openheart

Adiposity, fat-free mass and incident heart failure in 500 000 individuals

Ayodipupo S Oguntade ,[1,2] Hannah Taylor,[1] Ben Lacey,[1,3] Sarah Lewington[1,4]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2024-002711).

To cite: Oguntade AS, Taylor H, Lacey B, *et al*. Adiposity, fat-free mass and incident heart failure in 500 000 individuals. *Open Heart* 2024;**11**:e002711. doi:10.1136/openhrt-2024-002711

BL and SL contributed equally.

BL and SL are joint senior authors.

Received 14 April 2024
Accepted 20 June 2024

[1]Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK
[2]Department of Cardiology, Hull University Teaching Hospitals NHS Trust, Hull, UK
[3]UK Biobank, Stockport, UK
[4]MRC Population Health Research Unit, Nuffield Department of Population Health (NDPH), University of Oxford, Oxford, UK

Correspondence to
Dr Ayodipupo S Oguntade; ayodipupooguntade@gmail.com

ABSTRACT

Background and aims The independent role of body fat distribution and fat-free mass in heart failure (HF) risk is unclear. We investigated the role of different body composition compartments in risk of HF.

Methods Present analyses include 428 087 participants (mean age 55.9 years, 44% male) from the UK Biobank. Associations of long-term average levels of body composition measures with incident HF were determined using adjusted Cox proportional hazards regression models.

Results Over a median follow-up of 13.8 years, there were 10 455 first-ever incident HF events. Overall, HF risk was more strongly associated with central adiposity (waist circumference (WC) adjusted for body mass index (BMI); HR 1.38, 95% CI 1.32 to 1.45) than general adiposity (BMI adjusted for WC; HR 1.22, 95% CI 1.16 to 1.27). Although dual X-ray absorptiometry-derived body fat remained positively related to HF after adjustment for fat-free mass (HR 1.37, 95% CI 1.18 to 1.59), the association of fat-free mass with HF was substantially attenuated by fat mass (HR 1.12, 95% CI 1.01 to 1.26) while visceral fat (VAT) remained associated with HF independent of subcutaneous fat (HR 1.20, 95% CI 1.09 to 1.33). In analyses of HF subtypes, HF with preserved ejection fraction was independently associated with all fat measures (eg, VAT: HR 1.23, 95% CI 1.12 to 1.35; body fat: HR 1.36, 95% CI 1.17 to 1.57) while HF with reduced ejection fraction was not independently associated with fat measures (eg, VAT: HR 1.29, 95% CI 0.98 to 1.68; body fat: HR 1.29, 95% CI 0.80 to 2.07).

Conclusions This large-scale study shows that excess adiposity and fat mass are associated with higher HF risk while the association of fat-free mass with HF could be explained largely by its correlation with fat mass. The study also describes the independent relevance of body fat distribution to HF subtypes, suggesting different mechanisms may be driving their aetiopathogenesis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Obesity as defined by the body mass index is a risk factor for heart failure (HF) but the independent role of body fat distribution and fat-free mass using whole body imaging in incident HF and its subtypes risk is unclear.

WHAT THIS STUDY ADDS

⇒ Central adiposity especially visceral fat is an independent risk factor for HF while the association of fat-free mass with HF is explained by its correlation with fat mass. HF with preserved ejection fraction was independently associated with excess visceral and body fat while HF with reduced ejection fraction was not.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may be important for preventative population health strategies for tackling the current obesity pandemic in the general population.

INTRODUCTION

The associations of adiposity, body fat distribution and fat-free mass (collectively termed 'body composition') with cardiac dysfunction have been an area of active investigation. The most widely studied measure of body composition is body mass index (BMI), used as a measure of general adiposity.[1–3] However, BMI is an imprecise measure as it does not differentiate between body fat (and its distribution in different body compartments) and fat-free mass. Moreover, there is emerging evidence that measures of central adiposity may be more strongly associated with heart failure (HF) risk.[4–6] Furthermore, recent studies have shown that fat-free mass may be more strongly associated with cardiovascular risk than with adiposity measures, but the independent effects of fat-free mass and the various adiposity measures on HF risk are not well established.[7–9]

Anthropometric measures do not directly measure fat mass and fat-free mass and the use of other fat quantification measures like bioelectrical impedance analysis (BIA) and dual X-ray absprtiometry (DXA) could potentially provide insights into the role of fat distribution and fat-free mass in individuals who are at increased risk of HF in the population. To the best of our knowledge, no recent study has examined the relevance of fat and fat-free mass quantification using both BIA and DXA in HF risk, and fat and fat-free mass measurement are not yet routinely used in cardiovascular risk prediction in the general population.

HF can be subtyped using left ventricular ejection fraction (LVEF) obtained from cardiac imaging into HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF), and, more recently, HF with mildly reduced ejection fraction.[10 11] Obesity has been shown to be a risk factor for HFpEF in some observational studies but data on HFrEF is sparse.[12–16] However, LVEF is not commonly recorded in routine data and as such, there is little evidence on the relationship between measures of body composition and HF subtypes in large-scale observational studies. UK Biobank (UKB) and its extensive record linkage provide a good opportunity to investigate the relevance of excess adiposity and fat-free mass in relation to HF and its different subtypes. A better understanding of the aetiology of HF and its subtypes will inform prevention at individual and population levels.

In the present study, we determined the associations between measures of body composition and risk of incident HF and its subtypes. We also explored the independent and joint effects of general and central adiposity on HF. Finally, we explored the independent associations of longitudinal changes in body composition measures with incident HF in this contemporary population cohort.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[17] The design and data collection procedures of UKB have been previously described.[18] Briefly, the UKB is a prospective cohort of 502 000 adults (aged 40–70 years) recruited from the general population of the UK between 2006 and 2010.[19] All UKB participants have given written informed consent for the use of their data for health research. A repeat survey of the full baseline assessment including anthropometry and bioimpedance was conducted on approximately 20 000 participants in 2012–2013 and used to calculate regression dilution ratios (RDRs) of these measures as explained below in the statistical analysis section. The UKB imaging substudy started in 2014 and is ongoing.[20] So far, 57 670 participants without interval HF event between the initial and imaging visits over a mean interval of 10 years have additionally had further anthropometry and bioimpedance remeasured. Alongside a repeat of the baseline assessment, participants of the imaging substudy underwent whole body imaging for the assessment of cardiac function and body composition, using cardiac MRI (CMR) and DXA, respectively. The present analysis included 428 087 individuals with complete anthropometric and bioimpedance measures who were free of HF and other major cardiovascular conditions at the baseline assessment visit. Of these, about 36 000 individuals from the initial baseline assessment have had whole body DXA imaging and 2913 of these individuals have had repeat DXA body imaging.

All UKB participants have their data linked to their UK National Health Service (NHS) records and are followed up by electronic health records linkage (hospital episode statistics and Office for National Statistics cause of death).[21] All the authors had full access to all the data in the study and took responsibility for its integrity and the data analysis.

Data collection procedures

At recruitment participants reported lifestyle exposures, medical history and medications before undergoing standardised assessments including body size and biomarker measurements. Anthropometric measurements included body weight (using a Tanita BC418MA body composition analyser), standing height (Seca 240 cm height measure), and waist and hip circumference (Seca 200 cm tape measure around the narrowest part of the trunk and the widest part of the hips, respectively).[19 22 23] Waist-to-hip ratio (WHR) is the ratio of the waist circumference (WC) to hip circumference (both in cm). BMI is the ratio of the weight (kg) to the square of the height in metres. BIA measures of body fat mass (BFM) and fat-free mass (BFFM) were obtained from the same Tanita BC-418MA analyser. This involved the participants standing barefooted on the analyser's foot pads while holding onto metal conductor hand grips.[22 23]

During the imaging substudy, DXA (GE-Lunar, Madison, Wisconsin, USA) was used to estimate body fat-free mass and body fat distribution using a proprietor device algorithm.[20] Briefly, the android region is defined by transverse planes at the top of the iliac crest and at 20% of the distance between the iliac crest and the top of the trunk.[19] The Gynoid area is the area around the hips defined by transverse planes at 1.5 and 2.5 times the height of the android region below the iliac crest.[19] Subcutaneous adipose tissue (SAT) was defined as subcutaneous fat in the android and gynoid regions. The amount of SAT in the android region was estimated by measuring the fat between the abdominal wall and the skin line on both sides of the image, and this estimate of subcutaneous abdominal fat was subtracted from the android fat to obtain the visceral fat (VAT) estimate.[24] DXA-derived fat-free mass was calculated by subtracting the DXA-derived total body fat from total body mass.

HF incidence in UK Biobank

The primary outcome in this study was a first-ever recorded incident HF diagnosis after the baseline visit (for anthropometric and bioimpedance measures) or first imaging visit (for DXA-derived measures). Incident HF events were coded using the International Classification of Diseases, 10th Revision (ICD-10) and the OPCS Classification of Interventions and Procedures version 4 (OPCS-4). ICD-10 codes used to define HF include I11.0, I13.0, I13.2 and I50. OPCS-4 codes used to define HF procedures are K01 (transplantation of heart and lung), K02 (other transplantation of heart), K54 (Open heart assist operations), K56 (Transluminal heart assist operations) and K76 (Transluminal operations on cardiac conduit). A detailed list of ICD-10 and OPCS-4 codes

used in the present analysis can be found in online supplemental table S1.

Participants' primary care records were used to obtain the HF LVEF phenotype for a fraction of the participants with incident HF (1464 individuals) whose primary care records are linked to the UKB study and who have had echocardiography done in primary care using read codes and SNOMED CT codes (online supplemental table S2). HFrEF was identified from diagnostic codes of systolic dysfunction or reduced LVEF. HFpEF was identified using diagnostic codes of diastolic dysfunction, normal LVEF or preserved LVEF in the absence of concomitant codes for reduced ejection fraction. HF with midrange ejection fraction was not considered because this phenotype was not routinely coded in primary care. This was supplemented by LVEF obtained from CMR in the ongoing UKB imaging substudy where this was available. Thus, there were 901 HFrEF events and 563 HFpEF events which were categorised.

Statistical analysis

We excluded UKB participants who had withdrawn from the study (n=111), those outside the age group of 40–69 years (n=2431) and those with missing (n=11 894) or outlying body composition measures outside the 0.01th percentile and 99.99th percentiles of the distribution (n=530). Finally, to minimise reverse causation, we excluded individuals with HF at baseline (n=2501) or with other major cardiac and vascular conditions (n=59 747) (see online supplemental figure S1) leaving 428 087 participants in the main analysis. For the analysis of DXA-derived measures, we excluded individuals with interval HF or other major cardiac and vascular conditions at their first imaging visit and included 36 278 individuals in the analyses.

We summarised baseline characteristics of participants in proportions or means (SD). The inter-relationships between body composition measures were determined using Pearson's partial correlation method (online supplemental tables S3, S4). Participants were followed via electronic health record linkage from the date of recruitment at baseline (or first imaging visit in analyses of DXA measures) until the date of (1) first HF event, (2) death or (3) loss to follow-up. Cox proportional hazard regression models were used to estimate adjusted HRs stratified by age at risk, sex and UK region (England, Wales and Scotland), and further adjusted for ethnicity (European, South-Asian, African and others), education, quintiles of the Townsend deprivation index, smoking (never, past and current smokers), alcohol (lifetime abstainer, ex-drinker, occasional drinker (up to three times per month)) and regular drinker (weekly/daily) and physical activity (<10, 10–49.9, ≥50 metabolic equivalent [MET]-hour/week). For each of these potential confounders, individuals with missing values were assigned to the largest category. Analyses that use values of body composition measures obtained on a single occasion at baseline which do not take into account within person variability over time, are prone to systematic underestimation of the strength of associations between measured body composition and HF risk ('regression dilution bias').[25 26] As such, in this analysis, RDRs were calculated using the age-adjusted and sex-adjusted Pearson partial correlations (r) between baseline and resurvey measures (4.3 years after baseline visit) in 17 450 individuals of the present analysis who attended both visits (online supplemental table S5). In the case of DXA-derived measures, RDRs were calculated using the age and sex adjusted Pearson partial correlations (r) between initial imaging and imaging resurvey measures (2 years after the initial imaging visit) in 2913 individuals who attended both visits (online supplemental table S5). This method has been described in detail elsewhere.[27 28] Associations were corrected for regression dilution bias by dividing the beta coefficients (and standard errors) by the RDR and described as association with usual (long-term average) body composition measures. Previous population studies have shown the SD of BMI in the general population to be approximately 5 kg/m^2 and large population studies often express the excess risk attributable to BMI per 5 kg/m^2 higher.[29–32] As such in the present analyses, HRs were reported as per usual 5 BMI units equivalent higher of each body composition measure based on the measured SD of the different body composition measures in the UKB as shown in online supplemental table S6 (eg, 5 BMI units is equivalent to 12.2 WC units, 0.07 WHR units, 9.8 BFM units, 4.9 BFFM units, 0.6 VAT units and 2.1 SAT units) so that the strength of associations can be easily compared.

The shapes of the association between 'usual' levels of body composition and HF risk were described by plotting the floating absolute risks against the mean body composition at resurvey within each baseline quintiles of each body composition measure.[33] The variance of the logHR (95% CI) in each group, including the reference, was calculated (from the variances and covariances of the logHR in all groups except the reference group) and used to obtain group-specific logHR (95% CIs) as previously described.[27 33] HRs (ie, floated absolute risks) were estimated for each quintile with the bottom fifth designated as the reference.

Independent effects of general (BMI) and central adiposity (WC and WHR), and of fat and fat-free mass were investigated by comparing the strength of associations before and after mutual adjustment for each other. In the mutual adjustment analyses, because of the correlations between the body composition measures, the residuals obtained from a first-step linear regression of the body composition measures against each other (which are uncorrelated) were used in the second stage Cox regression analyses. The χ^2 values of the different models were compared and used to explain which of the different body composition measures was most informative of HF risk. The joint effects of both general and central fat distribution on incident HF were assessed by determining the associations of tertiles of central adiposity measures (WC, WHR and VAT) with incident HF among normal weight,

overweight and obese individuals (as defined by BMI). Effect modifications by age at risk (5 years age groups), sex, ethnicity, smoking and alcohol were assessed by including an interaction term in the multivariable model. Heterogeneity between subgroups was assessed using χ^2 tests for heterogeneity while χ^2 tests for trend were used to assess if the HRs differed in any ordered subgroups. A semi-quantitative estimate of mediation was evaluated for each body composition measure by assessing the change in the χ^2 statistic for that body composition measure following sequential adjustment for intermediate factors considered to lie on the causal pathway of associations between body composition and HF. Intermediate factors included systolic blood pressure (SBP), type 2 diabetes mellitus (T2DM), blood glucose, glycated haemoglobin (HbA1c), C reactive protein, estimated glomerular filtration rate (eGFR), serum high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C).

We then determined the associations of decadal longitudinal changes in anthropometric and bioimpedance measures and incident HF from initial visit to imaging visit (mean interval of 10 years) in analyses of subset of participants with repeat body composition measures (57 670 participants) without interval HF event before the imaging visit. Briefly, per cent changes in each body composition measure were calculated ((imaging value–baseline value)/baseline value×100%).[9 34] Participants were divided into five groups based on percent change in each body composition measure (Δ% <– 8%, –8% ≤Δ% < –2%, –2% ≤Δ% < 2% (reference group), ≥2% Δ %<10% and Δ% ≥10%). Stable body composition was defined as – 2% ≤ Δ body composition measure <2% based on previous literature on age-related changes in body fat and fat-free mass.[34–36]

Sensitivity analyses were performed to assess the potential for reverse causality and residual confounding. Separate analyses excluded the first 2 years of follow-up and the shape and strength of associations were compared with those of the main analyses. Analyses excluding underweight individuals were also performed to investigate residual confounding from undernutrition at baseline.

Proportional hazards assumption was tested by checking the Schoenfeld residuals of each body composition measure in the association between HF incidence and natural log of the follow-up time. Considerations were given to multiple testing using a Bonferroni-corrected p value threshold that accounted for the total number of body composition measures tested (ie, p<0.006). All analyses were done using Stata V.17.0 (StataCorp) while plots were made using the Jasper package (developed by Matt Arnold) in R V.4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall incident HF

Over a median follow-up of 13.8 years, there were 10 455 incident HF events in the main analysis of anthropometric and BIA measures while in online supplemental figure S5 analysis of DXA-derived measures, there were 292 incident HF events over a median follow-up of 4 years among individuals without pre-existing HF or major cardiovascular conditions. Participants had a mean (SD) age of 55.9 (8.1) years, 188 312 (44%) were male and 405 177 (94.2%) were European. Overall, there were more HF events in men (6197 vs 4258 incident HF) than women (table 1). On average, those who developed HF were older, more socioeconomically deprived, more likely to be current smokers and had higher adiposity, VAT and fat-free mass. Participants who developed HF were twice as likely to have hypertension and three times more likely to have T2DM than those who did not develop HF and also had higher SBP, diastolic BP, plasma glucose and HbA1c. Participants with HF were also more likely to have chronic kidney disease, be on BP and lipid-lowering medications and insulin than those without HF. Participants with HF also had lower eGFR than participants without HF.

All the body composition measures showed positive and log-linear associations with incident HF in both sexes (figure 1). Associations were stronger for usual WC and WHR than BMI or fat measures (table 2). Each 5 kg/m^2 higher usual BMI was associated with 57% higher HF risk (95% CI 1.54 to 1.60). Both usual WC and WHR were associated with 67% higher HF risk per 12.2 cm (95% CI 1.64 to 1.71) and per 0.07units (95% CI 1.62 to 1.73), respectively. The strength of associations for both usual BIA-derived and DXA-derived body fat was comparable (HR 1.55 and HR 1.44, respectively) and similar to that for BMI. BIA-derived and DXA-derived fat-free mass showed comparable but weaker association with incident HF (HR 1.25 (95% CI 1.23 to 1.27) and HR 1.26 (95% CI 1.14 to 1.38)). Both VAT and SAT were associated with a higher risk of incident HF (HR 1.26 (95% CI 1.16 to 1.35) and HR 1.44 (95% CI 1.26 to 1.65), respectively). Associations did not significantly differ by sex, age, ethnicity, smoking or alcohol consumption (online supplemental figures S2, S3) and were not substantially different from the main analyses when expressed per usual SD of each body composition measure (online supplemental figures S4, S5).

The association of BMI with HF was substantially attenuated when adjusted for WC (HR 1.22 (95% CI 1.16 to 1.27; χ^2=77)). By contrast, adjustment of WC for BMI attenuated its association with incident HF risk to HR 1.38 (95% CI 1.32 to 1.45; χ^2=169) while adjustment of WHR for BMI attenuated its association with incident HF risk to HR 1.30 (95% CI 1.25 to 1.34;χ^2=203) (see table 2).

Adjustment of BIA-derived body fat for fat-free mass did not substantially attenuate its association with incident HF risk (HR 1.46 (95% CI 1.41 to 1.50; χ^2=617)). However, adjustment of BIA-derived fat-free mass for body fat substantially attenuated its association with incident HF (HR 1.06 (95% CI 1.04 to 1.08; χ^2=31)) (table 2). Associations of DXA-derived body fat and fat-free mass when mutually adjusted for each other were comparable with

Table 1 Participants' characteristics by incident heart failure in UK Biobank*

Characteristics at baseline	Incident heart failure		
	No	Yes	Total
Baseline visit	N=**417 632**	N=**10 455**	N=**428 087**
Age (years)	55.8 (8.0)	61.4 (6.4)	55.9 (8.1)
Men	182 116 (43.6%)	6196 (59.3%)	188 312 (44.0%)
England	370 390 (88.7%)	9845 (94.2%)	380 235 (88.8%)
European	395 222 (94.6%)	9955 (95.2%)	405 177 (94.6%)
Higher education	269 783 (64.6%)	7079 (67.7%)	276 862 (64.7%)
Most deprived	82 826 (19.9%)	2684 (25.7%)	85 510 (20.0%)
Current smoker	42 349 (10.1%)	1670 (16.0%)	44 019 (10.3%)
Regular/daily drinker	293 908 (70.4%)	6874 (65.7%)	300 782 (70.3%)
Low physical activity	72 643 (17.4%)	1973 (18.9%)	74 616 (17.4%)
BMI (kg/m^2)	27.2 (4.6)	29.4 (5.6)	27.2 (4.7)
Waist circumference (cm)	89.4 (13.0)	97.4 (14.5)	89.6 (13.1)
Waist-to-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
BIA-body fat mass (kg)	24.5 (9.3)	27.7 (11.3)	24.5 (9.4)
BIA-body fat-free mass (kg)	52.8 (11.4)	56.8 (12.0)	52.9 (11.4)
Hypertension	99 287 (23.8%)	4880 (46.7%)	104 167 (24.3%)
Diabetes	17 162 (4.1%)	1344 (12.9%)	18 506 (4.3%)
Chronic kidney disease	2298 (0.6%)	161 (1.5%)	2459 (0.6%)
BP lowering medication usage	67 234 (16.1%)	3818 (36.5%)	71 052 (16.6%)
Insulin usage	3190 (0.8%)	341 (3.3%)	3531 (0.8%)
Lipid-lowering medication usage	49 506 (11.9%)	2674 (25.6%)	52 180 (12.2%)
Systolic BP (mm Hg)	137.5 (18.5)	146.2 (19.4)	137.7 (18.6)
Diastolic BP (mm Hg)	82.4 (10.1)	84.3 (10.5)	82.4 (10.1)
Glucose (mmol/L)	5.1 (1.1)	5.5 (1.9)	5.1 (1.2)
HbA1c (mmol/mol)	35.7 (6.1)	38.7 (10.0)	35.8 (6.3)
HDL-C (mmol/L)	1.5 (0.4)	1.4 (0.4)	1.5 (0.4)
LDL-C (mmol/L)	3.6 (0.8)	3.5 (0.9)	3.6 (0.8)
eGFR (mL/min)	90.5 (15.3)	79.9 (17.7)	90.3 (15.4)
C reactive protein (mg/L)†	2.8 (0.7)	2.7 (0.8)	2.8 (0.7)†
DXA imaging visit‡			
DXA-body fat mass (kg)	25.5 (9.3)	27.9 (10.7)	25.5 (9.3)
DXA-visceral fat (kg)	1.2 (0.9)	1.7 (1.2)	1.2 (0.9)
DXA-subcutaneous adipose tissue (kg)	5.3 (2.0)	5.3 (2.1)	5.3 (2.0)
DXA-fat-free mass (kg)	49.7 (10.1)	53.8 (10.7)	49.8 (10.1)

*Data are presented as arithmetic mean (SD), geometric mean (SD) or n (%).
†Geometric mean (SD).
‡Imaging visit occurred 10 years after the baseline visit.
BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; DXA, dual X-ray absprtiometry; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

the results of the main analyses of BIA-derived measures. Both VAT and SAT remained independently associated with HF risk after mutual adjustment for each other (HR 1.20 (95% CI 1.09 to 1.33; p<0.001)) and (HR 1.22 (95% CI 1.02 to 1.47; p=0.03)), respectively, although the CI for SAT was wider.

Table 3 shows the joint associations of general and central fat distribution with incident HF risk. Across all tertiles of WC, WHR and VAT, there was a graded log-linear higher risk of HF from normal weight to overweight and obese individuals which was higher in individuals in upper tertiles than lower tertiles of each central fat distribution measure.

All the body composition measures remained positively associated with HF risk in models adjusted for cardiometabolic intermediate factors except for SAT which association was completely attenuated after adjustment for CRP (table 4). SBP, glycaemic status, eGFR and CRP mediated approximately 80% of the association as shown by the percentage reduction in the χ^2 value. Serum lipids did not appear to be important mediators of the observed associations. The shape and strength of associations between

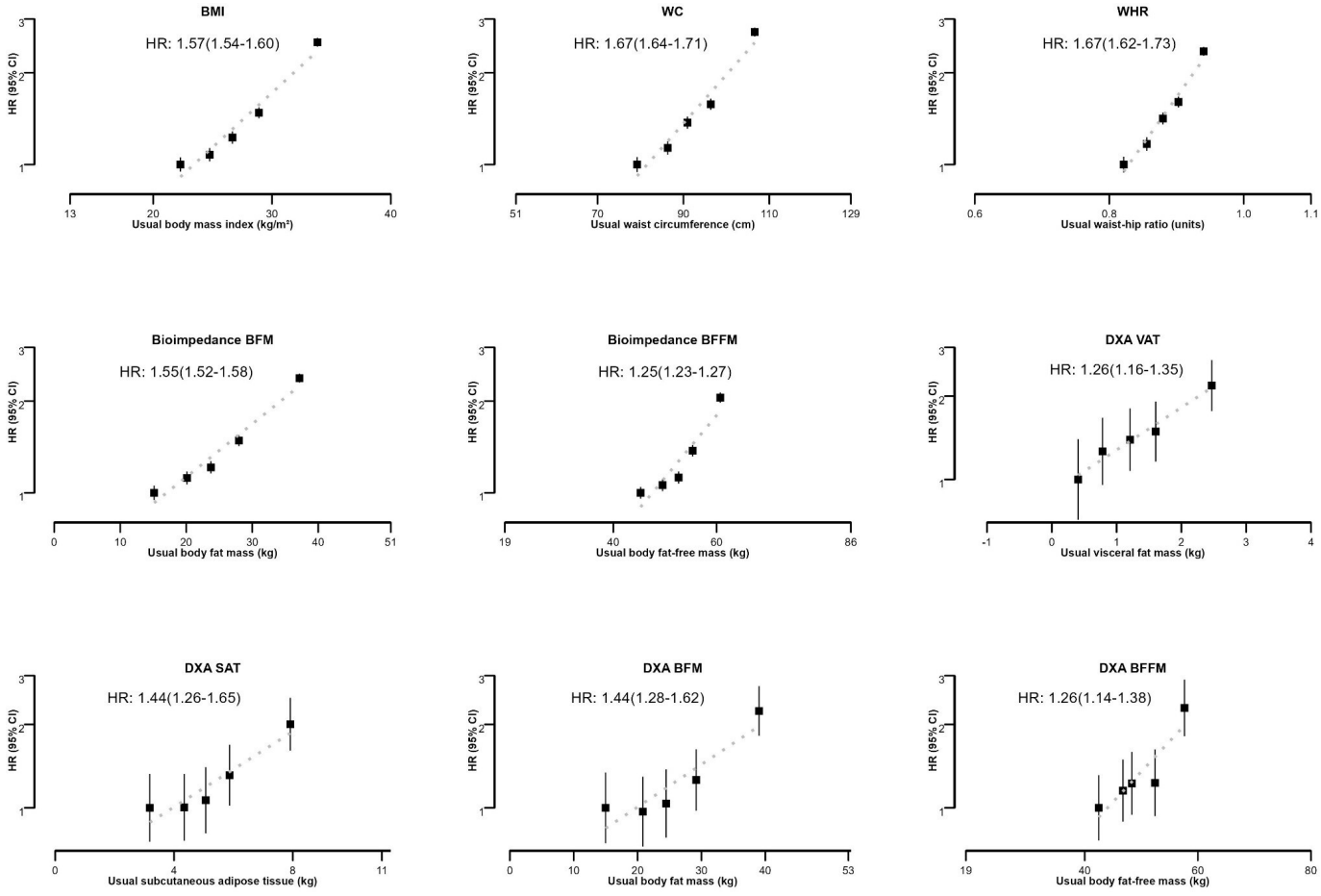

Figure 1 Shape of associations of body composition measures with incident HF in the UK Biobank. Error bars denote group-specific 95% CIs. Group-specific HRs were plotted against the resurvey means of each body composition measure in each baseline quintile. HR estimates were stratified by age at risk (5-year age groups), sex and UK region and were adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity. BFM, body fat mass; BFFM, body fat-free mass; BMI, body mass index; DXA, dual X-ray absorptiometry; SAT, subcutaneous adipose tissue; VAT, visceral fat; WC, waist circumference; WHR, waist-to-hip ratio.

body composition measures and HF did not also differ from the main analyses when the first 2 years of follow-up or underweight individuals were excluded (online supplemental figures S5, S6). Associations did not differ appreciably for fatal HF events and use of BP lowering or lipid-lowering medications had no appreciable effect on the overall estimates (online supplemental figure S7).

Table 5 shows the associations of decadal change in body composition measures with incident HF. Individuals with ≥10% decadal increase in BMI from baseline had about twofold higher risk of HF compared with individuals with stable BMI. Individuals with more than 8% decadal decrease in BMI from baseline also had a 35% higher risk of incident HF than those with stable BMI while individuals with decadal BMI decrease of 2%–8% or decadal increase of 2%–10% had no significant increased risk of HF when compared with individuals with stable BMI. Decadal changes in each of WC and WHR were not associated with incident HF risk. There was a 33% higher risk of HF among individuals with 2%–8% decadal decrease in body fat but further decrease in body fat or increase in body fat was not associated with higher risk of HF when compared with individuals with stable body fat mass. On the contrary, compared with those with stable fat-free mass, there was a significant graded increase in HF risk with decadal increase in fat-free mass (42% higher HF risk for decadal increase of 2% to <10% and 4-fold higher HF risk for ≥10% decadal increase in fat-free mass). Decadal decrease in fat-free mass was, however, not associated with higher HF risk when compared with individuals with stable fat-free mass.

Body fat distribution and HF LVEF subtypes

As shown in figure 2, DXA-derived fat-free mass was independently associated with both HFpEF (HR 1.20 (95% CI 1.06 to 1.35)) and HFrEF (HR 1.44 (95% CI 1.03 to 2.02)). Higher body fat mass was significantly associated with higher HFpEF risk (HR 1.36 (95% CI 1.17 to 1.57)) but was not associated with HFrEF risk (HR 1.29 (95% CI 0.80 to 2.07)). Excess VAT and SAT were significantly associated with HFpEF risk (23% and 35% higher risk respectively) but were not associated with HFrEF risk.

Table 2 Independent associations of usual levels of body composition measures with incident heart failure

Models*	HR (95% CI)	P value	χ^2
Anthropometry			
BMI	1.57 (1.54 to 1.60)	<0.001	1994
+WC	1.22 (1.16 to 1.27)	<0.001	77
WC	1.67 (1.64 to 1.71)	<0.001	1992
+BMI	1.38 (1.32 to 1.45)	<0.001	169
WHR	1.67 (1.62 to 1.73)	<0.001	1083
+BMI	1.30 (1.25 to 1.34)	<0.001	203
Bioimpedance			
Body fat mass	1.55 (1.52 to 1.58)	<0.001	1700
+Fat free mass	1.46 (1.41 to 1.50)	<0.001	617
Fat-free mass	1.25 (1.23 to 1.27)	<0.001	874
+Body fat mass	1.06 (1.04 to 1.08)	<0.001	31
DXA-imaging			
Body fat mass	1.44 (1.28 to 1.62)	<0.001	36
+Fat-free mass	1.37 (1.18 to 1.59)	<0.001	18
Fat-free mass	1.26 (1.14 to 1.38)	<0.001	22
+Body fat mass	1.12 (1.01 to 1.26)	0.04	4
Visceral fat	1.26 (1.16 to 1.35)	<0.001	33
+Subcutaneous adipose tissue	1.20 (1.09 to 1.33)	<0.001	12
Subcutaneous adipose tissue	1.44 (1.26 to 1.65)	<0.001	28
+Visceral fat	1.22 (1.02 to 1.47)	0.03	5

*All models were stratified by age at risk (in 5-year ranges), sex and UK region and were adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.
BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio.

DISCUSSION

Association shape and magnitude

In this large study, all body composition measures showed strong positive log-linear associations with incident HF across the range of distribution measured. The independent association with HF was stronger for central adiposity (WC) than general adiposity (BMI). Body fat mass was strongly associated with higher incident HF risk independent of fat-free mass while the association of fat-free mass with incident HF was largely explained by fat mass.

Previous studies have reported weaker associations for WC with respect to HF risk than described in the present report and tended to report stronger HF risk for general adiposity (BMI) than central adiposity (WC).[3] The HUNT study[37] and Cooper Centre Longitudinal study[38] found a 27% and 28% higher HF risk, respectively, per 5 kg/m^2 higher measured BMI. Similarly, some European cohorts such as the British Regional Heart Study,[39] Rotterdam study,[40] PREVEND study,[41] Cohort of Swedish Men,[42] Swedish Mammography Cohort[42] and PPSWG study[43] have reported risk estimates ranging from 10 to 40% higher HF risk per 5 kg/m^2 higher measured BMI. However, Aune *et al*[3] in a meta-analysis of 23 studies on BMI and 12 studies on WC reported a 41% higher risk per 5 kg/m^2 higher BMI and 29% higher risk per 10 cm higher WC.

Some other recent epidemiological studies have, however, shown that central adiposity measures like WC are more strongly associated with cardiovascular disease risk than BMI.[5 42 44–50] The disparities between the findings of the studies may be partly explained by methodological problems such as reverse causation, measurement errors, poor quality data or non-exclusion of participants with cardiovascular diseases at baseline. In addition, none of the studies to date have corrected their results for measurement error and regression

Table 3 Joint associations of general and central fat distribution on heart failure (HF) risk

	Normal weight		Overweight		Obese	
Body composition	HF events	HR (95% CI)	HF events	HR (95% CI)	HF events	HR (95% CI)
Waist circumference						
Tertile 1	1515	1.00 (0.95 to 1.05)	626	1.11 (1.02 to 1.20)	11	1.67 (0.92 to 3.01)
Tertile 2	592	1.21 (1.12 to 1.32)	2143	1.32 (1.26 to 1.38)	278	1.68 (1.49 to 1.89)
Tertile 3	38	1.08 (0.79 to 1.49)	1470	1.63 (1.55 to 1.71)	3742	2.64 (2.56 to 2.73)
Waist-to-hip ratio						
Tertile 1	989	1.00 (0.94 to 1.06)	768	1.20 (1.12 to 1.29)	217	2.25 (1.97 to 2.57)
Tertile 2	777	1.28 (1.20 to 1.38)	1545	1.44 (1.37 to 1.52)	802	2.22 (2.07 to 2.38)
Tertile 3	379	1.40 (1.27 to 1.55)	1926	1.73 (1.65 to 1.81)	3012	3.03 (2.92 to 3.14)
Visceral fat						
Tertile 1	43	1.00 (0.74 to 1.35)	17	1.22 (0.75 to 1.96)	4	3.04 (1.14 to 8.13)
Tertile 2	17	0.84 (0.52 to 1.36)	43	1.07 (0.79 to 1.45)	13	2.37 (1.37 to 4.08)
Tertile 3	3	1.16 (0.37 to 3.61)	45	1.31 (0.98 to 1.75)	70	2.09 (1.65 to 2.65)

HR estimates are floated absolute risks of heart failure and models were stratified by age at risk (5-year age groups), sex and UK region and adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.

Table 4 HR (95% CI) for HF per five usual BMI units equivalent higher usual body composition measures with adjustment for potential intermediate risk factors

	Model 1		Model 2		Model 3		Model 4	
Models	**HR (95% CI)**	χ^2	**HR (95% CI)**	χ^2	**HR (95% CI)**	χ^2	**HR (95% CI)**	χ^2
Usual levels of anthropometry								
Body mass index	1.57 (1.54 to 1.60)	1994	1.48 (1.45 to 1.52)	1017	1.37 (1.33 to 1.40)	599	1.11 (1.02 to 1.20)	399
Waist circumference	1.67 (1.64 to 1.71)	1992	1.57 (1.52 to 1.61)	1014	1.43 (1.39 to 1.48)	620	1.36 (1.33 to 1.41)	426
Waist-to-hip ratio	1.67 (1.62 to 1.73)	1083	1.49 (1.43 to 1.54)	451	1.38 (1.33 to 1.44)	299	1.32 (1.27 to 1.37)	207
Usual levels of bioimpedance measures								
Body fat mass	1.55 (1.52 to 1.58)	1700	1.46 (1.42 to 1.49)	872	1.34 (1.30 to 1.37)	488	1.27 (1.24 to 1.31)	304
Body fat-free mass	1.25 (1.23 to 1.27)	874	1.19 (1.17 to 1.21)	413	1.15 (1.13 to 1.17)	251	1.13 (1.11 to 1.15)	209
Usual levels of DXA imaging measures								
Visceral fat	1.25 (1.16 to 1.35)	33	1.18 (1.08 to 1.30)	13	1.15 (1.05 to 1.26)	8	1.12 (1.02 to 1.23)	5
Subcutaneous fat	1.44 (1.26 to 1.65)	28	1.29 (1.10 to 1.51)	10	1.22 (1.04 to 1.43)	6	1.15 (0.98 to 1.36)	3
Body fat mass	1.44 (1.28 to 1.62)	36	1.30 (1.13 to 1.50)	13	1.23 (1.06 to 1.43)	8	1.17 (1.00 to 1.36)	4
Body fat-free mass	1.26 (1.14 to 1.38)	22	1.19 (1.07 to 1.33)	10	1.17 (1.05 to 1.30)	8	1.15 (1.03 to 1.28)	7

Model 1: stratified by age at risk (5-year age groups), sex and UK region and adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.
Model 2: model 1+systolic blood pressure, glycated haemoglobin, blood glucose, diabetes, low density lipoprotein cholesterol and high density lipoprotein cholesterol.
Model 3: model 2+estimated glomerular filtration rate.
Model 4: model 3+C reactive protein.
BMI, body mass index; DXA, dual X-ray absprtiometry; HbA1c, glycated haemoglobin; HF, heart failure.

dilution bias. Despite the methodological differences in the cohort design between this analysis of the UKB and reports from other studies, the reported risk estimates in this study are comparable to other well-designed cohorts in Europe and the USA.[51–54]

This present study has shown that central adiposity is a stronger risk factor for HF than general adiposity, after adjustment for each other, in this middle-aged adult population. This is in keeping with findings from a few other studies.[55 56] Nicklas *et al*[55] in the Health ABC study of community-dwelling Americans aged 70–79 years found that WC remained significantly associated with HF after adjustment for BMI (HR 1.27; 95% CI 1.04 to 1.54 per SD) while BMI was not significantly associated with HF after adjustment for WC (HR 1.08; 95% CI 0.86 to 1.35). A similar finding was reported from the Cardiovascular Health Study (CHS) of elderly Americans.[56] Conversely, this present UKB study found a significant independent association of BMI (though weaker than WC) when adjusted for WC unlike the aforementioned studies. This may be because this study has a larger number of HF events to detect this association. Moreover, the American studies recruited older individuals.

Increase in BMI often reflects a complex interrelationship in the distribution of both fat mass and fat-free mass. Body fat mass is the total amount of adipose tissue in the body while fat-free mass is a surrogate for lean mass and includes all the body components except adipose tissue (ie, skeletal muscle mass, bone mineral mass, total body water and other organs).[57 58] Body fat mass measured either by bioimpedance or DXA showed comparable strength of associations of risk of incident HF (~50% higher risk) while for fat-free mass, there was a weaker association. There is a dearth of studies that

Table 5 Independent associations of changes in body composition measures and incident HF from baseline to imaging visit (mean 10 years from baseline visit) in analyses restricted to subset of participants with repeat body composition measures (57 670 participants) and without interval HF event before the imaging visit*

	⊿ % < –8% in body composition	–8% ≤ ⊿ % < –2% in body composition	Stable body composition –2% ≤ % change <2%	≥ 2% ⊿ %< 10% in body composition	≥ 10% ⊿ in body composition
Body composition	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Anthropometry					
Body mass index	1.35 (1.02 to 1.79)	1.07 (0.89 to 1.29)	1.00 (0.82 to 1.22)	0.87 (0.70 to 1.09)	1.96 (1.36 to 2.82)
Waist circumference	1.07 (0.81 to 1.41)	1.06 (0.871.29)	1.00 (0.79 to 1.27)	1.15 (0.96 to 1.39)	1.23 (0.89 to 1.71)
Waist-to-hip ratio	1.40 (0.96 to 2.05)	1.07 (.87 to 1.33)	1.00 (0.81 to 1.23)	1.19 (1.00 to 1.40)	1.04 (0.72 to 1.50)
Bioimpedance					
Body fat mass	1.10 (0.90 to 1.34)	1.33 (1.04 to 1.70)	1.00 (0.72 to 1.38)	0.96 (0.75 to 1.22)	0.89 (0.73 to 1.09)
Body fat-free mass	1.07 (0.77 to 1.50)	1.12 (0.96 to 1.30)	1.00 (0.82 to 1.23)	1.42 (1.08 to 1.87)	4.26 (2.12 to 8.55)

*HR estimates are floated absolute risks of HF and models were stratified by age at risk (in 5-year ranges), sex and UK region and adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.
HF, heart failure.

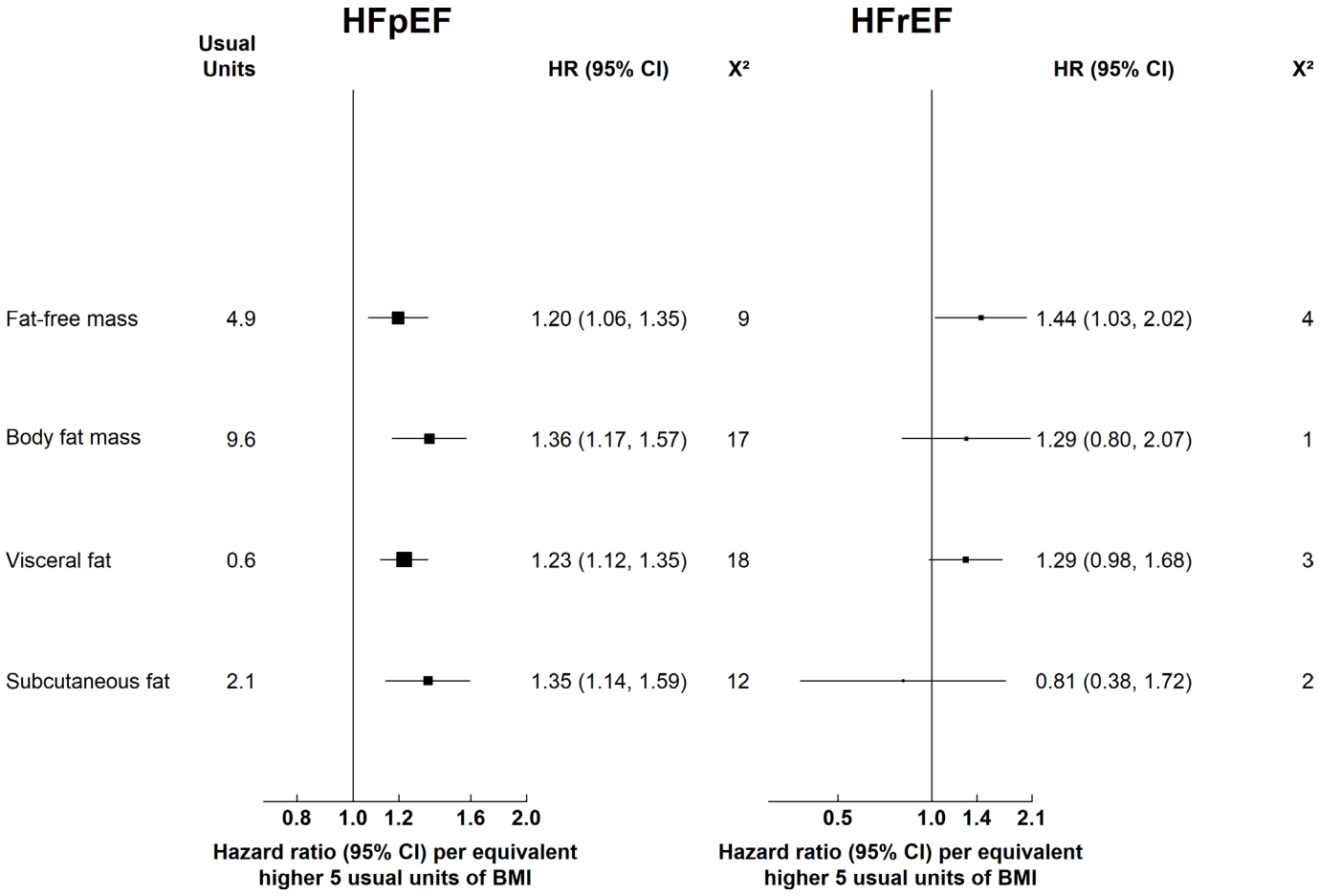

Figure 2 Associations of usual adiposity and fat measures with incident HF subtypes Cox regression models were stratified by age at risk (5-year age groups), sex and UK region and were adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity. BMI, body mass index; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with preserved ejection fraction.

have examined the association of either fat mass or fat-free mass with HF risk. In the Health ABC,[51] total body fat measured by DXA was associated with 31% higher HF risk per 8.76 kg increase.[51] In a pooled analysis of two cohorts of elderly individuals from the CHS and Health ABC study, Zhang *et al*[57] did not find a significant association between any of the total fat mass and fat-free mass measured by DXA and incident HF in confounder-adjusted models. All the above studies had fewer HF events than the UKB and none of them evaluated the role of fat mass and fat-free mass independent of one another. In UKB, adjustment of body fat mass for fat-free mass did not substantially attenuate the observed association between body fat and incident HF, thus confirming that fat distribution independent of fat-free mass is more strongly associated with incident HF. To the best of our knowledge, no study has reported the independent associations of fat-free mass with incident HF. In the present study, fat-free mass showed weaker independent association with HF independent of fat mass. It could be argued that increased skeletal muscle mass and accompanying increase in blood volume could lead to higher BP and increased cardiac workload with consequent LV remodelling that predisposes to HF.[59] However, higher fat-free mass also reflects higher visceral organs' mass, non-fat soft tissue, fibrous tissue, bone mineral mass and extracellular water. Increased extracellular water and subclinical oedema could potentially explain the remaining excess risk of HF associated with higher fat-free mass. Indeed, in population studies, there is an inverse association between skeletal muscle mass and cardiovascular outcomes while increased extracellular fluid is associated with higher risk of cardiovascular outcomes.[60–65] There is a need for studies in other populations to confirm the role of fat-free mass and its components, independent of body fat distribution in HF.

Few studies have investigated the independent association of VAT and SAT with incident HF. In the present study, both VAT and SAT were independently associated with higher risk of HF (~20% higher risk). This is consistent with recent findings by Rao *et al*[66] in the Jackson Heart Study (JHS). However, the Multi-ethnic Study of Atherosclerosis (MESA) study[16] which had far fewer HF events than the UKB and JHS did not find a significant association for SAT despite the strong association seen for VAT with incident HF. Previous studies have found significant associations between each of VAT and SAT with cardiometabolic profile and LV function although

stronger for VAT, suggesting that central fat distribution and subcutaneous fat in android and gynoid regions have metabolic activity that drives insulin resistance, inflammation and lipotoxicity that have been implicated in cardiac dysfunction.[67–80] In our analyses of the joint association of general and central adiposity with incident HF, we have shown the log-linear increase in HF risk across tertiles of VAT, WC and WHR in normal weight, overweight and obese individuals. Although, HF risk increased log-linearly across categories of BMI regardless of central adiposity, the largest risk was seen in the top tertile of central fat distribution. Xu *et al*[81] in a recent analysis of the Atherosclerosis Risk in Communities (ARIC) study have also reported greater risk of HF with increasing tertiles of visceral adiposity index (calculated from WC and BMI). These findings corroborate the relevance of central fat distribution in cardiovascular risk. We have also recently shown in the UKB that VAT is the only body composition measure independently associated with LVEF after accounting for other body fat measures and fat-free mass.[82]

The stronger independent association of central adiposity with HF could be explained by the lipotoxic and depressive effects of VAT on myocardial fibres.[83] Lipid accumulation also occurs in cardiomyocytes and epicardial tissue and leads to mitochondrial dysfunction and apoptosis of myocardial cells.[84 85] This lipotoxicity has been associated with LV remodelling in the transition to HF.[83 86 87]

Intermediate factors and causal mediators

In this study, cardiometabolic factors explained up to three-quarters of the associations between the body composition measures and incident HF. This is concurrent with previous studies that have investigated the role of cardiometabolic factors in cardiovascular disease risk.[88–90] Increased adiposity is associated with elevated SBP, insulin resistance and a proatherogenic state that is associated with vascular inflammation and arterial stiffness.[91] In turn, these factors may lead to LV remodelling and hypertrophy, followed by diastolic and systolic dysfunction, resulting in HF.[72 92–96] This is especially true of central adiposity which has also been associated with increased sympathetic activity with attendant predisposition to tachyarrhythmias and HF.[97–99]

Decadal changes in body composition measures and incident HF risk

We found a significantly increased HF risk for individuals with ≥10% decadal increase in BMI (2-fold higher risk) and individuals with ≥8% decadal decrease in BMI from baseline (35% higher HF risk) compared with individuals with stable BMI while decadal increase in body fat was also associated with higher HF risk. There was also significant graded increase in HF risk with decadal increase in fat-free mass. Decadal changes in WC and WHR were not significantly associated with incident HF risk. Few studies have assessed the associations between longitudinal changes in body composition measures and cardiovascular risk in the general population. Hu *et al*[34] in 1048 middle-aged individuals in Shanghai have reported a 2-fold higher risk of cardiovascular events in individuals with a 2-year ≥2% increase in body fat compared with individuals with stable body fat and 4-fold higher risk of cardiovascular events in those with more than 8% decrease in fat-free mass. Cheng *et al*[100] in an analysis of four US cohorts (MESA, ARIC, CHS and Framingham Heart Study) have reported a significant higher risk of HF with significant weight loss and weight gain which became noticeable 10 years before incident events. These findings point to the deleterious effects of both weight gain (both fat and fat-free mass) and weight loss for cardiovascular risk.

Magnitude of associations in HF subtypes

The majority of studies on HF LV subtypes have come from cohorts in the USA[16 53 56 101 102] and recently from the Dutch PREVEND cohort.[103] Many of these studies have far fewer events than the UKB and the reported estimates are, therefore, more imprecise than UKB. We did not find a significant association between VAT or any of the other fat measures and HFrEF despite significant associations of these measures with HFpEF. Increased general and central adiposity has been associated with renin–angiotensin–aldosterone–system activation, resulting in greater blood volume, higher BP and elevated filling pressures, which causes increased LV mass and concentric hypertrophy, the hallmark of HFpEF.[91 104 105] The stronger independent association of VAT with HFpEF could be explained by the pro-inflammatory and metabolic activity of VAT.[83] Visceral adipose tissue, epicardial fat and vascular tissue secrete proinflammatory cytokines for example, TNFα, IL-1 and IL-6 which contribute to microvascular endothelial dysfunction and reduced vascular compliance.[69 70] Reduced vascular compliance and a rise in intracardiac pressures exacerbates LV remodelling and hypertrophy leading to eventual myocardial burn-out.[106 107] Systemic inflammation is upregulated in HF and detrimental to patients with HF and while inflammatory biomarkers are elevated in patients with HFpEF, this has not been well described in those with HFrEF, suggesting that this may not be a prominent pathway in HFrEF.[108]

Future perspectives

The present study was not adequately powered to investigate the ethnic differences in the associations of body composition measures with incident HF. The UKB is a 95% European Caucasian cohort and participants of African and South-Asian ethnicities were not well represented in the cohort. Afro-Caribbeans have been shown to be at greater risk of HF than other ethnicities in population studies, however, this has often been attributed to the higher prevalence of hypertension in them.[109] On the other hand, South-Asians have higher risk of coronary heart disease (CHD) and have more central adiposity and T2DM than other ethnicities in the UK.[110–114] CHD

is the most common aetiological subtype of HF in the UK and given the close link between adiposity and CHD in population studies, one would expect higher risk of adiposity-related HF events in people of South-Asian descent. Whether this is indeed the case in individuals of South-Asian descent remains unclear. The contributions of excess adiposity to HF risk in both ethnic minorities require further investigation.

The findings from the current study have important implications for population health. By demonstrating an independent relevance of fat distribution in addition to BMI on HF risk, our findings suggest that body fat imaging could be used for HF risk prediction in the general population. In addition, the added roles of different ectopic fat depots (epicardial fat, pericardial fat, intrahepatic fat, pancreatic fat and perinephric fat) in HF risk prediction in contemporary European populations and other ethnic groups require further research. Findings from such studies could contribute to HF risk prediction models by integrating fat imaging into current HF risk scores. Despite several population studies describing independent effects of central adiposity on HF outcomes beyond the BMI, many HF risk prediction scores do not currently include central adiposity measures and fat imaging.[5 6 103 115–125] Risk prediction models for individuals without CVD in the general population are important as such models could aid the early identification of those at high risk of HF who would benefit from intensive primary and secondary prevention interventions (eg, weight reduction, physical activity, BP control).

Strengths and limitations

To the best of our knowledge, this is the largest contemporary prospective cohort study with long follow-up that has investigated the association between multiple body composition measures and incident HF. We have been able to show the associations between body fat distribution and incident HF using different methods including direct fat imaging by DXA. Our findings provide insight into the potential role of fat and fat-free mass measurement in HF risk prediction in contemporary clinical practice. We have also been able to show the real-world associations of decadal changes in body composition measures and incident HF in a contemporary population free of cardiovascular disease. All measurements were done according to standard and validated methods. Correction for regression dilution bias addressed measurement error in the associations of different body composition measures with HF risk, unlike most previous studies. The electronic linkage of participants' data to their health records allowed accurate ascertainment of HF events in this contemporary population. Moreover, excluding participants with major cardiac and vascular conditions at baseline limited the impact of reverse causation and confounding; the results were also robust to several sensitivity analyses.

The study is not without limitations. First, the number of participants in the underweight BMI category was modest (0.5%) and the study may not have been sufficiently powered to investigate the shape of the association for these participants. However, the proportion of underweight individuals in the study mirrors contemporary UK population and the absolute number of underweight participants in this analysis is substantially more than in other similar studies. The shape and strength of the observed association were similar for both fat mass and BMI and probably holds valid for these individuals. Second, BIA-derived fat and fat-free mass were estimated from proprietary algorithms which may not estimate regional fat and fat-free mass reliably, however, our analyses of DXA-derived measures were similar to the main analyses. Furthermore, while attempts have been made to reduce potential confounding, residual or unmeasured confounding is likely to remain. Fourth, there is limited ethnic diversity in the UKB (which is a predominantly white European cohort) and the findings from the study may not be generalisable to other ethnicities. Fifth, analyses of HF LV phenotypes were limited by the smaller number of individuals for which LV function was available in the cohort. Moreover, in Cox regression analyses of the risk of the HF subtypes, non-events would have included everyone else without LV data in the total sample and could have led to potential misclassification that cannot be quantified, as some people without available primary care data or LV imaging data could have had HF events which were not subtyped. Finally, it is not possible to take the reported observational associations as proof of causality but our findings corroborate recent evidence from Mendelian randomisation studies of the causality between BMI and incident HF.[126–129]

Conclusion

In conclusion, adiposity, body fat distribution and fat-free mass are associated with a positive and log-linear risk of incident HF. Central fat distribution showed a stronger independent association for HF than the BMI. Body fat distribution was only independently associated with HFpEF and not HFrEF. These findings may be important for preventative population health strategies for tackling the current obesity pandemic.

X Ayodipupo S Oguntade @AyodipupoOgunt1 and Sarah Lewington @SarahLewington2

Acknowledgements This research has been conducted using the UK Biobank Resource under Application Number 31461. The study used data provided by patients and collected by the NHS as part of their care and support and made available by National Safe Haven as part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation.Copyright (2023), NHS England. Reused with the permission of the NHS England and UK Biobank. All rights reserved

Contributors ASO, HT, BL and SL conceptualised the study. ASO developed the statistical analyses plan, analysed and interpreted the data and wrote the first draft and revisions of the manuscript. BL and SL provided access to the data and secured funds for the study. HT, BL and SL supervised the project and contributed with data interpretation and critical revisions to manuscript draft and final revisions. All authors read and approved the final draft of the manuscript. ASO, HT, BL and SL are the guarantors of the paper.

Funding This work was funded by a doctoral scholarship to ASO from the Nuffield Department of Population Health (NDPH), University of Oxford (Oxford, UK). BL acknowledges financial support from UK Biobank, funded largely by the UK Medical Research Council and Wellcome Trust. The Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), NDPH receives research grants from industry that are governed by University of Oxford contracts that protect its independence and has a staff policy of not taking personal payments from industry; further details can be found at https://www.ndph.ox.ac.uk/files/about/ndphindependence-of-research-policy-jun-20.pdf.This research was funded in whole, or in part, by the UKRI (223600/Z/21/Z). For the purpose of Open Access, the authors have applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission

Competing interests SL reports grants from the Medical Research Council (MRC) and research funding from the US Centers for Disease Control and Prevention Foundation (with support from Amgen) during the conduct of the study.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the UK Biobank is approved by the National Information Governance Board for Health and Social care, and the National Health Service North west Centre for Research Ethics Committee (Ref: 11/NW/0382) Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data that support the findings of this study are available from the UK Biobank. The UK Biobank will make the data used for this study available to all bonafide researchers for health-related research that is in the public interest.

ORCID iD

Ayodipupo S Oguntade http://orcid.org/0000-0001-8802-8590

REFERENCES

1 Kenchaiah S, Evans JC, Levy D, *et al*. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305–13.
2 Pandey A, Kondamudi N, Patel KV, *et al*. Association between regional adipose tissue distribution and risk of heart failure among blacks. *Circ Heart Fail* 2018;11:e005629.
3 Aune D, Sen A, Norat T, *et al*. Body mass index, abdominal fatness, and heart failure incidence and mortality: a systematic review and dose–response meta-analysis of prospective studies. *Circ* 2016;133:639–49.
4 Farrell SW, Finley CE, Radford NB, *et al*. Cardiorespiratory fitness, body mass index, and heart failure mortality in men: Cooper center longitudinal study. *Circ Heart Fail* 2013;6:898–905.
5 Hu G, Jousilahti P, Antikainen R, *et al*. Joint effects of physical activity, body mass index, waist circumference, and waist-to-hip ratio on the risk of heart failure. *Circ* 2010;121:237–44.
6 Borné Y, Hedblad B, Essén B, *et al*. Anthropometric measures in relation to risk of heart failure hospitalization: a Swedish population-based cohort study. *Eur J Public Health* 2014;24:215–20.
7 Fenger-Grøn M, Overvad K, Tjønneland A, *et al*. Lean body mass is the predominant anthropometric risk factor for atrial fibrillation. *J Am Coll Cardiol* 2017;69:2488–97.
8 Carbone S, Billingsley HE, Rodriguez-Miguelez P, *et al*. Lean mass abnormalities in heart failure: the role of sarcopenia, sarcopenic obesity, and cachexia. *Curr Probl Cardiol* 2020;45:100417.
9 Patel KV, Bahnson JL, Gaussoin SA, *et al*. Association of baseline and longitudinal changes in body composition measures with risk of heart failure and myocardial infarction in type 2 diabetes: findings from the look AHEAD trial. *Circ* 2020;142:2420–30.
10 McDonagh TA, Metra M, Adamo M, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
11 Heidenreich PA, Bozkurt B, Aguilar D. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circ* 2022;145:895–1032.
12 Tsujimoto T, Kajio H. Abdominal obesity is associated with an increased risk of all-cause mortality in patients with HFpEF. *J Am Coll Cardiol* 2017;70:2739–49.
13 Oh A, Okazaki R, Sam F, *et al*. Heart failure with preserved ejection fraction and adipose tissue: a story of two tales. *Front Cardiovasc Med* 2019;6:1–10.
14 Lam CS, Fat CC. Female, fatigued features of the obese HFpEF phenotype. *JACC Hear Fail* 2018;6:710–3.
15 Pandey A, LaMonte M, Klein L, *et al*. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol* 2017;69:1129–42.
16 Rao VN, Zhao D, Allison MA, *et al*. Adiposity and incident heart failure and its subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). *JACC Heart Fail* 2018;6:999–1007.
17 Vandenbroucke JP, von Elm E, Altman DG, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12:1500–24.
18 Fry A, Littlejohns TJ, Sudlow C, *et al*. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026–34.
19 Malden D, Lacey B, Emberson J, *et al*. Body fat distribution and systolic blood pressure in 10,000 adults with whole-body imaging: UK biobank and Oxford biobank. *Obesity* 2019;27:1200–6.
20 Biobank UK. UK biobank imaging modality DXA version 1.0. 2015;6.
21 Littlejohns TJ, Holliday J, Gibson LM, *et al*. The UK biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun* 2020;11:1–12.
22 Malden DE. *Adiposity and coronary heart disease in the uk biobank: a prospective cohort study of 500 000 adults.* University of Oxford, 2020.
23 Franssen FME, Rutten EPA, Groenen MTJ, *et al*. New reference values for body composition by bioelectrical impedance analysis in the general population: results from the UK biobank. *J Am Med Dir Assoc* 2014;15:1–448.
24 Shetty S, Kapoor N, Thomas N, *et al*. DXA measured visceral adipose tissue, total fat, anthropometric indices and its association with cardiometabolic risk factors in mother-daughter pairs from India. *J Clin Densitom* 2021;24:146–55.
25 Frost C, Thompson SG. Correcting for regression dilution bias: comparison of methods for a single predictor variable. *J R Stat Soc Ser A Stat Soc* 2000;163:173–89.
26 Clarke R, Shipley M, Lewington S, *et al*. Underestimation of risk associations due to regression dilution in long- term follow-up of prospective studies. *Am J Epidemiol* 1999;150:341–53.
27 Clarke R, Emberson JR, Breeze E, *et al*. Biomarkers of inflammation predict both vascular and non-vascular mortality in older men. *Eur Heart J* 2008;29:800–9.
28 Easton DF, Peto J, Babiker A. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991;10:1025–35.
29 Lu Y, Hajifathalian K, Ezzati M, *et al*. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet* 2014;383:970–83.
30 Whitlock G, Lewington S, Sherliker P, *et al*. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083–96.
31 Fontvieille E, Viallon V, Recalde M, *et al*. Body mass index and cancer risk among adults with and without cardiometabolic diseases: evidence from the EPIC and UK biobank prospective cohort studies. *BMC Med* 2023;21:1–15.
32 Berrington de Gonzalez A, Hartge P, Cerhan JR, *et al*. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363:2211–9.
33 Alegre-Díaz J, Herrington W, López-Cervantes M, *et al*. Diabetes and cause-specific mortality in Mexico city. *N Engl J Med* 2016;375:1961–71.

34 Hu T, Shen Y, Cao W, *et al*. Two-year changes in body composition and future cardiovascular events: a longitudinal community-based study. *Nutr Metab (Lond)* 2023;20:1–9.
35 Newman AB, Lee JS, Visser M, *et al*. Weight change and the conservation of lean mass in old age: the health aging and body composition study. *Am J Clin Nutr* 2005;82:872–8.
36 Bell KE, von Allmen MT, Devries MC, *et al*. Muscle disuse as a pivotal problem in sarcopenia-related muscle loss and dysfunction. *J Frailty Aging* 2016;5:33–41.
37 Mørkedal B, Vatten LJ, Romundstad PR, *et al*. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag health study). *J Am Coll Cardiol* 2014;63:1071–8.
38 Pandey A, Cornwell WK, Willis B, *et al*. Body mass index and cardiorespiratory fitness in mid-life and risk of heart failure hospitalization in older age: findings from the Cooper center longitudinal study. *JACC Heart Fail* 2017;5:367–74.
39 Wannamethee SG, Shaper AG, Whincup PH, *et al*. Obesity and risk of incident heart failure in older men with and without pre-existing coronary heart disease: does leptin have a role. *J Am Coll Cardiol* 2011;58:1870–7.
40 Van Lieshout MAW, Verwoert GC, Mattace-Raso FUS, *et al*. Measures of body composition and risk of heart failure in the elderly: the Rotterdam study. *J Nutr Health Aging* 2011;15:393–7.
41 Brouwers FP, de Boer RA, van der Harst P, *et al*. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J* 2013;34:1424–31.
42 Levitan EB, Yang AZ, Wolk A, *et al*. Adiposity and incidence of heart failure hospitalization and mortality: a population-based prospective study. *Circ Heart Fail* 2009;2:202–8.
43 Halldin AK, Lissner L, Lernfelt B, *et al*. Impact of changes in physical activity or BMI on risk of heart failure in women–the prospective population study of women in Gothenburg. *Scand J Prim Health Care* 2020;38:56–65.
44 Taylor AE, Ebrahim S, Ben-Shlomo Y, *et al*. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. *Am J Clin Nutr* 2010;91:547–56.
45 Swainson MG, Batterham AM, Tsakirides C, *et al*. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS ONE* 2017;12:e0177175.
46 Ashwell M, Gibson S. Waist-to-height ratio as an indicator of early health risk: simpler and more predictive than using a matrix based on BMI and waist circumference. *BMJ Open* 2016;6:e010159.
47 Chen J, Li M, Hao B, *et al*. Waist to height ratio is associated with an increased risk of mortality in Chinese patients with heart failure with preserved ejection fraction. *BMC Cardiovasc Disord* 2021;21:1–11.
48 Shen S, Lu Y, Qi H, *et al*. Waist-to-height ratio is an effective indicator for comprehensive cardiovascular health. *Sci Rep* 2017;7:1–7.
49 Alshamiri MQ, Mohd A Habbab F, Al-Qahtani SS, *et al*. Waist-to-height ratio (WHtR) in predicting coronary artery disease compared to body mass index and waist circumference in a single center from Saudi Arabia. *Cardiol Res Pract* 2020.:4250793.
50 Page JH, Rexrode KM, Hu F, *et al*. Waist-height ratio as a predictor of coronary heart disease among women. *Epidemiol* 2009;20:361–6.
51 McTigue KM, Chang Y-F, Eaton C, *et al*. Severe obesity, heart disease, and death among white, African American, and hispanic postmenopausal women. *Obesity* 2014;22:801–10.
52 Ndumele CE, Matsushita K, Lazo M, *et al*. Obesity and subtypes of incident cardiovascular disease. *J Am Heart Assoc* 2016;5:e003921:1–10:.
53 Fliotsos M, Zhao D, Rao VN, *et al*. Body mass index from early-, mid-, and older-adulthood and risk of heart failure and atherosclerotic cardiovascular disease: MESA. *J Am Heart Assoc* 2018;7:e009599.
54 Campbell DJ, Gong FF, Jelinek MV, *et al*. Threshold body mass index and sex-specific waist circumference for increased risk of heart failure with preserved ejection fraction. *Eur J Prev Cardiol* 2019;26:1594–602.
55 Nicklas BJ, Cesari M, Penninx BWJH, *et al*. Abdominal obesity is an independent risk factor for chronic heart failure in older people. *J Am Geriatr Soc* 2006;54:413–20.
56 Djoussé L, Bartz TM, Ix JH, *et al*. Adiposity and incident heart failure in older adults: the cardiovascular health study. *Obesity* 2012;20:1936–41.
57 Zhang L, Bartz TM, Santanasto A, *et al*. Body composition and incident heart failure in older adults: results from 2 prospective cohorts. *J Am Heart Assoc* 2022;11:e023707.
58 De Ieso F, Mutke MR, Brasier NK, *et al*. Body composition analysis in patients with acute heart failure: the scale heart failure trial. *ESC Heart Fail* 2021;8:4593–606.
59 Korhonen PE, Mikkola T, Kautiainen H, *et al*. Both lean and fat body mass associate with blood pressure. *Eur J Intern Med* 2021;91:40–4.
60 Srikanthan P, Horwich TB, Tseng CH. Relation of muscle mass and fat mass to cardiovascular disease mortality. *Am J Cardiol* 2016;117:1355–60.
61 Sedlmeier AM, Baumeister SE, Weber A, *et al*. Relation of body fat mass and fat-free mass to total mortality: results from 7 prospective cohort studies. *Am J Clin Nutr* 2021;113:639–46.
62 Xu Y, Hu T, Shen Y, *et al*. Contribution of low skeletal muscle mass in predicting cardiovascular events: a prospective cohort study. *Eur J Intern Med* 2023;114:113–9.
63 Wong JCH, O'Neill S, Beck BR, *et al*. Association of change in fat and lean mass with incident cardiovascular events for women in midlife and beyond: a prospective study using dual-energy X-ray absorptiometry (DXA). *Maturitas* 2023;178.
64 Zhang D, Spiropoulos KA, Wijayabahu A, *et al*. Low muscle mass is associated with a higher risk of all–cause and cardiovascular disease–specific mortality in cancer survivors. *Nutrition* 2023;107:1–9.
65 Knudsen NN, Kjærulff TM, Ward LC, *et al*. Body water distribution and risk of cardiovascular morbidity and mortality in a healthy population: a prospective cohort study. *PLoS ONE* 2014;9:e87466.
66 Rao VN, Bush CG, Mongraw-Chaffin M, *et al*. Regional adiposity and risk of heart failure and mortality: the Jackson heart study. *J Am Heart Assoc* 2021;10:e020920.
67 Bower JK, Meadows RJ, Foster MC, *et al*. The association of percent body fat and lean mass with HbA1C in US adults. *J Endocr Soc* 2017;1:600–8.
68 Lin S-F, Fan Y-C, Chou C-C, *et al*. Body composition patterns among normal glycemic, pre-diabetic, diabetic health Chinese adults in community: NAHSIT 2013–2016. *PLoS ONE* 2020;15:e0241121:1–14:.
69 Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm* 2013;2013:139239:1–12:.
70 Coppack SW. Pro-inflammatory cytokines and adipose tissue. *Proc Nutr Soc* 2001;60:349–56.
71 Li C, Qin D, Hu J, *et al*. Inflamed adipose tissue: a culprit underlying obesity and heart failure with preserved ejection fraction. *Front Immunol* 2022;13:947147:1–18:.
72 Neeland IJ, Gupta S, Ayers CR, *et al*. Relation of regional fat distribution to left ventricular structure and function. *Circ Cardiovasc Imaging* 2013;6:800–7.
73 Pérez-Pevida B, Díaz-Gutiérrez J, Miras AD, *et al*. High body adiposity drives glucose intolerance and increases cardiovascular risk in normoglycemic subjects. *Obesity* 2018;26:672–82.
74 Majili Z, Kinabo J. Science C. Body fat content, distribution and blood glucose concentration among adults population in Ilala municipality, Dar es Salaam. *Tanz* 2015;14:119–28.
75 de Ritter R, Sep SJS, van Greevenbroek MMJ, *et al*. Sex differences in body composition in people with prediabetes and type 2 diabetes as compared with people with normal glucose metabolism: the Maastricht study. *Diabetologia* 2023;66:861–72.
76 Takase M, Nakamura T, Hirata T, *et al*. Association between fat mass index, fat-free mass index and hemoglobin A1C in a Japanese population: the Tohoku medical megabank community-based cohort study. *J Diabetes Investig* 2022;13:858–67.
77 Zhen J, Liu S, Zhao G, *et al*. Association of waist circumference with haemoglobin A1C and its optimal cutoff for identifying prediabetes and diabetes risk in the Chinese population. *Intern Emerg Med* 2022;17:2039–44.
78 Williams ES, Shah SJ, Ali S, *et al*. C-reactive protein, diastolic dysfunction, and risk of heart failure in patients with coronary disease: heart and soul study. *Eur J Heart Fail* 2008;10:63–9.
79 Gutiérrez-Cuevas J, Sandoval-Rodriguez A, Meza-Rios A, *et al*. Molecular mechanisms of obesity-linked cardiac dysfunction: an up-date on current knowledge. *Cells* 2021;10:1–27.
80 Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. *Circ Res* 2005;96:939–49.
81 Xu C, Guo Y, Zhang S, *et al*. Visceral adiposity index and the risk of heart failure, late-life cardiac structure, and function in ARIC study. *Eur J Prev Cardiol* 2023;30:1182–92.

82 Oguntade AS, Lacey B, Taylor H, *et al*. Body fat distribution, fat-free mass and cardiovascular function in the UK biobank. *Art Res* 2023;29:121–33.
83 Sletten AC, Peterson LR, Schaffer JE. Manifestations and mechanisms of myocardial lipotoxicity in obesity. *J Intern Med* 2018;284:478–91.
84 Larsen TS, Jansen KM. Impact of obesity-related inflammation on cardiac metabolism and function. *J Lipid Atheroscler* 2021;10:8–23.
85 Zhang Y, Ren J. Role of cardiac steatosis and lipotoxicity in obesity cardiomyopathy. *Hypertension* 2011;57:148–50.
86 Li C, Liu H, Xu F, *et al*. The role of lipotoxicity in cardiovascular disease. *Emerg Crit Care Med* 2022;2:214–8.
87 Marín-Royo G, Ortega-Hernández A, Martínez-Martínez E, *et al*. The impact of cardiac lipotoxicity on cardiac function and mirnas signature in obese and non-obese rats with myocardial infarction. *Sci Rep* 2019;9:444:1–11:.
88 Wilson PWF, Meigs JB. Cardiometabolic risk: a framingham perspective. *Int J Obes* 2008;32:S17–20.
89 Lu Y, Hajifathalian K, Rimm EB, *et al*. Mediators of the effect of body mass index on coronary heart disease. *Epidemiol* 2015;26:153–62.
90 Khafagy R, Dash S. Obesity and cardiovascular disease: the emerging role of inflammation. *Front Cardiovasc Med* 2021;8:1–10.
91 Ebong IA, Goff DC, Rodriguez CJ, *et al*. Mechanisms of heart failure in obesity. *Obes Res Clin Pract* 2014;8:e540–8.
92 van Hout MJP, Dekkers IA, Westenberg JJM, *et al*. The impact of visceral and general obesity on vascular and left ventricular function and geometry: a cross-sectional magnetic resonance imaging study of the UK biobank. *Eur Heart J Cardiovasc Imaging* 2020;21:273–81.
93 Corden B, de Marvao A, Dawes TJ, *et al*. Relationship between body composition and left ventricular geometry using three dimensional cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2016;18:32.
94 Sawada N, Daimon M, Kawata T, *et al*. The significance of the effect of visceral adiposity on left ventricular diastolic function in the general population. *Sci Rep* 2019;9:1–8.
95 Rayner JJ, Banerjee R, Holloway CJ, *et al*. The relative contribution of metabolic and structural abnormalities to diastolic dysfunction in obesity. *Int J Obes (Lond)* 2018;42:441–7.
96 Hatani Y, Tanaka H, Mochizuki Y, *et al*. Association of body fat mass with left ventricular longitudinal myocardial systolic function in type 2 diabetes mellitus. *J Cardiol* 2020;75:189–95.
97 Patel KHK, Reddy RK, Sau A, *et al*. Obesity as a risk factor for cardiac arrhythmias. *BMJ Med* 2022;1:e000308.
98 Davy KP, Orr JS. Sympathetic nervous system behavior in human obesity. *Neurosci Biobehav Rev* 2009;33:116–24.
99 Alvarez GE, Beske SD, Ballard TP, *et al*. Sympathetic neural activation in visceral obesity. *Circ* 2002;106:2533–6.
100 Cheng Y-J, Chen Z-G, Wu S-H, *et al*. Body mass index trajectories during mid to late life and risks of mortality and cardiovascular outcomes: results from four prospective cohorts. *E Clin Med* 2021;33.
101 Eaton CB, Pettinger M, Rossouw J, *et al*. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. *Circ Heart Fail* 2016;9:e002883:1–9:.
102 Gaziano L, Cho K, Djousse L, *et al*. Risk factors and prediction models for incident heart failure with reduced and preserved ejection fraction. *ESC Heart Fail* 2021;8:4893–903.
103 Suthahar N, Meems LMG, Withaar C, *et al*. Relative fat mass, a new index of adiposity, is strongly associated with incident heart failure: data from PREVEND. *Sci Rep* 2022;12:147.
104 Alpert MA, Lavie CJ, Agrawal H, *et al*. Obesity and heart failure: epidemiology, pathophysiology, clinical manifestations, and management. *Transl Res* 2014;164:345–56.
105 Rider OJ, Lewis AJM, Neubauer S. Structural and metabolic effects of obesity on the myocardium and the aorta. *Obes Facts* 2014;7:329–38.
106 Nauta JF, Hummel YM, Tromp J, *et al*. Concentric vs. eccentric remodelling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment. *Eur J Heart Fail* 2020;22:1147–55.
107 Azevedo PS, Polegato BF, Minicucci MF, *et al*. Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. *Arq Bras Cardiol* 2016;106:62–9.
108 Albar Z, Albakri M, Hajjari J, *et al*. Inflammatory markers and risk of heart failure with reduced to preserved ejection fraction. *Am J Cardiol* 2022;167:68–75.
109 Piña IL, Jimenez S, Lewis EF, *et al*. Race and ethnicity in heart failure JACC focus seminar 8/9. *J Am Coll Cardiol* 2021;78:2589–98.
110 Tillin T, Hughes AD, Mayet J, *et al*. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans. *J Am Coll Cardiol* 2013;61:1777–86.
111 Volgman AS, Palaniappan LS, Aggarwal NT. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments a scientific statement from the American heart association. *Circ* 2018;138:e1–34.
112 Kuppuswamy VC, Gupta S. Excess coronary heart disease in South Asians in the United Kingdom. *BMJ* 2005;330:1223–4.
113 Rao G, Powell-Wiley TM, Ancheta I, *et al*. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations a scientific statement from the American heart association. *Circ* 2015;132:457–72.
114 Patel AP, Wang M, Kartoun U, *et al*. Quantifying and understanding the higher risk of atherosclerotic cardiovascular disease among South Asian individuals: results from the UK biobank prospective cohort study. *Circ* 2021;144:410–22.
115 Loehr LR, Rosamond WD, Poole C, *et al*. Association of multiple anthropometrics of overweight and obesity with incident heart failure: the atherosclerosis risk in communities study. *Circ Heart Fail* 2009;2:18–24.
116 Kannel WB, D'Agostino RB, Silbershatz H, *et al*. Profile for estimating risk of heart failure. *Arch Intern Med* 1999;159:1197.
117 Ho JE, Enserro D, Brouwers FP, *et al*. Predicting heart failure with preserved and reduced ejection fraction the international collaboration on heart failure subtypes. *Circ Heart Fail* 2016;9:1–9.
118 Butler J, Kalogeropoulos A, Georgiopoulou V, *et al*. Incident heart failure prediction in the elderly the health ABC heart failure score. *Circ Heart Fail* 2008;1:125–33.
119 Chahal H, Bluemke DA, Wu CO, *et al*. Heart failure risk prediction in the multi-ethnic study of atherosclerosis. *Heart* 2015;101:58–64.
120 Agarwal SK, Chambless LE, Ballantyne CM, *et al*. Prediction of incident heart failure in general practice the atherosclerosis risk in communities (ARIC) study. *Circ Heart Fail* 2012;5:422–9.
121 Codina P, Lupón J, Borrellas A, *et al*. Head-to-head comparison of contemporary heart failure risk scores. *Eur J Heart Fail* 2021;23:2035–44.
122 Khan SS, Ning H, Shah SJ, *et al*. 10-year risk equations for incident heart failure in the general population. *J Am Coll Cardiol* 2019;73:2388–97.
123 Khan SS, Ning H, Allen NB, *et al*. Development and validation of a long-term incident heart failure risk model. *Circ Res* 2022;130:200–9.
124 Shea S, Blaha MJ. Long-term risk prediction for heart failure, disparities, and early prevention. *Circ Res* 2022;130:210–2.
125 Tragante V, Pilbrow A, Poppe K. Editorial: improving early detection and risk prediction in heart failure. *Front Cardiovasc Med* 2022;9:930935.
126 Larsson SC, Bäck M, Rees JMB, *et al*. Body mass index and body composition in relation to 14 cardiovascular conditions in UK biobank: a mendelian randomization study. *Eur Heart J* 2020;41:221–6.
127 Lumbers RT, Katsoulis M, Henry A. Body mass index and heart failure risk: a cohort study in 1.5 million individuals and Mendelian Randomisation analysis. *Cardiovascular Medicine* [Preprint].
128 Lind L, Ingelsson M, Sundstrom J, *et al*. Impact of risk factors for major cardiovascular diseases: a comparison of life-time observational and mendelian randomisation findings. *Open Heart* 2021;8:e001735.
129 Benn M, Marott SCW, Tybjærg-Hansen A, *et al*. Obesity increases heart failure incidence and mortality: observational and Mendelian randomization studies totalling over 1 million individuals. *Cardiovasc Res* 2023;118:3576–85.

Table S1: Operational codes used to define incident heart failure

Disease category	Disease code category	Code definition
ICD-10 HES and national death records		
Hypertensive heart disease	I11	I11.0 Hypertensive heart disease with (congestive) heart failure
Hypertensive heart and renal disease	I13	I13.0 Hypertensive heart and renal disease with (congestive) heart failure I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
Heart failure	I50	I50.0 Congestive heart failure I50.1 Left ventricular failure I50.9 Heart failure, unspecified
OPCS 4		
Transplantation of heart and lung	K01	K01 Transplantation of heart and lung K01.1 Allotransplantation of heart and lung K01.2 Revision of transplantation of heart and lung K01.8 Other specified transplantation of heart and lung K01.9 Unspecified transplantation of heart and lung
Other transplantation of heart	K02	K02 Other transplantation of heart K02.1 Allotransplantation of heart NEC K02.2 Xenotransplantation of heart K02.3 Implantation of prosthetic heart K02.4 Piggyback transplantation of heart K02.5 Revision of implantation of prosthetic heart K02.6 Revision of transplantation of heart NEC K02.8 Other specified other transplantation of heart K02.9 Unspecified other transplantation of heart
Open heart assist operations	K54	K54 Open heart assist operations K54.1 Open implantation of ventricular assist device K54.2 Open removal of ventricular assist device K54.8 Other specified open heart assist operations K54.9 Unspecified open heart assist operations
Transluminal heart assist operations	K56	K56 Transluminal heart assist operations K56.1 Transluminal insertion of pulsation balloon into aorta K56.2 Transluminal insertion of heart assist system NEC K56.3 Transluminal maintenance of heart assist system K56.4 Transluminal removal of heart assist system K56.8 Other specified transluminal heart assist operations K56.9 Unspecified transluminal heart assist operations
Transluminal operations on cardiac conduit	K76	K76 Transluminal operations on cardiac conduit K76.1 Percutaneous transluminal balloon dilation of cardiac conduit K76.8 Other specified transluminal operations on cardiac conduit K76.9 Unspecified transluminal operations on cardiac conduit

HES: Hospital Episodes Statistics, **OPCS:** Office of Population Censuses and Surveys.

Table S2: Diagnosis codes for HF ejection fraction subtypes in primary care

Heart failure subtype	Code type	Diagnosis codes
HFpEF	Read codes	585g G5yyA G5yyC G583. XaJ99 XaItG XaYYs XaWyi 585k. XaJvY 585R. 58530 5C20. XaJKz XaItG Left ventricular diastolic dysfunction XaJ99 Echocardiogram shows left ventricular diastolic dysfunction XaWyi Heart failure with normal ejection fraction XaYYs Diastolic dysfunction
	SNOMED CT	"3545003" "418304008" "443343001" "441530006" "120891000119109" "120881000119106" "443344007" "446221000" "395704004" "441530006" "443344007"
HFrEF	Read codes	585f. G5yy9 XaJ98 XaIIq XafeB G5yyD G581.13 33BA. XM1Qn Impaired left ventricular function XaIIq Left ventricular systolic dysfunction XaJ98 Echocardiogram shows left ventricular systolic dysfunction XafeB Heart failure with reduced ejection fraction
	SNOMED CT	"441481004" "153931000119109" "153951000119103" "153941000119100" "442304009" "134401001" "698592004" "430396006" "443253003" "371037005" "417996009" "443254009" "120861000119102" "120851000119104" "15629741000119102" "15629641000119107" "703272007" "703275009" "703273002 "703276005" "703274008"

Table S3: Age-adjusted sex-specific partial correlation coefficients between body composition measures at baseline visit*†

		WC	WHR	Body fat mass	Body fat-free mass
BMI	**Women**	0.87	0.45	0.94	0.69
	Men	0.88	0.60	0.92	0.65
WC		**Women**	0.74	0.88	0.66
		Men	0.80	0.89	0.65
WHR			**Women**	0.44	0.28
			Men	0.61	0.32
Body fat mass				**Women**	0.71
				Men	0.60

*Analysis among 428,087 UKB participants included in the main analysis.
†Pearson partial correlation coefficients are reported in this table. BMI: body mass index; WC: waist circumference; WHR: waist hip ratio.

Table S4: Age-adjusted sex-specific partial correlation coefficients between DXA-derived fat measures at baseline imaging visit*†

		Visceral fat	Subcutaneous fat	Fat-free mass
Body fat	**Women**	0.82	0.96	0.53
	Men	0.87	0.93	0.44
Visceral fat		**Women**	0.67	0.40
		Men	0.65	0.37
Subcutaneous fat			**Women**	0.52
			Men	0.41

*Analysis among 36,278 UKB participants (men=17309; women=18969) included in the DXA-imaging analysis. †Pearson partial correlation coefficients are reported in this table. BMI: body mass index; WC: waist circumference; WHR: waist hip ratio.

Table S5: Regression Dilution Ratios (RDR) of body composition measures

Body composition	Women*	Men*	All†
Anthropometric and bio-impedance measures			
BMI	0.92	0.93	0.92
Waist circumference	0.82	0.82	0.82
Waist-hip ratio	0.65	0.66	0.65
Body fat mass	0.90	0.90	0.90
Body fat-free mass	0.91	0.95	0.94
DXA			
Visceral fat mass	0.93	0.92	0.92
Subcutaneous fat mass	0.93	0.92	0.93
Body fat mass	0.93	0.93	0.93
Body fat-free mass	0.97	0.98	0.97

Number of resurvey participants=17,450 (men=8286; women-=9164) for anthropometric and bio-impedance measures while number of resurvey participants=2913 (men=1425; women-=1488) for DXA measures. *adjusted for 5year age-group; †adjusted for 5 year age-group and sex.

Table S6: Baseline characteristics of UK Biobank participants by sex*

Characteristics at baseline	Women	Men	Total
Number of participants	**N=239,775**	**N=188,312**	**N=428,087**
Demographic and lifestyle factors			
Age (years)	55.9 (8.0)	55.9 (8.2)	55.9 (8.1)
Recruitment regions			
England	212,710 (88.7%)	167,525 (89.0%)	380,235 (88.8%)
Wales	9,870 (4.1%)	7,843 (4.2%)	17,713 (4.1%)
Scotland	17,195 (7.2%)	12,944 (6.9%)	30,139 (7.0%)
Ethnicity			
White	227,100 (94.7%)	178,077 (94.6%)	405,177 (94.6%)
Asian	3,970 (1.7%)	4,147 (2.2%)	8,117 (1.9%)
African	3,898 (1.6%)	2,946 (1.6%)	6,844 (1.6%)
others	4,807 (2.0%)	3,142 (1.7%)	7,949 (1.9%)
Higher education	153,256 (63.9%)	123,606 (65.6%)	276,862 (64.7%)
Most deprived	47,030 (19.6%)	38,480 (20.4%)	85,510 (20.0%)
Current smoker	20,911 (8.7%)	23,108 (12.3%)	44,019 (10.3%)
Regular/daily drinker	152,909 (63.8%)	147,873 (78.5%)	300,782 (70.3%)
Low physical activity	42,807 (17.9%)	31,809 (16.9%)	74,616 (17.4%)
Anthropmetry			
BMI (kg/m^2)	26.9 (5.0)	27.7 (4.1)	27.2 (4.7)
Waist circumference (cm)	84.2 (12.2)	96.4 (10.9)	89.6 (13.1)
Hip circumference (cm)	103.1 (10.1)	103.2 (7.3)	103.1 (9.0)
Waist-hip ratio	0.81 (0.07)	0.93 (0.06)	0.87 (0.09)
Waist-height ratio	0.52 (0.08)	0.55 (0.06)	0.53 (0.07)
Bioimpedance			
Body fat percentage (%)	36.4 (6.8)	25.0 (5.7)	31.4 (8.5)
Whole body fat mass (kg)	26.6 (9.8)	21.9 (8.0)	24.5 (9.4)
Whole body fat-free mass (kg)	44.5 (4.9)	63.7 (7.7)	52.9 (11.4)
Trunk fat percentage (%)	33.9 (7.7)	27.3 (6.5)	31.0 (7.9)
Trunk fat mass (kg)	13.5 (5.2)	13.6 (4.8)	13.5 (5.0)
Trunk fat-free mass (kg)	25.0 (2.6)	35.1 (3.9)	29.4 (5.9)
†**DXA imaging visit**			
DXA body fat mass	26.4 (9.6)	24.6 (8.8)	25.5 (9.3)
DXA visceral fat	0.8 (0.6)	1.7 (1.0)	1.2 (0.9)
DXA-subcutaneous adipose tissue (kg)	6.0 (2.1)	4.5 (1.6)	5.3 (2.0)
DXA fat-free mass (kg)	41.9 (4.9)	58.4 (6.7)	49.8 (10.1)
Medical conditions			
Hypertension	52,564 (21.9%)	51,603 (27.4%)	104,167 (24.3%)
Diabetes	7,869 (3.3%)	10,637 (5.6%)	18,506 (4.3%)
Chronic kidney disease	1,328 (0.6%)	1,131 (0.6%)	2,459 (0.6%)
BP lowering medication usage	35,916 (15.0%)	35,136 (18.7%)	71,052 (16.6%)
Insulin usage	1,522 (0.6%)	2,009 (1.1%)	3,531 (0.8%)
Lipid lowering medication usage	22,968 (9.6%)	29,212 (15.5%)	52,180 (12.2%)
Systolic blood pressure (mmHg)	135.0 (19.1)	141.1 (17.3)	137.7 (18.6)
Diastolic blood pressure (mmHg)	80.8 (9.9)	84.6 (9.9)	82.4 (10.1)
Blood biomarkers			
Glucose (mmol/L)	5.0 (1.0)	5.1 (1.3)	5.1 (1.2)
HbA1c (mmol/mol)	35.6 (5.6)	36.0 (7.0)	35.8 (6.3)
HDL-C (mmol/L)	1.6 (0.4)	1.3 (0.3)	1.5 (0.4)
LDL-C (mmol/L)	3.7 (0.9)	3.6 (0.8)	3.6 (0.8)
eGFR (ml/min)	96.8 (16.3)	84.2 (14.7)	91.2 (16.8)
‡C-reactive protein (mg/L)	2.8 (0.7)	2.9 (0.6)	2.8 (0.7)

* Data are presented as arithmetic mean (SD), geometric mean (SD) or n(%);

‡Geometric mean (SD); BMI: body mass index; eGFR: estimated glomerular filtration rate; †Imaging visit occurred 10 years after the baseline visit.

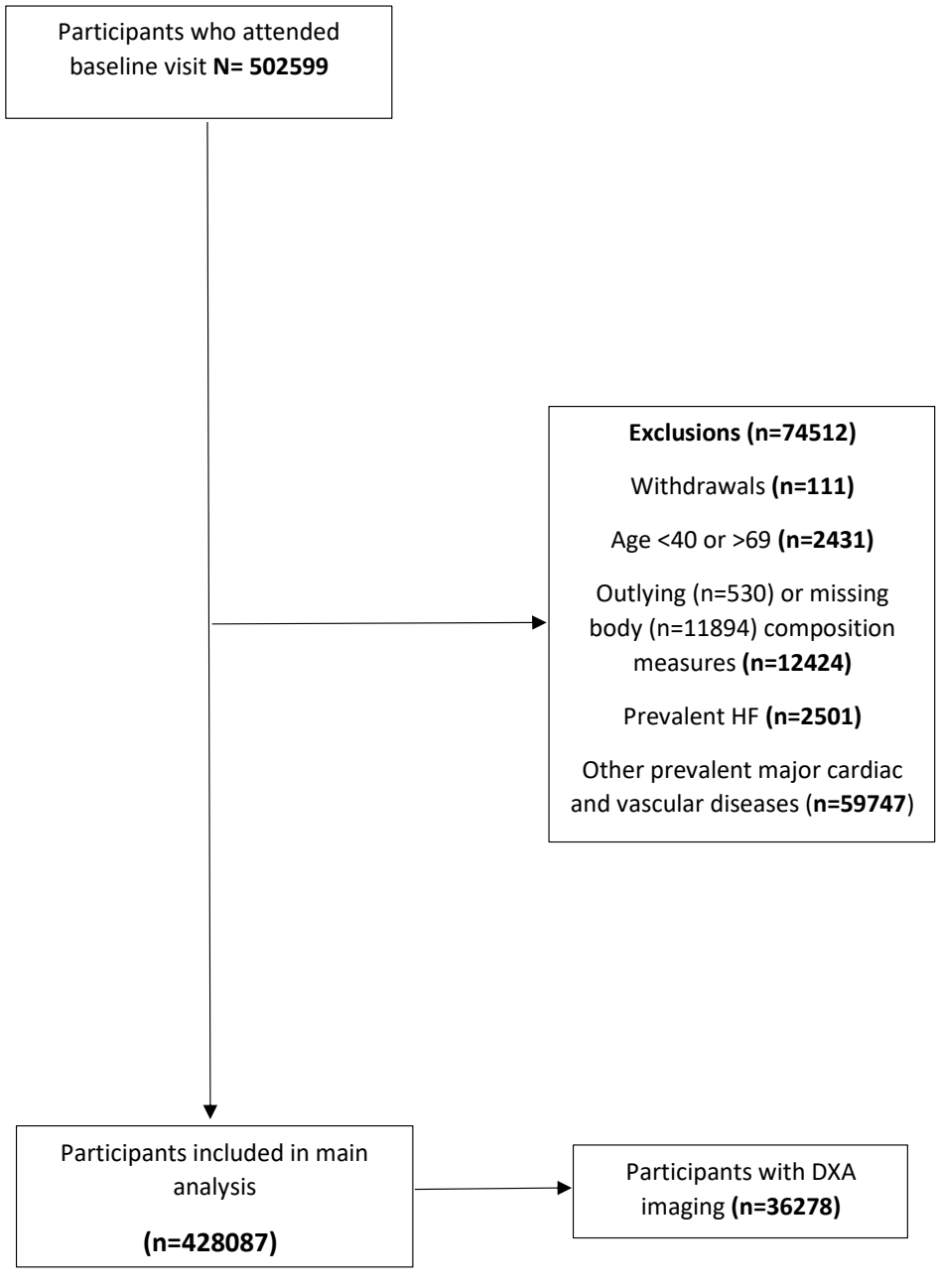

Figure S1: Flow diagram of UK Biobank study population

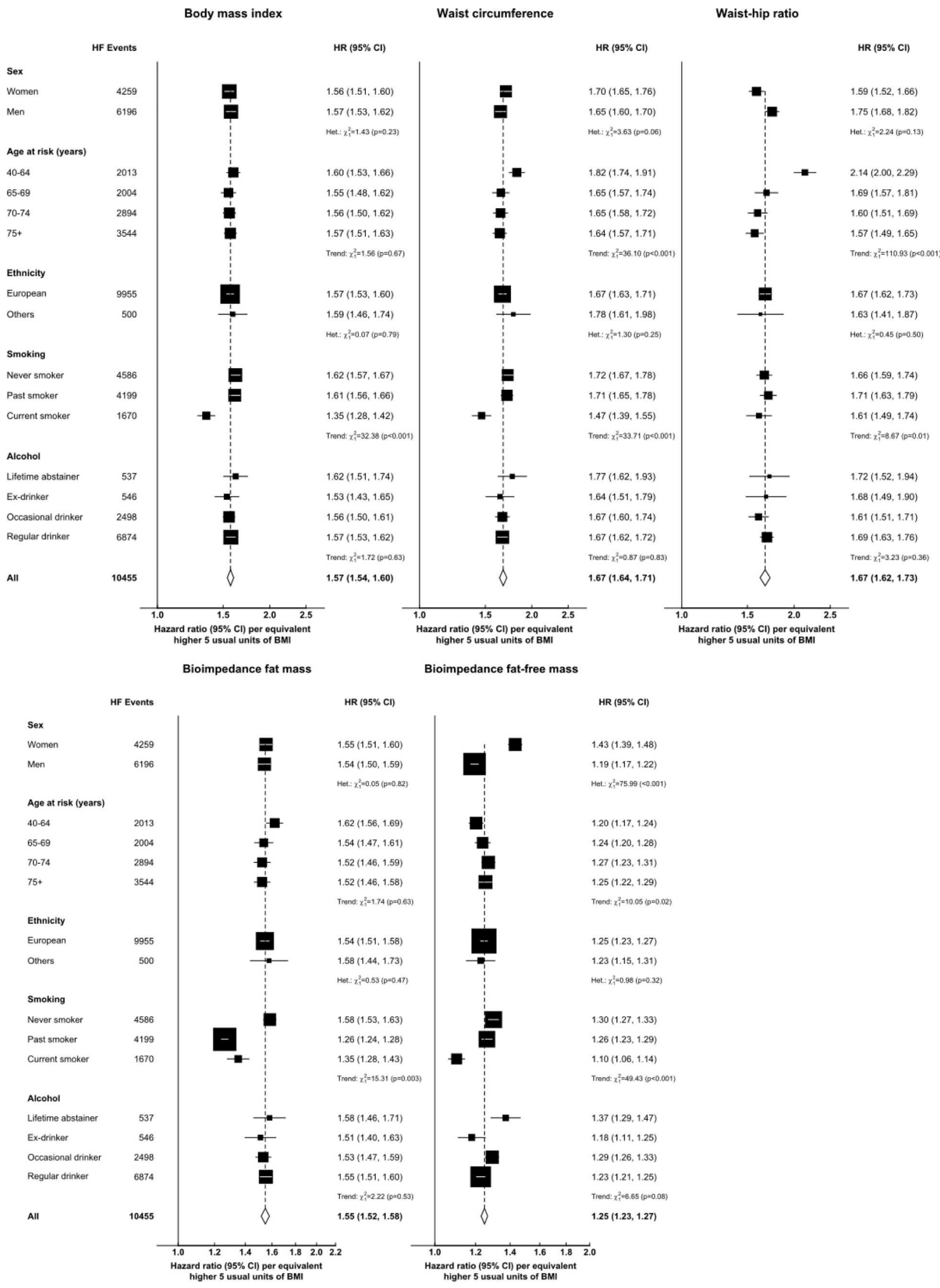

Figure S2: Hazard ratios (95% CI) of HF per 5 usual BMI units equivalent of anthropometric and bio-impedance measures by potential confounders

Box area is inversely proportional to the variance of the log risk. Where appropriate, hazard ratio (HR) estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.

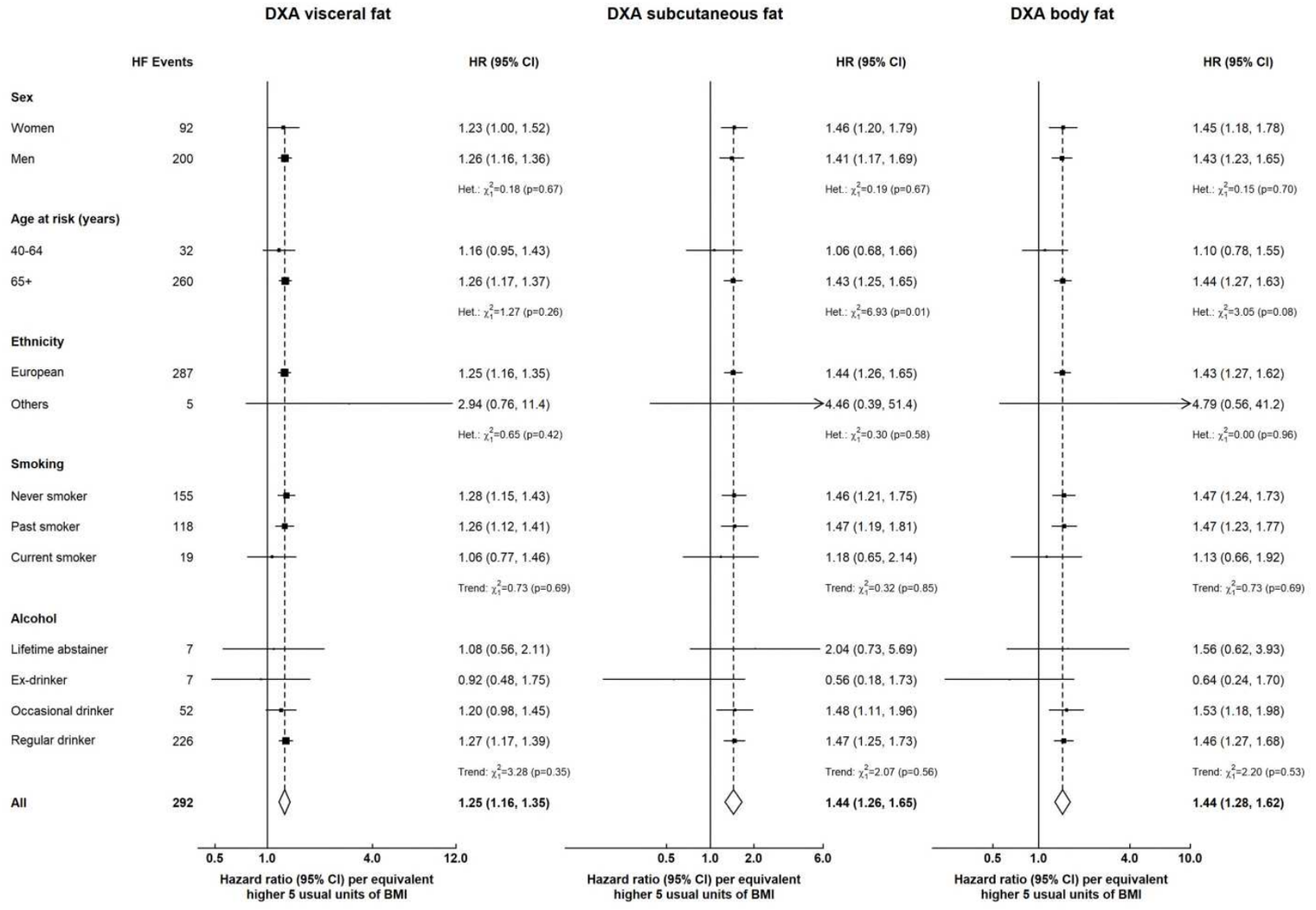

Figure S3: Hazard ratios (95% CI) of HF per 5 usual BMI units equivalent of DXA fat measures by potential confounders

Box area is inversely proportional to the variance of the log risk. Where appropriate, hazard ratio (HR) estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.

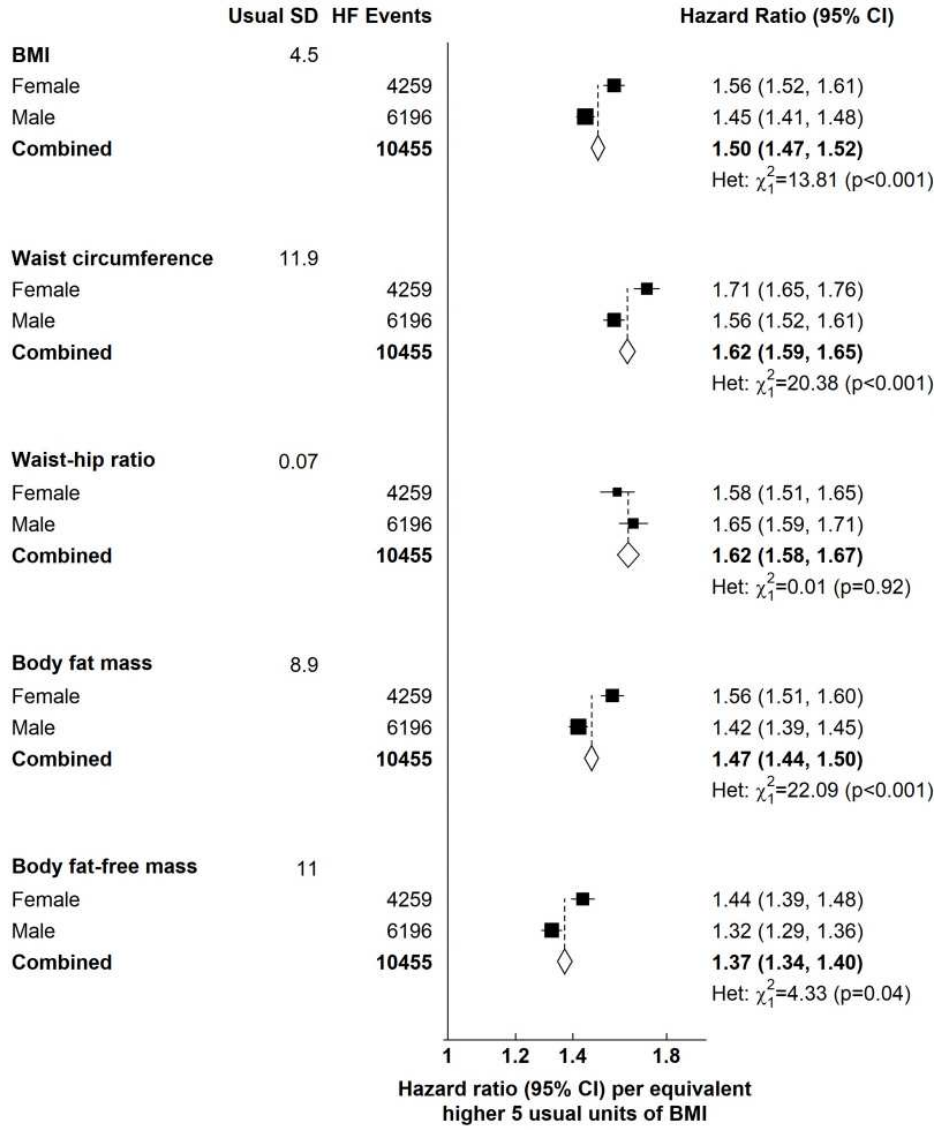

Figure S4: Hazard ratios (95% CI) of HF per usual SD of anthropometric and bio-impedance measures in main analyses

Box area is inversely proportional to the variance of the log risk. Where appropriate, hazard ratio (HR) estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.

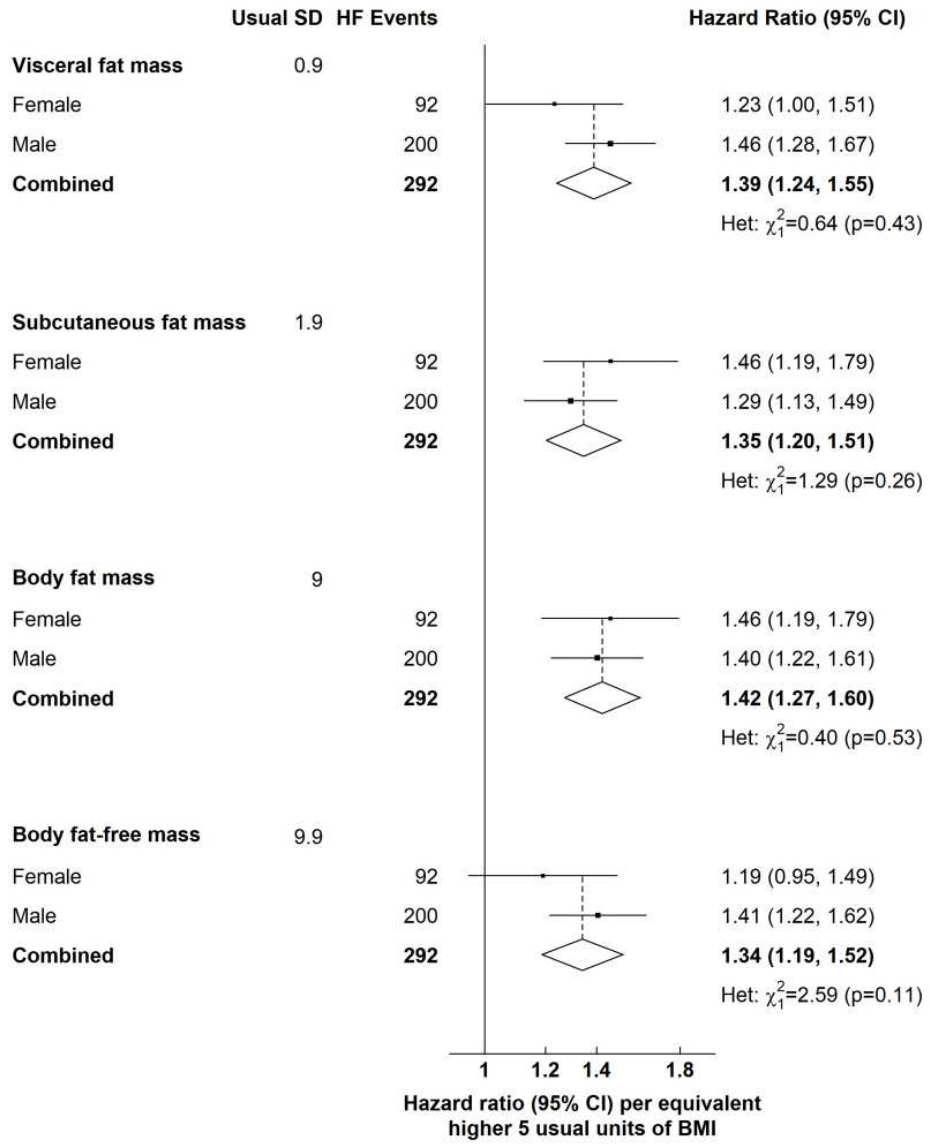

Figure S5: Hazard ratios (95% CI) of HF per usual SD of DXA-derived measures in supplementary analyses

Box area is inversely proportional to the variance of the log risk. Where appropriate, hazard ratio (HR) estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.

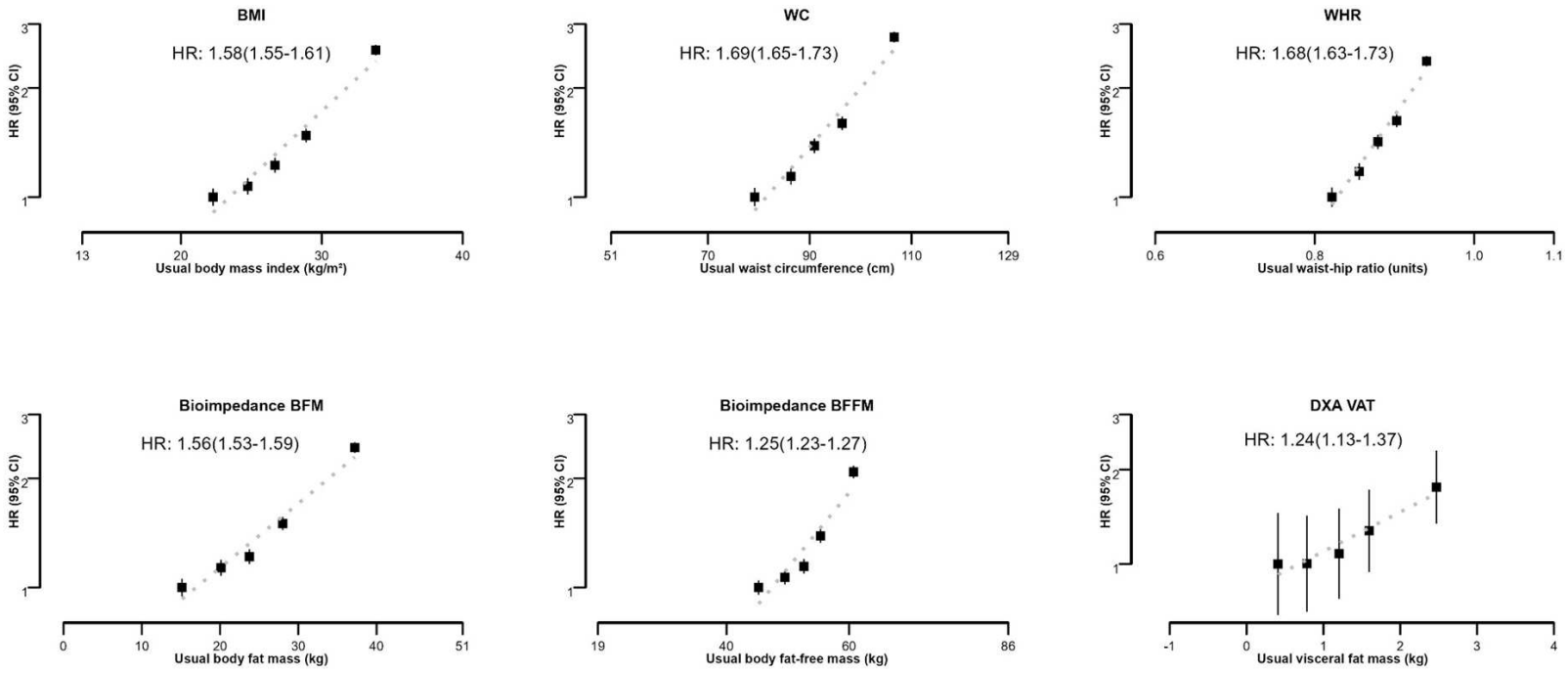

Figure S5: Hazard ratios (95% CI) of incident HF with increasing usual units of body composition measures in all participants excluding first 2 years of follow-up.

Error bars denote group-specific 95% CIs. Hazard ratio estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity

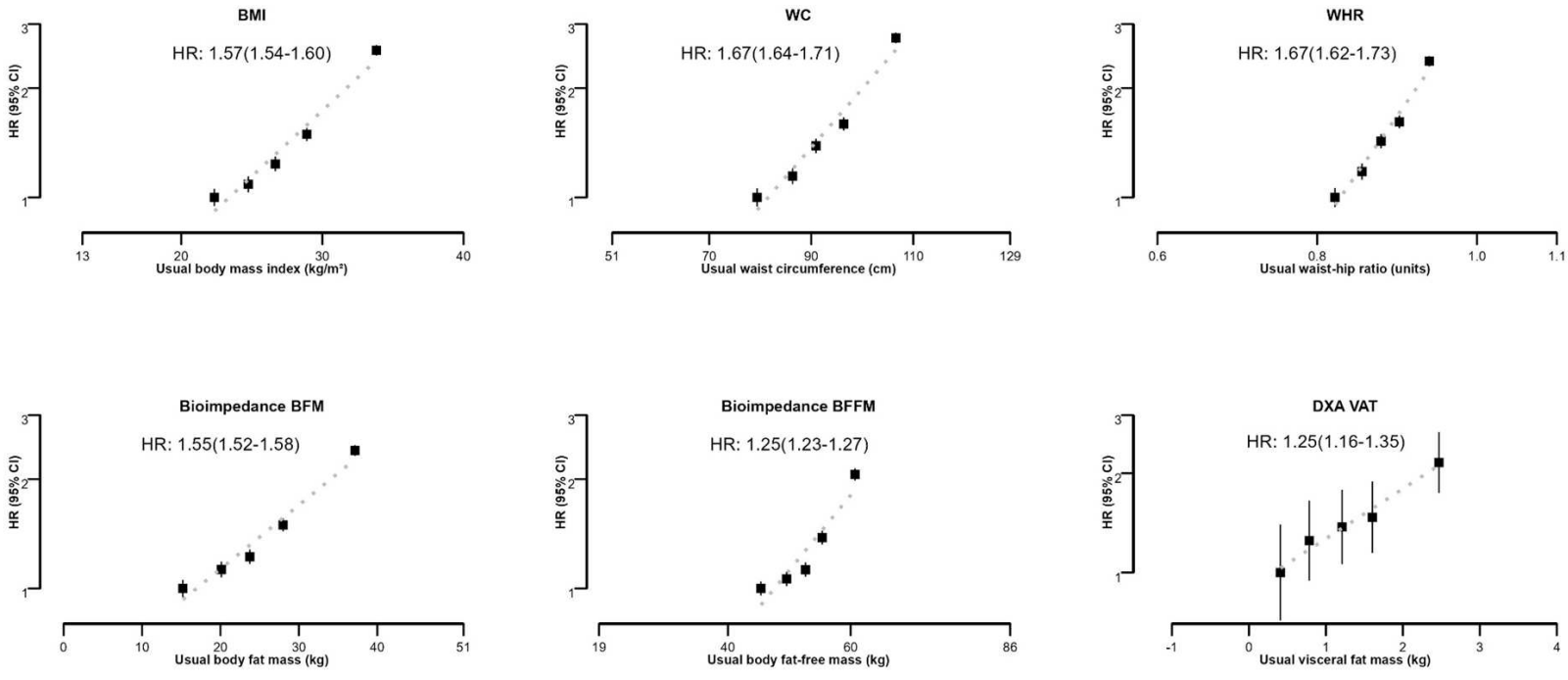

Figure S6: Hazard ratios (95% CI) of incident HF with increasing usual units of body composition measures in all participants excluding underweight participants

Error bars denote group-specific 95% CIs. Hazard ratio estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity

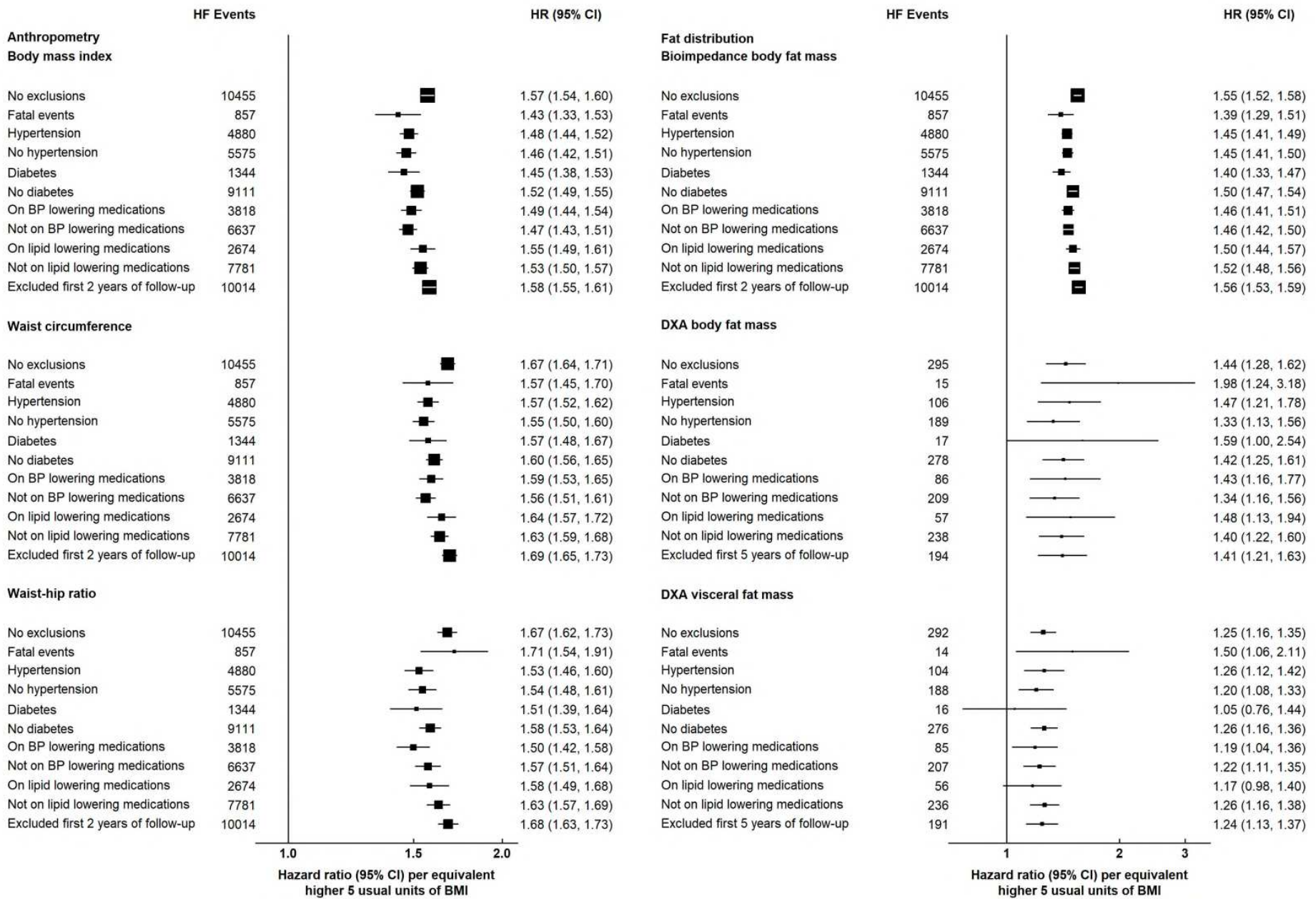

Figure S7: Hazard ratios of HF per equivalent 5 BMI usual units higher body composition measures before and after various exclusions

Box area is inversely proportional to the variance of the log risk. Where appropriate, hazard ratio (HR) estimates are stratified by age at risk (in 5-year ranges), sex and UK region, and are adjusted for ethnicity, education, social deprivation, smoking, alcohol and physical activity.

Oguntade AS, *et al. Open Heart* 2024; 11:e002711. doi: 10.1136/openhrt-2024-002711