American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2015. This work is written by (a) US Government employee(s) and is in the public domain in the US.

Vol. 183, No. 1
DOI: 10.1093/aje/kwv153
Advance Access publication:
December 6, 2015

Original Contribution

Muscle Quality and Myosteatosis: Novel Associations With Mortality Risk

The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study

Ilse Reinders*, Rachel A. Murphy, Ingeborg A. Brouwer, Marjolein Visser, Lenore Launer, Kristin Siggeirsdottir, Gudny Eiriksdottir, Vilmundur Gudnason, Palmi V. Jonsson, Thomas F. Lang, and Tamara B. Harris for the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study

* Correspondence to Ilse Reinders, Laboratory of Epidemiology and Population Sciences, National Institute on Aging, 7201 Wisconsin Avenue, 3C-309 Gateway Building, Bethesda, MD 20814 (e-mail: ilse.reinders@nih.gov).

Initially submitted February 18, 2015; accepted for publication June 4, 2015.

Muscle composition may affect mortality risk, but prior studies have been limited to specific samples or less precise determination of muscle composition. We evaluated associations of thigh muscle composition, determined using computed tomography imaging, and knee extension strength with mortality risk among 4,824 participants aged 76.4 (standard deviation (SD), 5.5) years from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (2002–2006). Cox proportional hazards models were used to estimate hazard ratios. After 8.8 years of follow-up, there were 1,942 deaths. For men, each SD-increment increase in muscle lean area, muscle quality, and strength was associated with lower mortality risk, with decreases ranging between 11% and 22%. Each SD-increment increase in intermuscular adipose tissue and intramuscular adipose tissue was associated with higher mortality risk (hazard ratio (HR) = 1.13 (95% confidence interval (CI): 1.06, 1.22) and HR = 1.23 (95% CI: 1.15, 1.30), respectively). For women, each SD-increment increase in muscle lean area, muscle quality, and strength was associated with lower mortality risk, with decreases ranging between 12% and 19%. Greater intramuscular adipose tissue was associated with an 8% higher mortality risk (HR = 1.08, 95% CI: 1.01, 1.16). This study shows that muscle composition is associated with mortality risk. These results also show the importance of improving muscle strength and area and lowering muscle adipose tissue infiltration.

adipose tissue; aging; computed tomography; mortality risk; muscle; muscle composition; strength

Abbreviations: AGES, Age, Gene/Environment Susceptibility; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; HR, hazard ratio; HU, Hounsfield units; SD, standard deviation.

Loss of muscle strength and muscle mass occurs with aging (1). Low muscle strength has consistently been associated with increased mortality risk (2–8), whereas muscle mass, based on bioelectrical impedance analysis or dual-energy x-ray absorptiometry, shows inconsistent associations with mortality risk (9–14). The use of computed tomography (CT) imaging can provide more precise estimates of muscle mass.

Besides the loss of muscle mass and strength, aging also results in a redistribution of adipose tissue, where subcutaneous adipose tissue relocates to more detrimental locations, as intramuscular and intermuscular adipose tissue, or moves between and within muscles or organs (15). The result is that older people have greater levels of intramuscular or intermuscular adipose tissue compared with younger people with the same body mass index (BMI). The presence of intramuscular and intermuscular adipose tissue, defined as myosteatosis, is in turn inversely associated with loss of muscle strength (16) or mobility disability (17). The redistribution of adipose tissue can also be measured using CT imaging. However, few studies have used CT imaging to determine the association between muscle composition measures and mortality risk, particularly

in a general older population. In the Health, Aging and Body Composition Study, thigh muscle strength, but not muscle mass from CT, was associated with mortality risk after 4.9 years among 2,292 participants aged 70–79 years (18). In the InCHIANTI Study, cross-sectional muscle or fat areas of the calf assessed with peripheral quantitative CT were also not associated with mortality after 5.1 years among 934 participants aged ≥65 years (19).

Investigation of novel muscle composition measures, muscle quality, and myosteatosis in a large study population with a longer follow-up period is needed to clarify associations between muscle composition measures and mortality risk. Therefore, our aim in this study was to examine the relationship of thigh muscle composition, including muscle lean area, knee extension strength, muscle quality (defined as the ratio between knee extension strength and muscle lean area), and myosteatosis (defined as intermuscular adipose tissue and intramuscular adipose tissue), with all-cause mortality risk after 8.8 years of follow-up in a large study of older men and women.

METHODS

Study population

We used data from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, a prospective population study of survivors from the Reykjavik Study (20, 21). The baseline examination of 5,764 men and women took place in Iceland between 2002 and 2006 (22). Participants with missing data on CT ($n = 457$), muscle strength ($n = 396$), and covariates ($n = 87$) were excluded, resulting in 4,824 participants with complete data in the analytical cohort. Male participants who were excluded were older, were more likely to be nonsmokers, had slower gait speed, had higher C-reactive protein (CRP) values, and were more likely to have diabetes than men included in the analytical cohort. Excluded women were older, had less education, were more likely to be nonsmokers, reported less moderate-to-vigorous physical activity in the previous 12 months, had slower gait speed, had higher CRP values, and were more likely to have diabetes and coronary heart disease than women included in the analytical cohort ($P < 0.05$ for all).

All participants provided written informed consent. The study was approved by the National Bioethics Committee in Iceland, as well as the Institutional Review Board of the Intramural Research Program at the National Institute on Aging, US National Institutes of Health.

Measures

Computed tomography. CT imaging of the midthigh was part of the baseline examination (2002–2006) and was performed with a 4-row detector system (Sensation; Siemens Medical Systems, Erlangen, Germany) as previously described (23). Thigh muscle cross-sectional area (cm^2) represents muscle lean area and was determined from a single 10-mm transaxial section using a 120-kV peak (24). Prior to the transaxial imaging, the right position for imaging at the midfemur was determined by measuring the maximum length of the femur on an anterior-posterior scout image and then finding the center of the long axis of the femur. Muscle lean area was segmented using the outline along the fascial plane between the muscle and subcutaneous fat.

Myosteatosis was defined as the presence of intermuscular and intramuscular adipose tissue. Intermuscular adipose tissue is the visible fat within the fascia surrounding skeletal muscles (25); lakes of adipose tissue between and within muscle were determined as the number of pixels with Hounsfield units (HU) between −200 and −50 multiplied by the area of a pixel. Intramuscular adipose tissue was calculated as the mean attenuation coefficient of the muscle lean area after subtraction of intermuscular adipose tissue, expressed in HU. Higher HU values indicate lower muscle adipose tissue infiltration and higher muscle strength (26). To facilitate interpretation of study results on intermuscular adipose tissue and intramuscular adipose tissue in relation to mortality risk, we multiplied the values for intramuscular adipose tissue by −1.

An operator used a manual contouring program to draw the contours of the total muscle bundle. Within each region, a threshold was chosen to select voxels with a CT density greater than the maximal density of fat, as documented in the paper by Lang et al. (27). The muscle lean area of each region was calculated as the number of voxels above the threshold, and the lean tissue attenuation was the mean CT density of the thresholded voxels. The average of the values for the left and right legs was used; if data for one leg were missing or invalid, then the nonmissing thigh was used. This was the case for 34 participants (0.70%).

Visceral adipose tissue was determined with CT imaging of the abdomen at the L4/L5 vertebrae. Visceral adipose tissue was distinguished from subcutaneous adipose tissue by tracing along the facial plane defining the internal abdominal wall.

Analysis of the CT images was performed using specialized software developed at the University of California, San Francisco. Twenty-six randomly selected participants underwent a second CT scan after repositioning. The coefficient of variation was 3.5% for muscle lean area, 1.3% for intermuscular adipose tissue, and 5.9% for intramuscular adipose tissue. There was no significant difference between the repeated measurements (24).

Maximal isometric knee extension measurement and muscle quality. Maximal isometric knee extension strength was measured on the dominant side using an adjustable dynamometer chair. Knee extension strength was measured (in newtons) with the knee angle at 60° from flexion toward full extension (24, 28). The ankle was fastened by a belt to a strain-gauge system, and the participant was positioned with both hands gripping the side edge of the seat. Before the measurement, participants completed 1 trial to ensure that they understood the standardized verbal instructions. Three maximal efforts, separated by 30 seconds' rest, were conducted, and the highest value was used. Muscle quality was ascertained by taking the ratio of strength to muscle lean area.

Mortality

Mortality was ascertained from the Icelandic National Roster (http://www.statice.is/Statistics/Population/Births-and-death), an adjudicated registry of deaths. Person-years

of follow-up were calculated from the date of the baseline examination to the date of death or September 30, 2014, for persons who were censored. Information on cause-specific mortality was available only through December 31, 2009. Among participants with cause-specific mortality ($n = 143$), the main causes of death were cardiovascular disease ($n = 68$ (47.6%)) and cancer ($n = 40$ (28.0%)). Eight deaths (5.6%) were attributed to diabetes. These numbers were too small to investigate cause-specific mortality.

Baseline covariates

All confounders were assessed at baseline. BMI (weight (kg)/height $(m)^2$) was calculated from measured height (cm) and weight (kg), and waist circumference (cm) was measured using standardized protocols (22). Information on education (less than high school, high school, or postsecondary), smoking status (never, former, or current smoking), and physical activity was self-reported. The physical activity variable was based on the following question on activity during the past year: "How often did you participate in moderate or vigorous physical activities?" Participants could choose from these answers: never, rarely, weekly but less than 1 hour per week, 1–3 hours per week, 4–7 hours per week, or more than 7 hours per week. Because of low numbers in some categories, we combined "never" with "rarely" and "4–7 hours per week" with "more than 7 hours per week." Normal 6-m gait speed (m/second) was used to assess mobility functioning (29, 30). Blood pressure was assessed from the mean value of 2 measurements with a large-cuff mercury sphygmomanometer. High-density lipoprotein cholesterol, CRP, and glucose were analyzed from fasting blood samples using reagents from Roche Diagnostics (Mannheim, Germany) on a Hitachi 912 analyzer (Hitachi Ltd., Tokyo, Japan) according to the manufacturer's instructions. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. Current medication use was determined from medication containers brought to the clinic and the questionnaire. Medical conditions (diabetes, chronic obstructive pulmonary disease, coronary heart disease) were defined according to self-reports, medications, or clinical assessments.

Statistical analysis

Analyses were stratified by sex because of a significant interaction of muscle composition measures and strength with sex in relation to mortality risk. Baseline characteristics are presented as mean values and standard deviations (SDs) for continuous variables and numbers and percentages for categorical variables. Differences between men and women were assessed using t tests and χ^2 tests. Correlations between muscle composition measures and strength were examined using Spearman's correlation coefficient (r).

Cox proportional hazards analyses were performed to determine associations of muscle composition measures and strength (determined at baseline) with time to death. The proportional hazards assumption was tested using Schoenfeld residuals. The assumption was not met for age and CRP among men; these variables were therefore modeled as time-varying covariates. Hazard ratios and 95% confidence intervals were estimated for the association of muscle composition, per SD increment, with mortality risk. Model results were adjusted for demographic variables and potential confounders selected a priori on the basis of available literature. Model 1 adjusted for age, BMI, educational level, smoking status, and physical activity level. Additionally, we investigated whether the associations between muscle composition measures and mortality risk were influenced by factors that reflect potential pathways or factors that could mediate these associations. In model 2, we adjusted for gait speed, diabetes, chronic obstructive pulmonary disease, coronary heart disease, and CRP.

To investigate linearity for continuous variables, we divided muscle composition measures and potential confounding variables into quartiles and used these as single determinants for mortality risk. We explored whether the regression coefficients were increasing or decreasing at the same rate for every quartile as compared with the previous quartile. This was the case for all of the variables except BMI among men and intermuscular adipose tissue among women; however, the direction remained the same. Therefore, we analyzed age, BMI, gait speed, and CRP as continuous variables.

In sensitivity analyses, we adjusted for visceral adipose tissue as a more precise measure of adiposity instead of BMI. Complete data for those analyses were available for 4,790 men and women. We also tested whether associations were driven by participants with extreme BMI values. Persons who are underweight are likely to have sarcopenia (age-related loss of skeletal muscle mass), which in turn is associated with an increased risk of mortality (2, 31). Extremely obese individuals also have increased risk of mortality (32–34). Therefore, we excluded participants with BMIs indicative of underweight (<18.5) (20 men and 44 women) or extreme obesity (>35.0) (61 men and 154 women), because they might have influenced the results. All P values were 2-tailed ($\alpha = 0.05$), and data were analyzed with STATA, version 12.1 (StataCorp LP, College Station, Texas).

RESULTS

Baseline characteristics of the 4,824 participants (2,065 men and 2,759 women) are shown in Table 1. Compared with women, men were more likely to have comorbid conditions, to be former smokers, to have higher education, to report more moderate-to-vigorous physical activity, and to have a faster 6-m gait speed. Men also had significantly greater values for muscle lean area, muscle quality, and strength, while women had more myosteatosis ($P < 0.05$ for all). Correlations between muscle composition measures and strength are presented in Web Table 1 (available at http://aje.oxfordjournals.org/).

During a mean follow-up period of 8.8 (SD, 2.8) years, 978 (47%) men died (56.5 per 1,000 person-years) and 964 (35%) women died (38.6 per 1,000 person-years). Table 2 depicts mortality risk per SD-increment increase in thigh muscle composition and strength. All of the muscle composition measures in men were associated with mortality in the model that adjusted for age, BMI, educational level, smoking status, and physical activity level (model 1). Associations were not substantially changed after additional adjustment

Table 1. Baseline Characteristics of 4,824 Participants From the AGES-Reykjavik Study, 2002–2006

	Men ($n = 2,065$)			Women ($n = 2,759$)			*P* Value
	Mean (SD)	No.	%	Mean (SD)	No.	%	
Demographic Factors							
Age at baseline, years	76.5 (5.4)			76.3 (5.6)			0.094
Education							
Less than high school		1,431	69		2,104	76	
High school		257	12		488	18	<0.001
Postecondary		377	18		167	6	
Diabetes mellitus		314	15		259	9	<0.001
Chronic obstructive pulmonary disease		63	3		96	3	0.409
Coronary heart disease		633	31		353	13	<0.001
Lifestyle Factors							
Body mass index[a]	26.8 (3.8)			27.2 (4.7)			0.015
Waist circumference, cm	102.3 (10.5)			99.3 (12.6)			<0.001
Smoking status							
Never smoker		584	28		1,451	53	
Former smoker		1,240	60		953	35	<0.001
Current smoker		241	12		355	13	
Moderate-to-vigorous physical activity							
Rarely or never		1,196	58		1,799	65	
Occasionally		145	7		18	7	<0.001
Moderate to high		724	35		771	28	
Gait speed, m/second	0.98 (0.20)			0.92 (0.20)			<0.001
Metabolic Variables							
Systolic blood pressure, mm Hg	143 (20)			142 (20)			0.059
Diastolic blood pressure, mm Hg	76 (9)			72 (9)			<0.001
LDL cholesterol, mmol/L	3.25 ± 0.98			3.68 (1.04)			<0.001
HDL cholesterol, mmol/L	1.41 (0.38)			1.73 (0.45)			<0.001
C-reactive protein, mg/L	3.65 (6.58)			3.67 (6.16)			0.929
Thigh Muscle Parameters							
Muscle lean area, cm^2	127 (21)			93 (15)			<0.001
Muscle quality, strength/area	3.16 (0.70)			2.79 (0.75)			<0.001
Knee extension strength, N	401 (107)			257 (76)			<0.001
Intermuscular adipose tissue, cm^2	18 (7.9)			19 (7.9)			<0.001
Intramuscular adipose tissue, HU	42 (5.2)			39 (5.1)			<0.001

Abbreviations: AGES, Age, Gene/Environment Susceptibility; HDL, high-density lipoprotein; HU, Hounsfield units; LDL, low-density lipoprotein; N, newtons; SD, standard deviation.

[a] Calculated as weight (in kilograms) divided by squared height (in meters).

for gait speed, diabetes, chronic obstructive pulmonary disease, coronary heart disease, and CRP (model 2). Greater muscle lean area and strength showed an approximate 20% lower mortality risk for each SD-increment increase, whereas greater muscle quality (strength/area) was associated with an 11% decreased risk. Greater intermuscular adipose tissue and intramuscular adipose tissue were associated with increased mortality risks (hazard ratio (HR) = 1.13 (95% confidence interval (CI): 1.06, 1.22) and HR = 1.23 (95% CI: 1.15, 1.30), respectively) (model 2). In women, each SD-increment increase in muscle lean area, muscle quality, and strength was associated with lower mortality risk, with the lowest hazard ratio being that for strength (HR = 0.81, 95% CI: 0.75, 0.88) (model 2). Intramuscular adipose tissue, but not intermuscular adipose tissue, was associated with mortality among women (HR = 1.08, 95% CI: 1.01, 1.16).

To assess how the associations of muscle composition and strength with mortality risk were affected by other muscle composition measures, we additionally adjusted for other muscle composition measures separately in 1 model. Given that muscle quality is based on muscle lean area and knee extension strength, we did not put these 3 components into

Table 2. Associations of Thigh Muscle Composition and Strength (per Standard-Deviation Increment) With All-Cause Mortality in Participants From the AGES-Reykjavik Study, 2002–2006

	Men[a] ($n = 2,065$)				Women ($n = 2,759$)			
	Model 1[b]		Model 2[c]		Model 1		Model 2	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Muscle lean area, cm^2	0.77	0.64, 0.76	0.78	0.71, 0.85	0.80	0.72, 0.85	0.85	0.78, 0.93
Thigh muscle quality (strength/area)	0.83	0.78, 0.89	0.89	0.83, 0.95	0.81	0.76, 0.87	0.88	0.82, 0.94
Knee extension strength, N	0.72	0.67, 0.77	0.79	0.73, 0.86	0.73	0.68, 0.79	0.81	0.75, 0.88
Intermuscular adipose tissue, cm^2	1.14	1.06, 1.22	1.13	1.06, 1.22	1.00	0.93, 1.07	0.99	0.92, 1.07
Intramuscular adipose tissue, HU	1.28	1.21, 1.36	1.23	1.15, 1.30	1.16	1.08, 1.25	1.08	1.01, 1.16

Abbreviations: AGES, Age, Gene/Environment Susceptibility; CI, confidence interval; HR, hazard ratio; HU, Hounsfield units; N, newtons.

[a] Among men, age and C-reactive protein did not meet the Schoenfeld criteria in all models and therefore were modeled as time-varying covariates.

[b] In model 1, results were adjusted for age, body mass index, educational level, smoking status, and physical activity level.

[c] Model 2 adjusted for all of the factors in model 1 plus gait speed, diabetes, chronic obstructive pulmonary disease, coronary heart disease, and C-reactive protein.

1 model—that is, we only adjusted for intermuscular adipose tissue or intramuscular adipose tissue within the association between muscle quality and mortality. Another example would be adjusting for strength within the association between intermuscular adipose tissue and mortality (Table 3). These models showed that muscle lean area and strength influenced each other, but the associations were modest and did not materially alter the results. The coefficient for muscle lean area was weakened by the addition of strength, with a similar but less dramatic change being seen after adjustment for intermuscular adipose tissue or intramuscular adipose tissue; however, associations between muscle lean area and mortality risk remained significant in men. Among men, risk associated with intermuscular adipose tissue was diminished by adjustment for muscle lean area, while strength had little influence.

In sensitivity analyses, adjustment for visceral adipose tissue instead of BMI resulted in similar hazard ratios in comparison with the main analyses, where greater values of muscle lean area, muscle quality, and strength and lower values of myosteatosis were associated with lower mortality risk. The coefficients most affected were those for intermuscular adipose tissue in both men and women, whereas the association remained significant among men. Among women, adjustment for visceral adipose tissue resulted in a lower mortality risk for muscle lean area (HR = 0.80, 95% CI: 0.74, 0.87) (Web Table 2) as models adjusted for BMI.

In addition, the influences of strength and direction of muscle composition on mortality risk were comparable with the original associations after exclusion of participants with extreme BMI values. The coefficient most affected was muscle lean area among women, and the association became borderline-significant (HR = 0.92, 95% CI: 0.84, 1.01) (Web Table 3).

DISCUSSION

In this study of older adults, we examined thigh muscle composition and knee extension strength in relation to mortality risk. Our results indicate that the composition and function of muscle may determine mortality risk in older persons. Greater intramuscular adipose tissue was associated with higher mortality risk in both men and women, while greater intermuscular adipose tissue was associated with increased mortality risk among men only. We further showed that among both men and women, muscle quality and strength remained associated with lower mortality risk independently of other muscle composition measures. Associations between muscle composition measures were independent of visceral adipose tissue. In addition, associations remained after exclusion of participants with BMIs less than 18.5 and greater than 35.0. This suggests that muscle composition measures may be important mortality risk factors, regardless of weight or adiposity, that may be helpful for refining mortality estimates in older adults.

Muscle quality is an important measure, since it represents muscle strength relative to muscle size and is associated with survival. Previous studies have shown that the loss of muscle strength is greater than the loss of muscle mass in older adults, leading to a decrease in muscle quality with age (35–38). This indicates that the decline in muscle mass alone cannot explain the decrease in muscle quality and that other changes in muscle composition might explain the deterioration of muscle quality (37). Myosteatosis might contribute to the decrease in muscle quality due to the proinflammatory properties of the adipose tissue infiltrated into the muscle (39). However, in our analyses, adjustment for a general indicator of inflammation did not attenuate results. As Newman et al. (40) mentioned, the prevention of muscle quality decline is likely to be accomplished through preservation of muscle mass and that effect on the maintenance of strength; however, body fat and myosteatosis also play a role in muscle quality. Since this was (to our knowledge) the first study investigating the association between thigh muscle quality and mortality risk, future studies are needed to corroborate our findings, and mechanistic studies are warranted to determine how better muscle quality and myosteatosis are associated with survival. In addition, determining sex-specific cutpoints for muscle quality might be a useful tool in gerontology to identify persons at greater mortality risk, especially since sarcopenia definitions

Table 3. Risk of Mortality per Standard-Deviation Increment of Thigh Muscle Composition and Strength After Additional Adjustment for Other Muscle Parameters (Model 3[a]) in Participants From the AGES-Reykjavik Study, 2002–2006

	Men[b] ($n = 2,065$)		Women ($n = 2,759$)	
	HR	95% CI	HR	95% CI
Muscle lean area, cm^2	0.78	0.71, 0.85	0.85	0.78, 0.93
+ Knee extension strength	0.84	0.76, 0.92	0.91	0.83, 1.00
+ Intermuscular adipose tissue	0.80	0.73, 0.88	0.86	0.78, 0.93
+ Intramuscular adipose tissue	0.82	0.75, 0.90	0.86	0.79, 0.94
+ Intermuscular adipose tissue + knee extension strength	0.86	0.78, 0.94	0.91	0.83, 1.00
+ Intramuscular adipose tissue + knee extension strength	0.87	0.79, 0.95	0.91	0.83, 1.00
Thigh muscle quality (strength/area)	0.89	0.83, 0.95	0.88	0.82, 0.94
+ Intermuscular adipose tissue	0.89	0.83, 0.95	0.88	0.82, 0.94
+ Intramuscular adipose tissue	0.91	0.86, 0.97	0.89	0.82, 0.95
Knee extension strength, N	0.79	0.73, 0.86	0.81	0.75, 0.88
+ Muscle lean area	0.84	0.77, 0.91	0.83	0.77, 0.90
+ Intermuscular adipose tissue	0.80	0.74, 0.87	0.81	0.75, 0.88
+ Intramuscular adipose tissue	0.83	0.77, 0.90	0.82	0.76, 0.89
+ Muscle lean area + intermuscular adipose tissue	0.84	0.77, 0.91	0.83	0.77, 0.90
+ Muscle lean area + intramuscular adipose tissue	0.86	0.79, 0.94	0.84	0.77, 0.91
Intermuscular adipose tissue, cm^2	1.13	1.06, 1.22	0.99	0.92, 1.07
+ Muscle lean area	1.07	0.99, 1.15	1.00	0.93, 1.07
+ Knee extension strength	1.10	1.02, 1.18	0.99	0.92, 1.07
+ Intramuscular adipose tissue	1.04	0.96, 1.12	0.97	0.89, 1.04
+ Muscle lean area + knee extension strength	1.06	0.98, 1.14	1.00	0.93, 1.07
+ Muscle lean area + knee extension strength + intramuscular adipose tissue	0.99	0.92, 1.08	0.98	0.91, 1.06
Intramuscular adipose tissue, HU	1.23	1.15, 1.30	1.08	1.01, 1.16
+ Muscle lean area	1.18	1.11, 1.26	1.08	1.00, 1.16
+ Knee extension strength	1.18	1.11, 1.26	1.05	0.98, 1.13
+ Intermuscular adipose tissue	1.21	1.13, 1.29	1.09	1.01, 1.18
+ Muscle lean area + knee extension strength	1.16	1.09, 1.24	1.05	0.98, 1.13
+ Muscle lean area + knee extension strength + intermuscular adipose tissue	1.16	1.08, 1.25	1.06	0.98, 1.14

Abbreviations: AGES, Age, Gene/Environment Susceptibility; CI, confidence interval; HR, hazard ratio; HU, Hounsfield units; N, newtons.

[a] Results were adjusted for age, body mass index, educational level, smoking status, physical activity level, gait speed, diabetes, chronic obstructive pulmonary disease, coronary heart disease, and C-reactive protein, with additional adjustment for other muscle composition measures.

[b] Among men, age and C-reactive protein did not meet the Schoenfeld criteria in all models and therefore were modeled as time-varying covariates.

include muscle and strength/gait speed but do not consider other muscle measures that could potentially improve mortality estimates. Furthermore, more studies are needed to easily measure muscle composition measures in a clinical setting.

Greater strength was associated with decreased mortality risk, which is comparable to numerous other studies that have investigated strength (both grip and leg strength) in relation to survival (2–8, 18). The inverse association between muscle strength and mortality risk likely reflects the association between strength and better physical functioning and thereby lower mortality risk. Our results for other muscle composition measures are supported by several prior studies. However, the majority of previously published studies used bioelectrical impedance analysis or dual-energy x-ray absorptiometry imaging to measure muscle composition. Results from the National Health and Nutrition Examination Survey ($n = 3,659$) showed that participants with the lowest muscle mass index (muscle mass/height^2) had higher mortality risk (13), which was also observed in a study carried out among 1,512 Taiwanese elderly (14). In contrast, in a study of 4,107 British men, fat mass index or fat-free mass index was not associated with mortality (9). Similar results were

observed in a study with 3,793 French women, where greater total lean mass was not associated with better survival (11). CT imaging provides a more precise description of muscle composition and allows determination of muscle adipose tissue infiltration. Thereby it provides further understanding of relationships between muscle composition and mortality. Our results parallel those found in unhealthy populations (peripheral arterial disease), where lower calf skeletal muscle density (41) or leg strength (42) has been associated with higher mortality risk. However, Cesari et al. (19) observed no independent associations between calf muscle composition and mortality risk among 934 Italian community-dwelling older adults. Important study differences may have contributed to discrepancies between results. Compared with the study by Cesari et al., AGES-Reykjavik may have had greater power to detect risk, since there was a longer follow-up period (8.8 years vs. 5.1 years) and a greater number of deaths (1,942/4,824 (40.3%) vs. 263/934 (28.2%)). However, it is not possible to compare mean values for the muscle components, since the site of the CT imaging was not consistent between studies (thigh vs. calf). Additional studies are needed to clarify relationships between muscle composition measures and mortality.

Strength and limitations

A major strength of this study was the availability of CT data, which enabled determination of muscle lean area, as well as myosteatosis. While there are many studies of body weight, body fat, and mortality risk, less focus has been put on the relationships of muscle size and muscle adipose tissue infiltration with mortality risk. In addition, the large sample size was a further benefit and allowed us to perform sex-specific analyses. A further strength was the well-characterized study population, which allowed for adjustment of many potential confounders and provided evidence that muscle composition measures are associated with mortality independently of other lifestyle and demographic factors.

Some limitations should be noted, however. First, a single time point for measurement of muscle composition and strength was used in this paper; thus, we were not able to investigate the role of gains or losses in these parameters. Second, information on cause-specific mortality was not available for all participants, and further studies are needed to determine whether associations between muscle composition measures and mortality are driven by mortality from specific causes. Third, the study population consisted of survivors from the Reykjavik Study. A limitation is the nonparticipation of frail individuals or persons with more disease in the AGES-Reykjavik Study, which may have caused a bias towards healthier persons at baseline in this study. In addition, participants who were excluded from the analytical cohort due to missing measurements were older and more likely to have comorbidity at baseline, resulting in a healthier analytical sample, and this might have caused a potential survival bias, which may have led to underestimation of the associations observed. Finally, the AGES-Reykjavik Study population consists of persons of European ancestry, which limits external validity for other ethnic groups.

In conclusion, in this study, the composition and strength of the thigh muscle were associated with mortality risk among 4,824 older men and women. These results may be useful for refining mortality estimates, and they show the importance of improving muscle strength and area and lowering muscle adipose tissue infiltration.

ACKNOWLEDGMENTS

Author affiliations: Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, Maryland (Ilse Reinders, Rachel A. Murphy, Lenore Launer, Tamara B. Harris); EMGO$^+$ Institute for Health and Care Research and Department of Health Sciences, Faculty of Earth and Life Sciences, VU University Amsterdam, Amsterdam, the Netherlands (Ilse Reinders, Ingeborg A. Brouwer, Marjolein Visser); Department of Nutrition and Dietetics, Internal Medicine Unit, VU University Medical Center, Amsterdam, the Netherlands (Marjolein Visser); Icelandic Heart Association Research Institute, Kopavogur, Iceland (Kristin Siggeirsdottir, Gudny Eiriksdottir, Vilmundur Gudnason); Faculty of Medicine, University of Iceland, Reykjavik, Iceland (Vilmundur Gudnason, Palmi V. Jonsson); Department of Geriatrics, Landspitali National University Hospital, Reykjavik, Iceland (Palmi V. Jonsson); and Department of Radiology and Biomedical Imaging, School of Medicine, University of California, San Francisco, San Francisco, California (Thomas F. Lang).

This work was supported by the National Institute on Aging, US National Institutes of Health (grant N01-AG-12100), the National Institute on Aging Intramural Research Program, Hjartavernd (Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

We thank the Icelandic Heart Association clinic staff for their invaluable contribution.

The views represented herein are our own, and the decision to submit the manuscript for publication was solely ours.

R.A.M. is currently an employee of DSM Nutritional Products (Parsippany, New Jersey). Her employment was subsequent to the analyses conducted in this study.

REFERENCES

1. Cruz-Jentoft AJ, Landi F, Topinková E, et al. Understanding sarcopenia as a geriatric syndrome. *Curr Opin Clin Nutr Metab Care*. 2010;13(1):1–7.
2. Rantanen T. Muscle strength, disability and mortality. *Scand J Med Sci Sports*. 2003;13(1):3–8.
3. Cooper R, Kuh D, Hardy R, et al. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ*. 2010;341:c4467.
4. Rantanen T, Volpato S, Ferrucci L, et al. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc*. 2003;51(5):636–641.
5. Metter EJ, Talbot LA, Schrager M, et al. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med Sci*. 2002;57(10):B359–B365.
6. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ*. 2008;337:a439.

7. Legrand D, Vaes B, Matheï C, et al. Muscle strength and physical performance as predictors of mortality, hospitalization, and disability in the oldest old. *J Am Geriatr Soc*. 2014;62(6): 1030–1038.
8. Al Snih S, Markides KS, Ray L, et al. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc*. 2002; 50(7):1250–1256.
9. Wannamethee SG, Shaper AG, Lennon L, et al. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr*. 2007;86(5): 1339–1346.
10. Han SS, Kim KW, Kim KI, et al. Lean mass index: a better predictor of mortality than body mass index in elderly Asians. *J Am Geriatr Soc*. 2010;58(2):312–317.
11. Rolland Y, Gallini A, Cristini C, et al. Body-composition predictors of mortality in women aged ≥75 y: data from a large population-based cohort study with a 17-y follow-up. *Am J Clin Nutr*. 2014;100(5):1352–1360.
12. Szulc P, Munoz F, Marchand F, et al. Rapid loss of appendicular skeletal muscle mass is associated with higher all-cause mortality in older men: the prospective MINOS study. *Am J Clin Nutr*. 2010;91(5):1227–1236.
13. Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. *Am J Med*. 2014;127(6): 547–553.
14. Chuang SY, Chang HY, Lee MS, et al. Skeletal muscle mass and risk of death in an elderly population. *Nutr Metab Cardiovasc Dis*. 2014;24(7):784–791.
15. Addison O, Marcus RL, Lastayo PC, et al. Intermuscular fat: a review of the consequences and causes. *Int J Endocrinol*. 2014; 2014:309570.
16. Goodpaster BH, Carlson CL, Visser M, et al. Attenuation of skeletal muscle and strength in the elderly: the Health ABC Study. *J Appl Physiol (1985)*. 2001;90(6):2157–2165.
17. Reinders I, Murphy RA, Koster A, et al. Muscle quality and muscle fat infiltration in relation to incident mobility disability and gait speed decline: the Age, Gene/Environment Susceptibility-Reykjavik Study. *J Gerontol A Biol Sci Med Sci*. 2015;70(8):1030–1036.
18. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*. 2006;61(1):72–77.
19. Cesari M, Pahor M, Lauretani F, et al. Skeletal muscle and mortality results from the InCHIANTI Study. *J Gerontol A Biol Sci Med Sci*. 2009;64(3):377–384.
20. Bjornsson OJ, Davidsson D, Olafsson H, et al. *Stages I–III, 1967–1968, 1970–1971 and 1974–1975. Participants, Invitation, Response etc*. Reykjavik, Iceland: Icelandic Heart Association; 1979.
21. Bjornsson G, Bjornsson OJ, Davidsson D, et al. *Report XXIV. Health Survey in the Reykjavik Area—Women. Stages I–III, 1968–1969, 1971–1972 and 1976–1978. Participants, Invitation, Response etc*. Reykjavik, Iceland: Icelandic Heart Association; 1982.
22. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, Gene/ Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol*. 2007;165(9):1076–1087.
23. Sigurdsson G, Aspelund T, Chang M, et al. Increasing sex difference in bone strength in old age: the Age, Gene/ Environment Susceptibility-Reykjavik study (AGES-Reykjavik). *Bone*. 2006;39(3):644–651.
24. Johannesdottir F, Aspelund T, Siggeirsdottir K, et al. Mid-thigh cortical bone structural parameters, muscle mass and strength, and association with lower limb fractures in older men and women (AGES-Reykjavik Study). *Calcif Tissue Int*. 2012; 90(5):354–364.
25. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. *Curr Opin Clin Nutr Metab Care*. 2010;13(3):260–264.
26. Goodpaster BH, Kelley DE, Thaete FL, et al. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *J Appl Physiol (1985)*. 2000; 89(1):104–110.
27. Lang T, Koyama A, Li C, et al. Pelvic body composition measurements by quantitative computed tomography: association with recent hip fracture. *Bone*. 2008;42(4): 798–805.
28. Era P, Rantanen T, Avlund K, et al. Maximal isometric muscle strength and anthropometry in 75-year-old men and women in three Nordic localities. *Scand J Med Sci Sports*. 1994;4(1): 26–31.
29. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2): M85–M94.
30. Ostir GV, Markides KS, Black SA, et al. Lower body functioning as a predictor of subsequent disability among older Mexican Americans. *J Gerontol A Biol Sci Med Sci*. 1998; 53(6):M491–M495.
31. Woo J, Leung J, Morley JE. Defining sarcopenia in terms of incident adverse outcomes. *J Am Med Dir Assoc*. 2015;16(3): 247–252.
32. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309(1):71–82.
33. Flegal KM, Kit BK, Graubard BI. Body mass index categories in observational studies of weight and risk of death. *Am J Epidemiol*. 2014;180(3):288–296.
34. Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. *Epidemiol Rev*. 2013;35(1):51–65.
35. Delmonico MJ, Harris TB, Visser M, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. *Am J Clin Nutr*. 2009;90(6):1579–1585.
36. Kennis E, Verschueren S, Van Roie E, et al. Longitudinal impact of aging on muscle quality in middle-aged men. *Age (Dordr)*. 2014;36(4):9689.
37. Moore AZ, Caturegli G, Metter EJ, et al. Difference in muscle quality over the adult life span and biological correlates in the Baltimore Longitudinal Study of Aging. *J Am Geriatr Soc*. 2014;62(2):230–236.
38. Doherty TJ. Invited review: aging and sarcopenia. *J Appl Physiol (1985)*. 2003;95(4):1717–1727.
39. Beasley LE, Koster A, Newman AB, et al. Inflammation and race and gender differences in computerized tomography-measured adipose depots. *Obesity (Silver Spring)*. 2009;17(5):1062–1069.
40. Newman AB, Haggerty CL, Goodpaster B, et al. Strength and muscle quality in a well-functioning cohort of older adults: the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2003;51(3):323–330.
41. McDermott MM, Liu K, Tian L, et al. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: a longitudinal study. *J Am Coll Cardiol*. 2012; 59(13):1159–1167.
42. Singh N, Liu K, Tian L, et al. Leg strength predicts mortality in men but not in women with peripheral arterial disease. *J Vasc Surg*. 2010;52(3):624–631.