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EDITORIAL COMMENT

Obesity and Outcomes in Heart Failure

Revisiting the Obesity Paradox?

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Obesity has become a leading cause of premature mortality globally, with most deaths having cardiovascular causes.[1] Obesity increases the risk for all forms of cardiovascular disease and is associated with a particularly potent risk for the development of heart failure (HF).[2] The relationship between obesity and incident HF is largely independent from comorbidities commonly associated with excess weight, such as hypertension and diabetes, suggesting that weight management is necessary for optimal HF risk mitigation. Among individuals with existing HF, the degree of obesity correlates with impairment in functional status and quality of life and the likelihood of HF hospitalizations.[3]

The interrelationship among obesity, HF, and mortality has been complicated by the consistent finding of an "obesity paradox" in epidemiologic studies, wherein among individuals with existing HF, those patients with higher body mass index (BMI) appear to have a lower risk of mortality than their counterparts with normal weight.[4] It has long been unclear whether this reflects a selection bias or a true protective effect of obesity. A key concern is index event bias, wherein analyses conducted within a group of individuals with a given condition, such as HF, can cause falsely protective associations for related risk exposures, such as obesity. In addition, advanced HF is associated with unintentional weight loss from cachexia, making lower BMI in that circumstance a marker of disease severity. Obesity is also often associated with earlier onset of HF, resulting in systematic differences in age and age-related comorbidities from HF patients with lower weight, which may bias outcome comparisons. In terms of a protective explanation, HF patients with higher BMI may have greater metabolic reserve, which can buffer against the chronic wasting associated with severe HF. Traditional epidemiologic analyses are limited in distinguishing whether the obesity paradox represents the biases described above or actual risk mitigation related to excess weight.

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In this issue of *JACC*, Sunderland et al[5] challenge the validity of the obesity paradox, using analytical approaches designed to address the methodologic biases that may have generated it. They performed a genome-wide association study (GWAS) and mendelian randomization (MR) among 50,636 individuals from 22 cohorts to evaluate the association of genetically predicted higher BMI with mortality and cardiovascular outcomes among HF patients.[5] They first recapitulated the obesity paradox within the UK Biobank, again showing that HF patients with overweight and class I obesity (BMI 30-34.9 kg/m^2) had lower mortality than HF patients with normal weight. They subsequently used 947 independent variants to develop a genetic instrument for obesity, showing similar effects on BMI for those with and without HF. They then demonstrated that among patients with HF, each 1-SD higher genetically predicted BMI (4.3 kg/m^2 in men and 5.1 kg/m^2 in women) was associated with 21% higher risk of all-cause mortality, and 29% higher risk of CV mortality or HF hospitalization.

Given that genes are randomly assorted at conception, MR analyses minimize confounding and

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approximate the causal relationship between a genetically determined exposure and an outcome. As such, the analysis by Sunderland et al[5], similarly to previous such work, is an elegant and unbiased way of examining the impact of obesity on clinical outcomes among individuals with HF. Their findings were robust to sensitivity analyses adjusting for index event bias to account for the survival bias in HF cohorts. Their finding that genetically predicted BMI is associated with increased mortality among HF patients, contrasting with the inverse mortality associations for obesity seen in observational HF studies, supports the notion that the obesity paradox may reflect methodologic bias rather than true protection. However, there are important caveats to consider.

"Clinicians should be cautious about interpreting higher weight as protective in HF, but the optimal approach to weight management for HF patients remains an important and unresolved question."

First, the genetic predisposition to obesity generally reduces longevity for all individuals. It is challenging to separate the shorter life expectancy generally associated with excess weight from short-term mortality after HF development (with an average of ~2 years follow-up after HF diagnosis in the present analysis). It would be helpful to confirm that there is no attenuation over time after HF diagnosis in the harm associated with genetically predicted obesity, but this analysis is unable to provide such data. In addition, the weight association with mortality among HF patients has been U-shaped, and MR analyses, which assume linear associations, are limited for evaluating nonlinear associations. MR analyses also presume a constant and proportional hazard of lifelong genetic BMI risk associated with HF outcomes. These analyses are not well designed to account for bidirectional associations, secular trends, or environmental impacts on body weight. The study population here, largely derived from clinical trials, is demographically homogenous (with >95% European ancestry), so results may not be widely generalizable.

There is particular caution regarding implications for weight loss. Matched observational studies of bariatric surgery indicate that marked weight loss is associated with improved outcomes among HF patients.[6] Randomized trials of high-potency incretin analogues (glucagon-like peptide 1 receptor agonist (GLP-1RA) and glucose-dependent insulinotropic polypeptide/GLP-1RA) in obesity and HF with preserved ejection fraction demonstrate improved symptoms and functional capacity and reduced risk of worsening HF events.[7] In contrast, the picture is more unclear for those with heart failure with reduced ejection fraction (HFrEF), where earlier trials of the GLP-1RA liraglutide demonstrated no mortality benefit, with signals toward increased risk of adverse events, including arrhythmias and worsening HF.[8,9] Indications of increased harm with GLP-1RA use in these trials were most notable among individuals with severe HF (NYHA functional class III-IV HF). It is unclear whether these adverse outcomes were related to weight loss, to known effects of GLP-1RA on raising heart rate, or to other causes. While the recent SELECT trial of the GLP-1RA semaglutide demonstrated cardiac benefits of semaglutide among the subset of the patients with HFrEF, more than 90% of those individuals had NYHA functional class I-II HF.[10] Notably, in the present study, the magnitude of the adverse associations between BMI and adverse outcomes was stronger among individuals with ejection fractions ≥40% vs <40%, although there was no statistically significant interaction.

While this MR analysis demonstrates the harmful impact of lifelong exposure to obesity, it does not necessarily indicate beneficial effects of weight reduction after HF development. MR analyses of other exposures, such as hemoglobin A1c and triglycerides, have demonstrated causal associations with CVD, but clinical trials of reducing glycemia and triglycerides have had modest or null effects on cardiovascular event rates. Because the severity of HF was not described in this analysis, it is unclear the extent to which this study population reflects those with advanced HF for whom weight loss is most in question. This is particularly relevant for patients with obesity and end-stage HFrEF, in whom excess weight often precludes candidacy for advanced HF therapies. We agree with the study investigators that clinical trials of GLP-1RA are warranted and needed to assess the impact of weight reduction on clinical outcomes among patients with HFrEF.

The investigators of this study conducted a robust MR analysis, demonstrating that genetically predicted higher weight was associated with increased risk of mortality and HF hospitalization among patients with HF. The contrast with the protective associations for obesity seen in epidemiologic studies of HF patients suggests that methodologic bias is a likely explanation for the obesity paradox. However, the analysis is somewhat limited by difficulty disentangling the pre- and post-HF diagnosis impacts of

obesity on longevity, linear modeling of the nonlinear association between weight and HF mortality, and the use of a demographically homogenous study population. Randomized clinical trials of GLP-1RA or other weight loss therapies are needed to truly understand the clinical impact of weight loss among HF patients, particularly for those with advanced HFrEF. Clinicians should be cautious about interpreting higher weight as protective in HF, but the optimal approach to weight management for HF patients remains an important and unresolved question.

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KEY WORDS GLP-1 RA, heart failure, Mendelian randomization, obesity, selection bias, weight loss

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Body Mass Index, Clinical Outcomes, and Mortality in Heart Failure

A Mendelian Randomization Study

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ABSTRACT

BACKGROUND Excess adiposity, most commonly indexed through body mass index (BMI), is strongly associated with the development of heart failure (HF). Weight loss therapies improve outcomes in patients with obesity and HF with preserved left ventricular ejection fraction (LVEF), but their effects in HF with reduced LVEF remain unclear.

OBJECTIVES The aim of this work is to determine whether higher BMI is associated with adverse clinical outcomes in patients with HF and whether there is effect modification by LVEF subgroup.

METHODS Two-sample Mendelian randomization (MR) was used, with genome-wide significant loci associated with BMI as instrumental variables and outcome data from a genome-wide association study (GWAS) of time-to-event clinical outcomes in patients with HF. A total of 50,636 individuals of European ancestry with established HF from 22 cohorts were included in the genetic analysis: 12 HF trials, 1 prospective case-cohort study, 9 cohorts nested within non-HF cardiovascular trials, and 1 population-based cohort derived from the UK Biobank.

The exposure was genetically predicted BMI and the outcome measures were all-cause mortality and a composite of cardiovascular mortality or HF hospitalization. Genetic associations for the outcomes were derived from our GWAS and MR was used to estimate the unbiased association of genetically predicted BMI with these clinical outcomes.

RESULTS The mean BMI was 29.2 ± 5.8 kg/m^2. Over a median follow-up of 27.0 months, all-cause mortality occurred in 11,454 patients (23%), and 11,360 participants (22%) experienced the composite endpoint. Genetically predicted BMI was associated with an increased rate of both all-cause mortality (HR per SD [4.8 BMI units] 1.21; 95% CI: 1.13-1.29; $P = 9 \times 10^{-8}$) and the composite outcome (HR 1.29; 95% CI: 1.20-1.38; $P = 8 \times 10^{-13}$). Associations were consistent across LVEF ≤40% and >40%: for all-cause mortality, HR: 1.16 (95% CI: 0.99-1.37) and 1.20 (95% CI: 0.94-1.53); and for the composite outcome, HR: 1.30 (95% CI: 1.15-1.48) and 1.57 (95% CI: 1.29-1.91), respectively.

CONCLUSIONS Among patients with HF, higher BMI was associated with increased all-cause mortality and cardiovascular death or HF hospitalization, supporting the potential role of weight-management strategies across the ejection fraction spectrum. (JACC. 2026;87:2981-2992) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BMI = body mass index

CKD = chronic kidney disease

COPD = chronic obstructive pulmonary disease

CV = cardiovascular

DM = diabetes mellitus

GIP = glucose-dependent insulinotropic polypeptide

GLP = glucagon-like peptide

GWAS = genome-wide association study

HES = Hospital Episode Statistics

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

ICD = International Classification of Diseases, 10th Revision

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MR = Mendelian randomization

NICOR = National Institute for Cardiovascular Outcomes Research

SGLT = sodium-glucose cotransporter

Heart failure (HF) is a growing public health concern, and obesity—defined as having a body mass index (BMI) (the weight in kilograms divided by the square of the height in meters) of 30.0 kg/m^2 or more—is increasingly recognized as a major causal risk factor.[1-4] Incretin-based therapies, including GLP-1 and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide (GIP/GLP)-1 receptor agonists, and—to a lesser extent—SGLT2 inhibitors, promote weight loss and reduce HF hospitalization in at-risk populations.[5-7] Mendelian randomization (MR) studies further support a positive association between higher BMI and new-onset HF, regardless of whether left ventricular ejection fraction (LVEF) is reduced or preserved.[8,9]

However, the effect of intentional weight reduction on mortality among patients with established HF remains debated, partly because of the obesity survival paradox, in which observational studies report a protective association between higher BMI and mortality.[10,11] This paradox may be explained by index event bias, in which higher BMI appears protective in observational studies because affected individuals have fewer or less severe alternative HF risk factors.[10,12,13] Recent trials in patients with heart failure with preserved ejection fraction (HFpEF) have shown that GLP-1 receptor agonists reduce BMI, improve quality of life, and increase 6-minute walk distance,[14] whereas GIP/GLP-1 receptor agonists have demonstrated improvements in clinical outcomes.[15] Although subgroup analyses from the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity) trial suggested that GLP-1 receptor agonists improve clinical outcomes in patients with both HFpEF and heart failure with reduced ejection fraction (HFrEF), the findings are debated, and uncertainty remains regarding the role of incretin-based therapies in patients with HFrEF with other studies showing signals for harm.[16-20]

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Understanding the relationship between BMI and clinical outcomes in HFpEF and HFrEF is essential for determining the potential role of incretin-based therapies and other weight-loss interventions. MR uses genetic variation to estimate causal relationships, minimizing biases such as reverse causation, confounding, and misclassification.[21] Applying this approach to estimate the association between BMI and clinical outcomes in HF offers an opportunity to provide evidence that may support the conduct of outcomes-driven randomized controlled trials of incretin-based therapies and other interventions aimed at reducing BMI.

In this study, we investigate the impact of higher BMI on clinical outcomes in HF, using genetic

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approaches to minimize bias to test the hypothesis that its true effects are adverse. First, we recapitulate the obesity survival paradox in HF using observational data from the UK Biobank. Next, we perform a time-to-event genome-wide association study (GWAS) of clinical outcomes stratified by LVEF and apply methods to account for bias inherent to prognostic study design. Finally, we use MR to estimate the association of genetically predicted higher BMI with all-cause mortality and a composite of cardiovascular (CV) mortality or HF hospitalization in patients with HF.

METHODS

OBSERVATIONAL ASSOCIATION BETWEEN BMI AND HF: THE PARADOX. Data source. The UK Biobank is a prospective cohort study of >500,000 UK residents aged between 40 and 69 years old and recruited between 2006 and 2010. The project has curated detailed health and genetic information from the participants alongside linked discharge data from secondary care (Hospital Event Statistics [HES]), and mortality data.[22]

Procedures and outcomes. HF was defined by the occurrence of any HF diagnosis code in the electronic health records: International Classification of Disease (ICD)-10 codes I110, I130, I132, I50*; and ICD9 codes 428*, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, as well as UK Biobank self-reported illness code 1076.[8] HF admission followed the National Institute for Cardiovascular Outcomes Research (NICOR) definition of an unscheduled admission, of >1 day in duration, with primary diagnosis code for HF (defined above) and/or 4254/I255 (ischemic cardiomyopathy), 4251/I420 (dilated cardiomyopathy), or 4254/I429 (cardiomyopathy, unspecified).[23] CV death was defined as any death resulting from HF, acute myocardial infarction (MI), stroke, or death due to other CV causes. Clinical outcome endpoints were defined according to the 2013 European Society of Cardiology Heart Failure Association guidelines[24] and the 2014 American

Flipping the Paradox: Unmasking the True Influence of Obesity on Heart Failure (HF) Prognosis

The Obesity Survival Paradox in HF

Obesity is an established causal risk factor for the development of HF. Paradoxically, among patients with established HF, higher body mass index (BMI) appears to protect against mortality in clinical studies, a phenomenon termed the "obesity survival paradox." This observation has led to uncertainty about the role of weight reduction in patients with HF. Such paradoxical associations are common in prognosis research.

Why Risk Factors Can Appear Protective After Disease Onset

HF can arise from multiple risk factors such as obesity, coronary artery disease, and hypertension. In populations with established HF, associations between these risk factors can be distorted by index event bias (a form of collider bias); this bias can attenuate or even reverse risk-factor associations with prognosis. For example, obesity may appear protective in HF not because it improves outcomes but because affected individuals developed HF with fewer or less severe alternative risk factors that carry worse prognoses. Conventional covariate adjustment cannot correct for index-event bias and indeed may amplify it, and confounding and reverse causation can further bias prognostic associations.

How Genetic Approaches Can Enable Unbiased Estimates of Risk Factors on Prognosis

Genetic variants can be used as proxies for risk factors to estimate their effects on disease outcomes under the Mendelian paradigm, mitigating bias because of confounding and reverse causation. Genome-wide association studies (GWAS) of disease prognosis (the outcome) are susceptible to index event bias, but unlike conventional observational analyses, this bias can be modeled and corrected. Mendelian randomization can then be applied to estimate the effects of risk factors on prognosis, minimizing bias from confounding, reverse causation, and index-event bias.

Broader Implications for Prognostic Research Across Clinical Medicine

Paradoxical associations between risk factors and disease outcomes are common in prognosis research across clinical medicine, and often underappreciated. Genetic studies of disease progression can provide unbiased evidence on the influence of risk factors to inform clinically important questions about disease management.

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College of Cardiology/American Heart Association (ACC/AHA) Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials.[25]

Study population. Individuals enrolled in the UK Biobank (N = 502,411) were considered for study inclusion. The following exclusions were made: 54 participants who withdrew consent, 3,107 with missing baseline BMI data, and 2,618 with prevalent HF at recruitment (including a 6-month lag period postrecruitment). After exclusions, 496,678 individuals were included in the analysis, 14,366 of whom were subsequently diagnosed with HF (Supplemental Table 1).

Statistical analysis. To illustrate the HF obesity survival paradox observed in observational data, we investigated the association between BMI and the clinical outcomes of interest in people with HF compared with the general UK Biobank population. BMI was modeled as a categorical variable with strata defined as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), class I obesity (30.0-34.9 kg/m^2), class II obesity (35.0-39.9 kg/m^2), and class III obesity (>40 kg/m^2). In addition, we modeled BMI as a continuous variable by fitting a 4-knot restricted cubic spline with knots at the 5th, 25th, 75th, and 95th BMI percentiles.[26]

Survival analysis was conducted using Cox proportional hazards regression to estimate the hazard of all-cause death and the Fine-Gray method to estimate the subdistribution hazard of CV death or HF hospitalization, with non-CV death as a competing risk. Individuals with established HF at enrollment were excluded, and for cases of HF occurring during follow-up, the baseline (t = 0) was set as the date of HF diagnosis. Models were run with no adjustment; adjustment for sex and age at enrollment or HF diagnosis in HF cases; and adjusted for sex, age, smoking status (never, previous, current), and baseline atrial fibrillation (AF), diabetes mellitus (DM), chronic kidney disease (CKD), hypertension, hyperlipidemia, MI, stroke, and chronic obstructive pulmonary disease (COPD). The proportional hazards assumption was assessed and validated by the inspection of the scaled Schoenfeld residuals plotted against time.

GWAS. Study population. Twenty-two cohorts participating in the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium, comprising 50,636 individuals with established HF of European ancestry, were included in the genetic study (Supplemental Table 2).[27] Twelve were HF cohorts (trials or prospective research cohorts), 9 were nested HF cohorts within non-HF cardiovascular trials or cohorts, and 1 cohort was derived from individuals in the UK Biobank with genetic data. Study-level LVEF data were available for 16 studies. For subgroup meta-analyses, cohorts were dichotomized by LVEF: ≤40% (trial entry criterion LVEF ≤40% or study mean LVEF ≤35%; 11 studies; 12,608 patients; mean LVEF 30.6%) or LVEF >40% (trial entry criterion LVEF >40% or study mean LVEF >45%; 5 studies; 9,597 patients; mean LVEF 54.3%).

Procedures and outcomes. The majority of cohorts were HF clinical trials and used standard HF inclusion criteria to define cases (Supplemental Table 2). For the UK Biobank, HF was defined using the diagnostic codes detailed here. Two clinical endpoints were investigated in the genetic analyses: all-cause mortality and a composite endpoint of CV mortality or HF hospitalization, as defined here.

Statistical analysis. Procedures for genotyping, imputation, and quality control have been previously reported.[8] For each HF cohort, GWAS of time-to-event outcomes were performed using Cox proportional hazards regression. An additive genetic model with adjustment for sex, age at study initiation, HF status at enrollment (prevalent or incident), and other study-specific covariates, including principal components for genetic ancestry, randomization arm, or recruitment center. For cases with prevalent HF at study enrollment, the date of study enrollment was set at the baseline (t = 0). For cases of HF occurring during follow-up, the baseline (t = 0) was set as the date of HF diagnosis, if available, or the date of the first recorded HF diagnosis. GWAS meta-analyses were performed using Genome-Wide Association Meta-Analysis (GWAMA [version 2.2.2]) with an inverse-variance weighted fixed-effects model.[28] Genetic variants are reported for which results were derived from at least 2 studies, pruned for independence using PLINK 2.0 (r^2 < 0.001, 10,000 kb) with a reference panel consisting of 10,000 unrelated European ancestry participants.[29,30] We investigated whether genetic variants previously associated with new-onset HF were also associated with clinical outcomes in patients with established HF, using summary statistics from our previous work[8] and those from a recent multiancestry meta-analysis of all-cause HF.[31] This analysis compared the observed replication rate with the expected rate, adjusted for statistical power, as previously described.[32]

We used the recently developed bivariate MR with corrected weighted least squares (CWBLS) adjustment to assess and adjust for index-event bias in the association of genetic variants identified in the GWAS (Supplemental Methods).[33,34] In further index-event bias sensitivity analyses we used the Dudbridge,[35]

standard CWLS,[34] Slope-Hunter,[36] and traditional 2-sample MR approaches,[37] to estimate bias correction factors and analyzed the impact of these index-event bias adjustments on our primary MR analysis (Supplemental Methods).

MR. Data sources. The genetic instrument for BMI was derived from genome-wide association summary statistics from a Genetic Investigation of Anthropometric Traits (GIANT) consortium meta-analysis of >700,000 individuals of predominantly European ancestry.[38] The GWAS data sources are listed in Supplemental Table 3. All contributing studies received approval from local institutional review boards. Meta-analysis of summary-level GWAS data was conducted in accordance with guidelines for study procedures provided by the University College London (UCL) Research Ethics Committee.

Selection of instruments. Variants were selected based on genome-wide significance for BMI ($P < 5 \times 10^{-8}$) and pruned for independence using PLINK 2.0 ($r^2 < 0.001$, 10,000 kb) with a reference panel consisting of 10,000 unrelated European ancestry participants from the UK Biobank (Supplemental Table 4).[29,30] To confirm the validity of this instrument in patients with established HF, we estimated the associations of the included variants in a GWAS of BMI in individuals with HF compared with non-HF controls in UK Biobank, testing for heterogeneity using Cochrane's Q statistic.

Statistical analysis. MR was performed in a 2-sample framework, using the MendelianRandomization R package.[39] The genetic instrument used in MR should satisfy 3 core instrumental variable assumptions. 1) Relevance: each variant is robustly associated with BMI, confirmed through genome-wide significance. 2) Independence: there are no measured or unmeasured confounders of the instrument and the outcome. 3) Exclusion restriction: the variants affect outcomes only through BMI, not via alternative biological pathways. The primary analysis used an inverse variance weighted (IVW) method, with sensitivity analyses conducted using MR Egger, weighted median, and weighted-mode methods designed to address the core MR assumptions, accounting for pleiotropy and imperfect instruments. The MR estimates represent the change in log hazard for HF clinical outcomes per standard deviation increase in BMI. The Z-test was used to assess for interaction between the LVEF stratified MR estimates.

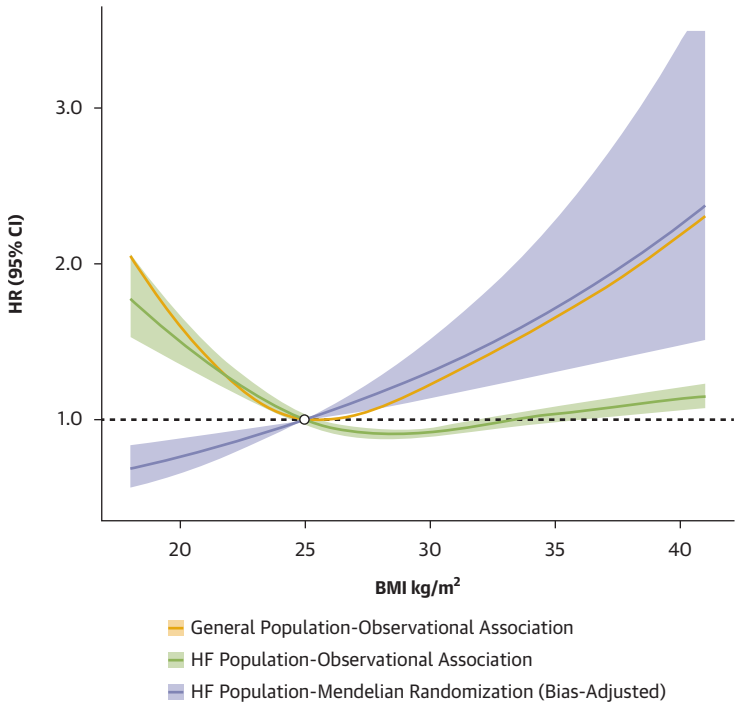
RESULTS

RECAPITULATING THE OBESITY SURVIVAL PARADOX IN HF. To demonstrate the survival paradox in HF, we first estimated the association between measured BMI and clinical outcomes using conventional observational analysis of data from 14,366 individuals with HF in the UK Biobank. Baseline demographics are presented in Supplemental Table 1. Our findings replicated the HF obesity survival paradox: compared with normal weight (18.5-24.9 kg/m^2), patients with HF in the overweight (25.0-29.9 kg/m^2) and obesity class I (30.0-34.9 kg/m^2) categories had an apparent lower rate of all-cause mortality, contrasting with that seen in the total UK Biobank population, in which overweight and obesity were associated with higher mortality rates relative to normal weight (**Figure 1**, Supplemental Table 5). Interestingly, conventional covariate adjustment for common CV risk factors appeared to strengthen the inverse association of higher BMI with clinical outcomes in patients with HF (Supplemental Table 5).

GWAS OF CLINICAL OUTCOMES IN HF. Next, to enable the MR study, we conducted a time-to-event GWAS meta-analysis of all-cause mortality and the composite of CV mortality or HF hospitalization in patients with established HF. We analyzed a population comprising 50,636 individuals with HF of European ancestry from 22 studies—all of whom had available genetic data—and follow-up data on the clinical outcomes of interest (**Table 1**, Supplemental Table 2). Over a median follow-up of 27.0 months (IQR: 17.2-35.3 months), 11,454 participants (23%) reached the endpoint of all-cause mortality, and 11,360 participants (22%) experienced the composite endpoint of cardiovascular death or hospitalization for HF (**Table 2**). The mean age of participants was 66 ± 9.5 years, with 68% male. The mean BMI was 29 ± 5.8 kg/m^2. A high proportion had comorbidities at enrollment: 46% had a history of MI, 51% had AF, 79% had hypertension, and 34% had DM. Eleven studies were classified as LVEF ≤40% (12,608 patients) and 5 as LVEF >40% (9,597 patients) (**Table 1**).

Although no genetic variants reached genome-wide significance ($P < 5 \times 10^{-8}$), 21 independent variants were associated with all-cause mortality and 27 with the composite outcome at a suggestive significance level ($P < 5 \times 10^{-6}$) (Supplemental Tables 6 and 7). None of the variants with suggestive associations with HF outcomes were associated with

FIGURE 1 Association Between BMI and Mortality: Observational and MR Analyses



Association between BMI and all-cause mortality. The plot presents data from 2 separate of analyses: observational BMI restricted cubic spline survival models using nongenetic data from either all individuals (yellow curve), or individuals with HF (green curve), within the UK Biobank and the MR estimate of the association between BMI and HF mortality, log-linearly extrapolated assuming a constant HR per standard deviation increase in genetically predicted BMI (purple curve), adjusted for index-event bias using the primary bias adjustment method (Bivariate MR CWBLS). Observational curves are derived from the models adjusted for age and sex, with estimates shown at the median age and for male sex, consistent with the covariate adjustment used in the GWAS of time-to-event outcomes. The observational analyses capture non-linear relationships between measured BMI and outcomes, whereas MR estimates assume a linear relationship on the log-hazard scale based on genetic instruments. All HRs are referenced to BMI = 25 kg/m^2 (open circle). Shaded areas represent 95% CIs. BMI = body mass index; CWBLS = corrected weighted least squares; GWAS = genome-wide association studies; HF = heart failure; MR = Mendelian randomization.

new-onset HF in previous GWAS ($P > 0.01$).[8] We also evaluated the replication of previously reported genetic variants associated with new-onset HF in European ancestry individuals (59 variants) against our GWAS of clinical outcomes in HF. Of these 59 variants, only 4 (11%) were associated with all-cause mortality at a nominal significance of $P < 0.05$, and 7 (20%) were associated with CV mortality or HF hospitalization (35 expected given power difference). The same analysis, but using the 176 genetic variants reported in a multiancestry HF meta-analysis by Lee et al[31] revealed comparably low replication rates (18% and 16%, respectively) (Supplemental Tables 8 to 11). This limited replication may reflect fundamental differences in the underlying pathobiology of disease onset vs progression or the modifying effects of treatment. To explore potential effect modification by LVEF, we conducted a subgroup GWAS meta-analysis restricted to cohorts with available LVEF data. No additional variants at the genome-wide significance threshold ($P < 5 \times 10^{-8}$) were identified (Supplemental Tables 12 to 15).

We then applied a range of approaches to identify and correct potential index-event bias influencing the genetic variant associations (Supplemental Methods, Supplemental Figures 1 to 9). To explore the range of bias correction factors under different models of bias adjustment, we conducted sensitivity analyses using multiple bias model and parameter combinations (Supplemental Methods). No genome-wide significant loci were identified after correcting for index-event bias.

MR STUDY OF BMI AND CLINICAL OUTCOMES IN HF. Finally, we applied MR to assess the association between genetically predicted BMI and clinical outcomes in individuals with HF. A total of 947 independent variants formed the genetic instrument for BMI (Supplemental Table 4). For the variants included, we did not find evidence of heterogeneity of effects between individuals from the UK Biobank with HF and those without. This confirms that the instrument, derived from a general population, is also valid in patients with HF ($P > 0.05/947$, Bonferroni-adjusted) (Supplemental Figure 10). One SD increment in genetically predicted BMI, corresponding to 4.8 kg/m^2,[22] was associated with a 21% higher rate of all-cause mortality (HR: 1.21 per SD; 95% CI: 1.13-1.29; $P = 9 \times 10^{-8}$). The bias-adjusted CWBLS multivariable MR was consistent with this finding (adjusted HR 1.30 per SD; 95% CI: 1.13-1.48; $P = 2 \times 10^{-4}$) (**Figure 1**). There was no evidence of interaction between the association of genetically predicted BMI and all-cause mortality and LVEF subgroup (P for interaction 0.84). In subgroup meta-analyses based on study-level LVEF categorization, the association of genetically predicted BMI with all-cause mortality was consistent across LVEF strata. In the LVEF ≤40% subgroup, defined as trials with entry criterion LVEF ≤40% or study mean LVEF ≤35%, the HR was 1.16 per SD BMI (95% CI: 0.92-1.49), whereas in LVEF >40% subgroup—defined as trials with entry criterion LVEF >40% or study mean LVEF >45%—the HR was 1.20 per SD BMI (95% CI: 0.94-1.53) (**Figure 2**). The bias-adjusted CWBLS multivariable MR results were consistent with these findings (adjusted HR 1.17 per SD; 95% CI: 0.92-1.49 and 1.33 per SD; 95% CI: 0.79-2.23, respectively).

For the composite outcome of CV mortality or HF hospitalization, an SD increment in genetically predicted BMI was associated with a 29% higher rate (bias-adjusted HR 1.29 per SD BMI, 95% CI: 1.20-1.38; $P = 8 \times 10^{-13}$) (Supplemental Figure 11). The bias-adjusted CWBLS multivariable MR was consistent with this finding (adjusted HR 1.16 per SD; 95% CI: 1.00-1.33; $P = 0.044$). The association was consistent across LVEF strata in subgroup meta-analyses (P for interaction 0.13). In the LVEF ≤40% subgroup, each SD increase in BMI was associated with a 31% higher rate of the composite outcome (HR: 1.31 per SD BMI; 95% CI: 1.16-1.48) and in the LVEF >40% subgroup a 57% higher rate (HR: 1.57 per SD BMI; 95% CI: 1.29-1.91) (**Figure 2**). The bias-adjusted CWBLS multivariable MR results were consistent with these findings (adjusted HR 1.46 per SD; 95% CI: 1.24-1.72 and 1.25 per SD; 95% CI: 0.81-1.95, respectively).

TABLE 1 Demographics and Clinical Characteristics of the Participants at Baseline

	All (N = 50,636)	LVEF ≤40% (n = 12,608)	LVEF >40% (n = 9,597)
Number of studies	22	11	5
Study type			
RCT	26,514 (52)	7,495 (59)	9,207 (96)
Research cohort	6,981 (14)	5,113 (41)	390 (4)
Genomic biobank	17,141 (34)	0 (0)	0 (0)
Race or ethnic group			
White	50,636 (100)	12,608 (100)	9,597 (100)
BMI, kg/m^2	29.2 ± 5.8	27.8 ± 5.3	29.9 ± 5.8
Age, y	65.6 ± 9.5	67.3 ± 11.5	68.5 ± 9.9
Male[a]	33,159/49,122 (68)	8,383/11,094 (76)	5,894/9,597 (61)
MI[a]	21,521/46,480 (46)	4,428/8,452 (52)	2,583/9,597 (27)
Hypertension[a]	38,394/48,827 (79)	7,064/10,799 (65)	8,591/9,597 (90)
Diabetes mellitus[a]	16,508/48,827 (34)	3,275/10,799 (30)	3,056/9,597 (32)
AF[a]	22,720/44,240 (51)	33,955/9,774 (40)	7,440/8,296 (90)
LVEF, %	34.3 ± 13.0	30.6 ± 9.6	54.3 ± 11.4
NT-proBNP, pg/mL (range)	1,234 (56-19,922)	1,683 (22-28,744)	891 (104-3,651)
Follow-up, mo (range)	37.5 (0.7-112.7)	31.7 (0.2-40.2)	34.0 (1.9-49.8)

Values are n (%), mean ± SD, or n/N (%), unless otherwise indicated. [a]Denominator numbers differ as some data are not available for all cohorts. The total cohort (All) sample size is not the sum of the LVEF strata, as only a subset of cohorts have available LVEF data.

AF = atrial fibrillation; BMI = body mass index; LVEF = left ventricular ejection fraction: MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RCT = randomized controlled trial.

We conducted sensitivity analyses to assess the robustness of these estimates. The weighted median, weighted mode, and MR-Egger regression methods all confirmed the direction of effect for both outcomes, with no evidence of directional horizontal pleiotropy detected (Supplemental Table 16, Supplemental Figures 12 and 13). We then repeated the primary IVW-MR analysis using GWAS outcome data adjusted using different index-event bias correction methods. For all-cause mortality in patients with HF, the bias-adjusted HRs ranged from 1.13 to 1.30, with CIs exceeding the null. For the composite outcome of CV or HF hospitalization, point estimates were all positive (range: 1.03-1.19) but were accompanied by wider CIs, with estimates from 2 methods (Dudbridge and CWLS) overlapping the null (Supplemental Table 16, Supplemental

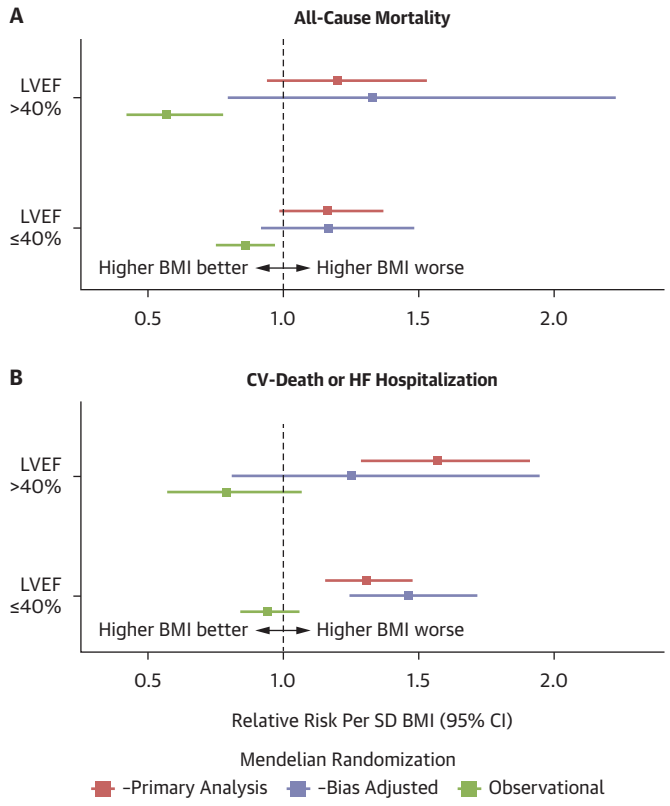
TABLE 2 Heart Failure Clinical Endpoints

	All (N = 50,636)	LVEF ≤40% (n = 12,608)	LVEF >40% (n = 9,597)
Death	11,454 (23)	2,711 (22)	1,029 (11)
CV death or HF hospitalization	11,360 (22)	4,229 (35)	1,600 (17)

Values are n (%).

CV = cardiovascular; HF = heart failure.

FIGURE 2 Association of Genetically Predicted BMI with HF Outcomes in Individuals With HFrEF and HFpEF



(A) All-cause mortality and (B) cardiovascular death or heart failure hospitalization show the change in HR per standard deviation increase in body mass index in individuals with diagnosed heart failure. Green data points represent previously reported observational associations for HFpEF (Guo et al[52]) and HFrEF (Butt et al[53]) Red data points represent the association derived from the MR analysis of body mass index on HF outcomes. Bars indicate the 95% CI. Purple data points represent the bias-adjusted estimate using the primary bias adjustment method (Bivariate MR CWBLS). HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.

Figure 14). Bias-adjusted estimates in LVEF-stratified analyses were consistently positive but imprecise, with wide CIs that in many cases overlapped the null, reflecting reduced statistical power (Supplemental Table 16, Supplemental Figure 15). The Slope-Hunter method proved highly sensitive to minor variations in input parameters and was deemed unreliable in our dataset (Supplemental Methods, Supplemental Figures 5 to 7). Finally, we repeated the study with a BMI instrument containing no overlapping samples (UK Biobank individuals) and found similar associations with reduced precision (Supplemental Figure 16).

DISCUSSION

In this study, we investigate the apparent obesity-survival paradox that has influenced clinical thinking about the role of weight loss in the management of patients with HF and obesity. Our observational analysis recapitulated the widely reported finding that higher BMI is associated with lower mortality in patients with established HF. Conversely, our genetic study, which accounts for relevant biases, found that higher BMI is associated with increased mortality in patients with HF. Our index-event bias adjusted estimate of the association of higher BMI on all-cause mortality was similar to the association estimated in the general population using observational analysis. These findings suggest the potential role for weight-loss interventions in the management of HF and provide a rationale for clinical trials.

We did not find evidence of an interaction with LVEF subgroup for the association of BMI on clinical outcomes. However, the magnitude of the effect was numerically greater for HFpEF than HFrEF, consistent with findings from clinical trials of drug-induced weight loss.[14-16] Our results are consistent with a previous 1-sample MR study, which reported a positive association between higher BMI and HF mortality.[40] Although the effects of specific weight-loss interventions may not be directly comparable with those estimated using genetic proxies, which reflect lifelong exposure to elevated body weight, our findings suggest that weight loss may improve outcomes in HF. Clinical trials of incretin-based therapies are underway in HFpEF, and our findings suggest a rationale for conducting similar trials in patients with HFrEF.

The HF obesity survival paradox was first described >20 years ago, with the observation replicated across numerous studies.[41,42] Numerous mechanistic theories have been proposed to explain the paradox, assuming a causal relationship, whereas others suggest that the association is caused by index event bias, a form of collider bias that can arise when studying disease cohorts. Consequently, there persists uncertainty regarding the role of weight reduction in management of patients with HF.[43-45] Selecting populations with HF to study the effects of BMI creates the potential for index-event bias to distort associations between risk factors and their association with prognosis. People with HF and obesity may appear to have a better prognosis not because obesity is causally protective but because they developed HF with fewer or less severe

alternative risk factors that have worse effects on prognosis than BMI.[10] Conventional covariate adjustment cannot mitigate this bias and indeed may amplify it, as we demonstrate in our analysis.[45,46]

MR describes an approach whereby genetic proxies are used as instrumental variables to model relationships between risk factors and outcomes to mitigate bias. Provided certain assumptions are met, MR can provide estimates that are less susceptible to bias arising from confounding and reverse causation. The associations of genetic variants with prognosis (the outcome), which are necessary for MR, remain vulnerable to index-event bias. However, this bias can be modeled and corrected by using genetic associations with disease onset.[33,37] In this study, we apply this by first performing a large time-to-event GWAS in a population with established HF, correct for index event bias, and then performing MR of BMI on clinical outcomes. We demonstrate how this analysis framework can be used to estimate unbiased associations of risk factors on prognosis.

STUDY LIMITATIONS. The GWAS study of clinical outcomes in HF was the largest yet performed; however, larger studies are needed to improve statistical power and to improve the precision of estimates from MR. Furthermore, the study population was limited to individuals of European ancestry because of the limited availability of samples from diverse genetic backgrounds. This is especially relevant, given differing adiposity-cardiovascular risk relationships across populations: for example, higher cardiometabolic risk at lower BMI in South-East Asian individuals, limiting generalizability beyond European ancestry populations.[47,48] The subgroup GWAS meta-analysis was limited by the availability of LVEF data in certain studies (only ∼44% of the total cohort, primarily randomized control trials) and by only having access study level LVEF. This will have reduced the power to detect effect modification by LVEF and may affect the external validity of the study. The CIs for the LVEF-stratified estimates were wide and did not consistently exclude the null, indicating limited precision for subgroup-specific causal estimates. Future studies should aim to model the interaction of LVEF as a continuous variable using individual participant-level data.

Our MR analyses, focused on the overall linear association of genetically predicted BMI, acknowledging the J-shaped relationship between BMI and mortality, with underweight individuals (BMI <18.5 kg/m^2) at higher risk in observational data. Nonlinear MR methods are controversial, and existing methods are insufficient to model this relationship reliably with genetic data.[49] The small proportion of underweight individuals (for example, $<0.5\%$ in the UK Biobank HF population) makes the likely impact on the MR estimates minimal, but if there truly is a causal U-shaped BMI-mortality relationship, the elevated risk at low BMI would be expected to attenuate the MR estimate toward the null (type II error).[50] BMI is also an imperfect measure of adiposity, as it does not distinguish between fat and lean mass or capture fat distribution, which may influence HF outcomes differentially. In our primary analyses, we used bivariate MR CWBLS to identify and correct the GWAS of HF outcomes for index-event bias. In sensitivity analyses, the majority of alternative bias-adjustment methods produced consistent findings, but the estimates varied, and—in some cases—the CI included the null. Although our MR sensitivity analyses showed consistent direct effects for the primary outcomes, this does not completely exclude pleiotropic bias via mechanisms other than BMI.

CONCLUSIONS

Our findings suggest that obesity is associated with adverse clinical outcomes in HF, similar to the association observed in the general population. They indicate that the obesity survival paradox is likely an artifact of bias, reinforcing the need for caution when making causal interpretations of prognostic associations from observational analyses. Taken together our findings support the potential benefit of weight-loss interventions for patients with HF and may provide a rationale for clinical trials.

DATA AVAILABILITY The GWAS summary statistics will be published in full on OpenGWAS, the GWAS catalog (study accessions GCST90827692 and GCST90827693), and the Cardiovascular Knowledge Portal.

The analysis was conducted using a *Snakemake* (version 7.26) workflow.[51] The code is available in GitHub repositories: https://github.com/nicksunderland/hf_progression_bmi and https://github.com/nicksunderland/hf_progression_bmi_ukbb.

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Chemicals & Pharmaceuticals, Lupin Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, Translational Medicine Academy, Regeneron, MCI India, Hilton Pharmaceuticals, IMEDIC Pharmaceuticals Micro Labs Ltd, At the Limits Ltd, and ARMGO Pharmaceuticals; has served on Data Safety Monitoring Boards for WCG Clinical Services; and is director of Global Clinical Trial Partners Ltd (which provides clinical trial services such as endpoint committees and educational programs). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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CLINICAL PERSPECTIVE

WHAT'S KNOWN? Observational studies suggest consistently that obesity may be paradoxically protective in patients with heart failure, creating uncertainty about the role of weight loss in clinical management.

WHAT'S NEW? Using genetic approaches, this study finds that higher BMI increases the risk of all-cause mortality and cardiovascular events in heart failure, irrespective of ejection fraction, suggesting that the apparent "obesity paradox" is likely caused by bias inherent to conventional observational study designs.

WHAT'S NEXT? These findings provide evidence that supports the clinical potential of targeted weight management in care of heart failure. Randomized controlled trials are needed to confirm these findings and to identify specific weight-loss interventions that are safe and effective.

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KEY WORDS heart failure, obesity, genome-wide association study, Mendelian randomization, index-event bias

APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this article.