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Authors

Langston, Marvin
Cawthon, Peggy
Lu, Kaiwei
et al.

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Associations of Lower Extremity Muscle Strength, Area, and Specific Force With Lower Urinary Tract Symptoms in Older Men: The Baltimore Longitudinal Study of Aging

Marvin E. Langston, MPH, PhD,[1] Peggy M. Cawthon, PhD, MPH,[2,3] Kaiwei Lu, MS,[4] Rebecca Scherzer, PhD,[4,5] John C. Newman, MD, PhD,[6] Kenneth Covinsky, MD,[4,5] Luigi Ferrucci, MD, PhD,[7] Eleanor M. Simonsick, PhD,[7] and Scott R. Bauer, MD, ScM[5,8]

[1]Department of Epidemiology and Population Health, Stanford University School of Medicine, Palo Alto, California, USA.
[2]Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA.
[3]Research Institute, California Pacific Medical Center, San Francisco, California, USA.
[4]Department of Medicine, University of California, San Francisco, California, USA.
[5]San Francisco VA Medical Center, Division of General Internal Medicine, San Francisco, California, USA.
[6]Buck Institute for Research on Aging, Novato, California, USA.
[7]National Institute on Aging, Intramural Research Program, Baltimore, Maryland, USA.
[8]Department of Medicine, Urology, Epidemiology and Biostatistics, University of California, San Francisco, California, USA.

*Address correspondence to: Scott R. Bauer, MD, ScM. E-mail: Scott.Bauer@ucsf.edu

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Abstract

Background: Lower urinary tract symptoms (LUTS) in older men are associated with an increased risk of mobility limitations. Lower extremity muscle quality may represent a novel shared mechanism of both LUTS and mobility limitations.

Methods: We evaluated associations of thigh skeletal muscle measures (strength, area, and specific force) with total LUTS severity (American Urologic Association Symptom Index; AUASI) and voiding and storage subscores among 352 men aged ≥60 years enrolled in the Baltimore Longitudinal Study of Aging. Thigh muscle strength (Nm) was defined as maximum concentric 30°/s knee extensor torque, area (cm^2), and specific force (Nm/cm^2) defined as strength/area. Associations with AUASI score were estimated using multivariable linear regression and linear mixed models.

Results: Mean thigh muscle strength at baseline was 139.7Nm. In cross-sectional multivariable models, each 39Nm increment in thigh muscle strength and $0.28Nm/cm^2$ increment in specific force was associated with −1.17 point (95% CI: −1.93 to −.41) and −0.95 point (95% CI: −1.63 to −0.27) lower AUASI score, respectively. Similar associations were observed for voiding and storage subscores, although somewhat attenuated. In longitudinal analyses, baseline muscle measures were not associated with annual change in AUASI, and current changes in muscle measures and AUASI were unrelated.

Conclusions: Cross-sectionally, higher thigh muscle strength and specific force were associated with decreased LUTS severity in older men. However, we did not observe concurrent worsening LUTS severity with declining thigh muscle strength, area, or specific force in longitudinal analyses.

Keywords: Aging, Mobility limitation, Prostatic diseases, Sarcopenia, Urinary bladder diseases

Lower urinary tract symptoms (LUTS) affect more than half of older men and LUTS severity is associated with risk of mobility impairment, functional decline, and falls (1–3). Male LUTS are often attributed to enlargement of the prostate gland with bladder outlet obstruction due to benign prostatic hyperplasia (BPH). However, LUTS in older men is more likely multifactorial with causality linked to various chronic conditions and nonurologic sources. For example, frailty has been associated with greater LUTS severity and BPH treatment failure in various clinical and population-based studies as well as clinical trials in older men (4–8).

Aging induces changes in body composition, including an increase in visceral adipose tissue and a decrease in skeletal muscle quality and function (9,10). Sarcopenia, an age-related decline in muscle mass and strength, is a major determinant of functional decline, loss of independence, frailty, and mobility limitations in older adults (11). Skeletal muscle measures including lower extremity muscle strength, area, and specific force have been strongly associated with declines in gait speed, functional limitations, and physical disability in older adults and key indicators of age-related muscle changes (12–14).

Although skeletal muscle measures and LUTS are both related to frailty and mobility limitations, their temporal

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association and causality remain unknown. Understanding this association is important due to the high prevalence of both conditions in older men, current male LUTS clinical guidelines that do not include screening for or co-managing geriatric syndromes, and a need to identify non-BPH-related drivers of LUTS in older men. Furthermore, the relationship between skeletal muscle and LUTS in older men remains poorly understood due to the use of inaccurate or surrogate muscle measures, lack of longitudinal data, and lack of standardized LUTS outcome measures. In contrast, the Baltimore Longitudinal Study of Aging (BLSA) provides an excellent opportunity to explore this relationship with repeated assessments of LUTS, muscle parameters, and other age-related phenotypic risk factors for LUTS.

To address ongoing gaps in knowledge, we evaluated (a) the cross-sectional relationship of lower extremity muscle strength, area, and specific force with LUTS severity, (b) the longitudinal relationship of baseline lower extremity muscle strength, area, and specific force with annual change in LUTS severity, and (c) the relationship of change in lower extremity muscle strength, area, and specific force with concurrent change in LUTS severity in a cohort of older, community-dwelling men who participated in the BLSA. We hypothesized that lower muscle strength, area, and specific force in the lower extremity at baseline as well as decreases during follow-up would be associated with worse LUTS severity.

Method

Participants

The BLSA, a long-running and continuously enrolled cohort since 1958 with a protocol updated in 2003 was used for this analysis. Although the full study design and detailed inclusion/exclusion criteria has been previously described (15,16), BLSA was initially designed to assess normative aging in community-dwelling adults aged 20 years and older. All participants had to be free of major chronic conditions upon enrollment with additional exclusion criteria relevant to this analysis such as a body mass index of ≥40, inability to perform daily self-care without assistance, inability to walk for at least 400 meters independently without assistance, and muscle-skeletal conditions due to diseases. Participants are recruited from the greater Baltimore community and actively followed with study visits occurring every 1–4 years depending on accumulated age (<60 every 4 years, 60–79 every 2 years, ≥80 every year) and examined at the National Institute on Aging Intramural Research Program Clinical Research Unit in Baltimore, Maryland. BLSA was approved by the Institutional Review Boards of participating institutions, and all participants provided signed informed consent.

Men who participated in BLSA aged 65–97 and underwent a physical examination, health history assessment, functional testing, cognitive testing, and imaging between February, 2011 and March, 2020, when Biodex dynamometer data was collected, were eligible for the current study. Measures collected at the index study visit (analytic baseline) and up to 7 subsequent study visits in this eligibility window were considered for the cross-sectional and longitudinal analyses, respectively. In the cross-sectional analysis, we excluded men with a self-reported history of stroke or Parkinson's disease who could have LUTS associated with neurogenic bladder which represents a distinct etiology (n = 42), and those missing lower extremity muscle measurements or LUTS assessments (n = 304) at baseline. In the longitudinal analyses, we additionally excluded those with prevalent moderate-to-severe LUTS at baseline and those without repeated muscle measures or LUTS assessments. Our final analytic samples included 352 and 188 older men for cross-sectional and longitudinal analyses, respectively.

Primary Exposure of Interest: Lower Extremity Muscle Measures

Three measures of thigh skeletal muscle (strength, area, and specific force) were used as our primary exposures. Maximum thigh muscle strength (Nm) was defined as the highest value of torque from either leg in up to 3 consecutive measures of concentric knee extensor strength at an angular velocity of 0.52 rad/s (30°/seconds) (17). This peak torque was measured using a Biodex Multi-Joint System-PRO (Biodex Medical System, Advantage Software V.4X, Inc., Shirley, NY) dynamometer (18). Thigh muscle area (cm^2) was estimated using 10-mm computed tomography (CT) images captured at the mid-femur using a CT scanner (Somatom Sensation 10; Siemens, Malvern, PA) and quantified (Geanie software, version 2.1; BonAlyse, Jyvaskyla, Finland). These methods allowed for the separation of distinct tissue types (eg, muscle and fat) according to density thresholds of 35 mg/mm to separate fat from muscle tissue and 180 mg/mm to separate the muscle from bone. CT images were checked for mistakes in the identification and contouring of tissue types. Macroscopically detectable intramuscular fat was not included in the estimation of the total thigh muscle area. The specific force of thigh skeletal muscle was defined as muscle strength divided by area (Nm/cm^2).

Primary Outcome of Interest: LUTS Severity

Lower urinary tract symptoms (LUTS) severity was estimated by the American Urological Association Symptom Index (AUASI) score via structured interviews at baseline and follow-up visits (19). The AUASI includes individual items assessing urinary frequency, urgency, intermittency, straining, weak urinary stream, incomplete bladder emptying, and nocturia ranging from 0 (no symptoms) to 5 (highest symptom burden) for each item. Total AUASI scores range from 0 to 35. These scores are clinically used to define LUTS categories: 0–7 (none/mild), 8–19 (moderate), and 20–35 (severe) with a minimum detectable difference of 3 points (20). Secondary outcomes included calculations of AUASI subscores separately for storage symptoms (urgency, frequency, and nocturia) and voiding symptoms (incomplete emptying, intermittency, weak stream, and straining) (21).

Other Measures

We included as potential covariates factors that might influence thigh muscle measures and LUTS severity. Age, race/ethnicity, and marital status were assessed at baseline via structured interviews while height, weight, calculated body mass index (BMI), waist circumference, physical activity (minutes of any walking and vigorous activity every week), and comorbid conditions were updated at every study visit (15). Study participants recorded a history of cardiovascular disease, diabetes mellitus, pulmonary disease, prostate cancer, and treatment for LUTS, including self-reported surgery for benign prostatic enlargement and LUTS-related medication use (eg, α-Antagonist and 5α-Reductase inhibitors).

Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (22).

Data Analysis

For this study, we assessed cross-sectional and longitudinal associations of thigh muscle measures (strength, area, and specific force) and LUTS severity based on AUASI score (total, storage subscore, and voiding subscore). Initially, we compared the distribution of potential covariates across tertiles of thigh muscle measures using Chi-square tests for categorical variables and ANOVA or Kruskal–Wallis tests for continuous variables. To examine the cross-sectional association of baseline thigh muscle measures and baseline LUTS severity, we used linear regression. For longitudinal analyses, we excluded men with moderate-to-severe LUTS (AUASI ≥ 8) at baseline in order to assess incident LUTS and men without repeated muscle measures or LUTS assessments (total longitudinal analytic sample $n = 188$). Men excluded due to no follow-up measurements ($n = 75$) had higher a higher body mass index than those in the analytic sample. We estimated the association of baseline thigh muscle measures with annual change in LUTS severity using linear mixed-effect models. Additionally, we examined the within-person changes in muscle measures with concurrent changes in AUASI score using linear mixed-effect models. All linear mixed models included both random intercepts and slopes while using an unstructured variance–covariance matrix. Muscle measures were modeled at baseline and time-varying variables were adjusted for baseline (measurement at each visit minus measurement at baseline) to separate between and within-person coefficient estimates. Muscle measures were modeled as both continuous and categorical exposures (cross-sectional analysis only) using tertiles. We sequentially adjusted our models for potential confounders at baseline using known risk factors and present 4 models: (a) crude, (b) adjusted for sociodemographic factors (age and race) and biometric measures (height, weight, and height × weight), (c) additionally adjusted for physical activity, (d) additionally adjusted for comorbid conditions (cardiovascular disease, diabetes mellitus, and pulmonary disease). Given univariate associations for baseline CES-D score and smoking status in our population, Model 4 was additionally adjusted for these factors. Because this additional adjustment did not affect point estimates, we present Model 4 as the fully adjusted model. In sensitivity analyses, we additionally accounted for LUTS treatment (eg, BPH surgery or LUTS medication use) as a baseline or time-varying covariate (longitudinal analysis only).

In order to evaluate the effect measure modification of age (above vs below the median), prostate-specific antigen as a surrogate of prostate volume (above vs below 1.6 ng/mL-the median value in this population), and reported presence of any comorbid conditions, we added an interaction term between muscle measures and the potential modifier to the fully adjusted model and assessed the p value for interaction. Additional sensitivity analyses were performed because some muscle measures were missing due to the inability of participants to use a BioDex machine. We created a multiple imputation model using 20 imputations with our entire initially eligible study population ($n = 656$) and included model covariates and factors associated with muscle measures or missingness. We also reran our analyses among men without a self-reported history of prostate cancer and considered thigh muscle area divided by height as an alternative definition. A p value < .05 was considered statistically significant. All analyses were performed using STATA version 15.1 (StataCorp LLC, College Station, TX) and R version 4.1.2, http://www.r-project.org.

Results

Characteristics of the 352 community-dwelling older men from the BLSA who comprise the cross-sectional analytic study population at baseline are shown in Table 1. Men in the highest tertile of thigh muscle-specific force were on average taller, more likely to be current or former smokers, exhibited better measures of cognitive function, engaged in more minutes of vigorous physical activity per week, and reported fewer depressive symptoms than men in the lower 2 tertiles. Those missing muscle measures were on average older and more likely to have a history of smoking (data not shown). At baseline, 53% of men presented with none/mild LUTS, 42% with moderate LUTS, and 5% with severe LUTS.

Cross-sectional associations of baseline muscle measures and AUASI in this cohort are shown in Table 2. Mean thigh muscle strength was 147.4 ± 41.4, 131.4 ± 36.3, and 125.9 ± 33.9 Nm among men with none/mild, moderate, and severe LUTS, respectively. Each 1 standard deviation (*SD*) increment in thigh muscle strength was associated with 1.17 points lower baseline AUASI score (95% CI: −1.93 to −0.41) in fully adjusted models (Model 4). Compared to crude models, the association was slightly attenuated, yet remained statistically significant across each successive model adding confounders representing demographic and biometric (Model 2), physical activity (Model 3), and comorbid conditions (Model 4). In terms of muscle-specific force, each 1 *SD* increment was associated with 0.95 points lower baseline AUASI score (95% CI: −1.63 to −0.27) in fully adjusted models with little variation in estimates across models. Thigh muscle strength and specific force were also associated with 2.29 (95% CI: −4.13 to −0.45) and 2.01 (95% CI: −3.61 to −0.42) points lower baseline AUASI scores when comparing the highest to lowest tertile of each respective muscle measure. Thigh muscle area was not associated with baseline AUASI score. The patterns of association with the AUASI voiding and storage subscores were similar for thigh muscle strength and specific force, yet muscle area was not associated with either subscore at baseline (Supplementary Table 1).

Characteristics of the 188 men included in the longitudinal analyses are included in Supplementary Table 2. Men in the highest tertile of thigh muscle-specific force were on average taller, engaged in more minutes of vigorous physical activity per week, and exhibited slightly lower baseline AUASI scores. Annual change estimates for AUASI and associations with baseline muscle measures are shown in Table 3. The mean follow-up time was 3.9 (*SD* 2.7) years. In crude models, each baseline muscle measure showed a very small positive association with annual change in AUASI. These associations were statistically significant for muscle area and force, but not strength. However, after multivariable adjustment, these baseline muscle measures were no longer significantly associated with annual change in AUASI. In time-updated models (Table 4), within-person change in muscle measures was not significantly associated with concurrent change in AUASI. When coefficients for baseline and within-person change in muscle measures were examined separately, each 1 *SD* between-person difference in baseline muscle strength was associated

Table 1. Summary of Baseline Characteristics Among Older Men in BLSA, by Tertiles of Thigh Muscle-Specific Force

Variable	Overall (*N* = 352)	Thigh muscle-specific force (Nm/cm²)		
		Tertile 1: 0.37–1.04 (*N* = 118)	Tertile 2: 1.05–1.25 (*N* = 117)	Tertile 3: 1.25–2.28 (*N* = 117)
AUASI, mean ± *SD*	7.2 ± 5.3	8.2 ± 5.5	7.1 ± 5.4	6.3 ± 5.0
Demographics				
Age, years, mean ± *SD*	74.3 ± 8.18	75.2 ± 8.4	74.2 ± 8.1	73.4 ± 8.0
Married status, *n* (%)	266 (75.8)	84 (71.2)	87 (75.0)	95 (81.2)
Race, *n* (%)				
White	259 (74.0)	80 (68.4)	86 (74.1)	93 (79.5)
Black or African American	71 (20.3)	32 (27.4)	21 (18.1)	18 (15.4)
Asian	14 (4.0)	4 (3.4)	7 (6.0)	3 (2.6)
Multi-race	6 (1.7)	1 (0.9)	2 (1.7)	3 (2.6)
Hispanic Ethnicity, *n* (%)	10 (2.8)	4 (3.4)	4 (3.4)	2 (1.7)
Biometrics, mean ± *SD*				
Height, cm	174.3 ± 6.8	172.0 ± 6.3	173.7 ± 7.1	177.1 ± 6.0
Weight, kg	84.5 ± 14.9	83.3 ± 15.2	85.3 ± 15.5	84.8 ± 13.9
BMI, kg/m²	27.8 ± 4.3	28.1 ± 4.3	28.2 ± 4.3	27.0 ± 4.1
Waist circumference, cm	95.0 ± 11.5	95.4 ± 10.5	95.6 ± 13.3	93.9 ± 10.7
Questionnaires, mean ± **SD**				
SF-12 MCS	55.8 ± 5.1	55.5 ± 5.8	56.0 ± 4.8	55.8 ± 4.8
CES-D, median (IQR)	3.0 (6.0)	5.0 (7.0)	3.0 (5.0)	3.0 (4.0)
California verbal learning test	46.2 ± 12.6	43.5 ± 12.3	46.2 ± 12.1	49.0 ± 12.9
Trail-making test Part A	34.0 ± 13.0	35.9 ± 15.4	33.3 ± 10.6	32.9 ± 12.4
Trail-making test Part B	86.2 ± 39.0	94.4 ± 47.9	82.9 ± 33.2	81.5 ± 33.3
Vigorous activity, minutes/wk, median (IQR)	35.0 (137.5)	16.3 (93.8)	40.0 (105.0)	60.0 (160.0)
Health behaviors				
Smoking, *n* (%)				
Never	213 (60.5)	76 (64.4)	80 (68.4)	57 (48.7)
Quit 10+ years ago	130 (36.9)	38 (32.2)	34 (29.1)	58 (49.6)
Quit < 10 years ago	3 (0.9)	1 (0.8)	1 (0.9)	1 (0.9)
Current	6 (1.7)	3 (2.5)	2 (1.7)	1 (0.9)
Drinking, *n* (%)				
No drink	59 (16.8)	25 (21.2)	13 (11.2)	21 (17.9)
<1 drink/wk	60 (17.1)	18 (15.3)	26 (22.4)	16 (13.7)
1-14 drinks/wk	211 (60.1)	72 (61.0)	67 (57.8)	72 (61.5)
>14 drinks/wk	21 (6.0)	3 (2.5)	10 (8.6)	8 (6.8)
Health conditions, *n* (%)				
Angina	19 (5.4)	9 (7.6)	5 (4.3)	5 (4.3)
Heart failure	7 (2.0)	3 (2.5)	2 (1.7)	2 (1.7)
Hypertension	182 (51.9)	61 (52.1)	60 (51.3)	61 (52.1)
High cholesterol	233 (67.1)	77 (65.3)	80 (70.8)	76 (65.5)
Coronary artery disease	36 (10.3)	13 (11.0)	8 (6.8)	15 (12.9)
Peripheral artery disease	4 (1.1)	0 (0.0)	2 (1.7)	2 (1.7)
Diabetes mellitus	87 (24.7)	28 (23.7)	29 (24.8)	30 (25.6)
Prostate cancer	53 (15.1)	23 (19.5)	18 (15.5)	12 (10.3)
Prostate-specific antigen, median (IQR)	1.6 (2.4)	1.8 (2.0)	1.6 (3.2)	1.6 (2.1)
LUTS treatments, *n* (%)				
Anti-cholinergic	10 (2.8)	5 (4.2)	4 (3.4)	1 (0.9)
α-Antagonist	45 (12.8)	15 (12.7)	10 (8.5)	20 (17.1)
5α-Reductase	33 (9.4)	7 (5.9)	8 (6.8)	18 (15.4)
Other	29 (8.2)	12 (10.2)	9 (7.7)	8 (6.8)
Self-reported BPH Surgery	51 (23.9)	16 (21.1)	21 (30.4)	14 (20.6)
Diuretic medication use	40 (11.4)	14 (11.9)	15 (12.8)	11 (9.4)

Table 1. Continued

Variable	Overall ($N = 352$)	Thigh muscle-specific force (Nm/cm^2)		
		Tertile 1: 0.37–1.04 ($N = 118$)	Tertile 2: 1.05–1.25 ($N = 117$)	Tertile 3: 1.25–2.28 ($N = 117$)
Participant study visits, mean ± *SD*	4.2 ± 2.1	4.3 ± 2.0	4.0 ± 2.0	4.4 ± 2.2

Note: AUASI = American Urological association symptom index overall score; BMI = Body Mass Index; BPH = benign prostatic hyperplasia; CES-D = center for epidemiologic studies depression scale; IQR = interquartile range; wk = week; LUTS = lower urinary tract symptoms; SF-12 MC = medical outcomes study short-form.

Table 2. Cross-sectional Associations of Lower Extremity Muscle Measures with LUTS Severity Among Older Men in BLSA

	Model 1-unadjusted[*]	Model 2[†]	Model 3[‡]	Model 4-fully adjusted[§]
	Effect estimate (95% CI)	Effect estimate (95% CI)	Effect estimate (95% CI)	Effect estimate (95% CI)
Thigh muscle strength[‖], per 40 Nm	−1.30 (−1.91, −0.70)	−1.14 (−1.90, −0.37)	−1.16 (−1.93, −0.39)	−1.17 (−1.93, −0.41)
Tertile 1 (42.8–121.3 Nm)	Ref.	Ref.	Ref.	Ref.
Tertile 2 (122.2–154.1 Nm)	−1.41 (−2.89, 0.08)	−1.23 (−2.82, 0.35)	−1.25 (−2.85, 0.35)	−1.27 (−2.86, 0.33)
Tertile 3 (154.3–257.9 Nm)	−2.64 (−4.13, −1.16)	−2.03 (−3.83, −0.23)	−2.19 (−4.02, −0.37)	−2.29 (−4.13, −0.45)
Thigh muscle area[‖], per 24 cm^2	−0.90 (−1.51, −0.29)	−0.59 (−1.51, 0.33)	−0.57 (−1.49, 0.35)	−0.44 (−1.37, 0.50)
Tertile 1 (60.8–110.7 cm^2)	Ref.	Ref.	Ref.	Ref.
Tertile 2 (110.8–129.7 cm^2)	−2.07 (−3.56, −0.58)	−1.49 (−3.10, 0.13)	−1.35 (−2.99, 0.28)	−1.31 (−2.95, 0.33)
Tertile 3 (129.8–202.7 cm^2)	−1.75 (−3.24, −0.26)	−0.47 (−2.50, 1.56)	−0.37 (−2.42, 1.68)	−0.07 (−2.14, 2.00)
Thigh muscle-specific force[‖], per 0.28 Nm/cm^2	−0.88 (−1.49, −0.26)	−0.83 (−1.49, −0.16)	−0.86 (−1.54, −0.19)	−0.95 (−1.63, −0.27)
Tertile 1 (0.37–1.04 Nm/cm^2)	Ref.	Ref.	Ref.	Ref.
Tertile 2 (1.05–1.24 Nm/cm^2)	−1.06 (−2.55, 0.44)	−0.97 (−2.46, 0.53)	−1.00 (−2.51, 0.51)	−0.89 (−2.41, 0.62)
Tertile 3 (1.25–2.28 Nm/cm^2)	−2.10 (−3.59, −0.61)	−1.80 (−3.38, −0.23)	−1.88 (−3.47, −0.29)	−2.01 (−3.61, −0.42)

Notes: CI = confidence interval; LUTS = lower urinary tract symptoms.
[*]Effect estimates calculated using linear regression models.
[†]Model 1 + adjusted for sociodemographic factors (age and race) and biometric measures (height, weight, and height × weight).
[‡]Model 2 + additionally adjusted for physical activity.
[§]Model 3 + additionally adjusted for comorbid conditions (cardiovascular disease, diabetes mellitus, and pulmonary disease).
[‖]Muscle measures modeled continuously.

with a 0.40 lower AUASI (95% CI: −0.86 to −0.06). Similarly, each 1 *SD* between-person difference in baseline muscle-specific force was associated with a 0.48 lower AUASI (95% CI: −0.92 to −0.05). When AUASI storage and voiding subscores were examined separately, no significant associations were detected for any of the muscle measures and storage or voiding LUTS changes in any of the longitudinal models (Supplementary Tables 3 and 4).

We did not observe effect modification by age, prostate-specific antigen level, or reported history of any comorbid condition for the association between muscle measures and LUTS severity (data not shown). In sensitivity analyses, excluding men with a history of prostate cancer, using thigh muscle area divided by height as the primary exposure, inclusion of all initially eligible men using multiple imputation models, and adjusting for LUTS treatment did not materially impact observed associations (Supplementary Tables 5–7).

Discussion

In this study of community-dwelling and relatively healthy older men, thigh muscle strength and specific force, but not thigh muscle area, were inversely associated with LUTS severity (total, storage, and voiding) in cross-sectional models. However, we did not observe a significant association between baseline lower extremity muscle measures with annual change in LUTS or changes in lower extremity muscle measures with concurrent changes in LUTS severity among older men in longitudinal analyses.

Despite the clear importance of properly functioning lower extremity skeletal muscles for preserving mobility (14,23,24), we are not aware of any prior studies evaluating the relationship between lower extremity strength, area, or specific force and LUTS in older men. However, previous analyses by our group and others have demonstrated both cross-sectional and longitudinal relationships between phenotypic frailty, of which poor lower extremity muscle function is a key component, and LUTS severity in older men. In the Osteoporotic Fractures in Men (MrOS) study, our group previously found the prevalence of severe LUTS to be 2.5 times higher among men with phenotypic frailty than in robust men (25) and that older men without LUTS at baseline who developed phenotypic frailty were also more likely to report greater LUTS severity during follow-up (8). Older men seeking subspecialty treatment for LUTS are also more likely to have slow Timed-Up-And-Go-Test times than those with other urologic conditions (7). Other groups have reported similar associations with phenotypic frailty among older Korean and Japanese men (5,26). Lower total lean body mass on dual-energy X-ray

Table 3. Associations of Baseline Lower Extremity Muscle Measures with Annual Change in LUTS Severity Among Older Men in BLSA

Thigh Muscle Measure	Model 1-Unadjusted*	Model 2†	Model 3‡	Model 4-fully adjusted§
	Annual change estimate (95% CI)	Annual change estimate (95% CI)	Annual change estimate (95% CI)	Annual change estimate (95% CI)
Strength, per 40 Nm	0.04 (–0.06, 0.14)	0.04 (–0.06, 0.15)	0.03 (–0.07, 0.13)	0.02 (–0.08, 0.13)
Area, per 23 cm^2	0.07 (0.04, 0.09)	0.10 (–0.05, 0.24)	0.08 (–0.06, 0.23)	0.08 (–0.06, 0.23)
Specific Force, per 0.29 Nm/cm^2	0.08 (0.06, 0.11)	–0.01 (–0.14, 0.13)	–0.01 (–0.15, 0.12)	–0.02 (–0.15, 0.12)

Notes: CI = Confidence Interval; LUTS = Lower Urinary Tract Symptoms.
*Annual change estimate for American Urological Association Symptom Index overall score calculated using linear mixed effects models.
†Model 1 + adjusted for sociodemographic factors (age and race) and biometric measures (height, weight, and height × weight).
‡Model 2 + additionally adjusted for physical activity.
§Model 3 + additionally adjusted for comorbid conditions (cardiovascular disease, diabetes mellitus, and pulmonary disease).

Table 4. Associations of Changes in Lower Extremity Muscle Measures with Concurrent Changes in LUTS Severity Among Older Men in BLSA

Parameter	Model 1-Unadjusted*	Model 2†	Model 3‡	Model 4-Fully Adjusted§
	Effect estimate (95% CI)	Effect estimate (95% CI)	Effect estimate (95% CI)	Effect estimate (95% CI)
Thigh muscle strength, per 40 Nm				
Baseline (between-person differences)	–0.28 (–0.57, 0.01)	–0.45 (–0.81, –0.10)	–0.43 (–0.79, –0.07)	–0.40 (–0.76, –0.05)
Time-updated (within-person change)	–0.37 (–0.83, 0.09)	0.38 (–0.19, 0.94)	0.37 (–0.19, 0.93)	0.38 (–0.17, 0.93)
Thigh muscle area, per 23 cm^2				
Baseline (between-person differences)	0.08 (–0.18, 0.34)	0.10 (–0.34, 0.53)	0.10 (–0.34, 0.53)	0.14 (–0.29, 0.58)
Time-updated (within-person change)	–0.54 (–1.45, 0.37)	–0.16 (–0.70, 0.37)	–0.17 (–0.70, 0.35)	–0.12 (–0.65, 0.40)
Thigh muscle-specific force, per 0.29 Nm/ cm^2				
Baseline (between-person differences)	–0.40 (–0.71, –0.10)	–0.46 (–0.78, –0.15)	–0.45 (–0.77, –0.13)	–0.44 (–0.76, –0.11)
Time-updated (within-person change)	–0.07 (–0.61, 0.47)	0.30 (–0.25, 0.85)	0.30 (–0.26, 0.85)	0.29 (–0.26, 0.85)

Notes: CI = confidence interval; LUTS = lower urinary tract symptoms.
*Effect estimates calculated using linear mixed effects models.
†Model 1 + adjusted for sociodemographic factors (age and race) and biometric measures (height, weight, and height × weight).
‡Model 2 + additionally adjusted for physical activity.
§Model 3 + additionally adjusted for comorbid conditions (cardiovascular disease, diabetes mellitus, and pulmonary disease).

absorptiometry, a surrogate of skeletal muscle mass, is also associated with LUTS among men in the National Health and Nutrition Examination Study (27). Given the lack of existing literature examining associations with lower extremity muscle measures, our novel study requires validation and replication, particularly in larger cohort studies with repeated muscle, lower extremity physical performance, and LUTS assessments.

Interpretation of our findings is somewhat complicated by the conflicting cross-sectional and longitudinal results. Overall, our findings suggest that older men with weaker lower extremity muscles are more likely to report greater LUTS severity. This relationship appears largely independent of age, body size, physical activity, and several of the most common diseases known to cause both LUTS and sarcopenia. Although we observed modest associations that did not reach the minimal detectable difference in the AUASI (3 points) (20), the mean differences did reach the threshold used to conclude a clinically meaningful difference in an Agency for Healthcare Research and Quality comparative effectiveness review of BPH medications (28). Furthermore, as lower extremity muscle strength (as well as muscle area and specific force) slowly declines with age, we did not observe a concurrent increase in LUTS severity. There are several possible explanations for the lack of longitudinal associations in our study. First, the mean change in lower extremity muscle strength, area, and specific force may have been too small and the follow-up period too short to observe modest concurrent changes in LUTS severity. Although some older men have remained enrolled in BLSA long enough to develop sarcopenia and concurrent LUTS over many years, this shared mechanism may require longer follow-up to detect longitudinal associations. Second, the potential contribution of age-related changes in lower extremity muscle to LUTS development may not be immediate and we did not have sufficient sample size to evaluate time lags or threshold effects. Last, the cross-sectional findings may be due to residual confounding by baseline differences between individuals which do not influence the longitudinal models because we focused on associations between within-person change in muscle and LUTS. To determine whether older men should be screened for frailty, sarcopenia, and mobility impairments during initial and subsequent LUTS evaluations, additional longitudinal studies with larger sample sizes, longer follow-up, and/or greater change in muscle and LUTS measures are needed to contextualize the suggestive cross-sectional findings in this study.

Regardless of whether muscle strength and specific force directly cause LUTS or share a common mechanism, there are important clinical and public health implications of this study. Although screening for falls and mobility limitations is widely recommended in all older adults (29), multiple barriers have led to the slow adoption of these guidelines (30,31). Older

men with LUTS have an increased risk of developing new mobility limitations and recurrent falls, independent of age and other comorbidities (1,3). Older men with greater LUTS severity are also more likely to be frail, sedentary, and, based on the novel findings of the current study, more likely to have weaker lower extremity muscles and lower thigh muscle-specific force, which are all major risk factors for mobility limitations and falls (23,24). Thus, older men with moderate-to-severe LUTS may represent a high-risk population to screen for frailty or sarcopenia and target interventions to prevent falls and major mobility disability, particularly when presenting for a LUTS-focused evaluation. One such intervention is physical activity, which was demonstrated in the Lifestyle Interventions and Independence for Elders trial to lower the risk of incident major mobility disability by 18% and persistent mobility disability by 28% in older adults at risk for disability (32). A recent Cochrane review based on 59 clinical trials also determined that exercise reduces the rate of falls by 23% among community-dwelling older adults (33). Although awaiting confirmatory studies to validate our findings and to determine the temporality and mechanism of observed associations and greater implementation of universal fall screening guidelines, we believe there is sufficient evidence to justify assessing older men with severe LUTS for contributors to frailty, falls, and mobility limitations, such as lower extremity weakness, in both primary care and urology clinics and intervening when appropriate to prevent irreversible loss of mobility and independence.

Although not supported by the results of our longitudinal analysis, in theory, regular physical activity could decrease LUTS severity through multiple integrated physiologic systems, including skeletal muscle, neuromuscular, immune, cardiovascular, and neurologic (34). A Cochrane review of clinical trials testing physical activity for LUTS due to bladder outlet obstruction attributable to BPH rated the level of evidence as "very low," indicating the need for additional high-quality randomized controlled trials (35). In this review, several studies examined the efficacy of targeted pelvic floor exercise but only 2 trials examined the effects of aerobic or resistance exercise. A 12-week clinical trial among 56 Korean men with suspected BPH found that those randomized to a supervised tai chi class intervention reported a clinically meaningful decrease in LUTS severity compared to watchful waiting (36). In another trial, 130 obese men with BPH were randomized to a weight reduction program, which included exercise, compared to weight reduction advice alone, but no effect on LUTS severity was observed (37). However, these trials had major limitations, including high drop-out, lack of appropriate control or blinding, and a multimodal intervention that did not cause expected changes in anthropometrics, body composition, or metabolic markers. Sedentary older men with severe and/or bothersome LUTS may be particularly motivated to increase their physical activity if it is shown to improve their urinary symptoms while simultaneously lowering their risk of falls and mobility limitation, which is currently being tested in the PRescription exercise for Older men with Urinary Disease (PROUD) pilot randomized clinical trial (38).

Strengths of this study include repeated measurements of well-characterized lower extremity muscle and LUTS assessments and significant representation of Black and African American men. We also acknowledge several limitations. First, our cohort of older adults was exceptionally healthy upon enrollment and needed to remain relatively healthy, cognitive, and mobile throughout follow-up to continue study assessments. Our results may not generalize to a less healthy population, although we would expect associations to be stronger in populations with greater heterogeneity in muscle strength and LUTS. Pelvic floor muscle measures were not captured by BLSA, therefore, we cannot assess the correlation between lower extremity muscle and pelvic floor muscle strength, area, or specific force. Muscle measures were assessed using a BioDex machine which led to missing data due to safety concerns, pain, or participant refusal. We developed a multiple imputation model to account for this missing data and our main findings were relatively unchanged when associations were examined with the imputed data. The sample size for longitudinal models was significantly smaller and therefore we were underpowered to detect small, but potentially biologically meaningful, associations. Finally, our findings must be thoughtfully interpreted given the limited prior literature, relatively short follow-up, and possible residual confounding.

In conclusion, we found that thigh muscle strength and specific force, but not thigh muscle area, are inversely associated with LUTS severity in older men. However, we did not observe concurrent worsening LUTS severity among older men with declining muscle strength, area, or specific force in longitudinal analyses. Although prospective studies with larger sample sizes are needed to confirm our cross-sectional findings, low thigh muscle strength, and specific force may reflect emerging sarcopenia, an unexplored mechanism of LUTS that could partially explain why older men with LUTS have an increased risk of mobility limitations and frailty. In the meantime, we believe that older men being evaluated for severe LUTS should be screened for frailty, falls, and mobility limitations, and modifiable risk factors for these geriatric outcomes should be promptly addressed.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None.

Author Contributions

M.L.: conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval of the version to be published; P.C.: conception and

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