Title: The role of obesity-related cardiovascular remodelling in mediating incident cardiovascular outcomes: a population-based observational study

Running title: A link between obesity and cardiovascular outcomes

Liliana Szabo[1,2,3]*, Celeste McCracken[4]*, Jackie Cooper[1], Oliver J Rider[4], Hajnalka Vago[3], Bela Merkely[3], Nicholas C. Harvey[5,6], Stefan Neubauer[4], Steffen E. Petersen[†1,2,7,8], Zahra Raisi-Estabragh[†1,2]

1. William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK

2. Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, West Smithfield, London, EC1A 7BE, UK

3. Semmelweis University, Heart and Vascular Center, Budapest Hungary

4. Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, OX3 9DU, UK

5. MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

6. NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

7. Health Data Research UK, London, UK

8. Alan Turing Institute, London, UK

*LS and CM are joint first authors.

[†]SEP and ZRE are joint senior authors.

Corresponding author: Dr Zahra Raisi-Estabragh; William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK; E-mail: zahraraisi@doctors.org.uk, Telephone: +44 (20) 37658766

Abstract

Aims: We examined associations of obesity with incident cardiovascular outcomes and cardiovascular magnetic resonance (CMR) phenotypes, integrating information from body mass index (BMI) and waist-to-hip-ratio (WHR). Then, we used multiple mediation to define the role of obesity-related cardiac remodelling in driving obesity-outcome associations, independent of cardiometabolic diseases.

Methods and results: In 491,606 UK Biobank participants, using Cox proportional hazard models, greater obesity (higher WHR, higher BMI) was linked to significantly greater risk of incident ischaemic heart disease, atrial fibrillation (AF), heart failure (HF), all-cause mortality, and cardiovascular disease mortality. In combined stratification by BMI and WHR thresholds, elevated WHR was associated with greater risk of adverse outcomes at any BMI level. Individuals with overweight BMI but normal WHR had weaker disease associations. In the subset of participants with CMR (n=31,107), using linear regression, greater obesity was associated with higher left ventricular (LV) mass, greater LV concentricity, poorer LV systolic function, lower myocardial native T1, larger left atrial (LA) volumes, poorer LA function and lower aortic distensibility. Of note, higher BMI was linked to higher, whilst greater WHR was linked to lower LVEDV. In Cox models greater LVEDV and LVM were linked to increased risk of cardiovascular disease, most importantly HF and an increased LAV was the key predictive measure of new onset AF. In multiple mediation analyses, hypertension and adverse LV remodelling (higher LVM, greater concentricity) were major independent mediators of the obesity-outcome associations. Atrial remodelling and native T1 were additional mediators in the associations of obesity with AF and HF, respectively.

Conclusions: We demonstrate associations of obesity with adverse cardiovascular phenotypes and their significant independent role in mediating obesity-outcome relationships. Additionally, our findings support the integrated use of BMI and WHR to evaluate obesity-related cardiovascular risk.

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Ethical approval

This study complies with the Declaration of Helsinki; the work was covered by the ethical approval for UK Biobank studies from the National Health Service (NHS) National Research Ethics Service on 17th June 2011 (Ref 11/NW/0382) and extended on 18th June 2021 (Ref 21/NW/0157) with written informed consent obtained from all participants.

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Introduction

The obesity pandemic is a global public health priority and represents a major risk factor for cardiovascular disease (CVD) and premature mortality[1]. Obesity is traditionally defined using body mass index (BMI), a correlate of subcutaneous adiposity. However, growing evidence supports a more heterogeneous nature of obesity phenotype, incorporating differential patterns of regional body fat distribution, broadly comprising subcutaneous and visceral adiposity. Visceral fat tissue is located around solid organs and has distinct metabolic features[2]. Waist-to-hip ratio (WHR) is a simple measure of central obesity that approximates body shape and correlates with abdominal visceral adiposity[3]. Expert panels increasingly recommend integration of BMI and WHR for characterisation of obesity[4,5]. However, few studies have assessed the utility of incorporating both measures for evaluating relationships of obesity with cardiovascular outcomes in large population cohorts.

Despite widespread recognition of obesity as a major risk factor for CVD, the mechanisms through which it promotes disease are incompletely understood. A large proportion of adverse cardiovascular associations of obesity are attributed to obesity as a driver of cardiometabolic diseases, such as hypertension and diabetes[1]. However, obesity may also impact cardiovascular health through other independent biological pathways[1]. For example, myocardial accumulation of triglycerides and their products have been linked to direct cardiac lipotoxicity[6]. This and many other direct and indirect pathways may lead to myocardial disarray, dysfunction, and fibrosis[2,7]. The role of obesity-related cardiovascular remodelling in driving associated cardiovascular risk has not been previously examined.

Cardiovascular imaging phenotypes reflect organ-level remodelling in response to a wide range of exposures and provide reliable indicators of cardiovascular health[8]. Evaluating the relationships between obesity and cardiovascular imaging phenotypes may provide novel insights into the mechanisms driving the adverse relationships between obesity and cardiovascular outcomes. Previous studies demonstrate unhealthy cardiac remodelling patterns in obesity[7], using echocardiography worse diastolic function and adverse deformation pattern have also been described[9,10]. However, cohort studies using cardiovascular magnetic resonance (CMR) imaging are limited to simplistic volumetric indices[11–14].

In this study of the UK Biobank cohort, we evaluate the role of obesity-related cardiovascular remodelling in mediating incident cardiovascular outcomes. First, we examine the links between obesity and incident cardiovascular events, integrating information from BMI and WHR. Second, we examine associations of obesity with CMR measures of cardiac structure, function, and myocardial tissue composition. Finally, we use multiple mediation analysis to quantify the role of obesity-related cardiovascular remodelling in driving associations with incident outcomes, independent of cardiometabolic diseases.

Methods

Study population

The UK Biobank is a cohort study including more than 500,000 individuals from across the UK. Participants aged 40-69 years old were identified through National Health Service (NHS). Baseline assessment incorporated socio-demographics, lifestyle, environmental factors, medical history, and physical measures described in the study protocol[15]. Incident health outcomes are prospectively tracked through linkages with national electronic health records, including hospital episode statistics (HES) and death registers. The UK Biobank Imaging Study aims to scan a randomly selected 20% (n=100,000) subset of the original UK Biobank participants. The pre-defined imaging protocol consists of multiorgan multimodality imaging, including CMR[16].

Measures of obesity

Body size measures were performed as part of the UK Biobank assessments using standardised protocols and equipment. Height was measured using the Seca 202 height measure (Seca, Germany). Waist (natural indent) and hip (widest point) circumferences were measured over light clothes with the Seca-200 tape measure. Weight measures were taken using the Tanita BC418MA body composition analyser (Tanita, Japan).

We calculated BMI by dividing weight in kilograms by height in meters squared. We calculated WHR by dividing waist circumference by hip circumference. We considered BMI and WHR as both continuous and categorical variables. BMI categories were as follows: 1) Normal BMI 18.5-24.9 kg/m^2, 2) Overweight BMI 25-29.9 kg/m^2, 3) Obese BMI >30 kg/m^2. For WHR, we used abdominal obesity cut-off points of 0.85 for women and 0.90 for men.

Ascertainment of outcomes

The following incident CVDs were considered: any CVD, ischaemic heart disease (IHD), heart failure (HF), atrial fibrillation (AF). We also included all-cause mortality and CVD mortality (any CVD recorded as the primary cause of death). Outcomes were extracted using record linkage to HES and death register data with diseases recorded according to international classification of disease (ICD) codes ***(Supplementary Table 1)***.

CMR measures

Native CMR scans were performed according to a pre-defined acquisition protocol[17] using 1.5 Tesla scanners (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare). The protocol included standard long-axis images and a short-axis stack covering both ventricles from base to apex, all acquired using balanced steady-state free precession sequences. CMR images were analysed using a fully automated quality controlled pipeline[18]. We included the following measures of left ventricular (LV) and left atrial (LA) structure and function: LV end-diastolic volume (LVEDV), mass (LVM), concentricity index (LVM:LVEDV), ejection fraction (LVEF), LA maximal volume (LAV), LA ejection fraction (LAEF). We included LV global function index (LVGFI) as an additional measure of LV function. We included LV global function index (LVGFI) as an additional measure of LV function, defined as LVSV/LV global volume x 100, where LV global volume was calculated as the sum of the LV mean cavity volume [(LV end-diastolic volume + LV end-systolic volume)/2] and myocardium volume (LV mass/density). Density of LV was specified as 1.05 g/mL. LVGFI is a measure of LV function which incorporates ventricular structure and has been shown to have more reliable associations with disease in population cohorts compared to LVEF[8,19,20].

The CMR protocol also included myocardial native T1 mapping sequence[21] in one midventricular short-axis slice. Global myocardial native T1 was calculated from the entire short-axis slice using a fully automated quality-controlled analysis tool[22]. We include global native T1 in our analysis, as a measure of myocardial tissue character. The pre-specified UK Biobank protocol does not contain contrast administration.

We also considered aortic distensibility (AoD) and arterial stiffness index (ASI), as measures of arterial health[23]. AoD provides an estimate of aortic compliance and is an indicator of local aortic bio-elastic function. We derived AoD measures from transverse cine images of the thoracic aorta using a previously validated automated quality controlled tool. ASI is an indicator of large artery stiffness derived from a pulse waveform contour obtained from finger plethysmography.

Definition of covariates

Covariates were selected based on biological plausibility and reported associations with obesity and incident cardiovascular outcomes in existing literature (***Figure 1, Supplementary Table 2***). We adjusted for potential confounders (age, sex, ethnicity, material deprivation, education, smoking, alcohol intake, poor dietary practises and physical activity) to estimate the magnitude of the exposure-outcome associations. We also identified the following cardiometabolic diseases as potentially lying on the causal pathway: diabetes, hypertension, and hypercholesterolaemia. We used age and sex as recorded at baseline.

Statistical analysis

Statistical analysis was performed using R version 4.1.0. and RStudio. For associations with incident outcomes, we used the baseline set with obesity exposures (BMI, WHR) defined at baseline recruitment and incident outcomes tracked thereafter; this allowed the inclusion of a large sample with sufficient long-term follow-up[15] (***Figure 1***). We used Cox proportional hazard regression to estimate the associations of BMI and WHR exposures (as continuous metrics) with incident CVDs (IHD, AF, HF, any CVD) and mortality outcomes (all-cause, CVD)[24]. The results are reported as hazard ratios (HR), per 1 standard deviation (SD) increase in BMI or WHR, and 95% confidence intervals (CI). We created hierarchical models with incremental inclusion of covariates to understand their influence on the main obesity-outcome associations. Model 1 was adjusted by age and sex; Model 2 was adjusted by Model 1 variables plus ethnicity, Townsend deprivation score, education, physical activity, alcohol consumption frequency, smoking and processed meat intake (i.e., true confounders). Our fully adjusted model, Model 3, was adjusted by Model 2 variables plus diabetes, hypertension, and high cholesterol.

To understand potential interactions between obesity subtypes and usefulness of their integration in clinical assessments, we created obesity strata based on WHO cut-offs for BMI and WHR, as outlined previously. We stratified the sample based on both BMI and WHR expressed as categorical exposures, creating six obesity subtypes. Individuals with normal BMI and normal WHR were considered the reference level. We report HR and 95% CI related to each obesity category against the reference level, adjusting for confounders as before.

In participants with CMR data available, we used multivariable linear regression to estimate the associations of BMI and WHR (as continuous variables) with selected cardiovascular phenotypes. To allow comparison of the magnitude of effects across CMR metrics, we report standardised beta-coefficients and raw unit coefficients with corresponding 95% CIs and p-values. As the main exposures (BMI and WHR) of our study are highly correlated with body size measures, we did not scale CMR metrics in our models to such measures (body surface area or height square).

Finally, we explored the role of cardiometabolic disease and CMR measures in mediating the relationships between obesity and incident outcomes. Towards this, we first describe the links between CMR measures and incident CVD outcomes, using Cox regression models. Next, we applied the Multiple Mediation Analysis for Big Data Sets package (mmabig[25]) to quantify the proportion of obesity-outcome effects mediated through cardiac remodelling (CMR metrics), hypertension, diabetes, and high cholesterol. CIs for coefficients in the mediation models were estimated across 500 bootstrapped replicates.

P-values were for two-tailed tests and were adjusted for multiple testing using a false discovery rate of 5% across exposure variables, giving an overall cutoff of 0.01.

Results

Description of baseline characteristics

The baseline dataset was available for 491,606 participants (***Supplementary Table 3, Supplementary Figure 1***). The mean age was 56.5 (±8.1) years and the sample included 54.3% women. A total of 24.5% of participants had BMI in the obese range (>30 kg/m^2), and almost half (49.2%) had elevated WHR. A notable proportion of participants with normal BMI had elevated WHR (21.5% in the baseline set), rising to 55.7% in the overweight BMI group at and a majority 74.8% in the obese BMI group. CMR data were available for 31,107 participants. Participant characteristics in the baseline and CMR set were broadly comparable, although the imaging set was healthier with fewer vascular risk factors and prevalent CVDs.

Incident events

The censor date was 26th March 2021 for mortality data and HES outcomes, giving an average follow-up of 12.2(±0.9) years for the baseline set and 3.8(±1.3) years for the imaging. Within the baseline set, we observed incidence of any CVDs in 10.4% of participants, with the most common incident CVD being IHD occurring in 6.4% of participants. Within the baseline set, 6.8% of participants died, and 12% of deaths were primarily attributed to CVDs. Within the CMR set, 1.2% of participants died, with 11.5% of deaths due primarily to CVD causes (***Supplementary Table 1***).

Associations between obesity and incident cardiovascular events

In fully adjusted Cox regression models, higher BMI and WHR were associated with significantly higher risk of all outcomes considered (***Table 1***). In fully adjusted models, for every SD (4.4kg/m^2) increase in BMI, there was 34% greater risk of incident HF, 27% greater risk of incident AF, 18% greater risk of incident IHD, 5% greater risk of all-cause mortality, and 23% greater risk of CVD mortality. Similarly, every SD increase in WHR (0.09) was associated with 33% greater risk of incident HF, 18% greater risk of incident AF, 24% greater risk of incident IHD, 19% greater risk of all-cause, and 32% greater risk of CVD mortality.

We observed a significantly larger magnitude of effect with WHR compared to BMI in the associations with incident IHD (HR 1.46 vs 1.33) and with both CVD mortality (HR 1.80 vs 1.56) and all-cause mortality (HR 1.39 vs 1.17). BMI showed a larger effect size (but with overlap of CIs) in the association with incident AF.

In the combined stratification by both WHR and BMI (***Supplementary table 4, Figure 2***), elevated WHR was linked to adverse outcomes in any BMI combination. Individuals with "normal BMI-elevated WHR" had a significantly higher risk of incident outcomes (all significant except AF) compared to those with "normal BMI-normal WHR" (***Figure 2***). Individuals in the "overweight-normal WHR" category had significant but weaker associations with disease than their "elevated WHR" counterparts, and a significantly lower risk of overall death. For individuals in the "obese-elevated WHR" group, adverse outcome associations were augmented compared to when each exposure was assessed alone (in both categorical and continuous approaches).

Association of obesity exposure with CMR metrics

We summarise the mean CMR metrics for the whole imaging set and in combined stratification by both WHR and BMI obesity cut-offs. (***Supplementary Table 5***). In fully adjusted models, greater obesity (both BMI and WHR) was associated with an adverse pattern of cardiovascular remodelling across all metrics considered (***Figure 3***). Specifically, greater obesity was linked to higher LVM, a more concentric pattern of LV hypertrophy (higher LVM: LVEDV), and poorer LV function (lower LVGFI). Higher BMI was linked to higher, whilst greater WHR was linked to lower LVEDV. Higher obesity metrics were linked to significantly lower myocardial native T1. With regards to LA remodelling, greater obesity was linked to larger LA volumes (higher LAV), and poorer LA function (lower LAEF). Higher BMI and WHR were also linked to lower (unhealthy) arterial compliance by both AoD and ASI.

While the direction of associations was broadly consistent between the two obesity metrics, we observed a larger magnitude of effect with BMI compared to WHR in the associations with LVM, native T1, LAV and LAEF. Whilst WHR showed stronger associations with LVM:LVEDV and ASI. BMI and WHR showed similar strength of effect with LVGFI (***Figure 3***).

The association of CMR metrics with incident outcomes

Towards considering mediation of obesity-outcome associations through cardiac alterations, we tested the association of selected CMR metrics with our outcomes of interest. In fully adjusted Cox regression models, larger LVEDV, higher LVM, and poorer LV function by both LVEF and LVGFI were associated with incident CVD (***Supplementary Table 6)***. These relationships appeared most prominent for HF. Higher native T1 relaxation times were linked to greater incident AF, HF, CV mortality, and all-cause mortality. Higher LVM:LVEDV was associated with any CVD and IHD. Not surprisingly, the relationships with LA metrics were strongest in case of AF. ASI showed no association with any of the considered incident outcomes.

Mediation analysis

We used multiple mediation analysis to investigate the potential mechanisms driving the obesity-outcome associations, considering mediation through cardiometabolic diseases (diabetes, high cholesterol, hypertension) and CMR alterations. The mediation analysis considered three key outcomes of incident IHD, AF, and HF. Granular results are available in ***Supplementary Table 7*** and ***Supplementary Table 8***, and a visual summary is presented in ***Figure 4***. Overall, we found that the effects of both BMI and WHR on incident outcomes were potentially mediated by obesity-induced adverse cardiac remodelling and hypertension, with a smaller mediating effect of diabetes.

Adverse alterations of LV structure and function (high LVM, higher LV concentricity, lower LVGFI) appeared as potential mediators for all three incident CVDs, potentially contributing a large proportion of the mediated effect, independent of cardiometabolic diseases. Atrial remodelling (larger LAV) was identified as an additional independent mediator of the relationship between obesity and AF. Native T1 mediated a significant fraction of the relationship between obesity and incident HF (BMI: -36%, WHR: -77%). This relationship is negative, meaning that while BMI and WHR are associated with a decreasing T1, increasing T1 value is linked to incident HF.

Discussion

Summary of findings

In this large population-based cohort, we consider the role of obesity-related cardiovascular remodelling in potentially driving key incident cardiovascular outcomes. We first demonstrate independent associations of BMI and WHR as independent predictors of incident outcomes. In combined stratification by both WHR and BMI, individuals with elevated WHR had greater risk of all outcomes at any BMI group. Second, greater BMI and WHR were linked to adverse LV structure, poorer LV function, lower myocardial native T1, large LA size, poorer LA function, and lower arterial compliance. Third, we showed that greater LVM is linked to an increased risk of all cardiovascular disease considered in our study, moreover greater LVEDV and LAV are linked to an increased risk of heart failure, atrial fibrillation. Finally, we found that hypertension and adverse LV remodelling were the two strongest mediating factors between excess weight and incident IHD, AF, and HF using multiple mediation analysis.

Comparison with existing research

Previous researchers have demonstrated associations of obesity with adverse CVD and mortality outcomes[26]. Our work extends these observations through integrated modelling of BMI with WHR in a population-based cohort and by considering a wider range of CVD outcomes. We demonstrate that an elevated WHR at any BMI level is linked to adverse incident CVD and mortality outcomes. Furthermore, our findings suggest that WHR may provide better discrimination of "pathological" obesity than BMI alone. In particular, we observed inconsistent outcome associations for individuals classified as overweight per BMI but who had a normal WHR. These individuals had weaker associations with incident CVDs, non-significant association with heart failure and CVD death, and lower risk of all-cause death. Thus, it is likely that some individuals in this category were healthy, contrary to the BMI classification of overweight. In comparison, those with elevated WHR but normal BMI had elevated risk of all-cause death, CVD death, and all incident CVDs (non-significant for AF).

The paradoxical associations between mortality and overweight BMI have been previously reported[27]. A growing body of evidence supports methodological explanations rather than a true mechanistic relationship, such as misclassification bias caused by using BMI as a sole measure of obesity or unmeasured confounding[2]. Our findings support characterisation of obesity with integration of BMI and WHR to better distinguish health from disease (minimise misclassifications) and to strengthen cardiovascular outcome prediction.

Previous studies have reported associations of greater obesity with adverse cardiac remodelling across a limited range of phenotypes. In a study of 5,098 participants of the MESA cohort, Turkbey et al.[28] demonstrate, consistent with our observations, association of greater obesity with greater LVM and concentric LV remodelling without change in LV ejection fraction. In an echocardiography study of 4,343 participants of the ARIC study, Bello et al.[29] also observed association of greater obesity with greater LVM. Our findings support these existing reports in a much larger cohort and using the reference standard modality of CMR. A novel finding of our research is that higher BMI was linked to higher, whilst greater WHR was linked to lower LVEDV. Clearly showing the disparity of the effect of BMI and WHR on remodelling. Possible explanations for this observation include higher cardiac output as opposed to increased load in the driving mechanisms of obesity related cardiac remodelling, as well as an increased arterial stiffness (causing increased afterload) and/or metabolic dysregulation. Furthermore, whilst we also observed non-significant associations of obesity with LV ejection fraction (as per Turkbey et al.[28]), we demonstrate associations of greater obesity with poorer LV function by lower LVGFI, an emerging marker of LV systolic function[30].

We are first to report associations of obesity with myocardial native T1 in a large cohort. . This metric provides a non-invasive indicator of myocardial tissue character. Generally higher native

T1 is linked to greater myocardial fibrosis and adverse outcomes. Adipose tissue shortens T1 relaxation time[31]. We demonstrate association of greater obesity with lower native T1; however, higher native T1 was found to be linked to greater risk of incident HF. A possible interpretation is that these associations indicate different stages of obesity-related cardiac disease. The associations of greater obesity with lower native T1 observed in the whole sample, may indicate subclinical myocardial lipid accumulation as a feature of early-stage obesity remodelling. Whilst in later stages, fibrotic degeneration replaces lipid accumulation leading to clinical disease and pump failure, hence the association of higher native T1 with incident HF. Previous studies have made the link between myocardial steatosis and poorer cardiac health[32] and between myocardial fibrosis and adverse cardiovascular outcomes[33]. Notably, native T1 may also be elevated by other potentially pathologic processes, such as subacute inflammation and myocardial hyper-perfusion[31]. Such alterations may represent other biologic pathways through which obesity-mediated HF occurs. Thus, our findings present new insight into potential disease mechanisms driving the adverse cardiovascular consequences of obesity, which merit further study.

Our findings indicate association of greater obesity with greater LA dilatation and poorer LA function. These observations likely indicate elevated LV filling pressures and diastolic dysfunction. Consistently, Al Jaroudi et al.[34] also demonstrate association of higher BMI with poorer diastolic function in an echocardiography study of 21,666 participants. In the mediation analysis, we additionally demonstrate that LA remodelling (higher LAV) is a potential mediator of the associations between obesity and incident AF. This observation supports previous reports proposing a direct mechanistic role for obesity in driving AF through the promotion of electroanatomic remodelling[35].

Overall, our results show that from the cluster of metabolic pathologies associated with obesity, hypertension is the most important cardiometabolic disease linking adiposity exposure to adverse CVD outcomes. This is consistent with many previous studies linking obesity to greater risk for hypertension, which in turn is widely recognised as major risk factor for CVD occurrence[1]. However, here we formally illustrate the role of hypertension in mediating the adverse clinical consequences of obesity.

Although we demonstrate a probable mediating role for hypertension, a large proportion of the obesity-outcome associations are possibly attributed to CMR alterations. CMR alterations do not occur spontaneously but rather are a response to an exposure. Firstly, obesity itself may have a direct role in altering the cardiac phenotype. Second, it is possible that obesity mediates cardiovascular remodelling through variables other than the cardiometabolic factors considered in our analysis – that is obesity is acting through other indirect biological pathways. Thirdly, a proportion of the CMR mediated effects may be related to residual confounding from incomplete capture of cardiometabolic conditions. LV structure and function metrics had conceivable roles mediating associations of obesity

with all three conditions (AF, HF, IHD). These adverse remodelling patterns are incompletely explained by known cardiometabolic factors. Our work encourages further research to identify direct and indirect biological pathways that may be driving obesity-related cardiac remodelling.

Clinical and research implications

Our findings demonstrate potential shortcomings rooted in the oversimplification of excess weight using BMI alone. We highlight merit in characterisation of obesity using both BMI and WHR for better capture of obesity-related cardiovascular risk. Given that these measures are highly accessible, cheap, and non-invasive their integration into existing clinical pathways is likely to be feasible across a wide range of settings. Further validation of our findings and examining practicalities of integrative BMI-WHR phenotyping of obesity in routine practice are warranted.

Our work encourages research into possible direct pathways such as lipotoxicity, obstructive sleep apnea[36], changes in the intracellular homeostasis, circulating hormones[37], oxidative stress, inflammation, and fibrosis that may all contribute to the myocardial structure's deterioration[7], providing therapeutic targets for medical intervention and lifestyle modification.

Limitations

Incident outcomes are based on HES data which limits us to incident diseases recorded in a hospital setting. The UK Biobank imaging study CMR protocol did not include more extensive tissue characterisation sequences such as T2 or gadolinium contrast-enhanced images. A limitation of the mediation analyses is it provides a means of apportioning variance, but does not permit inference of causal associations. Thus whilst it is possible to speculate on causal pathways on the basis of our findings and what is known from the pre-existing literature, we are not able to draw any definitive conclusions from the present study. Indeed, we cannot exclude residual confounding or reverse causation due to the study's observational nature. Finally, at the time of our analysis, UK Biobank's primary care linkage was incomplete, and medication history could be ascertained only from baseline recorded self-reports which has several limitations, therefore we did not address this area in our current analysis.

Conclusions

The combined use of BMI and WHR to characterise obesity may provide better discrimination of "pathologic" obesity and provide better estimations of cardiovascular risk than either metric alone. We demonstrate novel associations of obesity with a wide range of adverse CMR phenotypes, which along with hypertension have important independent roles in potentially mediating

obesity-outcome associations. The mediated effects attributed to "CMR metrics" may represent direct obesity-related damage and/or residual effect of other metabolic exposures which are associated with obesity.

Authors contribution

L.S., C.M., Z.R.-E., and S.E.P. conceived the idea and developed the analysis plan. C.M. led the statistical analysis and provided all figures and tables for the manuscript. J.C. supervised the statistical analysis and figure creation. C.M., L.S. and Z.R.-E. have verified the underlying data. All authors had full access to all the data in the study and accept responsibility to submit for publication. L.S. and Z.R.-E. wrote the original manuscript. L.S., O.R., H. V., B. M., S. N., N.C.H., S.E.P. and Z.R.E contributed to the interpretation of the data. S.E.P and Z.R.E. jointly supervised the work. All co-authors critically reviewed the manuscript and approved the final submitted version.

Data availability statement

This research was conducted using the UK Biobank resource under ac- cess application 2964. UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any persons. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: http://www.ukbiobank.ac.uk/ register-apply.

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Figure legends:

Figure 1: Study flowchart. Covariates considered in the relationship between obesity exposure and incident cardiovascular outcomes. Abbreviations: BMI: body mass index, WHR, wait-to-hip ratio

Figure 2: Results from Cox proportional hazards models relating obesity category to incident disease in the full sample. Each panel represents one fully adjusted model, where the baseline category is Normal BMI- normal WHR. Rectangles indicate the 95% confidence interval for the hazard ratio.

Figure 3: Linear regression results for raw CMR metrics displaying beta coefficients and 95% confidence intervals per 1SD increase in (log)BMI or WHR in the imaging subset.

Figure 4: Results from fully adjusted multiple mediation models between obesity and incident cardiovascular disease, mediated by the one raw CMR metric and the three cardiometabolic conditions in each iteration. The overall size of the bars corresponds to the strength of the total effect between obesity and incident disease, measured by (log)BMI on the top row and waist-hip ratio on the bottom row. The coloured areas reflect the size of the mediated effects via each mediator.

Table 1. Associations of obesity metrics (as continuous variables) with incident cardiovascular diseases and mortality outcomes

	BMI (log)			WHR		
Incident disease	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Any CVD	1.33* [1.32, 1.34] $< 1.0 \times 10^{-300}$	1.30* [1.29, 1.32] $< 1.0 \times 10^{-300}$	1.22* [1.20, 1.23] $< 1.0 \times 10^{-300}$	1.38* [1.37, 1.40] $< 1.0 \times 10^{-300}$	1.33* [1.31, 1.34] $< 1.0 \times 10^{-300}$	1.22* [1.20, 1.23] 7.05×10^{-225}
Ischaemic heart disease	1.33* [1.31, 1.34] $< 1.0 \times 10^{-300}$	1.29* [1.27, 1.30] $< 1.0 \times 10^{-300}$	1.18* [1.16, 1.19] 1.89×10^{-155}	1.46* [1.44, 1.48] $< 1.0 \times 10^{-300}$	1.38* [1.36, 1.40] $< 1.0 \times 10^{-300}$	1.24* [1.22, 1.26] 3.17×10^{-166}
Atrial fibrillation	1.36* [1.35, 1.38] $< 1.0 \times 10^{-300}$	1.35* [1.33, 1.37] $< 1.0 \times 10^{-300}$	1.27* [1.25, 1.28] 3.11×10^{-281}	1.30* [1.28, 1.32] 8.66×10^{-239}	1.27* [1.25, 1.29] 2.85×10^{-190}	1.18* [1.16, 1.20] 1.04×10^{-80}
Heart failure	1.59* [1.57, 1.62] $< 1.0 \times 10^{-300}$	1.52* [1.49, 1.54] $< 1.0 \times 10^{-300}$	1.34* [1.32, 1.37] 3.43×10^{-237}	1.67* [1.64, 1.71] $< 1.0 \times 10^{-300}$	1.54* [1.51, 1.57] $< 1.0 \times 10^{-300}$	1.33* [1.30, 1.36] 7.38×10^{-132}
All-cause mortality	1.17* [1.16, 1.18] 1.51×10^{-174}	1.12* [1.11, 1.14] 4.74×10^{-91}	1.05* [1.03, 1.06] 1.49×10^{-13}	1.39* [1.37, 1.41] $< 1.0 \times 10^{-300}$	1.28* [1.27, 1.30] 1.15x10-256	1.19* [1.18, 1.21] 1.76×10^{-119}
CVD mortality	1.56* [1.51, 1.61] 5.19×10^{-176}	1.46* [1.42, 1.51] 2.38×10^{-127}	1.23* [1.19, 1.27] 3.38×10^{-34}	1.80* [1.73, 1.87] 1.09×10^{-199}	1.61* [1.55, 1.68] 2.17×10^{-121}	1.32* [1.26, 1.38] 1.74×10^{-37}

Table 1 footnote. Results are hazard ratios associated with 1 SD increase in obesity (BMI (log) or WHR), 95% confidence intervals and p-values from Cox models relating the exposures to incident disease/events in the full sample. 1SD BMI (log) = 4.4 kg/m^2 and 1 SD WHR =0.09.

Figure 1. Study flowchart

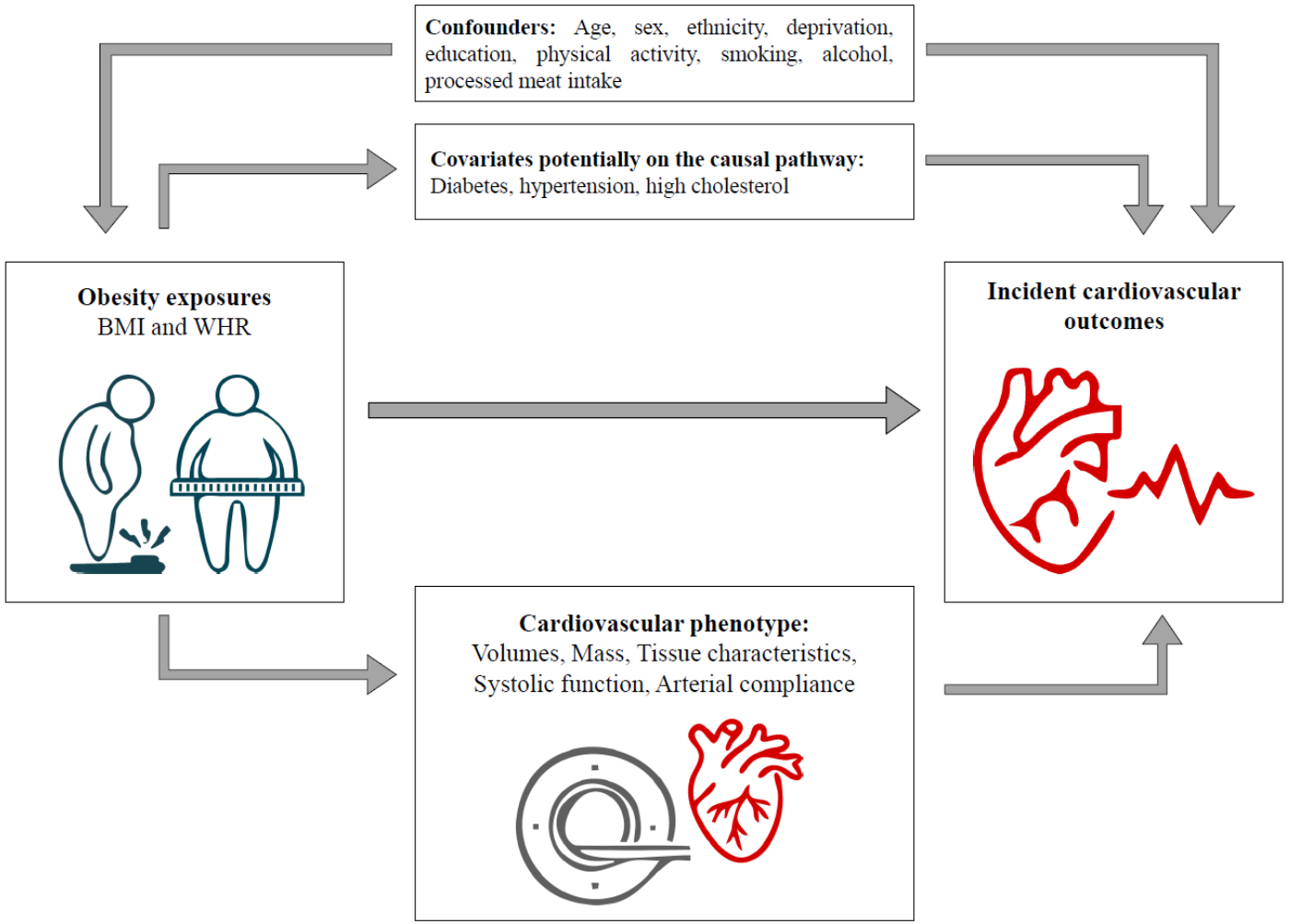


Figure 2. Association between obesity categories and incident disease

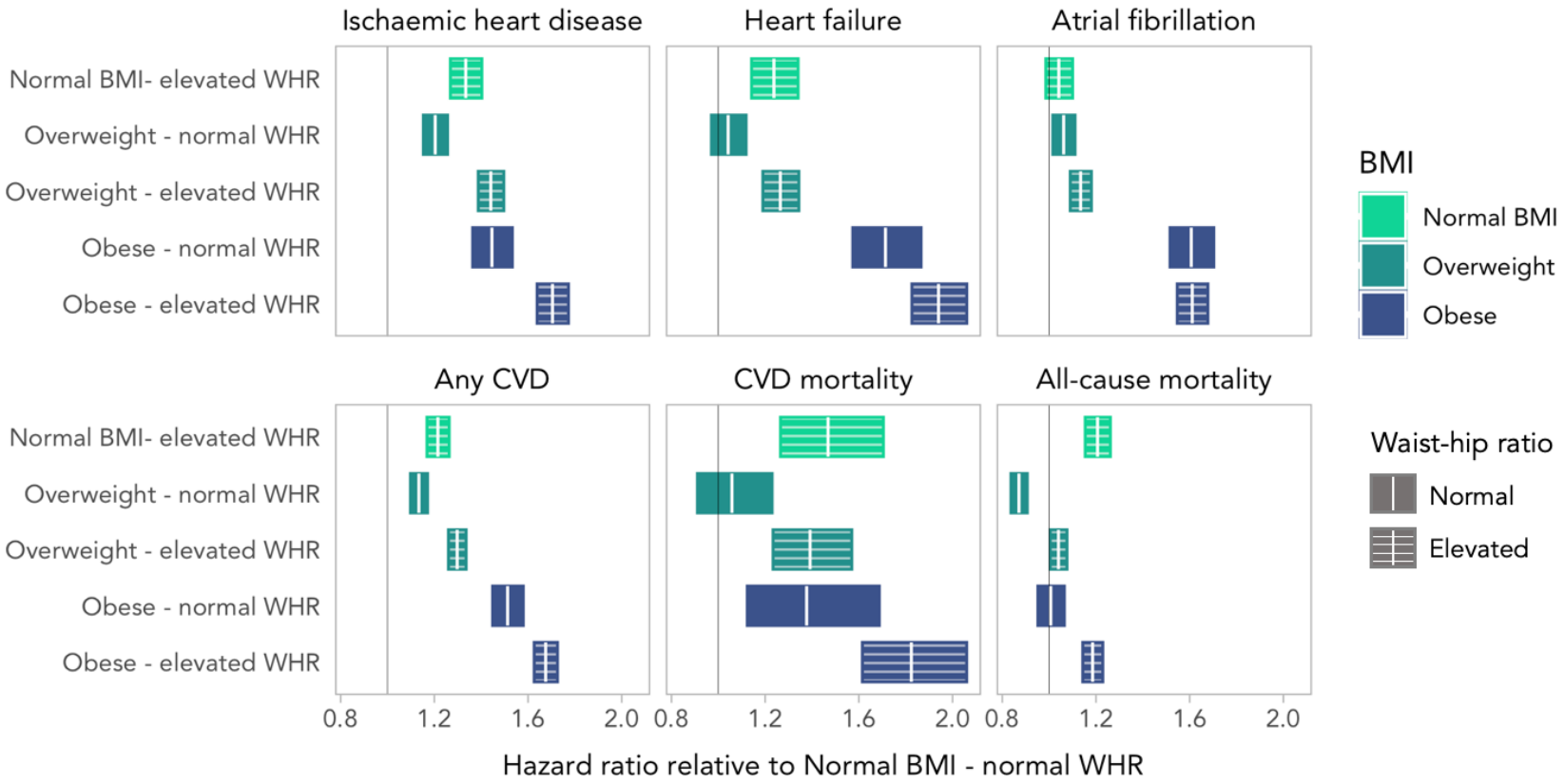


Figure 3. Associations between obesity and CMR metrics

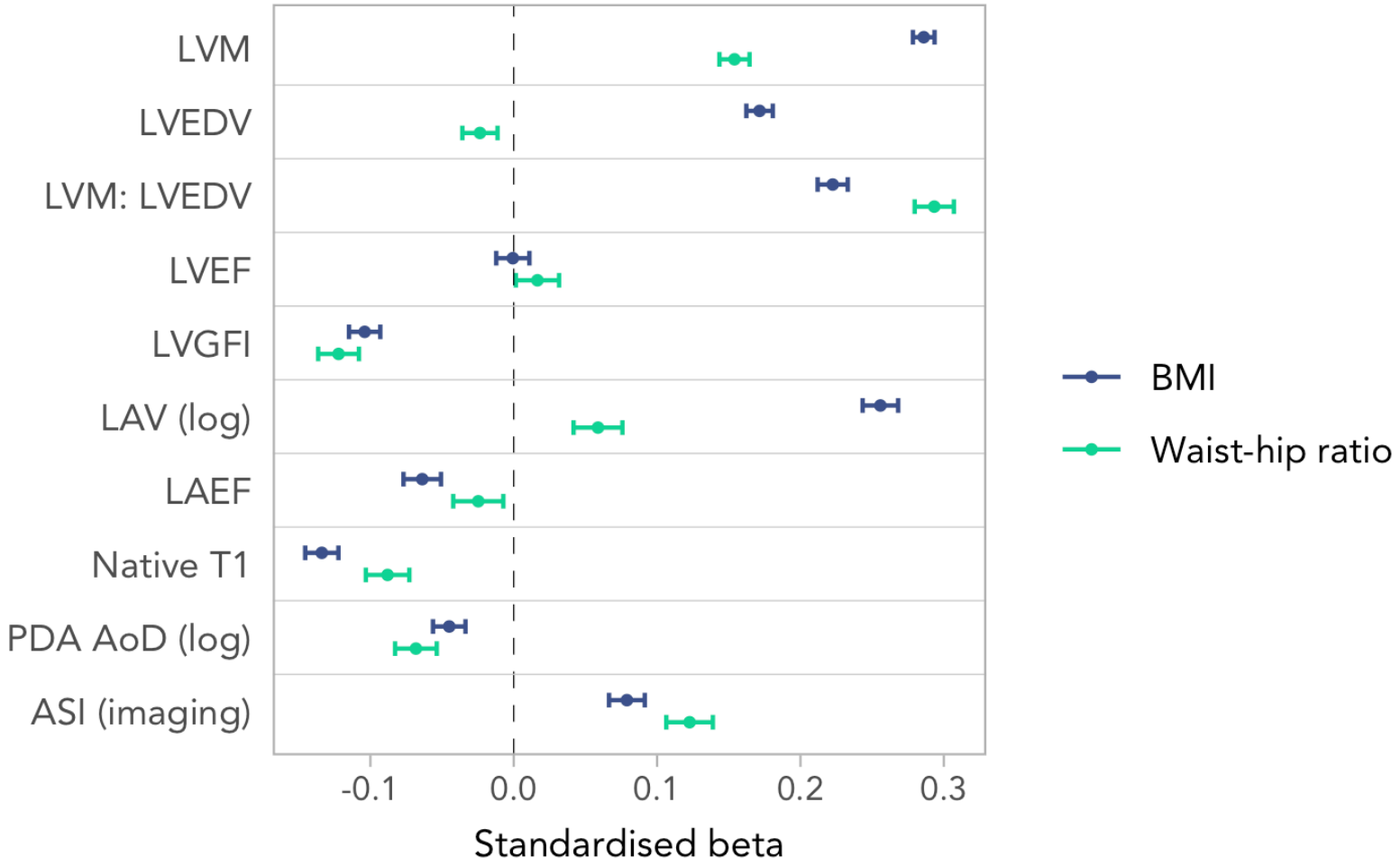
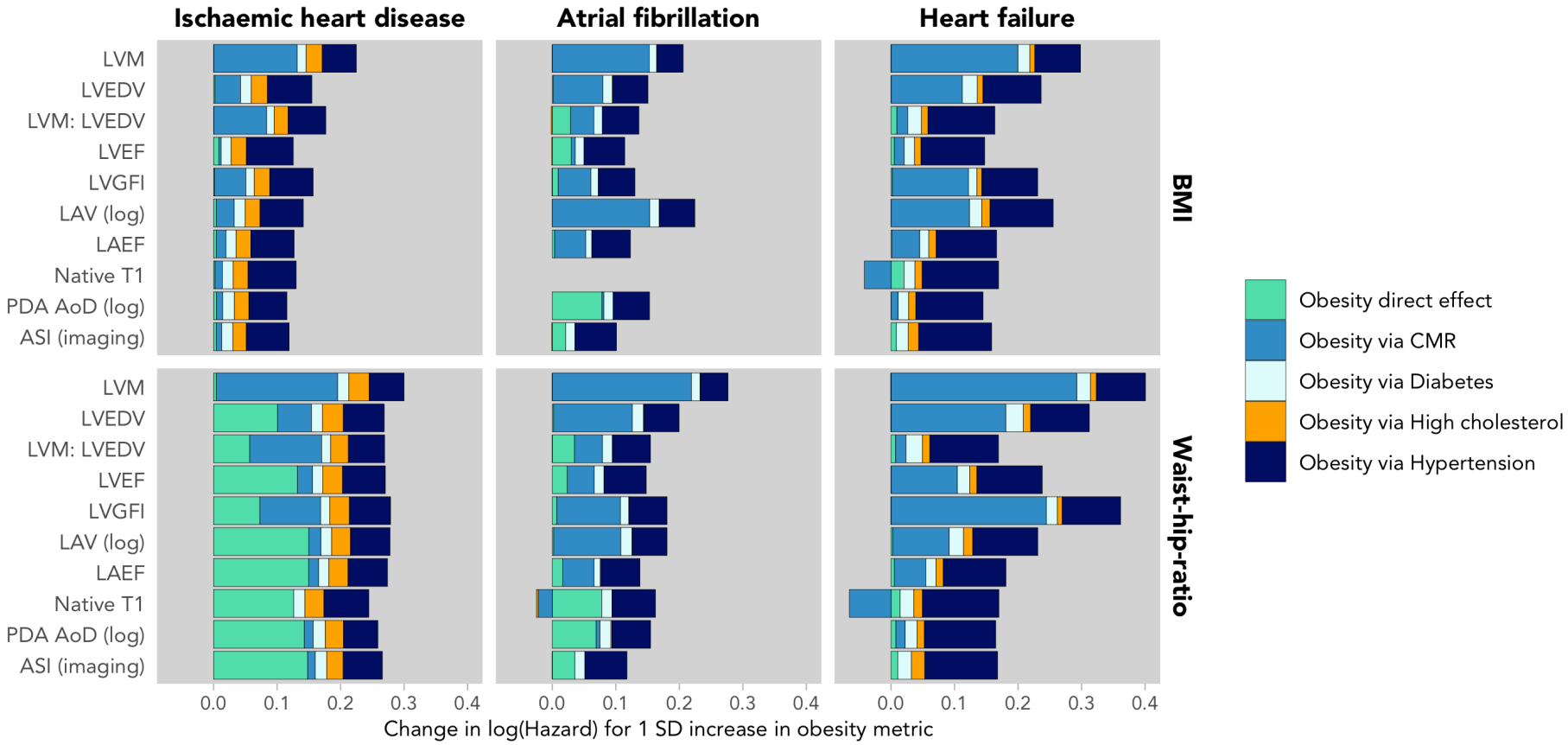
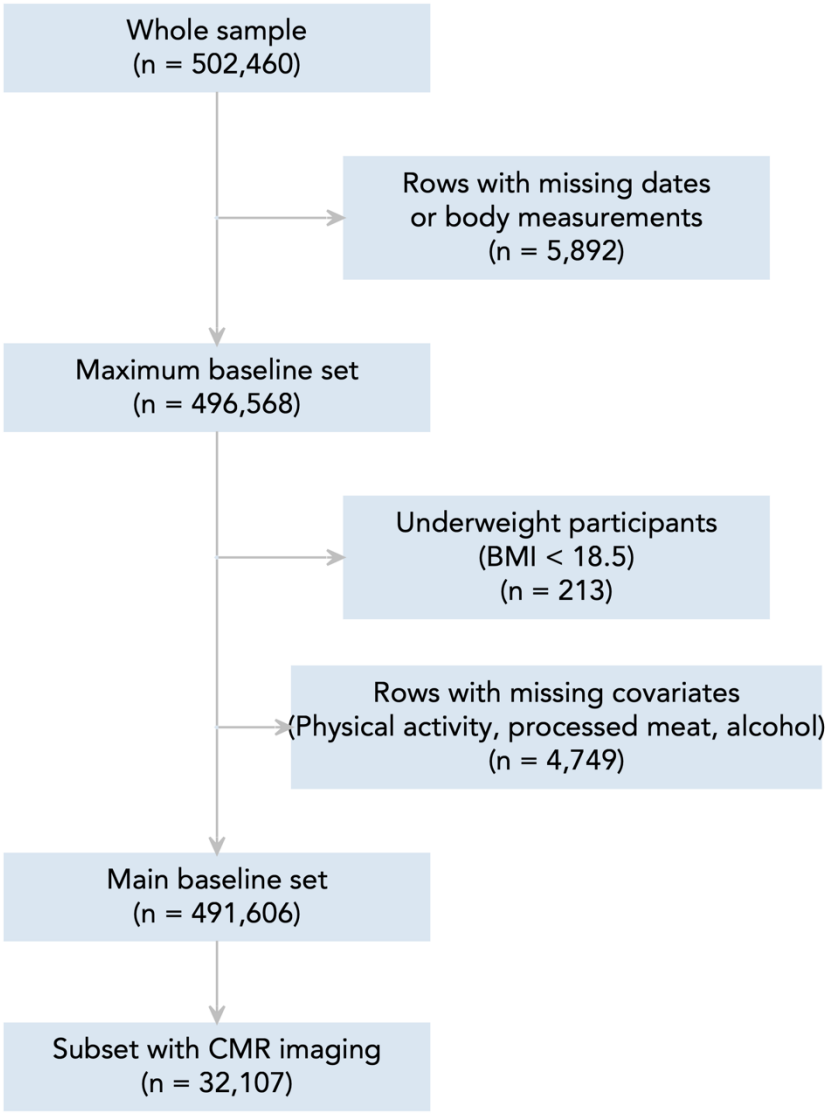


Figure 4. CMR and the relationship between obesity and incident events



Supplementary Figure 1. Sample selection



Supplementary Figure 1 footnote. BMI: body mass index, CMR: cardiovascular magnetic resonance.

Supplementary Table 1. UK Biobank fields/codes for cardiovascular disease

Source	Field ID or code	CVD death	Description
Ischaemic heart disease			
Self-report	20004		coronary angioplasty (ptca) +/- stent
	20004		coronary artery bypass grafts (cabg)
	20002		heart attack/myocardial infarction
	20002		heart failure/pulmonary odema
OPCS4	K504		K50.4 Percutaneous transluminal atherectomy of coronary artery
	K503		K50.3 Percutaneous transluminal injection of therapeutic substance into coronary artery NEC
	K502		K50.2 Percutaneous transluminal coronary thrombolysis using streptokinase
	K40		K40 Saphenous vein graft replacement of coronary artery
	K41		K41 Other autograft replacement of coronary artery
	K42		K42 Allograft replacement of coronary artery
	K43		K43 Prosthetic replacement of coronary artery
	K44		K44 Other replacement of coronary artery
	K45		K45 Connection of thoracic artery to coronary artery
	K46		K46 Other bypass of coronary artery
	K49		K49 Transluminal balloon angioplasty of coronary artery
	K501		K50.1 Percutaneous transluminal laser coronary angioplasty
	K75		K75 Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
ICD9	410		410 Acute myocardial infarction
	411		411 Other acute and subacute forms of ischaemic heart disease
	412		412 Old myocardial infarction
	4140		4140 Coronary atherosclerosis
	4141		4141 Aneurysm of heart
	4148		4148 Other specified forms of chronic ischaemic heart disease
	4149		4149 Chronic ischaemic heart disease, unspecified
ICD10	I210	yes	I21.0 Acute transmural myocardial infarction of anterior wall
	I211	yes	I21.1 Acute transmural myocardial infarction of inferior wall
	I212		I21.2 Acute transmural myocardial infarction of other sites
	I213	yes	I21.3 Acute transmural myocardial infarction of unspecified site
	I214	yes	I21.4 Acute subendocardial myocardial infarction
	I219	yes	I21.9 Acute myocardial infarction, unspecified
	I21X		I21.X Presumed acute myicardial infaction (unconfirmed)
	I22		I22 Subsequent myocardial infarction
	I23		I23 Certain current complications following acute myocardial infarction
	I240		I24.0 Coronary thrombosis not resulting in myocardial infarction
	I241		I24.1 Dressler's syndrome
	I248	yes	I24.8 Other forms of acute ischaemic heart disease
	I249	yes	I24.9 Acute ischaemic heart disease, unspecified
	I251	yes	I25.1 Atherosclerotic heart disease
	I252	yes	I25.2 Old myocardial infarction
	I255	yes	I25.5 Ischaemic cardiomyopathy
	I256	yes	I25.6 Silent myocardial ischaemia
	I258	yes	I25.8 Other forms of chronic ischaemic heart disease
	I259	yes	I25.9 Chronic ischaemic heart disease, unspecified
First occurrences	131298		acute myocardial infarction
	131300		subsequent myocardial infarction
	131302		certain current complications following acute myocardial infarction
	131304		other acute ischaemic heart diseases
Diagnosed by doctor	6150: 1		Heart attack
	3894		Age heart attack diagnosed
Algorithm	42000		42000 Date of myocardial infarction

Supplementary Table 1 continues…

Supplementary Table 1 (continued)

Source	Field ID or code	CVD death	Description
Atrial fibrillation			
Self-report	20002		atrial fibrillation
ICD9	4273		4273 Atrial fibrillation and flutter
ICD10	I480	yes	I48.0 Paroxysmal atrial fibrillation
ICD10	I481		I48.1 Persistent atrial fibrillation
ICD10	I482		I48.2 Chronic atrial fibrillation
ICD10	I489	yes	I48.9 Atrial fibrillation and atrial flutter, unspecified
First occurrences	131350		Date I48 first reported (atrial fibrillation and flutter)
Heart failure			
Self-report	20002		heart failure/pulmonary odema
ICD9	428		428 Heart failure
ICD9	4020		4020 Hypertensive heart disease, specified as malignant
ICD9	4029		4029 Hypertensive heart disease, not specified as malignant or benign
ICD9	4040		4040 Hypertensive heart and renal disease, specified as malignant
ICD9	4049		4049 Hypertensive heart and renal disease, not specified as malignant or benign
ICD10	I110	yes	I11.0 Hypertensive heart disease with (congestive) heart failure
ICD10	I130	yes	I13.0 Hypertensive heart and renal disease with (congestive) heart failure
ICD10	I132	yes	I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
ICD10	I500	yes	I50.0 Congestive heart failure
ICD10	I501	yes	I50.1 Left ventricular failure
ICD10	I509	yes	I50.9 Heart failure, unspecified
First occurrences	131354		Date I50 first reported (heart failure)
Additional codes included under "Any CVD"			
Self-report	20002		cardiomyopathy
Self-report	20002		hypertrophic cardiomyopathy (hcm / hocm)
ICD9	4274		4274 Ventricular fibrillation and flutter
ICD9	4275		4275 Cardiac arrest
ICD9	4255		4255 Alcoholic cardiomyopathy
ICD10	I46	yes	I46 Cardiac arrest
ICD10	I472	yes	I47.2 Ventricular tachycardia
ICD10	I490	yes	I49.0 Ventricular fibrillation and flutter
ICD10	I420	yes	I42.0 Dilated cardiomyopathy
ICD10	I426	yes	I42.6 Alcoholic cardiomyopathy
ICD10	I42		I42 Cardiomyopathy
ICD10	I43		I43 Cardiomyopathy in diseases classified elsewhere
ICD10	I11	yes	I11 Hypertensive heart disease
ICD10	I13		I13 Hypertensive heart and renal disease
First occurrences	131346		Date I46 first reported (cardiac arrest)
First occurrences	131338		cardiomyopathy
First occurrences	131340		cardiomyopathy in diseases classified elsewhere
First occurrences	131288		hypertensive heart disease
First occurrences	131292		hypertensive heart and renal disease

Supplementary Table 1 footnote. ICD10 codes are drawn from fields 41270, 41280, 41234 and 41259; ICD9 codes are drawn from fields 41271, 41281, 41234 and 41259; OPCS4 codes are drawn from fields 41272, 41282, 41149 and 41259; Deaths codes are drawn from fields 40000, 40001 and 40023. Where a 3-digit code is given, this includes all 4-digit sub-codes, for example, I46 includes I462, I468 and I469.

Supplementary Table 2. UK Biobank fields/codes for risk factors

Source	Field ID or code	Description
Diabetes		
Self-report	20002	Diabetes
	20002	Type 1 diabetes
	20002	Type 2 diabetes
Medications	6153, 6177: 3	Insulin
ICD9	250	Diabetes mellitus
ICD10	E10	E10 Insulin-dependent diabetes mellitus
ICD10	E11	E11 Non-insulin-dependent diabetes mellitus
ICD10	E12	E12 Malnutrition-related diabetes mellitus
ICD10	E13	E13 Other specified diabetes mellitus
ICD10	E14	E14 Unspecified diabetes mellitus
ICD10	O24	O24 Diabetes mellitus in pregnancy
ICD10	R73	R73 Elevated blood glucose level
First occurrences	130706	Date E10 first reported (insulin-dependent diabetes mellitus)
First occurrences	130708	Date E11 first reported (non-insulin-dependent diabetes mellitus)
First occurrences	130710	Date E12 first reported (malnutrition-related diabetes mellitus)
First occurrences	130712	Date E13 first reported (other specified diabetes mellitus)
First occurrences	130714	Date E14 first reported (unspecified diabetes mellitus)
Diagnosed by doctor	2443	Diabetes diagnosed by doctor
Diagnosed by doctor	2976	Age diabetes diagnosed by doctor
Biochemistry	30740	Serum glucose >11.1 mmol/L
Biochemistry	30750	Glycated haemoglobin (HbA1c) > 48
Hypertension		
Self-report	20002	Essential hypertension
	20002	Hypertension
Medications	6153, 6177: 2	Blood pressure medication
ICD10	I10	Essential (primary) hypertension
First occurrences	131286	Date I10 first reported (essential (primary) hypertension)
Diagnosed by doctor	6150: 4	High blood pressure
	2966	Age high blood pressure diagnosed
High cholesterol		
Self-report	20002	high cholesterol
Medications	6153, 6177: 1	Cholesterol lowering medication
ICD10	E780	E78.0 Pure hypercholesterolaemia
ICD10	E781	E78.1 Pure hyperglyceridaemia
ICD10	E782	E78.2 Mixed hyperlipidaemia
ICD10	E783	E78.3 Hyperchylomicronaemia
ICD10	E784	E78.4 Other hyperlipidaemia
ICD10	E785	E78.5 Hyperlipidaemia, unspecified
First occurrences	130814	Date E78 first reported (disorders of lipoprotein metabolism and other lipidaemias)
Biochemistry	30690	serum total cholesterol >7 mmol/L

Supplementary Table 2 footnote:

We accessed self-reported fields for participants' educational level, smoking status, processed meat intake, and alcohol intake. Ethnicity was categorised as White or BAME (Black, Asian and Minority Ethnic). Material deprivation is reported as the Townsend index, which measures location-based socioeconomic deprivation relative to national averages. Physical activity was measured via self-reported responses to the International

Physical Activity Questionnaire (IPAQ). Participants reported their time spent in different types of exercise (walking, moderate, or vigorous), from which their overall summed metabolic equivalent (MET) minutes/week was calculated as per published guidance. Diabetes was ascertained from any of: self-report, reported use of insulin, hospital records, blood biomarkers (serum glucose > 11.1 mmol/L, or serum glycosylated haemoglobin >48 mmol/mol). Hypertension was coded based on hospital records, self-reports or self-reported use of blood pressure medication. High cholesterol was coded based on self-report, self-reported use of cholesterol-lowering medication, hospital records, or serum total cholesterol >7 mmol/L. ICD10 codes are drawn from fields 41270, 41280, 41234 and 41259; ICD9 codes are drawn from fields 41271, 41281, 41234 and 41259; Where a 3-digit code is given, this includes all 4-digit sub-codes, for example, E10 includes E100, E101 and E102 etc

Supplementary Table 3. Participant characteristics

Characteristic	Baseline set (n=491,606)	Imaging set (n= 31,107)
Age	56.5 (±8.1)	63.3 (±7.5)
Female sex*	266,997 (54.3%)	16,519 (51.4%)
Ethnicity - white	466,354 (94.9%)	31,246 (97.3%)
Ethnicity - BAME	25,252 (5.1%)	861 (2.7%)
Townsend deprivation index*	-2.2 [-3.7, 0.5]	-2.7 [-3.9, -0.6]
Post-secondary education/qualification*	292,232 (59.4%)	23,384 (72.8%)
Smoking – never smoked	268,208 (54.6%)	19,809 (61.7%)
Smoking – previous smoker	170,558 (34.7%)	10,793 (33.6%)
Smoking – current smoker	51,122 (10.4%)	1,148 (3.6%)
Alcohol frequency – never	38,587 (7.8%)	2,064 (6.4%)
Alcohol frequency – less than once per week	111,300 (22.6%)	6,892 (21.5%)
Alcohol frequency – once or more per week	341,719 (69.5%)	22,891 (71.3%)
Processed meat frequency – less than weekly	195,390 (39.7%)	13,702 (42.7%)
Processed meat frequency – weekly	143,778 (29.2%)	8,745 (27.2%)
Processed meat frequency – two or more times/week	152,438 (31.0%)	9,386 (29.2%)
Physical activity – inactive (<600 summed METS /week)	128,981 (26.2%)	5,295 (16.5%)
Physical activity – active (600 – 2,999 summed METS /week)	231,028 (47.0%)	16,413 (51.1%)
Physical activity – very active (>3,000 summed METS/week)	131,597 (26.8%)	10,123 (31.5%)
Median BMI (kg/m^2)	26.8 [24.2, 29.9]	26.0 [23.6, 28.9]
Normal BMI (18.5 – 24.9)	161,106 (32.8%)	12,815 (39.9%)
Overweight BMI (25 – 29.9)	210,150 (42.7%)	13,377 (41.7%)
Obese BMI (≥ 30)	120,350 (24.5%)	5,915 (18.4%)
Mean waist-hip ratio	0.87 (±0.09)	0.87 (±0.09)
Normal WHR	249,758 (50.8%)	16,344 (50.9%)
Elevated WHR	241,848 (49.2%)	15,763 (49.1%)
Normal BMI - normal WHR	126,475 (25.7%)	9,432 (29.4%)
Normal BMI - elevated WHR	34,631 (7.0%)	3,383 (10.5%)
Overweight - normal WHR	92,994 (18.9%)	5,446 (17.0%)
Overweight - elevated WHR	117,156 (23.8%)	7,931 (24.7%)
Obese - normal WHR	30,289 (6.2%)	1,466 (4.6%)
Obese - elevated WHR	90,061 (18.3%)	4,449 (13.9%)
Diabetes status	30,344 (6.2%)	1,923 (6.0%)
Hypertension status	147,071 (29.9%)	10,644 (33.2%)
High cholesterol status	149,398 (30.4%)	11,263 (35.1%)
Prevalent conditions		
Any CVD	27,168 (5.5%)	2,327 (7.2%)
Ischaemic heart disease	20,327 (4.1%)	1,533 (4.8%)
Atrial fibrillation	8,137 (1.7%)	922 (2.9%)
Heart failure	2,646 (0.5%)	196 (0.6%)
Incident events		
Any CVD	51,077 (10.4%)	943 (2.9%)
Ischaemic heart disease	31,474 (6.4%)	578 (1.8%)
Atrial fibrillation	27,247 (5.5%)	505 (1.6%)
Heart failure	13,865 (2.8%)	235 (0.7%)
All-cause mortality	33,525 (6.8%)	382 (1.2%)
CVD mortality	4,033 (0.8%)	44 (0.1%)

Supplementary Table 3 footnote. * Sex, education and Townsend deprivation measured only at baseline. All other factors including prevalent conditions are measured at baseline for the full set, and at imaging for the imaging subset. Incident events are counted after baseline for the whole set, and after imaging for the imaging subset. Abbreviations: BAME, Black Asian and Minority ethnicities; BMI, body mass index; CVD, cardiovascular disease; METS, metabolic equivalents, WHR, waist-to-hip ratio.

Supplementary Table 4. Associations of obesity categories with incident cardiovascular diseases and mortality outcomes

	WHR category	BMI category		Combined BMI – WHR category				
Incident outcome	**Elevated WHR**	**Overweight (BMI 25- 29.9)**	**Obese (BMI > 30)**	**Normal BMI - elevated WHR**	**Overweight - normal WHR**	**Overweight - elevated WHR**	**Obese - normal WHR**	**Obese - elevated WHR**
Any CVD	1.27* [1.25, 1.30] $1.58x10^{-119}$	1.16* [1.13, 1.18] $1.30x10^{-35}$	1.53* [1.49, 1.57] $1.09x10^{-247}$	1.22* [1.17, 1.26] $1.45x10^{-22}$	1.13* [1.10, 1.17] $1.72x10^{-14}$	1.30* [1.26, 1.34] $5.32x10^{-70}$	1.51* [1.45, 1.58] $4.42x10^{-79}$	1.68* [1.63, 1.73] $8.66x10^{-254}$
Ischaemic heart disease	1.34* [1.30, 1.37] $2.09x10^{-103}$	1.22* [1.18, 1.25] $2.72x10^{-39}$	1.48* [1.44, 1.53] $3.28x10^{-126}$	1.33* [1.27, 1.40] $4.00x10^{-29}$	1.20* [1.15, 1.26] $1.99x10^{-17}$	1.44* [1.39, 1.50] $9.83x10^{-80}$	1.45* [1.36, 1.53] 4.94x10-35	1.70* [1.64, 1.77] $6.72x10^{-157}$
Atrial fibrillation	1.18* [1.14, 1.21] $2.18x10^{-29}$	1.09* [1.06, 1.13] $3.25x10^{-8}$	1.58* [1.53, 1.64] $1.61x10^{-155}$	1.04 [0.99, 1.10] 0.1494	1.06* [1.02, 1.11] 0.0082	1.13* [1.09, 1.18] $5.29x10^{-10}$	1.61* [1.52, 1.70] $9.80x10^{-58}$	1.61* [1.55, 1.68] $5.89x10^{-118}$
Heart failure	1.36* [1.30, 1.42] $5.75x10^{-48}$	1.10* [1.04, 1.15] $1.71x10^{-4}$	1.74* [1.66, 1.83] $2.17x10^{-109}$	1.24* [1.14, 1.34] $1.93x10^{-7}$	1.04 [0.97, 1.12] 0.2557	1.26* [1.19, 1.34] $3.37x10^{-14}$	1.71* [1.57, 1.87] $1.82x10^{-35}$	1.94* [1.83, 2.06] $4.14x10^{-103}$
All-cause mortality	1.18* [1.15, 1.21] $2.24x10^{-36}$	0.91* [0.89, 0.94] $3.72x10^{-11}$	1.07* [1.04, 1.10] $1.53x10^{-5}$	1.21* [1.15, 1.26] $1.24x10^{-16}$	0.87* [0.84, 0.91] $1.26x10^{-11}$	1.04 [1.00, 1.08] 0.0273	1.01 [0.95, 1.06] 0.8099	1.19* [1.14, 1.23] $1.99x10^{-20}$
CVD mortality	1.46* [1.35, 1.59] $6.43x10^{-19}$	1.09 [0.99, 1.19] 0.0649	1.47* [1.34, 1.61] $5.72x10^{-16}$	1.47* [1.27, 1.70] $4.29x10^{-7}$	1.06 [0.91, 1.23] 0.4596	1.39* [1.23, 1.57] $7.66x10^{-8}$	1.38* [1.12, 1.69] 0.0020	1.82* [1.62, 2.06] $3.67x10^{-22}$

Supplementary Table 4 footnote. Results are hazard ratios, 95% confidence intervals and p-values from Cox proportional hazards regression in the full data set. Each cell represents one model. Hazard ratios reflect the increased hazard associated with category status, compared to normal obesity (normal WHR, normal BMI respectively). All models are adjusted by age, sex, ethnicity, deprivation, smoking, alcohol consumption frequency, processed meat intake, education, physical activity, diabetes, hypertension and high cholesterol.
Abbreviations: CVD, cardiovascular disease, BMI, body mass index; METS, metabolic equivalents, WHR waits-to-hip ratio

Supplementary Table 5: CMR metrics by obesity category

CMR	Imaging set	Normal BMI - normal WHR	Normal BMI - elevated WHR	Overweight - normal WHR	Overweight - elevated WHR	Obese - normal WHR	Obese - elevated WHR
N	32,107	9,432	3,383	5,446	7,931	1,466	4,449
LVEDV (ml)	148.2 (33.8)	139.4 (31.1)	145.8 (33.8)	145.5 (33.3)	155.0 (33.7)	146.8 (29.4)	160.7 (35.2)
LVEDV index (ml/m^2)	79.1 (14.1)	80.7 (13.9)	80.2 (15.0)	78.7 (14.0)	79.3 (14.2)	75.1 (12.1)	76.7 (13.8)
LVM (g)	86.6 (22.4)	76.0 (18.5)	84.4 (19.2)	82.4 (20.7)	94.8 (20.7)	83.4 (18.6)	102.3 (24.2)
LVM index (g/m^2)	46.0 (8.7)	43.9 (8.2)	46.4 (8.2)	44.5 (8.6)	48.4 (8.5)	42.6 (7.6)	48.7 (9.2)
LVM: LVEDV	0.59 (0.09)	0.55 (0.07)	0.58 (0.08)	0.57 (0.08)	0.62 (0.09)	0.57 (0.08)	0.64 (0.10)
LVEF (%)	59.5 (6.1)	60.0 (5.8)	59.2 (6.2)	59.9 (5.9)	58.8 (6.4)	60.5 (5.9)	59.1 (6.5)
LVGFI (%)	47.5 (6.9)	49.4 (6.7)	47.3 (6.7)	48.5 (6.6)	45.7 (6.7)	49.0 (6.6)	45.3 (6.8)
T1 mapping (ms)	932 (36)	942 (35)	931 (34)	932 (35)	922 (35)	935 (37)	926 (36)
LAV (ml)	73.0 (23.3)	67.3 (20.3)	67.3 (22.2)	72.8 (21.4)	75.2 (23.5)	79.2 (22.0)	83.6 (26.8)
LAV index (ml/m^2)	39.1 (11.3)	39.1 (11.2)	37.1 (11.6)	39.5 (10.7)	38.6 (11.4)	40.6 (10.4)	40.0 (12.1)
LAEF (%)	61.3 (9.1)	61.8 (8.5)	62.0 (9.2)	61.9 (8.6)	61.0 (9.6)	60.9 (8.6)	59.3 (10.1)
PDA AoD(10^{-3}/mmHg)	2.42 (1.14)	2.57 (1.27)	2.35 (1.13)	2.48 (1.19)	2.29 (0.99)	2.46 (1.12)	2.28 (0.96)
ASI (m/s)	9.56 (2.69)	9.02 (2.69)	9.72 (2.74)	9.36 (2.64)	10.05 (2.67)	9.33 (2.57)	10.06 (2.52)

Supplementary Table 5 footnote: Continuous data are given in mean (standard deviation).

Abbreviations: index, indexation to body surface area; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; LVM:LVEDV, concentricity index; LVEF, left ventricular ejection fraction; LVGFI, left ventricular global function index, LAV, left atrial volume, LAEF, left atrial ejection fraction, PDA AoD, aortic distensibility at the proximal descending aorta; ASI, arterial stiffness index

Supplementary Table 6. Associations between CMR metrics and incident outcomes

		Model 1		Model 2		Model 3	
Exposure	**Outcome**	**HR, 95% CI**	**p-value**	**HR, 95% CI**	**p-value**	**HR, 95% CI**	**p-value**
LVEDV	Any CVD	1.32* [1.23, 1.42]	9.13x10-14	1.34* [1.25, 1.44]	2.15x10-15	1.32* [1.23, 1.42]	2.14x10-14
	Ischaemic heart disease	1.11 [1.01, 1.22]	0.0367	1.14* [1.04, 1.26]	0.0071	1.13 [1.03, 1.24]	0.0119
	Atrial fibrillation	1.51* [1.39, 1.63]	1.91x10-24	1.52* [1.41, 1.65]	1.76x10-26	1.50* [1.39, 1.62]	3.52x10-24
	Heart failure	1.93* [1.76, 2.11]	4.73x10-44	1.94* [1.77, 2.13]	9.08x10-45	1.89* [1.72, 2.08]	1.00x10-40
	All-cause mortality	1.15 [1.03, 1.29]	0.0144	1.17* [1.05, 1.31]	0.0048	1.17* [1.05, 1.31]	0.0047
	CVD mortality	1.74* [1.43, 2.12]	3.92x10-8	1.74* [1.43, 2.12]	2.52x10-8	1.69* [1.39, 2.06]	1.07x10-7
LVM	Any CVD	1.68* [1.57, 1.80]	1.70x10-48	1.69* [1.58, 1.81]	7.49x10-50	1.60* [1.49, 1.72]	6.75x10-38
	Ischaemic heart disease	1.55* [1.42, 1.70]	2.16x10-21	1.57* [1.43, 1.72]	2.07x10-22	1.47* [1.34, 1.61]	1.74x10-15
	Atrial fibrillation	1.71* [1.57, 1.86]	7.76x10-37	1.72* [1.59, 1.88]	2.27x10-37	1.67* [1.53, 1.82]	2.29x10-30
	Heart failure	2.26* [2.03, 2.50]	7.15x10-54	2.27* [2.05, 2.52]	2.42x10-54	2.14* [1.92, 2.38]	1.40x10-42
	All-cause mortality	1.28* [1.14, 1.45]	3.85x10-5	1.29* [1.14, 1.45]	2.99x10-5	1.28* [1.13, 1.45]	7.31x10-5
	CVD mortality	1.90* [1.51, 2.38]	4.09x10-8	1.92* [1.53, 2.42]	2.79x10-8	1.86* [1.46, 2.37]	5.18x10-7
LVM: LVEDV	Any CVD	1.26* [1.19, 1.34]	2.75x10-15	1.25* [1.18, 1.33]	4.69x10-14	1.19* [1.12, 1.27]	1.51x10-8
	Ischaemic heart disease	1.35* [1.26, 1.45]	6.59x10-17	1.33* [1.24, 1.42]	7.06x10-15	1.25* [1.16, 1.35]	2.62x10-9
	Atrial fibrillation	1.14* [1.05, 1.24]	0.0013	1.13* [1.04, 1.23]	0.0037	1.09 [1.00, 1.18]	0.0605
	Heart failure	1.14 [1.01, 1.29]	0.0382	1.12 [0.99, 1.27]	0.0669	1.04 [0.91, 1.18]	0.5919
	All-cause mortality	1.12 [1.02, 1.23]	0.0160	1.10 [1.00, 1.21]	0.0461	1.08 [0.99, 1.19]	0.0962
	CVD mortality	1.13 [0.87, 1.47]	0.3711	1.12 [0.86, 1.46]	0.4101	1.07 [0.81, 1.40]	0.6323
LVEF	Any CVD	0.83* [0.78, 0.89]	2.07x10-8	0.83* [0.78, 0.89]	1.51x10-8	0.83* [0.77, 0.88]	3.24x10-9
	Ischaemic heart disease	0.90 [0.83, 0.98]	0.0109	0.90* [0.83, 0.97]	0.0085	0.89* [0.82, 0.96]	0.004
	Atrial fibrillation	0.78* [0.72, 0.85]	4.68x10-9	0.79* [0.72, 0.85]	3.83x10-9	0.79* [0.73, 0.85]	4.09x10-9
	Heart failure	0.52* [0.47, 0.57]	2.29x10-47	0.52* [0.48, 0.57]	2.46x10-46	0.54* [0.49, 0.58]	3.90x10-44
	All-cause mortality	0.84* [0.77, 0.93]	3.54x10-4	0.84* [0.77, 0.93]	3.21x10-4	0.85* [0.77, 0.93]	3.66x10-4
	CVD mortality	0.58* [0.47, 0.70]	5.36x10-8	0.58* [0.48, 0.71]	6.97x10-8	0.59* [0.48, 0.72]	1.41x10-7
LVGFI	Any CVD	0.74* [0.69, 0.80]	6.60x10-17	0.75* [0.69, 0.80]	1.81x10-16	0.76* [0.71, 0.82]	3.54x10-14
	Ischaemic heart disease	0.76* [0.70, 0.83]	7.88x10-10	0.77* [0.70, 0.84]	2.33x10-9	0.79* [0.72, 0.86]	9.52x10-8
	Atrial fibrillation	0.74* [0.68, 0.81]	2.58x10-10	0.75* [0.68, 0.82]	5.07x10-10	0.76* [0.69, 0.84]	8.24x10-9
	Heart failure	0.44* [0.39, 0.50]	3.11x10-41	0.45* [0.40, 0.51]	3.84x10-40	0.47* [0.42, 0.53]	8.12x10-36
	All-cause mortality	0.80* [0.72, 0.88]	1.57x10-5	0.80* [0.72, 0.89]	3.23x10-5	0.81* [0.73, 0.90]	6.72x10-5
	CVD mortality	0.49* [0.38, 0.63]	4.63x10-8	0.49* [0.38, 0.64]	6.79x10-8	0.50* [0.38, 0.65]	2.31x10-7
Native T1	Any CVD	1.09 [1.01, 1.16]	0.0199	1.07 [1.00, 1.15]	0.0425	1.08 [1.01, 1.16]	0.0206
	Ischaemic heart disease	0.96 [0.88, 1.05]	0.4293	0.95 [0.87, 1.04]	0.2374	0.96 [0.88, 1.05]	0.3437
	Atrial fibrillation	1.21* [1.11, 1.33]	3.92x10-5	1.20* [1.09, 1.31]	1.01x10-4	1.21* [1.10, 1.32]	5.57x10-5
	Heart failure	1.42* [1.26, 1.61]	1.35x10-8	1.39* [1.23, 1.57]	1.20x10-7	1.40* [1.24, 1.58]	3.94x10-8
	All-cause mortality	1.25* [1.13, 1.38]	1.02x10-5	1.23* [1.12, 1.36]	4.06x10-5	1.23* [1.11, 1.36]	4.54x10-5

Native T1	CVD mortality	1.52* [1.17, 1.98]	0.002	1.51* [1.16, 1.96]	0.0021	1.51* [1.17, 1.96]	0.0018
LAV (log)	Any CVD	1.40* [1.30, 1.50]	2.27x10-20	1.41* [1.32, 1.52]	2.16x10-21	1.37* [1.28, 1.47]	2.93x10-18
	Ischaemic heart disease	1.14* [1.04, 1.24]	0.0031	1.15* [1.06, 1.25]	0.0012	1.11 [1.02, 1.21]	0.0127
	Atrial fibrillation	1.92* [1.74, 2.12]	7.88x10-39	1.94* [1.75, 2.13]	8.57x10-40	1.87* [1.70, 2.07]	5.67x10-36
	Heart failure	1.74* [1.52, 1.98]	1.46x10-16	1.75* [1.53, 1.99]	6.34x10-17	1.65* [1.45, 1.88]	8.57x10-14
	All-cause mortality	1.11 [1.00, 1.23]	0.0425	1.12* [1.01, 1.24]	0.0296	1.11 [1.00, 1.23]	0.0498
	CVD mortality	1.57* [1.16, 2.13]	0.0035	1.56* [1.15, 2.12]	0.004	1.50* [1.11, 2.04]	0.0091
LAEF	Any CVD	0.62* [0.58, 0.66]	2.20x10-44	0.63* [0.59, 0.67]	1.09x10-43	0.64* [0.60, 0.68]	3.77x10-40
	Ischaemic heart disease	0.81* [0.75, 0.87]	7.88x10-8	0.81* [0.75, 0.88]	1.45x10-7	0.83* [0.77, 0.90]	2.83x10-6
	Atrial fibrillation	0.47* [0.44, 0.51]	2.30x10-79	0.48* [0.44, 0.52]	1.18x10-77	0.49* [0.45, 0.53]	1.26x10-71
	Heart failure	0.57* [0.52, 0.63]	1.38x10-31	0.58* [0.53, 0.63]	2.94x10-30	0.60* [0.55, 0.66]	8.11x10-26
	All-cause mortality	0.88* [0.80, 0.96]	0.0061	0.88* [0.81, 0.97]	0.0092	0.89 [0.81, 0.98]	0.0172
	CVD mortality	0.66* [0.52, 0.83]	4.79x10-4	0.66* [0.52, 0.84]	6.06x10-4	0.67* [0.53, 0.86]	0.0012
PDA AoD (log)	Any CVD	0.83* [0.76, 0.91]	5.19x10-5	0.84* [0.77, 0.92]	1.03x10-4	0.88* [0.80, 0.96]	0.0039
	Ischaemic heart disease	0.81* [0.72, 0.90]	1.43x10-4	0.81* [0.73, 0.91]	2.42x10-4	0.85* [0.76, 0.95]	0.0057
	Atrial fibrillation	0.95 [0.84, 1.08]	0.4487	0.97 [0.85, 1.09]	0.5848	1.00 [0.88, 1.14]	0.9467
	Heart failure	0.88 [0.73, 1.05]	0.1506	0.89 [0.74, 1.06]	0.1889	0.94 [0.78, 1.13]	0.4907
	All-cause mortality	0.93 [0.81, 1.07]	0.3317	0.94 [0.82, 1.08]	0.3573	0.94 [0.82, 1.08]	0.3899
	CVD mortality	0.74 [0.50, 1.09]	0.1262	0.74 [0.50, 1.09]	0.1286	0.77 [0.52, 1.14]	0.1943
ASI (imaging)	Any CVD	1.08 [1.00, 1.15]	0.0364	1.07 [1.00, 1.15]	0.0479	1.06 [0.99, 1.14]	0.0974
	Ischaemic heart disease	1.07 [0.98, 1.17]	0.1277	1.06 [0.97, 1.16]	0.1647	1.05 [0.96, 1.15]	0.2772
	Atrial fibrillation	0.99 [0.90, 1.09]	0.8338	0.98 [0.90, 1.08]	0.7523	0.98 [0.89, 1.07]	0.6392
	Heart failure	0.92 [0.80, 1.05]	0.2249	0.91 [0.80, 1.05]	0.1877	0.90 [0.79, 1.03]	0.1348
	All-cause mortality	1.03 [0.93, 1.14]	0.5857	1.02 [0.92, 1.14]	0.6725	1.02 [0.92, 1.13]	0.7195
	CVD mortality	1.08 [0.79, 1.47]	0.6341	1.08 [0.80, 1.48]	0.6120	1.07 [0.79, 1.46]	0.6465

Supplementary Table 6 footnote. Hazard ratios associated with 1 SD increase in CMR measures, 95% confidence intervals and p-values from Cox proportional hazards models relating LVEDV, LVM, LVM:LVEDV, LVEF, LVGFI, Native T1, LAEF, PDA AoD (log) and ASI to incident disease/events in the imaging subset. Each cell represents a different model. Model 1 = adjusted by age and sex, Model 2 = adjusted by Model 1 variables plus ethnicity, Townsend deprivation score, education, physical activity, alcohol consumption frequency, smoking and processed meat intake. Model 3 = adjusted by Model 2 variables plus diabetes, hypertension and high cholesterol.

Abbreviations: LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; LVM:LVEDV, concentricity index; LVEF, left ventricular ejection fraction; LVGFI, left ventricular global function index, LAV, left atrial volume, LAEF, left atrial ejection fraction, PDA AoD, aortic distensibility at the proximal descending aorta; ASI, arterial stiffness index

Supplementary Table 7. Mediation results for BMI-outcome associations

Outcome	CMR metric	Total effect	Direct effect of obesity	Obesity via CMR	Obesity via Diabetes	Obesity via High cholesterol	Obesity via Hypertension
Ischaemic heart disease	LVEDV	0.155* (100%)	0.002 (1%)	0.040* (26%)	0.017* (11%)	0.025* (17%)	0.070* (45%)
	LVM	0.225* (100%)		0.132* (59%)	0.014 (6%)	0.025* (11%)	0.054* (24%)
	LVM: LVEDV	0.177* (100%)		0.083* (47%)	0.012* (7%)	0.022* (12%)	0.059* (34%)
	LVEF	0.125* (100%)	0.008 (5%)	0.004* (3%)	0.016* (13%)	0.024* (19%)	0.074* (60%)
	LVGFI	0.157* (100%)	0.001 (1%)	0.049* (32%)	0.013* (8%)	0.025* (16%)	0.068* (43%)
	Native T1	0.130* (100%)	0.002 (1%)	0.011* (9%)	0.017* (13%)	0.023* (18%)	0.076* (59%)
	LAV (log)	0.141* (100%)	0.004 (3%)	0.028* (19%)	0.018* (13%)	0.023* (17%)	0.068* (49%)
	LAEF	0.127* (100%)	0.004 (3%)	0.015* (12%)	0.016* (13%)	0.023* (18%)	0.068* (54%)
	PDA AoD (log)	0.115* (100%)	0.005 (3%)	0.009* (8%)	0.019* (16%)	0.023* (20%)	0.060* (52%)
	ASI (imaging)	0.119* (100%)	0.004 (3%)	0.009 (7%)	0.018* (15%)	0.021* (18%)	0.068* (57%)
Atrial fibrillation	LVEDV	0.151* (100%)	0.001 (0%)	0.079* (53%)	0.015* (10%)	0.001 (1%)	0.055* (37%)
	LVM	0.206* (100%)		0.153* (74%)	0.012 (6%)		0.041* (20%)
	LVM: LVEDV	0.135* (100%)	0.029 (16%)	0.037* (29%)	0.013 (11%)	-0.002 (-1%)	0.058* (46%)
	LVEF	0.113* (100%)	0.030 (18%)	0.006* (6%)	0.014 (13%)		0.064* (63%)
	LVGFI	0.130* (100%)	0.009 (5%)	0.052* (41%)	0.011 (9%)		0.058* (46%)
	Native T1	0.131 (100%)	0.073 (47%)	-0.018 (-16%)	0.013* (12%)	-0.004 (-3%)	0.066* (59%)
	LAV (log)	0.224* (100%)		0.153* (68%)	0.015* (7%)		0.056* (25%)
	LAEF	0.123* (100%)	0.003 (2%)	0.049* (41%)	0.010 (8%)		0.060* (49%)
	PDA AoD (log)	0.153* (100%)	0.078 (43%)	0.003 (2%)	0.015* (11%)		0.057* (43%)
	ASI (imaging)	0.100* (100%)	0.021 (14%)		0.015 (15%)		0.065* (71%)
Heart failure	LVEDV	0.236* (100%)		0.112* (48%)	0.024* (10%)	0.009 (4%)	0.092* (39%)
	LVM	0.298* (100%)		0.200* (67%)	0.019* (6%)	0.008 (3%)	0.072* (24%)
	LVM: LVEDV	0.163* (100%)	0.009 (4%)	0.017 (10%)	0.022* (13%)	0.010 (7%)	0.105* (66%)
	LVEF	0.147* (100%)	0.005 (3%)	0.016* (11%)	0.016 (11%)	0.010 (7%)	0.100* (69%)
	LVGFI	0.231* (100%)	0.002 (1%)	0.120* (52%)	0.013 (6%)	0.008 (3%)	0.088* (38%)
	Native T1	0.127* (100%)	0.020 (11%)	-0.042* (-36%)	0.017* (15%)	0.011 (9%)	0.120* (101%)
	LAV (log)	0.255* (100%)		0.123* (48%)	0.019* (8%)	0.013 (5%)	0.099* (39%)
	LAEF	0.166* (100%)		0.044* (27%)	0.014 (8%)	0.012 (7%)	0.095* (57%)
	PDA AoD (log)	0.145* (100%)		0.011 (9%)	0.017 (11%)	0.011 (8%)	0.106* (72%)
	ASI (imaging)	0.158* (100%)	0.008 (4%)		0.019 (12%)	0.016* (10%)	0.115* (74%)

Supplementary Table 7 footnote. BMI: body mass index. Average effect and proportion mediated (effect / total effect) for multiple mediation models between BMI (exposure) and incident events in the imaging subset. Mediated via diabetes, hypertension and high cholesterol plus one cardiovascular metric at a time. Each row represents one model. All models are adjusted by age, sex, smoking, alcohol intake frequency, ethnicity, Townsend deprivation score, education, physical activity and processed meat intake. Mediation analyses were conducted with the mmabig package in R, with 400 bootstrapped samples. An asterisk indicates an effect where the semiparametric confidence interval does not contain zero.

Supplementary Table 8. Mediation summary for WHR-outcome associations

Outcome	CMR metric	Total effect	Direct effect of obesity	Obesity via CMR	Obesity via Diabetes	Obesity via High chol	Obesity via Hypertension
Ischaemic heart disease	LVEDV	0.269* (100%)	0.101 (35%)	0.054* (21%)	0.018* (7%)	0.032* (13%)	0.065* (25%)
	LVM	0.300* (100%)	0.004 (1%)	0.191* (64%)	0.018* (6%)	0.032* (11%)	0.055* (19%)
	LVM: LVEDV	0.269* (100%)	0.057* (19%)	0.113* (43%)	0.014 (5%)	0.028* (11%)	0.057* (22%)
	LVEF	0.270* (100%)	0.132* (47%)	0.024* (9%)	0.016* (6%)	0.031* (12%)	0.067* (26%)
	LVGFI	0.279* (100%)	0.073 (24%)	0.096* (35%)	0.014* (5%)	0.031* (11%)	0.065* (24%)
	Native T1	0.244* (100%)	0.126* (49%)		0.018* (7%)	0.030* (13%)	0.071* (30%)
	LAV (log)	0.278* (100%)	0.150* (52%)	0.019* (7%)	0.017* (6%)	0.030* (11%)	0.062* (23%)
	LAEF	0.274* (100%)	0.150* (53%)	0.016* (6%)	0.016* (6%)	0.030* (12%)	0.062* (24%)
	PDA AoD (log)	0.259* (100%)	0.143* (52%)	0.014* (6%)	0.019* (8%)	0.029* (12%)	0.054* (22%)
	ASI (imaging)	0.266* (100%)	0.148* (54%)	0.012 (5%)	0.018* (7%)	0.026* (10%)	0.062* (24%)
Atrial fibrillation	LVEDV	0.200* (100%)	0.002 (1%)	0.124* (62%)	0.018* (9%)		0.055* (28%)
	LVM	0.277* (100%)		0.219* (79%)	0.014 (5%)		0.044* (16%)
	LVM: LVEDV	0.155* (100%)	0.035 (17%)	0.044* (30%)	0.016 (11%)		0.060* (42%)
	LVEF	0.148* (100%)	0.024 (12%)	0.042* (30%)	0.015 (11%)		0.066* (47%)
	LVGFI	0.181* (100%)	0.007 (3%)	0.100* (56%)	0.013 (7%)		0.060* (34%)
	Native T1	0.137* (100%)	0.078* (48%)	-0.022 (-24%)	0.016 (14%)	-0.003 (-2%)	0.068* (64%)
	LAV (log)	0.181* (100%)	0.002 (1%)	0.106* (59%)	0.018 (10%)		0.055* (30%)
	LAEF	0.138* (100%)	0.016 (9%)	0.049* (37%)	0.010 (7%)	0.001 (1%)	0.061* (46%)
	PDA AoD (log)	0.155* (100%)	0.069 (37%)	0.006 (4%)	0.017 (13%)	0.002 (1%)	0.061* (45%)
	ASI (imaging)	0.118* (100%)	0.035 (23%)		0.016 (15%)		0.066* (63%)
Heart failure	LVEDV	0.312* (100%)		0.181* (58%)	0.027* (9%)	0.012 (4%)	0.092* (30%)
	LVM	0.400* (100%)		0.293* (73%)	0.022 (5%)	0.009 (2%)	0.077* (20%)
	LVM: LVEDV	0.169* (100%)	0.007 (3%)	0.016 (9%)	0.026* (16%)	0.012 (7%)	0.108* (66%)
	LVEF	0.238* (100%)		0.104* (44%)	0.019 (8%)	0.011 (5%)	0.103* (43%)
	LVGFI	0.362* (100%)		0.245* (68%)	0.017 (5%)	0.007 (2%)	0.092* (25%)
	Native T1	0.104* (100%)	0.014 (10%)	-0.066* (-77%)	0.022 (22%)	0.014 (14%)	0.120* (131%)
	LAV (log)	0.231* (100%)	0.003 (1%)	0.089* (39%)	0.023* (10%)	0.015 (6%)	0.102* (44%)
	LAEF	0.181* (100%)	0.005 (2%)	0.050* (29%)	0.016 (9%)	0.012 (6%)	0.099* (55%)
	PDA AoD (log)	0.165* (100%)	0.008 (3%)	0.015 (10%)	0.019 (11%)	0.011 (7%)	0.112* (69%)
	ASI (imaging)	0.168* (100%)	0.011 (5%)		0.021 (13%)	0.021 (13%)	0.115* (70%)

Supplementary Table 8 footnote: WHR: waist-hip-ratio. Average effect and proportion mediated (effect / total effect) for multiple mediation models between waist-hip-ratio (exposure) and incident events in the imaging subset. Mediated via diabetes, hypertension and high cholesterol plus one cardiovascular metric at a time. Each row represents one model. All models are adjusted by age, sex, smoking, alcohol intake frequency, ethnicity, Townsend deprivation score, education, physical activity and processed meat intake. Mediation analyses were conducted with the mmabig package in R, with 400 bootstrapped samples. An asterisk indicates an effect where the semiparametric confidence interval does not contain zero.