear performance difference among the different combinations among the men. Yet among women, the weak + ALM$_{BMI}$ combination was the only one for which there was no evidence of heterogeneity among cohorts in the women. Based on our overall findings, we recommend weak and ALM$_{BMI}$

as potential criteria for clinically relevant weakness and low lean mass, respectively, among older men and women.

Those classified as weak had significantly greater odds of mobility impairment compared to those who were not weak, yet among the weak, the odds were similar for those with and without low lean mass. This finding suggests that among those without mobility problems, weakness is likely the key to identifying individuals at risk for future mobility impairment. Our results are consistent with the literature in that muscle strength is a stronger predictor of mobility problems than lean mass (5,24,25). The observed higher risk for mobility impairment in the group that was weak but had normal lean mass also highlights the important contributions of nonmass factors for muscle function, such as inter- and intramuscular fat infiltration (26,27), excitation-contraction coupling (28), and functions of the central nervous system and neuromuscular junction (29). Yet while weakness is clearly clinically important, there may be a specific subgroup among the weak for whom low muscle mass is an important cause of their weakness. It is important for clinicians to be able to identify these patients because they are the most likely to benefit from therapies that increase muscle mass. Our cutpoints may be useful for finding these individuals who are
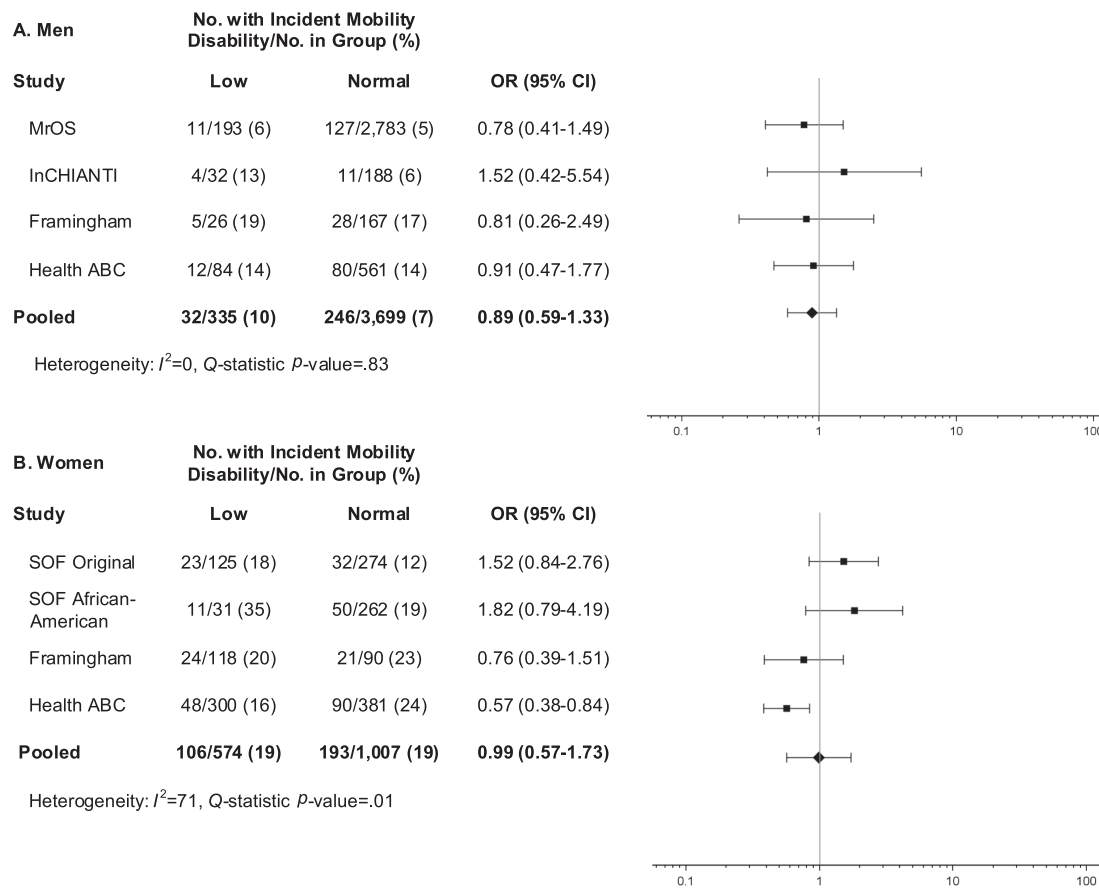
A. Men

Study	No. with Incident Mobility Disability/No. in Group (%)		OR (95% CI)
	Low	Normal	
MrOS	11/193 (6)	127/2,783 (5)	0.78 (0.41-1.49)
InCHIANTI	4/32 (13)	11/188 (6)	1.52 (0.42-5.54)
Framingham	5/26 (19)	28/167 (17)	0.81 (0.26-2.49)
Health ABC	12/84 (14)	80/561 (14)	0.91 (0.47-1.77)
Pooled	**32/335 (10)**	**246/3,699 (7)**	**0.89 (0.59-1.33)**

Heterogeneity: I^2=0, Q-statistic P-value=.83

B. Women

Study	No. with Incident Mobility Disability/No. in Group (%)		OR (95% CI)
	Low	Normal	
SOF Original	23/125 (18)	32/274 (12)	1.52 (0.84-2.76)
SOF African-American	11/31 (35)	50/262 (19)	1.82 (0.79-4.19)
Framingham	24/118 (20)	21/90 (23)	0.76 (0.39-1.51)
Health ABC	48/300 (16)	90/381 (24)	0.57 (0.38-0.84)
Pooled	**106/574 (19)**	**193/1,007 (19)**	**0.99 (0.57-1.73)**

Heterogeneity: I^2=71, Q-statistic P-value=.01

Figure 3. Age-adjusted odds ratios (OR) for incident mobility impairment (gait speed ≤ 0.8 m/s) after approximately 3 years of follow-up for proposed low appendicular lean mass criteria (ALM) among men (**A**) and women (**B**) in the FNIH Sarcopenia Project.

both weak and have low lean mass. The low numbers of individuals who were classified as having both weakness and low lean mass in our analyses (≤8% of women and ≤4% of men), was due, in part, to the fact that our studies were composed of generally healthy, nondisabled older adults. Future research is needed to determine whether improvements in lean mass among those who are weak translate into improved mobility.

Two recent prospective studies evaluated the validity of the European Working Group on Sarcopenia in Older People sarcopenia criteria (7) for predicting mortality in older adults: Arango-Lopera and colleagues (30) examined 345 residents of Mexico City, who were aged 70 years or older, over 3 years of follow-up, and Landi and colleagues (31) followed 364 men and women, who were aged 80–85 years and living in the Sirente area of Italy, for 7 years. In both cohorts, sarcopenia, defined by the European Working Group on Sarcopenia in Older People as slow gait speed or low grip strength combined with low lean mass, was associated with a greater than twofold higher risk for all-cause mortality. Because the European Working Group on Sarcopenia in Older People criteria combines both weakness and low lean mass in a single classification of sarcopenia, these prior studies could not determine which of these two elements may be most important for predicting mortality. Similar to incident mobility impairment, our all-cause mortality results support weakness

over low lean mass as the predominant predictor of clinical outcomes. Both of our weakness criteria predicted mortality among men, although in women only weakness by absolute grip strength was associated with mortality. Conversely, low lean mass was not a consistent predictor of mortality in either men or women. Combining weakness and low lean mass criteria resulted in no consistent patterns of associations for the four groups, though results suggested that those classified as weak had the highest mortality rates regardless of their lean mass status. Our mortality results were not fully consistent with the mobility impairment results perhaps because death is farther down the causal pathway from strength and lean mass than mobility impairment. Additional studies are needed to examine the relation of our criteria with other, more proximal relevant clinical geriatric outcomes (eg, self-reported disability, active vs disabled life expectancy, falls).

This study has some important limitations. First, mobility impairment analyses included only those who were not impaired at baseline. Thus, further investigation of the ability of our criteria to predict relevant clinical outcomes within more impaired populations is needed. Nevertheless, our criteria may identify subgroups of older adults that may be targeted for prevention of mobility problems. Second, results may have been influenced by differences among the pooled cohorts, including the varying follow-up times for gait speed assessments.
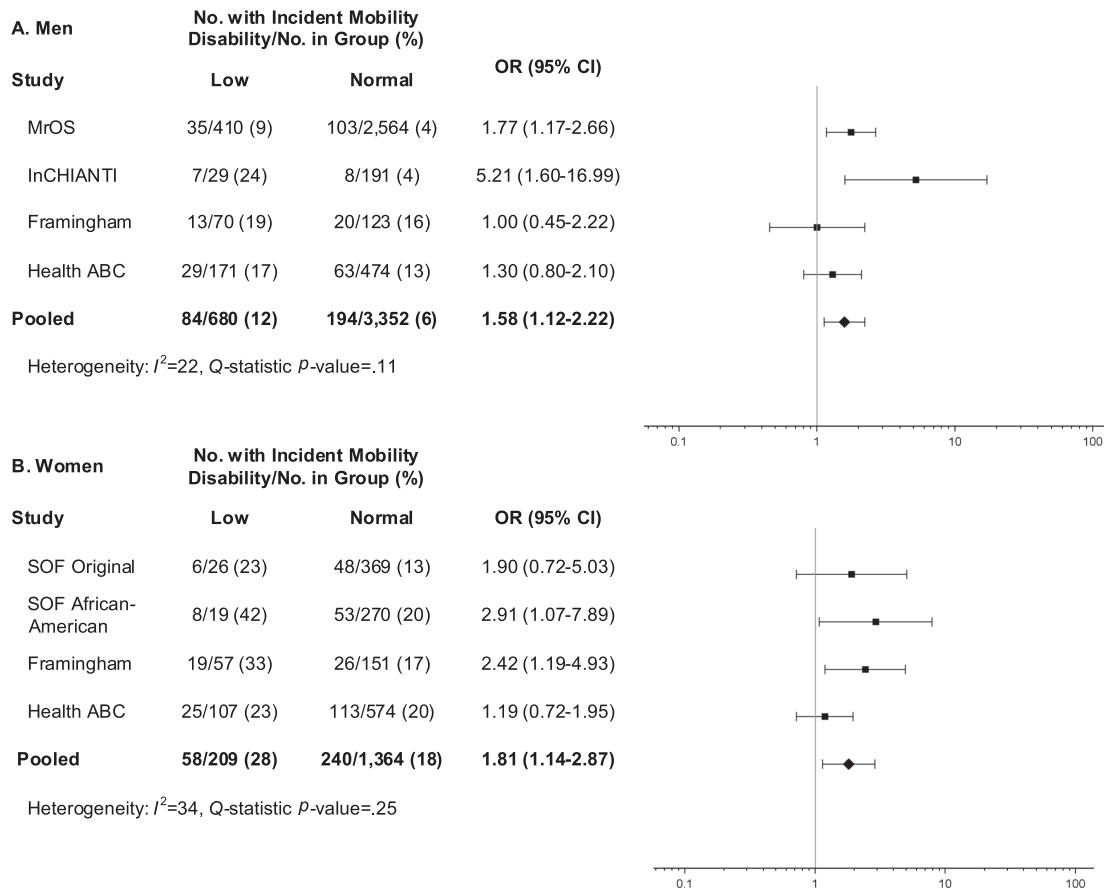
Figure 4. Age-adjusted odds ratios (OR) for incident mobility impairment (gait speed ≤ 0.8 m/s) after approximately 3 years of follow-up for proposed low appendicular lean mass-to-BMI ratio criteria (ALM$_{BMI}$) among men (**A**) and women (**B**) in the FNIH Sarcopenia Project.

In our meta-analyses, however, we did assess the heterogeneity across cohorts for associations of weakness and low lean mass criteria with mobility impairment and mortality, and we selected our recommended criteria only from among those without statistically significant evidence for heterogeneity. Third, over 26,000 individuals were included in the Sarcopenia Project, yet only 6,280 were included in the current analysis, limiting generalizability. Fourth, it is important to note that there are many other factors apart from muscle strength and mass that contribute to incident mobility impairment in older adults, which we did not account for in our analyses. In particular, several co-morbid conditions can influence the amount of strength required to ambulate (32). Nevertheless, in this initial phase of the Sarcopenia Project, our goal was to establish the predictive validity of our criteria for the general population of community-dwelling older adults. Future work should assess the performance of these preliminary criteria within relevant disease states as well as other specific populations (eg, institutionalized older adults, racial/ethnic groups). Finally, the methods used to derive our cut-points for weakness and low lean mass do not provide estimates of precision nor do they evaluate any underlying biologic relation among strength, lean mass, and mobility (10,11). Thus, our proposed criteria should be interpreted as preliminary recommendations.

Our study has several strengths. This is the largest endeavor to date to develop data-driven criteria for clinically relevant weakness and low lean mass. Our analyses included a large number of men and women from six diverse, community-based cohorts with information on objective measures of lean mass, strength, and mobility, as well as longitudinal information on incident mobility impairment and mortality, two clinically important aging outcomes. We analyzed pooled, individual-level data, which has advantages over aggregating results from individual studies, including assessment of individual-level missing data, standardized statistical analysis, and consistent adjustment for confounders (33).

Conclusion

Among older adults without mobility impairment, our criteria for clinically relevant weakness and low lean mass predict incident mobility impairment over 3 years of follow-up. Our analyses suggest that grip strength (<26 kg in men and <16 kg in women) and ALM standardized to BMI (<0.789 in men and <0.512 in women) are preliminary candidate criteria for weakness and low lean mass, respectively. These cut-points must be evaluated in additional studies to

determine whether they identify the groups of older adults with mobility problems that are likely to benefit from interventions designed to maintain or improve mobility.

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