

# UCSF

## UC San Francisco Previously Published Works

### Title

Appendicular Lean Mass, Grip Strength, and the Development of Knee Osteoarthritis and Knee Pain Among Older Adults

### Permalink

<https://escholarship.org/uc/item/54p3621c>

### Journal

ACR Open Rheumatology, 3(8)

### ISSN

2578-5745

### Authors

Andrews, James S  
Gold, Laura S  
Nevitt, Michael  
[et al.](#)

### Publication Date

2021-08-01

### DOI

10.1002/acr2.11302

Peer reviewed

# Appendicular Lean Mass, Grip Strength, and the Development of Knee Osteoarthritis and Knee Pain Among Older Adults

James S. Andrews,<sup>1</sup>  Laura S. Gold,<sup>1</sup> Michael Nevitt,<sup>2</sup> Patrick J. Heagerty,<sup>1</sup> and Peggy M. Cawthon<sup>3</sup>

**Objective.** The association of sarcopenia with development of knee osteoarthritis (OA) or knee pain in older adults is uncertain. We examined the relationship of grip strength and appendicular lean mass (ALM) with the likelihood of developing knee OA and knee pain in older adults in the Health ABC (Health, Aging, and Body Composition) Study.

**Methods.** ALM and grip strength were assessed at baseline by dual-energy x-ray absorptiometry and handheld dynamometry, respectively. Incident clinically diagnosed, symptomatic knee OA, defined as new participant report of physician-diagnosed knee OA and concurrent frequent knee pain, and incident frequent knee pain over 5 years of follow-up were examined. Separate regression analyses, stratified by sex, modeled associations of baseline ALM and grip strength with the likelihood of incident clinically diagnosed, symptomatic knee OA and incident knee pain over follow-up, adjusting for covariates.

**Results.** Among the 2779 subjects without OA at baseline, 95 men (6.9%) and 158 women (11.3%) developed clinically diagnosed, symptomatic knee OA, and, among the 2182 subjects without knee pain at baseline, 315 men (28.3%) and 385 women (36.1%) developed knee pain over follow-up. Among men only, each SD decrement of ALM was associated with decreasing likelihood of incident knee OA (odds ratio [OR] per SD decrement: 0.68; 95% confidence interval [CI]: 0.47-0.97), and each SD decrement of grip strength was associated with increasing likelihood of incident knee pain (OR per SD decrement: 1.20; 95% CI: 1.01-1.42).

**Conclusion.** In older men, ALM and grip strength may be associated with the development of knee OA and knee pain, respectively.

## INTRODUCTION

Knee osteoarthritis (OA) and knee pain are leading causes of impaired mobility and physical disability among older adults, with approximately 1 in 4 Americans over the age of 55 years reporting knee pain on most days in a month within the last year (1,2). Despite how common knee OA and knee pain are among older adults and their significant negative impact on these individuals' physical functioning, there are relatively few known risk factors for the development of knee OA and knee pain. These risk factors include obesity, joint trauma or altered

joint mechanics, female sex, and possibly race/ethnicity (1), of which only obesity and, in some cases, altered joint mechanics are potentially modifiable. The identification of novel, potentially modifiable risk factors for incident knee OA and knee pain among older adults could advance the understanding of the pathogenesis of OA in this population, improve physicians' ability to risk-stratify patients, and ultimately facilitate the development of preventive interventions.

Sarcopenia, or aging-related declines in muscle mass and strength, is strongly associated with development of physical disability and lower-extremity mobility impairment over time in

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supported by National Institute of Aging grant 1K23AG058756. Research reported in this publication was supported by a University of Washington Clinical Evidence, Learning, and Research (CLEAR) Center Pilot & Feasibility award. The University of Washington CLEAR Center is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under award number P30AR072572. Lastly, this research was supported by National Institute on Aging contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106; National Institute on Aging grant R01-AG028050; and National Institute of Nursing Research grant R01-NR012459. This research was funded in

part by the Intramural Research Program of the National Institutes of Health, National Institute on Aging.

<sup>1</sup>James S. Andrews, MD, Laura S. Gold, PhD, Patrick J. Heagerty, PhD: University of Washington, Seattle; <sup>2</sup>Michael Nevitt, PhD, MPH: University of California, San Francisco; <sup>3</sup>Peggy M. Cawthon PhD, MPH: California Pacific Medical Center Research Institute and University of California, San Francisco.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to James Andrews, MD, Division of Rheumatology, University of Washington, Box 359755, 401 Broadway, PS5095, Seattle, WA 98122. Email: jsa1@uw.edu.

Submitted for publication February 1, 2021; accepted in revised form June 11, 2021.

### SIGNIFICANCE & INNOVATIONS

- Prior studies of relationships between muscle mass or muscle strength and the development of knee osteoarthritis (OA) have not examined the associations of lean mass and grip strength, commonly used measures of aging-related sarcopenia, with the incidence of knee OA or knee pain.
- Among older men, but not women, higher baseline appendicular lean mass (ALM) was associated with increased risk of incident clinically diagnosed, symptomatic knee OA, and lower baseline grip strength was associated with increased risk of incident knee pain.
- Among older men, but not women, ALM and grip strength may be important risk factors for the development of clinically diagnosed, symptomatic knee OA and knee pain, respectively.

older adults (3–6); therefore, it may be an important and potentially modifiable risk factor for the development of knee OA and knee pain in these individuals. Previous studies of the relationship of muscle mass and strength with knee OA have tended to focus specifically on thigh muscles (primarily quadriceps and hamstrings) given their role in knee joint function and mechanics, and observed trends have been conflicting or inconsistent. Thigh muscle size has not been associated with the development of either symptomatic or radiographic knee OA among adults at risk for OA (7,8). In comparison, relationships between thigh muscle strength and the development of knee OA have been inconsistent. Lower quadriceps strength was associated with increasing risk of incident symptomatic, but not radiographic, knee OA among adults aged 50 to 79 years at risk for OA in the Multicenter OA Study (9). However, among a subset of individuals with meniscal pathology from this same cohort, high quadriceps strength was associated with a lower risk of incident radiographic knee OA in women but not men and was not associated with risk of incident symptomatic OA in women or men (10). In contrast, in another cohort of adults aged 45 to 79 years old at risk of knee OA in at least one knee, neither lower baseline thigh muscle strength nor declines in thigh muscle strength over time were associated with a risk of radiographic progression of early OA (11). Lastly, in this same cohort, lower thigh muscle strength was observed to be associated with an increased risk of incident radiographic knee OA in women but not in men; however, this relationship was attenuated after adjustment for differences in body mass index (BMI) (12).

The aim of this study is to examine the relationships of grip strength and whole body appendicular lean mass (ALM) (both commonly used measures of aging-related sarcopenia) with the likelihood of developing clinically diagnosed, symptomatic knee OA and knee pain in older adults.

### PATIENTS AND METHODS

**Participants.** Data were obtained from the first 6 years of the Health ABC (Health, Aging, and Body Composition) Study, a prospective cohort study of the relationships between body composition and changes in physical function among older adults. Details of the Health ABC Study have been previously published (13). Briefly, white and Black individuals aged 70 to 79 years were recruited from April 1997 to June 1998 from a sample of Medicare beneficiaries living in Pittsburgh, Pennsylvania, and Memphis, Tennessee (13). In order to be eligible, individuals had to report no difficulty walking one-quarter mile, climbing 10 steps, or performing basic activities of daily living (ADLs). A total of 3075 men and women were included in the Health ABC Study.

**Measures. Muscle.** At baseline, in Health ABC Study Year 1, the following were assessed: ALM and grip strength. ALM was assessed by whole body dual-energy x-ray absorptiometry (DXA) according to a standardized procedure (13). Briefly, ALM represents the sum of lean mass from all four extremities. DXA is a commonly used method of assessing body composition, including lean mass, in clinical outcomes research among older adults, such as the Health ABC Study from which the data for the current study derive (3,4). In general, DXA has good reproducibility and is sensitive to small changes in body composition (13). The precision errors  $\pm 1$  SD are 1.0 kg for fat mass and 0.8 kg for lean tissue mass (14). Grip strength was assessed by Jamar dynamometer according to a standardized procedure in which two trials were conducted in each hand and the maximum grip strength recorded in any single trial was used as the value for grip strength (15). Assessment of grip strength by Jamar dynamometer has high inter-rater reliability in older adults (intraclass correlation coefficient = 0.91–0.95) (16). Low (versus not low) ALM and low grip strength were calculated on the basis of published definitions of clinically relevant low lean mass and low grip strength (4). For men, low ALM was defined as less than 19.75 kg and low grip strength was defined as less than 26 kg. For women, low ALM was defined as less than 15.02 kg and low grip strength as less than 16 kg.

**Knee OA and knee pain.** Incident clinically diagnosed, symptomatic knee OA and knee pain were assessed in Health ABC Study Years 2 to 6. Incident clinically diagnosed, symptomatic knee OA was defined as new 1) participant report that a physician has ever told them that they have OA or degenerative arthritis of the knee and 2) self-report of knee pain on most days of the last month or knee pain lasting for more than 1 month in the past 12 months. This definition of knee OA was used to facilitate comparison with other large epidemiologic studies of knee OA (17,18). Knee pain was defined as self-report of knee pain most days of the last month or knee pain lasting for more than 1 month in the past 12 months (19).

*Other variables.* Sociodemographic variables (age, sex, and race) and BMI were assessed in Health ABC Study Year 1. Prevalent medical comorbidities (non-skin cancer, pulmonary disease, cardiac disease, cerebrovascular disease, and diabetes mellitus) were assessed annually in Health ABC Study using a standard algorithm combining participant report and medical record review (15). Chronic oral glucocorticoid and nonsteroidal anti-inflammatory drug (NSAID) use was assessed annually in the Health ABC Study using a standardized approach (20). Physical activity was assessed annually in the Health ABC Study as self-reported number of minutes of walking per week (expressed as kCal/kg/week).

**Statistical analysis.** *Primary analyses.* All analyses were stratified by sex because the relationship between body composition and development of clinically diagnosed, symptomatic knee OA or knee pain likely differs by sex (10,12). Separate logistic regression analyses modeled the association between baseline ALM or baseline grip strength and the likelihood of incident 1) clinically diagnosed, symptomatic knee OA or 2) knee pain at the end of follow-up with and without adjusting for covariates (race, baseline age, baseline BMI, walking per week, NSAID use, oral glucocorticoid use, and prevalent medical comorbidities). Baseline ALM and grip strength were analyzed as both continuous and categorical (low versus not low) variables. Because death and loss to follow-up were relatively rare (in the knee OA group, 166 [12.0%] men and 95 [6.8%] women died and 65 [4.7%] men and 87 [6.2%] women were lost to follow-up; in the knee pain group, 139 [12.5%] men

and 80 [7.5%] women died and six [0.5%] men and 10 [0.9%] women were lost to follow-up), those who died or were lost prior to the end of follow-up were considered as not having developed the outcomes in the primary analyses. For continuous measures of ALM and grip strength, odds ratios (ORs) are expressed per SD decrement in the predictor variable. To assess the correlation between ALM and grip strength, we calculated Pearson correlation coefficients.

*Sensitivity analysis.* To examine whether the association of baseline grip strength or ALM with the likelihood of clinically diagnosed, symptomatic knee OA or knee pain at the end of follow-up is affected by loss to follow-up and death, those individuals who died or were lost prior to the end of follow-up were excluded, and analyses were repeated.

## RESULTS

**Participant characteristics.** A total of 3075 men and women were included in the Health ABC Study. Those missing ALM or grip strength (men,  $n = 61$ ; women,  $n = 76$ ) and those with prevalent clinically diagnosed, symptomatic knee OA (men,  $n = 45$ ; women,  $n = 114$ ) or knee pain (men,  $n = 315$ ; women,  $n = 441$ ) at baseline were excluded, leaving 1385 men and 1394 women for the knee OA analysis and 1115 men and 1067 women for the knee pain analysis. Participant baseline characteristics for men and women are shown in Table 1. Overall, men and women in both the knee OA and knee pain groups had a mean age of approximately 74 years old, were slightly more likely to be white than Black, and had an average BMI of approximately 27

**Table 1.** Participant baseline characteristics stratified by sex

Characteristics	Men		Women	
	Knee OA Group ( $n = 1385$ ) <sup>a</sup>	Knee Pain Group ( $n = 1115$ )	Knee OA Group ( $n = 1394$ ) <sup>a</sup>	Knee Pain Group ( $n = 1067$ )
Age, years, mean $\pm$ SD	73.8 $\pm$ 2.9	73.8 $\pm$ 2.8	73.5 $\pm$ 2.9	73.5 $\pm$ 2.8
White race, n (%)	869 (62.7)	699 (62.7)	747 (53.6)	596 (55.9)
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	27.0 $\pm$ 3.9	26.7 $\pm$ 3.8	27.5 $\pm$ 5.4	27.0 $\pm$ 5.2
ALM, mean $\pm$ SD, kg	23.9 $\pm$ 3.6	23.7 $\pm$ 3.6	16.6 $\pm$ 3.1	16.3 $\pm$ 3.0
Grip strength, mean $\pm$ SD, kg	37.5 $\pm$ 8.6	37.7 $\pm$ 8.6	22.7 $\pm$ 6.0	22.9 $\pm$ 6.0
Walking, mean $\pm$ SD, kCal/kg/wk	9.0 $\pm$ 19.9	9.6 $\pm$ 21.3	6.5 $\pm$ 14.7	6.4 $\pm$ 12.5
Low ALM, <sup>b</sup> n (%)	159 (11.5)	145 (13.0)	475 (34.1)	402 (37.7)
Low grip strength, <sup>b</sup> n (%)	84 (6.1)	68 (6.1)	116 (8.3)	77 (7.2)
Use of NSAIDs, <sup>c</sup> n (%)	236 (17.0)	161 (14.4)	322 (23.1)	217 (20.3)
Use of oral glucocorticoids, <sup>c</sup> n (%)	19 (1.4)	16 (1.4)	39 (2.8)	32 (3.0)
Prevalent comorbidities, n (%)				
Malignancy	360 (26.0)	294 (26.3)	246 (17.7)	199 (18.7)
Pulmonary disease	158 (11.4)	114 (10.2)	156 (11.2)	121 (11.3)
Cardiac disease	414 (29.9)	324 (29.1)	242 (17.4)	166 (15.6)
Cerebrovascular disease	94 (6.8)	74 (6.6)	103 (7.4)	75 (7.0)
Diabetes mellitus	230 (16.6)	177 (15.9)	198 (14.2)	150 (14.1)

Abbreviation: ALM, appendicular lean mass; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis.

<sup>a</sup> All individuals in the knee pain group are included in the knee OA group.

<sup>b</sup> Low ALM: men, <19.75 kg; women, <15.02 kg. Low grip strength: men, <26kg; women, <16 kg (4).

<sup>c</sup> NSAIDs include Cox-2 inhibitors. Glucocorticoids include cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisone, triamcinolone, betamethasone, and prednisolone.

kg/m<sup>2</sup>. Among men, the percentage with low ALM was 11.5% in the knee OA group and 13% in the knee pain group, whereas among women the percentage was 34.1% in the knee OA group and 37.7% in the knee pain group. Among men, the percentage with low grip strength was 6.1% in both the knee OA and knee pain groups, and among women the percentage was 8.3% in the knee OA group and 7.2% in the knee pain group. The most common medical comorbidities at baseline among men and women in both groups were malignancy and cardiac disease. Among men, the percentage reporting chronic NSAID use was 17% in the knee OA group and 14.4% in the knee pain group, and among women the percentage was 23.1% in the knee OA group and 20.3% in the knee pain group.

#### Association of baseline ALM and grip strength on development of knee OA and knee pain.

A total of 95 men (6.9%) and 158 women (11.3%) developed clinically diagnosed, symptomatic knee OA, and 315 men (28.3%) and 385 women (36.1%) developed knee pain over follow-up. Among men, baseline ALM was associated with the likelihood of incident clinically diagnosed, symptomatic knee OA such that, for each SD decrement in ALM, the adjusted odds of knee OA decreased by 32% (OR: 0.68; 95% CI: 0.47-0.97) (Table 2). In addition, among men, baseline low ALM (compared with not low ALM) was associated with an adjusted OR for incident clinically diagnosed, symptomatic knee OA of 0.21 (95% CI: 0.05-0.87). Lastly, among men, baseline grip strength was associated with the likelihood of incident knee pain such that for each SD decrement in grip strength the adjusted odds of knee pain increased by 20% (OR: 1.20; 95% CI: 1.01-1.42). Among women, baseline ALM and grip strength measures were not statistically significantly associated with either incident clinically diagnosed, symptomatic knee OA or knee pain. Supplementary Tables 1A and 1B depict the unadjusted and stepwise adjusted ORs for the association of baseline ALM or grip strength measures with the likelihood of incident clinically diagnosed, symptomatic knee OA or knee pain. Lastly, the

correlation coefficient (*r*) between ALM and grip strength in our sample is 0.35 among women and 0.41 among men.

**Sensitivity analysis.** When men and women who died or were lost to follow-up prior to the end of the study period were excluded from the analysis, the overall trends were unchanged. Lower ALM (as a continuous measure) and low ALM (as a categorical measure) were each associated with a lower likelihood of incident clinically diagnosed, symptomatic knee OA in men only, and lower baseline grip strength (as a continuous measure) was associated with increased risk of knee pain in men only (Supplementary Table 2).

## DISCUSSION

In this cohort of older men and women, ALM and grip strength were associated with risk of clinically diagnosed, symptomatic knee OA and knee pain, respectively, among men but not women. Even when adjusting for covariates, including BMI, physical activity, and medication use, higher ALM and lower grip strength were associated with increased likelihood of incident clinically diagnosed, symptomatic knee OA and knee pain, respectively, over 5 years of follow-up in older men but not older women. These findings suggest that differences in muscle mass and strength, such as in ALM and grip strength, in older adults may be relevant, albeit modest, risk factors for the development of clinically diagnosed, symptomatic knee OA and knee pain in older men. To our knowledge, this is among the first studies to demonstrate an association of lower grip strength, a key component of sarcopenia in older adults, with the development of knee pain. Given the frequency of knee pain and its significant contribution to decreased physical function in older adults, these findings suggest that further examination of grip strength as a risk factor for the development of knee pain in older adults (in particular, older men) could facilitate efforts to prevent this important source of physical disability for these individuals.

**Table 2.** Odds ratios and 95% confidence intervals for the effect of baseline ALM or grip strength on the likelihood of incident clinically diagnosed, symptomatic knee OA or knee pain over the first 5 years of follow-up in the Health ABC Study, stratified by sex

	Men		Women	
	Knee OA Cohort (n = 1385)	Knee Pain Cohort (n = 1115)	Knee OA Cohort (n = 1394)	Knee Pain Cohort (n = 1067)
ALM, <sup>a</sup> kg	<b>0.68 (0.47-0.97)<sup>b</sup></b>	0.93 (0.74-1.18)	1.12 (0.76-1.65)	0.76 (0.56-1.05)
Grip strength, <sup>a</sup> kg	1.00 (0.76-1.32)	<b>1.20 (1.01-1.42)<sup>b</sup></b>	1.14 (0.83-1.55)	1.07 (0.84-1.37)
Low ALM (yes/no) <sup>c</sup>	<b>0.21 (0.05-0.87)<sup>b</sup></b>	0.82 (0.52-1.28)	0.94 (0.59-1.50)	0.88 (0.63-1.22)
Low grip strength (yes/no) <sup>c</sup>	1.08 (0.45-2.60)	1.17 (0.68-2.02)	1.32 (0.73-2.38)	1.49 (0.92-2.41)

Abbreviation: ALM, appendicular lean mass; OA, osteoarthritis.

All models are adjusted for race, baseline age, baseline body mass index, walking per week, nonsteroidal anti-inflammatory drug use, oral glucocorticoid use, and prevalent comorbidities (malignancy, pulmonary disease, cardiac disease, cerebrovascular disease, and diabetes mellitus).

<sup>a</sup> Odds ratios are expressed per SD decrement in the predictor variable.

<sup>b</sup> Bold font indicates *P* < 0.05.

<sup>c</sup> Low ALM: men, <19.75 kg; women, <15.02 kg. Low grip strength: men, <26 kg; women, <16 kg (4).



Our findings corroborate prior studies in which relationships of body composition (specifically of muscle mass and strength) with knee OA differ between men and women. Although ours is the first study, to our knowledge, to examine the association between grip strength and incident clinically diagnosed, symptomatic knee OA, lower quadriceps muscle strength was associated with increased risk of incident radiographic knee OA in women, but not men, in two large observational cohort studies (10,12). In the present study, we similarly observed that decreased strength, assessed as grip strength, was associated with increased risk of incident knee pain (although not with clinically diagnosed, symptomatic knee OA); however, we identified this association in men but not women. With respect to muscle mass, women with both low ALM and high fat mass measured by DXA were at increased risk of incident radiographic knee OA compared with women with normal ALM and fat mass in the Multicenter Osteoarthritis Study (21). However, when obesity was instead defined by BMI rather than by a DXA-based definition, this association was observed only in men. Moreover, low ALM alone was not statistically significantly associated with incident radiographic knee OA, although the point estimates of the effects trended toward a protective effect in men but not in women, similar to our results. We also observed that the associations between DXA-based measures of lean mass with incident knee OA differed between men and women. To our knowledge, however, ours is the first study to identify a statistically significant negative longitudinal association between ALM and incident clinically diagnosed, symptomatic knee OA in men or women. Ours is also the first study to identify a similar relationship between low ALM, defined using the foundation for the National Institutes of Health Sarcopenia Project's definition of clinically relevant low ALM, and incident clinically diagnosed, symptomatic knee OA in older men. Our findings suggest that further studies of sex-specific relationships of muscle mass and strength, such as ALM and grip strength, with incident clinically diagnosed, symptomatic knee OA and knee pain are needed.

The negative association that we observed between lower ALM and lower likelihood of incident clinically diagnosed, symptomatic knee OA in older men was not consistent with our hypothesis that aging-related declines in ALM would be associated with an increased risk of knee OA. The observed protective association between ALM and clinically diagnosed, symptomatic knee OA persisted after adjustment for BMI, suggesting that this potential relationship between ALM and incident knee OA may be separate from the well-established strong association between higher overall body mass and higher risk of incident knee OA (1). Nevertheless, as with any observational study, various potential threats to the validity of this observed association remain. Although we adjusted for medication (NSAID and glucocorticoid) use, physical activity (walking), and medical comorbidities, further unmeasured confounders may be responsible for the observed, protective association. We also acknowledge the limitations of assessing lean mass by DXA as a surrogate measure of muscle mass.

DXA does not directly measure lean mass, only fat mass and bone mass. Lean mass is then calculated by subtracting fat mass and bone mass from total body mass. Lean mass, which includes not only muscle but also water and connective tissue, is then taken as an approximation of skeletal muscle mass. Others have hypothesized that the inconsistent relationships between lean mass measured by DXA and various physical function outcomes in older adults may largely be due to the measurement error introduced by these inherent methodologic limitations (22). Moreover, greater measurement error in DXA-derived ALM may occur as body mass increases (23). This possible systematic bias could introduce spurious associations between ALM and knee OA or knee pain. Thus, we suggest interpreting the observed protective effect of ALM on the risk of clinically diagnosed, symptomatic knee OA in older men with caution and as hypothesis-generating. One hypothesis, which would require further study, is that sex-specific metabolic processes, such as circulating steroid sex hormone levels, that affect both the loss of skeletal muscle mass and the risk of knee OA could contribute to this potential protective association between lower ALM and lower risk of clinically diagnosed, symptomatic knee OA in men. For example, circulating sex hormones levels, such as those of androstenedione or estradiol, have sex-specific associations with lower risk of knee OA and arthroplasty (24,25). In addition, stratifying our analyses by sex could also introduce spurious associations. However, we adopted this sex-stratified approach because body composition and its relationship to functional outcomes, such as knee OA and knee pain, is thought to differ between men and women. Future studies, likely incorporating alternative methods of directly assessing skeletal muscle mass in older adults, will be needed to further clarify potential relationships between ALM and incident clinically diagnosed, symptomatic knee OA in older men.

The observed relationship of grip strength with incident knee pain in older men may have important implications for the prevention of disability and the promotion of healthy aging. Muscle strength, including grip strength, decreases with age as part of the normal aging process (3). Among the general population of older adults, these age-related declines in grip strength are strongly associated with various adverse physical function outcomes, including mobility impairment and ADL dependence (4–6). Knee pain is a leading cause of physical disability, including mobility and ADL impairment, in older adults (1). Therefore, identifying grip strength as a modest risk factor for the development of knee pain in older men has the potential to 1) help advance understanding of the potential contribution of muscle strength to the pathogenesis of knee pain and physical disability in older men, 2) facilitate risk stratification of older male patients with respect to future likelihood of knee pain-related disability and thus improve our ability to apply existing interventions to those individuals most likely to benefit, and 3) ultimately aid in the development of novel strategies or interventions (such as strength training or improved nutrition) to prevent knee pain and knee pain-related disability in

this population. Lastly, grip strength, in particular, is a reliable (26), objective, and practical measure; therefore, it may be a particularly useful tool in both the clinical and research settings.

Although lower grip strength is not expected to be a direct cause of knee pain in older adults, these findings suggest that grip strength may be a useful surrogate measure of overall muscle strength in studies of knee pain in older men. Grip strength correlates with muscle strength in other areas of the body. For example, among all older adults in the Health ABC Study (from which the current study's participants derive), grip strength is associated with leg extension strength ( $r = 0.40$ ;  $P < 0.001$  in men and  $r = 0.44$ ;  $P < 0.001$  in women) (27). Therefore, grip strength may have utility as a surrogate measure for age-related declines in muscle strength elsewhere in the body and as an outcome in studies aimed at reducing the risk of knee pain in older men by increasing total body strength with systemic interventions. In studies of knee pain, grip strength also has the advantage over leg extension strength of avoiding the potential confounding influence of knee pain on the assessment of leg strength.

Incident clinically diagnosed, symptomatic knee OA was relatively rare in our study, and the low event rate reduces the statistical power to detect associations with candidate risk factors. Nevertheless, we observed statistically significant associations between higher ALM measures and greater risk of incident clinically diagnosed, symptomatic knee OA. Incident knee pain, on the other hand, was common in this cohort of older adults, who had relatively preserved physical functioning. Despite all subjects being free of significant mobility and ADL impairment at baseline, as required by the eligibility criteria of the Health ABC Study, 32% of individuals (28% of men and 36% of women) in the present study newly developed knee pain during the 5 years of follow-up. This observation underscores the relevance of knee pain to healthy aging of older adults. As the global population ages, advancing our understanding of the pathogenesis of knee pain in older adults and developing effective strategies to prevent it both may be fundamental in improving physical health outcomes for a rapidly growing segment of the global community.

The present study has certain limitations. Most importantly, the measure of knee OA used in our study requires, in addition to the presence of active knee pain symptoms, self-report of physician-diagnosed knee OA. Report of knee pain symptoms most days of the last month is a standard method of defining symptomatic knee OA and knee pain dating back to the Framingham and NHANES (National Health and Nutrition Examination Survey) studies (19). The combination of self-report of physician diagnosis of knee OA and active knee pain symptoms was used to facilitate comparison with other large epidemiologic studies (17,18). However, self-report of physician-diagnosed knee OA in older adults may tend to under-report knee OA compared with definitions based on radiographs or symptoms (28,29). To address this potential limitation, we also examined the relationship of sarcopenia measures with knee pain itself. Future studies will need to

examine the relationship between sarcopenia and radiographically defined knee OA in this and other cohorts of older adults. Second, the Health ABC Study includes only nondisabled white and Black older adults; thus, it is unknown how our findings may generalize to other groups of older adults. Third, although all analyses are adjusted for history of cerebrovascular disease, specific data on history of hemiparesis or hemiplegia were not available. Lastly, assessing physical activity by self-report of walking per week, as done in the present study, may not capture all of an individual's regular physical activity. Thus, our results may be influenced by unresolved confounding. Despite these limitations, the study has several strengths. One strength of the study is that it leverages a large, well-characterized cohort of older men and women. In addition, the measures of sarcopenia used in the current study, ALM and grip strength, are well-validated and commonly used and facilitate comparison with other studies of sarcopenia and functional outcomes in older adults.

In conclusion, we observed that, among older men, higher ALM and lower grip strength at baseline were associated with increased likelihood of incident clinically diagnosed, symptomatic knee OA and incident knee pain, respectively, over follow-up. Given the important negative effects of knee OA and chronic knee pain on physical functioning among older adults, these findings suggest that further studies, including using alternative non-DXA-based methods of ascertaining skeletal muscle mass (such as magnetic resonance imaging, computed tomography, or  $D_3$ -creatinine urinary dilution) should explore the relationship of ALM and grip strength with the development of knee OA and knee pain in older men and the potential for interventions targeting muscle strength to prevent knee pain for these individuals.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Andrews had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Andrews, Gold, Nevitt, Heagerty, Cawthon.

**Acquisition of data.** Andrews, Gold.

**Analysis and interpretation of data.** Andrews, Gold, Nevitt, Heagerty, Cawthon.

## REFERENCES

1. Felson DT. Clinical practice: osteoarthritis of the knee. *N Engl J Med* 2006;354:841–8.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35.
3. Cawthon PM. Recent progress in sarcopenia research: a focus on operationalizing a definition of sarcopenia. *Curr Osteoporos Rep* 2018;16:730–7.
4. McLean RR, Shardell MD, Alley DE, Cawthon PM, Fragala MS, Harris TB, et al. 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. *J Gerontol A Biol Sci Med Sci* 2014;69:576–83.
5. Roshanravan B, Patel KV, Fried LF, Robinson-Cohen C, de Boer IH, Harris T, et al. Association of muscle endurance, fatigability, and strength with functional limitation and mortality in the health aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2017;72:284–91.
  6. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. *J Am Geriatr Soc* 2002;50:897–904.
  7. Segal NA, Findlay C, Wang K, Torner JC, Nevitt MC. The longitudinal relationship between thigh muscle mass and the development of knee osteoarthritis. *Osteoarthritis Cartilage* 2012;20:1534–40.
  8. Ruhdorfer AS, Dannhauer T, Wirth W, Cotofana S, Roemer F, Nevitt M, et al. Thigh muscle cross-sectional areas and strength in knees with early vs knees without radiographic knee osteoarthritis: a between-knee, within-person comparison. *Osteoarthritis Cartilage* 2014;22:1634–8.
  9. Segal NA, Torner JC, Felson D, Niu J, Sharma L, Lewis CE, et al. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. *Arthritis Rheum* 2009;61:1210–7.
  10. Thorlund JB, Felson DT, Segal NA, Nevitt MC, Niu J, Neogi T, et al. Effect of knee extensor strength on incident radiographic and symptomatic knee osteoarthritis in individuals with meniscal pathology: data from the multicenter osteoarthritis study. *Arthritis Care Res* 2016;68:1640–6.
  11. Eckstein F, Hitzl W, Duryea J, Kent Kwok C, Wirth W, OAI Investigators. Baseline and longitudinal change in isometric muscle strength prior to radiographic progression in osteoarthritic and pre-osteoarthritic knees—data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2013;21:682–90.
  12. Culvenor AG, Felson DT, Niu J, Wirth W, Sattler M, Dannhauer T, et al. Thigh muscle specific-strength and the risk of incident knee osteoarthritis: the influence of sex and greater body mass index. *Arthritis Care Res* 2017;69:1266–70.
  13. Visser M, Pahor M, Tylavsky F, Kritchevsky SB, Cauley JA, Newman AB, et al. One- and two-year change in body composition as measured by DXA in a population-based cohort of older men and women. *J Appl Physiol* (1985) 2003;94:2368–74.
  14. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. *Am J Clin Nutr* 1990;51:1106–12.
  15. Cawthon PM, Fox KM, Gandra SR, Delmonico MJ, Chiou C-F, Anthony MS, et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? *J Am Geriatr Soc* 2009;57:1411–9.
  16. Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. *J Hand Ther* 2005;18:426–7.
  17. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation - United States, 2013–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:246–53.
  18. Deshpande BR, Katz JN, Solomon DH, Yelin EH, Hunter DJ, Messier SP, et al. Number of persons with symptomatic knee osteoarthritis in the us: impact of race and ethnicity, age, sex, and obesity. *Arthritis Care Res* 2016;68:1743–50.
  19. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. *Arthritis Rheum* 1987;30:914–8.
  20. Marcum ZA, Perera S, Donohue JM, Boudreau RM, Newman AB, Ruby CM, et al. Analgesic use for knee and hip osteoarthritis in community-dwelling elders. *Pain Med* 2011;12:1628–36.
  21. Misra D, Fielding RA, Felson DT, Niu J, Brown C, Nevitt M, et al. Risk of knee osteoarthritis with obesity, sarcopenic obesity, and sarcopenia. *Arthritis Rheumatol* 2019;71:232–7.
  22. Cawthon PM, Blackwell T, Cummings SR, Orwoll ES, Duchowny KA, Kado DM, et al. Muscle mass assessed by D3-Creatine dilution method and incident self-reported disability and mortality in a prospective observational study of community dwelling older men. *J Gerontol A Biol Sci Med Sci* 2021;76:123–30.
  23. Cawthon PM, Orwoll ES, Peters KE, Ensrud KE, Cauley JA, Kado DM, et al. Strong relation between muscle mass determined by d3-creatine dilution, physical performance, and incidence of falls and mobility limitations in a prospective cohort of older men. *J Gerontol A Biol Sci Med Sci* 2019;74:844–52.
  24. Hussain SM, Cicuttini FM, Bell RJ, Robinson PJ, Davis SR, Giles GG, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to circulating sex steroid hormone concentrations in women. *Arthritis Rheumatol* 2014;66:2144–51.
  25. Hussain SM, Cicuttini FM, Giles GG, Graves Se, Wang Y. Relationship between circulating sex steroid hormone concentrations and incidence of total knee and hip arthroplasty due to osteoarthritis in men. *Osteoarthritis Cartilage* 2016;24:1408–12.
  26. Harkonen R, Harju R, Alaranta H. Accuracy of the Jamar dynamometer. *J Hand Ther* 1993;6:259–62.
  27. Fragala MS, Alley DE, Shardell MD, Harris TB, McLean RR, Kiel DP, et al. Comparison of handgrip and leg extension strength in predicting slow gait speed in older adults. *J Am Geriatr Soc* 2016;64:144–50.
  28. Szoek CE, Dennerstein L, Wluka AE, Guthrie JR, Taffe J, Clark MS, et al. Physician diagnosed arthritis, reported arthritis and radiological non-axial osteoarthritis. *Osteoarthritis Cartilage* 2008;16:846–50.
  29. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol* 2000;27:1513–7.