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Greater skeletal muscle fat infiltration is associated with higher all-cause mortality among men of African ancestry

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Abstract

Background: fat infiltration within and around skeletal muscle (i.e. myosteatosis) increases with ageing, is greater in African versus European ancestry men and is associated with poor health. Myosteatosis studies of mortality are lacking, particularly among African ancestry populations.
Methods: in the Tobago Health study, a prospective longitudinal study, we evaluated the association of all-cause mortality with quantitative computed tomography (QCT) measured lower leg myosteatosis (intermuscular fat (IM fat) and muscle density) in 1,652 African ancestry men using Cox proportional hazards models. Date of death was abstracted from death certificates and/or proxy.
Results: one hundred and twelve deaths occurred during follow-up (mean 5.9 years). In all men (age range 40–91 years), higher all-cause mortality was associated with greater IM fat (HR (95% CI) per SD: 1.29 (1.06–1.57)) and lower muscle density (HR (95% CI) per SD lower: 1.37 (1.08–1.75)) in fully adjusted models. Similar mortality hazard rates were seen in the subset of elderly men (aged ≥65 years) with greater IM fat (1.40 (1.11–1.78) or lower muscle density (1.66 (1.24–2.21)) in fully adjusted models.
Conclusions: our study identified a novel, independent association between myosteatosis and all-cause mortality in African ancestry men. Further studies are needed to establish whether this association is independent of other ectopic fat depots and to identify possible biological mechanisms underlying this relationship.

Keywords: *obesity, myosteatosis, all-cause mortality, African American, older people*

Introduction

Ectopic fat infiltration within and around skeletal muscle (myosteatosis) is associated with metabolic disorders and poor musculoskeletal health [1–6]. In particular, myosteatosis may play an important role in the development of insulin resistance and type 2 diabetes (T2D) [1, 2, 5, 7–10], decreased muscle strength [11, 12] and mobility loss [3, 13]. Versus Caucasians, African ancestry individuals have greater myosteatosis [14], shorter lifespan expectancy and higher mortality from diabetes and heart disease [15]. Despite the emerging clinical importance of myosteatosis, studies examining the relationship of this important fat depot and mortality are sparse, particularly among high-risk African ancestry individuals. Therefore, we assessed myosteatosis and mortality in a large population-based cohort of African ancestry men aged 40 and above, regardless of their health status. We hypothesised that greater myosteatosis would be associated with elevated risk of all-cause mortality independent of age, lifestyle, co-morbidities and BMI.

Methods

Tobago health study

Between 1997 and 2003, 3,376 men aged 40 and above were recruited for population-based prostate cancer screening on the Caribbean island of Tobago [16]. To be eligible, men had

to be ambulatory, non-institutionalised and not terminally ill. Recruitment for the initial screening was accomplished by flyers, public service announcements, posters, informing healthcare workers at local hospital and health centres, and word of mouth. The population representative sample included 97% African, 2% East Indian, <1% white and <1% 'other' [17].

Between 2003 and 2007, men from the prostate cancer study were invited via phone for peripheral quantitative computed tomography (pQCT) scan of calf skeletal muscle composition, which serves as the baseline for the analysis. Death dates were obtained from death certificates and/or reports from a proxy (58 versus 42% of study participants, respectively) between November 2003 and May 2013. Of the 2,029 with some adiposity measurements at baseline, 377 men lost to follow-up with no information on date-of-censor were excluded. Therefore, our analysis is limited to men with baseline pQCT, known vital status at follow-up and African ancestry ($n = 1{,}652$). Written informed consent was obtained from all participants. This study has been approved by the Institutional Review Boards of the Tobago Division of Health and Social Services and the University of Pittsburgh.

Myosteatosis measures

Myosteatosis measures included intermuscular fat (IM fat, visible fat beneath the fascia lata) and muscle density (fat between muscle fibres and fat within the muscle cell) from pQCT scan of the calf performed with a Stratec XCT-2000 scanner (Orthometrix, Inc., White Plains, NY, USA). Lower skeletal muscle density from CT is indicative of greater intramuscular fat content [18]. A site at 66% of the calf length, proximal to the terminal end of the tibia was scanned, since it has the largest circumference and the lowest variability among individuals [6]. All images were analysed with STRATEC analysis software version 5.5D (Orthometrix, Inc.) and performed by a trained investigator unaware of the participant's disease status.

With the pQCT scan, fat, muscle and bone can be distinguished by different mineral equivalent density of 0, 80 and 1,200 mg/cm^3, respectively. IM fat can be detected as a shift of mineral equivalent density from 80 (muscle) to 0 (fat) mg/cm^3. Muscle density was determined as the ratio of muscle mass (mg) and muscle area (cm^2) [19]. Similarly, total muscle area (mm^2), total fat (mm^2) and subcutaneous fat (mm^2) were obtained. The coefficients of variation (CV) determined by repeat pQCT scanning in 15 individuals were 1.0, 1.5, 7.6, 0.9 and 1.1% for total, subcutaneous and IM fat, muscle area and muscle density, respectively.

General adiposity measures

Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm. Weight was measured on a balance beam scale to the nearest 0.1 kg. Body mass index (BMI) was calculated from measured height and weight (kg/m^2). Waist circumference was measured at the narrowest point of waist, or at umbilicus, if the narrowest point could not be identified.

Medical conditions

T2D was defined as fasting serum glucose ≥126 mg/dl or currently taking anti-diabetic medication. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or currently taking antihypertensive medication. Other co-morbidities including 'ever having' cancer, CVD, renal disease, stroke and MI were self-reported yes/no using questionnaire.

Other measures

Covariate information was collected with standardised interviewer-administered questionnaires. Participants were instructed to bring in all prescription medications taken in the past 30 days to their clinic visit and interviewers recorded the medications. Smoking status was categorised as non-smoker (men who smoked <100 cigarettes total in their lifetime), former smoker (men who smoked >100 cigarettes but did not currently smoke) or current smoker and treated as nominal variables. Walking is the predominant form of physical activity in Tobago, so physical activity was assessed by whether or not participants walked for exercise, to work, the store or church four or more times in the past 7 days. Hours of television watching was assessed, with the cut-off point of '21 or more hours' per week as showing some versus no sedentary behaviour. Self-reported health status was categorised as good/excellent versus fair/poor/very poor. All baseline information provided by pQCT measures or questionnaires was obtained at the same day.

Statistical analysis

Outliers were defined as any value outside the interval of Quartile_3 (75%ile) + 3 × IQR (IQR = inter-quartile range) and Quartile_1 (25%ile) − 3 × IQR and were deleted (11 were deleted for muscle density and 27 were deleted for IM fat) to increase the statistical power. All continuous variables were normally distributed. Distributions of continuous and categorical variables were presented as mean ± standard deviation (SD) or frequency and analysed with Student's *t*-test, χ^2 test or Fisher exact test, as necessary. Age-adjusted *P* values were presented.

Age- and multivariable-adjusted hazard ratio (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. The proportional hazards assumptions were confirmed by Schoenfeld residuals. The adjusted covariates were selected based on previous studies, biological plausibility and results from Table 1, including age, height, smoking status, alcohol intake, physical activity, TV viewing time, health status, and the presence or absence of T2D, renal disease, stroke, cancer, MI and hypertension. Subcutaneous fat, IM fat and skeletal muscle density models were additionally adjusted for BMI and calf muscle area. Due to missing covariate data, the final *n* in multivariable models was 1,495 for IM fat and 1,375 for muscle density. Lastly, we performed fully adjusted, stratified analyses by age groups (<65 and 65+).

Table 1. The distributions of baseline demographic characteristics, lifestyle factors and co-morbidity by vital status in 1,652 Tobago men

	All (n = 1,652)	Survivors (n = 1,540)	Deceased (n = 112)	P value*	Age-adjusted P value
Socio-demographic					
Age	57.7 ± 9.6	56.9 ± 9.1	68.9 ± 9.4	<0.001	–
Education level, n (%)					
High school and above	181 (11.1)	172 (11.3)	9 (8.0)	0.287	0.737
Marriage status, n (%)					
Married or live with a spouse	1,167 (71.1)	1,089 (71.1)	78 (70.9)	0.969	0.993
Lifestyle factors					
Smoking, n (%)					
Former smoker	364 (22.0)	334 (21.7)	30 (26.8)	0.137	0.020
Current smoker	176 (10.7)	160 (10.4)	16 (14.3)		
Alcohol consumption, n (%)					
>3 drinks per week	172 (10.4)	163 (10.6)	9 (8.0)	0.393	0.899
Physical activity, n (%)					
>3 times per week	822 (49.8)	766 (49.7)	56 (50.0)	0.958	0.759
TV viewing, n (%)					
>21 h per week	290 (17.6)	272 (17.7)	18 (16.1)	0.654	0.864
Health status, n (%)					
Excellent/good	1,530 (93.2)	1,444 (94.3)	86 (78.2)	<0.001	<0.001
Co-morbidities					
Prevalence of type 2 diabetes, n (%)	305 (18.9)	258 (17.1)	47 (42.3)	<0.001	<0.001
Renal disease, n (%)	5 (0.3)	3 (0.2)	2 (1.8)	0.039	0.059
Cardiovascular disease, n (%)	62 (3.8)	52 (3.4)	10 (8.9)	0.007	0.096
Stroke, n (%)	26 (1.6)	21 (1.4)	5 (4.5)	0.027	0.169
Cancer, n (%)	129 (7.8)	100 (6.5)	29 (25.9)	<0.001	0.002
Myocardial infarction, n (%)	13 (0.8)	11 (0.7)	2 (1.8)	0.218	0.204
Hypertension, n (%)	823 (49.8)	746 (48.4)	77 (68.8)	<0.001	0.506
Medication use					
Antihypertensive drugs, n (%)	342 (60.5)	301 (61.1)	41 (56.9)	0.505	0.148
Lipid-lowering drugs, n (%)	71 (4.5)	69 (4.6)	2 (2.8)	0.769	0.413
Anti-diabetic drugs, n (%)	189 (11.7)	156 (10.4)	33 (29.7)	<0.001	0.004
Body composition characteristic					
BMI (kg/m^2)	27.4 ± 4.4	27.5 ± 4.4	26.3 ± 4.6	0.005	0.148
Waist circumference (cm)	93.1 ± 11.1	93.1 ± 11.1	92.9 ± 11.3	0.853	0.664
Calf total fat (mm^2)	1,794.8 ± 765.7	1,792.8 ± 762.0	1,823.2 ± 817.5	0.689	0.718
Calf subcutaneous fat (mm^2)	1,367.0 ± 669.1	1,375.1 ± 670.8	1,254.3 ± 636.6	0.069	0.625
Calf intermuscular fat (mm^2)	249.7 ± 17.3	241.9 ± 210.5	361.8 ± 276.6	<0.001	0.014
Calf skeletal muscle density (mg/cm^3)	73.5 ± 3.9	73.7 ± 3.7	70.4 ± 5.2	<0.001	<0.001
Calf muscle area (mm^2)	7,556.4 ± 1,295.5	7,614.2 ± 1,279.8	6,757.2 ± 1,251.5	<0.001	0.006

Values are unadjusted mean ± SD, unless indicated otherwise. Age-adjusted P values were obtained from logistic regression for categorical variables and linear regression for continuous variables.

*P values for comparisons between the survivors and deceased from two-sample t-tests or χ^2 tests or Fisher's exact test.

Multicollinearity was checked with variation inflation factor (VIFs of included variables were <10). Sensitivity analyses with the outliers included confirmed the results (Supplementary data, Appendix 1, available in *Age and Ageing* online). Analyses were performed with SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Of the 2,029 men with baseline data, 377 were lost to follow-up. Of the 1,652 men with known mortality status and baseline pQCT, 112 participants died during a mean follow-up of 5.9 years (median (IQR) 6.0 years (5.5–6.4 years); Table 1). At baseline, the mean age of the men was 57.7 years (Table 1). The majority reported excellent or good health (93.2%). Deceased men were older and with a poorer health status and a lower BMI, had higher prevalence of T2D, renal disease, cardiovascular disease, stroke, cancer and hypertension, and higher anti-diabetic drug use. Additionally, deceased men had greater IM fat and lower muscle density after adjustment for age (both $P < 0.05$).

Myosteatosis and all-cause mortality

IM fat (per SD greater) and muscle density (per SD lower) were associated with 21% (95% CI: 2–44%) and 36% (95% CI: 11–67%) higher hazard of mortality, respectively, independent of age (Table 2). These results slightly attenuated after additionally adjusted for co-morbidities and lifestyle factors (HR (95% CI) per SD greater IM fat: 1.20 (0.99–1.45)

Table 2. Hazard ratios (95% confidence interval) for all-cause mortality per SD greater baseline adiposity or muscle measure

	Age adjusted	Multivariable[a]	Multivariable[a] + BMI and muscle area
BMI (kg/m^2)	0.88 (0.71–1.10)	0.88 (0.70–1.11)	–
Waist circumference (cm)	1.01 (0.82–1.25)	1.01 (0.80–1.28)	–
Calf total fat (mm^2)	1.01 (0.84–1.21)	1.04 (0.85–1.26)	–
Calf subcutaneous fat (mm^2)	0.94 (0.76–1.16)	0.94 (0.76–1.16)	1.04 (0.78–1.39)
Calf intermuscular fat (mm^2)	1.21 (1.02–1.44)*	1.20 (0.99–1.45)	1.29 (1.06–1.57)*
Calf skeletal muscle density (mg/cm^3)[b]	1.36 (1.11–1.67)**	1.30 (1.03–1.63)*	1.37 (1.08–1.75)**
Calf muscle area (mm^2)	0.77 (0.61–0.98)*	0.85 (0.65–1.09)	–

Hazard ratios and *P* values were obtained with Cox proportional hazard models. Fully adjusted multivariable model *n*'s for BMI, waist circumference, calf total fat, calf subcutaneous fat, and calf muscle area were 88 deaths and 1,435 survivors. *n* for calf intermuscular fat was 82 deaths and 1,413 survivors. *n* for calf muscle density was 72 deaths and 1,303 survivors.

[a]Adjusted for age, height, smoking status, alcohol consumption, physical activity, TV viewing time, health status, cancer, T2D, renal disease, stroke, myocardial infarction and hypertension.

[b]Per SD lower.

*$P < 0.05$.

**$P < 0.01$.

and per SD lower muscle density: 1.30 (1.03–1.63)) and in models with further adjustment for BMI and muscle area (HR (95% CI) per SD greater IM fat: 1.29 (1.06–1.57) and per SD lower muscle density: 1.37 (1.08–1.75)). No other measure of adiposity was associated with mortality, regardless of the degree of adjustment.

Myosteatosis and all-cause mortality by age groups

Among the 1,242 middle-aged men (aged 40–64), 35 deaths occurred. Neither IM fat nor muscle density was associated with all-cause mortality among middle-aged men in any model (Table 3). Among 410 elderly men (aged 65+), 77 deaths occurred. In these men, both greater IM fat and lower muscle density were associated with greater all-cause mortality in both age-adjusted and fully adjusted models ($P < 0.05$ for all).

Table 3. Age stratified adjusted hazard ratios (95% confidence interval) of all-cause mortality risk by baseline myosteatosis measures[a]

Model	Age group			
	Under 65 years (*n* died/survived: 35/1,207)		65 years and above (*n* died/survived: 77/333)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Intermuscular fat (mm^2)				
Age adjusted	1.08 (0.75–1.55)	0.675	1.26 (1.03–1.53)	0.025
Multivariable[b] adjusted	1.16 (0.74–1.82)	0.527	1.40 (1.11–1.78)	0.005
Muscle density (mg/cm^3)				
Age adjusted	0.97 (0.61–1.53)	0.880	1.50 (1.19–1.90)	<0.001
Multivariable[b] adjusted	0.87 (0.51–1.48)	0.601	1.66 (1.24–2.21)	0.007

Hazard ratios and *P* values were obtained with Cox proportional hazard models.

[a]Per 1 SD increase in IM fat and 1 SD decrease in muscle density.

[b]Adjusted for age, height, smoking status, alcohol consumption, physical activity, TV viewing time, health status, cancer, T2D, renal disease, stroke, myocardial infarction, hypertension, BMI and calf muscle cross-sectional area.

Discussion

We report an association between both intermuscular fat and muscle density and increased hazards of all-cause mortality among African ancestry men, even after adjustment for important lifestyle and medical covariates, and general adiposity.

Despite the growing appreciation of a potential role for myosteatosis in metabolic health and ageing independent from overall adiposity [1, 2, 5, 7–10], few studies have examined the association between myosteatosis and mortality. Existing studies have focused exclusively on older Caucasians [20, 21] or highly selected individuals [22]. Similarly to our findings, the Walking and Leg Circulation Study II (WALCS II) reported a higher mortality risk associated with lower calf muscle density among 434 patients with lower extremity peripheral arterial disease (PAD) [22]. The Osteoporotic Fractures in Men Study (MrOS) further extended the finding to community-dwelling older Caucasian men ($n = 1{,}063$, mean age = 77) and found that muscle density, but not intermuscular fat, was associated with an increased risk of mortality [21]. The AGES-Reykjavik study [23] in Icelandic individuals aged 66–96 found that greater thigh intermuscular fat was independently associated with elevated mortality risk in men, but not in women, suggesting a potential gender difference in the adverse impact of intermuscular fat. Our study extends these findings to middle-aged and elderly African ancestry men, a high-risk population segment inadequately studied thus far. Contrary to our findings, the 'Invecchiare in Chianti' (InCHIANTI) study [20], a prospective population-based study among Italians ($n = 934$, mean age = 74.5) found no association between muscle density and all-cause mortality. The discrepancy may due to differences in the studied populations as ours is younger, yet, less healthy as determined by co-morbidity prevalence.

Ectopic fat increases with the ageing process. Our results showed an adverse impact of myosteatosis on mortality risk in a combined sample of middle-aged and elderly African ancestry man. In the fully adjusted model of men aged 65 and older, the mortality risk was 40% (95% CI: 11–78%) and

66% (95% CI: 24–121%) greater per 1 SD greater IM fat and 1 SD lower muscle density, respectively. This indicates that maintaining muscle density and prevention of muscle fat infiltration may be crucial for successful ageing in elderly men. However, we were unable to detect a significant association in middle-aged men alone. The adverse impact of greater myosteatosis on mortality risk may be due to an acceleration of muscle density loss and ectopic fat infiltration around age 65.

Insulin resistance is hypothesised to be a culprit linking myosteatosis and mortality. The accumulation of intermuscular fat may impair nutritive blood flow to muscles and lead to impaired insulin action and insulin diffusion capacity [1]. Additionally, the accumulation of intramuscular fat may impair the glucose metabolism via the insulin receptor substrate 1/phosphatidylinositol 3-kinase and growth-factor-regulated protein kinase B pathways [24] and eventually lead to impaired insulin signalling and insulin resistance [25]. Myosteatosis could also increase local inflammation in the muscle fibres [26]. This increased inflammation could lead to increases in oxidative stress, resulting in a decrease in insulin-stimulated tyrosine phosphorylation [27] and a decrease in the activity of downstream signalling molecules, thus resulting in insulin resistance [27]. However, in our study, the significant association between myosteatosis and all-cause mortality risk persists even after adjusting for T2D or HOMA-IR (results not shown), which suggests that there are also other mechanisms underlying these associations.

Subcutaneous fat is generally thought to be protective for health outcomes, because it stores excess fat and prevents it from overflowing into other deleterious ectopic depots [8]. Several studies have linked thigh subcutaneous fat to a favourable glucose or lipid profile, independent of abdominal fat [28]. Although we have previously linked lower calf subcutaneous fat to a higher prevalence of T2D [8], we found no association between subcutaneous fat and all-cause mortality.

No other measures of adiposity were associated with mortality, despite the fact that some previous studies revealed a relation of BMI or waist circumference with mortality risk [29]. However, it has been hypothesised that this association may be attenuated with increasing age due to the associated redistribution of body fat or shrinkage of height [30]. Thus, it is possible that the wide age range of our population (40–91 years) may have weakened the associations between BMI or waist circumference and mortality.

However, the inclusion of men with a wide age range is also a major strength of our study as we were able to test for an age effect. Other strengths of our study include the population-based design, which allows us to study the effects of myosteatosis within the normal process of ageing. And, most importantly, ours is the first mortality study of myosteatosis in African ancestry men. Given similar total body fat across ethnicities, the greater myosteatosis observed in African ancestry men might explain the relatively higher risk of mortality, especially from T2D and heart disease [15]. However, further analyses in comparable, ethnically diverse cohorts are needed to definitively address this hypothesis.

Our study has some limitations. First, our study is observational, and causality cannot be determined. Second, 377 men were lost to follow-up. Compared with individuals with complete follow-up information, the censored individuals were older and less healthy (Supplementary data, Appendix 2, available in *Age and Ageing* online) and, therefore, likely had a greater risk of mortality. Even with a possibly underestimated mortality rate, we were still able to identify a significant association of myosteatosis and mortality. Third, some bias may have been introduced from missing covariate data in multivariable models. Fourth, the bias caused by reverse causation, a phenomenon that obesity-related disease may lead to both greater myosteatosis and elevated risk of mortality, is unavoidable. To minimise this bias, our analyses were adjusted for several major co-morbidities related to obesity at baseline. Fifth, including only the men who were well enough to have pQCT measures may have resulted in a 'healthy participant' bias and could limit the generalisability of our findings. Sixth, fat located in other ectopic storage depots, such as the liver, pancreas and heart, should be taken into consideration. Lastly, other untested potential mechanisms such as inflammation or mitochondrial function may be residual confounders.

In conclusion, our study identified a previously unreported, independent association of both intra- and intermuscular fat with mortality in middle-aged and elderly African ancestry men. Further, it highlights the potential importance of maintaining muscle density in the elderly. These results illustrate that myosteatosis may be a novel independent marker of ageing with a potential impact on healthy ageing and expected lifespan. Future studies are needed to replicate our findings in other populations of African ancestry, to establish whether the association is independent of other ectopic fat depots and to identify the precise biological mechanisms underlying this relationship.

Key points

- Fat infiltration within and around skeletal muscle (i.e. myosteatosis) increases with ageing and is greater in African versus Caucasians.
- Previous studies of myosteatosis and mortality are lacking, especially in high-risk African ancestry populations.
- This is the first study to test for and identify a significant association between greater myosteatosis and excess mortality risks among African ancestry men with a wide age range.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Conflicts of interest

None declared.

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References

1. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr 2000; 71: 885–92.
2. Goodpaster BH, Krishnaswami S, Resnick H *et al*. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. Diabetes Care 2003; 26: 372–9.
3. Visser M, Goodpaster BH, Kritchevsky SB *et al*. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 2005; 60: 324–33.
4. Lang T, Cauley JA, Tylavsky F *et al*. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. J Bone Miner Res 2010; 25: 513–9.
5. Miljkovic I, Cauley JA, Wang PY *et al*. Abdominal myosteatosis is independently associated with hyperinsulinemia and insulin resistance among older men without diabetes. Obesity 2013; 21: 2118–25.
6. Simonsick EM, Maffeo CE, Rogers SK *et al*. Methodology and feasibility of a home-based examination in disabled older women: the Women's Health and Aging Study. J Gerontol A Biol Sci Med Sci 1997; 52: M264–74.
7. Yim JE, Heshka S, Albu J *et al*. Intermuscular adipose tissue rivals visceral adipose tissue in independent associations with cardiovascular risk. Int J Obes 2007; 31: 1400–5.
8. Miljkovic-Gacic I, Gordon CL, Goodpaster BH *et al*. Adipose tissue infiltration in skeletal muscle: age patterns and association with diabetes among men of African ancestry. Am J Clin Nutr 2008; 87: 1590–5.
9. Gallagher D, Kelley DE, Yim J-E *et al*. Adipose tissue distribution is different in type 2 diabetes. Am J Clin Nutr 2009; 89: 807–14.
10. Boettcher M, Machann J, Stefan N *et al*. Intermuscular adipose tissue (IMAT): association with other adipose tissue compartments and insulin sensitivity. J Magn Reson Imaging 2009; 29: 1340–5.
11. Marcus RL, Addison O, Dibble LE *et al*. Intramuscular adipose tissue, sarcopenia, and mobility function in older individuals. J Aging Res 2012; 2012: 629637.
12. Tuttle LJ, Sinacore DR, Mueller MJ. Intermuscular adipose tissue is muscle specific and associated with poor functional performance. J Aging Res 2012; 2012: 172957.
13. Goodpaster BH, Park SW, Harris TB *et al*. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci 2006; 61: 1059–64.
14. Torriani M, Grinspoon S. Racial differences in fat distribution: the importance of intermuscular fat. Am J Clin Nutr 2005; 81: 731–2.
15. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci 2002; 57: B359–65.
16. Bunker CH, Patrick AL, Konety BR *et al*. High prevalence of screening-detected prostate cancer among Afro-Caribbeans: the Tobago Prostate Cancer Survey. Cancer Epidemiol Biomarkers Prev 2002; 11: 726–9.
17. Miljkovic-Gacic I, Ferrell RE, Patrick AL, Kammerer CM, Bunker CH. Estimates of African, European and Native American ancestry in Afro-Caribbean men on the island of Tobago. Hum Hered 2005; 60: 129–33.
18. Larson-Meyer DE, Smith SR, Heilbronn LK *et al*. Muscle-associated triglyceride measured by computed tomography and magnetic resonance spectroscopy. Obesity 2006; 14: 73–87.
19. Wong AKO, Hummel K, Moore C *et al*. Improving reliability of pQCT-derived muscle area and density measures using a watershed algorithm for muscle and fat segmentation. J Clin Densitom 2015; 18: 93–101.
20. Cesari M, Pahor M, Lauretani F *et al*. Skeletal muscle and mortality results from the InCHIANTI Study. J Gerontol A Biol Sci Med Sci 2009; 64: 377–84.
21. Miljkovic I, Kuipers AL, Cauley JA *et al*. Greater skeletal muscle fat infiltration is associated with higher all-cause and cardiovascular mortality in older men. J Gerontol A Biol Sci Med Sci 2015; 70: 1133–40.
22. McDermott MM, Liu K, Tian L *et al*. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: a longitudinal study. J Am Coll Cardiol 2012; 59: 1159–67.
23. Koster A, Murphy RA, Eiriksdottir G *et al*. Fat distribution and mortality: the AGES-Reykjavik Study. Obesity (Silver Spring) 2015; 23: 893–7.
24. Petersen KF, Shulman GI. Etiology of insulin resistance. Am J Med 2006; 119(5 Suppl 1): S10–6.
25. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science 2005; 307: 384–7.
26. Beasley LE, Koster A, Newman AB *et al*. Inflammation and race and gender differences in computerized tomography-measured adipose depots. Obesity 2009; 17: 1062–9.
27. Evans JL, Maddux BA, Goldfine ID. The molecular basis for oxidative stress-induced insulin resistance. Antioxid Redox Signal 2005; 7: 1040–52.
28. Snijder M, Visser M, Dekker J *et al*. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. Diabetologia 2005; 48: 301–8.
29. Cerhan JR, Moore SC, Jacobs EJ *et al*., eds. A pooled analysis of waist circumference and mortality in 650,000 adults. In: Mayo Clinic Proceedings, 2014. Elsevier.
30. Thinggaard M, Jacobsen R, Jeune B, Martinussen T, Christensen K. Is the relationship between BMI and mortality increasingly U-shaped with advancing age? A 10-year follow-up of persons aged 70–95 years. J Gerontol A Biol Sci Med Sci 2010; 65: 526–31.

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