*Journal of Gerontology: MEDICAL SCIENCES*
2005, Vol. 60A, No. 3, 324–333


# Muscle Mass, Muscle Strength, and Muscle Fat Infiltration as Predictors of Incident Mobility Limitations in Well-Functioning Older Persons

Marjolein Visser,[1,2] Bret H. Goodpaster,[3] Stephen B. Kritchevsky,[4] Anne B. Newman,[5] Michael Nevitt,[6] Susan M. Rubin,[6] Eleanor M. Simonsick,[7] and Tamara B. Harris,[2]
for the Health ABC Study

[1]Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands.
[2]National Institute on Aging, Laboratory of Epidemiology, Demography, and Biometry, Bethesda, Maryland.
[3]Department of Medicine, University of Pittsburgh, Pennsylvania.
[4]Sticht Center on Aging, Wake Forest University School of Medicine, Winston-Salem, North Carolina.
[5]Division of Geriatric Medicine, University of Pittsburgh.
[6]Prevention Sciences Group, University of California, San Francisco.
[7]National Institute on Aging, Gerontology Research Center, Baltimore, Maryland.

***Background.*** Lower muscle mass has been correlated with poor physical function; however, no studies have examined this relationship prospectively. This study aims to investigate whether low muscle mass, low muscle strength, and greater fat infiltration into the muscle predict incident mobility limitation.

***Methods.*** Our study cohort included 3075 well-functioning black and white men and women aged 70–79 years participating in the Health, Aging, and Body Composition study. Participants were followed for 2.5 years. Muscle cross-sectional area and muscle tissue attenuation (a measure of fat infiltration) were measured by computed tomography at the mid-thigh, and knee extensor strength by using a KinCom dynamometer. Incident mobility limitation was defined as two consecutive self-reports of any difficulty walking one-quarter mile or climbing 10 steps.

***Results.*** Mobility limitations were developed by 22.3% of the men and by 31.8% of the women. Cox's proportional hazards models, adjusting for demographic, lifestyle, and health factors, showed a hazard ratio of 1.90 [95% confidence interval (CI), 1.27–2.84] in men and 1.68 (95% CI, 1.23–2.31) in women for the lowest compared to the highest quartile of muscle area ($p < .01$ for trend). Results for muscle strength were 2.02 (95% CI, 1.39–2.94) and 1.91 (95% CI, 1.41–2.58), $p < .001$ trend, and for muscle attenuation were 1.91 (95% CI, 1.31–2.83) and 1.68 (95% CI, 1.20–2.35), $p < .01$ for trend. When included in one model, only muscle attenuation and muscle strength independently predicted mobility limitation ($p < .05$). Among men and women, associations were similar for blacks and whites.

***Conclusion.*** Lower muscle mass (smaller cross-sectional thigh muscle area), greater fat infiltration into the muscle, and lower knee extensor muscle strength are associated with increased risk of mobility loss in older men and women. The association between low muscle mass and functional decline seems to be a function of underlying muscle strength.

MUSCLE weakness is an important determinant of physical function in older persons. Low muscle strength is predictive of future decline in functional performance and incident disability (1). In addition, strength training in frail older persons is paralleled by improvements in physical function (2). Whereas the role of muscle strength in physical function is well established, less is known about the relationship between muscle mass and physical function.

Recent cross-sectional studies have shown that low muscle mass is associated with poor functional performance (3,4) and self-reported disability (4–6). Because muscle mass is highly correlated with muscle strength (7), the observed relationship between muscle mass and physical function could be simply a function of muscle strength. Whether low muscle mass itself contributes to decline in physical function, or whether this association is mediated by muscle strength remains unclear. Moreover, this research question has never been addressed using a prospective study design.

With aging, declines in both muscle mass and muscle strength are well documented (8–10). In addition, the composition of muscle changes (11–13) with increasing infiltration of fat. Recent studies by our group (3,14) have shown a cross-sectional association between the amount of fat infiltration into the muscle, determined by the attenuation of mid-thigh muscle tissue using computed tomography, and muscle strength and mobility performance. The increasing fat infiltration into the muscle with aging may be an important, if not central, aspect of sarcopenia (the loss of muscle mass and muscle strength with aging; 15). Whether greater fat infiltration into the muscle is prognostic for future mobility limitations, independent of muscle strength, has never been studied.

Muscle mass, muscle strength, and fat infiltration into the muscle can be modified by behavioral and pharmacological interventions in older persons. Hormone supplementation, nutritional interventions, and strength and exercise training are most often used to increase muscle mass and strength (16–19), and may decrease the amount of fat infiltration into the muscle (17,20). To prevent or slow the decline in physical function with aging, it is important to know which muscle components independently contribute to functional loss in old age. This information will help to optimize intervention strategies focused on the muscles, as different aspects of muscle integrity may respond to different treatments.

This prospective study aims to investigate the independent and joint contributions of low muscle mass, low muscle strength, and greater fat infiltration into the muscle on incident mobility limitations in older men and women.

## Methods

### *Study Population*

The Health, Aging, and Body Composition (Health ABC) study cohort includes 3075 black and white men and women. White participants were recruited from a random sample of Medicare beneficiaries residing in ZIP codes from the metropolitan areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Black participants were recruited from all age-eligible residents in the same geographic areas. After receiving information describing the study, potential participants were screened for eligibility. Eligibility criteria included: age 70–79 years in the recruitment period from March 1997 through July 1998; self-report of no difficulty walking one-quarter mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches, or other special equipment to get around; no history of active treatment for cancer in the prior 3 years; no enrollment in a lifestyle intervention trial; and no plan to move out of the area in the next 3 years.

Of the 3075 participants, we excluded those with missing data on incident mobility limitations ($n = 7$), muscle area or muscle attenuation ($n = 53$), total body fat mass ($n = 14$), or muscle strength ($n = 370$, see muscle strength section). A total of 2631 participants (85.6% of original cohort, 1286 men and 1345 women) were available for analysis, of whom 117 died during the follow-up period used for this analysis.

### *Incident Mobility Limitations*

Mobility limitations were assessed by self-reported level of difficulty walking one-quarter mile and climbing 10 steps without resting. Response categories were: no difficulty, a little difficulty, some difficulty, a lot of difficulty, and unable to do. Because of the eligibility criteria of the study, all participants had no self-reported mobility limitations at baseline. The 2.5-year incidence of mobility limitations was assessed using information collected during the Year 2 and Year 3 clinic examinations and the 6-, 18-, and 30-month telephone contacts. Persistent mobility limitation was based on two consecutive reports of either having any difficulty walking one-quarter mile or having any difficulty climbing 10 steps without resting.

### *Muscle Mass*

The cross-sectional area of muscle in both thighs was used as a measure of muscle mass. Muscle area was measured by computed tomography (Memphis clinic site: Somatom Plus 4, Siemens, Erlangen, Germany, or PQ 2000S, Marconi Medical Systems, Cleveland, OH; at Pittsburgh clinic site: 9800 Advantage, General Electric, Milwaukee, WI) as described previously (3). In short, a single 10-mm-thick axial image (120 kVp, 200–250 mA) of both thighs was obtained at the midpoint of the distance between the medial edge of the greater trochanter and the intercondyloid fossa of the right leg. For each participant, the determination of soft tissue type was made using the bimodal image distribution histogram resulting from the distribution numbers in adipose tissue and muscle tissue. Intermuscular and visible intramuscular adipose tissue was separated from subcutaneous adipose tissue by drawing a line along the deep fascial plane surrounding the thigh muscles. The total area of nonadipose, nonbone tissue within the deep fascial plane was used as a measure of muscle area ($cm^2$). Reproducibility of muscle mass by computed tomography was assessed by reanalyzing a 5% convenience sample of the study cohort, showing a coefficient of variation of less than 5%.

### *Muscle Strength*

The maximal isokinetic strength of the knee extensors (Nm) was assessed by a KinCom 125 AP Dynamometer (Chattanooga, TN) at 60°/s and was calculated from the average of three reproducible and acceptable trials of a maximum of six trials. Participants with a systolic blood pressure $\geq$200 mmHg, diastolic blood pressure $\geq$110 mmHg, or who reported a history of cerebral aneurysm, cerebral bleeding, bilateral total knee replacement, or severe bilateral knee pain were excluded from testing (12.7% of original cohort).

### *Muscle Fat Infiltration*

The mean attenuation (Hounsfield Units, HU) of thigh muscle tissue obtained by computed tomography, excluding intermuscular and intramuscular adipose tissue lying interior to the deep fascial plane surrounding the muscle, was used as an indicator of fat infiltration into the muscle. Lower muscle attenuation indicates greater fat infiltration. The validity of this noninvasive measure has been previously established (21). In 45 men and women between 25 and 49 years old with a BMI ranging from 18.5 to 35.9 kg/$m^2$, the correlation between muscle attenuation and muscle fiber lipid content determined with histological Oil Red O staining was –0.43 ($p < .01$). In a subset of 19 volunteers, the correlation between muscle attenuation and triglyceride content in percutaneous biopsy specimens from vastus lateralis was –0.58 ($p = .02$) (21). Reproducibility of muscle attenuation was assessed by reanalyzing a 5% convenience sample of the study cohort, showing a coefficient of variation of less than 5%.

### *Covariates*

Covariates included demographic variables (clinic site, age, race, sex, and education), lifestyle indicators (physical activity, smoking status, alcohol consumption, total body fat mass, and body height) and health status variables (prevalent disease, self-rated health, depression, and cognitive status). Education was categorized into three groups: less than high school, high school graduate, and postsecondary school. Physical activity of the past 7 days was assessed by an interviewer-administered questionnaire. The time spent climbing stairs, walking for exercise, walking for other purposes, aerobics, weight or circuit training, high intensity exercise activities, and moderate intensity exercise activities was obtained as well as information on the intensity level at which each activity was carried out. A metabolic equivalent value was assigned to each activity–intensity combination and was used to calculate the number of kilocalories per week per kilogram of body weight spent on that activity (22). For each participant, the scores of all performed activities were summed and multiplied by body weight to create an overall physical activity score in kilocalories per week. Smoking status was categorized as current, former, or never smoker. Alcohol consumption in a typical week during the past 12 months was categorized as none, 1–7 per week, or $>7$ per week. Total body fat mass was included as a covariate, because higher fat mass is associated with greater muscle mass (23), greater muscle strength (24), but poorer physical function (23). Total body fat mass was assessed using fan-beam dual-energy x-ray absorptiometry (software version 8.21, QDR4500A; Hologic, Waltham, MA). Body height was measured to the nearest millimeter using a wall-mounted stadiometer, and body weight was assessed using a standard balance beam scale. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. Current presence of disease was determined using self-reported physician-diagnosed disease information, clinic data, and medication use. The diseases included individually in the analysis were cerebrovascular disease (self-reported history of stroke, transient ischemic attack, or carotid endarterectomy), coronary heart disease (self-reported history of coronary artery bypass graft/percutaneous transarterial coronary angioplasty or coronary heart disease), peripheral arterial disease (self-reported history of claudication or history of lower extremity bypass/angioplasty), congestive heart failure (self-reported history of congestive heart failure), hypertension (systolic blood pressure $\geq 140$ or diastolic blood pressure $\geq 90$ mmHg), current symptomatic hip or knee osteoarthritis (self-reported history of knee/hip osteoarthritis and a history of knee/hip symptoms in the past year), osteoporosis (self-reported history of osteoporosis or use of osteoporosis medication), pulmonary disease (self-reported history of current asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, and medication use), diabetes mellitus (self-reported diagnosis of diabetes and medication use, or a fasting glucose concentration $\geq 126$ mmol/L), and depression (use of antidepressants). Self-rated health was categorized as: excellent/very good, good, or fair/poor. Cognitive status was assessed using the Teng-modified Mini-Mental Status Examination (25).

### *Statistical Analyses*

Analyses were performed for men and women separately using SAS software (SAS Institute, Cary, NC). Each muscle parameter was categorized by race- and sex-specific quartiles; the highest quartile served as the reference group. When a threshold in the relationship was suspected, additional analyses were performed using race-and sex-specific deciles. The main outcome of the study was incident mobility limitations. Person-time for each participant was calculated from the date of the baseline examination to the date of the first of the two consecutive self-reports of mobility limitations, date of death, or date of the last study contact, whichever came first. Cox's proportional hazards models were used to test the association of each muscle parameter with incident mobility limitations, adjusting for the selected covariates. The results are presented as hazard ratios with 95% confidence intervals (CIs). To test for trend, we ordered the muscle parameter quartiles from lowest to highest, and included this variable in the models as a linear variable. To investigate which muscle parameters were independently associated with incident mobility limitations, we used a Cox's proportional hazards model that included all muscle parameters and the selected covariates. The results from log(–log) plots and time interactions terms indicated that the proportional hazards model assumption was valid in all models. Potential interaction between the muscle parameters and race was investigated in stratified analyses by sex, and was tested using the muscle parameter * race product term in models stratified by sex.

A comparison of the 444 participants excluded from the present analysis with the 2631 who were included showed that those excluded were slightly older (74.0 vs 73.6 years), were more likely to be black (50.5% vs 40.2%), were less physically active (27.7% vs 20.6% in the low-activity group), had a higher BMI (28.0 vs 27.3 kg/m$^2$), had poorer cognitive scores (87.8 vs 89.9 on the Mini-Mental State Examination), had greater fat infiltration into the muscle (33.9 vs 35.6 HU), had more prevalent disease ($p < .05$), and were less likely to rate their health as excellent/very good (32.0% vs 45.9%). No significant differences were observed for sex, muscle mass, muscle strength (when available), and total body fat mass.

## Results

The characteristics of the study sample are shown in Table 1. Within sex, blacks had greater mid-thigh muscle area, muscle strength, fat infiltration into the mid-thigh muscle (statistically significant for women only), and body fat mass compared to whites. The 2631 older persons contributed 5561 person-years during the 2.5-year follow-up. During follow-up, incident mobility limitations were reported by 287 men (22.3%, event rate 101 per 1000 person-years) and 428 women (31.8%, event rate 156 per 1000 person-years). Of the 117 persons who died during follow-up, 64 (54.7%) had incident mobility limitations before death. Event rates were 131 and 207 per 1000 person-years for black men and women, and 87 and 121 per 1000 person-years for white men and women, respectively.

### *Muscle Mass*

Table 2 shows the results of multiple Cox's proportional hazards regression analyses for mid-thigh muscle area. After

Table 1. Baseline Characteristics of the 2631 Health, Aging, and Body Composition Study Participants

| | White Men $N = 827$ | Black Men $N = 459$ | White Women $N = 747$ | Black Women $N = 598$ |
|---|---|---|---|---|
| Characteristics | Mean (*SD*) | Mean (*SD*) | Mean (*SD*) | Mean (*SD*) |
| Age, y | 73.9 (2.9) | 73.4 (2.8)* | 73.5 (2.80) | 73.3 (2.9) |
| Height, m | 1.74 (0.06) | 1.73 (0.07) | 1.59 (0.06) | 1.60 (0.06) |
| Body mass index, kg/m$^2$ | 27.0 (3.7) | 27.1 (4.3) | 26.0 (4.5) | 29.6 (5.7)** |
| Total body fat, kg | 21.7 (6.7) | 22.3 (7.4)** | 26.3 (7.7) | 30.9 (9.9)** |
| Mid-thigh muscle area, cm$^2$ | 255.7 (38.2) | 277.6 (50.0)** | 170.5 (27.7) | 203.1 (33.2)** |
| Mid-thigh muscle attenuation, HU | 37.6 (6.3) | 37.0 (6.5) | 34.9 (6.8) | 32.7 (6.8)** |
| Knee extensor strength, Nm | 130.6 (33.1) | 134.6 (37.4)* | 78.1 (19.8) | 85.6 (23.7)** |
| Teng cognitive score | 92.0 (6.2) | 84.0 (10.2)** | 93.5 (5.6) | 87.1 (9.0)** |
| | % | % | % | % |
| Memphis study site | 49.3 | 48.6 | 53.6 | 46.8* |
| Low education | 14.4 | 48.9** | 10.1 | 37.8** |
| Smoking status | | | | |
| Never | 29.8 | 29.7 | 58.6 | 55.8 |
| Former | 65.5 | 48.9 | 33.6 | 32.8 |
| Current | 4.7 | 21.4** | 7.8 | 11.4 |
| Alcohol (drinks/wk) | | | | |
| 0 | 36.1 | 53.1 | 45.7 | 68.7 |
| 1–6 | 51.0 | 37.9 | 48.9 | 29.6 |
| 7+ | 12.9 | 9.0** | 5.4 | 1.7** |
| Physical activity (kcal/wk) | | | | |
| <2500 | 16.2 | 25.7 | 19.7 | 24.1 |
| 2500–4499 | 23.9 | 22.9 | 29.4 | 25.4 |
| 4500–8499 | 33.4 | 24.2 | 33.9 | 29.3 |
| 8500+ | 26.5 | 27.2** | 17.0 | 21.2* |
| Self-rated health | | | | |
| Excellent/very good | 55.3 | 34.6 | 52.2 | 33.8 |
| Good | 36.4 | 36.6 | 41.9 | 41.4 |
| Fair/poor | 8.3 | 28.8** | 5.9 | 24.8** |
| Prevalent disease | | | | |
| Cerebrovascular disease | 3.6 | 1.7 | 2.0 | 2.5 |
| Heart disease | 29.9 | 22.2** | 12.6 | 17.7** |
| Hypertension | 52.4 | 64.7** | 52.2 | 72.1** |
| Symptomatic hip/knee osteoarthritis | 5.1 | 2.4* | 8.7 | 7.9 |
| Osteoporosis | 1.8 | 1.1 | 26.2 | 9.0** |
| Pulmonary disease | 5.0 | 6.8 | 5.4 | 5.9 |
| Diabetes mellitus | 16.8 | 25.7** | 7.2 | 21.4** |
| Depression | 5.2 | 2.6* | 10.6 | 4.2** |

*Notes*: *$p < .05$, **$p < .01$ black men versus white men, or black women versus white women, Student's *t* test for differences of means and chi-square test for proportions.

adjustment for demographic variables (Model 1), persons in the lowest quartile of muscle area were 2.25 (95% CI, 1.54–3.29 for men) and 1.70 (95% CI, 1.25–2.31 for women) times more likely to develop mobility limitations during follow-up. After additional adjustment for lifestyle factors (including physical activity, Model 2) and health factors (Model 3), the relationship was only slightly attenuated (hazard ratio = 1.90 (95% CI, 1.27–2.84) for men and hazard ratio = 1.68 (95% CI, 1.23–2.31) for women). The association between mid-thigh muscle area and incident mobility limitations is also illustrated in Figure 1. Women in the lowest quartile of muscle area (<152 cm$^2$ for white women and <181 cm$^2$ for black women) had an increased risk of incident mobility limitations, whereas the risk for women in the highest three quartiles was similar (hazard ratios = 1.0–1.14). When the women were categorized into deciles of muscle area, the increased risk (hazard ratio = 2.37; 95% CI, 1.49–3.79) was only observed for those in the lowest decile (<136 cm$^2$ for white women and <158 cm$^2$ for black women). In contrast, for men there was evidence of a graded association. All associations were similar for blacks and whites within sex.

### *Muscle Strength*

As expected, low muscle strength was associated with a higher risk of mobility limitations (Figure 2, Table 3). After adjustment for age, race, study site, body height, and total body fat mass, men and women in the lowest quartile of muscle strength were 2.64 (95% CI, 1.83–3.80) and 2.15 (95% CI, 1.61–2.87) times more likely to develop mobility limitations compared to those in the highest quartile. Furthermore, a clear trend across quartiles was observed

Table 2. Adjusted Hazard Ratios (With 95% Confidence Intervals) for Incident Mobility Limitations According to Quartiles of Mid-Thigh Muscle Cross-Sectional Area ($cm^2$)

| Quartile of Mid-Thigh Muscle Cross-Sectional Area | *N* | Event Rate* | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| Men | | | | | |
| 1 = low | 320 | 130 | 2.25 (1.54–3.29) | 2.11 (1.44–3.11) | 1.90 (1.27–2.84) |
| 2 | 322 | 100 | 1.58 (1.10–2.29) | 1.47 (1.01–2.14) | 1.40 (0.96–2.05) |
| 3 | 322 | 100 | 1.50 (1.05–2.15) | 1.42 (0.99–2.04) | 1.53 (1.06–2.21) |
| 4 = high | 322 | 80 | 1.0 | 1.0 | 1.0 |
| *p* Value trend | | | .001 | .0003 | .006 |
| Women | | | | | |
| 1 = low | 335 | 170 | 1.70 (1.25–2.31) | 1.68 (1.23–2.29) | 1.68 (1.23–2.31) |
| 2 | 337 | 140 | 1.10 (0.82–1.48) | 1.06 (0.79–1.43) | 1.14 (0.84–1.54) |
| 3 | 338 | 150 | 1.04 (0.79–1.36) | 1.05 (0.79–1.38) | 1.05 (0.79–1.38) |
| 4 = high | 335 | 170 | 1.0 | 1.0 | 1.0 |
| *p* Value trend | | | .001 | .003 | .002 |

*Notes*: Model 1: adjusted for age, race, study site, body height, total body fat mass. Model 2: additionally adjusted for lifestyle factors, including education, alcohol consumption, smoking status, and physical activity. Model 3: additionally adjusted for prevalent disease, self-rated health, depression, and cognitive status. Cut-points for white men were: <230, 230–253, 254–280, 281+; for black men: <245, 245–276, 277–307, 308+; for white women: <152, 152–168, 169–188, 189+; for black women: <181, 181–203, 204–224, 225+$cm^2$.

*Events/1000 person-years.

($p < .0001$). After additional adjustment for other potential confounders, including lifestyle and health factors, the relationship remained statistically significant. Associations were similar for blacks and whites within sex.

### *Muscle Fat Infiltration*

A lower mid-thigh muscle attenuation, indicative of a greater fat infiltration into the muscle, was associated with a greater incidence of mobility limitations (Figure 3, Table 4). After adjustment for age, race, study site, body height, and total body fat mass, persons in the lowest quartile of muscle attenuation had an increased risk of mobility limitations [hazard ratio = 2.16 (95% CI, 1.48–3.14) for men and hazard ratio = 1.98 (95% CI, 1.43–2.76) for women]; this risk remained statistically significant after additional adjustment for lifestyle and health factors (Model 3).

### *Muscle Parameters and Incident Mobility Limitations*

To investigate whether the associations of mid-thigh muscle area and mid-thigh muscle attenuation with decline in physical function were mediated by muscle strength, we included both measures as well as muscle strength and all potential confounders in a single regression model (Table 5). As expected, muscle strength remained an independent determinant of incident mobility limitations in both men and women. After muscle strength was taken into account, low muscle area did not remain a significant factor associated with incident mobility limitations. These results suggest that muscle strength mediates the relationship between muscle area and incident mobility limitations. These results are also illustrated in Figure 4, showing the association of sex- and race-specific quartiles of muscle strength versus muscle area with incident mobility limitations for men and women, after adjustment for muscle attenuation, total body fat mass, and potential confounders. Again, the association of muscle strength with incident mobility limitations was more pronounced compared to the association with muscle area. The pattern of the associations was not different between men and women ($p = .5$).

Not only muscle strength but also muscle attenuation remained an independent determinant of incident mobility limitations (Table 5). Persons in the lowest quartile of muscle attenuation (with the greatest amount of fat

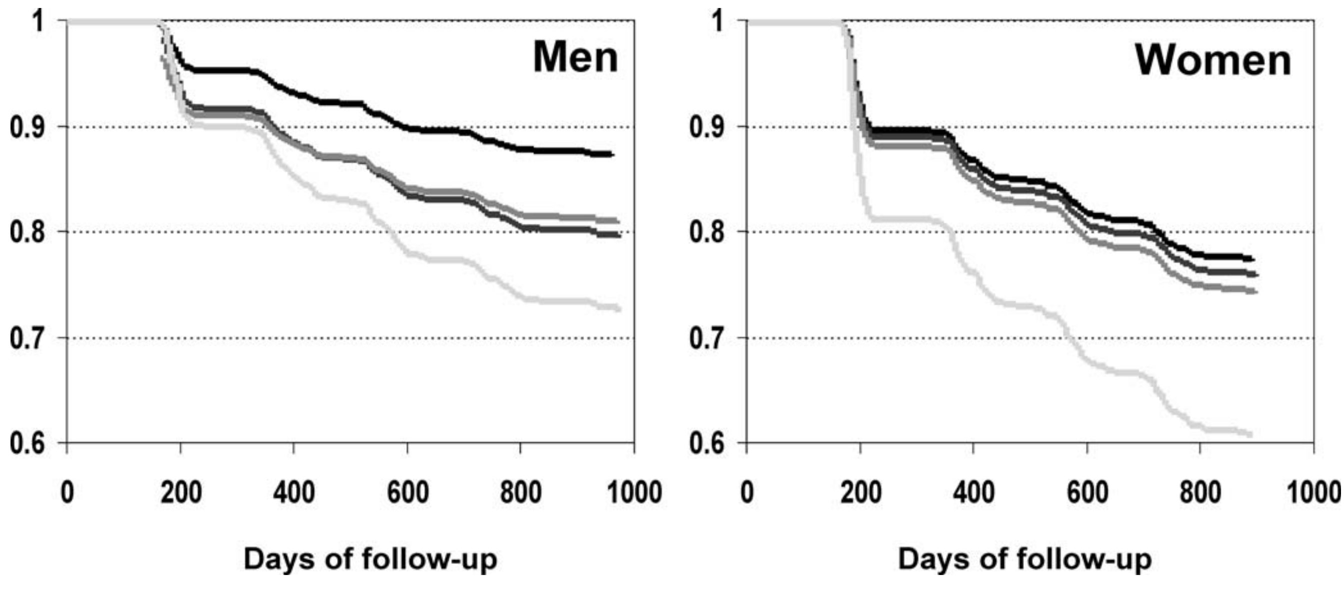


Figure 1. Probability of having no mobility limitations in men and women according to quartiles of mid-thigh muscle area. ▬ Highest quartile (=4), ▬ (=3), ▬ (=2), ▬ Lowest quartile (=1 = lowest muscle area). Adjusted for all potential confounders.

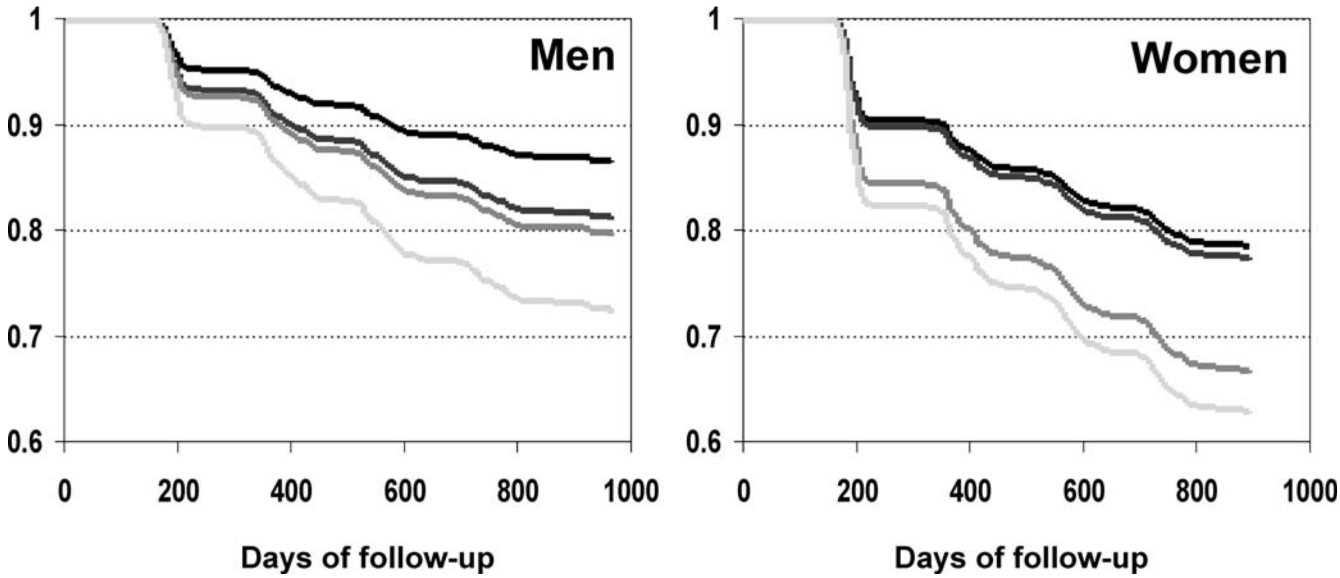


Figure 2. Probability of having no mobility limitations in men and women according to quartiles of knee extensor strength. ▬ Highest quartile (=4), ▬ (=3), ▬ (=2), ▬ Lowest quartile (=1 = lowest muscle strength). Adjusted for all potential confounders.

infiltration into the muscle) were 50%–80% more likely to develop mobility limitations during follow-up, independent of muscle area, muscle strength, or total body fat mass ($p$ value for trend <.001 for men and women). The hazard ratios for the lowest quartiles of muscle attenuation were similar to, if not slightly stronger than, those for muscle strength. The adjusted hazard ratio of incident mobility limitations according to sex- and race-specific quartiles of muscle strength versus muscle attenuation for men and women is shown in Figure 5. Both lower muscle strength and lower muscle attenuation were associated with an increased risk for incident mobility limitations.

Table 3. Adjusted Hazard Ratios (With 95% Confidence Intervals) for Incident Mobility Limitations According to Quartiles of Knee Extensor Strength (Nm)

| Quartile of Knee Extensor Strength | *N* | Event Rate* | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| Men | | | | | |
| 1 = low | 320 | 151 | 2.64 (1.83–3.80) | 2.45 (1.70–3.54) | 2.02 (1.39–2.94) |
| 2 | 322 | 105 | 1.75 (1.20–2.55) | 1.65 (1.13–2.42) | 1.51 (1.03–2.12) |
| 3 | 322 | 97 | 1.54 (1.05–2.24) | 1.48 (1.01–2.17) | 1.36 (0.92–1.99) |
| 4 = high | 322 | 60 | 1.0 | 1.0 | 1.0 |
| *p* Value trend | | | .0001 | .0001 | .0002 |
| Women | | | | | |
| 1 = low | 336 | 216 | 2.15 (1.61–2.87) | 2.00 (1.49–2.69) | 1.91 (1.41–2.58) |
| 2 | 335 | 183 | 1.73 (1.30–2.30) | 1.64 (1.22–2.19) | 1.60 (1.19–2.15) |
| 3 | 338 | 126 | 1.18 (0.87–1.60) | 1.12 (0.83–1.52) | 1.10 (0.80–1.50) |
| 4 = high | 336 | 112 | 1.0 | 1.0 | 1.0 |
| *p* Value trend | | | .0001 | .0001 | .0001 |

*Notes*: Model 1: adjusted for age, race, study site, body height, total body fat mass. Model 2: additionally adjusted for lifestyle factors, including education, alcohol consumption, smoking status, and physical activity. Model 3: additionally adjusted for prevalent disease, self-rated health, depression, and cognitive status. Cut-points for white men were: <109, 190–128, 129–150, 151+; for black men: <110, 110–136, 137–158, 158+; for white women: <67, 67–78, 79–90, 91+; for black women: <71, 71–86, 87–101, 102+ Nm.

*Events/1000 person-years.

## Discussion

To our knowledge, this is the first study investigating the independent role of multiple muscle parameters on physical function using prospective data. The outcome measure is an important endpoint because it represents an early transition in the disablement pathway (26,27). In addition, rigorous methodology was used to assess these muscle parameters in a community-based cohort. Although lower mid-thigh muscle area was associated with increased risk of mobility limitations in older men and women, this risk was not independent of poor knee extensor muscle strength and greater fat infiltration into the mid-thigh muscle. These findings suggest that older persons with low muscle mass have an increased risk of functional decline because their muscles are generally weaker. The relationship between muscle mass and muscle strength is well known; muscle mass explains most of the variance in muscle strength (28,29). Nevertheless, older women with very low muscle area (lowest decile) were still at increased risk of mobility limitation (hazard ratio = 1.70; 95% CI, 1.02–2.81). These results suggest that a threshold may exist for women below which muscle area may be independently associated with physical function; this threshold should be explored in future studies.

We used computed tomography attenuation values of muscle tissue as indicators of fat infiltration into the muscle. A greater fat infiltration into the mid-thigh muscle was a strong predictor of incident mobility limitations, confirming previous cross-sectional associations by our group. Increasing fat infiltration into the muscle with aging may be a crucial aspect of sarcopenia influencing functional status

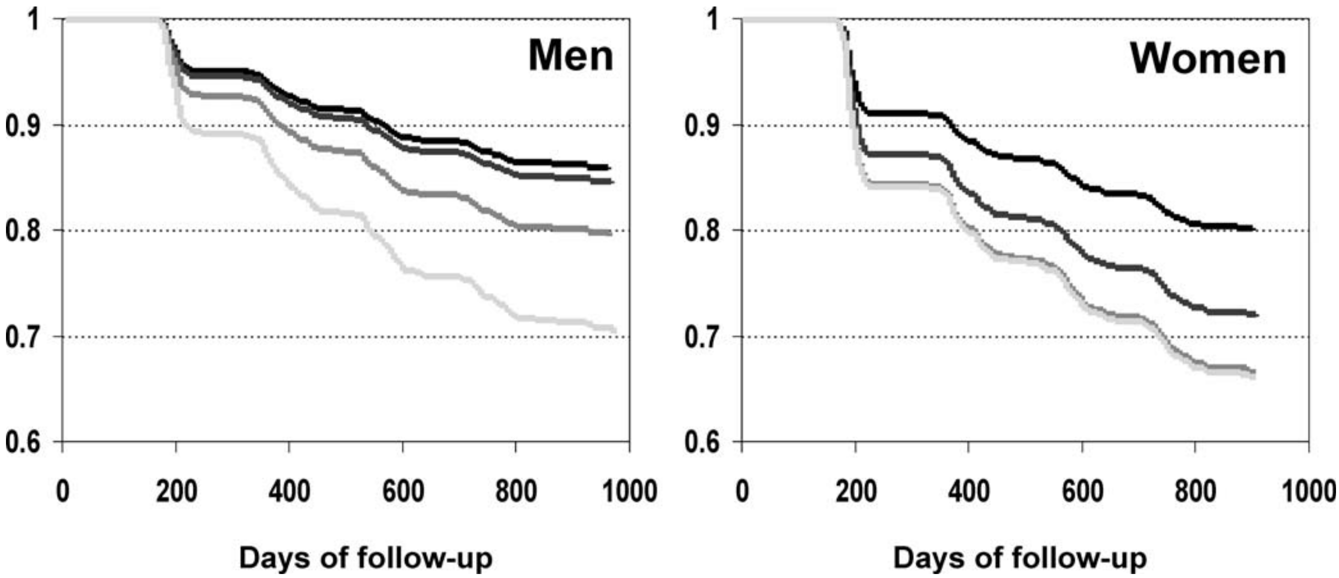


Figure 3. Probaility of having no mobility limitations in men and women according to quartiles of mid-thigh muscle attenuation. ▬ Highest quartile (=4), ▬ (=3), ▬ (=2), ▬ Lowest quartile (=1 = greatest fat infiltration into the muscle). Adjusted for all potential confounders.

in old age. Fat infiltration into the muscle is known to be positively correlated with overall body fatness (30–32). Moreover, our group previously showed a cross-sectional association between greater fat infiltration into the muscle and lower muscle strength (14). However, after adjustment for total body fat mass and knee extensor muscle strength, greater fat infiltration into the mid-thigh muscle remained an independent risk factor for incident mobility limitations. It remains unclear what mechanism(s) might explain the observed, independent association. Muscle attenuation may be a marker of functional aspects of the muscle other than muscle strength, such as muscle metabolism or neural factors, or may be the result of early-life lifestyle (e.g., physical activity history). Alternatively, knee extensor muscle strength may not be representative of strength in the collateral leg muscle groups and/or may not fully capture

Table 4. Adjusted Hazard Ratios (With 95% Confidence Intervals) for Incident Mobility Limitations According to Quartiles of Mid-Thigh Muscle Tissue Attenuation (HU)

| Quartile of Mid-Thigh Muscle Tissue Attenuation | *N* | Event Rate* | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| Men | | | | | |
| 1 = low | 320 | 170 | 2.16 (1.48–3.14) | 2.04 (1.40–2.98) | 1.92 (1.31–2.83) |
| 2 | 322 | 100 | 1.34 (0.92–1.94) | 1.32 (0.91–1.91) | 1.38 (0.94–2.01) |
| 3 | 322 | 80 | 1.11 (0.76–1.63) | 1.17 (0.80–1.71) | 1.08 (0.73–1.60) |
| 4 = high | 322 | 70 | 1.0 | 1.0 | 1.0 |
| *p* Value trend | | | .0001 | .0002 | .0002 |
| Women | | | | | |
| 1 = low | 336 | 230 | 1.98 (1.43–2.76) | 1.97 (1.42–2.75) | 1.68 (1.20–2.35) |
| 2 | 336 | 200 | 1.92 (1.40–2.64) | 1.93 (1.40–2.65) | 1.68 (1.22–2.33) |
| 3 | 337 | 140 | 1.50 (1.09–2.08) | 1.50 (1.08–2.07) | 1.35 (0.97–1.87) |
| 4 = high | 336 | 80 | 1.0 | 1.0 | 1.0 |
| *p* Value trend | | | .0001 | .0001 | .002 |

*Notes*: Model 1: adjusted for age, race, study site, body height, total body fat mass. Model 2: additionally adjusted for lifestyle factors, including education, alcohol consumption, smoking status, and physical activity. Model 3: additionally adjusted for prevalent disease, self-rated health, depression, and cognitive status. Cut-points for white men were: <34, 34–37, 38–41, 42+; for black men: <33, 33–36, 37–42, 43+; for white women: <31, 31–34, 35–39, 40+; for black women: <28, 28–32, 33–37, 38+ HU. Lower muscle tissue attenuation indicates greater fat infiltration into the muscle.

*Events/1000 person-years.

Table 5. Adjusted Hazard Ratios (With 95% Confidence Intervals) for Incident Mobility Limitations According to Quartiles of all Muscle Parameters

| Muscle Parameter | Men | Women |
|---|---|---|
| Mid-thigh muscle area | | |
| 1 = low | 1.45 (0.92–2.27) | 1.34 (0.95–1.88) |
| 2 | 1.18 (0.79–1.77) | 1.01 (0.74–1.38) |
| 3 | 1.39 (0.96–2.02) | 1.00 (0.75–1.32) |
| 4 = high | 1.0 | 1.0 |
| Mid-thigh muscle attenuation | | |
| 1 = low* | 1.79 (1.22–2.65) | 1.55 (1.10–2.17) |
| 2 | 1.38 (0.94–2.02) | 1.69 (1.23–2.34) |
| 3 | 1.06 (0.72–1.58) | 1.33 (0.96–1.85) |
| 4 = high | 1.0 | 1.0 |
| Knee extensor strength | | |
| 1 = low | 1.66 (1.10–2.51) | 1.69 (1.22–2.35) |
| 2 | 1.34 (0.89–2.02) | 1.53 (1.11–2.10) |
| 3 | 1.23 (0.83–1.82) | 1.08 (0.78–1.49) |
| 4 = high | 1.0 | 1.0 |

*Notes*: Adjusted for age, race, study site, body height, total body fat mass, education, alcohol consumption, smoking status, physical activity, prevalent disease, self-rated health, depression, cognitive status, and the other variables listed in the table.

*Lower muscle tissue attenuation indicates greater fat infiltration into the muscle.


Figure 4. Adjusted hazard ratio (HR) for incident mobility limitations in men and women according to sex- and race-specific quartiles (1 = low, 4 = high) of knee extensor strength and mid-thigh muscle cross-sectional area.

the true strength of the muscle because it is a volitional measure, explaining why muscle strength did not mediate the association between muscle attenuation and mobility limitation.

As stated in the Methods section, we included total body fat mass in all regression models because it is positively associated with muscle mass and muscle strength, and negatively associated with physical function (3,23,24). Of interest was our observation that total body fat mass was a strong predictor of incident mobility limitations in women but not in men. In women, the hazard ratios for mobility limitations were 1.0 (reference), 1.57 (95% CI, 1.13–2.19), 1.75 (95% CI, 1.24–2.47), and 2.73 (95% CI, 1.91–3.91) with increasing quartile of total body fat mass. In men, the corresponding hazard ratios were 1.0 (reference), 0.96 (95% CI, 0.66–1.39), 1.14 (95% CI, 0.76–1.70), and 1.18 (95% CI, 0.77–1.80). This association was independent of the three muscle parameters. The results of the present study suggest that interventions designed to prevent or delay disability should focus not only on increasing muscle strength, but also on optimizing body composition, especially in older women.

The prevalence and incidence of functional limitation is generally higher in women and blacks compared to men and whites (33,34). Although socioeconomic and health-related factors may (partly) explain these differences, sex and race differences in muscle integrity and total body fat mass may also contribute to the difference in functional status in old age. In our study, women had less muscle mass, greater fat infiltration into the muscle, lower muscle strength, and more

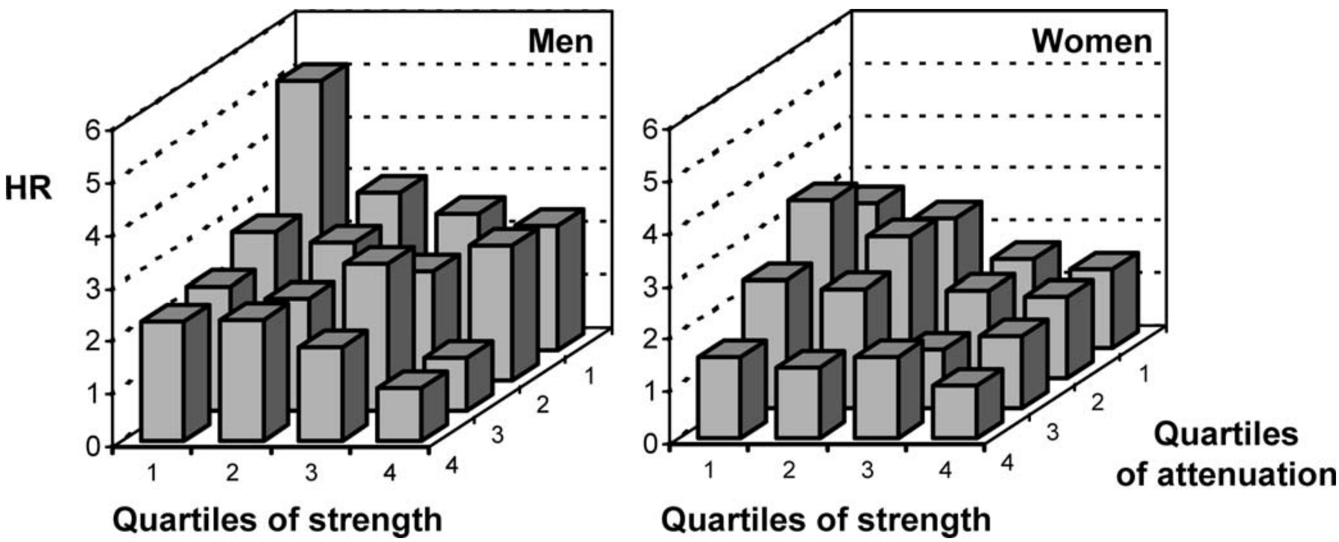


Figure 5. Adjusted hazard ratio (HR) for incident mobility limitations in men and women according to sex- and race-specific quartiles (1 = low, 4 = high) of knee extensor strength and mid-thigh muscle tissue attenuation. Low attenuation indicated greater fat infiltration into the muscle.

total body fat compared to men. Similarly, blacks had a greater fat infiltration into the muscle and more body fat than whites.

Some limitations of the study need to be addressed. Due to the strict exclusion criteria for the strength-testing procedure, a relatively healthier sample may have been included in the statistical analyses. However, when we repeated the analyses for muscle area and muscle attenuation including persons with missing muscle strength data, the associations were similar. Including self-reported weight loss greater than 2.3 kg (5 lbs) in the 12 months prior to the start of the study also did not markedly affect the observed hazard ratios. Incident mobility limitation was based on self-report; this subjective measure may have been influenced by cognitive status, perceived mastery, and depressive symptoms (35,36) leading to potential misclassification (26). Because the study participants had to report mobility limitations on two consecutive contacts, our study outcome is unlikely to be influenced by short-term fluctuations in mobility. Future studies should include prospective measurements of objective function tests and a longer follow-up time to complement our results. Because the study cohort was selected to have no self-reported mobility limitation at baseline, the observed associations may be an underestimation of the true associations in the general population. Muscle attenuation was used as an indicator of fat infiltration into the muscle. No muscle biopsies were available in the study to directly assess the fat content of muscle tissue. However, the fat and triglyceride content of the vastus lateralis has been shown to be negatively associated with mid-thigh muscle attenuation (21). In addition, good correlations between tissue attenuation measured by computed tomography and histological or chemical assessment of tissue fat content has been observed for other organs (37).

## *Conclusion*

Lower muscle mass (smaller cross-sectional muscle area), lower muscle strength, and greater fat infiltration into the muscle are associated with incident mobility limitations in older men and women. The association between low muscle mass and incident mobility limitations seems to be a function of lower muscle strength.

Acknowledgments

The research of Dr. Visser has been made possible by a fellowship from the Royal Netherlands Academy of Arts and Sciences. This study was supported by National Institute on Aging grants NO1-AG-6-2101, NO1-AG-6-2103, and NO1-AG-6-2106.

Address correspondence to Dr. M. Visser, Institute for Research in Extramural Medicine, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. E-mail: m.visser@vumc.nl

References

1. Rantanen T, Guralnik JM, Ferrucci L, et al. Coimpairments as predictors of severe walking disability in older women. *J Am Geriatr Soc*. 2001;49:21–27.
2. Fiatarone MA, O'Neill E, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330:1769–1775.
3. 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.
4. Sternfeld B, Ngo L, Satariano WA, Tager IB. Associations of body composition with physical performance and self-reported functional limitation in elderly men and women. *Am J Epidemiol*. 2002;156:110–121.
5. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among elderly in New Mexico. *Am J Epidemiol*. 1998;147:755–763.
6. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc*. 2002;50:889–896.
7. Landers KA, Hunter GR, Wetzstein CJ, Bamman MM, Weinsier RL. The interrelationship among muscle mass, strength, and the ability to perform physical tasks of daily living in younger and older women. *J Gerontol*. 2001;56:B443–B448.
8. Metter EJ, Lynch N, Conwit R, Lindle R, Tobin J, Hurley B. Muscle quality and age: cross-sectional and longitudinal comparisons. *J Gerontol*. 1999;54:B207–B218.
9. Gallagher D, Ruts E, Visser M, Heshka S, Baumgartner RN, Wang J, et al. Weight stability masks body composition changes in elderly men: visceral fat increase and lean tissue loss. *Am J Physiol*. 2000;279:E366–E375.
10. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol*. 2000;88:1321–1326.
11. Borkan GA, Hults DE, Gerzof SG, Robbins AH, Silbert CK. Age changes in body composition revealed by computed tomography. *J Gerontol*. 1983;38:673–677.
12. Forsberg AM, Nilsson E, Werneman J, Bergstrom J, Hultman E. Muscle composition in relation to age and sex. *Clin Science*. 1991;81:249–256.
13. Overend TJ, Cunningham DA, Paterson DH, Lefcoe MS. Thigh composition in young and elderly men determined by computed tomography. *Clin Physiol*. 1992;12:629–640.
14. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. The association between skeletal muscle composition and strength in the elderly: the Health ABC study. *J Appl Physiol*. 2001;90:2157–2165.
15. Roubenoff R, Hughes VA. Sarcopenia: current concepts. *J Gerontol*. 2000;55:M716–M724.
16. Morganti CM, Nelson ME, Fiaterone MA, Dallal GE, Economos CD, Crawford BM, et al. Strength improvements with 1 yr of progressive resistance training in older women. *Med Sci Sports Exerc*. 1995;27:906–912.
17. Sipilä S, Taaffe DR, Cheng S, Puolakka J, Toivanen J, Suominen H. Effects of hormone replacement therapy and high-impact physical exercise on skeletal muscle in post-menopausal women a randomized placebo-controlled study. *Clin Sci*. 2001;101:147–157.
18. Roth SM, Ivey FM, Martel GF, Lemmer JT, Hurlbut DE, Siegel EL, et al. Muscle size responses to strength training in young and older men and women. *J Am Geriatr Soc*. 2001;49:1428–1433.
19. Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, et al. Growth hormone and sex steroid administration in healthy aged women and men. *JAMA*. 2002;288:2282–2292.
20. Ryan AS, Nicklas BJ, Berman DM, Dennis KE. Dietary restriction and walking reduce fat deposition in the midthigh in obese older women. *Am J Clin Nutr*. 2000;72:708–713.
21. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined with computed tomography is a marker of skeletal muscle lipid content. *J Appl Physiol*. 2000;89:104–110.
22. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25:71–80.
23. Visser M, Harris TB, Langlois J, Hannan MT, Roubenoff R, Felson DT, et al. Body fat and skeletal muscle mass in relation to physical disability in very old men and women of the Framingham Heart Study. *J Gerontol Med Sci*. 1998;53:M214–M221.

24. Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, et al. Strength and muscle quality in a cohort of well-functioning older adults: the Health ABC Study. *J Am Geriatr Soc.* 2003;51:323–330.
25. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry.* 1987;48:314–318.
26. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, 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; 49A:M85–M94.
27. Fried LP, Bandeen-Roche K, Chaves PHM, Johnson BA. Preclinical mobility disability predicts incident mobility disability in older women. *J Gerontol.* 2000;55A:M43–M52.
28. Reed RL, Pearlmutter L, Yochum K, Meredith KE, Mooradian AD. The relationship between muscle mass and muscle strength in the elderly. *J Am Geriatr Soc.* 1991;39:555–561.
29. Metter EJ, Lynch N, Conwit R, Lindle R, Tobin J, Hurley B. Muscle quality and age: cross-sectional and longitudinal comparisons. *J Gerontol.* 1999;54A:B207–B218.
30. Kelley DE, Slasky BS, Janosky J. Skeletal muscle density: effects of obesity and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr.* 1991;54:509–515.
31. Ryan AS, Nicklas BJ. Age-related changes in fat deposition in mid-thigh muscle in women: relationships with metabolic cardiovascular disease risk factors. *Int J Obes.* 1999;23:126–132.
32. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, et al. Assessment of skeletal muscle triglyceride content by 1H nuclear magnetic resonance spectroscopy in lean and obese adolescents. *Diabetes.* 2002;51:1022–1027.
33. Ostchega Y, Harris TB, Hirsch R, Parsons VL, Kington R. The prevalence of functional limitations and disability in older persons in the US: data from the National Health and Nutrition Examination Survey III. *J Am Geriatr Soc.* 2000;48:1132–1135.
34. Dunlop DD, Manheim LM, Sohn MW, Liu X, Chang RW. Incidence of functional limitation in older adults: the impact of gender, race, and chronic conditions. *Arch Phys Med Rehabil.* 2002;83:964–971.
35. Kempen GIJM, Steverink N, Ormel J, Deeg DJ. The assessment of ADL among frail elderly in an interview survey: self-report versus performance-based tests and determinants of discrepancies. *J Gerontol.* 1996;51B:254–260.
36. Hoeymans N, Wouters ERCM, Feskens EJM, van den Bos GA, Kromhout D. Reproducibility of performance-based and self-reported measures of functional status. *J Gerontol.* 1997;52A:M363–M368.
37. Bydder GM, Chapman RW, Harry D, Bassan L, Sherlock S, Kreel L. Computed tomography attenuation values in fatty liver. *J Comput Tomogr.* 1981;5:33–35.

*Received July 31, 2003*
*Accepted January 2, 2004*
*Decision Editor: John E. Morley, MB, BCh*