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Research Article

Application of Selected Muscle Strength and Body Mass Cut Points for the Diagnosis of Sarcopenia in Men and Women With or at Risk for HIV Infection

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Abstract

Background: Persons with HIV may experience greater mobility limitations than uninfected populations. Accurate tools are needed to identify persons at greatest risk of decline. We evaluated the performance of novel muscle weakness metrics (grip, grip/body mass index [BMI], grip/weight, grip/total body fat, grip/arm lean mass) and association with slowness and falls in older persons with or at risk for HIV infection as part of the work of the Sarcopenia Definitions and Outcomes Consortium (SDOC).

Methods: We assessed the prevalence of sarcopenia among 398 men (200 HIV+, 198 HIV–) from the Multicenter AIDS Cohort Study and 247 women (162 HIV+, 85 HIV–) from the Women's Interagency HIV Study using previously validated muscle weakness metrics discriminative of slowness. Sensitivity and specificity were used to compare new muscle weakness and slowness criteria to previously proposed sarcopenia definitions.

Results: The prevalence of muscle weakness ranged from 16% to 66% among men and 0% to 47% among women. Grip/BMI was associated with slowness among men with HIV only. Grip/BMI had low sensitivity (25%–30%) with moderate to high specificity (68%–89%) for discriminating of slowness; all proposed metrics had poor performance in the discrimination of slowness (area under the curve [AUC] < 0.62)

or fall status (AUC < 0.56). The combination of muscle weakness and slowness was not significantly associated with falls ($p \geq .36$), with a low sensitivity in identifying those sustaining one or more falls (sensitivity ≤ 16%).

Discussion: Clinical utility of new sarcopenia metrics for identification of slowness or falls in men and women with or at risk for HIV is limited, given their low sensitivity.

Keywords: Falls, Gait speed, Muscle, Weakness

With the widespread availability of potent antiretroviral therapy (ART), morbidity and mortality has decreased markedly among persons with HIV (PWH) and survival now approaches that of the general population (1). However, compared to uninfected, demographically similar controls without HIV, PWH with suppressed, treated HIV have a higher burden of aging-related comorbidities and appear to experience a greater burden of, and earlier onset of, geriatric syndromes including frailty, osteoporotic fractures, and physical and cognitive impairment (2–4). As a result, it has been speculated that HIV may represent an accelerated aging phenotype (5).

One manifestation of an "accelerated aging" phenotype in PWH may be the accelerated loss of muscle mass and function, a cardinal indicator of risk of mobility disability in older persons. We have previously shown that, compared to uninfected populations at risk for HIV infection, those aging with HIV have a greater decline in grip strength and gait speed, with a more pronounced decline beginning between ages 55–60 years. These functional impairments and frailty may be the consequence of low muscle mass (6) or poor muscle quality (7). Indeed, loss of lean mass (an overestimate of muscle quantity) and increased fatty infiltration within skeletal muscle (a measure of muscle quality) are also greater among PWH compared to populations without HIV (7,8). Furthermore, impairments in physical function and frailty, even among middle-aged PWH, have been linked to important clinical outcomes including falls, disability, and mortality (9,10). The underlying mechanisms are likely multifaceted and may include inflammation, chronic immune activation, ART-specific or HIV-associated mitochondrial dysfunction, and effects of HIV-related metabolic dysfunction leading to proteolysis (11–13).

The best measures for identifying PWH in the clinical setting that are at greatest risk for poor outcomes, such as slow gait and falls, are currently unknown. Given the skeletal muscle abnormalities observed in PWH, tools are needed to identify those at greatest risk for impaired physical function, enabling targeted prevention and treatment strategies. One such metric may be identifying those with sarcopenia, the loss of muscle mass and muscle quality that is strongly associated with physical function, frailty, and disability with aging (14). "Sarcopenia" definitions historically relied on assessment of lean mass, generally by use of dual-energy X-ray absorptiometry (DXA) (15–18). More recent definitions have included measures of both lean mass and muscle function (19,20). As described in this volume of the Journal, the Sarcopenia Definitions and Outcomes Consortium (SDOC) used pooled analyses of epidemiologic cohorts of community-dwelling older adults to develop and assess clinically relevant cut points for muscle weakness and lean mass to identify those with slowness, and then assessed the application of a combined sarcopenia metric of muscle weakness and slowness to clinical outcomes (21,22). In the work described in this manuscript, we applied the SDOC proposed metrics derived from those analyses to two well-characterized cohorts of men and women with or at risk for HIV infection. We assessed the sensitivity and specificity of the muscle weakness metrics to identify slowness and falls to determine whether measures validated in an older, HIV-uninfected a population would perform similarly in a population with HIV that is chronologically younger but biologically experiencing similar geriatric outcomes. We then compared the putative sarcopenia metrics of both muscle weakness and slowness to those previously proposed by the Foundation of the National Institutes of Health (FNIH) Sarcopenia Project (23) and the European Working Group on Sarcopenia in Older People (EWGSOP) (24).

Method

Participants

The current analysis used data collected in the Multicenter AIDS Cohort Study (MACS) Bone Strength Substudy (BOSS) and the Women's Interagency HIV Study (WIHS) Musculoskeletal Substudy (MSK). The MACS is an ongoing, prospective cohort study of men who have sex with men, established in 1984, with enrollment at four U.S. sites: Los Angeles, CA; Pittsburgh, PA; Baltimore, MD/Washington, DC, and Chicago, IL. The WIHS is a prospective cohort study of women who initially enrolled in 1994–1995 from six U.S. sites: Bronx/Manhattan, NY; Brooklyn, NY; Chicago, IL; Washington, DC; San Francisco, CA; and Los Angeles, CA, with additional enrollment in 2001–2002 and 2011–2012. In 2014–2015, the WIHS closed its Los Angeles site and added four additional U.S. sites: Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS. In both the MACS and WIHS, participants attend semiannual visits, which include an interviewer-administered questionnaire, physical examination, and collection of laboratory specimens.

BOSS enrolled men with HIV on ART and men without HIV (ages 50–69) from the four MACS sites between 2012 and 2015. Exclusion criteria included a history of osteoporosis medication use, weight >300 pounds, and a plasma HIV-1 RNA level ≥200 copies/mL. MSK enrolled women with and without HIV (≤65 years) from three WIHS sites (San Francisco, Bronx, and Chicago). Exclusion criteria included weight >264 pounds, height >6 feet, pregnant or breast-feeding within the past 6 months, type I diabetes, use of corticosteroids, use of exogenous hormones including growth hormone and hormonal contraceptives in the past 12 months, and drugs used to treat osteoporosis. Both substudies were specifically designed to understand the contribution of chronic HIV and ART to fracture risk. The institutional review boards of participating institutions approved the study protocol. All participants provided written, informed consent.

Body Composition Assessment

Participants underwent whole-body DXA for ascertainment of total and appendicular lean mass (LM). In BOSS, scans were completed on a Lunar Prodigy (GE Medical Systems, Madison, WI) with Encore 2002 software at the Pittsburgh site and Hologic 4500A machines with QDA4500A software version 9.03 (Hologic Inc., Waltham, MA) at the other sites. Scans were read centrally at Tufts

Body Composition Analysis Center (Boston, MA). In MSK, scans were completed on Lunar Prodigy (GE Medical Systems) at all three sites. Scans were read centrally at the Image Analysis Lab (New York, NY).

Physical Function and Fall Measures

Grip strength and walking speed were assessed during a semiannual cohort visit at or closest to the time of DXA scan using a common protocol (25). Grip strength was determined using the average of three measures in the dominant hand with a Jamar hydraulic handheld dynamometer (in contrast to the maximum grip strength in the SDOC metrics). Walking speed was defined by the faster of two measurements at a "normal, comfortable pace" over a 4-m course. Given the younger age and the low prevalence of slowness in the MSK and BOSS, a well-established threshold of 1.0 m/s (26) was taken to define slowness, rather than the threshold of 0.8 m/s used to define slowness in the older cohorts in other SDOC analyses. A fall was defined as an event, including a slip or trip, in which a participant lost their balance and landed on the floor or ground or lower level, or hit an object like a table or chair. MACS participants were asked to report each fall in real-time (within 24 hours) for two years. WIHS participants reported whether a fall had occurred in the prior 6-month period.

Putative Sarcopenia Risk Measurements

In the SDOC, classification and regression tree analyses were used to determine the variables and cut points for muscle weakness that could best discriminate those with and without slowness (22). The leading risk markers selected by this methodology were: grip strength divided by body mass index (grip/BMI; men <1.05 and women <0.79), maximal grip strength (men <35.5 kg, women <20.0 kg), grip strength divided by total body fat (TBF; men <1.66, women <0.65), grip strength divided by arm lean mass (arm LM; men <6.08, women <3.26), and grip strength divided by weight (men <0.45, women <0.34). Maximum grip strength and grip/BMI were chosen as the preferred muscle weakness metrics; muscle weakness in combination with gait speed <0.8 m/s was the ultimate SDOC recommendation for risk stratification. The new SDOC recommendations were contrasted to existing definitions, including FNIH (23) and EWGSOP (24). In the FNIH, sarcopenia was defined as grip <26.0 kg (men) and <16.0 kg (women), or grip/BMI <1.00 (men) and <0.56 (women). In EWGSOP, sarcopenia was defined as both ALM/ht^2 of <7.23 (men) and 5.67 kg/m^2 (women) and either low grip strength (<30 and <20 kg for men and women, respectively) or slowness (<0.8 m/s).

Statistics

Statistical analyses were performed using R version 3.5.3 and stratified by sex and HIV serostatus. We applied the cut points in the grip strength variables to our population to describe the proportion below a given cut point (ie, those who exhibit muscle weakness), and assessed the sensitivity and sensitivity in detecting slowness or falls. We used logistic regression to assess the association between the muscle weakness metrics and slowness. We stratified the number of falls into three categories: no fall, one fall, and two or more falls, and then used ordinal logistic regression to assess the association. In their ability to predict slowness or falls, the proposed muscle weakness metrics were compared to published definitions of sarcopenia using receiver operator characteristic (ROC) curves and associated condordance (*c*) statistics.

Results

We included 398 men (200 with and 198 without HIV) and 247 women (162 with and 85 without HIV) in this analysis. As shown in Table 1, the average age among men with and without HIV was approximately 60 years while women were nearly 10 years younger than the men. Additional characteristics are summarized in Table 1.

Physical Function, Falls, and Body Composition

Although grip strength was similar by HIV serostatus, a greater proportion of both men and women with HIV met criteria for slowness (<1.0 m/s) compared to men or women without HIV. Arm LM was considerably higher among men compared to women, and total body fat higher among women than men, with few differences by HIV serostatus (Table 1). Among men, 43% of men with and 43% of men without HIV had sustained at least one fall compared to 25%–27% of women with or without HIV.

The Prevalence of Muscle Weakness Based on SDOC Cut Points

The prevalence of muscle weakness ranged from 16% to 66% among men and 0% to 47% among women (Table 2). Men with HIV generally had a similar or lower prevalence of muscle weakness compared to men without HIV, with the exception of metrics correcting for arm LM. Women with HIV had similar prevalence of muscle weakness as women without HIV on most measures except for metrics correcting for BMI or weight (grip/BMI and grip/weight).

Muscle Weakness as a Determinant of Slowness

We examined associations between muscle weakness and the presence of slowness (<1.0 m/s), stratified by sex and HIV serostatus, Table 3. Grip/BMI was associated with greater odds of slowness in men with HIV (OR 3.35 [95% CI 1.54, 7.36]); grip/TBF (OR 2.58 [95% CI 1.18 5.93]) and grip/weight (OR 2.12 [95% CI 1.11, 4.15]) were significantly associated with a greater odds of slowness among men without HIV. Among women, none of the proposed putative sarcopenia risk markers were significantly associated with slowness.

Sensitivity and specificity estimates for discriminating slowness using the muscle weakness and low mass markers are shown in Table 4. Among both men and women, grip/BMI had low sensitivity (25%–31%) with moderate to high specificity (68%–89%). In contrast, grip strength had moderate sensitivity (41%–57%) and specificity (54%–57%) among men, and very low sensitivity (6%–10%) but high specificity (91%–92%) among women. Among both men and women, all the proposed metrics had poor discrimination of slowness with area under the curve (AUC) ≤ 0.62, and consistently poorer performance among PWH compared to controls without HIV.

Comparisons of SDOC Definitions to Other Definitions of Sarcopenia

The co-occurrence of low grip strength and slow gait (<1.0 m/s) was associated with a similar prevalence of sarcopenia compared to existing sarcopenia metrics (Table 2), in this population of men and women with or without HIV. When the lower gait speed cut point of 0.8 m/s was applied, the sarcopenia prevalence fell to ≤2% among men and women.

Table 1. Baseline Characteristics of Men and Women With and at Risk for HIV

	Men		Women	
	HIV (*N* = 200)	Uninfected (*N* = 198)	HIV (*N* = 162)	Uninfected (*N* = 85)
Characteristics				
Age, years (*SD*)	59 ± 5	60 ± 5	50 ± 5	49 ± 6
Male	200 (100)	198 (100)	—	—
Female	—	—	162 (100)	85 (100)
Black	54 (27)	34 (17)	104 (64)	61 (72)
White	144 (72)	162 (82)	27 (17)	11 (13)
Hispanic ethnicity	9 (4)	7 (4)	35 (22)	20 (24)
Current smoker	36 (18)	32 (16)	63 (39)	16 (19)
Diabetes mellitus	32 (18)	21* (12)	115 (71)	60 (71)
Hypertension	124 (63)	98 (50)	90 (56)	46 (54)
BMI, kg/m^2	25.9 ± 4.2	26.6 ± 4.7	29.5 ± 6	30.7 ± 6.1
HIV-1 RNA < 50 copies/mL	179 (90)	—	103 (65)	—
CD4 + T cells < 500 cells/μL	48 (24)	—	62 (39)	—
Sarcopenia measures				
Grip (absolute strength, kg)	36.2 ± 8.5	36.4 ± 7.8	27.4 ± 7.8	28.3 ± 5.7
Grip/BMI	1.43 ± 0.38	1.41 ± 0.38	0.97 ± 0.32	0.95 ± 0.29
Grip/TBF	1.81 ± 0.77	1.74 ± 0.79	1.06 ± 0.55	1.00 ± 0.50
Grip/arm LM	5.50 ± 1.28	5.71 ± 1.21	6.11 ± 1.38	6.09 ± 1.48
Grip/weight	0.45 ± 0.12	0.45 ± 0.12	0.36 ± 0.12	0.36 ± 0.10
Outcomes				
Gait speed, m/s	1.07 ± 0.17	1.13 ± 0.21	1.01 ± 0.21	1.02 ± 0.21
<1.0 m/s, %	59 (30)	53 (27)	77 (48)	40 (47)
<0.8 m/s, %	11 (6)	2 (1)	23 (14)	9 (11)
No fall	113 (57)	113 (57)	106* (75)	55* (73)
1 fall	45 (23)	50 (25)	19* (13)	8* (11)
Multiple falls (2+)	41 (21)	35 (18)	16* (11)	12* (16)

Notes: Data presented as mean (*SD*) or proportion (%). BMI = body mass index; LM = lean mass; TBF = total body fat.
*Data not available on all participants.

Muscle Weakness, Sarcopenia, or Both as Determinants of Fall Status

Among both men and women, low grip, slow gait, and the SDOC sarcopenia metric of both low grip and slow gait were not significantly associated with the odds of falls ($p \geq .36$); Table 5. Overall the combination of low grip and slow gait had low sensitivity but high specificity for discriminating the number of falls among both men (sensitivity 16% and 12% and specificity 87% and 86% for 1 or ≥2 falls, respectively) and women (sensitivity 4% and specificity 96% for both 1 or ≥2 falls).

Discussion

In this report, we applied new muscle weakness cut points developed within a pooled data analysis of over 18,000 older adults (22) to two large, well-characterized cohorts of men and women with or at risk for HIV infection, a population at increased risk for mobility limitations. In the pooled data analysis, grip strength with and without adjustments for body size and composition, not DXA-measured lean mass, consistently discriminated older adults with slowness (22), and both low grip strength and low usual gait speed independently predicted multiple other outcomes including falls, mobility limitations, hip fractures, and mortality (27). Application of these gender-specific absolute grip, grip/weight, or grip/BMI cut points in other previously published clinical cohorts with mobility limitations led to a categorization of >50% of adults having muscle weakness (28), a proportion far greater than prevalence estimates using previously recommended criteria for diagnosing sarcopenia (range: 6%–32%). When applied to men and women with or at risk for HIV in the BOSS and MSK cohorts, a group approximately 10–20 years younger than other evaluated cohorts, less than one third of adults were categorized with muscle weakness by grip/BMI. In contrast, absolute grip identified nearly 50% of men but <10% of women as having muscle weakness, regardless of HIV serostatus. SDOC absolute grip or grip/BMI thresholds had moderate to high specificity but low sensitivity (particularly among women) in determining the presence or absence of slowness. Although the SDOC sarcopenia metric utilizing both muscle weakness and slowness with a <1 m/s cut point resulted in a similar proportion of sarcopenic individuals compared to existing metrics (Table 2), the SDOC slowness metric of <0.8 m/s identified ≤2% of individuals with sarcopenia, suggesting limited utility of the identification of sarcopenia among adults younger than those in the cohort for which this was established, and among individuals with or at risk for HIV. Finally, the SDOC metric of muscle weakness had low sensitivity (≤16%) and high specificity (≥86%) for discrimination of fall status.

The poor performance (ie, the low sensitivity, specificity, and AUC) of muscle weakness measures in discriminating slow gait or falls could be explained by the low prevalence of muscle weakness among our participants. This was true regarding some of the measures of interest, especially among the women: weak absolute grip strength was present in only 8% of the women in our cohort compared to 30% of older women in the SDOC cohorts. In contrast, the men in our cohort had a 10% *greater* prevalence of weak grip compared to older adults in the pooled data analysis (21). Thus,

Table 2. Prevalence of Muscle Weakness and Existing Sarcopenia Metrics, Count and Percent

	Men			Women		
	Cut point	HIV	Uninfected	Cut point	HIV	Uninfected
Muscle weakness metric						
Grip/BMI	<1.05	32/198 (16%)	35/195 (18%)	<0.79	40/150 (27%)	24/75 (32%)
Grip	<35.5 kg	88/199 (44%)	92/197 (47%)	<20.0 kg	14/153 (9%)	5/76 (7%)
Grip/TBF	<1.66	70/152 (46%)	77/147 (52%)	<0.65	29/115 (25%)	12/53 (23%)
Grip/arm lean mass	<6.08	101/152 (66%)	94/147 (64%)	<3.26	1/115 (1%)	1/53 (2%)
Grip/weight	<0.45	92/198 (46%)	103/196 (53%)	<0.34	65/150 (43%)	35/75 (47%)
Existing sarcopenia metric						
SDOC Grip + gait (<1.0 m/s)		24/200 (12%)	30/198 (15%)		7/156 (4%)	2/81 (2%)
SDOC Grip + gait (<0.8 m/s)		3/200 (2%)	1/198 (1%)		4/160 (2%)	1/83 (1%)
FNIH Grip/BMI	<1.00	27/198 (14%)	25/195 (13%)	<0.56	11/150 (7%)	5/75 (7%)
FNIH Grip	<26.0	22/199 (11%)	15/197 (8%)	<16.0	5/153 (3%)	1/76 (1%)
EWGSOP	—	23/187 (12%)	13/178 (7%)	—	5/149 (3%)	2/74 (3%)

Note: BMI = body mass index; EWGSOP = European Working Group on Sarcopenia in Older People (inclusive of walking speed, grip strength, skeletal muscle index); FNIH = Foundation of the National Institutes of Health Sarcopenia Project; SDOC = Sarcopenia Definitions and Outcomes Consortium, where weak grip was defined as <35.5 kg for a man and <20.0 kg for a woman + slow gait of either <1.0 m/s or 0.8 m/s; TBF, total body fat.

Table 3. Prediction of Slowness by Muscle Weakness Metrics[†]

	Men		Women	
Muscle weakness metric	HIV	Uninfected	HIV	Uninfected
Grip/BMI	3.35 (1.54, 7.36)**	1.77 (0.80, 3.81)	1.64 (0.79, 3.43)	0.95 (0.36, 2.52)
Grip	0.81 (0.44, 1.50)	1.73 (0.92, 3.28)	1.17 (0.38, 3.59)	0.73 (0.09, 4.63)
Grip/TBF	1.34 (0.67, 2.68)	2.58 (1.18, 5.93)*	1.88 (0.80, 4.49)	0.24 (0.05, 0.92)
Grip/arm lean mass	0.85 (0.41, 1.76)	1.97 (0.87, 4.80)	—	—
Grip/weight	1.28 (0.70, 2.37)	2.12 (1.11, 4.15)*	1.40 (0.73, 2.70)	1.15 (0.46, 2.88)

Notes: BMI = body mass index; TBF = total body fat; grip/arm lean mass excluded in women due to small numbers.

[†]Odds ratios and 95% confidence intervals shown. Odds ratios quantify the estimated multiplicative increase in odds of slowness for those individuals below the relevant weakness threshold (Table 2) relative to those above said threshold.

*$p < .05$; **$p < 0.01$.

regardless of prevalence of muscle weakness, these cut points do not appear to perform well (in terms of sensitivity and specificity) among men or women with or at risk for HIV infection. Notably, our outcome measures of slow gait and falls were not uncommon in this cohort of individuals primarily between 50 and 60 years of age: nearly 50% of women had a gait speed of <1.0 m/s and 43% of men reported one or more falls, regardless of HIV serostatus.

A second explanation for poor discrimination of slowness using muscle weakness measures in our population could be the time course to develop clinically relevant muscle weakness or slowness. Grip strength impairments may occur at a later age while more subtle changes in mobility measures involving the lower extremities (eg, chair stand time, walking speed) may be detectable at an earlier age. In our prior work within the MACS Cohort, subtle decline in walking speed began at approximately age 40 while grip strength decline was not apparent until after age 55 (2,29). Similarly, in a cohort of PWH aged 45–65, 18% had slowness (a score of ≤3 on Short Physical Performance Battery [SPPB], corresponding to ≤1.2 m/s) and 10% had weak grip (by Fried's frailty criteria), while 33% had impaired chair stand time (a score of ≤3 of SPPB) (30). Chair stand impairment was also apparent in the ALIVE Cohort of people using injection drugs and living with or without HIV infection (median age 51): 42% of participants had slow chair stand time (a score of ≤3 on SPPB) compared to 28% with slowness (score of ≤3 on SPPB) (31). Although these cut points for gait and grip differ from the SDOC definitions, the prevalence of lower extremity impairments are apparent. As discussed by Manini and colleagues (22), lower extremity strength impairments may be a more sensitive and specific determinant of slowness, especially in younger populations or those with less baseline impairment.

Although the risk of falls is closely intertwined with physical function, upper body strength and gait speed may not influence fall risk as much as balance or lower extremity strength. Indeed, in the BOSS cohort, we have previously shown that balance confidence and chair rise time but not other markers of physical function were associated with subsequent risk of falls (32). Similar, among women with HIV, frailty was associated with recurrent but not single falls, while gait and grip were not associated with fall risk (33); among men and women with HIV (mean age 52), frailty was associated with a greater odds of single or recurrent falls, while weak grip and slow gait were associated only with recurrent falls. Lastly, among middle-aged PWH, frailty or impairment on the SPPB tandem stand component were more strongly linked to fall risk than weak grip or slow gait (34).

Many factors besides strength influence gait speed and falls among PWH and may diminish the sensitivity of muscle weakness metrics within these cohorts. Another possible reason for the poor test performance may relate to prior exposure to mitochondrially toxic antiretroviral therapies. The profile of upper and lower extremity muscles differ both in fiber type, mitochondrial function

Table 4. Sensitivity and Specificity of Putative and Existing Sarcopenia Metrics for Slow Gait[†]

		HIV		Uninfected	
	Cut point	Sensitivity	Specificity	Sensitivity	Specificity
Muscle weakness metrics					
Men					
Grip/BMI	<1.05	17/59 (29%)	124/139 (89%)	13/53 (25%)	120/142 (85%)
Grip	<35.5	24/59 (41%)	76/140 (54%)	30/53 (57%)	82/144 (57%)
Grip/TBF	<1.66	24/47 (51%)	59/105 (56%)	25/36 (69%)	59/111 (53%)
Grip/arm lean mass	<6.08	30/47 (64%)	34/105 (32%)	27/36 (75%)	44/111 (40%)
Grip/weight	<0.45	30/59 (51%)	77/139 (55%)	35/53 (66%)	74/142 (52%)
Women					
Grip/BMI	<0.79	22/69 (32%)	63/81 (78%)	11/35 (31%)	27/40 (68%)
Grip	<20.0	7/71 (10%)	75/82 (91%)	2/36 (6%)	37/40 (92%)
Grip/TBF	<0.65	17/54 (31%)	49/61 (80%)	3/27 (11%)	17/26 (65%)
Grip/arm lean mass	<3.26	1/54 (2%)	61/61 (100%)	0/27 (0%)	25/26 (96%)
Grip/weight	<0.34	33/69 (48%)	49/81 (60%)	17/35 (49%)	22/40 (55%)
Putative and existing sarcopenia metrics					
Men					
FNIH Grip/BMI	<1.00	15/59 (25%)	127/139 (91%)	11/53 (21%)	128/142 (90%)
FNIH Grip	<26.0	10/59 (17%)	128/140 (91%)	6/53 (11%)	135/144 (94%)
EWGSOP	—	8/54 (15%)	118/133 (89%)	4/45 (9%)	124/133 (93%)
Women					
FNIH Grip/BMI	<0.56	6/69 (9%)	76/81 (94%)	2/35 (6%)	37/40 (92%)
FNIH Grip	<16.0	4/71 (6%)	81/82 (99%)	0/36 (0%)	39/40 (98%)
EWGSOP	—	3/68 (4%)	79/81 (98%)	2/35 (6%)	39/39 (100%)

Notes: BMI = body mass index; EWGSOP = European Working Group on Sarcopenia in Older People (inclusive of walking speed, grip strength, skeletal muscle index); FNIH = Foundation of the National Institutes of Health Sarcopenia Project; SDOC = Sarcopenia Definitions and Outcomes Consortium, where weak grip was defined as <35.5 kg for a man and <20.0 kg for a woman + slow gait of either <1.0 m/s or 0.8 m/s; TBF = total body fat.

[†]Sensitivity: count of individuals exhibiting muscle weakness among those with slowness (gait speed < 1.0 m/s) shown, with percentages. Specificity: count of individuals *not* exhibiting muscle weakness among those *not* exhibiting slowness (gait speed > 1.0 m/s) shown, with percentages.

and oxidative capabilities (35). While merely speculative, the impact of mitochondrial toxicity could have a greater impact on measures of sarcopenia in our population, which may have been reflected in differing effects on strength. This may be particularly true among the men from the BOSS study, who were diagnosed with HIV over a longer duration of time and had more extensive exposure to older, more toxic antiretroviral regimens. Cognitive impairment and neuropathy (secondary to HIV, exposure to older ART, or mitochondrial toxicity) are both common and have been associated with impairment in gait speed and falls among older adults with HIV (36–38). As a result of neuropathy or other etiologies (eg, polypharmacy, substance abuse), balance impairments may also have a more significant impact on slowness and falls than muscle weakness among older PWH (34,36). The substantial sedentary time observed among PWH has also been linked to both falls and slowness among older PWH (34,39–41).

Another notable finding was the striking sex difference that body weight adjustment had on the prevalence of muscle weakness. While muscle weakness by absolute grip strength was present in <10% of women, the prevalence of weakness tripled after accounting for body mass; this impact of body weight adjustment on grip strength was attenuated among the men. The implications of body weight among older adults with HIV may signal pathology resulting from ART effects (including lipoatrophy or lipohypertrophy), lifestyle, wasting, hormonal changes associated with aging, or substance abuse. Furthermore, the impact of interventions targeting body weight can have a contradictory impact on function. Among patients with massive weight loss following bariatric surgery, improvements in lower extremity function (chair stand time, gait) were substantial while grip strength declined (42). Similarly, in a physical activity intervention to improve physical function (the LIFE Trial), significant improvements were seen in chair stand time, accounting for 39% of the reduction in disability, while grip strength did not improve (43). As discussed above, lower extremity strength impairments may be a stronger predictor among those with less baseline impairment, although grip strength is more frequently used to assess strength in the research setting due to convenience and a strong association with mortality. Together these results demonstrate the impact of weight on strength and suggest that lower extremity strength measures (such as chair stand time) may be a stronger predictor of slowness in some populations, and may be more amenable to interventions than grip strength.

Key differences between the BOSS and MSK studies and the SDOC pooled data analysis cohorts should be emphasized: BOSS and MSK participants were 10–20 years younger than the other SDOC cohorts, with the greatest age differences among women. As such, the frequency of slowness (walking speed <0.8 m/s) was low and we instead used a higher but still clinically meaningful cut point of <1.0 m/s to define slowness. While we do not have data regarding substance use across all cohorts included in the SDOC analysis, in general, rates of smoking, alcohol use, and illicit substance use tend to be high among MACS and WIHS participants, which may influence the prevalence of and mechanisms underlying muscle weakness and slowness. Similarly, other socioeconomic differences between the MACS or WIHS participants and the SDOC cohorts may account for differing prevalence, including physical activity, physically demanding occupations, race and ethnicity. Small numbers in some of the categories limited the ability to detect associations with

Table 5. Relation Between Muscle Weakness, Slowness, and Falls†

	OR (95% CI)	*p* Value
Men		
Low grip	0.93 (0.63, 1.36)	.70
Slow gait (<1 m/s)	1.16 (0.76, 1.76)	.50
Low grip + slow gait	1.00 (0.57, 1.72)	.99
Women		
Low grip	1.57 (0.52, 4.23)	.39
Slow gait (<1 m/s)	1.34 (0.72, 2.51)	.36
Low grip + slow gait	0.94 (0.14, 4.09)	.94

Note: †Odds ratios derived from ordinal logistic regression estimate the multiplicative increase in odds of a greater number of falls relative to a lesser number of falls attending the presence of weakness, slowness or the combination of the two, relative to the presence of neither. Neither muscle weakness, slowness, nor the combination is consistently associated with fall risk in men or women.

the outcome measures. For example, only one woman with and one without HIV met the cut point criteria for grip/arm lean mass. Lastly, our analyses were cross-sectional and we did not evaluate whether grip strength was predictive of developing incident slowness or falls in those with or at risk of HIV.

In summary, among adults with or at risk for HIV, none of the putative sarcopenia risk markers consistently predicted slowness, and the combination metric of muscle weakness and slowness together had very low sensitivity for falls. In this population, muscle weakness may not be as closely related to slowness as in other populations, or slowness may precede muscle weakness, limiting the discriminative capabilities of grip strength. Furthermore, many other factors likely contribute to slowness or falls; thus, the discriminative ability of these cut points in people with or at risk of HIV may be limited. Adults aging with HIV continue to experience increasing risk of mobility limitations. Better screening tools are needed to identify those that may benefit most from interventions, and should perhaps incorporate additional measures of lower extremity strength (eg, chair stand time). For now, we can continue to recommend low cost and high-yield interventions such as increased physical activity that can reduce the risk of mobility impairment in older adults, regardless of HIV serostatus or sarcopenia (44).

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Conflict of Interest

K.M.E. has served as a consultant to Gilead Sciences and ViiV Pharmaceuticals, and has a grant pending from Gilead Sciences, outside of this project. J.M. has consulting and/or advisory board memberships with: Novartis, Pluristem, and UCB. P.C. serves as a consultant for Bioage, and had grants to her institution from Abbott and Nestle for work outside of this project. S.B. has received research grants from NIA, NICHD, NINR, FNIH, AbbVie, Alivegen, Transition Therapeutics, and MIB; these investigator-initiated grants are managed by Brigham and Women's Hospital. S.B. has also received consulting fees from AbbVie and OPKO and has equity interest in FPT, LLC. R.A.F. reports grants from National Institutes of Health (National Institute on Aging), during the conduct of the study; grants, personal fees, and other from Axcella Health, stock options from Inside Tracker, grants and personal fees from Biophytis, grants and personal fees from Astellas, personal fees from Cytokinetics, personal fees from Amazentis, grants and personal fees from Nestlé, personal fees from Glaxo Smith Kline, outside the submitted work. F.J.P. has received honoraria from Gilead Sciences, Janssen, ViiV, and Merck. J.E.L. has received grant support from Gilead Sciences and has consulted for Gilead Sciences and Merck, outside of this project. A.S. has received grant support from Gilead Sciences, HIV AGE Positively, outside of this project. P.C.T. has received grant support from Merck, outside of this project. T.G.T., H.Z., R.C.-A., T.M., L.K., K.M.W., M.T.Y., and T.T.B. report no conflict of interest.

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