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ORIGINAL RESEARCH

Imaging-Derived Sarcopenic Obesity and Cardiovascular Outcomes

Insights Into Heart Failure Risk and Muscle Biology

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ABSTRACT

BACKGROUND The prognostic value of obesity in cardiovascular disease is complex. Measures such as body mass index and waist-to-height ratio show differing associations with outcomes, especially in heart failure. Assessing sarcopenic obesity, the coexistence of excess fat and low muscle mass, may clarify this relationship; however, quantifying sarcopenia in clinical practice remains challenging.

OBJECTIVES The goal was to establish a translatable method of assessing sarcopenic obesity from cardiovascular imaging and assess its clinical relevance using long-term follow-up, genomic, and transcriptomic data.

METHODS We developed a deep learning pipeline to quantify pectoralis major muscle mass from 55,768 cardiovascular magnetic resonance examinations and combined this with body weight to derive a novel sarcopenic obesity index. Associations with cardiac remodeling phenotypes and adverse cardiovascular and mortality outcomes were tested in multivariable models. Genome-wide association analysis, colocalization, and polygenic risk score evaluation were performed for the sarcopenic obesity index. Transcriptomic profiling of skeletal muscle across 7 pathophysiological states assessed differential gene expression.

RESULTS A higher sarcopenic obesity index was associated with adverse cardiac remodeling, and with increased risk of incident heart failure (HR: 1.31; 95% CI: 1.16-1.49), cardiovascular death (HR: 1.51; 95% CI: 1.25-1.81), and all-cause mortality (HR: 1.37; 95% CI: 1.26-1.49). Genome-wide association analysis identified 16 loci for sarcopenic obesity. Loci included genes associated with heart failure and nonischemic cardiomyopathy, with colocalization implicating shared causal variants in heart failure. Transcriptomic profiling demonstrated that sarcopenic obesity loci were specifically modulated during muscle atrophy. Analyses identified *ACVR2B*, the target of bimagrumab, which is being tested with semaglutide to enhance fat loss while maintaining lean mass.

CONCLUSIONS These results establish sarcopenic obesity as a clinically meaningful cardiovascular risk phenotype and point to viable therapeutic targets. (JACC. 2026;■:■-■) © 2026 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BIA = bioelectrical impedance analysis

BMI = body mass index

CMR = cardiovascular magnetic resonance

CT = computed tomography

DEXA = dual-energy x-ray absorptiometry

EDV = end-diastolic volume

GWAS = genome-wide association study

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

IDI = integrated discrimination improvement

LDL = low-density lipoprotein

LV = left ventricle

LVEF = left ventricular ejection fraction

MVR = mass-to-volume ratio

NRI = net reclassification improvement

PRS = polygenic risk score

WHR = waist-to-hip ratio

WHtR = waist-to-height ratio

Sarcopenic obesity is the combination of increased adiposity and reduced skeletal muscle mass and strength. In the context of the inexorable rise of obesity rates globally and an aging population, it represents the intersection of 2 public health concerns.

Sarcopenic obesity has been linked to a broad range of clinical sequalae associated with aging, including frailty and cognitive impairment,[1,2] metabolic disturbances such as dyslipidemia and diabetes mellitus,[3] and effects on treatment outcomes including surgical complications and prolonged hospital inpatient stays.[4] From a cardiovascular disease perspective, sarcopenic obesity is of particular interest given the complex relationship between obesity and cardiovascular outcomes, particularly heart failure. It is known that obesity is a risk factor for the development of both heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF); however, when considering the role of obesity as a prognostic marker for individuals with established heart failure, the relationship is less clear.[5] For example, when considering all-cause mortality for individuals with HFpEF the nadir of risk has been shown to be at a body mass index (BMI) of 30 to 35 kg/m^2, whereas if one measures waist:height ratio (WHtR), the risk appears to be constant across the range.[6,7] Historically, this has been termed the "obesity paradox"; however, it appears clear that the relationship is more complex than this and that sarcopenic obesity may be a potentially more sensitive method for risk stratification in these patients.

A major limitation in the assessment of sarcopenic obesity are in the common modalities used to assess sarcopenia: bioelectrical impedance analysis (BIA) and dual-energy x-ray absorptiometry (DEXA). They are not routinely performed in patients with cardiometabolic disease, only indirectly estimate muscle mass and furthermore are subject to a number of limitations and assumptions such as hydration status and fat distribution, which limit their precision and accuracy.[8,9] By contrast, cross-sectional imaging of the chest is one of the most commonly performed radiological investigations within health care systems.[10] The pectoralis major muscle is a large skeletal muscle with well-defined anatomical boundaries. It is consistently captured within standard cardiac and thoracic imaging fields of view enabling reproducible and opportunistic quantification without additional imaging or radiation exposure, and therefore is a potentially scalable muscle mass surrogate.

In this study, we create a novel index to assess sarcopenic obesity in approximately 55,000 individuals by using a direct, 3-dimensional measurement of pectoralis major muscle mass from cardiovascular magnetic resonance (CMR) examinations in combination with body weight. Using this sarcopenic obesity index, we determine its association with prognostic markers of cardiac structure and function as well as cardiovascular and mortality outcomes. To further understand the biological mechanisms that might drive these associations, we also perform a systematic evaluation of its genetic architecture in a genome-wide association (GWAS) framework and derive a polygenic score. Finally, using candidate genes identified from our GWAS, we interrogate their in vivo differential expression in human muscle biopsy transcriptomes in physiological and pathological states including unloading, aging, and frailty.

METHODS

STUDY POPULATION. The UK Biobank is a large population-based prospective cohort study of 500,000 individuals aged between 40 and 69 years at the time of initial recruitment between 2006 and 2010. It has collected information on health and lifestyle data, physical measurements, biological samples, and genotype. Incident health events are prospectively tracked through linkage to electronic health record data (hospital episode statistics, death register).[11] CMR examinations, as part of the UK Biobank imaging enhancement, have been performed from 2015 onward. Information regarding the CMR protocol and derivation of CMR phenotypes, as well as the cardiovascular and mortality outcome (myocardial infarction, ischemic stroke, heart failure cardiovascular death related to these conditions,

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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all-cause mortality) definitions are described in the Supplemental Methods.

This study was conducted using UK Biobank access application 2964 in accordance with the principles in the Declaration of Helsinki concerning human subjects and tissues. It was covered by the general ethical approval for UK Biobank studies (June 18, 2021, Ref 21/NW/0157) with written informed consent obtained from all participants.

DEEP LEARNING ALGORITHM TO DERIVE SARCOPENIC OBESITY INDEX. The sarcopenic obesity index, adapted from the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity consensus statement on sarcopenic obesity,[12] was derived as follows:

$$\textit{Sarcopenic obesity index} = \frac{\textit{Weight } (kg)}{\textit{Pectoralis major muscle mass } (g)}$$

In this way, the 2 components of sarcopenic obesity are captured, with an increasing sarcopenic obesity index indicative of a more pathophysiological state (increasing obesity, increasing sarcopenia/lower muscle mass).

We developed a deep learning pipeline to measure pectoralis major muscle mass from the axial stack of UK Biobank CMR examinations. The axial stack provides thoracic coverage from around the cricothyroid junction to the liver. Ground truth composed of manual, 3-dimensional segmentation of pectoralis major in 200 cases (>2,100 slices). Of these 200 cases, participants were partitioned into training (n = 150) and test (n = 50) sets. We implemented nnU-Net (v2) in both 2-dimensional and 3-dimensional full-resolution U-Net architectures employing *z*-score intensity normalization, real-time data augmentation, and a composite loss comprising the Dice similarity coefficient and cross-entropy. Model parameters were optimized using stochastic gradient descent with Nesterov momentum across 1,200 training epochs. In the evaluation of 50 independent test studies (Supplemental Table 1), the highest performance was achieved by the 2-dimensional U-Net ensemble (over 5-fold) incorporating uncertainty estimation. This model demonstrated the best combination of overlap- and boundary-based performance metrics, with a mean Dice similarity coefficient of 0.832 ± 0.05, mean Jaccard index of 0.715 ± 0.07, mean 95th percentile Hausdorff distance of 5.20 ± 3.4 mm, and mean average surface distance of 0.96 ± 0.55 mm, outperforming the single-fold 2-dimensional and 3-dimensional models. Further methodological details are presented in the Supplemental Methods. Exemplar segmentation is shown in **Figure 1**.

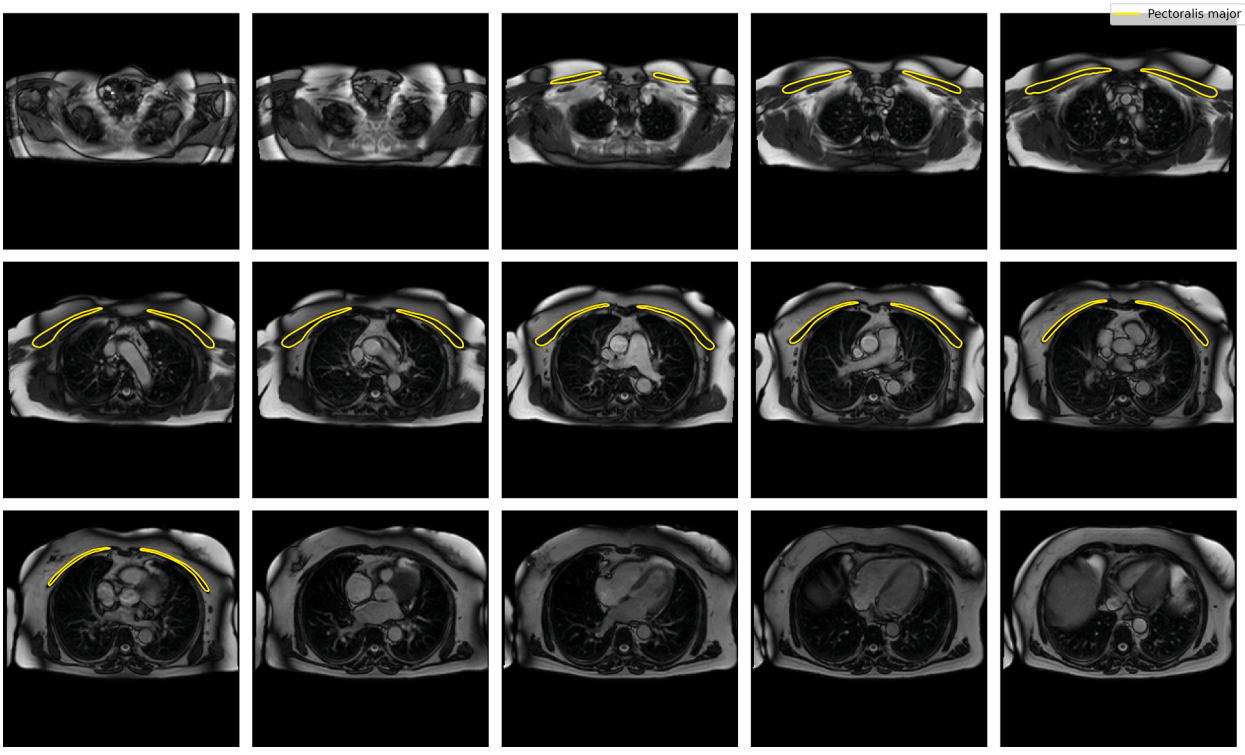
To evaluate the validity of pectoralis major muscle mass as a sarcopenia biomarker, correlation and agreement analyses against established body composition and functional measures available in the UK Biobank were performed. We compared pectoralis major muscle mass with appendicular lean mass derived from both BIA and DEXA, magnetic resonance imaging-derived thigh muscle volume, and maximal handgrip strength. Body composition metrics were normalized to both BMI and height.[2] Associations between measures were quantified using Spearman's rank correlation coefficients. Agreement between modalities were further assessed using Bland-Altman analyses with calculation of mean bias and 95% limits of agreement applied to normalized and *z*-standardized measurements.

OBSERVATIONAL ANALYSES. Baseline characteristics of the cohort are presented in categorized fashion with participants grouped into unequal bins based on their sarcopenic obesity percentile separately for male and female individuals to aid comparison and visualization. To examine trends across the groups, Cuzick's extension of the Wilcoxon rank sum test was used for continuous variables and the chi-square test for trend was used for categorical variables.[13,14]

To examine the association between sarcopenic obesity index and CMR parameters, multivariable linear regression models were fitted for each dependent variable (left ventricular [LV] end-diastolic volume [EDV], LV end-systolic volume [ESV], left ventricular ejection fraction [LVEF], LV mass, LV mass:volume ratio [MVR], LV global longitudinal strain, global native T1). The sarcopenic obesity index was scaled to a mean of zero and SD of 1 such that the coefficient is interpreted as the change in CMR parameter per SD increase in the sarcopenic obesity index. Covariates included age, sex, ethnicity (White vs non-White), systolic blood pressure, height, BMI, smoking status, current alcohol use, known type 2 diabetes mellitus, Townsend deprivation index, low-density lipoprotein (LDL) cholesterol levels and physical activity. When considering native T1, averaged wall thickness for basal and mid antero- and inferoseptal segments were included as an additional covariate. Physical activity was estimated using a modified version of the Recent Physical Activity Questionnaire approach.[15]

The relationships between sarcopenic obesity index and incident myocardial infarction, stroke, heart

FIGURE 1 Exemplar Deep Learning–Derived Segmentation of Pectoralis Major From CMR Images



Representative axial cardiac magnetic resonance (CMR) slices from the UK Biobank imaging protocol are shown, spanning the thoracic inlet to the upper abdomen. Automated 3-dimensional segmentation of the pectoralis major muscle, generated using an nnU-Net–based deep learning pipeline, is delineated in yellow. These segmentations provided volumetric estimates of pectoralis major mass for derivation of the sarcopenic obesity index. CMR images reproduced by kind permission of UK Biobank.

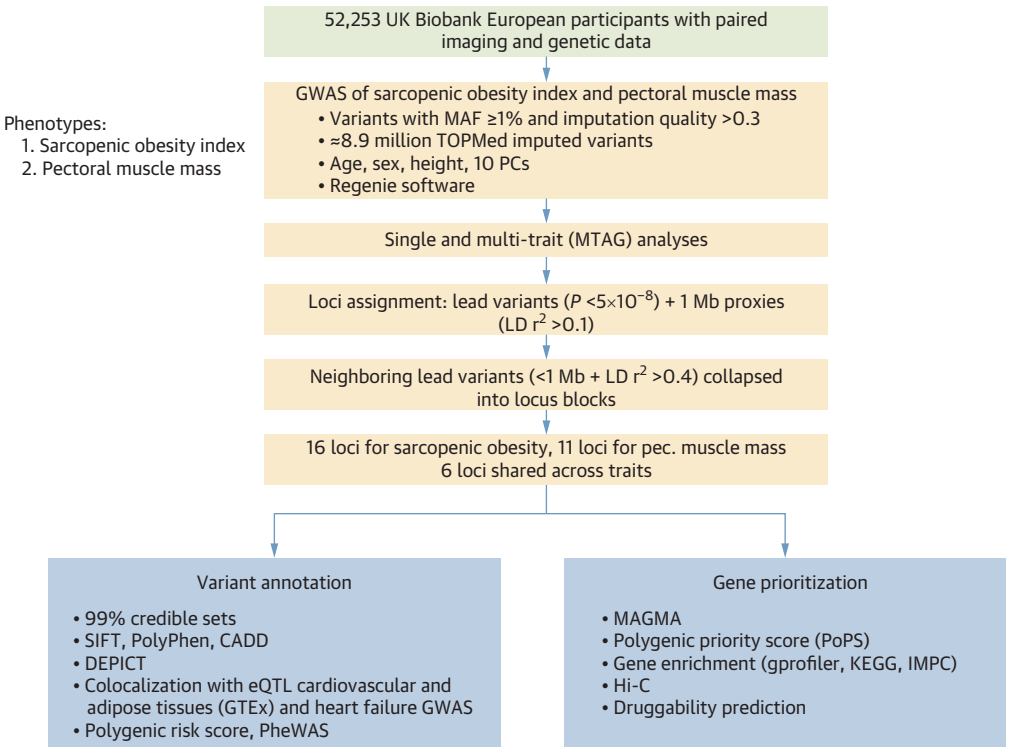
failure, cardiovascular mortality, and all-cause mortality were individually assessed using Cox proportional hazards regression models, providing HRs as measures of risk.[16] The outcome variable was time to incident diagnosis or death with the sarcopenic obesity index serving as the main predictor. The considered timeframe was date of imaging visit until the occurrence of the outcome being considered, or until a censor date of January 1, 2023. Cox models were adjusted for the following covariates: age, sex, ethnicity (White vs non-White), systolic blood pressure, height, smoking status, current alcohol use, known type 2 diabetes mellitus, Townsend deprivation index, LDL cholesterol levels, and physical activity.

To examine and compare the utility of the sarcopenic obesity index, additional models were constructed with pectoralis major muscle mass, weight, BMI, waist-to-hip ratio (WHR), and WHtR as exposures of interest for each assessed outcome. All body composition exposure variables were standardized (mean = 0, SD = 1) thus the HR is interpreted as the change in risk per SD increase. Plots of Schoenfeld residuals were visually examined to assess for model violations.[17] Cox models were constructed using the *survival* package in R.[18]

A number of complementary analyses were performed to assess the incremental predictive value of the sarcopenic obesity index relative to conventional anthropometric measures. Model discrimination was assessed using Harrell's C-statistic. Differences in C-statistics between models incorporating the sarcopenic obesity index and those incorporating BMI, WHR, or WHtR were formally compared using a Wald-type test (*compareC* R package).[19] Model fit was further evaluated using likelihood ratio testing. Reclassification performance was assessed using integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI).

Sensitivity analyses were undertaken to evaluate the robustness of the sarcopenic obesity index. First, alternative formulations of the index were

FIGURE 2 Study Flowchart for GWAS Analysis



CADD = combined annotation-dependent depletion; DEPICT = Data-driven Expression Prioritized Integration for Complex Traits; eQTL = expression quantitative trait loci; GTEx = genotype-tissue expression; GWAS = genome-wide association study; Hi-C = long-range chromatic interaction; IMPC = International Mouse Phenotyping Consortium; INFO = imputation quality score; KEGG = Kyoto Encyclopedia of Genes and Genomes; LD = linkage disequilibrium; MAF = minor allele frequency; MAGMA = Multi-marker Analysis of GenoMic Annotation; MTAG = multi-trait analysis of genome-wide association; PolyPhen-2 = Polymorphism Phenotyping 2; PRS = polygenic risk scores; SIFT = sorting intolerant from tolerant.

constructed: 1) replacing body weight with DEXA-derived fat mass as the numerator (fat mass/pectoralis muscle mass); and 2) normalizing pectoralis major muscle mass to height squared (height^2), with height removed as a covariate from the corresponding models. Second, to address potential reverse causation, analyses were repeated after excluding events occurring within the first year following imaging.

All analyses were conducted in R version 4.1.1.[20]

GENETIC ANALYSES. For both the sarcopenic obesity index and pectoralis major muscle alone, we conducted GWAS in 52,253 European ancestry individuals across 8.9 million TOPMed (Trans-Omics for Precision Medicine)-imputed common variants at a minor allele frequency of ≥0.01 and imputation quality score of >0.3. A flowchart describing the genomic analyses is presented in **Figure 2**. Further information describing the methods used for performing the GWAS, heritability and genetic correlation analyses, functional annotation of variants, cross-referencing against known obesity and other cardiovascular trait loci, colocalization analyses, candidate gene prioritization, druggability analyses, and polygenic risk score (PRS) computation and phenome-wide association study analysis in the UK Biobank and All of Us cohorts are presented in the Supplemental Methods.

TRANSCRIPTIONAL PROFILING OF SARCOPENIC OBESITY CANDIDATE GENES. To further explore the mechanistic relevance of the sarcopenic obesity GWAS loci, we examined whether the candidate genes mapped to these loci were transcriptionally responsive to mechanical loading, unloading, frailty, and aging in 1,082 human skeletal muscle samples.

We compared candidate genes against 7 independent human muscle biopsy data sets: 1) differentially expressed genes after short-term unloading with a

knee brace and 2) differentially expressed genes after 84-day bed rest[21]; 3) differentially expressed genes among endurance-training responders[22]; 4) resistance training differentially expressed genes in young and 5) older adults[23,24]; 6) differentially expressed genes associated with prefrailty[25] and 7) genes differing in healthy individuals by age (~35 vs ~65 years).[26] Details of the transcriptomic pipeline (sample processing, array hybridization, preprocessing, differential expression, and integration with GWAS) are presented in the Supplemental Methods.

RESULTS

VALIDATION OF PECTORALIS MAJOR MUSCLE PHENOTYPE. Correlations between pectoralis major muscle mass and established measures of skeletal muscle mass and function are presented in Supplemental Figure 1. When normalized to BMI, correlation coefficients were $\rho = 0.84$ for DEXA-derived appendicular lean mass and $\rho = 0.86$ for magnetic resonance imaging-derived thigh muscle volume. Similar correlations were observed when normalizing to height.[2] Correlation of pectoralis major muscle mass and handgrip strength was $\rho = 0.75$. Pectoralis major muscle mass demonstrated the highest correlation coefficient with handgrip compared with the other body composition metrics. Bland-Altman plots for agreement between pectoralis major muscle mass and appendicular lean mass and thigh muscle volume are shown in Supplemental Figure 2. For z-standardized measures normalized to BMI, 95% of individuals differed by no more than 1.15 SDs between DEXA appendicular lean mass and pectoralis major muscle mass (95% limits of agreement = 1.15, −1.12), and by no more than 1.14 SDs for thigh muscle volume and pectoralis major muscle mass (95% limits of agreement = 1.14, −1.12).

BASELINE CHARACTERISTICS. Baseline characteristics for the cohort, split into unequal percentile bins (1st-50th, 50th-75th, 75th-90th, and >90th) and divided into female and male individuals are presented in **Figure 3**, and Supplemental Tables 2 and 3. Further descriptive statistics of the sarcopenic obesity index are presented in Supplemental Table 4. There was a clear trend that individuals with higher (worsening) sarcopenic obesity indices were more likely to be older, have higher BMI, systolic blood pressure, HbA1c, and levels of deprivation. They were less likely to be physically active and had lower pectoralis major muscle mass. Opposing trends for LDL cholesterol (increasing levels with higher sarcopenic obesity index in women vs decreasing levels in men) were observed. It is possible that this is a result of patterns of statin prescribing in men vs women for primary prevention, which, in the United Kingdom, are mainly driven by QRISK scoring in general practice.[27]

ASSOCIATION OF SARCOPENIC OBESITY AND MARKERS OF CARDIAC REMODELING. The association of the sarcopenic obesity index with prognostically important LV CMR parameters in fully adjusted models are presented in **Table 1**. The following number of participants had paired sarcopenic obesity and CMR data and were included in the analyses: 55,599 individuals for LV EDV, LV ESV, LVEF, and LV MVR; 44,895 for LV global longitudinal strain and 42,052 for global native T1. A 1-SD increase in sarcopenic obesity index was associated with significantly lower LV EDV (effect size = −4.1 mL; 95% CI: −4.5 to −3.7; $P = 7.5 \times 10^{-114}$), lower LV mass (effect size = −3.5 g; 95% CI: −3.7 to −3.3; $P = 1.2 \times 10^{-281}$), higher LV MVR (effect size = 0.008; 95% CI: 0.007-0.009; $P = 1.9 \times 10^{-41}$), and higher native T1 values (effect size = 6.4 ms; 95% CI: 5.8-7.1; $P = 6.4 \times 10^{-101}$).

THE PREDICTIVE VALUE OF SARCOPENIC OBESITY FOR INCIDENT CARDIOVASCULAR OUTCOMES AND MORTALITY. Associations of the sarcopenic obesity index and conventional body composition metrics (BMI, WHR, WHtR), when modeled separately as exposures of interest, are detailed in **Table 2** and **Figure 4**. The median follow-up time was 4.18 years. A higher sarcopenic obesity index was associated with elevated risk of incident heart failure (HR: 1.31; 95% CI: 1.16-1.49; $P = 1.23 \times 10^{-5}$). For heart failure, the sarcopenic obesity index demonstrated the most robust association compared with BMI (HR: 1.11; 95% CI: 1.00-1.23; $P = 0.04$) and WHR (HR: 1.21; 95% CI: 1.06-1.39; $P = 0.006$); the association with WHtR was nonsignificant. For cardiovascular mortality, the sarcopenic obesity index was significantly associated (HR: 1.51; 95% CI: 1.25-1.82; $P = 2.05 \times 10^{-5}$), whereas BMI, WHtR, and WHR were not significantly associated with risk. For all-cause mortality, the sarcopenic obesity index was also significantly associated with risk (HR: 1.37; 95% CI: 1.26-1.49; $P = 2.57 \times 10^{-13}$), with a larger effect estimate than BMI (HR: 1.13; 95% CI: 1.05-1.22; $P = 0.0021$), WHtR (HR: 1.16; 95% CI: 1.07-1.25; $P = 3.4 \times 10^{-4}$), and WHR (HR: 1.20; 95% CI: 1.08-1.33; $P = 4.4 \times 10^{-4}$). For myocardial infarction, the sarcopenic obesity index was not associated with risk (HR: 1.08; 95% CI: 0.91-1.28), whereas BMI, WHtR, and WHR all showed significant positive associations.

Results describing the incremental predictive value of the sarcopenic obesity index in comparison

with BMI, WHR, and WHtR for heart failure, cardiovascular death, and all-cause mortality are shown in Supplemental Table 5. Across all 3 outcomes, incorporation of the sarcopenic obesity index in the model as opposed to a conventional anthropometric measure demonstrated a small but significant improvement in C-statistics. Improvements in discrimination of approximately 0.005 for heart failure, 0.008 to 0.009 for cardiovascular death, and 0.008 to 0.009 for all-cause mortality were observed. Likelihood ratio testing similarly demonstrated improved model fit for the sarcopenic obesity index across all comparisons. IDI, which quantifies the degree of separation in predicted risk between individuals who do and do not experience the event, was significantly higher for cardiovascular death in comparison with BMI (IDI = 0.003; 95% CI: 0.000-0.016; $P = 0.045$) and WHR (IDI = 0.003; 95% CI: 0.000-0.019; $P = 0.047$). For all-cause mortality, both IDI and NRI were significantly improved for the sarcopenic obesity index compared with BMI, WHR, and WHtR, with IDI of 0.002 (95% CI: 0.001-0.005; $P < 0.001$ for all comparisons) and NRI ranging from 0.100 to 0.111 (vs BMI: 0.100; 95% CI: 0.032-0.168; $P = 0.013$; vs WHR: 0.100; 95% CI: 0.044-0.169; $P < 0.001$; vs WHtR: 0.111; 95% CI: 0.048-0.173; $P = 0.007$).

Using alternative formulations of the sarcopenic obesity index in sensitivity analyses yielded similar observations (Supplemental Table 6). Substituting weight with DEXA-derived fat mass and normalizing pectoralis major muscle mass to height^2 produced concordant and similarly sized effect estimates for heart failure, cardiovascular mortality, and all-cause mortality. Associations with myocardial infarction and stroke remained nonsignificant when normalizing pectoralis major to height.[2] Substitution of fat mass resulted in this variation of the sarcopenic obesity index being associated with increased risk of myocardial infarction (HR: 1.23; 95% CI: 1.03-1.46; $P = 0.021$) and stroke (HR: 1.22; 95% CI: 1.02-1.45; $P = 0.03$).

In sensitivity analyses excluding events occurring within 1 year of imaging baseline, associations for the sarcopenic obesity index were largely unchanged (Supplemental Table 7). A higher sarcopenic obesity index remained associated with increased risks of incident heart failure (HR: 1.30; 95% CI: 1.13-1.49; $P = 1.75 \times 10^{-4}$), cardiovascular death (HR: 1.54; 95% CI: 1.26-1.88; $P = 2.49 \times 10^{-5}$), and all-cause mortality (HR: 1.35; 95% CI: 1.23-1.48; $P = 4.32 \times 10^{-10}$).

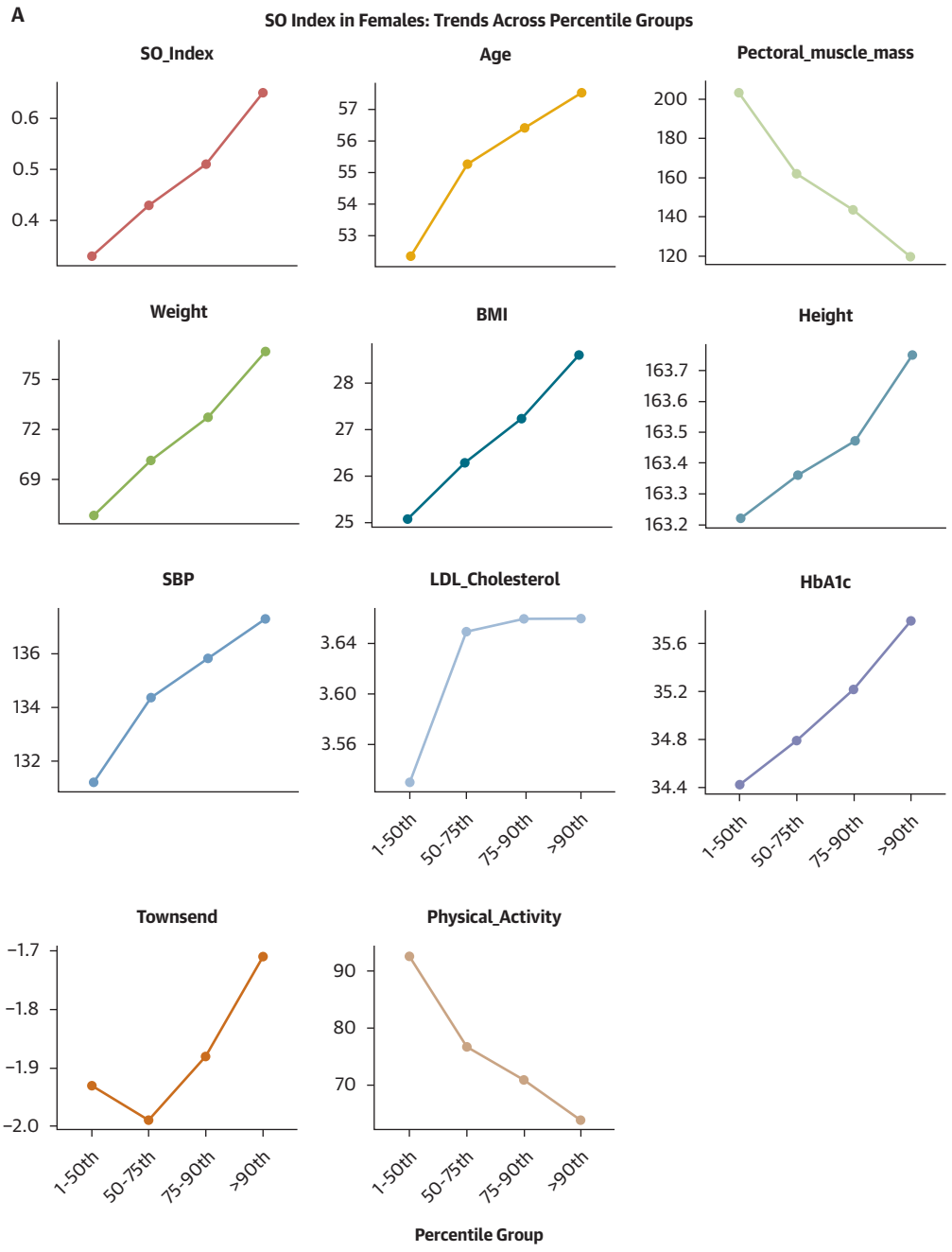
GWAS. Single nucleotide polymorphism-based heritability estimates for sarcopenic obesity index and pectoralis major muscle mass were 17.1% and 14.6%, respectively. A total of 16 loci were identified for sarcopenic obesity (**Table 2**). Eleven loci were identified for pectoralis major muscle mass (**Table 3**). Six loci were shared across both the sarcopenic obesity and pectoralis muscle mass traits (Supplemental Figure 3). Cross-referencing loci effect directions between the 2 traits demonstrated expected directionality as per the genetic correlation ($r_g = -0.762$). All sarcopenic obesity loci that were not genome-wide significant for pectoralis major muscle mass reached nominal significance with P values <0.05.

Six of 16 sarcopenic obesity loci (*SLC30A10, CAND2, CELF1,* LOC646736*, GSS, LOC101929664*) were known BMI loci. The overlap between loci identified for sarcopenic obesity, pectoralis muscle mass, and known BMI loci are shown in Supplemental Figure 3. There was overlap across a range of sarcopenic obesity loci with a number of cardiovascular phenotypes and endophenotypes including blood pressure, heart failure, coronary disease, LVEF, and LV mass. These are summarized in Supplemental Table 8.

GENE PRIORITIZATION. Gene prioritization was performed for 86 candidate genes using a scoring system described in the Supplemental Methods. Prioritized genes for the sarcopenic obesity index and pectoralis major muscle are listed in **Table 3** and Supplemental Table 9, respectively, with full locus-level scoring provided in Supplemental Table 10. Among sarcopenic obesity loci, several prioritized genes were notable for established links to cardiac structure, contractile function, and heart failure susceptibility. These included *TTN, EYA4, PLEC, CAND2, MYBPC3,* and *MYH7B*.

TTN encodes titin, a sarcomeric protein central to passive stiffness and stretch sensing in the cardiomyocyte and is a well-established cause of dilated cardiomyopathy involved in stretch sensing.[28] Variants (rs3731750, rs2042995, rs2042996, rs1001238) in the 99% credible set at the *TTN* locus have previously been demonstrated to be genome-wide significant for dilated cardiomyopathy[29] as well as quantitative traits of cardiac structure and function.[30] *EYA4* is prominently expressed in both the LV and skeletal muscle, and *EYA4* mutations have been demonstrated to result in a dilated cardiomyopathy and heart failure phenotype. *PLEC* encodes plectin, a cytoskeletal cross-linking protein important for structural integrity in striated muscle, with disruption linked to both skeletal and cardiac myopathic phenotypes. *MYBPC3*, which encodes the cardiac

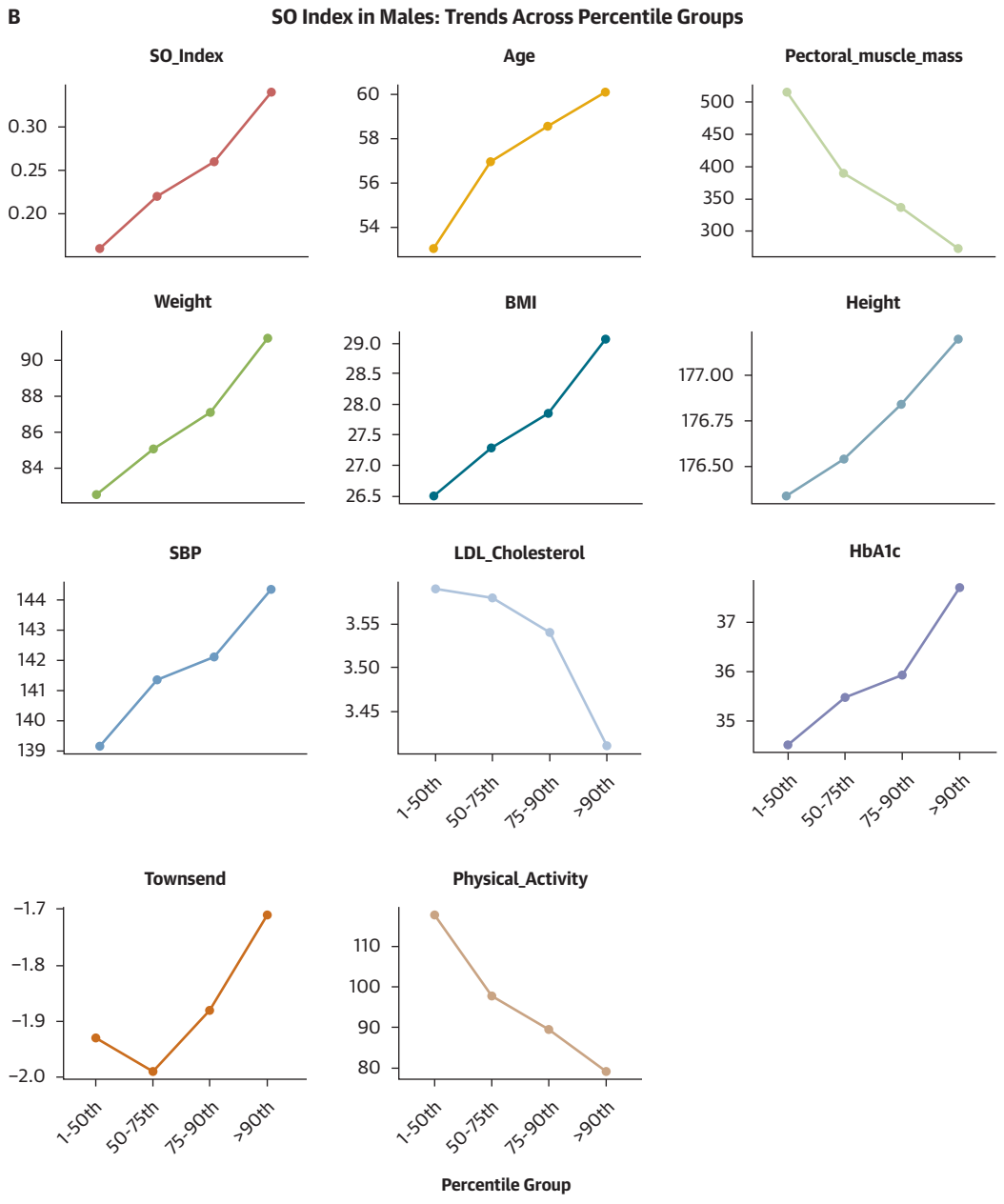
FIGURE 3 **Visual Representation of Body Composition and Cardiovascular Risk Factor Trends Across SO Groups in Female and Male Patients**



Baseline characteristics for the cohort, split into unequal percentile bins (1st-50th, 50th-75th, 75th-90th, and >90th) and divided into female (A) and male (B) patients. Individuals with higher (worsening) sarcopenic obesity (SO) indices were more likely to be older, have higher body mass index (BMI), systolic blood pressure (SBP), HbA1c, and levels of deprivation. They were less likely to be physically active and had lower pectoralis major muscle mass. LDL = low-density lipoprotein.

Continued on the next page

FIGURE 3 Continued



isoform of myosin-binding protein C, is a canonical cardiomyopathy gene with established roles in hypertrophic and dilated cardiomyopathy.[31] *MYH7B*, a myosin heavy chain family member, has also been implicated in cardiac contractile biology and cardiomyopathic processes.[32] In colocalization analysis with a recent all-cause heart failure GWAS, the lead variant at the *CAND2* locus (rs7650482) showed strong evidence of colocalization (PP4 >0.8) for sarcopenic obesity and heart failure[33] (H4 posterior probability = 0.94) indicating the potential for the same underlying causal variant to influence both traits.[34] Taken together, these prioritized genes may suggest a biological overlap between sarcopenic obesity and myocardial remodeling or heart failure susceptibility. The *IRS1* gene was prioritized at the

TABLE 1 Association Between Sarcopenic Obesity Index and Prognostically Important LV CMR Phenotypes

CMR Parameter	Effect Size	Lower 95% CI	Upper 95% CI	*P* Value
LV end-diastolic volume, mL	−4.1	−4.5	−3.7	7.5×10^{-114}
Indexed LV end-diastolic volume, mL/m^2	−1.3	−1.5	−1.1	5.7×10^{-43}
LV end-systolic volume, mL	−1.7	−1.9	−1.4	1.3×10^{-48}
Indexed LV end-systolic volume, mL/m^2	−0.4	−0.5	−0.3	9.5×10^{-13}
LV ejection fraction, %	−0.03	−0.12	0.06	0.57
LV mass, g	−3.5	−3.7	−3.3	1.2×10^{-281}
Indexed LV mass, g/m^2	−0.95	−1.05	−0.85	1.6×10^{-84}
LV mass:volume ratio	0.008	0.007	0.009	1.9×10^{-41}
LV GLS, %	0.02	−0.02	0.05	0.34
LV native T1, ms	6.4	5.8	7.1	6.4×10^{-101}

Effect sizes are interpreted as change in LV CMR parameter per 1 SD increase in sarcopenic obesity index. Models are adjusted for age, sex, ethnicity, systolic blood pressure, height, body mass index, smoking status, current alcohol use, known type 2 diabetes mellitus, Townsend deprivation index, low-density lipoprotein cholesterol levels, and physical activity. Indexed parameters are indexed to body surface area with height and body mass index removed as covariates from the model.

CMR = cardiac magnetic resonance; GLS = global longitudinal strain; LV = left ventricular.

TABLE 2 Associations of the SO Index and Conventional Anthropometric Measures With Incident Cardiovascular Outcomes and Mortality

Outcome	Exposure	Events	Event Rate (%)	HR	95% CI	*P* Value
Heart failure		390	0.81			
	SO index			1.31	1.163-1.486	1.23×10^{-5}
	BMI			1.11	1.003-1.226	0.043
	WHtR			1.11	0.999-1.228	0.052
	WHR			1.21	1.057-1.389	0.006
Myocardial infarction		385	0.79			
	SO index			1.08	0.913-1.284	0.36
	BMI			1.2	1.081-1.323	5.0×10^{-4}
	WHtR			1.22	1.097-1.357	2.5×10^{-4}
	WHR			1.32	1.151-1.515	7.36×10^{-5}
Stroke		312	0.64			
	SO index			1.13	0.955-1.334	0.16
	BMI			0.97	0.861-1.098	0.65
	WHtR			1	0.884-1.133	0.99
	WHR			1.07	0.919-1.255	0.37
Cardiovascular death		109	0.23			
	SO index			1.51	1.247-1.818	2.05×10^{-5}
	BMI			1.15	0.941-1.405	0.17
	WHtR			1.16	0.946-1.423	0.15
	WHR			1.24	0.957-1.614	0.10
All-cause mortality		707	1.46			
	SO index			1.37	1.261-1.494	2.57×10^{-13}
	BMI			1.13	1.045-1.219	0.0021
	WHtR			1.16	1.068-1.252	3.4×10^{-4}
	WHR			1.2	1.084-1.330	4.4×10^{-4}

Results are presented as HR per SD increase in body composition metric. Models were adjusted for the following covariates: age, sex, ethnicity (White vs non-White), systolic blood pressure, height, smoking status, current alcohol use, known type 2 diabetes mellitus, Townsend deprivation index, low-density lipoprotein cholesterol levels and physical activity, left ventricular mass, and left ventricular ejection fraction.

BMI = body mass index; SO = sarcopenic obesity; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio.

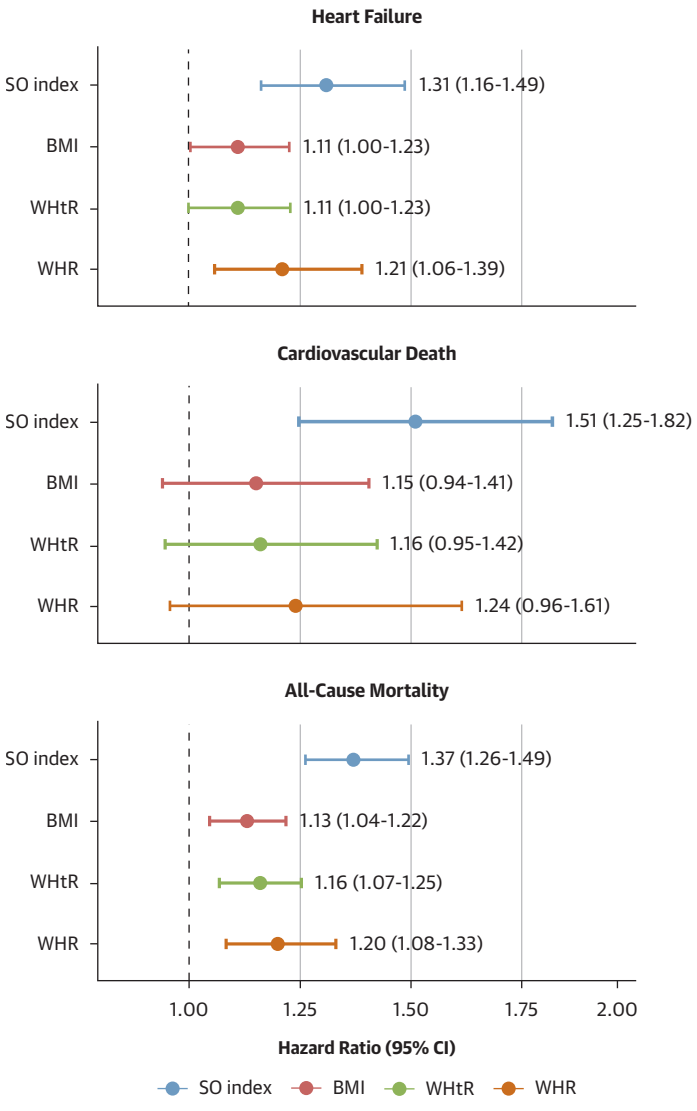
LOC646736 locus. Colocalization analyses suggested the signal at the LOC646736 locus was an expression quantitative trait locus in visceral adipose tissue that reduced *IRS1* expression, providing a potential link between sarcopenic obesity and insulin signaling.

PRS AND PHENOME-WIDE ASSOCIATION STUDY. In addition to obesity, the strongest associations as indicated by the most significant *P* values were as follows: for every SD increase in the sarcopenic obesity index PRS, there was an associated increased risk of hypertension (OR: 1.05; 95% CI: 1.038-1.053; $P = 8.29 \times 10^{-36}$), heart failure (OR: 1.05; 95% CI: 1.035-1.071; $P = 6.28 \times 10^{-11}$), and type 2 diabetes (OR: 1.05; 95% CI: 1.042-1.065; $P = 3.86 \times 10^{-21}$). There was also increased risk of developing severe sepsis (OR: 1.05; 95% CI: 1.032-1.068; $P = 4.94 \times 10^{-9}$) indicating pleiotropic effect of sarcopenic obesity above and beyond cardiometabolic diseases.

The PRS for sarcopenic obesity was deployed in the All of Us cohort for validation purposes. There were concordant, significant findings in the All of Us cohort for all of the top associations identified in the UK Biobank: hypertension (OR: 1.04; 95% CI: 1.071-1.097; $P = 4.43 \times 10^{-10}$), heart failure (OR: 1.05; 95% CI: 1.025-1.076; $P = 4.91 \times 10^{-5}$), type 2 diabetes (OR: 1.05; 95% CI: 1.030-1.061; $P = 2.59 \times 10^{-9}$), sepsis (OR: 1.03; 95% CI: 1.002-1.063; $P = 3.73 \times 10^{-2}$). The wider CIs observed in results derived from the All of Us cohort results reflects the smaller sample size and the more inconsistent data capture of diagnoses as a result of a noncentralized health care system. Figure 5 demonstrates associations of the sarcopenic obesity index PRS with the most significant clinical phenotypes.

TRANSCRIPTIONAL PROFILING OF SARCOPENIC OBESITY CANDIDATE GENES. A striking pattern of overlap was observed in states of muscle unloading (Figure 6). Sixty-four of 86 sarcopenic obesity genes (74.4%) were significantly modulated in at least 1 unloading model and 48 (55.8%) exceeded the 1.25-fold-change threshold (Supplemental Table 11). Twenty-eight candidates were regulated during short-term knee-brace unloading and 36 after 84-day bed rest. This indicated broad sensitivity of sarcopenic obesity loci genes to reduced mechanical input. By contrast, overlap with growth-promoting or fitness-associated states was substantially more modest. Only 6 candidate overlapped genes associated with hypertrophy after resistance training. Eight overlapped with the endurance-training responder signature and 4 overlapped with the prefrailty profile. Aging regulated 8 candidates among age-differentially expressed genes. These findings suggest that genes mapping to sarcopenic obesity loci are disproportionately related to withdrawal of mechanical load. Our analysis positions these genes as possible load-sensing or load-effector nodes indicating that genetic susceptibility to sarcopenic

FIGURE 4 Comparative Associations of SO Index and Other Anthropometric Measures With Incident Cardiovascular and Mortality Outcomes



Results are presented as HR per SD increase in body composition metric. Models were adjusted for the following covariates: age, sex, ethnicity (White vs non-White), systolic blood pressure, height, smoking status, current alcohol use, known type 2 diabetes mellitus, Townsend deprivation index, low-density lipoprotein cholesterol levels, and physical activity, LV mass, LV ejection fraction. LV = left ventricular; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio; other abbreviations as in Figure 3.

TABLE 3 Sarcopenic Obesity Index Loci

Locus Name (Locus Number)	Lead Variant	rsID	Chromosome	Position (hg38)	Reference Allele
SLC30A10 (1)	1:219570796:C:A	rs2785988	1	219570796	C
LOC101927709 (2)	2:118632640:C:G	rs56279633	2	118632640	C
TTN (3)	2:178612605:AT:A	rs774777095	2	178612605	AT
LOC646736 (4)	2:226183055:C:T	rs2943653	2	226183055	C
CAND2 (5)	3:12800724:T:G	rs4642101	3	12800724	T
ACVR2B (6)	3:38454574:C:T	rs3749386	3	38454574	C
LOC101928448 (7)	5:56564954:A:G	rs3936511	5	56564954	A
LINC00461 (8)	5:88673046:A:G	rs6882046	5	88673046	A
EYA4 (9)	6:133520910:A:T	rs10872408	6	133520910	A
HDAC9 (10)	7:18806501:A:G	rs12699982	7	18806501	A
PLEC (11)	8:143944186:C:T	rs11786896	8	143944186	C
LOC102724316 (12)	10:29417831:A:G	rs66520641	10	29417831	A
CELF1 (13)	11:47491256:AG:A	rs71475920	11	47491256	AG
GSS (14)	20:34952197:G:A	rs2025096	20	34952197	G
LOC101929664 (15)	22:30011375:G:A	rs41159	22	30011375	G
TNRC6B (16)	22:40283358:C:G	rs5995842	22	40283358	C

hg38 = Genome Reference Consortium Human Build 38; MAF = minor allele frequency; MTAG = multi-trait analysis of genome-wide association study; rsID = reference single nucleotide polymorphism identifier; SE = standard error.

Continued on the next page

obesity may reflect an enhanced susceptibility to inactivity-mediated atrophy.

DRUGGABILITY. There were a number of candidate genes that represented targets for small molecular and protein therapeutics as defined in The Open Targets platform, PharmGKB, and the Side Effect Resource (SIDER v4.1).[35,36] These analyses revealed a clinically relevant finding at the *ACVR2B* locus. Bimagrumab is a human monoclonal antibody agent that binds to activin receptor type 2B (encoded by *ACVR2B*) and activin receptor type 2A. The resultant blockade of myostatin and activins diminishes inhibitory signaling on muscle development thereby promoting increased muscle mass. It has been studied in several settings including sarcopenia and obesity.[37-41] It is currently under investigation as part of a phase 2 randomized trial to investigate whether bimagrumab in addition to the glucagon-like peptide receptor 1 agonist semaglutide is able to preserve or increase muscle mass in the presence of weight loss.[42]

DISCUSSION

This study used a novel phenotype of sarcopenic obesity, derived from a direct, accurate, 3-dimensional measurement of pectoralis major muscle mass from CMR imaging at population scale (**Central Illustration**). A worsening sarcopenic obesity index was associated with prognostically important LV parameters as derived by CMR, in particular lower LV mass, greater LV MVR, and higher global native T1 indicative of myocardial diffuse fibrosis. The sarcopenic obesity index was associated with an increased risk of incident heart failure, cardiovascular mortality, and all-cause mortality and showed more consistent associations with adverse outcomes when compared with traditional measures of anthropometry (BMI, WHR, WHtR). Sixteen genome-wide significant loci associated with sarcopenic obesity were identified with bioinformatic interrogation demonstrating associations with cardiometabolic genes, pathways, and diseases. Data from muscle biopsy demonstrate that genes mapping to sarcopenic obesity loci have a unique expression profile, being disproportionately regulated by unloading of muscle. This integrative analysis of sarcopenic obesity suggests that it may be a distinct and high-risk body composition phenotype with relevance for cardiovascular risk stratification.

Comparative analyses of pectoralis major muscle mass with established measures of muscle mass supported its validity as an imaging-derived surrogate of skeletal muscle status at a population level. Pectoralis major muscle mass demonstrated excellent concordance with appendicular lean mass measured using both BIA and DEXA, as well as thigh muscle volume. Bland-Altman analyses indicated

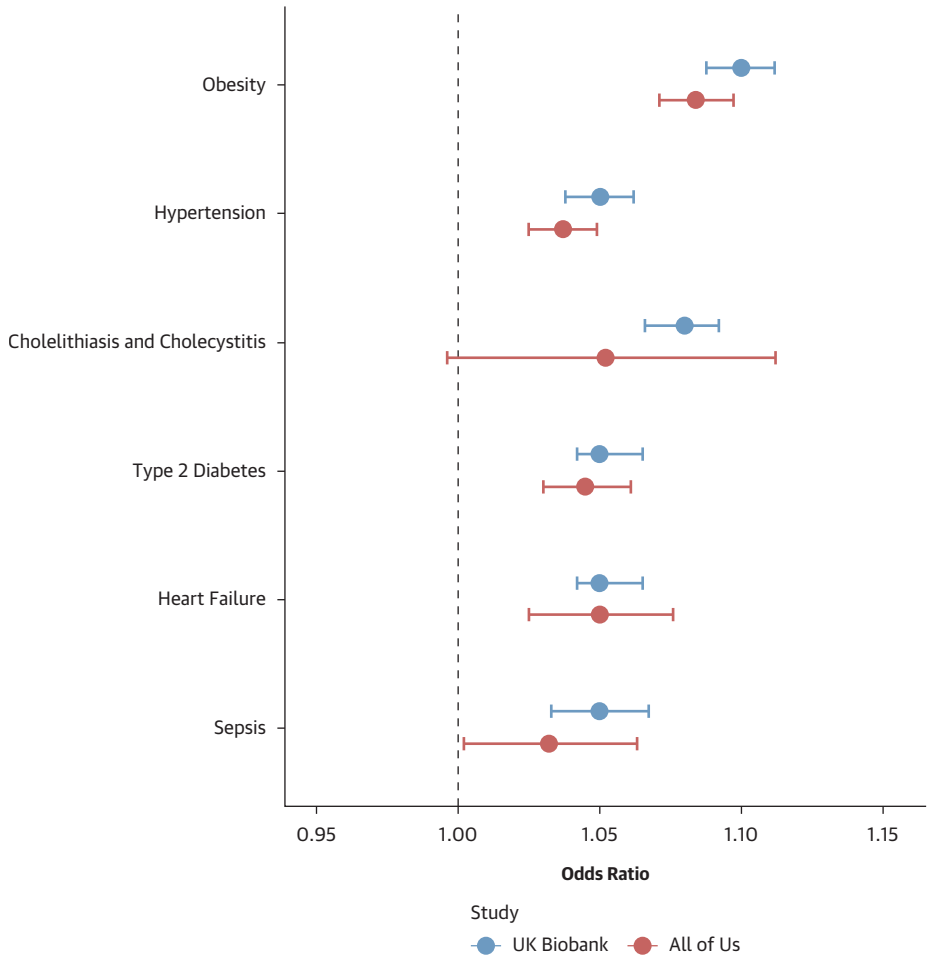
TABLE 3 Continued

Alternate Allele	MAF	Beta	SE	*P*	Prioritized Gene(s)	Pectoralis Major Muscle Mass Locus	Identified From MTAG Analysis
A	0.30	0.0388	0.0068	1.20E-08	*SLC30A10*	Yes	Yes
G	0.10	−0.0557	0.0102	4.93E-08	*LOC101927709*	Yes	
A	0.21	0.0410	0.0075	4.63E-08	*TTN*		
T	0.33	−0.0457	0.0066	5.18E-12	*IRS1*		
G	0.35	−0.0437	0.0065	2.31E-11	*RAF1, TMEM40, CAND2*		Yes
T	0.45	−0.0431	0.0062	4.91E-12	*ACVR2B*	Yes	
G	0.19	−0.0435	0.0078	2.51E-08	*LOC101928448*		
G	0.27	0.0421	0.0070	2.01E-09	*MEF2C, LINC00461*		
T	0.46	0.0363	0.0062	4.44E-09	*EYA4*	Yes	
G	0.27	0.0395	0.0070	1.82E-08	*HDAC9*		
T	0.05	−0.0830	0.0141	4.39E-09	*PLEC*		Yes
G	0.13	−0.0533	0.0091	3.91E-09	*SVIL*		
A	0.26	−0.0428	0.0070	1.11E-09	*NDUFS3, RAPSN, MTCH2, MYBPC3, DDB2, FAM180B, FNBP4*		
A	0.19	−0.0459	0.0079	6.01E-09	*MYH7B, MAP1LC3A*		Yes
A	0.42	−0.0530	0.0062	2.08E-17	*MTMR3*	Yes	
G	0.34	0.0371	0.0065	9.75E-09	*TNRC6B, ADSL*	Yes	

moderate individual-level agreement with greater dispersion of differences at the upper end of the muscle mass distribution. This divergence from appendicular/lower-limb muscle measures at higher muscle mass may reflect heterogeneity in regional hypertrophy, particularly in individuals performing physical activity which preferentially load-specific muscle groups. Although agreement was closer in individuals with lower muscle mass, which is where the sarcopenic obesity index is potentially most clinically important and applicable, the pectoralis-based phenotype may be best interpreted as a population-scale surrogate rather than a precise, individual-level substitute for established measures of muscle mass. Pectoralis major derived from CMR imaging has been used in 2 prior studies of patients with heart failure. These were relatively small scale, however, and only quantified pectoralis major area in a single slice.[43,44] A key advantage of this study is the 3-dimensional assessment of pectoralis major using the entirety of the axial stack thus providing a more accurate measurement of muscle mass, in addition to large sample size of approximately 55,000 participants.

The choice of using pectoralis major as a muscle mass surrogate in constructing the sarcopenic obesity index was deliberate, as it may facilitate translation through "opportunistic screening." Within cardiac imaging, opportunistic screening refers to leveraging potentially valuable information that is incidental to the clinical indication for the examination.[45] Pectoralis major is an anatomically distinct structure and is captured as part of routine examinations across all cross-sectional imaging common in cardiovascular disease pathways: CMR, computed tomography (CT) coronary angiography, and CT for structural intervention planning. The number of CMR and cardiac CT examinations continues to rise substantially. In the UK, ~115,000 CMR examinations were performed in 2018 and ~172,000 cardiac CTs in 2023-2024.[46,47] In the United States, ~243,000 cardiac CT examinations were billed to Medicare in 2022.[48] The CMR-based deep learning segmentation framework described in this study is adaptable to CT using transfer learning and fine-tuning on a modest, annotated CT data set.[49] It is acknowledged that an assessment of muscle strength, in addition to muscle mass, is optimal in the evaluation of sarcopenic obesity[12]; however, we have demonstrated that pectoralis major muscle mass displays good concordance with maximal handgrip strength and given that handgrip strength is not routinely captured in clinical practice, it was not included in the present evaluation of sarcopenic obesity. It is further acknowledged that although use of pectoralis major offers a potentially pragmatic and scalable method for muscle mass assessment in individuals undergoing cross-sectional imaging, it is not a method described in contemporary guidelines for the assessment of sarcopenia and sarcopenic obesity that focus on BIA, DEXA, and CT at the third lumbar vertebra.[12,50]

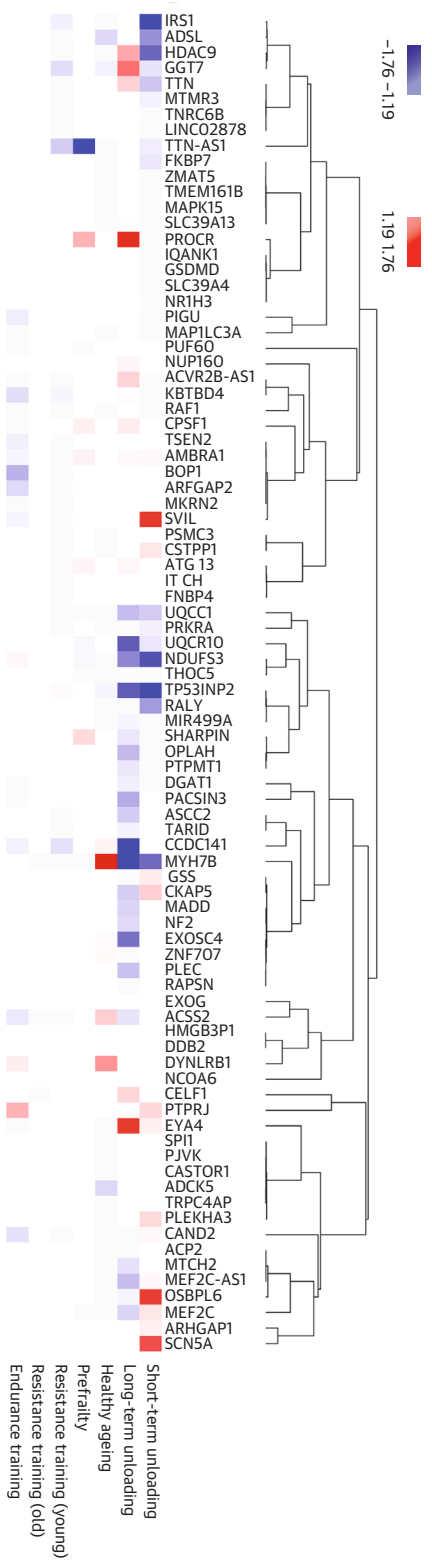
FIGURE 5 **Top Phenome-Wide Association Study Associations in UK Biobank and All of Us for Sarcopenic Obesity Polygenic Risk Score**



ORs are shown per SD increase in the sarcopenic obesity polygenic risk score, highlighting the strongest associations across diagnostic phenotypes. Analyses were adjusted for age, sex, genotyping array, and the first 10 principal components of ancestry. Results are displayed for both the discovery cohort (UK Biobank: >430,000 individuals without cardiac magnetic resonance imaging) and the validation cohort (All of Us: >240,000 individuals).

That sarcopenic obesity is associated with lower LV mass is of interest, particularly given the large effect size (−3.5 g per SD increase in sarcopenic obesity index) and that BMI alone is independently associated with higher LV mass.[51] This appears to highlight the importance of the relationship between skeletal muscle mass and myocardial mass. The relationship between skeletal muscle mass and imaging phenotypes of LV mass has not been well studied, however. A study of 378 participants using bioelectrical impendence for muscle mass assessment and echocardiography for LV mass assessment demonstrated that sarcopenic participants had lower LV mass.[52] The traditional paradigm is that high LV mass is clinically unfavorable and has been demonstrated in other cohort studies such as the Framingham Heart Study[53] and the Multi-Ethnic Study of Atherosclerosis[54] but it is possible that low LV mass is also of significant clinical relevance. Studies from autopsy specimens demonstrate that aging is associated with a smaller heart and that there is progressive attrition of myocyte numbers but this is accompanied by hypertrophy of the remaining myocytes.[55] From our genomic analyses to understand the genetic architecture of sarcopenic obesity we have identified that 13 of 16 sarcopenic obesity loci overlap with known GWAS signals for cardiovascular diseases and/or cardiac imaging endophenotypes, in addition

FIGURE 6 Overlap of Sarcopenic Obesity-Associated Genes With Differential Expression in Human Muscle Across Experimental and Physiological States



to a number of prioritized genes at these loci that are implicated in cardiac structure, heart failure, and cardiomyopathies (*TTN, EYA4, PLEC, CAND2, MYBPC3, MYH7B*). This raises the possibility of shared biology underlying the adverse remodeling observed in association with sarcopenic obesity.

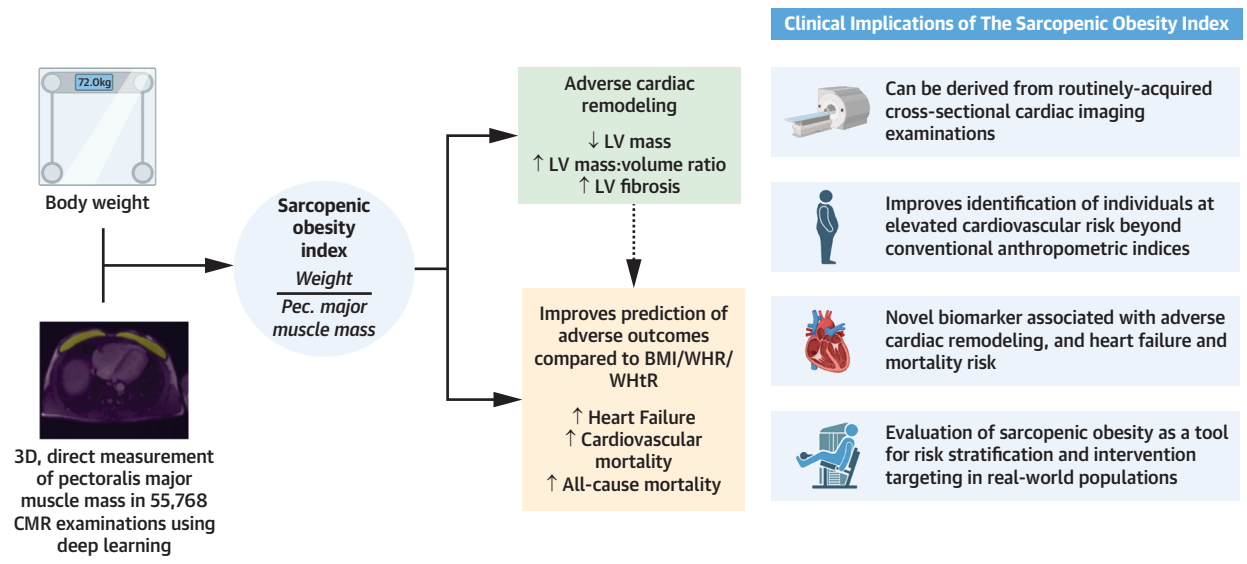
A key finding of this study is that the sarcopenic obesity index was a prognostically informative body composition phenotype for incident heart failure and cardiovascular and all-cause mortality outcomes when compared with traditional anthropometrics. Relative to BMI, WHR, and WHtR, the sarcopenic obesity index demonstrated strong and consistent associations with these outcomes in addition to modest but statistically significant improvements in discrimination and model fit. In addition, reclassification analyses suggested that, particularly for all-cause mortality, the sarcopenic obesity index provided a meaningful, albeit modest, improvement in risk stratification beyond conventional parameters. These findings may suggest that assessment of sarcopenic obesity provides incremental clinical value. It was also noteworthy that when a more granular metric of adiposity was used to derive the sarcopenic obesity index (ie, fat mass from DEXA imaging), associations with adverse outcomes were stronger, supporting the biological plausibility of the phenotype and suggesting that direct quantification of adiposity, in addition to sarcopenia, may further improve risk stratification. It has been long acknowledged, in the setting of heart failure, that there are paradoxical associations between higher BMI and better outcomes but these are increasingly attributed to confounding and misclassification, particularly the inability of BMI to separate adiposity from muscle mass and fluid status. A recent analysis of 5 large HFmrEF/HFpEF trials reported that

FIGURE 6 Continued

Heat map showing expression patterns of genes mapped from sarcopenic obesity loci across multiple conditions: knee-brace short-term unloading (7-14 days), long-term unloading (84 days) with bed rest, aging, prefrailty, resistance training in young individuals, resistance training in older individuals, and endurance training. Rows represent experimental states and columns represent sarcopenic obesity–mapped genes, with colors indicating direction and magnitude of differential expression (red = upregulation, blue = downregulation). There is negligible overlap with resistance or endurance training and few associations with healthy aging or prefrailty differentially expressed genes. However, there is approximately 3 times enrichment overlap with differential expression gene lists for short- and long-term unloading.

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CENTRAL ILLUSTRATION **Imaging-Derived Sarcopenic Obesity Index and Associations With Cardiovascular Outcomes**



Sanghvi MM, et al. JACC. 2026;■(■):■-■.

This study creates a deep-learning-derived sarcopenic obesity index (pectoralis muscle mass from CMR combined with weight). A higher sarcopenic obesity index predicted adverse remodeling and incident heart failure, cardiovascular death, and all-cause mortality, outperforming BMI/waist measures. 3D = 3-dimensional; BMI = body mass index; CMR = cardiac magnetic resonance; LV = left ventricular; Pec. = pectoralis; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio.

although ~46% met BMI ≥30 kg/m^2, ~95% had elevated waist circumference or WHtR.[56] In the PARAGON-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin-Receptor Blocker Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial, central adiposity defined by WHtR ≥0.5 characterized ~96% of participants.[7] Because elevated WHtR is near ubiquitous in this setting, in the context of our findings, it is possible that identification of individuals with concurrent excess adiposity and low muscle mass may be a fruitful mechanism by which to identify those who are at greatest risk of adverse outcomes.

Associations of the sarcopenic obesity PRS with clinical outcomes in both the UK Biobank and All of Us cohorts reinforced its importance in cardiometabolic disease. We identified strong associations for genetically determined sarcopenic obesity with hypertension, type 2 diabetes, and heart failure. Data from transcriptomic analyses demonstrated that genes associated with sarcopenic obesity loci were highly enriched in experimental models of both shorter-term and long-term atrophy, whereas overlap with resistance/hypertrophy and endurance expression profiles was minimal. This enrichment suggests that individuals who are genetically susceptible to sarcopenic obesity may be particularly prone to inactivity-mediated atrophy. Recent cardiovascular prevention guidelines have emphasized the importance of resistance training[57] and assessment of sarcopenic obesity may identify individuals who stand to benefit most significantly from these recommendations.

Measurement of the sarcopenic obesity index may also be of relevance in the context of the expanding usage of weight loss therapies. Although glucagon-like peptide-1 receptor agonists have transformed the management of obesity, emerging evidence has suggested that these agents may cause unintended reductions in skeletal muscle mass with estimates ranging from 15% to 60%. It was of interest, therefore, that downstream druggability analyses from our sarcopenic obesity GWAS identified the *ACVR2B* gene as a high-confidence target in our druggability assessment. It encodes the activin type 2 receptor that is antagonized by bimagrumab, a first-in-class monoclonal antibody, which exerts an anabolic effect on skeletal muscle. The Phase 2b BELIEVE (Safety and Efficacy of Bimagrumab and Semaglutide

in Adults Who Are Overweight or Obese) trial evaluated the therapeutic value of combining bimagrumab with the glucagon-like peptide-1 receptor agonist semaglutide. The combination of bimagrumab and semaglutide produced greater reductions in body weight, fat mass, visceral adiposity, and inflammatory markers than either agent alone, with 92.8% of weight loss attributable to fat mass (vs 71.8% for semaglutide). Overall, combination therapy reduced body weight by 22.1% (−10.8% with bimagrumab, −15.7% with semaglutide), whereas bimagrumab monotherapy uniquely increased lean mass by 2.5%.[42] These results highlight a potential application of the sarcopenic obesity index as a biomarker for nominating individuals in whom targeted therapies that preserve or augment muscle mass, while reducing adiposity, may be of greatest utility.

A higher sarcopenic obesity index was associated with significantly higher native T1 values from CMR. T1 mapping permits the detection of diffuse myocardial structural alterations that are not readily captured via other noninvasive means. Low-grade inflammatory states have been shown to promote monocyte infiltration into cardiomyocytes, which, following macrophage differentiation, results in cardiac inflammation and myocardial fibrosis that, in turn, can increase T1 values.[58] As obesity develops, adipose tissue can become progressively dysfunctional with increased adipocyte macrophage infiltration and release of excess free fatty acids, reactive oxygen species, and pro-inflammatory cytokines fostering inflammation and insulin resistance.[59,60] Both inflammation and insulin resistance have been shown to promote the state of anabolic resistance, with consequent impairment of muscle protein synthesis.[61] Our sarcopenic obesity GWAS identified *IRS1* as a candidate gene with evidence of its downregulation in visceral adipose tissue when examining differential gene expression. The *IRS1* gene encodes IRS-1, a key adaptor in insulin signaling that mediates the effects of activated insulin receptors on glucose uptake in skeletal muscle. Collectively, these findings raise the possibility that inflammation and insulin resistance may contribute to the downstream sequalae of sarcopenic obesity, although further work is required to clarify these mechanisms.

Results from phenome-wide association study analysis demonstrated associations of sarcopenic obesity beyond cardiometabolic disorders with the association with sepsis being particularly noteworthy; sarcopenia is known to predict increased risk of mortality in both the short- and long-term in individuals with septic shock. The relationship of obesity with sepsis, is, in an almost identical fashion to heart failure, less clear, with an "obesity paradox" being observed when using BMI as the obesity measurement of choice.[62] It is possible that the presence of sarcopenic obesity can identify those who are more at risk of the catabolic stress of sepsis in those who overweight or obese. In observational data, the sarcopenic obesity index was the strongest predictor of all-cause mortality compared with other body composition metrics and this is concordant with previous findings.[3,63,64] Its ability to discriminate and reclassify individuals at greatest risk of mortality indicates that it may also be an important biomarker beyond cardiovascular disease

STUDY LIMITATIONS. First, this is an observational study and although all analyses have been adjusted for a range of covariates, residual confounding cannot be ruled out. Second, in the UK Biobank, International Classification of Diseases, 10th Revision coding schedule does not contain heart failure subtypes, so heart failure outcomes could not be differentiated between HFpEF and HFrEF. Third, it is known that the UK Biobank participant population is affected by a "healthy volunteer" selection bias with respect to the overall cohort being generally healthier than the general UK population. Fourth, ethnic diversity in the studied cohort is low, with approximately 95% of individuals being White and genetic analyses were restricted to individuals of European ancestry due to sample size. Finally, the work used a single-stage study design for discovery of genetic loci and as such, replication in the future in independent cohorts will be essential to strengthen the credibility of the results.

CONCLUSIONS

We have performed a comprehensive analysis of the syndrome of sarcopenic obesity using a novel imaging-derived phenotype. These analyses demonstrated the importance and mechanistic underpinnings of the relationship between sarcopenic obesity and cardiovascular disease. Observational, genomic, and transcriptomic analyses performed in this work may aid in incorporating cross-sectional imaging-derived assessment of sarcopenic obesity into clinical risk assessment, stratification, and identification of individuals for targeted intervention.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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KEY WORDS cardiovascular magnetic resonance, deep learning, genome-wide association study, heart failure, obesity, sarcopenia

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.