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Early body composition, but not body mass, is associated with future accelerated decline in muscle quality

Elisa Fabbri[1,2*], Nancy Chiles Shaffer[1], Marta Gonzalez-Freire[1], Michelle D. Shardell[1], Marco Zoli[2], Stephanie A. Studenski[1] & Luigi Ferrucci[1]

[1]*Longitudinal Study Section, Translational Gerontology Branch, Intramural Research Program, National Institute on Aging, National Institutes of Health, 251 Bayview Boulevard, Baltimore, MD 21224-6825, USA;* [2]*Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*

Abstract

Background Muscle quality (MQ) or strength-to-mass ratio declines with aging, but the rate of MQ change with aging is highly heterogeneous across individuals. The identification of risk factors for accelerated MQ decline may offer clues to identity the underpinning physiological mechanisms and indicate targets for prevention and treatment. Using data from the Baltimore Longitudinal Study of Aging, we tested whether measures of body mass and body composition are associated with differential rates of changes in MQ with aging.

Methods Participants included 511 men and women, aged 50 years or older, followed for an average of 4 years (range: 1–8). MQ was operationalized as ratio between knee-extension isokinetic strength and CT-thigh muscle cross-sectional area. Predictors included body mass and body composition measures: weight (kg), body mass index (BMI, kg/m^2), dual-energy x-ray absorptiometry-measured total body fat mass (TFM, kg) and lean mass (TLM, kg), and body fatness (TFM/weight). Covariates were baseline age, sex, race, and body height.

Results Muscle quality showed a significant linear decline over the time of the follow up (average rate of decline 0.02 Nm/cm^2 per year, $P < .001$). Independent of covariates, neither baseline body weight ($P = .756$) nor BMI ($P = .777$) was predictive of longitudinal rate of decline in MQ. Instead, higher TFM and lower TLM at baseline predicted steeper longitudinal decline in MQ ($P = .036$ and $P < .001$, respectively). In particular, participants with both high TFM and low TLM at baseline experienced the most dramatic decline compared with those with low TFM and high TLM (about 3% per year vs. 0.5% per year, respectively). Participants in the higher tertile of baseline body fatness presented a significantly faster decline of MQ than the rest of the population ($P = .021$). Similar results were observed when body mass, TFM, and TLM were modeled as time-dependent predictors.

Conclusions Body composition, but not weight nor BMI, is associated with future MQ decline, suggesting that preventive strategies aimed at maintaining good MQ with aging should specifically target body composition features.

Keywords Muscle quality; Body composition; BMI; Aging; Longitudinal study

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**Correspondence to: Elisa Fabbri, MD, National Institute on Aging, NIH, 251 Bayview Blvd, Baltimore, MD 21224, USA. Phone: +39 3294540198, Fax: 410-350-7304, Email: elisa.fabbri@nih.gov*

Introduction

One of the most pervasive and remarkable features of aging is a progressive loss of muscle strength, which contributes to reduced capability of movement and independence.[1] Individuals who maintain good muscle strength also better compensate for the presence of other impairments, such as pain and balance problems, and therefore have lower risk of developing mobility loss.[2] Previous evidence demonstrated that age-associated decline in muscle strength exceeds what is expected on the basis of the decline in muscle mass alone, particularly after the age of 60–70 years, suggesting that the intrinsic capacity of muscle tissue to generate force, often referred to as muscle biomechanical quality, is progressively

reduced.[1,3–6] Muscle quality (MQ), often operationalized as the ratio between some measure of muscle strength or power per unit of muscle mass, is almost constant in children and young adults but, for unknown reasons, there is large inter-individual variability in older adults, with MQ well-preserved in some individuals but not in others. Proposed hypotheses include an intrinsic reduction of contractility, fat micro and macro-infiltrations, increase in collagen, denervation only partially compensated by re-innervation, and progressively less efficient neurological control of contraction.[2] Muscle quality has also emerged as a better predictor of functional limitation and poor health in older adults than muscle mass alone.[3,7,8]

Previous cross-sectional studies suggested that body composition may strongly affect MQ. Specifically, intramuscular and intermuscular fat infiltration, as well as intramyocellular lipid storage, may impair muscle force production in the elderly.[9]

A few previous cross-sectional studies explored the relationship of body mass and body composition with MQ and their interacting impact on physical function and performance, supporting a cross-sectional association between obesity and poor MQ.[10–12] However, longitudinal trajectories of decline of MQ in older adults have not been fully investigated, and the identification of early predictors of such decline had so far limited success. In the Baltimore Longitudinal Study of Aging (BLSA), the longitudinal decline in muscle strength significantly exceeded that predicted by the decline in muscle mass, but no risk factor for accelerated decline was identified.[14] The excess decline in muscle strength compared with muscle mass was confirmed in the Health, Aging, and Body Composition (Health ABC) and was interpreted as due to age-related increase in muscular fat infiltration.[13] Koster and colleagues also analysed data from the Health ABC participants and found that baseline higher fatness was cross-sectionally associated with poorer MQ, although no significant association was found with longitudinal decline in MQ.[14] However, these studies are limited to persons 70–79 years old who were highly functional at baseline.

Using data from men and women, aged 50 to 95 years, enrolled in the BLSA, we describe longitudinal trajectories of MQ, operationalized as ratio between knee-extension isokinetic torque and thigh muscle cross-sectional area. We also tested the hypothesis that high body mass and/or body composition measures predicted accelerated decline of MQ with aging, independent of baseline age, sex, race, and body height.

Methods

Study design and setting

The BLSA is a study of human aging established in 1958 and conducted by the National Institute on Aging Intramural Research Program. A general description of the sample and enrollment procedures and criteria has been previously reported.[15] Briefly, the BLSA continuously enrolls healthy volunteers aged 20 years and older who are followed for life with follow-up visits conducted at intervals of 1 to 4 years, with more frequent follow-up for older persons. Participants are assessed at the National Institute on Aging Intramural Research Program Clinical Research Unit in Baltimore, Maryland, over three days of testing. Certified nurse practitioners and certified technicians administer all assessments following standardized protocols. All participants receive an extensive description of the study protocol, procedures, and risk associated with participation and consent to be part of the study at each single visit.

Participants

The overall sample for the present study consists of 511 BLSA participants, aged 50 to 95 years old and with longitudinal data available on MQ, assessed between January 2006 and June 2014. The average follow-up time was 4 years (range 1–8 years). Also, the number of participants by length of follow-up and the number of observations by follow-up time (years) are, respectively, provided in *Tables* S1A and S1B (Supporting Information 1).

Measurements

Body mass

With participants in a gown, body weight was measured in kilograms with a calibrated scale to the nearest 0.1 kg. Body height was measured in centimeters by a stadiometer to the nearest 0.1 cm.[16] Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2).

Body composition

Total body dual-energy x-ray absorptiometry (DEXA) was performed using the Prodigy Scanner (General Electric, Madison, WI) and analysed with version 10.51.006 of the software. DEXA uses tissue absorption of x-ray beams to identify different components of the human body (bone mineral content, lean body mass, and fat mass) and to provide quantitative data on body composition.[17,18] Absolute measures of total body fat mass (TFM) and total body lean mass (TLM) in kilograms as well as body fatness (TFM/body weight) were included in the present analysis.

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Muscle quality

Muscle strength (peak torque) assessment

Maximum quadricep strength was defined as the highest value of torque (peak torque) from either leg in up to three consecutive measures of concentric knee extensor strength (Newton per meters, Nm) using isokinetic dynamometer at an angular velocity of 0.52 rad/s (30°/s).

The Kinetic Communicator (Kin-Com Model 125E, version 3.2; Chattanooga Group, Chattanooga, TN) dynamometer was used to assess strength in BLSA until 2010.[19] From 2010 up to now, muscle strength was tested by the Biodex Multi-Joint System-PRO (Biodex Medical System, Advantage Software V.4X, Inc., Shirley, NY, USA) dynamometer.[20] In Supporting Information 2, we provide a detailed description of the methods used to acquire strength measures for each of two instruments. Validity and reliability of both the dynamometers both were reported in previous studies.[21–23] The dynamometer's calibration settings were verified on a regular basis throughout the data collection period according to the manufacturers' guidelines.

To address the possibility of systematic differences in strength measures due to the change in instrument, we developed a conversion equation using data from 76 participants who underwent both Kin-com and Biodex strength tests at the same visit to (Supporting Information 3). After the conversion, sensitivity analyses excluded a residual effect of the type of instrument on baseline strength values and change overtime in strength values in the sample population (Supporting Information 4).

Thigh cross-sectional muscle area (CMA) assessment

Cross-sectional muscle area (CMA) of the thigh was measured from 10 mm CT images captured at midfemur by a Somatom Sensation 10 CT scanner (Siemens, Malvern, PA) and quantified using Geanie software version 2.1 (BonAlyse, Jyvaskyla, Finland; http:// www.bonalyse.com).[24] Different tissues in the analysis were separated according to different density thresholds: a density value of 35 mg/mm was used to separate fat from muscle tissue, and 180 mg/mm to separate muscle from bone tissue. Analysed images were visualized and individually checked for mistakes in the identification and contouring of different tissue. Macroscopically detectable intramuscular fat was not included in the calculation of muscle area.

Muscle quality definition

Muscle quality (Nm/cm^2) was operationalized as the ratio between the maximum quadriceps torque, measured by isokinetic dynamometer, and mid thigh CT-scan CMA. Then, MQ was calculated as: MQ = Strength peak torque / CMA.

Noteworthy, in a previous cross-sectional analysis in BLSA, a positive association between MQ and height was described.[10] This finding is probably explained by the fact that CMA is a two-dimensional measure that does not fully take into account differences due to body size. To verify whether differences in body size affect our findings, we also calculated two alternative versions of the MQ ratio after normalization of CMA according to body height (h). In particular, CMA was normalized using the following formulas: $N_{CMA1} = [(CMA_x) / (h_x^2)] \times (h_{mean}^2)$ or $N_{CMA2} = [(CMA_x) \times (h_x^2)] / (h_{mean}^2)$, where CMA_x and h_x denote the CMA and height, respectively, for the x^{th} observation, and h_{mean} denotes the mean height from all observations in our sample population. Then, N_{CMA1} and N_{CMA2} were used to calculate two additional metrics of normalized MQ ratio (N_{MQ} = strength peak torque / N_{CMA}).

Statistical analyses

Summary statistics of the population at the baseline are presented as mean (± standard deviation, SD) or number (percentage).

Longitudinal analyses were performed, and the endpoint was MQ operationalized as a continuous variable. Linear mixed models were used to describe change in MQ over the time of the follow-up and to exclude the influences of various unknown factors. First, a parsimonious model including only baseline age, sex, race (Caucasian vs. non-Caucasian), and body height as covariates was fitted (Model I). Then, the association between body mass/body composition measures and longitudinal decline in MQ was tested independent of covariates using linear mixed models (Models II and III, respectively). In particular, MQ was used as outcome variable, while body mass and body composition measures were used as predictors ('predictor', 'time', and 'predictor × time'). Baseline age, sex, race (Caucasian vs. non-Caucasian), and body height were included as covariates. Noteworthy, body mass and body composition were tested both as baseline variables and time-dependent variables (*Tables* 2 and 3, respectively). Furthermore, we performed some exploratory analyses stratifying our sample population according to sex-specific tertile cut-off of baseline TFM and TLM (not shown). We observed that participants in the highest tertile of TFM and lowest tertile of TLM experienced the steeper decline in MQ, while no significant differences were found among the other groups. Thus, we clustered our sample population according to three baseline body composition groups: 1. Reference group; 2. EITHER lowest tertile of TLM OR highest tertile of TFM; and 3. BOTH lowest tertile of TLM AND highest tertile of TFM. Then, we used linear mixed models to compare the longitudinal decline in MQ according to these three groups and independent of covariates. Moreover, we explored baseline and time-varying body fatness (operationalized as TFM divided by body weight) in relation to longitudinal change in MQ

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(Models I and III, *Table* 4). Baseline body fatness was also categorized as higher tertile (sex-specific cut points) vs. the rest of the population (Model 2, *Table* 4). *Figure* 1 represents estimated trajectories of longitudinal decline in MQ according to baseline categories of body fatness (higher tertile vs. rest of the population) for BLSA participants who entered the study in different age decades. Finally, sensitivity analyses were performed using the two version of normalized thigh CMA (NCMA1 and NCMA2) to compute MQ. Results of these additional analyses are shown in the appendix.

All the analyses were conducted using the SAS statistical package, version 9.3 (SAS institute Inc.,

Cary, NC). Figures were created in R 3.1.2.

Results

Baseline study sample characteristics

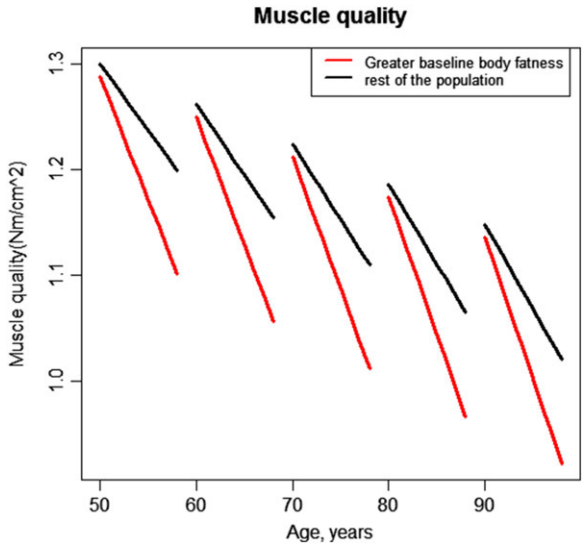
Baseline study sample included 511 BLSA participants (261 men and 250 women) aged 50–95 years (mean age ± SD: 70.2 ± 9.9 years). The mean BMI was 26.7 ± 4.0 kg/m^2. The mean values of DEXA-measured TFM and lean body mass were, respectively, 26.4 ± 9.5 kg and 47.3 ± 9.8 kg. The average knee extensors peak strength was 127.0 ± 38.8 (Nm). The mean CT-measured thigh cross-sectional area was 105.2 ± 27.5 cm^2. The average crude MQ ratio was 1.22 ± 0.26 Nm/cm^2. Baseline cross-sectional characteristics of the population according to (sex-specific) tertiles of MQ are presented in *Table* 1.

Longitudinal analysis

Independent of baseline age and sex, MQ ratio significantly declined with age (average rate of decline: −0.018 ± 0.002 Nm/cm^2 per year, $P < .001$). Women declined significantly faster than men (average rate of decline for women: −0.025 ± 0.003 Nm/cm^2 per year vs. for men: −0.010 ± 0.003 Nm/cm^2 per year, $P < .001$), while no significant association was found for baseline age ($P = .717$). Of note, when adjusting also for body height, sex differences were no longer significant. Moreover, we found no effect of race on longitudinal rate of decline, independent of baseline age, sex, and body height (Model I, *Table* 2).

Next, we tested the association between baseline measures of body mass/body composition and longitudinal decline in MQ. Independent of age, sex, race, and body height, no association was found between baseline body weight and longitudinal rate of decline in MQ ($P = .756$, Model II, *Table* 2). Similarly, no association was found for baseline BMI ($P = .777$) and even baseline BMI categories ($P = .615$), including obesity ($P = .701$). On the contrary, baseline measures of body composition were significantly and independently associated with longitudinal rate of decline in MQ. In particular, independent of covariates, higher TFM

Figure 1 Longitudinal trajectories of muscle quality decline estimated for Baltimore Longitudinal Study of Aging (BLSA) participants who entered the study in different age decades and according to higher (sex-specific) tertile of body fatness (red solid line) vs. rest of the population (dark solid line).



Note: Participants with greater body fatness experienced a decline in MQ almost twice faster than the rest of the population (P=.021, Model II, Table 4).

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Table 1 Baseline cross-sectional characteristics of the population according to (sex-specific) tertiles of muscle quality

	Muscle quality (Nm/cm^2)			
	Lowest tertile (n = 171)	Medium tertile (n = 169)	Highest tertile (n = 171)	P value[a]
Age (years)	71.5 (9.9)	70.1 (9.4)	68.9 (10.3)	.054
Sex (men)	87 (33%)	87 (33%)	87 (33%)	.992
Race (Caucasian)	100 (29.5%)	115 (33.9)	124 (36.6)	.019
Height, cm	167.6 (9.2)	168.3 (8.9)	170.5 (9.9)	.011
Weight, kg	77.4 (15.2)	75.8 (13.9)	75.9 (14.8)	.541
BMI, kg/m^2	27.4 (4.2)	26.6 (3.8)	26.01 (4.04)	.006
Total body fat mass (TFM), kg	26.8 (9.9)	26.2 (9.0)	26.2 (9.6)	.797
Body fatness (TFM/weight)	0.34 (0.9)	0.34 (0.8)	0.34 (0.9)	.978
Diabetes, *N* (%)	27 (15.8)	20 (11.8)	18 (10.5)	.315
Low (self-reported) physical activity, *N* (%)	62 (36.3)	66 (39.3)	58 (33.9)	.589

[a]*P* anova or chi-square.

Table 2 Results from linear mixed models testing associations of baseline body weight, total body fat mass (TFM), and total body lean mass (TLM) with longitudinal rate of decline in muscle quality (MQ), after adjustment for baseline age, sex, race, and time-varying height

Predictors	Muscle quality (Nm/cm^2)					
	Model I		Model II		Model III	
	β(SE)	P value	β(SE)	P value	β(SE)	P value
Baseline age (years)	−0.004 (0.001)	<.001	−0.005 (0.001)	<.001	−0.006 (0.001)	<.001
Sex (men)	−0.08 (0.03)	.015	−0.06 (0.03)	.046	0.06 (0.04)	.148
Race (Caucasian)	0.11 (0.02)	<.001	0.09 (0.02)	<.001	0.09 (0.02)	<.001
Height (cm)	0.004 (0.002)	.025	0.007 (0.002)	<.001	0.010 (0.002)	<.001
Baseline body weight (kg)			−0.004 (0.001)	<.001		
Baseline TFM (SD)					−0.009 (0.012)	.414
Baseline TLM (SD)					−0.013 (0.02)	<.001
Time (years)	−0.016 (0.002)	<.001	−0.015 (0.002)	<.001	−0.015 (0.002)	<.001
Baseline age (years) × time	0.0001 (0.002)	.783	0.0001 (0.0002)	.659	0.0003 (0.0002)	.226
Sex (men) × time	0.009 (0.007)	.181	0.009 (0.007)	.198	−0.015 (0.009)	.104
Race (Caucasian) × time	−0.0001 (0.005)	.989	0.0005 (0.005)	.907	0.0001 (0.005)	.978
Height (cm) × time	0.0004 (0.003)	.228	0.0004 (0.003)	.228	−0.0003 (0.0004)	.515
Baseline body weight (kg) × time			0.0001(0.0002)	.756		
Baseline TFM (SD) × time					−0.005 (0.002)	.036
Baseline TLM (SD) × time					0.019 (0.005)	<.001

and lower TLM predicted faster decline in MQ (P = .036 and $P < .001$ respectively; Model III, *Table* 2).

Results were also confirmed when body mass and measures of body composition were included in the model as time-dependent predictors (*Table* 3).

To better understand and interpret the findings described above, we ran some additional exploratory analyses by coding body composition according to sex-specific tertile cut-off of baseline TFM and TLM (Supporting Information 5). In particular, we identified three baseline body composition groups: 1. Reference group; 2. EITHER lowest tertile of TLM OR highest tertile of TFM; and 3. BOTH lowest tertile of TLM AND highest tertile of TFM. Comparing them, we found that participants who were either in the lowest tertile of TLM or in the highest tertile of TFM (group 2) experienced a significantly faster decrease in MQ compared with the reference group (β = −0.013, P = .006), but those who were in the highest tertile of TFM and the lowest tertile of TLM (group 3) experienced the most rapid decline (β = −0.031, P = .002, Supporting Information 6). In other word, participants with both high TFM and low TLM at baseline presented almost 6 times faster decline in MQ compared with those with low TFM and high TLM (about 3% per year vs. 0.5% per year, respectively).

Analysis using body fatness as predictor

Additional analyses were conducted using body fatness (operationalized as TBFM/body weight) as a measure of adiposity. The results, presented in *Table* 4, were substantially consistent with the original analysis. In particular, independent of covariates, an inverse association approaching statistical significance was found between baseline body fatness and longitudinal rate of decline in MQ (P = .053, Model I, *Table* 4). When comparing participants who were at baseline in the higher (sex-specific) tertile of body fatness to the rest of the population, we confirmed that those with

Table 3 Results from linear mixed models testing associations of time-varying body weight, total body fat mass (TFM), and total body lean mass (TLM) with longitudinal rate of decline in muscle quality (MQ), after adjustment for baseline age, sex, race, and time-varying height

Predictors	Muscle quality (Nm/cm^2)			
	Model I		Model II	
	β(SE)	*P* value	β(SE)	*P* value
Baseline age (years)	−0.005 (0.001)	<.001	−0.006 (0.001)	<.001
Sex (men)	−0.06 (0.03)	.046	0.07 (0.04)	.078
Race (Caucasian)	0.09 (0.02)	<.001	0.09 (0.02)	<.001
Height (cm)	0.01 (0.002)	<.001	0.01 (0.002)	<.001
Time-varying body weight (kg)	−0.004 (0.001)	<.001		
Time-varying TFM (SD)			−0.007 (0.01)	.517
Time-varying TLM (SD)			−0.014 (0.02)	<.001
Time (years)	−0.015 (0.002)	<.001	−0.015 (0.002)	<.001
Baseline age (years) × time	0.000005 (0.0002)	.985	0.0002 (0.0002)	.424
Sex (men) × time	0.009 (0.007)	.138	−0.014 (0.009)	.109
Race (Caucasian) × time	0.0002 (0.002)	.959	−0.0002 (0.005)	.946
Height (cm) × time	0.0004 (0.0004)	.242	−0.0002 (0.005)	.532
Time-varying body weight (kg) × time	−0.0001 (0.0002)	.666		
Time-varying TFM (SD) × time			−0.006 (0.002)	.011
Time-varying TLM (SD) × time			0.018 (0.005)	<.001

Table 4 Results from linear mixed models testing the association between body fatness (TBFM/weight) and the longitudinal rate of decline in muscle quality (MQ), independent of baseline age, sex, race, and body height. In Model I, body fatness was expressed as baseline continuous variable, in Model II as baseline binary variable (sex-specific higher tertile vs. the rest of the population), and in Model III as time-varying variable

Predictors	Muscle quality (Nm/cm^2)					
	Model I		Model II		Model III	
	β(SE)	*P* value	β(SE)	*P* value	β(SE)	*P* value
Baseline age (years)	−0.005 (0.001)	<.001	−0.005 (0.001)	<.001	−0.005 (0.001)	<.001
Sex (men)	−0.09 (0.04)	.015	−0.08 (0.03)	.013	−0.07 (0.03)	.038
Race (Caucasian)	0.11 (0.02)	<.001	0.11 (0.02)	<.001	0.11 (0.02)	<.001
Height (cm)	0.004 (0.002)	.023	0.004 (0.002)	.024	0.004 (0.002)	.025
Baseline body fatness	−0.09 (0.016)	.572				
Higher (sex-specific) tertile of baseline body fatness (vs. rest of the sample)			0.003 (0.02)	.897		
Time-varying body fatness					0.03 (0.14)	.828
Time (years)	−0.015 (0.002)	<.001	−0.012 (0.003)	<.001	−0.015 (0.002)	<.001
Baseline age (years) × time	0.0001 (0.0002)	.734	0.0001 (0.002)	.753	0.0001 (0.0002)	.811
Sex (men) × time	0.002 (0.007)	.749	0.010 (0.006)	.123	0.003 (0.007)	.703
Race (Caucasian) × time	−0.001 (0.005)	.798	−0.002 (0.005)	.725	−0.001 (0.005)	.771
Height × time	0.0005 (0.0003)	.183	0.0004 (0.0003)	.243	0.0005 (0.0003)	.174
Baseline body fatness × time	−0.06 (0.03)	.053				
Higher (sex-specific) tertile of baseline body fatness (vs. rest of the sample)			−0.11 (0.005)	.021		
Time-varying body fatness					−0.06 (0.03)	.038

Note: Average rate decline in MQ per year between baseline higher sex-specific tertile of body fatness vs. rest of the population (after adjustment for age, sex, race, and body height):

	Higher tertile of body fatness (n = 171)	Rest of the population (n = 340)	*P* value
Average rate of decline in MQ per year	−0.023	−0.012	.021

greater body fatness experienced a significantly accelerated decline in MQ (β = −0.011, *P* = .021; Model II, *Table* 4) and, in particular, almost twice faster than the rest of the population (about 2% per year vs. 1% per year, respectively). We also estimated longitudinal trajectories of age-related decline in MQ according to the two groups (sex-specific higher tertile of body fatness vs. rest of the population) for participants who entered in the study at different age decades (*Figure* 1). In addition, results were confirmed when body fatness was modeled as time-dependent variable (Model III, *Table* 4).

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Noteworthy, sex/body fatness and race/body fatness interactions have also been explored in relation to longitudinal change in MQ, but no significant interactions were found in our sample population (not shown).

Sensitivity analyses

Sensitivity analyses were also run using two versions of normalized MQ ratio according to body height (NMQ1 and NMQ2). Their results substantially confirmed the original findings. In particular, we found that body composition measures, but not body mass, were associated with accelerated decline overtime in both NMQ1 and NMQ2 (Supporting Information 7 and 8). In addition, we confirmed that greater baseline body fatness predicted future faster decline in NMQ1 and NMQ2 (Supporting Information 9).

Other supplemental analyses

Of note, in supplementary analyses, we tested whether baseline or time-dependent CT-measured intermuscular fat (IMAT) and muscle density, a surrogate for fat microinfiltration, predicted change in MQ. We found a cross-sectional negative association between MQ and IMAT, independent of age, sex, race, and body height. However, when the analysis was adjusted for weight or body fatness (i.e. TFM divided by body weight), the cross-sectional association was no longer statistically significant. Moreover, baseline and time-varying IMAT did not predict longitudinal change in MQ. In addition, no cross-sectional or longitudinal associations were found between muscle density and change in MQ.

Discussion

Using longitudinal data from the Baltimore Longitudinal Study of Aging participants aged 50 and older, we described the longitudinal rate of change in MQ with aging. We found that, independent of baseline age and sex, MQ declined about 0.02 Nm/cm^2 per year, with women declining significantly faster than men. Baseline age was not a significant predictor of the longitudinal rate of decline of MQ, meaning that, after the age of 50 years, MQ declines linearly with aging. Of note, when adjusting also for body height, sex differences in the rate of decline were no longer significant. Furthermore, we tested whether body mass and/or body composition measures predict accelerated rate of decline in MQ overtime. Independent of covariates, no association was found between baseline body weight and longitudinal rate of decline in MQ. Similarly, no association was found when baseline BMI was included as predictor. On the contrary, higher TFM and lower TLM at baseline predicted steeper longitudinal decline in MQ. In particular, individuals who have both high TFM and low TLM at baseline experienced the most dramatic decline compared with those with low TFM and high TLM. Consistently, participants in the higher tertile of baseline body fatness presented a significantly faster future decline than the rest of the population. Similar results were observed when body mass, TFM and TLM were modeled as time-dependent variables. Of note, no longitudinal association was found between IMAT/muscle density and decline in MQ. Finally, our results were confirmed by sensitivity analyses, including two versions of normalized MQ ratio according to body height (NMQ1 and NMQ2) as outcome variables.

The current study significantly contributes to previous literature and provides new insights on the relationship between body composition and age-related decline in MQ by showing that body composition characteristics (both high TFM and low TLM), but not body mass, are early predictors of impending faster decline in MQ, with potential implications for development of preventive strategies.

The relevance of body composition beyond body weight and body mass is not a new concept in gerontology. Several longitudinal studies have shown that changes in body composition may occur with aging even in individuals with stable weight overtime, but little work has been done to understand the consequences of these changes.[25] Our study demonstrated for the first time that body composition (body fatness), but not body mass, is the early risk factor for accelerated decline in MQ. In particular, our findings, if confirmed and validated in larger and more diverse population, may have relevant consequences for clinical translation. In fact, our results suggest that the assessment of body composition is even more meaningful and informative than the assessment of body mass alone for the prediction of future MQ deterioration, and it may be used as early screening tool in older adults, in order to identify individuals at higher risk to develop sarcopenia and its negative consequences who should be targeted for preventive interventions.[26]

Noteworthy, in our sample, no cross-sectional association was found between body fatness and MQ. On the contrary, higher body weight/BMI was strongly cross-sectionally associated with poorer MQ. This finding is only partially in contrast with a previous cross-sectional study from BLSA, where body weight was significantly and inversely associated with MQ, independent of age, sex, and body height. In fact, in that study, after matching within quartiles of height and muscle cross-sectional area, the association of weight with MQ ratio was actually reduced and no longer significant.[10]

Moreover, we acknowledge that, if participants with higher baseline BMI tended to have a shorter follow up, competing mortality may have biased our results. However, in our data, no significant correlation was found between baseline BMI and length of follow-up, suggesting that our finding was not biased by selective mortality. Therefore, although further studies are required to fully understand the underlying mechanisms,

our results suggest that, although body mass is strongly associated with occurring poor MQ, body composition features (specifically higher body fatness in relation to body mass) may represent a more sensitive biomarker at early stages of impending deterioration of MQ than body mass itself.

The mechanisms that link body composition features with MQ remain unclear. A complex ensemble of changes occurs in parallel in muscle and adipose tissue with aging. In particular, muscle mass progressively declines while fat mass increases, mainly as result of age-related unbalance in energy production and expenditure.[27] Of relevance, not only muscle and fat change in parallel with aging, but they also are interconnected by a tight and bidirectional cross-talk, which has an important role in maintaining an adequate ratio of skeletal muscle to fat and thus in the control of body weight.[28] Adipose tissue is not only a storage depot for excess energy, but also acts as an endocrine organ that secrets a large variety of adipokines that have both local and systemic effects.[29] An endocrine function is evident also for skeletal muscle,[30] and, interestingly, many myokines released by muscle at rest and during contraction are known to be also secreted by adipocytes. IL-6 is a remarkable example of adipo-myokine, released by both muscle and fat and acting on both tissues.[31] IL-6 released by enlarged adipocytes results in chronic elevation of IL-6 plasma levels with subsequent development of pro-inflammatory state that has been associated with accelerated decline of muscle mass and strength and probably contributes to the progressive insulin resistance that is often observed in aging individuals.[32] In turn, at muscular level chronic inflammation and insulin-resistance lead to cell dysfunction and atrophy, as attested by numerous studies performed in rodent model of obesity.[33,34] Also, skeletal muscle of obese subjects displays an impairment in oxidative capacity[35] and abnormal muscle fiber organization.[36,37] Moreover, evidence suggests that ectopic lipid storage in muscle (within muscle cells and/or in adipocytes located between muscle fibers), which tend to increase with age, does not just 'fill' the space left by lean mass loss but, it is independently regulated and may negatively affect muscle tissue.[38] Multiple studies in fact suggested that inter-muscular fat releases pro-inflammatory cytokines resulting in local inflammation within the muscle,[13,14,38–40] contributes to impaired muscle blood flow, and increases the rate of lipolysis resulting in an elevated concentration of glucose within the skeletal muscle itself, leading to insulin resistance.[41,42] Noteworthy, inter-muscular fat is positively associated with insulin resistance and an increased risk of developing type 2 diabetes, even when BMI is statistically accounted for, suggesting that these metabolic impairments are not simply due to obesity alone.[41,43] Finally, previous studies reported that older adults with higher levels of inter-muscular fat in lower extremities have lower muscle strength and quality,[44] supporting the idea that inter-muscular fat leads to muscular dysfunction, which in turn leads to further inactivity and increased ectopic lipid storage, resulting in a vicious circle with deleterious impact on muscle performance.

However, in our sample population, we found no longitudinal association between inter-muscular fat and muscle density, a surrogate of intra-muscular fat, and decline in MQ. Indeed, these results were not completely unexpected because both collagen and fat, which have opposite effects on density, tend to be deposited in muscle tissue with aging.[45]

Strengths of our study are the longitudinal design and the use of CT to assess muscle cross-sectional area. However, several limitations need to be addressed. First, the sample investigated is relatively small. Second, although all participants had at least one follow-up visit, loss of participants during the follow-up occurred and competing mortality might have affected the interpretation of our findings. However, we addressed this important issue performing additional analyses, and we found no significant correlation between baseline BMI and length of follow-up, supporting that our finding were not biased by competitive mortality. Moreover, in BLSA, the equipment for strength assessment was changed in 2010. However, a conversion equation was developed to avoid a systematic bias, and sensitivity analysis excluded the possibility that the change in methods could affect the longitudinal trajectories of strength in our sample population. Furthermore, because the BLSA continuously enrolls healthy volunteers followed for life, participation is very demanding and time consuming, and those enrolled in the study tend to be healthier and less disable than subjects of the same age in the overall population. Therefore, in order to generalize our findings, they should be validated in larger and more diverse populations, followed for a longer period. Also, we acknowledge that the decline in MQ and changes in body composition with aging can be influenced by a large variety of factors, including exercise, caloric intake, stressors, and diseases. However, the samples size we investigated was too small to test the effect of such a comprehensive group of factors. Consequently, we focused our analysis on the role of anthropometrics as predictors of MQ change. Other parameters that may be important were not considered and should be explored in future analyses. In addition, our measure of MQ is limited to knee extension strength, and there is no guarantee that our findings reflect what is happening in other muscles, for example upper extremity muscle, which are known to be affected differentially with aging.[46,47] Finally, it would also be interesting to determine whether baseline or change in abdominal visceral and subcutaneous fat predicts change in MQ independent of body size or body fatness. However, because abdominal CT data have been collected only in a subgroup of BLSA participants, we could not perform such analysis in our sample population, and we plan to follow up with such analysis as soon as enough data will be available.

In conclusion, after the age of 50, MQ declines linearly with aging. At an early stage, body composition (high fat mass and low lean mass), but not body mass, is associated

with future steeper decline in MQ in older adults suggesting that the early identification of individuals at high risk of decline in MQ should focus on body composition parameters. Whether interventions aimed at changing body composition may prevent the decline in MQ is unknown and should be tested in future randomized controlled trials.

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All the authors declare no conflicts of interest and certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia, and Muscle.[48]

Online supplementary material

Supporting information may be found in the online version of this article.

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