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ORIGINAL RESEARCH

Associations of Skeletal Muscle Mass and Fat Mass With Incident Cardiovascular Disease and All-Cause Mortality: A Prospective Cohort Study of UK Biobank Participants

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BACKGROUND: There is debate whether body mass index is a good predictor of health outcomes because different tissues, namely skeletal muscle mass (SMM) and fat mass (FM), may be differentially associated with risk. We investigated the association of appendicular SMM (aSMM) and FM with fatal and nonfatal cardiovascular disease (CVD) and all-cause mortality. We compared their prognostic value to that of body mass index.

METHODS AND RESULTS: We studied 356 590 UK Biobank participants aged 40 to 69 years with bioimpedance analysis data for whole-body FM and predicted limb muscle mass (to calculate aSMM). Associations between aSMM and FM with CVD and all-cause mortality were examined using multivariable Cox proportional hazards models. Over 3 749 501 person-years of follow-up, there were 27 784 CVD events and 15 844 all-cause deaths. In men, aSMM was positively associated with CVD incidence (hazard ratio [HR] per 1 SD 1.07; 95% CI, 1.06–1.09) and there was a curvilinear association in women. There were stronger positive associations between FM and CVD with HRs per SD of 1.20 (95% CI, 1.19–1.22) and 1.25 (95% CI, 1.23–1.27) in men and women respectively. Within FM tertiles, the associations between aSMM and CVD risk largely persisted. There were J-shaped associations between aSMM and FM with all-cause mortality in both sexes. Body mass index was modestly better at discriminating CVD risk.

CONCLUSIONS: FM showed a strong positive association with CVD risk. The relationship of aSMM with CVD risk differed between sexes, and potential mechanisms need further investigation. Body fat and SMM bioimpedance measurements were not superior to body mass index in predicting population-level CVD incidence or all-cause mortality.

Key Words: all-cause mortality ■ cardiovascular disease ■ cohort study ■ fat mass ■ skeletal muscle mass

The increasing prevalence of obesity is a significant public health concern because it is a known risk factor for several noncommunicable diseases,[1–5] estimated to account for 56 million deaths globally in 2017.[6] Evidence from prospective cohort studies[7–10] and meta-analyses of such studies[2,11,12] has repeatedly shown a J- or U-shaped relationship between body mass index (BMI), cardiovascular disease (CVD), and all-cause mortality, even after efforts to account for confounding and reverse causality.[12,13] A potential explanation for this is that BMI does not distinguish between fat mass (FM) and skeletal muscle mass

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CLINICAL PERSPECTIVE

What Is New?

- Reports of the relationship between muscle mass and cardiovascular disease (CVD) are inconsistent and have rarely been considered in the context of adiposity; analysis of body composition measured by bioimpedance in this large cohort of UK adults showed that fat mass showed strong positive associations with CVD events.
- Appendicular skeletal muscle mass had a curvilinear association with CVD events in women and a positive association in men; the associations of appendicular skeletal muscle mass and fat mass with all-cause mortality followed a J-shape in both men and women.
- Measurements of body fat and skeletal muscle mass were not superior to body mass index in predicting CVD events or mortality.

What Are the Clinical Implications?

- Body mass index has been criticized as an inaccurate measure of health risks, but at a population level, more specific measurements of body composition, namely appendicular skeletal muscle mass and fat mass, were generally not more predictive of CVD events or mortality.
- Although body mass index may be the simplest measurement to assess health risk, which is important from a public health perspective, some of this risk may not be attributable solely to adiposity, particularly if the association observed with appendicular skeletal muscle mass in men is confirmed.
- Further research is needed to better understand the biological mechanisms and impact of different body tissue compartment on health outcomes.

Nonstandard Abbreviations and Acronyms

aSMM	appendicular skeletal muscle mass
BIA	bioimpedance analysis
FM	fat mass
SMM	skeletal muscle mass

(SMM),[12,13] yet their contribution to the pathogenesis of disease is likely to be different.

A systematic literature review of the associations between body composition and CVD or mortality (Data S1, Tables S1 and S2) showed that the majority of studies found null or inverse associations with SMM, although a minority of studies reported positive or curvilinear associations. More studies have investigated the relationship of FM with these outcomes, with the majority of them reporting positive associations. Very few studies have investigated the combined impact of both types of tissues, yet weight change is associated with changes in both these body tissue compartments.

Dual energy X-ray absorptiometry (DEXA) or magnetic resonance imaging techniques are considered to be reference methods for the measurement of body composition because of their precision and reliability.[14] However, these are often not feasible for large studies given they are expensive and not easily portable.[15] Bioimpedance analysis (BIA) is a noninvasive and practical method to assess FM and SMM in clinical practice and at scale in population-based studies.[16–18] The UK Biobank uses a bioimpedance analyzer previously validated against DEXA in a mixed population of children and adults, and body composition estimates were found to be more accurate than those obtained from previous BIA estimates.[19] A recent validation study comparing BIA to DEXA in a subsample of the UK Biobank participants showed BIA to be a valid method for the assessment of appendicular skeletal muscle mass (aSMM) and FM.[20]

In this study we aimed to use BIA-derived aSMM and FM measurements to look at their associations with incident CVD and all-cause mortality in the UK Biobank population. Furthermore, to investigate the prognostic value of these BIA-derived measurements in comparison to more traditional measures such as BMI, grip strength, and waist circumference.

METHODS

Data Availability Statement

Researchers can apply to use the UK Biobank resource and access the data used. No additional data are available.

Study Design and Participants

The UK Biobank recruited 502 664 participants aged 40 to 69 years between 2006 and 2010 (response rate 5.5%) via mailed invitations to the general public living within 25 miles of one of the 22 assessment centers in England, Scotland, and Wales.[21,22] At the baseline assessment clinic, participants completed a touch-screen questionnaire and computer-assisted interview, had physical measurements taken, and biological samples collected.[23,24] UK Biobank received ethical approval from the North West Multicentre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was

conducted in accordance with the principles of the Declaration of Helsinki.

Participants were excluded from analyses if they had prior CVD (defined later) or diseases that may affect body composition including fractures in the past year, respiratory diseases, musculoskeletal conditions, and some infectious diseases (n=116 679; Figure S1).[25] Participants were also excluded if they had missing data for the exposures (n=6751) or were not of a White race (n=22 644), because BIA estimates are derived from algorithms in White populations, which represent ≈95% of the UK Biobank sample.[26–28]

Measurement of Exposures

Measures of body weight and body composition (muscle mass and fat mass) were derived from BIA in bare-footed participants wearing light clothing using a Tanita BC418MA single frequency segmental body-composition analyzer (Tanita, Tokyo, Japan) at the baseline assessment center visit. The aSMM (kg) was calculated as the sum of the predicted muscle mass from the 4 limbs. Whole body FM (kg) was also obtained from BIA. Standing height was measured using a Seca 202 scale (Seca, Hamburg, Germany). BMI was calculated by dividing weight (kg) by the squared height in meters.

Waist circumference (cm) was measured at the umbilicus using a tape measure. The mean grip strength (kg) of the left and right hands was taken once using a Jamar J00105 hydraulic hand dynamometer.

Ascertainment of Outcomes

Participants were followed via linkage to National Health Service hospital in-patient data from hospital episode statistics in England, the Scottish Morbidity Records, and the Patient Episode Database for Wales. Patients were identified if they died of any cause or developed incident CVD, defined using *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) categories: coronary heart disease (I21–I24, 125.6, I42, I43, K49, K50, K75, K40–K46), congestive heart failure or cardiomyopathy (I50, I50.1, 150.9, I11.0, I13.0, I13.2), and total stroke (I60–I64).[29] Follow-up was available until June 30, 2020, October 31, 2016, and February 29, 2016 for England, Scotland, and Wales respectively; and until July 31, 2020 for all-cause mortality for all regions.

Statistical Analysis

Association of Skeletal Muscle Mass and Fat Mass With CVD and Mortality

First, age-adjusted partial correlation coefficients between aSMM, FM, and height were calculated to examine the relationships between the body composition measurements and overall body size. As aSMM is highly correlated with FM and height,[30] aSMM was regressed on height and FM and the residuals from this model were divided into sex-specific quintiles for the main analysis.

Multivariable Cox regression analyses with age as the underlying timescale were used to estimate hazard ratios (HRs) and 95% CIs for the associations of sex-specific fifths of aSMM and fifths of FM as well as per 1 SD with incident CVD and all-cause mortality. All analyses were sequentially adjusted for height and height^2 (continuous), Townsend index of deprivation (quintiles), level of education (none, vocational qualifications, any degree, higher degree, other), smoking (never, previous, current), alcohol intake (none, <1 unit/week, 1–14 units/week, 14+ units/week), physical activity derived from metabolic equivalent of task scores (low, moderate, high),[31] and dietary factors (oily fish intake, saturated fat intake, fruit and vegetable intake [none, low, medium, high intake]), prior medical history (diabetes mellitus, cancer history >5 years ago, and menopausal status in women [binary for each]). We created a category for missing values for each of these covariates. Additionally, FM and aSMM were mutually adjusted for each other to assess the independent effects of each type of tissue. See Table S3 for the details on the derivation of these covariates.

The HRs and 95% CIs were computed using group-specific variances[32]; these reflect the uncertainty in the estimate of risk in each group (including the reference group), thereby allowing comparisons between any 2 quintiles independently of the reference group. Restricted cubic splines with 5 knots were also computed to visually explore nonlinear associations for continuous exposures, and departures from linearity were tested via the likelihood ratio statistic test used to evaluate if models with linear or categorical exposures were a better fit.[33] Five knots were specified to be consistent with the quintile analysis but also to provide enough flexibility to the model while also not being too many knots so that the model is oversensitive to the smallest fluctuations.[34,35] To correct for the measurement error that can arise from using a single baseline measurement to estimate long-term exposure status (ie, regression dilution bias),[36] mean values of BIA measurements at resurvey (2012–2013) from 15 694 participants were used in 2 ways. First, the HR (95% CI) in the baseline-defined groups of aSMM and FM were plotted against the mean resurvey values in those baseline-defined groups (termed the "usual" value). Second, where there was evidence of a log-linear relationship, regression dilution ratios were calculated using the MacMahon-Peto method.[37] The log HRs (and theirSEs) per 1 SD of baseline aSMM and FM were then divided by the relevant regression dilution

ratio to obtain HRs (and associated 95% CI) per 1 SD of usual aSMM and FM.[37]

Sensitivity analyses were conducted to assess potential residual confounding or reverse causality so additional exclusions were made for events that occurred during the first 2 years of follow-up to reduce the impact of reverse causality, for outliers, or for participants with BMI over 35 kg/m^2 for whom BIA measurements may be less accurate. Additional adjustments were made for BMI (instead of FM in the SMM model and instead of SMM in the FM model) as well as for hypertension (diagnosed by doctor, taking medication, or blood pressure measurement), and blood cholesterol (defined as taking medication, plus levels of non-high-density lipoprotein cholesterol and triglycerides) to investigate if these are potential mediators of the associations. Finally, Cox regression models were conducted with BMI as the exposure as a "positive control" to confirm that the specified models would produce the same association that has been documented previously.[9]

Associations of aSMM Within Tertiles of FM

To better assess the independent association of aSMM with the risk of disease, irrespective of its strong correlation with FM, we examined the sex-specific associations of aSMM within subgroups of FM tertiles (subsequently referred to as "body composition groups," because we looked at low/moderate/high groups [tertiles] of aSMM within groups of FM). Multivariable Cox models adjusting for all covariates listed previously were used to assess the associations with CVD and all-cause mortality using "moderate" aSMM as the reference category within each tertile of FM.

Prognostic Comparison of aSMM, FM, and Body Composition Groups With BMI, Waist Circumference, and Grip Strength

The relative importance of the various measures in prediction of CVD or mortality was assessed in several ways. First, where a linear association was present, the HRs associated with 1 usual SD change were compared for each measure. In order to assess the discriminatory ability of each measure with CVD and mortality Harrell's C-statistic from the area under the receiver operating curve was computed.[38] Third, the Wald test χ^2 statistic was used to compare a model with just confounders to a model with confounders plus the exposure of interest to explore how much of the variation in risk is explained by each exposure of interest, given confounders.[39]

All analyses were conducted using Stata 15.0 for analyses and R 3.5.2 for graphs. Analyses used 2-sided *P* values (α=0.05) without any correction for multiple testing.

RESULTS

Study Participants

After exclusions, the final sample included 356 590 adults who were followed for a median of 10.5 years during which there were 27 784 CVD events and 15 844 deaths due to all causes. The mean age at recruitment was 56 (SD 8) years. Men had a higher aSMM (median 27.2 kg in men; and 18.3 kg in women), although the difference between the sexes was smaller for FM (median 21.8 kg in men, 26.3 kg in women; Table 1, Tables S4 and S5). There were strong partial correlations between aSMM and FM (men *r*=0.71, women *r*=0.78) and aSMM and height (men *r*=0.52, women *r*=0.44) but not between FM and height (*r*=men 0.14, women 0.15; Table S6).

Participants in the highest quintiles of aSMM and FM had similar diets (ie, high saturated fat intake, low oily fish intake, but similar fruit and vegetable intakes), and a higher percentage of participants had low physical activity and a higher prevalence of type 2 diabetes mellitus and hypertension. A higher percentage of participants in the highest FM quintile were taking medication for cholesterol but there were no differences across aSMM quintiles (Table 1, Tables S4 and S5).

Associations of Skeletal Muscle Mass and Fat Mass With Health Outcomes

There was a potential curvilinear association between aSMM and CVD in women (likelihood ratio test statistic of nonlinearity [df=4], *P*<0.001) with the nadir approximately at the median; this curvilinear shape was even more pronounced in the cubic spline analysis (Figure 1, Figure S2, Table S7). There was a positive linear association in men with an HR per 1 usual SD of 1.07 (95% CI, 1.06–1.09). FM showed much stronger positive log-linear associations with the risk of CVD with HRs per 1 usual SD of 1.20 (95% CI, 1.19–1.22) in men and 1.25 (95% CI, 1.23–1.27) in women (Figure 1, Figure S2, Table S7). These associations were similar across CVD subtypes (nonfatal, fatal, coronary heart disease, congestive heart failure, and stroke) for both aSMM and FM (Figure S3). The associations of aSMM and FM with all-cause mortality generally followed a J-shape in both men and women, although the association with FM was more clear (Figure 2, Figure S2, Table S8).

These findings remained robust after sensitivity analyses (Tables S9 and S10). Exclusion of the first 2 years of follow-up to reduce the risk of reverse

Table 1. Baseline Characteristics of the Study Population According to Appendicular Skeletal Muscle Mass and Fat Mass Quintiles in 356 590 UK Biobank Participants

	Men Appendicular Skeletal Muscle Mass Quintiles, Range (kg)			Men Fat Mass Quintiles, Range (kg)			
	Q1 13.5 to ≤24.0	Q3 26.1 to ≤27.6	Q5 30.1 to ≤54.5	Q1 5.0 to ≤15.7	Q3 19.5 to ≤22.9	Q5 27.6 to ≤98.6	Total
Age at recruitment, y, mean (SD)	61.0 (6.4)	56.0 (7.8)	51.7 (7.8)	54.9 (8.3)	56.5 (8.1)	56.9 (7.8)	56.2 (8.1)
aSMM, kg, mean (SD)	24.6 (2.9)	26.9 (2.9)	30.5 (3.6)	24.6 (2.7)	26.7 (2.7)	31.0 (3.6)	27.2 (3.7)
FM, kg, mean (SD)	22.4 (7.1)	21.4 (7.4)	22.2 (9.2)	12.4 (2.4)	21.0 (1.0)	33.6 (6.2)	21.8 (7.8)
BMI, kg/m^2, mean (SD)	26.0 (3.5)	27.4 (3.6)	29.7 (4.4)	23.3 (1.8)	27.1 (1.6)	33.1 (3.5)	27.6 (4.0)
Higher education, n (%)	12 740 (39.7%)	13 140 (40.9%)	12 645 (39.3%)	13 909 (43.1%)	12 987 (40.6%)	11 735 (36.7%)	64 706 (40.2%)
Current smokers, n (%)	3714 (11.6%)	3573 (11.1%)	3724 (11.6%)	4366 (13.5%)	3368 (10.5%)	3286 (10.3%)	18 005 (11.2%)
Low fruit and vegetable intake, n (%)	14 779 (46.0%)	13 977 (43.5%)	13 367 (41.6%)	13 624 (42.2%)	14 191 (44.3%)	14 349 (44.8%)	70 241 (43.7%)
High saturated fat intake, n (%)	11 706 (36.4%)	11 647 (36.2%)	11 778 (36.6%)	10 457 (32.4%)	11 699 (36.6%)	12 933 (40.4%)	58 554 (36.4%)
Low oily fish intake, n (%)	10 919 (34.0%)	11 342 (35.3%)	11 988 (37.3%)	11 197 (34.7%)	11 518 (36.0%)	11 661 (36.4%)	57 348 (35.7%)
Heavy drinkers, n (%)	19 948 (62.1%)	19 841 (61.7%)	18 666 (58.1%)	17 562 (54.4%)	20 297 (63.4%)	19 695 (61.5%)	97 948 (60.9%)
Low physical activity, n (%)	7247 (22.6%)	6300 (19.6%)	5518 (17.2%)	4580 (14.2%)	6030 (18.8%)	8757 (27.4%)	31 636 (19.7%)
Hypertension, n (%)	20 146 (62.7%)	18 102 (56.3%)	17 370 (54.0%)	12 683 (39.3%)	18 523 (57.9%)	23 544 (73.5%)	91 858 (57.1%)
Type 2 diabetes mellitus, n (%)	1300 (4.1%)	1156 (3.6%)	1408 (4.4%)	388 (1.2%)	906 (2.8%)	2883 (9.0%)	6305 (3.9%)
Cancer history (>5 y ago), n (%)	1176 (3.7%)	816 (2.5%)	652 (2.0%)	780 (2.4%)	856 (2.7%)	889 (2.8%)	4233 (2.6%)
Cholesterol medication, n (%)	6204 (19.5%)	4646 (14.6%)	3842 (12.0%)	2175 (6.8%)	4664 (14.7%)	7440 (23.4%)	24 008 (15.0%)
	Women Appendicular Skeletal Muscle MassQuintiles, Range (kg)			Women Fat Mass Quintiles, Range (kg)			
	Q1 10.3 to ≤16.5	Q3 17.6 to ≤18.6	Q5 20.0 to ≤39.2	Q1 5.0 to ≤18.5	Q3 22.9 to ≤27.1	Q5 33.4 to ≤109.8	Total
Age at recruitment, y, mean (SD)	58.9 (7.0)	55.8 (7.9)	53.2 (8.1)	54.1 (8.1)	56.6 (7.9)	56.4 (7.8)	55.9 (8.0)
aSMM, kg, mean (SD)	17.0 (1.7)	18.0 (1.8)	20.3 (2.5)	16.6 (1.5)	17.9 (1.4)	21.1 (2.3)	18.3 (2.3)
FM, kg, mean (SD)	27.7 (8.5)	25.5 (8.8)	27.0 (11.9)	15.2 (2.6)	24.9 (1.3)	41.1 (7.4)	26.3 (9.6)
BMI, mean (SD)	25.9 (4.2)	26.3 (4.4)	28.5 (6.0)	21.6 (1.7)	25.9 (1.7)	33.9 (4.3)	26.7 (4.9)
Higher education, n (%)	14 330 (36.6%)	16 033 (40.9%)	17 056 (43.6%)	18 112 (45.5%)	15 834 (39.8%)	14 209 (36.4%)	79 178 (40.4%)
Current smokers, n (%)	3039 (7.8%)	3231 (8.2%)	3377 (8.6%)	3792 (9.5%)	3151 (7.9%)	2898 (7.4%)	16 069 (8.2%)
Low fruit and vegetable intake, n (%)	12 608 (32.2%)	11 874 (30.3%)	10 910 (27.9%)	12 125 (30.5%)	11 756 (29.6%)	12 234 (31.3%)	59 246 (30.3%)
High saturated fat intake, n (%)	11 699 (29.9%)	11 252 (28.7%)	11 212 (28.6%)	10 415 (26.2%)	11 615 (29.2%)	12 439 (31.9%)	57 055 (29.1%)
Low oily fish intake, n (%)	12 200 (31.2%)	12 619 (32.2%)	13 137 (33.6%)	12 971 (32.6%)	12 669 (31.8%)	13 082 (33.5%)	63 668 (32.5%)
Heavy drinkers, n (%)	12 955 (33.1%)	13 025 (33.2%)	12 318 (31.5%)	13 562 (34.1%)	13 525 (34.0%)	10 970 (28.1%)	64 272 (32.8%)
Low physical activity, n (%)	10 117 (25.8%)	8431 (21.5%)	7837 (20.0%)	6398 (16.1%)	8288 (20.8%)	12 160 (31.1%)	43 345 (22.1%)
Hypertension, n (%)	19 371 (49.5%)	16 440 (42.0%)	16 330 (41.7%)	11 345 (28.5%)	17 091 (43.0%)	23 766 (60.9%)	85 687 (43.8%)
Type 2 diabetes mellitus, n (%)	635 (1.6%)	669 (1.7%)	1250 (3.2%)	239 (0.6%)	524 (1.3%)	2046 (5.3%)	4032 (2.1%)
Cancer history (>5 y ago), n (%)	2540 (6.5%)	2010 (5.1%)	1845 (4.7%)	1912 (4.8%)	2278 (5.7%)	2170 (5.6%)	10 626 (5.4%)
Cholesterol medication, n (%)	4294 (11.0%)	3163 (8.1%)	3080 (7.9%)	1536 (3.9%)	3349 (8.5%)	5721 (14.8%)	17 157 (8.8%)
Postmenopausal, n (%)	28 352 (72.4%)	23 352 (59.6%)	17 594 (44.9%)	21 266 (53.5%)	24 686 (62.1%)	22 973 (58.8%)	116 065 (59.3%)

χ^2 test for trend was performed with $P<0.05$ for all characteristics across the aSMM and FM quintiles. All characteristics were determined at the baseline assessment clinic through touch-screen questionnaires, interviews, and/or physical measurements. Higher education: college or university degree or professional qualifications. Low physical activity: <600 metabolic equivalent (MET)-minutes per week.[31] Heavy alcohol drinker: >14 units of alcohol a week).[40] Hypertension: systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, was diagnosed by a doctor or were taking medication to lower blood pressure. Diabetes mellitus and cholesterol: taking medication for these conditions or diagnosed by a doctor. Cancer history: diagnosed with cancer >5 years ago (those with more recent cancer had been excluded). Low fruit and vegetable intake: the lowest consumption tertile (<21 portions per week). High saturated fat: the highest saturated fat tertile, based on portions per week of beef, lamb, pork, and whether they consumed animal- or plant-based spreads. Low oily fish: lowest consumption tertile (<1 portion per week). aSMM indicates appendicular skeletal muscle mass; BMI, body mass index; and FM, fat mass.

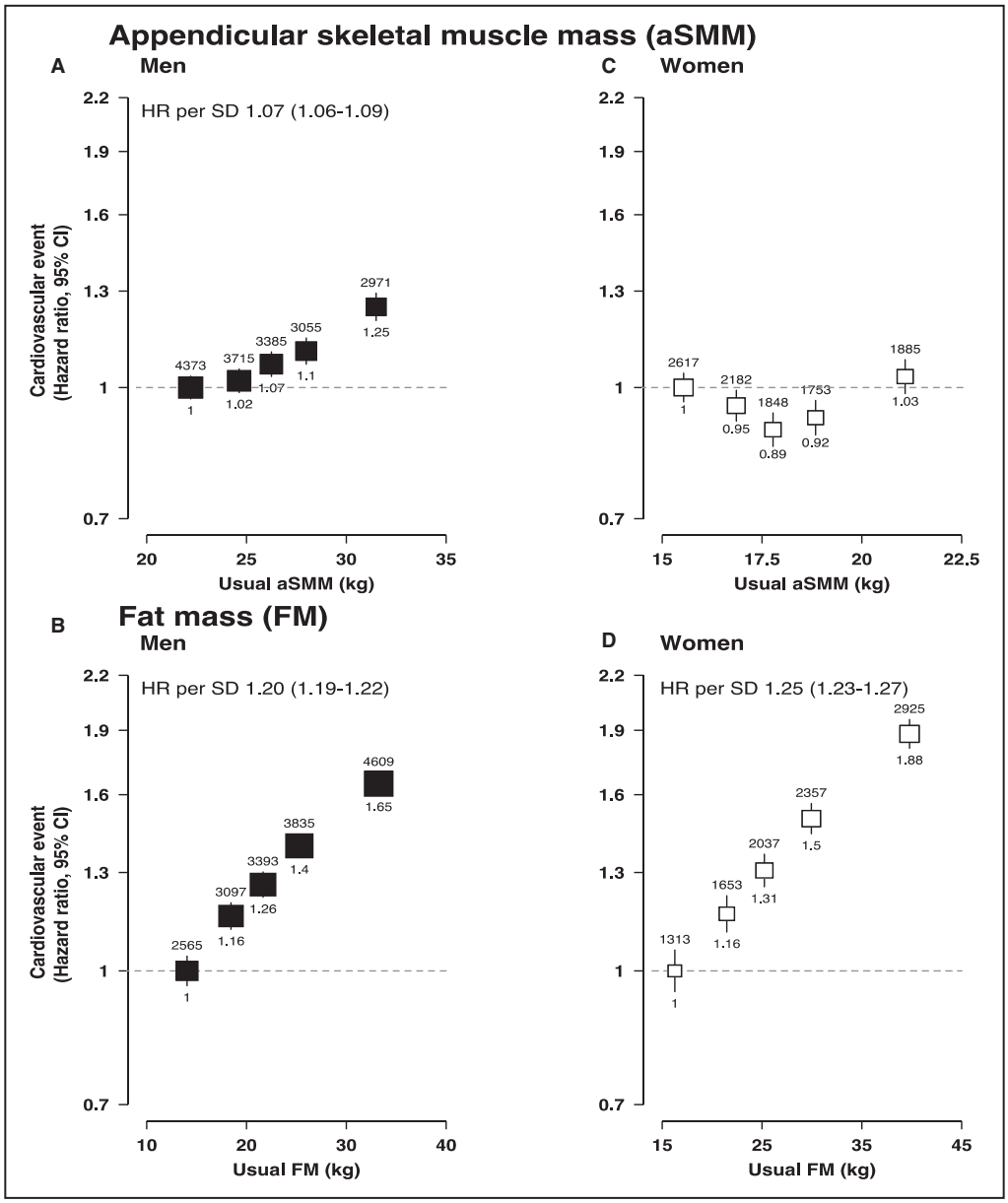


Figure 1. Adjusted hazard ratios (HRs) of incident cardiovascular disease associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM).
A, HRs of incident CVD associated with aSMM in men, 1 SD=5.66 kg. **B**, HRs of incident CVD associated with aSMM in women, 1 SD=1.45 kg. **C**, HRs of incident CVD associated with FM in men, 1 SD=6.75 kg. **D**, HRs of incident CVD associated with FM in women, 1 SD=8.28 kg. For all panels, likelihood ratio tests were used to estimate nonlinearity (aSMM in men, P=0.04; aSMM in women, P<0.001; FM in men, P=0.09; FM in women, P=0.09). Adjusted HRs and CIs obtained using the floated absolute risk method of Cox proportional hazards regression, number of cases shown above each estimate and HRs shown below. Adjusted for age (underlying timescale variable), height (as a continuous variable in FM and included by regression out of variation due to height for aSMM), Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes mellitus, cancer history, menopause (women), and mutually adjusted for FM (in the aSMM models) and aSMM (in the FM models). HRs are plotted at the mean of the resurvey values for the baseline-defined quintiles ("usual" values) to correct for measurement error. HRs per 1 SD given where there was no evidence of departure from linearity. CVD indicates cardiovascular disease.

causality, outliers, or participants with BMI >35 kg/m^2 did not affect the associations.

Adjustment for hypertension and high blood cholesterol as mediators did not affect associations of aSMM with CVD or all-cause mortality. These mediators explained ≈30% to 40% of the χ^2 statistic in models of FM and CVD, although the association between FM and all-cause mortality was affected less (Tables S11 and

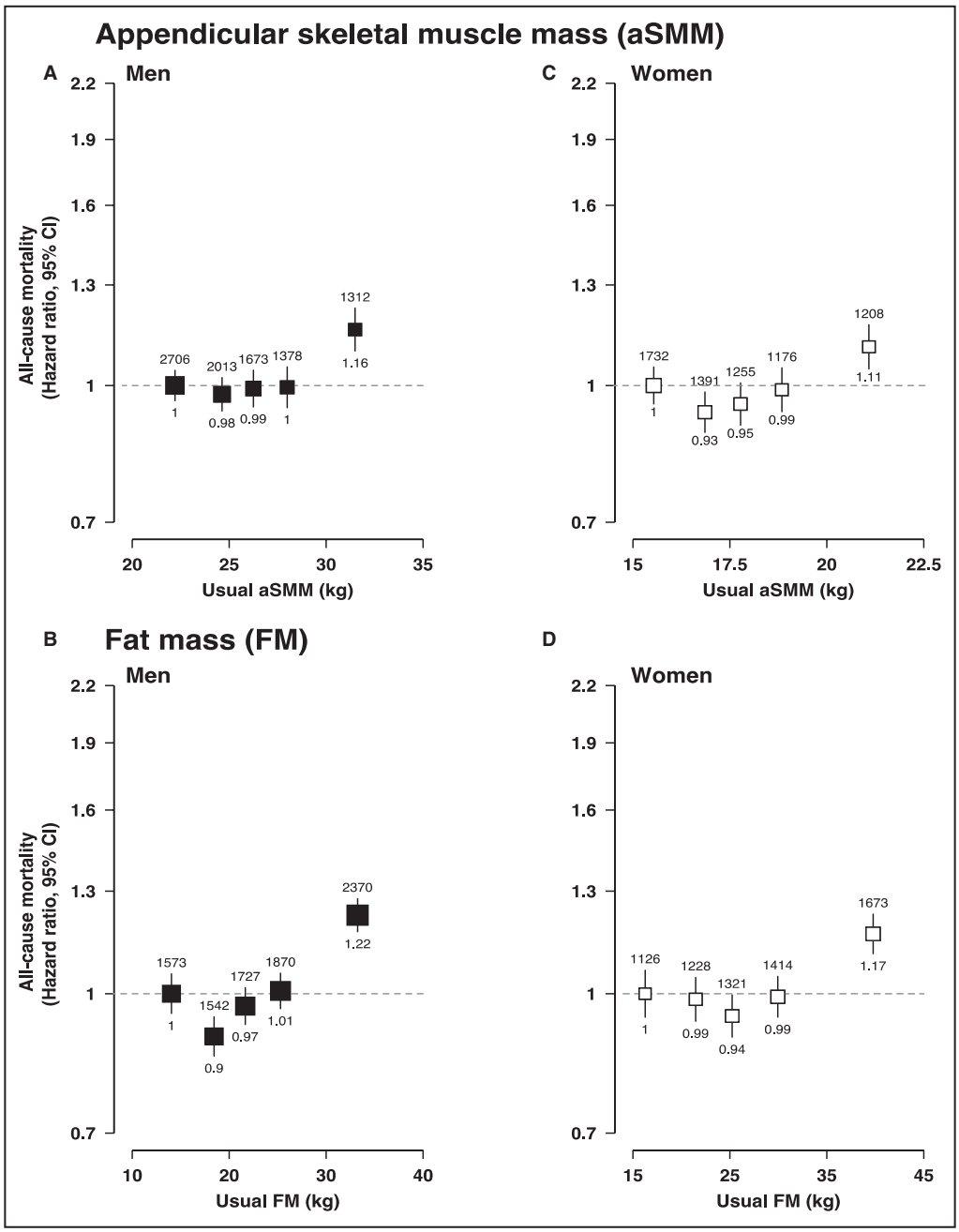


Figure 2. Adjusted hazard ratios (HRs) of all-cause mortality associated with appendicular skeletal muscle mass (ASMM) and fat mass (FM).

A, HRs of all-cause mortality associated with aSMM in men, 1 SD=5.66 kg. **B**, HRs of all-cause mortality associated with aSMM in women, 1 SD=1.45 kg. **C**, HRs of all-cause mortality associated with FM in men, 1 SD=6.75 kg. **D**, HRs of all-cause mortality associated with FM in women, 1 SD=8.28 kg. For all panels, likelihood ratio tests were used to estimate nonlinearity *P* values (aSMM in men, *P*=0.002; aSMM in women, *P*=0.008; FM in men, *P*<0.001; FM in women, *P*<0.001). Adjusted HRs and CIs obtained using the floated absolute risk method of Cox proportional hazards regression, number of cases shown above each estimate and HRs shown below. Adjusted for age (underlying timescale variable), height (as a continuous variable in FM and included by regression out of variation due to height for aSMM), Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes mellitus, cancer history, menopause (women), and mutually adjusted for FM (in the aSMM models) and aSMM (in the FM models). HRs are plotted at the mean of the resurvey values for the baseline-defined quintiles ("usual" values) to correct for measurement error.

S12). However, adjustment for BMI (instead of SMM or FM in their respective models) removed the positive association between aSMM and CVD in men but did not change the association observed in women. Associations between FM and CVD and all-cause mortality were largely attenuated after adjustment for BMI, with large % of the χ^2 statistic explained in both men and women.

Analyses of body composition groups (aSMM tertiles within each FM tertile) showed positive linear associations between aSMM and incident CVD risk in men in all FM tertiles, whereas women still had curvilinear associations with incident CVD except those in the highest FM tertile (Figure 3). The associations of aSMM with all-cause mortality within FM tertiles were broadly similar between men and women and to those observed in the main analysis, except for women in the middle tertile of FM, which showed a curvilinear association between aSMM and all-cause mortality.

Comparing the Prognostic Value of Body Composition Measures

For CVD risk, waist circumference and FM showed the strongest associations whereas aSMM and grip strength showed the weakest associations in both men and women. For all-cause mortality, waist circumference and grip strength showed the strongest associations, whereas aSMM remained the weakest (Figure 4, Table 2). However, the discriminatory performance (Harrell's C-statistics) for total CVD was slightly higher for BMI compared with all the other metrics in men (C=0.63; 95% CI, 0.63–0.64) and for BMI and waist circumference in women (C=0.45; 95% CI, 0.45–0.45). Similarly, for all-cause mortality, the discriminatory performance was highest for BMI (C=0.62; 95% CI, 0.62–0.63) and waist circumference (C=0.61; 95% CI, 0.61–0.62) in men, whereas in women it was FM (C=0.63; 95% CI, 0.62–0.63) and aSMM (C=0.63; 95% CI, 0.62–0.63). The χ^2 statistic was marginally higher in the BMI and waist circumference model in men and in the BMI and the combined aSMM/FM groups in women.

DISCUSSION

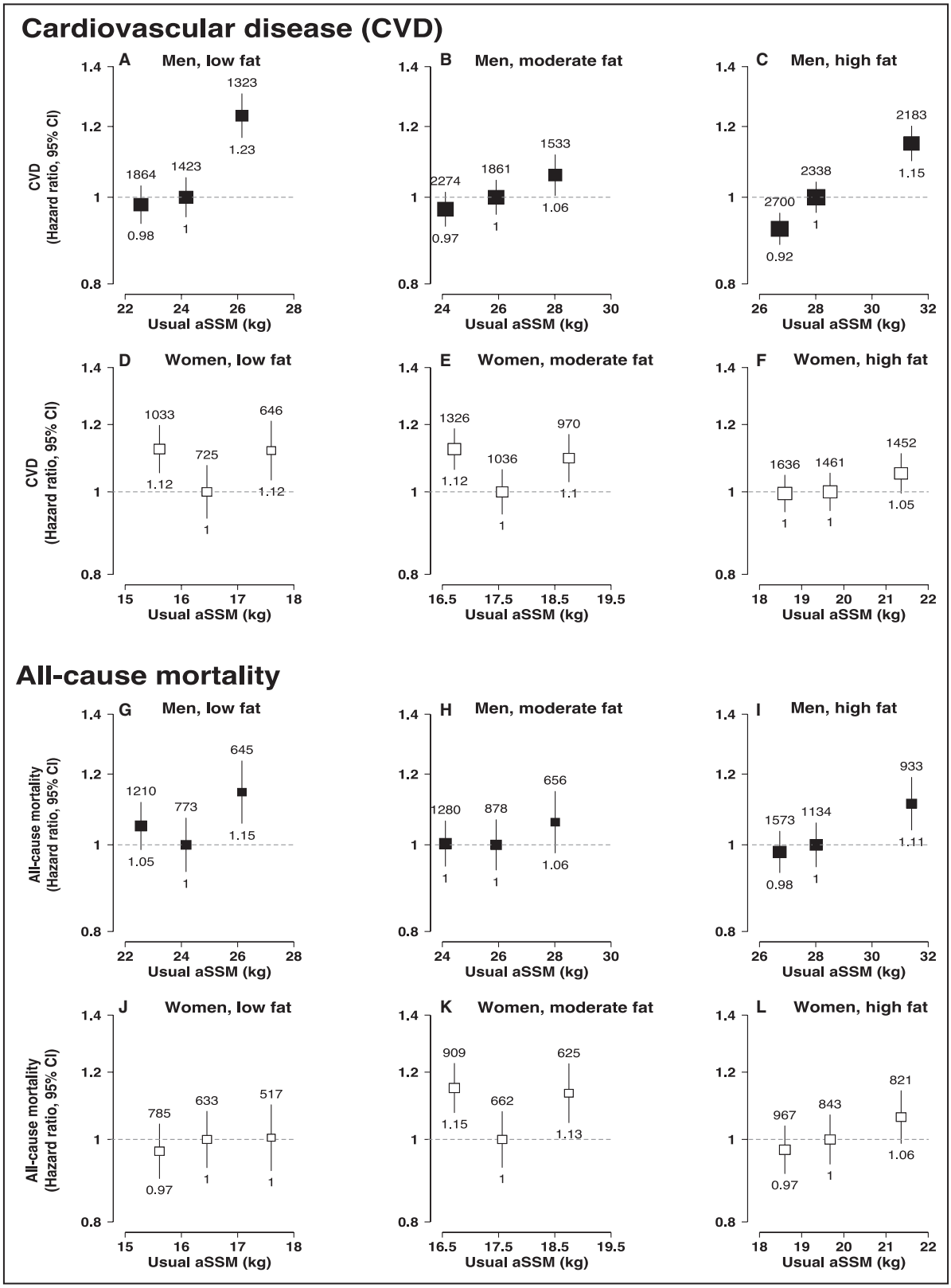
In this prospective study of 356 590 UK adults, FM had a strong positive log-linear association with the risk of CVD in both sexes. There was also a positive log-linear association with aSMM for men and a curvilinear association for women. The associations of aSMM and FM with all-cause mortality followed a J-shape in both men and women. Analysis of the association of aSMM within tertiles of FM supported these associations with CVD and all-cause mortality. The discriminatory ability of BMI was similar to, or better than, more specific measures of body composition (aSMM and FM), waist circumference, or grip strength in relation to CVD events or all-cause mortality.

Few previous studies have specifically examined the association between distinct body compartments with either incident CVD or mortality. In line with previous studies we consistently observed a positive association between FM and CVD. This is consistent with previous analyses from UK Biobank that found significant associations between body fat percentage, waist circumference, and waist-to-hip ratio on CVD outcomes[9] as well as meta-analyses of prospective cohort studies assessing various adiposity measures.[3,41]

The role of aSMM has been investigated in fewer studies, most of which used older populations with small sample sizes or a proxy for aSMM such as fat-free mass.[42–46] Our rationale for using aSMM as opposed to whole body muscle or fat-free mass is because this tissue is more likely to be modifiable by lifestyle factors such as physical activity than other components of fat-free mass and it is less likely to be confounded by FM given that higher abdominal FM is often accompanied by greater muscle in the trunk region.[30] However, aSMM is a large contributor to whole body muscle and it is likely that participants would be classified in the same quintile regardless of the measure used. Although some studies have shown an inverse association between aSMM and CVD risk, our finding of a positive log-linear association among men

Figure 3. Adjusted hazard ratios (HRs) of cardiovascular disease and all-cause mortality associated with appendicular skeletal muscle mass (aSMM) when participants are stratified into fat mass (FM) tertiles.
A, HRs of cardiovascular disease (CVD) associated with aSMM in low fat men. **B**, HRs of CVD associated with aSMM in moderate fat men. **C**, HRs of CVD associated with aSMM in high fat men. **D**, HRs of CVD associated with aSMM in low fat women. **E**, HRs of CVD associated with aSMM in moderate fat women. **F**, HRs of CVD associated with aSMM in high fat women. **G**, HRs of all-cause mortality associated with aSMM in low fat men. **H**, HRs of all-cause mortality associated with aSMM in moderate fat men. **I**, HRs of all-cause mortality associated with aSMM in high fat men. **J**, HRs of all-cause mortality associated with aSMM in low fat women. **K**, HRs of all-cause mortality associated with aSMM in moderate fat women. **L**, HRs of all-cause mortality associated with aSMM in high fat women. For all panels, adjusted hazard ratios (HR) and CIs obtained using Cox proportional hazards regression, number of cases shown above each estimate and HRs shown below. Adjusted for age (underlying timescale variable), height (included by regression out of variation due to height), Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes mellitus, cancer history, menopause (women), and mutually adjusted for FM (in the aSMM models) and aSMM (in the FM models). HRs are plotted at the mean of the resurvey values for the baseline-defined quintiles ("usual" values) to correct for measurement error.

has been observed previously. The Aerobics Center Longitudinal Study found a similar pattern with fat-free mass index measured by skinfold thicknesses as well as hydrostatic weighing (for which aSMM is the largest contributor) and had a comparably aged, predominantly male study population.[47] A plausible physiological mechanism linking higher aSMM with higher CVD risk may be a higher circulating blood



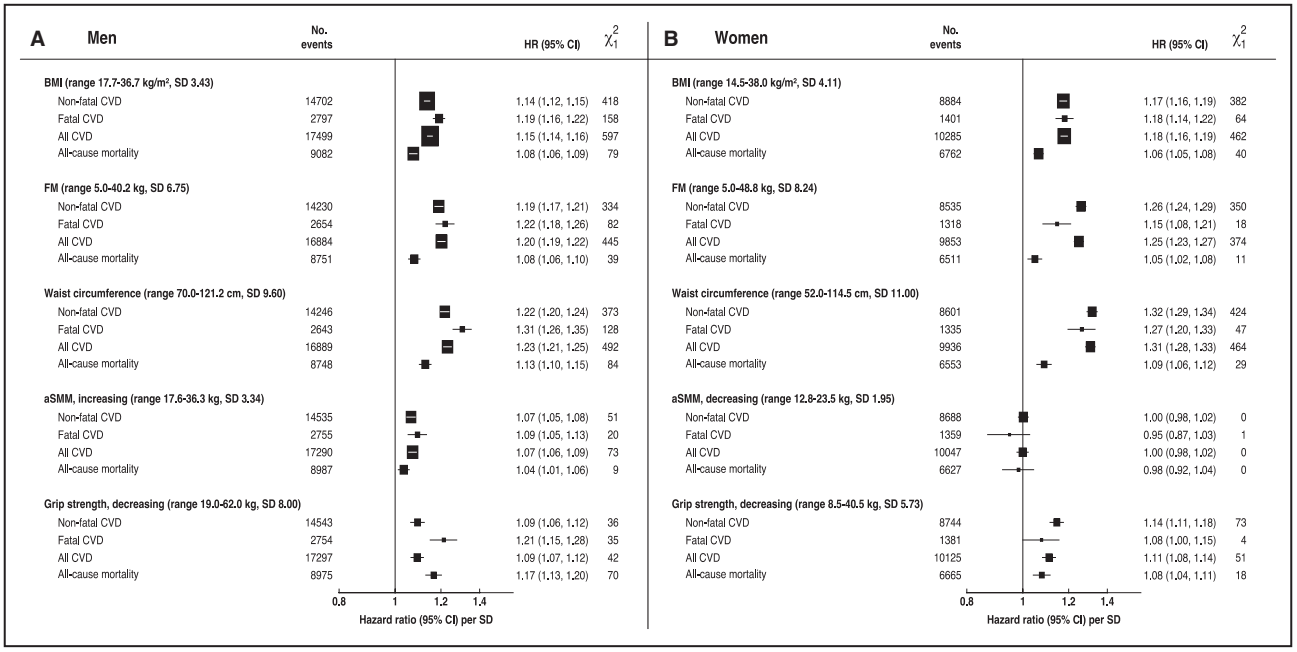


Figure 4. Independent effects of body mass index (BMI), fat mass (FM), waist circumference, appendicular skeletal muscle mass (aSMM), and grip strength on cardiovascular disease (CVD) subtypes and all-cause mortality. Adjusted hazard ratios (HRs) per SD change.

A, The independent effects of BMI, FM, waist circumference, aSMM and grip strength on CVD subtypes and all-cause mortality in men. **B**, The independent effects of BMI, FM, waist circumference, aSMM, and grip strength on CVD subtypes and all-cause mortality in women. Range excludes outliers. Adjusted hazard ratios (HR) and CIs obtained using Cox proportional hazard regression. Adjusted for age (underlying timescale variable), height (as a continuous variable in all models except aSMM where it was included by regression out of variation due to height for aSMM), Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes mellitus, cancer history, menopause (women), and mutually adjusted for FM (in the aSMM models) and aSMM (in the FM models). HRs are corrected for regression dilution bias by the MacMahon-Peto method.

volume, which increases cardiac output and increases systolic blood pressure and the risk of heart failure, a phenomenon previously described mainly among people with obesity.[48–50] A recent literature review has provided a more counterintuitive view of the role of lean mass on metabolic health, proposing the possibility of publication bias, especially if unexpected results were found.[51] Our analysis within tertiles of FM confirmed the increased risk of CVD with aSMM even among men with lower FM levels, reducing the possibility of residual confounding by FM although this cannot be completely ruled out. Our exploratory mediation analyses showed that the association between aSMM and CVD was no longer significant in men after adjusting for BMI. This implies that if aSMM increases, FM plus all the other body compartments have to decrease in order to hold BMI constant, such that changes in body composition that increase skeletal muscle while lowering total body fat, as expected with physical training, may not be associated with increased CVD risk. Furthermore, the large changes observed in the χ^2 statistic after adjustment for BMI in the aSMM model suggest a large part of the association may be explained by confounding by BMI, especially among men.

Nevertheless, it is unusual to find a CVD risk factor with such different associations between sexes.[52] A potential explanation for this disparity could be because of differences in lifestyle factors between men and women classified as high aSMM within each FM tertile. For example, compared with women, a higher percentage of men in the same aSMM and FM tertile, reported poorer diets (low fruit and vegetable intake, high saturated fat intake), heavy drinking (over 14 units/week, National Health Service guidelines), or presented a higher prevalence of hypertension and cholesterol medication. Our findings are largely consistent with those reported from a recent study of 38 000 middle-aged men that demonstrated a U-shaped association between predicted lean mass and CVD death and mortality; however, these participants may have been healthier because they recruited health professionals rather than the general population.[53] Although we adjusted for several potential lifestyle confounders our study may still have residual confounding in relation to lifestyle factors.

Table 2. The Discrimination Ability of Each Body Composition Measure for the Prediction of Cardiovascular Events and All-Cause Mortality, as Calculated by Harrell's C-Statistic From the Area Under the Receiver Operating Curve

	Men			Women		
	HR Per SD (95% CI)	Harrell's C-Statistic (95% CI)	χ^2_1	HR Per SD (95% CI)	Harrell's C-Statistic (95% CI)	χ^2_1
Cardiovascular disease						
BMI	1.15 (1.14–1.16)	0.63 (0.63–0.64)	597	1.18 (1.16–1.19)	0.45 (0.45–0.45)	462
FM	1.20 (1.19–1.22)	0.56 (0.55–0.56)	445	1.25 (1.23–1.27)	0.59 (0.58–0.59)	374
Waist circumference	1.23 (1.21–1.25)	0.61 (0.61–0.62)	492	1.31 (1.28–1.33)	0.45 (0.44–0.45)	464
aSMM	1.07 (1.06–1.09)	0.54 (0.54–0.54)	73	1.00 (0.98–1.02)	0.57 (0.56–0.57)	0
Decreasing grip strength	1.09 (1.07–1.12)	0.55 (0.54–0.55)	42	1.11 (1.08–1.14)	0.44 (0.43–0.44)	51
Body composition groups	…	0.56 (0.55–0.56)	504	…	0.45 (0.44–0.45)	400
All-cause mortality						
BMI	1.08 (1.06–1.09)	0.62 (0.62–0.63)	79	1.06 (1.05–1.08)	0.61 (0.61–0.62)	40
FM	1.08 (1.06–1.1)	0.60 (0.59–0.60)	39	1.05 (1.02–1.08)	0.63 (0.62–0.63)	11
Waist circumference	1.13 (1.1–1.15)	0.61 (0.61–0.62)	84	1.09 (1.06–1.12)	0.61 (0.6–0.62)	29
aSMM	1.04 (1.01–1.06)	0.60 (0.59–0.60)	9	0.98 (0.92–1.04)	0.63 (0.62–0.63)	0
Decreasing grip strength	1.17 (1.13–1.2)	0.60 (0.60–0.61)	70	1.08 (1.04–1.11)	0.61 (0.60–0.61)	18
Body composition groups	…	0.61 (0.61–0.62)	83	…	0.61 (0.61–0.62)	41

Harrell's C-statistic and hazard ratios (HR) per SD change calculated from the fully-adjusted model, which adjusted for: age (underlying timescale variable), height, Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes mellitus, cancer history, menopause (women), and mutually adjusted for FM (in the aSMM models) and aSMM (in the FM models). HRs are corrected for regression dilution bias using the MacMahon-Peto method. One SD of aSMM is 3.34 kg (men), 1.95 kg (women) and FM is 6.79 kg (men), 8.29 kg (women). The model for aSMM in men is for increasing aSMM; in women is for decreasing aSMM. Wald test χ^2_1 statistic was used to compare a model with just confounders to a model with confounders plus the exposure of interest. aSMM indicates appendicular skeletal muscle mass; BMI, body mass index; and FM, fat mass.

Clinical and Public Health Implications

BMI has been criticized as an inaccurate measure of health risks,[54,55] but at a population level, more specific measurements of body composition, namely aSMM and FM, were generally not more predictive of CVD events or mortality; an observation that also been reported elsewhere.[47,56,57] The moderately improved prognostic value of BMI may reflect the combined effects of height, FM, and SMM that are each individually associated with CVD risk.[58] In addition, BMI has less measurement error than other measures that could contribute to its marginally stronger prognostic ability.[50] Waist circumference and other measures of central adiposity have been reported to better discriminate CVD risk in some studies,[59] although not superior to BMI in others[60] as happened in our study. However, waist circumference is particularly liable to observer error,[50] whereas measures of central adiposity do not indicate whole-body adiposity, nor is there an equivalent measure for fat-free mass. Grip strength is often used as a functional indicator of SMM; however, it includes a volitional component and the European Working Group of Sarcopenia in Older People recommends measuring the amount of SMM to assess risk.[61] However, the commonly used measure of the mid-upper arm circumference is vulnerable to overestimation because it cannot distinguish between muscle fibers and intramuscular fat deposits.[61]

However, although BMI may be the simplest measurement to assess health risk, which is important from a public health perspective, some of this risk may not be attributable solely to adiposity, particularly if the association observed with aSMM in men is confirmed, although further research is needed to better understand the biological mechanisms and impact of different body tissue compartment on health outcomes. It could therefore be beneficial to reframe BMI as a composite measure of risk.[47,58] In addition, at the individual level, additional measurements of CVD risk factors (eg, blood lipids, blood pressure) in addition to BMI or body composition are needed to classify individuals at risk and propose adequate treatments.

Strengths and Weaknesses of the Study

The strengths of this study include its large sample size, which reduces the risk of chance findings owing to random error, and the detailed measurements of the exposures, potential confounders, and outcomes from the hospital episode statistics follow-up. Some participants had repeated measurements taken at resurvey, which allowed for the correction for random measurement error and consequent regression dilution bias.[36]

Although BIA has many practical strengths in research and clinical settings, it is not as accurate as other methods that use physical properties of the

body to measure composition, such as densitometry or DEXA or imaging methods such magnetic resonance imaging scans, and is vulnerable to estimation errors, especially at the extreme ranges of BMI or in people with conditions that affect water retention.[17,62] However, validation studies against DEXA show that it performs well in healthy individuals with a stable electrolyte and water balance.[20] Because algorithms to estimate body composition by BIA vary, it may be that our results can be replicated only using a Tanita BC-418 MA segmental body composition analyzer. However, studies comparing different analyzers from this manufacturer or others have reported only small differences in % body fat (eg, equivalent to 0.7 kg of difference in FM),[63] suggesting that a participant would likely fall into the same quintile regardless of the method used.

Despite the large sample of participants studied here, one of the main limitations is that the UK Biobank presents a low response rate for the United Kingdom (5.5%); however, the associations in this study should still be valid and not affected by selection bias.[64] The participants were predominantly people of White race, which limits the generalizability of our findings. Despite the performance of BMI in this high-income population of UK Biobank, there is emerging evidence that suggests that BMI is not an informative measure of risk for mortality in lean populations from low- and middle-income countries. For example, research from a large cohort study of 0.5 million adults in India found little association between BMI and cardiac mortality.[65] It may be that BMI is a better indicator of risk in populations where fat mass is the dominant type of body tissue, supported in the current study by the largely equivalent associations of BMI and fat mass with the risk of CVD. Research has also suggested that the distribution of fat mass within equivalent levels of BMI may have distinct associations with the risk of cardiometabolic diseases in different ethnic groups.[66] Thus, although BMI may be the most effective tool for risk assessment within high-income populations further work is needed to compare its prognostic ability with more detailed measures of body composition in diverse populations. Finally, as this is an observational study we cannot eliminate the possibility that residual confounding affected our results.

CONCLUSIONS

FM showed a strong positive association with CVD risk whereas SMM showed a positive log-linear association with CVD risk in men but curvilinear in women. Although BMI has been criticized as an inaccurate measure of risk, more specific measurements of body composition did not demonstrate improved prognostic ability to detect the risk of CVD or all-cause mortality.

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S12
Figures S1–S3
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SUPPLEMENTAL MATERIAL

Data S1.

Systematic literature review

Search terms used on PubMed and Embase (up to 18th October 2019):
("muscle mass" or "skeletal muscle" or “sarcopenia” or "fat mass" or "body fat" or "body composition" or "fat free mass" or "lean mass" or "adiposity") AND ("mortality" or "death" or "survival" or "cardiovascular disease" or "CVD" or "stroke" or "coronary heart disease" or "congestive heart failure")
Studies were excluded if they were done in patients or ill people (including but not limited to hospitalised, intensive care or dialysis patients, those with cancer, diabetes, COPD, CKD, dementia, HIV), done in children or adolescents, investigating a diet or exercise intervention, done in animals, molecular, cellular-level studies, or genetic studies. Only findings from prospective cohort studies published after 2000 with more than 600 participants are presented below.

Table S1. Summary of search findings.

Exposure	Outcome	Sex	Number of associations identified in studies			
			Null	Negative	Positive	U or J-shaped
Muscle mass	All-cause mortality	Combined men and women	7	8	3	
		Men only	10	7	1	3
		Women only	10	9	1	2
Muscle mass	CVD	Combined men and women	2	2	2	
		Men only	7	2	1	
		Women only	5	2	1	
Fat mass	All-cause mortality	Combined men and women	7	2	3	
		Men only	12	4	17	5
		Women only	13	10	19	3
Fat mass	CVD	Combined men and women	2	1	10	3
		Men only	11	2	16	
		Women only	12		13	
Low muscle, high fat	All-cause mortality	Combined men and women			1	
		Men only	2		2	
		Women only	2		1	
High Muscle, low fat	All-cause mortality	Combined men and women		1		
		Men only				
		Women only				
Low Muscle, high fat	CVD	Combined men and women			1	
		Men only	1			
		Women only	1			
High muscle, low fat	CVD	Combined men and women		1		
		Men only				
		Women only				

Each association assessed in the studies is counted distinctly (i.e. the number of associations exceeds the number of studies identified since some studies analysed more than one exposure/outcome combination). 'Muscle mass' includes studies that assessed measurements of lean mass from techniques such as bioimpedance analysis (BIA), dual energy x-ray absorptiometry (DEXA), mid upper arm circumference and calf circumference (it does not include studies of muscle quality such as grip strength). 'Fat mass' includes studies that assessed measurement of adiposity such as fat mass as determine by BIA or DEXA, percentage body fat, waist circumference, waist to hip ratio. Studies of BMI or body fat distribution indices are not included.

Table S2. Systematic literature review.

Reference		Study name (date of recruitment)	Study participants (location, N, age)	Body composition measurement	Exposure definition/coding	Outcome	Shape of association
68	Abramowitz, et al. (2018)	NHANES (1999-2004)	USA, n=11687 aged >20 yrs	DEXA (Appendicular skeletal muscle mass)	Low muscle defined as ASMI <5.45kg/m^2 (women) or <7.26kg/m^2 (men) [2,3]	All-cause mortality	BMI and mortality: U (low muscle group), 0 (preserved muscle group) ASMI and mortality (men and women combined): -
69	Allison, et al. (2002)	NHANES I & II	USA, n=10169 men aged 25-75yrs	Skinfolds (indicator of fat mass), upper arm circumference (fat free mass indicator), BMI	Modelled continuously	All-cause mortality	BMI and all-cause mortality: U (men) Fat free mass and mortality: linear - (men) Fat mass and mortality: linear + (men)
70	Andersen, et al. (2015)	Shanghai Men's Health Study and Shanghai Women's Health Study (1996-2000)	China, n=116442 aged 40-74yrs	Waist to hip ratio	Quintiles of WHR	All-cause and CVD mortality	WHR and mortality: linear + (men) WHR and mortality: linear + (women) WHR and CVD mortality: linear + (men) WHR and CVD mortality: linear + (women)
71	Atkins, et al. (2014)	NHANES (1999-2004)	USA, n=11687 aged >20yrs	Waist circumference, midupper arm circumference, triceps skinfold thickness	4 groups created: Optimal (MAMC >25.9cm and WC ≤102cm), sarcopenic (MAMC ≤25.9cm and WC ≤102cm), sarcopenic obese (MAMC ≤25.9cm and WC>102cm), obese (WC >102cm and MAMC >25.9cm)	All-cause mortality, CVD mortality, CVD events	Sarcopenia and mortality: 0 (men) Sarcopenia and mortality: + (women) Sarcopenia and CVD: 0 (men) Sarcopenia and CVD: + (women)
72	Bachettini et al. (2019)	n/a	Brazil, n=1291 aged >=60 years	Using the European Working Group on Sarcopenia in Older People (EWGSOP) definitions of sarcopenia	Sarcopenia, binary	All-cause mortality	Severe sarcopenia and mortality: + (men and women combined) Other sarcopenia and mortality: 0 (men and women combined)
73	Balogun, et al. (2017)	Tasmanian Older Adult Cohort study	Tasmania, n=1099 aged >50yrs	DEXA (Appendicular lean mass), lower limb strength	Calculated ALM/height^2 [2], ALM/BMI [1], ALM/weight*100 [12] from DEXA. Measured grip, lower-limb muscle, and upper-limb muscle strength and/or quality. Low muscle mass or function defined as participants in the lowest 20% of the sex-specific distribution for each measurement	Mortality, falls, fracture	Muscle strength or quality and mortality (men and women combined): 0 Low appendicular lean mass/BMI and mortality (men and women combined): + Low appendicular lean mass/height^2 and mortality (men and women combined): 0 Low appendicular lean mass/weight and mortality (men and women combined): 0
74	Batsis, et al. (2014)	NHANES III (1988-1994)	USA, n=4652 aged >60years	BIA (skeletal muscle index, % body fat)	4 definitions used: Normal if SMI ⩾10.76kg/m^2 (men) >6.76kg/m^2 (women); Class I sarcopenia if SMI 8.51–10.75 (men) 5.76–6.75 (women); Class II sarcopenia: ⩽8.50 kg/m2 ⩽5.75 [17]. Obesity defined as body fat >27% (men) >38% (women) [3]	All-cause mortality	Sarcopenia only and mortality: 0 (men) Sarcopenia only and mortality: + (women) Sarcopenic obese and mortality: 0 (men) Sarcopenic obese and mortality: 0 (women) Obese only and mortality: 0 (men) Obese only and mortality: 0 (women)
45	Batsis, et al. (2017)	NHAHES (1999-2004)	USA, n=4984 aged >60 yrs	DEXA (Appendicular lean mass), waist circumference, BMI	Low lean mass defined as: ALM <19.75kg (men) <15.02kg (women) [1] or ALM:BMI <0.789 (men), <0.512 (women). Obesity defined as body fat >25% (men) >35% (women) [9].	All-cause and CVD mortality	Low lean mass and mortality: + (men) Low lean mass and mortality: 0 (women) Low lean mass and CVD: + (men) Low lean mass and CVD: 0 (women) Low lean mass with obesity and mortality: + (men) Low lean mass with obesity and mortality: 0 (women) Low lean mass with obesity and CVD : 0 (men) Low lean mass with obesity and CVD : 0 (women) Obesity (body fat %) and mortality: - (men)

							Obesity (body fat %) and mortality: - (women) Obesity (body fat %) and CVD: 0 (men) Obesity (body fat %) and CVD: 0 (women)
75	Bea, et al. (2015)	Women's Health Initiative (1993-1998)	USA, n=10525 postmenopausal women aged 50-79yrs	DEXA (total body fat %, lean body mass %), BMI	Quintiles of each exposure	All-cause mortality	Fat mass and mortality (women aged 50-59): linear + Fat mass and mortality (women aged >70): linear - Lean mass and mortality (women aged 50-59): linear – Lean mass and mortality (women aged >70): linear +
76	Bigaard, et al (2004)	Diet, Cancer and Health study (1993-1997)	Denmark, n=51053 aged 50-64yrs	BIA (fat free mass index, body fat mass index)	Modelled continuously using linear splines, and relative risks estimated per 10% increase in waist circumference and per kg/m^2 increase in body fat mass index and fat free mass index Results stratified into high and low range corresponding to cut-offs at the 40th and 60th percentiles	All-cause mortality	Fat mass and mortality: J (men) Fat mass and mortality: J (women) Fat free mass and mortality: reverse J (men) Fat free mass and mortality: reverse J (women) WC and mortality: linear + (men) WC and mortality: linear + (women)
77	Bigaard, et al. (2005)	Diet, Cancer and Health (1993-1997)	Denmark, n=57058 adults	BIA (body fat mass index, fat free mass index), waist circumference	Modelled continuously using linear splines	All-cause mortality	Body fat mass index and all-cause mortality: J (men) Body fat mass index and all-cause mortality: J (women) Fat free mass index and mortality: reverse J (men) Fat free mass index and mortality: reverse J (women)
78	Boloukat, et al. (2018)	Tehran Lipid and Glucose Study	Iran, n=4631 aged >40yrs	BMI, waist circumference, waist-to-height ratio, WHR	Modelled continuously per 1 unit increase in each exposure	CHD or stroke incidence	WC and CVD: 0 (men) WC and CVD: 0 (women) WHR and CVD: 0 (men) WHR and CVD: 0 (women) Waist-to-height ratio and CVD: 0 (men) Waist-to-height ratio and CVD: 0 (women)
43	Brown, et al. (2016)	NHANES (1988-1994)	USA, n=4425 aged >60 yrs	BIA (skeletal muscle index), gait speed	Sarcopenia defined as low gait speed (<0.8m/s) and SMI <10.76 (men), <6.75 (women)	All-cause and CVD mortality	Sarcopenia and mortality: + (men) Sarcopenia and mortality: + (women) Sarcopenia and CVD: 0 (men) Sarcopenia and CVD: + (women)
79	Brown, et al. (2017)	NHANES III (1988-1994)	USA, n=1487 aged >65 yrs	BIA (Appendicular lean mass)	Modelled continuously per 1 SD of ALM	All-cause mortality	Appendicular lean mass and mortality: - linear (men) Appendicular lean mass and mortality: - linear (women)
44	Cesari, et al (2009)	InChianti study (1998-2000)	Italy, n=934 aged >65yrs	Peripheral quantitative computerised tomography (muscle density, muscle area, fat area)	Modelled continuously per 1 SD increase of each exposure	All-cause mortality	Muscle area and mortality (men and women combined): 0 Fat area and mortality (men and women combined): 0
80	Chen, et al. (2018)	China Kadoorie Biobank (2004-2008)	China, n=489301 aged 30-79yrs	BMI, body fat %, waist circumference	7 groups for each exposure, and BMI per 5kg/m^2, % body fat per 10%, waist circumference per 1 SD	Ischaemic and haemorrhagic stroke incidence	BMI and stroke/haemorrhage (men and women combined): + linear WC and stroke/haemorrhage (men and women combined): + linear Body fat % and stroke/haemorrhage (men and women combined): + linear
81	Chen et al. (2019)	Women's Health Initiative	USA, n=2,683 postmenopausal women with normal BMI	DEXA - % whole body and regional fat quartiles, fat mass index (dividing total or regional fat mass in kg by height squared)	Quartiles	CVD	Whole body fat mass and mortality: 0 (women) Leg fat and mortality: - (women) trunk fat and mortality: + (women)
82	Cheung, et al. (2016)	NHANES (1999-2004)	USA, n=2841 aged >65yrs	DEXA (Appendicular lean mass)	Calculated ALM, ALM/BMI, ALM/H^2 from DEXA. Sarcopenia defined using cut-points for each measure (given in their supplementary index).	All-cause mortality	Low appendicular lean mass and mortality: + (men and women combined)
83	Chin, et al (2013)	KNHANES (2008-2012)	South Korea, n=1578 aged >65yrs	DEXA (Appendicular skeletal muscle mass)	Sarcopenia defined as ASM/weight <1 SD below the gender-specific mean of a reference group aged 20-39 years. Equates to <32.2% men, <25.6% women.	CVD incidence	Sarcopenic and CVD (men and women combined): +

					Sarcopenic obesity if both sarcopenic and obese BMI		
84	Chuang, et al. (2014)	Elderly Nutrition and Health Survey (1999-2000)	Taiwan, n=1512 aged >65yrs	BIA (skeletal muscle mass index), BMI, waist circumference	Low/high risk groups defined as ASMI <11.45kg/m^2 (men) 8.51kg/m^2 (women) based off quartiles	All-cause mortality	Low skeletal muscle index and mortality: 0 (men) Low skeletal muscle index and mortality: + (women) Low skeletal muscle index and CVD: 0 (men) Low skeletal muscle index and CVD: + (women)
85	Chuang, et al. (2016)	Elderly Nutrition and Health Survey	Taiwan, n=1485 aged >65 yrs	BIA (skeletal muscle mass index)	Sarcopenia defined as SMMI men <11.45, women <8.51 [14] Sarcopenic obesity defined as being sarcopenic and having a high triglyceride (>150mg/dL) and high waist circumference (>90cm men, >80cm women)	All-cause and CVD mortality	Abdominal obesity and mortality: 0 (men and women combined) Abdominal obesity and CVD: 0 (men and women combined) Sarcopenic and mortality: 0 (men and women combined) Sarcopenic and CVD: 0 (men and women combined) Sarcopenic obesity and mortality: + (men and women combined) Sarcopenic obesity and CVD: + (men and women combined)
86	de Almeida Roediger, et al. (2019)	SABE (2000-2010)	Brazil, n=1504 aged >60yrs	BMI, waist circumference, wait-to-hip ratio skinfold, mid-upper arm circumference, calf circumference, arm muscle area	All exposures analysed as binary variables as either high vs low or adequate vs inadequate.	All-cause mortality	WC and mortality: 0 (men and women combined) WHR and mortality: 0 (men and women combined) MAMC (muscle) and mortality: - (men and women combined) Calf circumference (muscle) and mortality: - (men and women combined)
87	de Santana et al. (2019)	n/a	Brazil, n=839 aged >=65yrs	DEXA (total fat, appendicular lean mass)	Low lean mass, presence of visceral adipose issue	CVD mortality, all cause morality	Low muscle and CVD mortality: + (men and women combined) Low muscle and mortality: + (men and women combined) Fat mass and CVD mortality: + (men and women combined) Fat mass and mortality: + (men and women combined)
88	Dolan, et al. (2007)	Study of Osteoporotic Fractures	USA, n=8029 women aged >65	BIA (lean mass, fat mass, % body fat), BMI, waist girth	Quintiles of each exposure	All-cause mortality	Fat mass and mortality (women): U Lean mass and mortality (women): 0 BMI and mortality (women): U
89	Dong et al (2018)	NHANES III (1988-1994)	USA, n=16415) aged 18-89yrs	BIA (body fat %), WHR	Body fat % and WHR modelled continuously using cubic splines at 4 knots. Also created 9 groups to assess joint associations	All-cause mortality	Body fat % and mortality: U (men) Body fat % and mortality : U (women) WHR and mortality: U (men) WHR and mortality: + linear (women)
90	Gale, et al. (2007)	n/a	UK, n=800 aged >65yrs	Skinfolds (fat mass, fat free mass), BMI, grip strength	Modelled continuously per 1 SD increase in each exposure	All-cause and CVD mortality	Body fat % and CVD: 0 (men) Body fat % and CVD: 0 (women) Body fat % and mortality: 0 (men) Body fat % and mortality: 0 (women) MAMC (muscle) and CVD: 0 (men) MAMC (muscle) and CVD: 0 (women) Fat free mass and CVD: 0 (men) Fat free mass and CVD: 0 (women) MAMC (muscle) and mortality: 0 (men) MAMC (muscle) and mortality: 0 (women) Fat free mass and mortality: 0 (men) Fat free mass and mortality: 0 (women) Grip strength and CVD: + (men) Grip strength and CVD: 0 (women) Grip strength and mortality: + (men) Grip strength and mortality: 0 (women)
91	Gillum, et al. (2001)	NHANES I (1992)	USA, n=6936 aged 45-74yrs	BMI, Subscapular skinfold (SSF), subscapular to triceps skinfold thickness ratio (SFR)	Each exposure modelled in quartiles and results stratified by race, sex and smoking status	Stroke incidence	Trunk obesity and stroke: weak U (white men ex-smokers) Trunk obesity and stroke: 0 (women) Overall obesity and stroke: U (white men ex-smokers) Overall obesity and stroke: 0 (women)
92	Gnatiuc et al. (2019)	Mexico City cohort study	Mexico, n=159,755 aged 35 to <75	BMI, waist-to-hip ratio, waist circumference	Continuously	all-cause mortality	BMI and mortality: J (men and women cobined) WHR and mortality: + (men and women combined)

							WC and mortality: + (men and women combined)
93	Graf, et al. (2015)	n/a	Switzerland, n=3181 aged >65yrs	BIA (fat mass index, fat free mass index)	Quartiles of FMI and FFMI	All-cause mortality	Fat free mass index and mortality: 0 (women) Fat free mass index and mortality: - (men) Fat mass index and mortality: 0 (men) Fat mass index and mortality: 0 (women)
94	Han, et al. (2010)	Korean Longitudinal Study on Health and Aging	South Korea, n=877 aged >65yrs	BIA (lean mass, fat mass, fat percentage, lean mass index), BMI, waist circumference	3 groups for each exposure: <25th percentile, 25-75th percentile, >75th percentile	All-cause mortality	Lean mass and mortality: - (men and women combined) Fat mass and mortality: 0 (men and women combined)
95	Heitmann, et al. (2000)	n/a	Sweden, n=787 men aged 60yrs	Whole body potassium counter (lean body mass and fat mass calculated)	Quintiles, fractional polynomials	All-cause mortality	Fat free mass and mortality: reverse J (men) Fat mass and mortality: J (men) BMI and mortality: U (men)
96	Hirani, et al. (2017)	Concord Health and Aging in Men Project (2005-2013)	Australia, n=1666 men aged >70yrs	DEXA (Appendicular lean mass, fat %)	Low lean mass defined as ALM:BMI ratio <0.789 [6], Obesity defined as fat % > 30% [7]. 4 groups created: neither obese nor low muscle, obese only, low muscle only, sarcopenic obesity	Frailty, disability, institutionalisation and mortality	Obesity and mortality (men): 0 Low muscle and mortality (men): 0 Sarcopenic obesity and mortality (men): 0
97	Hotchkiss, et al. (2013)	Scottish Health Survey	Scotland, n=9329 aged 18-86yrs	BMI, Waist circumference, waist to hip ratio	Quartiles of WC and WHR. BMI groups (WHO classification)	All-cause mortality, CVD incidence and mortality	Adiposity and incident CHD: + (men) Adiposity and incident CHD: + (women) Adiposity and mortality: + (men) Adiposity and mortality: + (women) Adiposity and CHD mortality: 0 (men) Adiposity and CHD mortality: 0 (women)
98	Howell, et al. (2018)	NHANES III and NHANES (1999-2010)	USA, n=5849 Mexican Americans aged >20yrs	BIA (lean mass, fat mass, body fat %), waist circumference, waist-to-height ratio, skinfolds	Modelled continuously: BMI per 5kg/m^2, WC per 5cm, Waist to height ratioper 0.5, skinfolds per 5mm, % body fat per 5%, lean mass per 5kg, fat mass per 5kg	All-cause and CVD mortality	Fat mass and CVD mortality: - (men) Fat mass and CVD mortality: + (women) Fat mass and mortality: 0 (men) Fat mass and mortality: + (women) Lean mass and CVD mortality: 0 (men) Lean mass and CVD mortality: + (women) Lean mass and mortality: 0 (men) Lean mass and mortality: - (women)
9	Iliodromiti, et al. (2018)	UK Biobank (2006-2010)	UK, n=296535 aged 40-69yrs	BMI, waist-circumference, waist-to-hip ratio, BIA (body fat %)	All exposures treated as continuous variables (BMI 22kg/m^2 was referent value)	CVD incidence	BMI and CVD: J (men and women combined) WC and CVD: + linear (men and women combined) WHR and CVD: + linear (men and women combined) Body fat % and CVD: + linear (men and women combined)
99	Kahn, et al. (2012)	NHANES III (1988-1994)	USA, n=11437 aged 18-64 yrs	BMI, waist circumference, waist-to-hip ratio, waist-to-height ratio	Modelled continuously per 1 SD increase in each exposure and also in quartiles	All-cause mortality	WC and all-cause mortality: + (men) WC and all-cause mortality: + (women) WHR and all-cause mortality: + (men) WHR and all-cause mortality: + (women) Waist-to-height ratio and all-cause mortality: + (men) Waist-to-height ratio and all-cause mortality: + (women)
100	Katzmarzyk, et al. (2002)	Canada Fitness Survey	Canada, n=10323 aged 20-69yrs	Waist circumference, skinfolds principal component of skinfold residuals (indicates subcutaneous adipose tissue distribution)	Modelled each exposure continuously using polynomial models	All-cause mortality	WC and all-cause mortality: J (men) WC and all-cause mortality: linear + (women) Skinfolds (adiposity) and mortality: J (men), Skinfolds (adiposity) and mortality: linear + (women) BMI and mortality: J (men) BMI and mortality: linear + (women)
101	Kim, et al. (2017)	UK Biobank (2006-2010)	UK, n=403199 aged 40-69 yrs	Grip strength, BMI, waist circumference, % body fat	Per 5kg increase in GS, quintiles of GS within BMI/%body fat/waist circumference categories	All-cause and CVD mortality	Grip strength and all-cause mortality: linear – (men) Grip strength and all-cause mortality: linear – (women) Grip strength and CVD mortality: linear – (men) Grip strength and CVD mortality: linear – (women)

102	Kizer, et al. (2011)	Cardiovascular Health Study	USA, n=3754 aged 65-100yrs	BIA (fat free mass, fat mass) BMI, waist circumference, waist to hip ratio, waist to height ratio	Quintiles	Ischemic stroke incidence, CHD	Fat mass and stroke or CHD: 0 (men) Fat mass and stroke or CHD: 0 (women) Fat free mass and stroke or CHD: 0 (men) Fat free mass and stroke or CHD: 0 (women) WC and stroke: 0 (men) WC and stroke: 0 (women) WHR and stroke: 0 WC and CHD: + WHR and CHD: +
103	Kouvari et al. (2019)	ATTICA and GREECS	Greece, n=10428	Lean mass index and fat mass index created through total body lean and fat mass (indirectly calculated through population formals based on body weight, height, waist circumference) divided by height squared	Tertiles	CVD	Fat mass and CVD: + (men) Fat mass and CVD: + (women) Lean mass and CVD: U (men) Lean mass and CVD: U (women)
54	Lee et al (2018)	Health Professionals Follow-up Study (1987-2012)	USA, n=38006 men aged 40-75 years	Derived predicted lean body mass and fat mass using equations developed by NHANES and based on age, race, height, weight, waist circumference	Quintiles of predicted lean body mass and fat mass	All-cause and cause-specific (CVD, cancer, respiratory, other) mortality	BMI & all-cause mortality: J (men) Fat mass & all-cause mortality: linear (men) Lean mass & all-cause mortality: U (men) Fat & CVD: linear (men) Lean body mass & CVD: weak U (men) BMI & CVD: U (men)
104	Lee, et al. (2012)	n/a	China, n=3978 aged >65yrs	DEXA (body fat %), waist circumference, waist to hip ratio, relative abdominal fat (abdominal fat/whole body fat)	Quintiles	All-cause and CVD mortality	All-cause mortality and % body fat: - (men) All-cause mortality and % body fat: 0 (women) All-cause mortality and waist circumference: 0 (men) All-cause mortality and waist circumference: 0 (women) All-cause mortality and WHR: 0 (men) All-cause mortality and WHR: 0 (women) CVD mortality and WC: 0 (men) CVD mortality and WC: 0 (women) CVD mortality and % body fat: 0 (men) CVD mortality and % body fat: 0 (women) CVD mortality and WHR: 0 (men) CVD mortality and WHR: 0 (women)
105	Levitan, et al. (2009)	Swedish Mammography Cohort and the Cohort of Swedish Men	Sweden, n=80360 aged 45-79yrs	BMI, waist circumference, waist to hip ratio, waist to height ratio	Continuously (per 1 IQR increase in each exposure)	Heart failure hospitalisation or mortality	WC and CVD: linear + (men) WC and CVD: linear + (women) WHR and CVD: + (men) WHR and CVD: 0 (women) Waist-to-height ratio and CVD: + linear (men) Waist-to-height ratio and CVD: + linear (women)
106	Li, et al. (2018)	NHANES (1999-2002)	USA, n=4449 aged >50 yrs	DEXA (Appendicular lean mass)	Low muscle mass defined as appendicular lean mass (ALM) <19.75kg (M) or <15.02kg (F) and ALM/BMI <0.512 (M) and <0.789kg (F). Based on FNISH Sarcopenia Project definition [1]. Low muscle strength	All-cause mortality	Low muscle alone and mortality: 0 (men and women combined) Low muscle with low strength and mortality: + (men and women combined)
107	Myint, et al. (2014)	EPIC-Norfolk (1997-2000)	UK, n=15062 aged 40-79yrs	BIA (body fat %)	Quartiles of body fat %	All-cause mortality and CVD incidence	Body fat % and mortality: 0 (men) Body fat % and mortality: 0 (women) Body fat % and CVD: 0 (men) Body fat % and CVD: 0 (women)

108	Nalini et al. (2019)	Golestan Cohort Study	Iran, n=50,045 aged 40-75	BMI, waist circumference, waist to hip ratio, waist to height ratio	Quintiles	All cause and CVD mortality	BMI and all-cause mortality: 0 (men) BMI and all-cause mortality: 0 (women) BMI and CVD mortality: + (men) BMI and CVD mortality: + (women) Waist to height ratioand mortality: + (men) Waist to height ratioand mortality: + (women) Waist to height ratioand CVD mortality: + (men) Waist to height ratioand CVD mortality: + (women) WC and mortality: 0 (men) WC and mortality 0 (women) WC and CVD mortality: + (men) WC and CVD mortality: + (women) WHR and mortality: + (men) WHR And mortality: + (women) WHR and CVD mortality: + (men) WHR and CVD mortality: + (women)
109	Newman, et al. (2006)	Health, Aging and Body Composition study	USA, n=29292 aged 70-79yrs	DEXA (leg and arm lean mass), CT scan (thigh muscle area), knee extension strength	Per 1 SD increase	All-cause mortality	Arm or leg lean mass and mortality: 0 (men and women combined) Grip strength and mortality: + (men and women combined)
110	Ofstad et al (2019)	HUNT 2	Norway, n=61,016	BMI, WC, WHR, estimated total body fat (based on the YMCA's gender specific formulas), ABSI	Quartiles	CVD mortality	Body fat (estimated) and CVD mortality: + (men) Body fat (estimated) and CVD mortality: + (women) WC and CVD mortality: + (men) WC and CVD mortality: + (women) BMI and CVD mortality: +
48	Ortega, et al. (2016)	Aerobics Centre Longitudinal Study (1979-2003)	USA, n=60335 aged >20 years	BMI, body fat % determined by hydrostatic weighing or skinfold measurements, fat mass index, fat free mass index, fat free mass	For each exposure: very low <5th percentile, low 5-15th percentile, middle 15th-85th percentile, high 85-95th percentile, very high >95th	CVD mortality	BMI and CVD: + linear (men and women combined) Body fat % and CVD: J (men and women combined) Fat mass index and CVD: J (men and women combined) Fat free mass and CVD: 0 (men and women combined) Fat free mass index and CVD: + (men and women combined)
111	Otsuka, et al (2018)	Longitudinal Study of Aging (1997-2013)	Japan, n=1978 aged 40-79 yrs	DEXA (Appendicular lean mass excluding bones [4])	ALM/leg length, ALM/height, ALM/height^2, ALM/weight*100, ALM/BMI*10	All-cause mortality or disability	Lean mass and mortality: 0 (men) Lean mass and mortality: 0 (women)
112	Padwal, et al. (2016)	Population Health Research Data Repository	Canada, n=54420 aged >40yrs (91% women)	DEXA (body fat %), BMI	Quintiles of BMI and body fat %. Fully adjusted models included both BMI and body fat %	All-cause mortality	BMI and mortality: U (men) BMI and mortality: U (women) Body fat % and mortality: J (men) Body fat % and mortality: reverse J (women)
113	Park, et al. (2014)	KNHANES (2008-2012)	South Korea, n=7208 aged >50yrs	DEXA (ASM, SMI)	SMI normal >32% (men) >25.4% (women), class I sarcopenia 29-32% (men) 22.8-25.4% (women), class II sarcopenia <29% (men) <22.8% (women) - corresponded to 1 and 2 SDs below gender-specific means of younger population [18]	CVD incidence	Sarcopenia and CVD (men): + Sarcopenia and CVD (women): 0
114	Park, et al. (2018)	Korean National Health Insurance Cohort (2008-2013)	South Korea, n=465,629 adults	Weight-adjusted-waist index, waist circumference (WC), BMI, waist-to-height	10 groups of each index	All-cause and CVD mortality	BMI and all-cause mortality: U (men and women combined) WC and all-cause mortality: U (men and women combined) WHR and all-cause mortality: U (men and women combined)

				ratio (WHR), a body shape index (ABSI)			Weight-adjusted-waist index and all-cause mortality: U (men and women combined) ABSI and all-cause mortality: U (men and women combined) Weight-adjusted-waist index and CVD mortality: linear + (men and women combined) A Body Shape Index and CVD mortality: linear + (men and women combined) BMI and CVD: inverse J (men and women combined) WC and CVD: inverse J (men and women combined) WHR and CVD: inverse J (men and women combined)
115	Reis, et al. (2009)	NHANES III (1988-1994)	USA, n=12,228 aged 30-102ys	Waist-to-thigh ratio, waist-to-hip ratio, waist circumference, BMI	BMI categories, quintiles of WC, WHR and waist-to-thigh ratio	All-cause mortality	WHR and mortality: linear + (men) WHR and mortality: 0 (women) Waist-to-height ratio and mortality: + linear (men) Waist-to-height ratio and mortality: + (women) BMI and mortality: U (men) BMI and mortality: U (women) WC and mortality: J (women) WC and mortality: J (men)
116	Reis, et al. (2009)	NHANES III (1988-1994)	USA, n=5,780 aged 30-64yrs	BMI, waist circumference, waist to hip ratio, waist to thigh ratio	Quartiles of each exposure, results stratified by sex and race (white/black)	All-cause mortality	BMI and all-cause mortality: 0 (men) BMI and all-cause mortality: 0 (women) WHR and all-cause mortality: linear + (women) WHR and all-cause mortality: 0 (men) Waist-to-thigh ratio and all-cause mortality: linear + (men) Waist-to-thigh ratio and all-cause mortality: linear + (women) WC and all-cause mortality: 0 (men) WC and all-cause mortality: 0 (women)
117	Rexrode, et al. (2001)	Physicians Health Study	USA, n=16,164 men aged 40-84yrs	Waist circumference, waist to hip ratio, BMI	Quintiles of each exposure	CHD	WC and CVD: linear + (men) WHR and CVD: + linear (men) BMI and CVD: + linear (men)
118	Sim et al (2019)	Perth Longitudinal Study in Aging women	Australia, n=903 older women	DEXA (appendicular lean mass), BMI, grip strength, timed up and go	Various definitions of sarcopenia. Foundation of National Institues of Health (FNIH), European Working Group on Sarcopenia in Older People (EWGSOP), and the adapted FNIH (AUS-POPF) using Australian population-specific cut points (<2 standard deviation below mean of young healthy)	All cause mortality	Lean mass and mortality: 0 (women)
119	Simpson, et al. (2007)	Melbourne Collaborative Cohort Study	Australia, n=41313 aged 27-75yrs	BIA (fat mass, body fat %), BMI, waist circumference, waist to hip ratio	Quintiles	All-cause mortality	BMI and all-cause mortality: U (men) BMI and all-cause mortality: U (women) WC and all-cause mortality: linear + (men) WC and all-cause mortality: linear + (women) WHR and all-cause mortality: linear + (men) WHR and all-cause mortality: linear + (women) Fat mass and all-cause mortality: linear + (men) Fat mass and all-cause mortality: 0 (women) Body fat % and all-cause mortality: linear + (men) Body fat % and all-cause mortality: 0 (women)
46	Spahilari, et al. (2016)	Cardiovascular Health Study	USA, n=1355 aged >65yrs	DEXA (Total, appendicular lean and fat mass)	ALM, fat mass and lean principal components modelled linearly. Fat principal components modelled in quartiles	All-cause, CVD and non-CVD mortality	Appendicular lean mass and CVD: linear – (men and women combined) Appendicular lean mass and mortality: linear - (men and women combined) Fat mass and CVD: linear - (men and women combined) Fat mass and mortality: linear - (men and women combined)

47	Srikanthan, et al. (2014)	NHANES III (1988-1994)	USA, n=3659 men aged >55 and women aged >65yrs	BIA (SMI), non-muscle index (BMI - SMI)	Quartiles of SMI	All-cause mortality	Skeletal muscle index and mortality: weak – (men and women combined)
120	Srikanthan, et al. (2016)	NHANES (1999-2004)	USA, n=6541 aged >20yrs	DEXA (Appendicular skeletal muscle mass index, trunk fat mass index)	4 groups: Low muscle/low fat (ASMI<median, TRFI<median), Low muscle/high fat (ASMI<median, TRFI>=median), High muscle/low fat (ASMI>=median, TRFI<median), high muscle. High fat (ASMI>=median, TRFI>=median)	All-cause and CVD mortality	High muscle/low fat and CVD: - (men and women combined) High muscle/low fat and mortality: - (men and women combined) All other body composition groups and mortality: 0 (men and women combined) All other body composition group and CVD: 0 (men and women combined)
121	Stefan, et al. (2008)	Cooper Centre Longitudinal study (1970-2005)	USA, n=11335 women	BMI, skinfolds (% body fat), waist circumference, waist to height ratio, waist to hip ratio	Categorised as high or normal for each exposure. Cut-offs: Body fat 30%, Waist to hip ratio 0.75, waist to height ratio 0.5	All-cause mortality	Body fat % and all-cause mortality (women): 0 WC and all-cause mortality (women): 0 WHR and all-cause mortality (women): 0 Waist-to-height ratio and all-cause mortality (women): 0 BMI and all-cause mortality (women): 0
122	Sui, et al. (2007)	Aerobics Centre Longitudinal Study (1979-2001)	USA, n=2603 aged >60yrs	Hydrostatic weighing or skinfolds (% body fat, fat mass, fat free mass), waist circumference, BMI	BMI categories, WC categorised as abdominal obese if >88cm (men) or >102cm (women), % Body fat % categorised as obese if >25% (men), >30% (women), quintiles of FFM	All-cause mortality	WC and all-cause mortality: 0 (men and women combined) Body fat % and all-cause mortality: 0 (men and women combined) Fat free mass and all-cause mortality: + (men and women combined)
123	Tanne, et al. (2005)	Israeli Ischemic Heart Disease project	Israel, n=9151 men aged >23 ys	BMI, Subscapular skinfold (SSF), subscapular to triceps skinfold thickness ratio (SFR)	Exposures analysed per 1 SD increase	Stroke and CHD mortality	Trunk obesity and CVD mortality (men): 0 Body fat distribution and CHD (men): + linear Body fat distribution and stroke (men): 0
124	The DECODE Study Group (2008)	DECODE study	Europe, n=15521 aged 30-89yrs	Waist circumference	Abdominal obesity defined as waist circumference >94cm (men) or >80cm (women)	CVD mortality	WC and CVD mortality (men and women combined): 0
125	Thomson, et al. (2016)	Women's Health Initiative Observational Study	USA, n=77505 women	BMI, a body shape index, body adiposity index	Quintiles of ABSI and WC, BMI groups	All-cause mortality	A Body Shape Index and CVD: linear + (women) BMI and CVD: U (women) Body adiposity index and CVD: U (women)
126	Toss, et al. (2012)	n/a	Sweden, n=921 aged >65yrs	DEXA (fat and lean mass)	Assessed continuously per kg	All-cause mortality	Lean mass and mortality: linear - (men) Lean mass and mortality: linear - (women) Fat mass and mortality: linear - (women) Fat mass and mortality: 0 (men)
127	Van Aller et al (2018)	NHANES (1999-2004)	USA, n=3577 aged >=50yrs	DEXA	Body composition phenotype (4 categories based on having low adiposity or high adiposity and low muscle mass or high muscle mass), Trunk FM/ASM ratio, Fat mass/fat free mass ratio. Then defined sarcopenic obese from cut-offs at various percentiles for each of these measures	All cause mortality	Sarcopenic obesity and mortality: + (men) aged 50 - 70 yr Sarcopenic obesity and mortality: + (women) aged 50 - 70 yr Sarcopenic obesity and mortality: 0 (men) aged > 70 yr Sarcopenic obesity and mortality: 0 (women) aged >70 yr
128	Wang, et al. (2013)	Kailuan study	China, n=94733 aged 18-98yrs	BMI, waist circumference, waist-to-hip ratio, waist-to-height ratio	Quintiles	Total stroke, ischemic stroke, haemorrhagic stroke	WC and total stroke: + linear (men and women combined) WHR and total stroke: + linear (men and women combined) Waist-to-height ratio and total stroke: + linear (men and women combined)
129	Wannamethee, et al. (2007)	British Regional Heart Study (1998-2000)	UK, n=4107 men aged 60-79	Mid-upper arm circumference, mid arm muscle circumference, BMI, BIA (Fat mass index, fat free mass index)	Quartiles of each exposure	All-cause mortality	Fat mass and mortality: 0 (men) Fat free mass and mortality: 0 (men) MAMC (muscle) and mortality: - linear (men)

130	Wannamethee, et al. (2014)	British Regional Heart Study (1998-2000)	UK, n=4046 men aged 60-79yrs	Mid-upper arm circumference, mid arm muscle circumference, BMI	Tertiles of MAMC, and results stratified by prior CVD condition (none, coronary heart disease, heart failure)	All-cause mortality	MAMC (muscle) and CHD (men): linear - MAMC (muscle) and heart failure (men): 0
131	Yang, et al. (2019)	n/a	China, n=329 aged >=70yrs from 4 nursing homes	SARC-F and SARC-CalF questionnaires to screen for sarcopenia.	Score of >= 4 (SARC-F) or >=11 (SARC-CalF) indicate sarcopenia	All-cause mortality	Sarcopenia and mortality: + (men and women combined)
132	Yuki, et al. (2017)	Longitudinal Study of Aging (1997-2013)	Japan, n=700 aged 65-79yrs	DEXA (skeletal muscle mass index), grip strength, gait speed	Low muscle mass defined as SMI <7.0 (men), <5.4 (women) [15]. Low grip strength defined as <26kg (men) <18kg (women) [15]. Low gait speed defined as <0.8m/s [15]. Sarcopenia if low SMI and one of low grip strength or low gait speed	All-cause mortality	Sarcopenia and mortality: + (men) Sarcopenia and mortality: 0 (women)
133	Zaslavsky, et al. (2017)	Women's Health Initiative Observational Study (1993-1998)	USA, n=876 frail women aged >65	DEXA (Appendicular, central and total lean and fat mass)	Quartiles of each measurement	All-cause mortality	Lean mass & mortality: 0 (women) Fat mass & mortality: linear - (women)
134	Zhang, et al. (2007)	Shanghai Women's Health Study (1996-2000)	China, n=72773 women aged 40-70yrs	Waist to hip ratio	Quintiles	All-cause and CVD mortality	WHR and mortality: linear + (women) WHR and CVD mortality: linear + (women)
135	Zhu, et al. (2003)	NHANES I & II	USA, n=13369 women aged 25-75yrs	Skinfolds (fat mass, fat free mass)	All exposures analysed as continuous	All-cause mortality	BMI and mortality (women): U Fat free mass and mortality (women): linear - Fat mass and mortality (women): linear -
136	Zong, et al. (2016)	NHANES (1996-2006)	USA, n=9471 aged >20yrs	DEXA (body fat % for whole-body, trunk, leg)	Quartiles of each measure of FM%	All-cause and CVD mortality	Body fat % and CVD: U (men and women combined) Body fat % and all-cause mortality: U (men and women combined)

Acronyms: ABSI: A body shape index; ASMI: Appendicular skeletal muscle mass index (appendicular skeletal muscle mass, kg/height^2, m^2); BAI: Body adiposity index; BIA: bioimpedance analysis; BFMI: Body fat mass index (= fat mass index); BMI: Body mass index (body mass, kg/ height^2, m^2); DEXA: Dual energy x-ray absorptiometry; FFM: Fat free mass; FFMI: Fat free mass index (fat free mass, kg/ height^2, m^2); FM: Fat mass; FMI: Fat mass index (fat mass, kg/ height^2, m^2); GS: Grip strength; KNHANES: Korea National Health and Nutrition Examination Survey; NHANES: National Health and Nutrition Examination Survey; SMI: Skeletal muscle mass index (Skeletal muscle mass of whole body, kg/height^2, m^2)

Table S3. Derivation of variables used in analysis from the UK Biobank questionnaire and interviews.

Covariate	Categories used in analysis	UK Biobank variable used (question ID) and source
Body composition variables (exposures)		
Appendicular skeletal muscle mass (aSMM)	Quintiles of the residuals from the model of aSMM regressed on height	Arm predicted mass (left) (UKBBID: 23126) ‡, arm predicted mass (right) (UKBBID: 23122) ‡, leg predicted mass (left) (UKBBID: 23118)‡, leg predicted mass (right) (UKBBID: 23114). Height (UKBBID: 12144) ‡.
Fat mass (FM)	Quintiles	Whole body fat mass (UKBBID: 23100)‡
Body composition groups	1. Low aSMM / low FM 2. Low aSMM / moderate FM 3. Low aSMM / high FM 4. Moderate aSMM / low FM 5. Moderate aSMM / moderate FM 6. Moderate aSMM / high FM 7. High aSMM / low FM 8. High aSMM / moderate FM 9. High aSMM / high FM	Tertiles of aSMM within tertiles of FM derived from: arm predicted mass (left) (UKBBID: 23126) ‡, arm predicted mass (right) (UKBBID: 23122) ‡, leg predicted mass (left) (UKBBID: 23118)‡, leg predicted mass (right) (UKBBID: 23114), Whole body fat mass (UKBBID: 23100)‡, Height (UKBBID: 12144) ‡. Low aSMM, residuals of aSMM regressed on height: -10.82 - ≤-0.97 (men), -5.88 - ≤ -0.57 (women) Moderate aSMM: residuals of aSMM regressed on height: -0.97- ≤ 0.85 (men), -0.57 - ≤ 0.45 (women) High aSMM: residuals of aSMM regressed on height: 0.85 - ≤ 14.50 (men), 0.46 - ≤ 11.99 (women) Low FM, kg: 5.0 - ≤ 18.1 (men), 5.0 - ≤ 21.4 (women) Moderate FM: 18.2 - ≤ 24.1 (men), 21.5 - ≤ 28.8 (women) High FM: 24.2 - ≤ 98.6 (men), 28.9 - ≤ 109.8 (women)
BMI	Continuous (kg/m^2)	Body mass index (UKBBID: 21001)‡
Waist circumference	Continuous (cm)	Waist circumference (UKBBID: 48)‡
Grip strength	Continuous (kg)	Hand grip strength (left) (UKBBID: 46)‡, Hand grip strength (right) (UKBBID: 47)‡
Sociodemographic characteristics		
Sex	Men Women	Sex (UKBBID: 31)*
Education	Higher degree (college or university degree, or professional qualifications) Any school degree (A levels, AS levels, O levels, GCSEs or CSEs) Vocational qualifications (NVQ, HND or HNC) Other (none of the above qualifications)	Qualifications (UKBBID: 6138)†
Townsend index	Quintiles (high index indicates most deprivation)	Townsend index (UKBBID: 189)*
Lifestyle factors		
Smoking status	Never Current Previous	Smoking status (UKBBID: 20116)†
Alcohol intake	None Occasional (<1 unit/week) Moderate (1-14 units/week) Heavy (>14 units/week)	Alcohol intake frequency (UKBBID: 1558)† Depending on the participants' response, they were asked how much they consumed per week or month of the following alcoholic drinks:

		Red wine (UKBBID: 4407, 1568)†; champagne and white wine (UKBBID: 4418, 1578)†; beer and cider (UKBBID: 4429, 1588)†; spirits (UKBBID: 4440, 1598)†; fortified wine (UKBBID: 4451, 1608)†; other (UKBBID: 4462, 5364)†.
Saturated fat score	None Low Medium High Unknown	Beef intake (UKBBID: 1369)†, cheese intake (UKBBID: 1408)†, pork intake (UKBBID: 1389)†, lamb intake (UKBBID: 1379)†, processed meat intake (UKBBID: 1349), spread type (UKBBID: 1428)† The amount of each food eaten per week was totalled, then split into groups based off tertiles (with 'none' subsequently separated from the low category).
Fruit and vegetable score	None Low Medium High Unknown	Fresh fruit intake (UKBBID: 1309)†, raw vegetable intake (UKBBID: 1299)†, cooked vegetable intake (UKBBID: 1289). The amount of each food eaten per week was totalled, then split into groups based off tertiles (with 'none' subsequently separated from the low category).
Oily fish score	Unknown None Low Medium High	Oily fish intake (UKBBID: 1329)† The amount of oily fish per week was split into groups based off tertiles (with 'none' subsequently separated from the low category).
Physical activity (IPAQ MET scores)	Low Moderate High	Number of days/week of vigorous physical activity 10+ minutes (UKBBID: 904)†; Duration of vigorous activity (UKBBID: 914)† Number of days/week of moderate physical activity 10+ minutes (UKBBID: 884)†; Duration of moderate activity (UKBBID: 894)† Number of days/week walked 10+ minutes (UKBBID: 864)†; Duration of walks (UKBBID: 874)†
Medical history		
Type 2 diabetes	No Yes (if diagnosed by doctor or taking insulin for diabetes)	Diabetes diagnosed by doctor (UKBBID: 2443)† Medication for cholesterol, blood pressure or diabetes (men) (UKBBID: 6177)†; Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones (women) (UKBBID: 6153)†
Hypertension	No Yes (if diagnosed by doctor, had an SBP >140mmHg, DBP >90mmHg or taking medication for blood pressure)	Vascular/heart problems diagnosed by doctor (high blood pressure is one response) (UKBBID: 6150)† Systolic blood pressure, automated reading / manual reading (UKBBID: 4080 / 93)‡ Diastolic blood pressure, automated reading / manual reading (UKBBID: 4079 / 94)‡ Medication for cholesterol, blood pressure or diabetes (men) (UKBBID: 6177)†; Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones (women) (UKBBID: 6153)†
Cholesterol	No Yes (if taking cholesterol-lowering medication)	Medication for cholesterol, blood pressure or diabetes (men) (UKBBID: 6177)†; Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones (women) (UKBBID: 6153)†; blood lipids (UKBBID: 30690,30760,30870)
Prior cancer	No Yes (if cancer had been previously diagnosed by a doctor)	Cancer diagnosed by doctor (UKBBID: 2453)†
Menopause	No Yes (if responded to questions saying they have experienced the menopause)	Had menopause (women only) (UKBBID 2724)†

*Recruitment questions
†Touchscreen questions
‡Physical measurements

Table S4. Baseline characteristics of the study population according to appendicular skeletal muscle mass and fat mass quintiles.

	Men appendicular skeletal muscle mass (aSMM) quintiles, range (kg)					Men fat mass (FM) quintiles, range (kg)					Total
	13.5 - ≤ 24.0	24.1 - ≤ 26.0	26.1 - ≤ 27.6	27.7 - ≤ 30.0	30.1 - ≤ 54.5	5.0 - ≤ 15.7	15.8 - ≤ 19.4	19.5 - ≤ 22.9	23.0 - ≤ 27.5	27.6 - ≤ 98.6	
Age at recruitment, mean (SD)	61.0 (6.4)	58.2 (7.4)	56.0 (7.8)	54.0 (7.9)	51.7 (7.8)	54.9 (8.3)	56.0 (8.2)	56.5 (8.1)	56.7 (8.0)	56.9 (7.8)	56.2 (8.1)
aSMM (kg), mean (SD)	24.6 (2.9)	25.9 (2.8)	26.9 (2.9)	28.1 (3.0)	30.5 (3.6)	24.6 (2.7)	25.7 (2.7)	26.7 (2.7)	28.0 (2.8)	31.0 (3.6)	27.2 (3.7)
FM (kg), mean (SD)	22.4 (7.1)	21.6 (7.2)	21.4 (7.4)	21.5 (7.8)	22.2 (9.2)	12.4 (2.4)	17.5 (1.1)	21.0 (1.0)	24.9 (1.3)	33.6 (6.2)	21.8 (7.8)
Body mass index (BMI), mean (SD)	26.0 (3.5)	26.8 (3.5)	27.4 (3.6)	28.2 (3.8)	29.7 (4.4)	23.3 (1.8)	25.6 (1.6)	27.1 (1.6)	29.0 (1.8)	33.1 (3.5)	27.6 (4.0)
Weight (kg), mean (SD)	81.1 (12.1)	83.0 (12.1)	84.9 (12.4)	87.3 (13.0)	92.6 (15.1)	71.7 (7.0)	78.7 (6.3)	84.0 (6.2)	90.3 (6.5)	104.3 (11.8)	85.8 (13.6)
Height (cm), mean (SD)	176.6 (6.7)	175.9 (6.7)	175.8 (6.7)	176.0 (6.7)	176.6 (6.7)	175.3 (6.8)	175.5 (6.6)	176.0 (6.5)	176.6 (6.6)	177.6 (6.7)	176.2 (6.7)
Higher education, n (%)	12740 (39.7)	13085 (40.7)	13140 (40.9)	13096 (40.7)	12645 (39.3)	13909 (43.1)	13669 (42.1)	12987 (40.6)	12406 (38.8)	11735 (36.7)	64706 (40.2)
Current smokers, n (%)	3714 (11.6)	3431 (10.7)	3573 (11.1)	3563 (11.1)	3724 (11.6)	4366 (13.5)	3600 (11.1)	3368 (10.5)	3385 (10.6)	3286 (10.3)	18005 (11.2)
Low fruit and vegetable intake, n (%)	14779 (46.0)	14122 (43.9)	13977 (43.5)	13996 (43.5)	13367 (41.6)	13624 (42.2)	13909 (42.8)	14191 (44.3)	14168 (44.3)	14349 (44.8)	70241 (43.7)
High saturated intake, n (%)	11706 (36.4)	11786 (36.6)	11647 (36.2)	11637 (36.2)	11778 (36.6)	10457 (32.4)	11354 (34.9)	11699 (36.6)	12111 (37.9)	12933 (40.4)	58554 (36.4)
Low oily fish intake, n (%)	10919 (34.0)	11292 (35.1)	11342 (35.3)	11807 (36.7)	11988 (37.3)	11197 (34.7)	11452 (35.2)	11518 (36.0)	11520 (36.0)	11661 (36.4)	57348 (35.7)
Heavy drinkers, n (%)	19948 (62.1)	19885 (61.8)	19841 (61.7)	19608 (61.0)	18666 (58.1)	17562 (54.4)	19859 (61.1)	20297 (63.4)	20535 (64.2)	19695 (61.5)	97948 (60.9)
Low physical activity, n (%)	7247 (22.6)	6670 (20.7)	6300 (19.6)	5901 (18.3)	5518 (17.2)	4580 (14.2)	5351 (16.5)	6030 (18.8)	6918 (21.6)	8757 (27.4)	31636 (19.7)
Hypertension, n (%)	20146 (62.7)	18878 (58.7)	18102 (56.3)	17362 (54.0)	17370 (54.0)	12683 (39.3)	16508 (50.8)	18523 (57.9)	20600 (64.4)	23544 (73.5)	91858 (57.1)
Type 2 diabetes, n (%)	1300 (4.1)	1250 (3.9)	1156 (3.6)	1191 (3.7)	1408 (4.4)	388 (1.2)	666 (2.1)	906 (2.8)	1462 (4.6)	2883 (9.0)	6305 (3.9)
Cancer history (>5 years ago), n (%)	1176 (3.7)	927 (2.9)	816 (2.5)	662 (2.1)	652 (2.0)	780 (2.4)	836 (2.6)	856 (2.7)	872 (2.7)	889 (2.8)	4233 (2.6)
Cholesterol medication, n (%)	6204 (19.5)	5171 (16.2)	4646 (14.6)	4145 (13.0)	3842 (12.0)	2175 (6.8)	3807 (11.8)	4664 (14.7)	5922 (18.6)	7440 (23.4)	24008 (15.0)
	Women appendicular skeletal muscle mass (aSMM) quintiles, range (kg)					**Women fat mass (FM) quintiles, range (kg)**					**Total**
	10.3 - ≤ 16.5	16.6 - ≤ 17.5	17.6 - ≤ 18.6	18.6 - ≤ 19.9	20.0 - ≤ 39.2	5.0 - ≤ 18.5	18.6 - ≤ 22.8	22.9 - ≤ 27.1	27.2 - ≤ 33.3	33.4 - ≤ 109.8	
Age at recruitment, mean (SD)	58.9 (7.0)	57.1 (7.6)	55.8 (7.9)	54.6 (8.0)	53.2 (8.1)	54.1 (8.1)	55.7 (8.0)	56.6 (7.9)	57.0 (7.7)	56.4 (7.8)	55.9 (8.0)
aSMM (kg), mean (SD)	17.0 (1.7)	17.5 (1.7)	18.0 (1.8)	18.7 (1.9)	20.3 (2.5)	16.6 (1.5)	17.3 (1.4)	17.9 (1.4)	18.8 (1.5)	21.1 (2.3)	18.3 (2.3)
FM (kg), mean (SD)	27.7 (8.5)	26.0 (8.4)	25.5 (8.8)	25.3 (9.5)	27.0 (11.9)	15.2 (2.6)	20.7 (1.2)	24.9 (1.3)	29.9 (1.7)	41.1 (7.4)	26.3 (9.6)
Body mass index (BMI), mean (SD)	25.9 (4.2)	26.0 (4.2)	26.3 (4.4)	26.8 (4.8)	28.5 (6.0)	21.6 (1.7)	24.0 (1.5)	25.9 (1.7)	28.3 (2.0)	33.9 (4.3)	26.7 (4.9)
Weight (kg), mean (SD)	69.1 (11.6)	68.8 (11.6)	69.4 (12.1)	70.8 (12.9)	75.9 (16.3)	56.4 (4.7)	63.2 (3.7)	68.5 (3.7)	75.3 (4.2)	90.9 (11.1)	70.8 (13.3)
Height (cm), mean (SD)	163.4 (6.2)	162.6 (6.1)	162.5 (6.2)	162.6 (6.2)	163.3 (6.2)	161.6 (6.1)	162.5 (6.1)	162.9 (6.1)	163.3 (6.1)	164.0 (6.2)	162.9 (6.2)
Higher education, n (%)	14330 (36.6)	15246 (38.9)	16033 (40.9)	16513 (42.2)	17056 (43.6)	18112 (45.5)	16503 (42.6)	15834 (39.8)	14520 (37.7)	14209 (36.4)	79178 (40.4)
Current smokers, n (%)	3039 (7.8)	3164 (8.1)	3231 (8.2)	3258 (8.3)	3377 (8.6)	3792 (9.5)	3166 (8.2)	3151 (7.9)	3062 (8.0)	2898 (7.4)	16069 (8.2)
Low fruit and vegetable intake, n (%)	12608 (32.2)	12333 (31.5)	11874 (30.3)	11521 (29.4)	10910 (27.9)	12125 (30.5)	11518 (29.7)	11756 (29.6)	11613 (30.2)	12234 (31.3)	59246 (30.3)
High saturated intake, n (%)	11699 (29.9)	11407 (29.1)	11252 (28.7)	11485 (29.3)	11212 (28.6)	10415 (26.2)	10824 (27.9)	11615 (29.2)	11762 (30.6)	12439 (31.9)	57055 (29.1)
Low oily fish intake, n (%)	12200 (31.2)	12678 (32.4)	12619 (32.2)	13034 (33.3)	13137 (33.6)	12971 (32.6)	12521 (32.3)	12669 (31.8)	12425 (32.3)	13082 (33.5)	63668 (32.5)
Heavy drinkers, n (%)	12955 (33.1)	12840 (32.8)	13025 (33.2)	13134 (33.5)	12318 (31.5)	13562 (34.1)	13654 (35.2)	13525 (34.0)	12561 (32.6)	10970 (28.1)	64272 (32.8)
Low physical activity, n (%)	10117 (25.8)	8974 (22.9)	8431 (21.5)	7986 (20.4)	7837 (20.0)	6398 (16.1)	7114 (18.4)	8288 (20.8)	9385 (24.4)	12160 (31.1)	43345 (22.1)
Hypertension, n (%)	19371 (49.5)	17669 (45.1)	16440 (42.0)	15877 (40.5)	16330 (41.7)	11345 (28.5)	14192 (36.6)	17091 (43.0)	19293 (50.1)	23766 (60.9)	85687 (43.8)
Type 2 diabetes, n (%)	635 (1.6)	673 (1.7)	669 (1.7)	805 (2.1)	1250 (3.2)	239 (0.6)	363 (0.9)	524 (1.3)	860 (2.2)	2046 (5.3)	4032 (2.1)
Cancer history (>5 years ago), n (%)	2540 (6.5)	2298 (5.9)	2010 (5.1)	1933 (4.9)	1845 (4.7)	1912 (4.8)	2052 (5.3)	2278 (5.7)	2214 (5.8)	2170 (5.6)	10626 (5.4)
Cholesterol medication, n (%)	4294 (11.0)	3605 (9.3)	3163 (8.1)	3015 (7.8)	3080 (7.9)	1536 (3.9)	2350 (6.1)	3349 (8.5)	4201 (11.0)	5721 (14.8)	17157 (8.8)
Post-menopausal, n (%)	28352 (72.4)	25700 (65.6)	23352 (59.6)	21067 (53.8)	17594 (44.9)	21266 (53.5)	22970 (59.3)	24686 (62.1)	24170 (62.8)	22973 (58.8)	116065 (59.3)

χ^2 test for trend: p<0.05 for all characteristics across the aSMM and FM quintiles. All characteristics were determined at the baseline assessment clinic through touch-screen questionnaires, interviews and/or physical measurements. Higher education: college or university degree or professional qualifications. Low physical activity: <600 metabolic equivalent (MET)-minutes per week[32] . Heavy alcohol drinker: >14 units of alcohol a week)[137]. Hypertension: systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg, was diagnosed by a doctor or were taking medication to lower blood pressure. Diabetes and cholesterol: taking medication for these conditions or diagnosed by a doctor. Cancer history: diagnosed with cancer >5 years ago (those with more recent cancer had been excluded). Low fruit and vegetable intake: the lowest consumption tertile (< 21 portions per week). High saturated fat: the highest saturated fat tertile, based off portions per week of beef, lamb, pork and whether they consumed animal or plant-based spreads. Low oily fish: lowest consumption tertile (< 1 portion per week).

Table S5. Baseline characteristics of the study population according to body composition groups.

Men	Low Muscle / Low Fat	Med Muscle / Low Fat	High Muscle / Low Fat	Low Muscle / Med Fat	Med Muscle / Med Fat	High Muscle / Med Fat	Low Muscle / High Fat	Med Muscle / High Fat	High Muscle / High Fat
Age at recruitment, mean (SD)	59.0 (7.3)	55.1 (8.0)	51.7 (8.0)	60.3 (6.7)	56.3 (7.7)	52.6 (8.0)	60.7 (6.5)	56.7 (7.6)	53.2 (7.8)
Appendicular skeletal muscle (kg), mean (SD)	22.9 (2.1)	24.9 (1.9)	27.1 (2.3)	24.5 (1.9)	26.6 (1.8)	29.1 (2.2)	27.3 (2.6)	29.6 (2.5)	32.7 (3.3)
Fat mass (kg), mean (SD)	14.6 (2.8)	14.3 (2.8)	13.8 (3.1)	21.0 (1.7)	21.0 (1.7)	21.0 (1.7)	29.8 (5.5)	30.0 (5.8)	31.3 (7.2)
Body mass index (BMI), mean (SD)	22.8 (1.6)	24.1 (1.6)	25.4 (1.8)	25.7 (1.3)	27.2 (1.2)	28.6 (1.4)	29.7 (2.8)	31.4 (2.9)	33.5 (3.6)
Weight, mean (SD)	70.3 (6.3)	74.0 (6.3)	78.3 (7.0)	79.7 (5.3)	83.8 (5.1)	88.8 (5.9)	93.6 (9.7)	98.4 (10.0)	105.4 (12.3)
Height, mean (SD)	175.4 (6.8)	175.1 (6.7)	175.5 (6.7)	176.1 (6.6)	175.7 (6.5)	176.2 (6.6)	177.4 (6.6)	177.0 (6.6)	177.3 (6.7)
Higher education, n (%)	7753 (42.8)	7814 (43.2)	7626 (42.1)	7240 (41.0)	7309 (41.3)	6949 (39.3)	6488 (36.4)	6760 (37.9)	6767 (38.0)
Current smokers, n (%)	2406 (13.3)	2139 (11.8)	2285 (12.6)	1850 (10.5)	1882 (10.6)	1951 (11.0)	1768 (9.9)	1823 (10.2)	1901 (10.7)
Low fruit and vegetable intake, n (%)	8143 (45.0)	7708 (42.6)	7199 (39.8)	7903 (44.7)	7827 (44.3)	7593 (42.9)	8095 (45.5)	7900 (44.3)	7873 (44.2)
High saturated intake, n (%)	6078 (33.6)	6014 (33.2)	6006 (33.2)	6423 (36.4)	6406 (36.2)	6510 (36.8)	6978 (39.2)	7064 (39.6)	7075 (39.7)
Low oily fish intake, n (%)	6141 (33.9)	6302 (34.8)	6510 (36.0)	5948 (33.7)	6296 (35.6)	6698 (37.9)	6280 (35.3)	6539 (36.7)	6634 (37.2)
Heavy drinkers, n (%)	10276 (56.8)	10373 (57.3)	10233 (56.5)	11242 (63.6)	11271 (63.7)	10997 (62.2)	11508 (64.7)	11370 (63.8)	10498 (58.9)
Low physical activity, n (%)	3250 (18.0)	2669 (14.7)	2204 (12.2)	3657 (20.7)	3413 (19.3)	2993 (16.9)	4695 (26.4)	4475 (25.1)	4280 (24.0)
Hypertension, n (%)	8641 (47.7)	7727 (42.7)	7208 (39.8)	10898 (61.7)	10187 (57.6)	9600 (54.3)	12947 (72.7)	12437 (69.8)	12213 (68.6)
Diabetes, n (%)	298 (1.6)	245 (1.4)	274 (1.5)	558 (3.2)	505 (2.9)	500 (2.8)	1233 (6.9)	1245 (7.0)	1447 (8.2)
Cholesterol medication, n (%)	1930 (10.7)	1505 (8.4)	1195 (6.7)	3179 (18.1)	2527 (14.4)	2093 (11.9)	4515 (25.5)	3723 (21.0)	3341 (18.9)
Cancer diagnosed by doctor (>5 years ago), n (%)	573 (3.2)	407 (2.3)	373 (2.1)	591 (3.3)	480 (2.7)	340 (1.9)	651 (3.7)	468 (2.6)	350 (2.0)
Women	**Low Muscle / Low Fat**	**Med Muscle / Low Fat**	**High Muscle / Low Fat**	**Low Muscle / Med Fat**	**Med Muscle / Med Fat**	**High Muscle / Med Fat**	**Low Muscle / High Fat**	**Med Muscle / High Fat**	**High Muscle / High Fat**
Age at recruitment, mean (SD)	57.1 (7.7)	54.6 (8.0)	52.2 (7.9)	58.7 (7.1)	56.6 (7.8)	54.4 (8.1)	58.7 (7.1)	56.5 (7.7)	54.7 (8.0)
Appendicular skeletal muscle (kg), mean (SD)	15.7 (1.0)	16.7 (1.0)	18.0 (1.3)	16.7 (1.0)	17.8 (0.9)	19.2 (1.2)	18.7 (1.5)	20.0 (1.5)	22.1 (2.3)
Fat mass (kg), mean (SD)	17.8 (2.8)	17.1 (3.1)	16.4 (3.4)	25.1 (2.1)	24.9 (2.1)	24.9 (2.1)	36.1 (6.7)	36.3 (6.9)	38.8 (8.8)
Body mass index (BMI), mean (SD)	21.8 (1.7)	22.5 (1.8)	23.1 (1.9)	24.9 (1.6)	25.9 (1.6)	26.9 (1.8)	30.0 (3.5)	31.5 (3.7)	34.0 (4.7)
Weight, mean (SD)	56.8 (4.4)	58.6 (4.8)	60.9 (5.3)	66.1 (3.6)	68.4 (3.6)	71.5 (4.0)	80.9 (9.2)	84.0 (9.5)	90.9 (12.6)
Height, mean (SD)	161.6 (6.2)	161.6 (6.1)	162.5 (6.1)	163.1 (6.1)	162.6 (6.1)	163.1 (6.2)	164.2 (6.2)	163.5 (6.1)	163.6 (6.2)
Higher education, n (%)	9086 (41.3)	9855 (44.8)	10384 (47.2)	8069 (37.2)	8681 (39.9)	9277 (42.7)	7548 (35.0)	7976 (37.0)	8302 (38.5)
Current smokers, n (%)	1977 (9.0)	1946 (8.8)	2027 (9.2)	1652 (7.6)	1721 (7.9)	1795 (8.3)	1596 (7.4)	1618 (7.5)	1737 (8.1)
Low fruit and vegetable intake, n (%)	7248 (33.0)	6664 (30.3)	6047 (27.5)	6700 (30.9)	6491 (29.9)	6072 (28.0)	6863 (31.8)	6737 (31.2)	6424 (29.8)
High saturated intake, n (%)	5875 (26.7)	5960 (27.1)	5867 (26.7)	6416 (29.5)	6303 (29.0)	6340 (29.2)	6864 (31.8)	6720 (31.2)	6710 (31.1)
Low oily fish intake, n (%)	6984 (31.8)	7159 (32.5)	7342 (33.4)	6680 (30.8)	6845 (31.5)	7228 (33.3)	6969 (32.3)	7150 (33.1)	7311 (33.9)
Heavy drinkers, n (%)	7167 (32.6)	7649 (34.8)	7893 (35.9)	7415 (34.1)	7400 (34.0)	7428 (34.2)	6840 (31.7)	6542 (30.3)	5752 (26.7)
Low physical activity, n (%)	4468 (20.3)	3679 (16.7)	2965 (13.5)	4922 (22.7)	4536 (20.9)	4116 (19.0)	6478 (30.0)	6130 (28.4)	6051 (28.1)
Hypertension, n (%)	7938 (36.1)	6817 (31.0)	5918 (26.9)	9983 (46.0)	9342 (43.0)	8681 (40.0)	12572 (58.3)	11981 (55.5)	12455 (57.8)
Diabetes, n (%)	155 (0.7)	138 (0.6)	175 (0.8)	247 (1.1)	285 (1.3)	362 (1.7)	626 (2.9)	786 (3.7)	1258 (5.9)
Cholesterol medication, n (%)	1357 (6.2)	979 (4.5)	695 (3.2)	2057 (9.5)	1829 (8.5)	1607 (7.5)	3079 (14.4)	2720 (12.7)	2834 (13.3)
Cancer diagnosed by doctor (>5 years ago) , n (%)	1270 (5.8)	1077 (4.9)	932 (4.2)	1433 (6.6)	1173 (5.4)	1092 (5.0)	1358 (6.3)	1175 (5.5)	1116 (5.2)
Menopause, n (%)	14788 (67.3)	12378 (56.3)	9432 (42.9)	15674 (72.2)	13585 (62.5)	11126 (51.2)	15109 (70.1)	13077 (60.6)	10896 (50.6)

All characteristics were determined at the baseline assessment clinic through touch-screen questionnaires, interviews and/or physical measurements. Higher education: has a college or university degree or professional qualifications. Low physical activity: <600 metabolic equivalent (MET)-minutes per week[32]. Heavy alcohol drinker: drinking >14 units of alcohol a week[137]). Hypertension: if participants had a systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg, had been diagnosed by a doctor or were taking medication to lower blood pressure. Diabetes and high cholesterol: participants were taking medication for these conditions or diagnosed by a doctor. Cancer history: diagnosed with cancer >5 years ago (those with more recent cancer had been excluded). Low fruit and vegetable intake: the lowest consumption tertile (< 21 portions per week). High saturated fat: the highest saturated fat tertile, based off portions per week of beef, lamb, pork and whether they consumed animal or plant-based spreads. Low oily fish: lowest consumption tertile (< 1 portion per week).

Table S6. Partial correlation coefficients between appendicular skeletal muscle mass, fat mass and height, adjusted for age at recruitment.

Men	**aSMM**	**FM**	**Height**
aSMM	-	0.7132	0.5185
FM	0.7132	-	0.1375
Height	0.5185	0.1375	-
Women	**aSMM**	**FM**	**Height**
aSMM	-	0.7771	0.4403
FM	0.7771	-	0.1544
Height	0.4403	0.1544	-

Table S7. CVD sequential model adjustment.

Hazard ratios of CVD associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM)

	Quintile	No. events	Age and height adjusted	+ Socio-demographics*	+ Lifestyle factors†	+ Medical history‡	+ Mutual adjustment for ASM or FM
Appendicular skeletal muscle mass (aSMM)							
Men	1	4373	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	3715	0.99 (0.95 - 1.03)	1.00 (0.96 - 1.04)	1.01 (0.97 - 1.06)	1.01 (0.97 - 1.06)	1.02 (0.97 - 1.06)
	3	3385	1.03 (0.98 - 1.08)	1.04 (1.00 - 1.09)	1.06 (1.01 - 1.11)	1.06 (1.01 - 1.11)	1.07 (1.02 - 1.12)
	4	3055	1.07 (1.02 - 1.12)	1.08 (1.03 - 1.14)	1.11 (1.06 - 1.16)	1.10 (1.05 - 1.15)	1.10 (1.05 - 1.16)
	5	2971	1.25 (1.19 - 1.31)	1.26 (1.20 - 1.32)	1.29 (1.23 - 1.35)	1.27 (1.21 - 1.33)	1.25 (1.19 - 1.31)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001	p<0.001	0.014
		χ^2	103	106	120	106	87
Women	1	2617	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	2182	0.92 (0.87 - 0.97)	0.93 (0.88 - 0.98)	0.93 (0.88 - 0.99)	0.93 (0.88 - 0.98)	0.95 (0.90 - 1.01)
	3	1848	0.85 (0.80 - 0.91)	0.87 (0.82 - 0.92)	0.87 (0.82 - 0.93)	0.87 (0.82 - 0.92)	0.89 (0.84 - 0.95)
	4	1753	0.89 (0.83 - 0.94)	0.90 (0.85 - 0.96)	0.91 (0.86 - 0.97)	0.90 (0.85 - 0.96)	0.92 (0.87 - 0.98)
	5	1885	1.08 (1.02 - 1.15)	1.09 (1.03 - 1.16)	1.09 (1.03 - 1.16)	1.06 (1.00 - 1.13)	1.03 (0.97 - 1.09)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
		χ^2	69	63	59	51	26
Fat mass (FM)							
Men	1	2565	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	3097	1.14 (1.08 - 1.20)	1.14 (1.08 - 1.20)	1.15 (1.09 - 1.21)	1.14 (1.09 - 1.21)	1.16 (1.10 - 1.22)
	3	3393	1.25 (1.19 - 1.31)	1.24 (1.18 - 1.31)	1.25 (1.19 - 1.32)	1.24 (1.18 - 1.31)	1.26 (1.20 - 1.33)
	4	3835	1.42 (1.35 - 1.49)	1.40 (1.33 - 1.47)	1.40 (1.33 - 1.48)	1.38 (1.31 - 1.45)	1.40 (1.33 - 1.47)
	5	4609	1.76 (1.68 - 1.85)	1.71 (1.63 - 1.79)	1.71 (1.62 - 1.79)	1.65 (1.57 - 1.73)	1.65 (1.57 - 1.73)
	Non-linearity p-value		p<0.001	0.002	0.005	0.024	0.081
		χ^2	654	571	638	455	453
Women	1	1313	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	1653	1.16 (1.08 - 1.25)	1.15 (1.07 - 1.24)	1.16 (1.08 - 1.25)	1.16 (1.08 - 1.24)	1.16 (1.08 - 1.25)
	3	2037	1.32 (1.23 - 1.42)	1.30 (1.21 - 1.39)	1.31 (1.22 - 1.40)	1.30 (1.21 - 1.39)	1.31 (1.22 - 1.40)
	4	2357	1.56 (1.46 - 1.67)	1.51 (1.41 - 1.62)	1.51 (1.41 - 1.62)	1.49 (1.39 - 1.59)	1.50 (1.40 - 1.61)
	5	2925	2.07 (1.94 - 2.21)	1.97 (1.84 - 2.10)	1.95 (1.82 - 2.08)	1.88 (1.76 - 2.01)	1.88 (1.76 - 2.01)
	Non-linearity p-value		p<0.001	p<0.001	0.003	0.016	0.038
		χ^2	639	540	491	430	429

Test for non-linearity across quintiles conducted using LRTs with 4df (p<0.05 indicates significant departure from linearity). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) obtained using Cox proportional hazard regression. Age at risk adjusted for by using age during study as the underlying timescale for Cox regression. Height adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. *Sociodemographic characteristics: Townsend index of deprivation, education. †Lifestyle factors: smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake. ‡Medical history: diabetes, cancer history, menopause (women). χ^2 values were calculated from likelihood ratio tests to estimate the improvement in model fit.

Table S8. Mortality sequential model adjustment.

Hazard ratios of all-cause mortality associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM)

	Quintile	No. events	Age and height adjusted	+ Socio-demographics*	+ Lifestyle factors†	+ Medical history‡	+ Mutual adjustment for ASM or FM
Appendicular skeletal muscle mass (aSMM)							
Men	1	2706	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	2013	0.94 (0.88 - 0.99)	0.95 (0.90 - 1.01)	0.97 (0.92 - 1.03)	0.97 (0.92 - 1.03)	0.98 (0.92 - 1.04)
	3	1673	0.94 (0.88 - 1.00)	0.96 (0.90 - 1.02)	0.99 (0.93 - 1.05)	0.99 (0.93 - 1.05)	0.99 (0.93 - 1.06)
	4	1378	0.94 (0.88 - 1.00)	0.96 (0.89 - 1.02)	1.00 (0.93 - 1.07)	0.99 (0.93 - 1.06)	1.00 (0.93 - 1.06)
	5	1312	1.12 (1.05 - 1.20)	1.13 (1.06 - 1.21)	1.19 (1.11 - 1.27)	1.17 (1.09 - 1.25)	1.16 (1.08 - 1.24)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001	p<0.001	0.002
		χ^2	33	30	34	29	25
Women	1	1732	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	1391	0.91 (0.85 - 0.98)	0.92 (0.86 - 0.99)	0.93 (0.86 - 0.99)	0.92 (0.86 - 0.99)	0.93 (0.87 - 1.00)
	3	1255	0.92 (0.86 - 0.99)	0.93 (0.87 - 1.00)	0.94 (0.87 - 1.01)	0.94 (0.88 - 1.01)	0.95 (0.89 - 1.03)
	4	1176	0.96 (0.89 - 1.03)	0.97 (0.90 - 1.04)	0.98 (0.91 - 1.06)	0.98 (0.91 - 1.06)	0.99 (0.92 - 1.07)
	5	1208	1.11 (1.03 - 1.20)	1.11 (1.03 - 1.20)	1.13 (1.05 - 1.22)	1.12 (1.03 - 1.20)	1.11 (1.03 - 1.19)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001	p<0.001	0.003
		χ^2	31	28	29	26	21
Fat mass (FM)							
Men	1	1573	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	1542	0.89 (0.83 - 0.95)	0.89 (0.83 - 0.95)	0.90 (0.84 - 0.96)	0.89 (0.83 - 0.96)	0.90 (0.84 - 0.96)
	3	1727	0.97 (0.91 - 1.04)	0.96 (0.90 - 1.03)	0.97 (0.91 - 1.04)	0.96 (0.90 - 1.03)	0.97 (0.90 - 1.04)
	4	1870	1.05 (0.98 - 1.12)	1.02 (0.96 - 1.1)	1.02 (0.95 - 1.09)	1.00 (0.94 - 1.07)	1.01 (0.94 - 1.08)
	5	2370	1.35 (1.27 - 1.44)	1.28 (1.2 - 1.37)	1.27 (1.19 - 1.35)	1.22 (1.14 - 1.31)	1.22 (1.14 - 1.31)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
		χ^2	198	145	126	101	98
Women	1	1126	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	2	1228	0.97 (0.90 - 1.06)	0.97 (0.89 - 1.05)	0.98 (0.90 - 1.06)	0.98 (0.90 - 1.06)	0.99 (0.91 - 1.07)
	3	1321	0.95 (0.87 - 1.03)	0.94 (0.86 - 1.01)	0.94 (0.86 - 1.02)	0.93 (0.86 - 1.01)	0.94 (0.87 - 1.02)
	4	1414	1.02 (0.94 - 1.10)	0.99 (0.92 - 1.08)	0.98 (0.91 - 1.07)	0.98 (0.90 - 1.06)	0.99 (0.92 - 1.08)
	5	1673	1.27 (1.18 - 1.37)	1.21 (1.12 - 1.31)	1.18 (1.09 - 1.28)	1.16 (1.07 - 1.26)	1.17 (1.08 - 1.26)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
		χ^2	82	62	47	41	37

Test for non-linearity across quintiles conducted using LRTs with 4df (p<0.05 indicates significant departure from linearity). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) obtained using Cox proportional hazard regression. Age at risk adjusted for by using age during study as the underlying timescale for Cox regression. Height adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. *Sociodemographic characteristics: Townsend index of deprivation, education. †Lifestyle factors: smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake. ‡Medical history: diabetes, cancer history, menopause (women). χ^2 values were calculated from likelihood ratio tests to estimate the improvement in model fit.

Table S9. CVD sensitivity analyses.

Hazard ratios of CVD associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM)

	Quintile	Remove first 2 years of follow up		Remove outliers		Remove participants with BMI > 35	
		No. events	HR (95% CI)	No. events	HR (95% CI)	No. events	HR (95% CI)
Appendicular skeletal muscle mass (aSMM)							
Men	1	3804	1 (reference)	4316	1 (reference)	4283	1 (reference)
	2	3250	1.06 (1.01 - 1.11)	3715	1.02 (0.97 - 1.06)	3614	1.03 (0.98 - 1.08)
	3	2939	1.12 (1.06 - 1.17)	3385	1.07 (1.02 - 1.12)	3198	1.07 (1.02 - 1.12)
	4	2666	1.19 (1.13 - 1.25)	3055	1.1 0(1.05 - 1.16)	2800	1.11 (1.06 - 1.17)
	5	2597	1.37 (1.30 - 1.44)	2819	1.23 (1.17 - 1.29)	2448	1.25 (1.18 - 1.31)
Non-linearity p-value			0.038		0.057		0.046
Women	1	2327	1 (reference)	2582	1 (reference)	2505	1 (reference)
	2	1947	0.97 (0.91 - 1.03)	2182	0.95 (0.90 - 1.01)	2075	0.96 (0.90 - 1.01)
	3	1667	0.93 (0.87 - 0.99)	1848	0.89 (0.84 - 0.95)	1699	0.88 (0.83 - 0.94)
	4	1570	0.96 (0.90 - 1.02)	1753	0.92 (0.87 - 0.98)	1555	0.92 (0.86 - 0.98)
	5	1681	1.08 (1.01 - 1.15)	1682	1.01 (0.95 - 1.07)	1375	1.01 (0.94 - 1.08)
Non-linearity p-value			p<0.001		p<0.001		p<0.001
Fat Mass (FM)							
Men	1	2293	1 (reference)	2565	1 (reference)	2565	1 (reference)
	2	2701	1.13 (1.07 - 1.19)	3097	1.16 (1.1 - 1.22)	3097	1.16 (1.10 - 1.22)
	3	2907	1.20 (1.14 - 1.27)	3393	1.26 (1.19 - 1.32)	3393	1.26 (1.19 - 1.32)
	4	3341	1.36 (1.28 - 1.43)	3835	1.40 (1.33 - 1.47)	3828	1.40 (1.33 - 1.47)
	5	4014	1.60 (1.51 - 1.68)	3994	1.62 (1.54 - 1.71)	3460	1.61 (1.53 - 1.70)
Non-linearity p-value			0.038		0.211		0.286
Women	1	1173	1 (reference)	1313	1 (reference)	1313	1 (reference)
	2	1487	1.16 (1.07 - 1.25)	1653	1.16 (1.08 - 1.25)	1652	1.15 (1.07 - 1.24)
	3	1806	1.27 (1.18 - 1.37)	2037	1.30 (1.21 - 1.40)	2037	1.29 (1.21 - 1.39)
	4	2118	1.48 (1.37 - 1.59)	2357	1.50 (1.40 - 1.60)	2351	1.49 (1.39 - 1.59)
	5	2608	1.84 (1.71 - 1.98)	2493	1.82 (1.70 - 1.96)	1856	1.76 (1.63 - 1.89)
Non-linearity p-value			0.026		0.230		0.681

Test for non-linearity across quintiles conducted using LRTs with 4df (p<0.05 indicates significant departure from linearity). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) obtained using Cox proportional hazard regression. Adjusted for age at risk, Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes, cancer history, menopause (women), and mutually adjusted for FM and ASM. Height is adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. For the analysis without outliers, the top and bottom 25% of values were removed.

Table S10. CVD mediation analyses.

Hazard ratios of CVD associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM)

	Quintile	No. events	Adjust for BMI	Adjust for hypertension	Adjust for cholesterol
Appendicular skeletal muscle mass (aSMM)					
Men	1	2861	1 (reference)	1 (reference)	1 (reference)
	2	2457	0.96 (0.92 - 1.01)	1.02 (0.98 - 1.07)	1.03 (0.99 - 1.08)
	3	2209	0.97 (0.93 - 1.02)	1.06 (1.02 - 1.11)	1.08 (1.03 - 1.14)
	4	2004	0.98 (0.93 - 1.03)	1.10 (1.05 - 1.16)	1.14 (1.09 - 1.20)
	5	1907	1.04 (0.99 - 1.10)	1.23 (1.17 - 1.29)	1.28 (1.21 - 1.35)
	Non-linearity p-value		0.015	0.031	0.123
	Main model χ^2		106	87	74
	Adjusted model χ^2		12	79	92
	% Change		87%	9%	20%
Women	1	2617	1 (reference)	1 (reference)	1 (reference)
	2	2182	0.92 (0.87 - 0.97)	0.95 (0.90 - 1.01)	0.93 (0.88 - 0.99)
	3	1848	0.84 (0.79 - 0.89)	0.90 (0.84 - 0.95)	0.87 (0.82 - 0.93)
	4	1753	0.84 (0.79 - 0.90)	0.92 (0.87 - 0.98)	0.94 (0.88 - 1.00)
	5	1885	0.90 (0.85 - 0.96)	1.02 (0.96 - 1.09)	1.04 (0.98 - 1.11)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001
	Main model χ^2		51	26	29
	Adjusted model χ^2		43	23	30
	% Change		17%	12%	3%
Fat mass (FM)					
Men	1	2565	1 (reference)	1 (reference)	1 (reference)
	2	3097	1.05 (0.99 - 1.10)	1.12 (1.06 - 1.18)	1.09 (1.03 - 1.15)
	3	3393	1.06 (1.00 - 1.12)	1.19 (1.13 - 1.25)	1.15 (1.09 - 1.22)
	4	3835	1.09 (1.03 - 1.16)	1.29 (1.22 - 1.36)	1.27 (1.20 - 1.34)
	5	4609	1.10 (1.01 - 1.19)	1.48 (1.41 - 1.56)	1.49 (1.41 - 1.58)
	Non-linearity p-value		0.726	0.102	0.009
	Main model χ^2		455	453	398
	Adjusted model χ^2		8	274	252
	% Change		98%	40%	37%
Women	1	1313	1 (reference)	1 (reference)	1 (reference)
	2	1653	1.07 (0.99 - 1.16)	1.12 (1.05 - 1.21)	1.13 (1.05 - 1.23)
	3	2037	1.13 (1.05 - 1.22)	1.23 (1.15 - 1.32)	1.25 (1.16 - 1.35)
	4	2357	1.21 (1.11 - 1.32)	1.37 (1.28 - 1.47)	1.40 (1.30 - 1.52)
	5	2925	1.29 (1.15 - 1.46)	1.64 (1.54 - 1.76)	1.73 (1.60 - 1.87)
	Non-linearity p-value		0.991	0.119	0.047
	Main model χ^2		430	429	398
	Adjusted model χ^2		20	258	259
	% Change		95%	40%	35%

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) obtained using Cox proportional hazard regression. Adjusted for age at risk, Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes, cancer history, menopause (women), and mutually adjusted for FM and ASM ASM (except for the model adjusted for BMI). Height is adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. Test for non-linearity across quintiles conducted using LRTs with 4df (p<0.05 indicates significant departure from linearity). The χ^2 values were calculated from likelihood ratio tests to estimate the improvement in model fit.

Table S11. Mortality sensitivity analyses.

Hazard ratios of all-cause mortality associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM)

	Quintile	Remove first 2 years of follow up		Remove outliers		Remove participants with BMI > 35	
		No. events	HR (95% CI)	No. events	HR (95% CI)	No. events	HR (95% CI)
Appendicular skeletal muscle mass (aSMM)							
Men	1	2532	1 (reference)	2660	1 (reference)	2648	1 (reference)
	2	1897	1.00 (0.94 - 1.06)	2013	0.98 (0.92 - 1.04)	1941	0.98 (0.92 - 1.04)
	3	1566	1.02 (0.96 - 1.09)	1673	0.99 (0.93 - 1.06)	1568	0.98 (0.92 - 1.05)
	4	1283	1.03 (0.97 - 1.11)	1378	1.00 (0.93 - 1.07)	1259	0.99 (0.93 - 1.06)
	5	1219	1.22 (1.14 - 1.31)	1263	1.16 (1.08 - 1.24)	1076	1.13 (1.05 - 1.22)
Non-linearity p-value			0.004		0.002		0.011
Women	1	1647	1 (reference)	1712	1 (reference)	1663	1 (reference)
	2	1307	0.93 (0.86 – 1.00)	1391	0.93 (0.87 – 1.00)	1327	0.93 (0.86 - 1.00)
	3	1183	0.96 (0.89 - 1.03)	1255	0.95 (0.89 - 1.03)	1159	0.93 (0.86 - 1.00)
	4	1119	1.01 (0.93 - 1.09)	1176	0.99 (0.92 - 1.07)	1072	0.98 (0.90 - 1.05)
	5	1148	1.13 (1.05 - 1.22)	1093	1.09 (1.01 - 1.18)	932	1.06 (0.98 - 1.15)
Non-linearity p-value			0.001		0.008		0.006
Fat Mass (FM)							
Men	1	1468	1 (reference)	1573	1 (reference)	1573	1 (reference)
	2	1451	0.90 (0.84 - 0.97)	1542	0.90 (0.83 - 0.96)	1542	0.89 (0.83 - 0.96)
	3	1620	0.97 (0.90 - 1.04)	1727	0.97 (0.90 - 1.04)	1727	0.97 (0.90 - 1.03)
	4	1742	1.00 (0.93 - 1.07)	1870	1.01 (0.94 - 1.08)	1869	1.00 (0.94 - 1.07)
	5	2216	1.22 (1.14 - 1.30)	2039	1.19 (1.11 - 1.27)	1781	1.17 (1.09 - 1.25)
Non-linearity p-value			p<0.001		p<0.001		p<0.001
Women	1	1058	1 (reference)	1126	1 (reference)	1126	1 (reference)
	2	1162	0.99 (0.91 - 1.07)	1228	0.98 (0.90 - 1.06)	1228	0.98 (0.90 - 1.06)
	3	1244	0.94 (0.86 - 1.02)	1321	0.94 (0.87 - 1.02)	1321	0.93 (0.86 - 1.01)
	4	1336	0.99 (0.91 - 1.07)	1414	0.99 (0.91 - 1.07)	1409	0.98 (0.90 - 1.06)
	5	1604	1.18 (1.09 - 1.28)	1422	1.12 (1.03 - 1.22)	1069	1.08 (0.99 - 1.17)
Non-linearity p-value			p<0.001		0.001		0.018

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) obtained using Cox proportional hazard regression. Adjusted for age at risk, Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes, cancer history, menopause (women), and mutually adjusted for FM and ASM. Height is adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. Test for non-linearity across quintiles conducted using LRTs with 4df (p<0.05 indicates significant departure from linearity). For the analysis without outliers, the top and bottom 25% of values were removed.

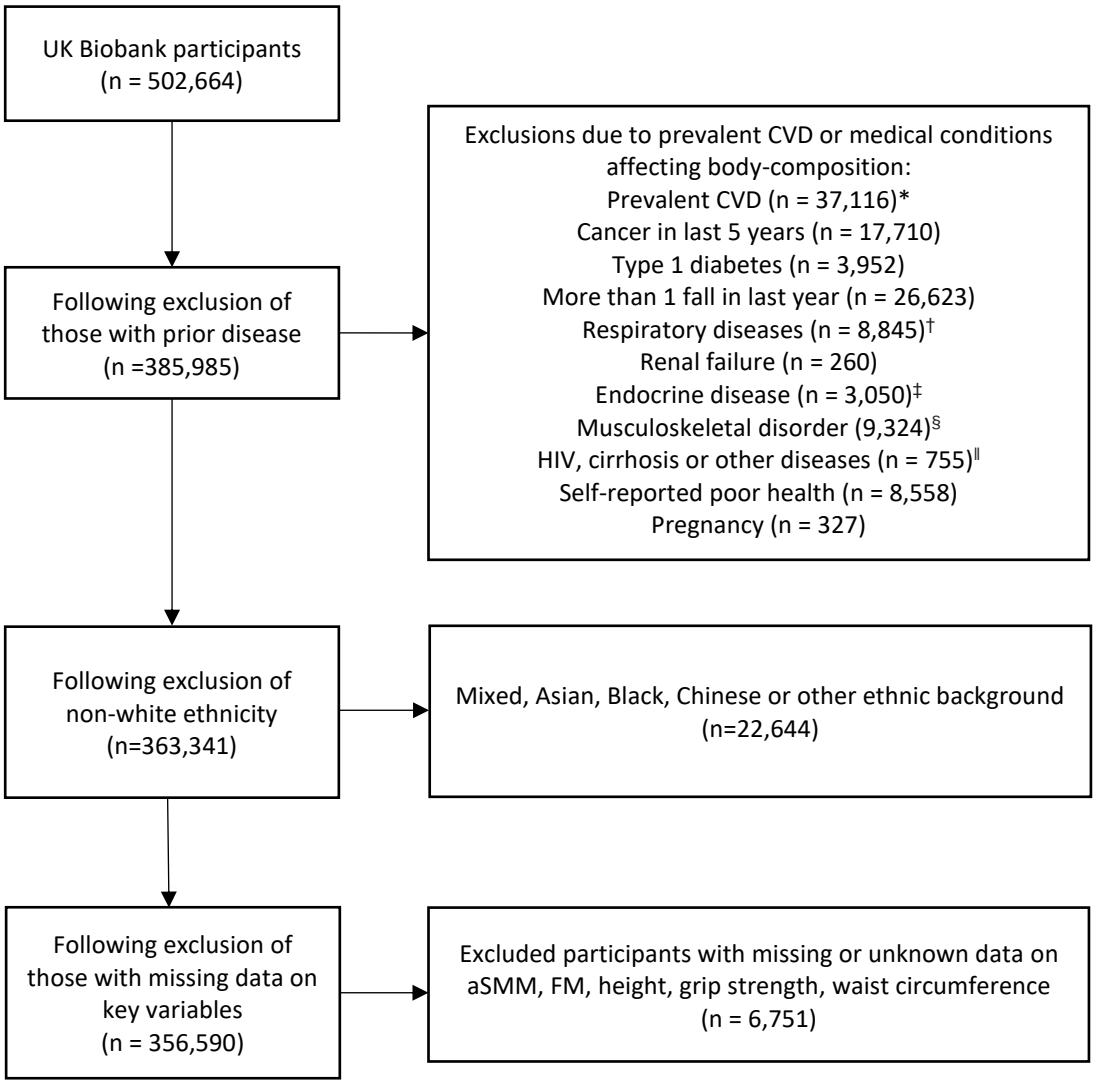
Table S12. Mortality mediation analyses.

Hazard ratios of all-cause mortality associated with appendicular skeletal muscle mass (aSMM) and fat mass (FM)

	Quintile	No. events	Adjust for BMI	Adjust for hypertension	Adjust for cholesterol
Appendicular skeletal muscle mass (aSMM)					
Men	1	2706	1 (reference)	1 (reference)	1 (reference)
	2	2013	0.95 (0.89 - 1.01)	0.98 (0.92 - 1.04)	0.98 (0.92 - 1.05)
	3	1673	0.95 (0.89 - 1.01)	0.99 (0.93 - 1.05)	0.97 (0.91 - 1.04)
	4	1378	0.93 (0.87 - 1.00)	0.99 (0.93 - 1.06)	0.96 (0.89 - 1.03)
	5	1312	1.06 (0.98 - 1.14)	1.15 (1.07 - 1.23)	1.13 (1.05 - 1.22)
	Non-linearity p-value		0.001	0.002	0.001
	Main model χ^2		29	25	21
	Adjusted model χ^2		16	24	20
	% Change		45%	4%	5%
Women	1	1732	1 (reference)	1 (reference)	1 (reference)
	2	1391	0.92 (0.86 - 0.99)	0.93 (0.87 - 1.00)	0.93 (0.86 - 1.00)
	3	1255	0.93 (0.87 - 1.00)	0.95 (0.89 - 1.03)	0.95 (0.88 - 1.03)
	4	1176	0.96 (0.89 - 1.03)	0.99 (0.92 - 1.07)	0.99 (0.91 - 1.07)
	5	1208	1.06 (0.98 - 1.14)	1.10 (1.02 - 1.19)	1.10 (1.02 - 1.20)
	Non-linearity p-value		0.003	0.003	0.004
	Main model χ^2		26	21	21
	Adjusted model χ^2		16	20	19
	% Change		38%	5%	9%
Fat mass (FM)					
Men	1	1573	1 (reference)	1 (reference)	1 (reference)
	2	1542	0.86 (0.79 - 0.92)	0.88 (0.82 - 0.95)	0.90 (0.84 - 0.97)
	3	1727	0.90 (0.83 - 0.97)	0.94 (0.88 - 1.01)	0.98 (0.91 - 1.06)
	4	1870	0.90 (0.82 - 0.98)	0.97 (0.91 - 1.04)	1.01 (0.94 - 1.09)
	5	2370	1.01 (0.90 - 1.13)	1.17 (1.09 - 1.25)	1.24 (1.15 - 1.34)
	Non-linearity p-value		p<0.001	p<0.001	p<0.001
	Main model χ^2		101	98	88
	Adjusted model χ^2		36	81	87
	% Change		64%	17%	1%
Women	1	1126	1 (reference)	1 (reference)	1 (reference)
	2	1228	0.91 (0.84 - 0.99)	0.98 (0.90 - 1.06)	0.97 (0.89 - 1.06)
	3	1321	0.82 (0.75 - 0.90)	0.93 (0.86 - 1.01)	0.97 (0.89 - 1.06)
	4	1414	0.81 (0.73 - 0.90)	0.97 (0.90 - 1.06)	1.00 (0.91 - 1.09)
	5	1673	0.83 (0.71 - 0.96)	1.13 (1.05 - 1.23)	1.16 (1.06 - 1.27)
	Non-linearity p-value		0.033	p<0.001	0.003
	Main model χ^2		41	37	31
	Adjusted model χ^2		22	31	26
	% Change		46%	16%	16%

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) obtained using Cox proportional hazard regression. Adjusted for age at risk, Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes, cancer history, menopause (women), and mutually adjusted for FM and ASM (except for the model adjusted for BMI). Height is adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. Test for non-linearity across quintiles conducted using LRTs with 4df (p<0.05 indicates significant departure from linearity). The χ^2 values were calculated from likelihood ratio tests to estimate the improvement in model fi

Figure S1. Exclusions and selection of the study population included in the analysis from the UK Biobank.



*Prior CVD: follows the same definition and codes from HES reported in the manuscript as well as self-reported from verbal interviews and touchscreen questionnaire including instances of heart attack/myocardial infarction, heart failure, angina, heart failure, stroke, transient ischaemic attack, subdural haemorrhage, aortic aneurysm rupture, cerebral aneurysm, peripheral vascular disease, leg claudication, arterial embolism, .

†Respiratory diseases: chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchiectasis (occurred anytime)

‡Endocrine diseases: Cushing's syndrome, hyperthyroidism (occurred anytime)

§Musculoskeletal diseases: motor neurone disease, osteoporosis, rheumatoid arthritis, fractures (occurred anytime)

‖HIV, cirrhosis or other disease: pancreatitis, encephalitis, meningitis, intracranial abscess, empyema, Stevens Johnson Syndrome and carcinoid syndrome/tumour (occurred in the last year); liver cirrhosis, HIV/AIDS (occurred anytime)

Figure S2. Splines.

Adjusted hazard ratios (HRs) of incident cardiovascular disease (CVD) and all-cause mortality associated with appendicular skeletal muscle mass (aSMM), whole body fat mass (FM) and body mass index (BMI) estimated using restricted cubic splines

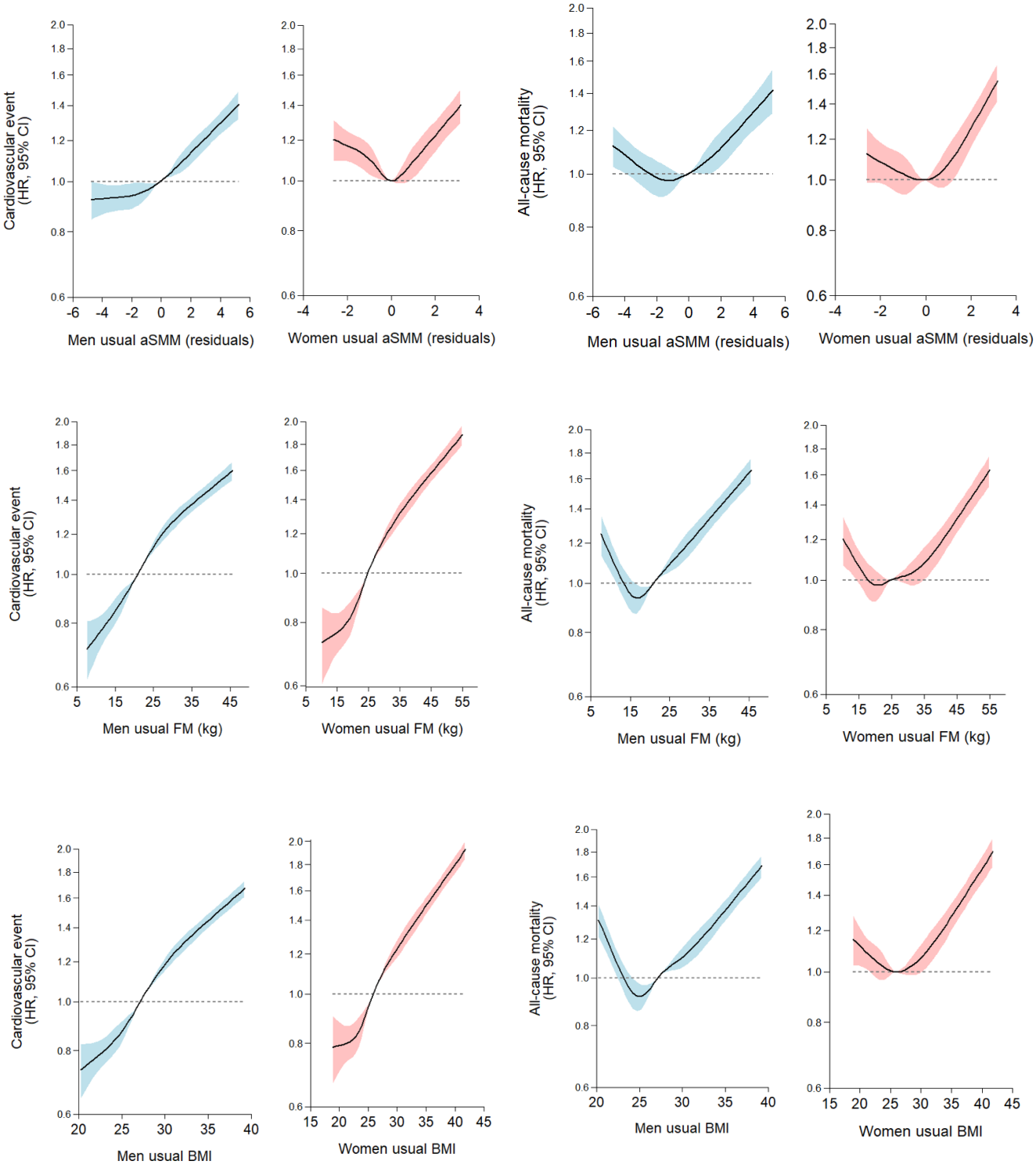
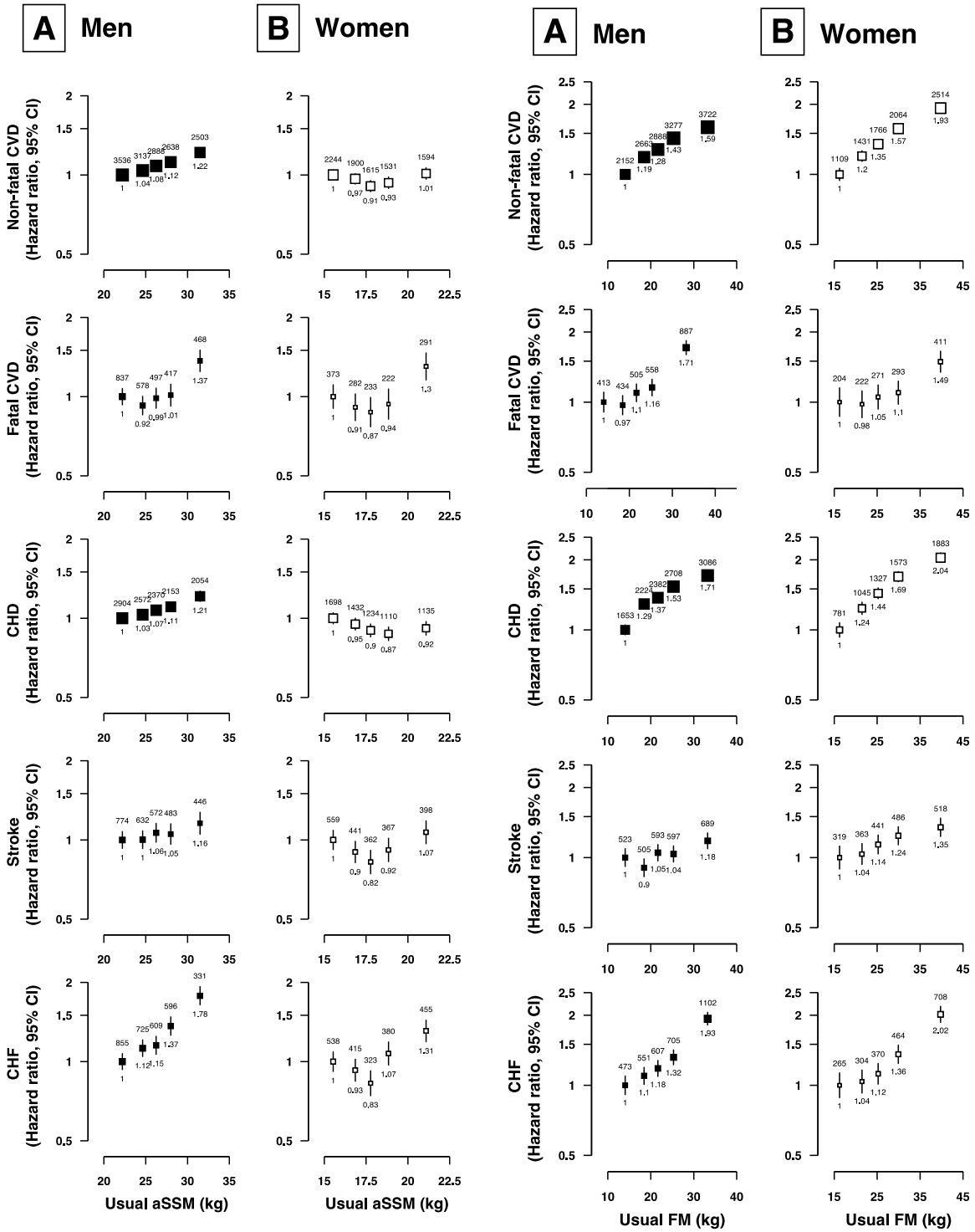


Figure S3. Associations with CVD subtypes.

Adjusted hazard ratios for the association between cardiovascular disease (CVD) subtypes (coronary heart disease, stroke and congestive heart failure) with i) appendicular skeletal muscle mass (aSMM) and ii) fat mass (FM)

i) Appendicular skeletal muscle mass ii) Fat mass



i A, adjusted hazard ratios for the association between CVD subtypes with aSSM in men. **i B**, adjusted hazard ratios for the association between CVD subtypes with aSSM in women. **ii A**, adjusted hazard ratios for the association between CVD subtypes with FM in men. **ii B**, adjusted hazard ratios for the association between CVD subtypes with FM in women

Adjusted hazard ratios (HR) and 95% group-specific confidence intervals (CI) obtained using floated absolute risk method of Cox proportional hazard regression. Adjusted for age at risk, Townsend index of deprivation, education, smoking status, alcohol intake, physical activity, oily fish intake, fruit and vegetable intake, saturated fat intake, diabetes, cancer history, menopause (women), and mutually adjusted for FM and ASM. Height is adjusted for by inclusion as continuous variable for FM and by regression out of variation due to height for ASM. HRs are plotted at the mean of the resurvey values for the baseline-defined quintiles ("usual" values) to correct for measurement error.