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Region-Specific Fat Mass and Muscle Mass and Mortality in Community-Dwelling Older Men and Women

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Key Words
Body composition · Thinness · Mortality in old age · Body mass components

Abstract
Background: Increased mortality risk at low body mass index values is well established for older persons. It is, however, unclear how the underlying body mass components (fat and muscle mass – FM and MM, respectively) are associated with mortality in old age. ***Objective:*** This study aimed to examine the mortality risk of four body composition measures (appendicular skeletal MM, leg, arm and trunk FM) with 12-year mortality in community-dwelling older men and women. As a secondary objective, the influence of cancer, obstructive lung disease, smoking and previous weight loss on these associations was examined. ***Methods:*** Data were used from the Longitudinal Aging Study Amsterdam, a random population-based cohort study (55–85 years) in the Netherlands. Body composition was determined in 1995–1996 by dual energy X-ray absorptiometry. The present study included 477 community-dwelling persons aged ≥65 years who were followed until 2007 for their vital status. ***Results:*** Twelve-year mortality rates were 133/242 (55%) in men and 92/235 (39%) in women. Since most associations were U- or J-shaped, only observations below the sample mean were included to calculate hazard ratios (HRs) per one SD lower value. Adjusted for height, age and each other, lower appendicular skeletal MM [HR 1.59 (95% CI: 1.04–2.42)] and lower leg FM [1.68 (1.04–2.72)] in men and lower trunk FM [1.61 (1.02–2.53)] in women were associated with an increased mortality risk. Associations attenuated and became statistically nonsignificant in men after adjustment for cancer, obstructive pulmonary disease and smoking and in women after additional adjustment for previous 3-year weight change. ***Conclusions:*** In older men, lower MM and lower leg FM are associated with an increased mortality risk, while in older women only lower trunk FM is associated with an increased risk. The causality of these associations is debated. Suggested sex differences deserve further study.

Introduction

The increased mortality risk at low body mass index (BMI) values is well established for older persons [1–4]. This association may be explained by weight loss that ac-

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companies a declining health in old age [5]. It is, however, unclear how the underlying body mass components (fat and muscle mass – FM and MM, respectively) are associated with mortality in old age and if thinness-related diseases or previous weight loss explain these associations.

Some studies suggest that low MM but not low FM is associated with an increased mortality risk [6–8], while in women only, there may be an association with low FM as well [9]. These studies were, however, performed in younger adults and used inaccurate measures to assess body composition like anthropometric measures [8, 9] or bioelectrical impedance [7]. Only one study in 60-year-old men used total body potassium counting [6], which is a more accurate method to estimate lean mass (LM).

There are only a limited number of studies performed in community-dwelling older persons based on more accurate imaging techniques, i.e. computed tomography (CT) scanning and/or dual energy X-ray absorptiometry (DXA), and results are inconsistent. One study found an association between low mid-thigh muscle area and mortality in older men only, but no associations were found for low MM in the legs or arms determined by DXA in both men and women [10]. Results on FM were not reported. Yet another study found that both low muscle area and fat area in the calf were associated with increased mortality in community-dwelling older persons after adjustment for height and weight, but did not distinguish between men and women. The associations disappeared after adjustment for age and gender [11].

Most previous studies that examined the association between low FM and mortality did not distinguish different regional fat depots [6–9, 11]. However, there are indications that a lower thigh or leg FM is associated with more unfavorable glucose and lipid levels in older persons after adjusting for the association with trunk FM which is in the opposite direction [12, 13]. A recent review summarized the evidence in favor on gluteofemoral body fat as a determinant of metabolic health [14]. Although this protective effect is suggested to be attributed to peripheral FM in the legs and not the arms [15], the role of arm FM is not often studied. As we recently showed that mid-upper arm circumference was more strongly associated with mortality than low BMI in old age [16], the association between arm FM and mortality also deserves further examination.

The primary objective of the current study was to examine the associations of different body composition measures (appendicular skeletal MM, leg FM, arm FM, and trunk FM) determined by DXA with 12-year all-cause mortality in community-dwelling older men and women. As a secondary objective, the influence of cancer, obstructive lung disease, smoking and previous weight loss on these associations was examined.

Subjects and Methods

Study Sample

This study uses prospective data from the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing study on predictors and consequences of changes in physical, emotional, cognitive and social functioning in older people in the Netherlands. A random sample stratified by age and sex according to expected mortality after 5 years was drawn from the population registries of 11 municipalities in three geographical areas of the Netherlands. A total of 3,107 men and women aged 55–85 years were enrolled at the baseline examination in 1992–1993. The total sample is representative of the Dutch general older population. Examination cycles are repeated every 3 years and consist of a general face-to-face interview and a medical interview in the respondent's home. The details of the LASA study have been described elsewhere [17]. The study was approved by the Ethics Review Board of the VU University Medical Center, and informed consent was obtained from all respondents.

For the present study, data from the second (1995–1996) examination cycle of LASA (n = 2,545) were used. During this examination cycle, respondents who lived in the Amsterdam region and who were born in or before 1930 (65 years and older as of January 1, 1996) were invited for an additional DXA examination (n = 698). Of the 698 respondents who were invited, 520 respondents (74%) participated in the whole body DXA examination. Nonresponders were older but had a similar gender distribution [18]. Of these 520 respondents, 4 were excluded because the DXA values of the left and right legs differed substantially (>1 standard deviation), 11 were excluded because of a bilateral hip or knee prosthesis, 2 because the soft tissue results were not calculated, and 22 because of missing data on body height. In addition, 4 institutionalized persons were excluded so that a more homogeneous population of older community-dwelling persons could be studied. Finally, 477 persons were left to be included in the analyses of the present study (242 men and 235 women).

Measures

Vital status and date of death were traced until June 1, 2007, through the registers of municipalities in which the respondents were living, which was 100% complete. Survival time was calculated in days from the 1995–1996 examination cycle until June 1, 2007.

Anthropometric data were collected during the medical interview by trained research nurses using a standardized protocol. Particularities during the measurements were reported using standard forms. Height was measured to the nearest 0.001 m using a stadiometer. In case no valid height measurement could be obtained due to the recorded particularities 'not able to stand', 'shoes', 'kyphosis', or 'scoliosis', or if height was missing, one of the following imputation methods was applied: (1) a valid follow-up measurement of height was used; (2) height was calculated for those with scoliosis or kyphosis using gender-specific prediction rules based on age and knee height [19] developed within the

LASA sample with a valid height and knee height measurement; (3) self-reported height was used. This imputation was performed in 42/477 (9%) respondents. Knee height of the left leg was measured using a Mediform sliding caliper (Medical Express, Beaverton, Oreg., USA) with the knee and ankle joints fixed at 90° angles. Weight was measured to the nearest 0.1 kg using a calibrated bathroom scale (Seca, model 100; Lameris, Utrecht, The Netherlands). Recorded weight particularities which led to exclusion of respondents were: 'amputation', 'brace', and 'prothesis'. In addition, weight was adjusted for 'clothing' (–1 kg), 'corset' (–1 kg), and 'shoes' (–1 kg) [20]. BMI was calculated as body weight (kg) divided by height (m) squared. Weight change (kg) between the first (1992–1993) and second (1995–1996) examination cycle of LASA was calculated.

A whole body DXA scan was performed at the VU University Medical Center, using a Hologic QDR 2000 scanner (Hologic Inc., Waltham, Mass., USA). The selected scanning mode was 'enhanced array whole body', and software version V5.70A was used to analyze the scan data. The software provides estimates of bone mineral content (in grams), LM (in grams), and FM (in grams) for the total body and for standard body regions (legs, arms, trunk and head). The amount of fat-free soft tissue (LM minus bone mineral content) of the extremities was used as an indicator of appendicular skeletal MM [21–23]. Leg FM and arm FM were calculated by adding FM of the left and right limbs. Total appendicular skeletal MM was calculated by adding fat-free soft tissue of both arms and legs. In the case parts of the arm (n = 24) or parts of the leg (n = 1) were not completely visible in the field of scanning, or a hip or knee prothesis was present in one leg only (n = 24), the opposite body part was used in duplicate instead.

The presence (yes or no) of obstructive lung disease (asthma, chronic bronchitis or pulmonary emphysema) and cancer (malignant neoplasms) was determined by explicitly asking the participants whether they had these diseases. The accuracy of self-report data for these diseases as compared to general practitioners' information was shown to be adequate [24]. Smoking status and history were assessed and categorized into current, former, and never smokers. Former smokers who stopped smoking more than 15 years ago were classified as never smokers since mortality in former smokers approaches the level of never smokers after a smoking cessation time of 10–20 years [25, 26].

Statistical Analyses

All statistical analyses were performed with SPSS 15.0 and R statistical software (version 2.6.2). A p value <0.05 was used to denote statistical significance. Separate analyses were performed for men and women because of expected potential sex differences in the associations between body composition measures and mortality [8, 9]. This stratification was also supported by adding an interaction term with sex to the crude Cox regression model adjusted for height (see below) that resulted in the following p values: 0.08 for trunk FM•sex and 0.09 for appendicular skeletal MM•sex. Pearson's correlation coefficients were calculated for determining associations between body composition measures. The association of appendicular skeletal MM, leg FM, arm FM, and trunk FM with 12-year all-cause mortality was examined using two methods: Cox regression models with restricted cubic spline functions and (linear) Cox regression models. The advantage of spline regression models over a categorical approach, such as the use of quintiles, is that it can fit complex distributions without assuming linear associations within categories, thus providing better insight into the true shape of the association [27]. The variables appendicular skeletal MM, leg FM, arm FM, and trunk FM were transformed to sex-specific Z scores to standardize across the different units of these independent variables. The Z score is a deviation from the sample mean value expressed in standard deviation units.

First, dose-response associations between appendicular skeletal MM, leg FM, arm FM, and trunk FM and 12-year mortality were examined using a Cox regression model with restricted cubic spline functions with 3 standard knots at the 5th, 50th and 95th percentile of the observed distribution of the independent variable. Based on the lower Akaike's Information Criterion [28], a model with 3 knots was found to have a superior fit over a model with 4 or 5 knots. Hazard ratios (HRs) were plotted against the Z score units, using a Z score of zero as the reference. Second, the same associations were examined by a linear Cox regression model. Since most associations were U- or J-shaped, only observations below the sample mean were included to calculate HR per one SD lower value. The assumption of proportional hazards was checked by a time interaction test (all were not statistically significant).

All associations were adjusted for body height since the amount of appendicular skeletal MM, and to a lesser extent the amount of leg and arm FM, is known to be strongly determined by body height (longer arms and legs contain more muscle and fat), and height is – although borderline not statistically significant in our study – associated with mortality. Secondly, we adjusted for age – which is strongly related to mortality – to account for the changes in body composition which normally occur with aging. Thirdly, we adjusted the association of each DXA measure (appendicular skeletal MM, leg FM, arm FM, and trunk FM) for the others. Only the analyses of leg FM, arm FM, and trunk FM were not adjusted for each other because these measures were highly correlated (Pearson's correlation coefficients of ≥ 0.75 in men and women) and the variance inflation factors (examined with collinearity statistics in SPSS) were between 2.2 and 7.0 where values above 2.5 may indicate collinearity problems in weaker models. Variance inflation factors with appendicular skeletal MM were below 1.3. Finally, we adjusted the associations for: (1) smoking status, presence of cancer or obstructive lung disease to examine if smoking status or these two diseases that are known to be associated with thinness [29] explained this association; (2) weight change in the previous 3 years to examine if previous weight loss would additionally explain the associations.

Results

During the follow-up period of 12 years, 133 (55%) men and 92 (39%) women died (table 1), with mortality rates of 69 and 43 per 1,000 person-years, respectively.

A description of the study sample is shown in table 1. The mean age of the study sample was 74.8 years (SD 6.4) in men and 74.0 years (SD 6.3) in women. Those who died during follow-up had a higher age, a lower BMI (in men only), a lower body height (in men only), lost more weight in the previous 3 years, and had a lower percentage of

Table 1. Description of the study sample by sex and 12-year all-cause mortality

	Men				Women			
	overall	survived	deceased	p	overall	survived	deceased	p
Total	242	109	133		235	143	92	
Age, years	74.8 (6.4)	71.6 (5.1)	77.4 (6.2)	0.000	74.0 (6.3)	71.7 (5.0)	77.6 (6.2)	0.000
BMI	25.8 (3.2)	26.3 (3.0)	25.4 (3.4)	0.045	27.5 (4.8)	27.5 (4.4)	27.5 (5.3)	0.911
Body height, cm	173.8 (6.4)	174.7 (6.4)	173.1 (6.3)	0.051	161.5 (6.1)	161.8 (6.3)	161.0 (5.6)	0.312
Weight change in past 3 years, kg	−0.4 (3.9)	0.4 (3.3)	−1.0 (2.3)	0.008	−0.2 (3.6)	0.2 (3.8)	−0.9 (3.3)	0.034
Obstructive lung disease, %	16.9	10.1	22.6	0.016	12.8	7.7	20.7	0.007
Cancer, %	8.7	1.8	14.3	0.001	13.6	11.9	16.3	0.442
Smoking (current or past <15 years ago), %	42.1	32.1	50.4	0.006	26.4	25.2	28.3	0.710
Body composition measures determined by DXA								
Body fat, %	28.3 (6.4)	28.8 (6.3)	27.8 (6.8)	0.252	42.8 (7.5)	43.7 (6.7)	41.4 (8.6)	0.020
Appendicular skeletal MM, kg	21.5 (2.7)	22.2 (2.4)	20.9 (2.8)	0.000	14.7 (2.2)	14.6 (2.3)	14.7 (2.2)	0.630
Leg FM, kg	4.4 (1.5)	4.6 (1.4)	4.3 (1.6)	0.150	7.4 (2.7)	7.5 (2.5)	7.3 (2.9)	0.645
Arm FM, kg	4.6 (1.5)	4.8 (1.4)	4.5 (1.5)	0.129	7.5 (2.8)	7.7 (2.7)	7.2 (2.9)	0.221
Trunk FM, kg	12.3 (5.0)	13.0 (5.0)	11.7 (5.0)	0.059	15.3 (5.6)	15.8 (5.3)	14.5 (6.1)	0.095

Values are mean (SD) unless stated otherwise. The difference between alive and deceased persons (p value) is tested by a Student t test or a general linear model. DXA measures are adjusted for age and body height.

Table 2. The HR of 12-year mortality per one SD lower value of the body composition measure as determined by DXA

	Total	Analysis adjusted for				
		height	height and age	height, age and other body comp. measures[1]	height, age, other body comp. measures[1], smoking, cancer, and obstructive lung disease	height, age, other body comp. measures[1], smoking, cancer, obstructive lung disease, and weight change in past 3 years
Men						
Appendicular skeletal MM	117	1.88 (1.22–2.89)	1.64 (1.08–2.50)	1.59 (1.04–2.42)	1.49 (0.97–2.28)	1.31 (0.84–2.06)
Leg FM	126	1.92 (1.18–3.12)	1.76 (1.09–2.86)	1.68 (1.04–2.72)	1.46 (0.89–2.41)	1.26 (0.73–2.16)
Arm FM	129	1.54 (0.96–2.48)	1.35 (0.83–2.17)	1.28 (0.79–2.08)	1.29 (0.80–2.09)	1.10 (0.65–1.85)
Trunk FM	118	1.32 (0.87–2.00)	1.37 (0.90–2.09)	1.36 (0.89–2.08)	1.39 (0.90–2.15)	1.30 (0.81–2.08)
Women						
Appendicular skeletal MM	127	0.83 (0.44–1.57)	0.92 (0.49–1.74)	0.80 (0.40–1.57)	0.72 (0.34–1.54)	0.63 (0.28–1.38)
Leg FM	131	1.51 (0.83–2.77)	1.18 (0.66–2.12)	1.18 (0.66–2.11)	1.21 (0.66–2.22)	0.97 (0.51–1.85)
Arm FM	130	2.05 (1.08–3.89)	1.20 (0.66–2.20)	1.20 (0.64–2.24)	1.22 (0.65–2.31)	0.91 (0.46–1.78)
Trunk FM	123	2.32 (1.43–3.75)	1.61 (1.02–2.52)	1.61 (1.02–2.53)	1.94 (1.20–3.14)	1.65 (0.94–2.88)

Analyses are performed on the left side of the dose-response curve, below a Z score of zero (see fig. 1).
[1] Analyses of appendicular skeletal MM are adjusted for leg FM, arm FM and trunk FM; analyses of leg FM, arm FM, and trunk FM are adjusted for appendicular skeletal MM.

body fat (in women only) than those who survived. In addition, men who died had a lower appendicular skeletal MM than men who survived. Leg FM, arm FM and trunk FM did not statistically significantly differ between those who died and those who survived. Pearson's correlation coefficients between appendicular skeletal MM and FM of the leg, arm or trunk FM varied from 0.35 to 0.38 in men and from 0.38 to 0.42 in women. Between trunk FM and FM of the leg or arm they varied from 0.75 to 0.78 in both men and women. The correlation coefficient between leg FM and arm FM was 0.89 in men and 0.92 in women.

In men, after adjustment for height, appendicular skeletal MM showed a reversed J-shaped association with 12-year mortality, while a U-shaped association was found for arm and leg FM and a linearly decreasing association

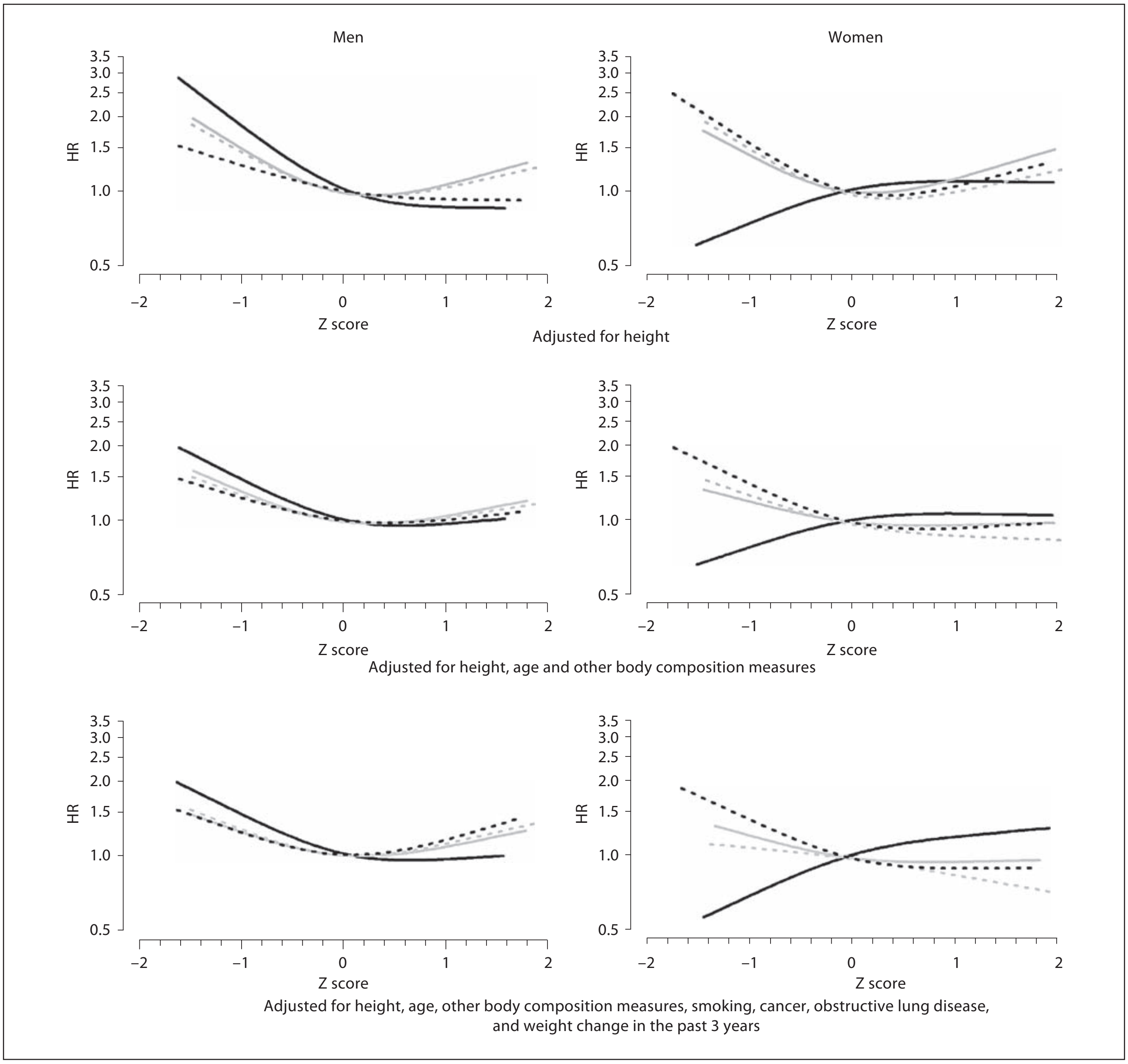

Fig. 1. Dose-response associations of different body composition measures determined by DXA with 12-year all-cause mortality, by sex. Black line: appendicular skeletal MM; grey line: leg FM; dashed grey line: arm FM; dashed black line: trunk FM. Analyses of appendicular skeletal MM are adjusted for leg FM, arm FM and trunk FM; analyses of leg FM, arm FM, and trunk FM are adjusted for appendicular skeletal MM.

for trunk FM (fig. 1). Below a Z score of zero (sample mean), the corresponding HRs per one SD lower value of the body composition measures are shown in table 2 and reveal a statistically significant association with mortality for lower appendicular skeletal MM and lower leg FM, also after additional adjustment for age and the other body composition measures. Adjustment for smoking status, obstructive lung disease and cancer attenuated the associations and they were no longer statistically significant. Additional adjustment for weight change in the past

3 years further attenuated the strength of the associations (table 2).

In women, after adjustment for height, appendicular skeletal MM showed a linearly increasing association with 12-year mortality until the sample mean, while a U-shaped association was found for the FM measures (fig. 1). Below a Z score of zero (sample mean), the corresponding HRs per one SD lower value of the body composition measures are shown in table 2 and reveal statistically significant associations with mortality for lower arm FM and lower trunk FM. The association with arm FM disappeared after adjustment for age, while the association with trunk FM remained statistically significant after adjustment for age, appendicular skeletal MM, and smoking status, obstructive lung disease and cancer. After adjustment for weight change in the past 3 years, the association with trunk FM was attenuated and became not statistically significant (table 2).

Discussion

In our study sample of Dutch community-dwelling persons aged 65 years and older, mostly reversed J-shaped (appendicular skeletal MM in men) and U-shaped (FM) associations were found between body composition measures and mortality. Below the sample mean, a 60% higher 12-year mortality risk was observed for one SD lower appendicular skeletal MM and one SD lower leg FM in men and for one SD lower trunk FM in women, after adjustment for height and age and each other. Associations attenuated and became statistically nonsignificant in men after adjustment for cancer, obstructive pulmonary disease and smoking and in women after additional adjustment for previous 3-year weight change.

The strengths of this study are the long (12-year) follow-up, the accurate assessment of regional body composition, the inclusion of different regional fat depots and the separate analysis of men and women. Another strength was the use of sophisticated spline regression techniques, which allowed a detailed study of the exact dose-response relationships which turned out to be nonlinear.

To our knowledge, there are only two previous comparable studies in a general older population using accurate imaging techniques. One study found an increased 6-year mortality risk for both low muscle and fat area of the calf using CT, which disappeared after adjustment for age and gender [11]. However, no data were presented for men and women separately. Another study found an increased 6-year mortality risk for low leg muscle area using CT in men but not in women, while no associations were found for arm muscle area using CT or leg or arm LM using DXA [10]. Results on FM were not reported. Linear models were used in both studies [10, 11], which may have weakened or obscured existing associations at low values, since our data show that the association of FM and MM with mortality is mostly non-linear.

With respect to differences in regional FM, in men only lower leg FM was found to be associated with mortality and not lower trunk or arm FM. These results are in line with previous studies suggesting a beneficial health effect of gluteofemoral FM and not of arm FM [15] or trunk FM [12–14]. Contrary to what we had expected based on previous studies [12–14], in women, a higher mortality risk was observed for low trunk FM and not for low leg FM. One potential explanation may be that there are sex-specific changes in body composition with weight loss as discussed later on.

An important issue to discuss is the causality of the observed associations. It is possible that underlying diseases cause weight loss as well as an increased mortality risk. For example, a recent meta-analysis of 57 studies suggests that the increased mortality risk at low BMI values may be explained by respiratory disease and lung cancer [30]. Adjustment for smoking status, obstructive lung disease and cancer indeed attenuated the observed associations in men but not in women. Nevertheless, also in men, the point estimates did not reduce to one, indicating that smoking and underlying diseases may partly explain the observed associations but not all. Subsequently, excluding all death occurring within the first year after baseline did not alter the associations [e.g. trunk FM in women changed from 1.94 (1.20–3.14) to 1.88 (1.16–3.05)]. Stratification by smoking status, obstructive lung disease, and heart disease generally did not alter the associations either (data not shown). It should be noted, however, that adjustment for presence of disease does not take into account its severity, and residual confounding can never be excluded.

Another explanation may be that lower body composition measures are markers of previous weight loss independent of underlying diseases. Indeed, after additional adjustment for weight change in the past 3 years, all associations with mortality attenuated and became statistically nonsignificant in women as well. Although this weight loss may be caused by underlying diseases not accounted for in the adjusted models, it is also possible that other (psychosocial or economic) factors lead to weight loss and (a subsequently) increased mortality risk. In other words, weight loss itself may also contribute to the higher mortality risk.

Sex-specific changes in body composition with weight reduction may explain the observed sex differences in the associations with low MM, e.g. that a low MM was associated with an increased mortality risk in men but not in women. This hypothesis is supported by a previous study in obese adults who lost weight through a diet intervention, which showed that men lose relatively more MM and women more FM [31]. Also in a general older population, men were shown to lose relatively more LM with weight loss than women, which was not explained by the men's greater initial LM or by their worse health status [32]. The finding that, in contrast to men, in women lower trunk FM and not leg FM was associated with an increased mortality risk may in part be explained by the fact that women show an evolutionary preference for FM storage in their legs [33]. Thus with weight loss, leg FM may be preserved and trunk FM lost.

Despite the causality discussion, there is also support for a causal link between low BMI or weight loss and mortality in older persons. A recent meta-analysis of 25 trials showed that oral protein and energy supplementation in older undernourished persons (often defined by a low BMI in combination with weight loss) led to a statistically significant increase in body weight as well as reduction in mortality [34]. In these trials, underlying body mass components were not assessed. There are a few hypothetical explanations for a causal link between a low FM and/or a low MM and mortality in older persons. One is the hypothesis that FM serves as a source of energy storage. Older persons who become ill may have a better chance to survive when they have more energy reserves. Likewise, MM may serve as an (extra) source of energy storage in men. Although this theory is hard to prove, there may be some support from observational studies in a clinical setting of hospitalized older persons [35], hemodialysis patients [36], and cancer patients [37], in which lower FM determined by DXA was associated with an increased mortality risk as well. No associations were found for lower LM or appendicular MM, but results were not stratified by sex, which may have obscured an existing association in men. However, the observed associations for low FM may also be explained by the confounding effects of disease severity. In women, yet another hypothesis might be that exogenous or adipose tissue-derived estrogens protect against certain health risks. This hypothesis is based on the observation that in older women who use hormone-replacement therapy mainly consisting of estrogens low BMI was not associated with mortality, while in women who did not use this therapy, low BMI was associated with an increased mortality risk [38]. Finally, gluteofemoral fat specifically is suggested to be a determinant of metabolic health in adults as well as in older persons, possibly through the long-term entrapment of excess fatty acids [14]. However, this does not explain why in our study in older women trunk FM seems to be beneficial and leg FM is not.

Although DXA measures cannot be assessed in all health care settings, it is important to disentangle the association of different body mass components with mortality because this may contribute to the ongoing debate on a consensus definition of cachexia or sarcopenia needed for clinical practice. At present, there are three consensus definitions of cachexia that only differ in minor points [39]. With respect to body composition, the definition of the European Palliative Care Research Collaborative [40] does not take into account fat loss, while the definition of the Special Interest Group on Cachexia and Anorexia of the ESPEN [41] does take into account fat loss. The Society for Cachexia and Wasting Disorders [42] includes loss of FM but only secondary to loss of MM. As our results show that a low FM is associated with an increased mortality risk, especially in women, this may favor the inclusion of fat loss in the cachexia definition. In addition, differences between men and women need to be explored in future studies and should be considered with respect to the definition of cachexia.

Our study has some limitations. Although the LASA sample is a representative sample of the general older Dutch population, nonresponders for the DXA examinations were older than responders [16]. When comparing the included study sample with the not included (overall) noninstitutionalized LASA sample aged ≥65 years stratified by sex, no statistically significant differences were observed for BMI, mid-upper arm circumference, or the number of chronic diseases (including obstructive lung disease, cardiac disease, peripheral arterial disease, stroke, diabetes mellitus, arthritis, and cancer). However, the included sample was somewhat younger for women only (mean age 74 vs. 76 years), had fewer functional limitations and a lower mortality rate (both sexes; $p < 0.05$) than the excluded sample. These data suggest that although no major differences were found, the study sample may have been somewhat healthier than the community-dwelling older Dutch population, which perhaps weakened the observed associations due to less contrast in the study measures. Furthermore, our study sample was relatively small and consequently confidence intervals were relatively wide. Another limitation of this study is that DXA measurements are not able to differentiate between different fat depots in the body (i.e. intra- or intermuscular fat tissue). Future, preferably larger, studies are needed to confirm our results, to further investigate the observed differences between men and women and to address how (the loss of) specific fat depots may influence health.

In summary, based on our study in community-dwelling older persons, both lower appendicular skeletal MM and lower leg FM are associated with an increased mortality risk in men, while in women, only lower trunk FM is associated with an increased mortality risk. The causality of these associations can be debated. The observed sex differences deserve further study.

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Disclosure Statement

None of the authors have a conflict of interest or financial interest with regard to the publication of this work.

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