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The Heart Failure Overweight/Obesity Survival Paradox : The Missing Sex Link

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Obesity is a key determinant of cardiovascular health and an independent risk factor for the development of heart failure (HF) (1,2). The "overweight" and "obese" states are defined by body mass index (BMI), with overweightness diagnosed in the BMI range ≥25 to <30 kg/m^2 and obesity ≥30 kg/m^2. Among 59,178 adults followed for a mean of 18 years, the adjusted hazard ratios for incident HF at BMIs <25, 25 to 29.9, and ≥30 kg/m^2 were 1.00, 1.25, and 1.99 ($p < 0.001$) for men and 1.00, 1.33, and 2.06 ($p < 0.001$) for women, respectively (3). However, multiple investigators have demonstrated an "obesity survival paradox" in HF with reduced (and preserved) ejection fraction, whereby overweight and obese patients have either no increased mortality risk compared with normal weight counterparts, or even a lower mortality risk (4-10). Several potential explanations have been

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

AF = atrial fibrillation

ARB = angiotensin receptor blocker

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

CRF = cardiorespiratory fitness

HF = heart failure

HR = hazard ratio

HRR = heart rate recovery

HTN = hypertension

LBM = lean body mass

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

MET = metabolic equivalent of task

NW = normal weight (18.5 to 24.99 kg/m^2)

NYHA = New York Heart Association

OB = obese (≥30 kg/m^2)

OW = overweight (25 to 29.99 kg/m^2)

RER = respiratory exchange ratio

SBP = systolic blood pressure

VE/VCO$_2$ = ratio of ventilation to increase in carbon dioxide output

VO$_2$ = oxygen uptake

Vt = tidal volume

postulated to explain these unexpected survival outcomes, including the potential confounding of cigarette smoking or undiagnosed systemic illness. There is also the possibility of "lead time bias" whereby obese individuals present with HF symptoms earlier in their disease course, or a "healthy survivor effect," whereby the most comorbid obese individuals die before developing HF, leaving the surviving obese HF patients with disproportionately favorable outcomes.

The paradox could alternatively be explained by the protection from cardiac cachexia afforded by baseline excess adiposity or by myocardial effects of adipokines secreted from adipose tissue. Both the biological mechanisms of the proposed paradoxical relationship between BMI and mortality in HF, and the role of sex in this relationship, remain incompletely understood. Given the female survival advantage in HF (11-13), and the recognition that female myocardium shows greater fatty acid metabolism and lower glucose utilization (14), we hypothesized that females with HF may derive a greater degree of protection from excess adiposity than males.

METHODS

STUDY POPULATION. We identified 4,380 consecutive adult patients with systolic HF who underwent cardiopulmonary exercise testing at Cleveland Clinic between January 1, 1995, and November 1, 2011. Institutional review board approval was granted both for the prospective recording of exercise testing data and the retrospective collection of additional data specific to this project; the requirement for informed consent was waived. We removed 253 patients from the cohort because of incomplete data, with either a missing stress test date (n 4), missing mortality follow-up data (n 46), no information in the electronic medical record to verify clinical data (n 116), or missing key cardiopulmonary stress test parameters (n 87). Patients with a baseline left ventricular ejection fraction (LVEF) in the 41% to 50% range were removed (n 130) to restrict analysis to individuals with LVEF ≤40%. We filtered out patients who had received a heart transplant (n 15) or left ventricular assist device (LVAD) (n 8) before their stress test date. Patients with a primary valvular cardiomyopathy etiology (n 85) or severe congenital heart disease (n 27) were also excluded from this analysis. We also excluded 51 patients with a BMI <18.5 kg/m^2 (below the "normal weight" range). Thus, the final cohort contained 3,811 subjects. If a patient underwent multiple cardiopulmonary stress tests, only the initial test was considered.

Baseline characteristics were prospectively recorded in the stress test database by the exercise physiologist conducting the test. Parameters such as HF etiology, presence of coronary artery disease (CAD), diabetes status, smoking status, and HF medications were ascertained by the physiologist through a combination of verbal history-taking and medical chart review. The patient's weight was always measured on the day of the test. Smoking and medication status were documented as current at the time of the test. The presence of CAD was defined as a prior myocardial infarction or any degree of obstruction on coronary imaging. Retrospective chart review was performed for >20% of database subjects to confirm the accuracy of the prospectively entered data.

CARDIOPULMONARY EXERCISE TESTING. Symptom-limited exercise stress testing was conducted by trained exercise physiologists and supervised by a physician. Exercise testing was performed using a treadmill stress in the majority of patients; the alternate option was a stationary bike. The exercise physiologist assigned the patient to the Bruce, modified Bruce, Cornell 0%, Cornell 5%, Cornell 10%, Naughton, or modified Naughton protocols, appropriate to the patient's physical abilities. Gas exchange data were collected throughout the test using a MedGraphics cardiopulmonary metabolic cart (St. Paul, Minnesota). Heart rate targets were not used as an endpoint or to judge the adequacy of the test. Blood pressure was manually measured every minute and the heart rate was recorded from an electrocardiogram printed each minute during the test. Electrocardiographic changes and symptoms were also recorded at the end of each stage. Heart rate recovery (HRR) was calculated as peak exercise heart rate minus the heart rate at 1 minute post-exercise. A standard walking cool-down was used during recovery.

The oxygen consumption (VO_2) was averaged over 30-s intervals throughout the test and the peak VO_2 was determined as the highest 30-s interval in the last 2 min of the test. The ventilatory threshold was defined as the VO_2 at which expired carbon dioxide increased nonlinearly relative to VO_2 (V-slope method). The ratio of the increase in ventilation to the increase in CO_2 output (VCO_2) was recorded at peak exercise (15). Estimated functional capacity was

calculated in metabolic equivalents of task (MET), where 1 MET 3.5 ml/kg/min of oxygen consumption. The test result parameters were prospectively entered into an institutional database. Peak VO_2 was calcu-lated per ml/kg/min of total body mass. Estimated lean body mass was calculated by the Boer formula: Men: estimated LBM 0.407 weight (kg) + 0.267 height (cm) 19.2; women: estimated LBM 0.252 weight (kg) + 0.473 height (cm) 48.3 (16). An addi-tional version of peak VO_2 was calculated corrected to estimated LBM to adjust for the differential oxygen consumption of muscle versus adipose tissue (17).

OUTCOME MEASURES. We retrospectively collected outcomes data for all subjects up until the date of death or to censor at November 1, 2011. All-cause mortality status and date of death were determined by linking our database with the U.S. Social Security Death Index. We also recorded the occurrence of heart transplantation or LVAD implantation during the follow-up period. We did not consider trans-plantation or LVAD implantation as an endpoint because physicians use peak VO_2 to determine advanced therapy eligibility. However, because these therapies do change the hazard of death, they were handled as time-dependent covariates to appropri-ately account for the impact of transplantation or LVAD implantation on the patient's subsequent survival.

STATISTICAL ANALYSES. **Baseline characteristics.** Base-line demographic and clinical data were stratified by both sex and BMI category, and comparisons were made between groups. Continuous data were evalu-ated for normality, and accordingly, between-group comparisons with Student *t* or Mann-Whitney testing were performed. Categorical data were compared with chi-square tests. Unadjusted survival was stratified by sex and normal weight/overweight/obese status. These weight categories were based on the World Health Organization classification of normal weight (NW) BMI as 18.5 to 24.99 kg/m^2, overweight (OW) as 25 to 29.99 kg/m^2, and obese (OB) as ≥30 kg/m^2.

Unadjusted and adjusted hazard ratios. Hazard ratios (HRs) were tabulated by sex and BMI category. Both the unadjusted and adjusted HRs were calcu-lated to better appreciate the relationship between BMI and mortality in each sex group and the role of potential confounders. Adjustment was performed for age, race, HF etiology, New York Heart Asso-ciation (NYHA) status, digoxin use, angiotensin-converting enzyme (ACE) inhibitor/angiotensin re-ceptor blocker (ARB) use, beta-blocker use, diabetes, smoking, hypertension (HTN), hypercholesterolemia, atrial fibrillation (AF), resting systolic blood pressure (SBP), heart rate recovery (HRR), peak VO_2, peak res-piratory exchange ratio (RER), peak tidal volume (Vt), and subsequent receipt of a heart transplant or LVAD as a time-dependent covariable. Not all patients in the cohort attained an acceptable RER; therefore, a sub-group analysis was performed to determine if the mortality HRs were consistent for subjects with peak RER ≥1.05.

Cox model with restricted cubic spline. Multi-variable analysis was performed using a Cox propor-tional hazards model for all-cause mortality. Because of the nonlinearity of the BMI-mortality relationship, a restricted cubic spline was used. This model permits appreciation of differential effects of BMI on mortal-ity through the recorded spectrum of low to high BMI

TABLE 1 Baseline Characteristics by Sex

Characteristic	Whole Cohort (n 3,811)	Female (n 969)	Male (n 2,842)	p Value
Age, yrs	54.1 ± 11.6	52.5 ± 11.7	54.6 ± 11.5	<0.0001
Female, %	25	100	0	<0.0001
Caucasian, %	84	79	85	<0.0001
LVEF, %	20 (15 25)	20 (15 25)	20 (15 25)	0.0100
BMI, kg/m^2	27.9 (24.7 31.8)	27.2 (23.7 31.9)	28 (25 31.7)	0.0015
Ischemic etiology, %	47	26	54	<0.0001
CAD, %	50	30	57	<0.0001
NYHA functional class, %				
I	8	5	9	<0.0001
II	31	29	31	0.2117
III	59	65	57	<0.0001
IV	2	2	3	0.0948
Digoxin, %	64	64	64	0.9752
ACE inhibitor/ARB, %	92	91	92	0.7745
Beta blocker, %	69	68	69	0.5795
Diabetes, %	28	27	28	0.7228
Smoking, %	21	19	22	0.0564
HTN, %	55	51	57	0.0013
Hyperlipidemia, %	56	50	58	<0.0001
AF, %	13	9	14	<0.0001
SBP, mm Hg	110 (98 122)	110 (98 122)	110 (98 122)	0.8871
Heart rate recovery	11 (6 18)	12 (6 18)	11 (6 18)	0.0907
Max METs	4.6 (3.6 5.8)	4.3 (3.5 5.3)	4.7 (3.7 5.9)	<0.0001
Peak VO_2, ml/kg/min	15.9 (12.6 20.1)	14.9 (12.2 18.4)	16.1 (12.9 20.5)	<0.0001
Peak RER	1.1 (1.0 1.2)	1.1 (1.0 1.1)	1.1 (1.1 1.2)	<0.0001
Peak Vt, ml	1,589 (1,235.5 1,990)	1,180 (983 1,430)	1,738.5 (1,411 2,109.8)	<0.0001
VE/VCO_2 ratio	37 (32 44)	36 (32 42)	37 (32 44)	0.1815

Values are mean ± SD or median (interquartile range).

ACE angiotensin-converting enzyme; AF atrial fibrillation; ARB angiotensin receptor blocker; BMI body mass index; CAD coronary artery disease; HTN hypertension; LVEF left ventricular ejection fraction; MET metabolic equivalent of task (metabolic equivalent); NYHA New York Heart Association functional status; peak RER peak respiratory exchange ratio; peak VO_2 peak oxygen uptake; peak Vt peak tidal volume; SBP systolic blood pressure; VE/VCO_2 ratio of ventilation to increase in carbon dioxide output.

TABLE 2 Baseline Characteristics by BMI Category

Characteristic	NW (n 1,044)	OW (n 1,432)	OB (n 1,335)	p Value
Age, years	55.4 ± 12.5	55.5 ± 11.2	51.5 ± 10.8	<0.0001
Female, %	32	21	25	<0.0001
Caucasian, %	85	85	81	0.0038
LVEF, %	20 (15 25)	20 (15 25)	20 (15 25)	<0.0001
BMI, kg/m^2	22.9 (21.4 24.1)	27.4 (26.2 28.6)	33.6 (31.4 36.7)	<0.0001
Ischemic etiology, %	46	51	44	0.0003
CAD, %	49	54	47	0.0009
NYHA functional class, %				
I	9	9	6	0.0072
II	29	30	32	0.4103
III	59	58	60	0.6144
IV	3	3	2	0.5060
Digoxin, %	69	62	61	0.0004
ACE inhibitor/ARB, %	91	92	92	0.5184
Beta blocker, %	63	69	73	<0.0001
Diabetes, %	17	26	38	<0.0001
Smoking, %	23	20	21	0.0654
HTN, %	44	54	66	<0.0001
Hyperlipidemia, %	46	59	60	<0.0001
AF, %	12	13	14	0.4413
SBP, mm Hg	104 (94 118)	110 (100 122)	110 (100 124)	<0.0001
Heart rate recovery	11 (6 17)	11 (6 18)	11 (6 18)	0.6478
Max METs	4.6 (3.7 5.8)	4.6 (3.7 5.9)	4.5 (3.5 5.6)	0.0016
Peak VO_2, ml/kg/min	16 (12.8 20.2)	16.1 (12.8 20.5)	15.6 (12.4 19.4)	0.0016
Peak RER	1.1 (1.0 1.2)	1.1 (1.1 1.2)	1.1 (1.0 1.1)	0.0006
Peak Vt, ml	1,404 (1,094 1,781)	1,630 (1,276 2,010)	1,703 (1,342 2,121)	<0.0001
VE/VCO_2 ratio	40 (34 48)	37 (32 44)	35 (31 40)	<0.0001

Values are mean ± SD or median (interquartile range).

NW normal weight; OB obese; OW overweight; other abbreviations as in Table 1.

measurements and so enables more accurate characterization of the influence of covariates on the BMI-mortality relationship. Use of a proportional hazards model that assumes linearity will give a hazard ratio for BMI that implies a constant and incremental effect on mortality throughout the BMI continuum, which is likely to miss effects that are not uniform throughout the normal weight, overweight, and obese ranges. The aim of this model was to define the association between sex- and mortality-adjusted for key potential confounders, and then examine for an interaction between sex and BMI. Model covariates were predefined within the study design based on their clinical and pathophysiologic relevance as a confounder, significance in prior literature, and frequency of occurrence in this cohort of patients. Covariates were excluded if they were found to be collinear with another key variable (e.g., both maximum METs and ventilatory threshold showed colinearity with peak VO_2 and therefore were excluded from the model). Sensitivity analyses were performed with the substitution of peak VO_2 by estimated LBM-adjusted peak VO_2 and then VE/VCO_2, and restriction of the model to only subjects with peak RER ≥1.05. All statistical analyses were performed using R 3.0.2 (R Foundation for Statistical Computing, Wien, Austria). Values of $p < 0.05$ were considered statistically significant and all tests were 2-tailed.

BMI-sex interaction. To address the study hypothesis of a differential response to the overweight and obese states in males versus females, an interaction term was introduced to the restricted cubic spline model for all-cause mortality, adjusted for sex, BMI, age, race, LVEF, etiology, NYHA functional class, digoxin use, ACE inhibitor/ARB use, beta-blocker use, diabetes status, smoking status, hypertension history, AF history, resting SBP, HRR, peak VO_2, peak RER, peak Vt, and subsequent heart transplantation or LVAD. The adjusted HR for all-cause mortality was plotted to a set of reference values based on median or mode values, as follows: age 54 years, white race, LVEF 21%, NYHA functional class 3, taking digoxin, taking ACE-inhibitor/ARB, taking beta-blocker, nonsmoker, no HTN, no hyperlipidemia, no AF, resting SBP 110.9 mm Hg, HRR 12.5, peak VO_2 16.8 ml/kg/min, peak RER 1.16, peak Vt 1,650.8 ml, and no transplantation or LVAD during follow-up. Cardiomyopathy etiology (ischemic/nonischemic) and diabetes status (yes/no) was varied to assess the persistence of the interaction under different conditions.

RESULTS

STUDY POPULATION. Tables 1 to 3 depict the baseline clinical characteristics and exercise test parameters from the study cohort. Within the cohort of 3,811 subjects, 3,765 (99%) underwent treadmill stress testing, with the most common exercise protocol being the modified Naughton (2,602 subjects, 68% of cohort). The median follow-up was 2,252 days (interquartile range: 955 to 3,821 days), during which time there were 1,537 mortality events (40.3% crude mortality). Females had a slight but significantly lower BMI (27.2 vs. 28.0 kg/m^2, $p < 0.0015$), were younger (52.5 vs. 54.6 years, $p < 0.0001$), had a lower burden of CAD (30% vs. 57%, $p < 0.0001$), and less ischemic etiology (26% vs. 54%, $p < 0.0001$) (Table 1) compared with males. Medication regimens and diabetes prevalence were equivalent between the sexes. Females attained significantly lower peak VO_2 and peak Vt than males ($p < 0.0001$ for both).

As expected, relative to the OW and OB groups NW patients had a lower prevalence of obesity-related conditions including diabetes, HTN, hyperlipidemia,

TABLE 3 Baseline Characteristics by Sex and BMI Category

Characteristic	Female NW (n 332)	Female OW (n 303)	Female OB (n 180)	Male NW (n 712)	Male OW (n 1,129)	Male OB (n 656)	p Value
Age, yrs	53.6 ± 12.3	54.6 ± 10.7	50.9 ± 10.9	53.6 ± 12.3	55.7 ± 11.4	53.0 ± 10.6	<0.0001
Female, %	100	100	100	0	0	0	<0.0001
Caucasian, %	83	79	79	86	87	85	0.0022
LVEF, %	20 (15 25)	20 (15 25)	20 (15 30)	20 (15 25)	20 (15 25)	20 (15 25)	<0.0001
BMI, kg/m^2	22.3 (20.9 23.8)	27.1 (26.2 28.7)	31.9 (30.9 33.4)	23.1 (21.7 24.2)	27.4 (26.2 28.6)	31.9 (30.9 33.4)	<0.0001
Ischemic etiology, %	24	29	26	56	57	53	<0.0001
CAD, %	27	33	31	60	60	56	<0.0001
NYHA functional class, %							
	6	5	0	10	10	8	0.0001
	31	27	36	29	31	34	0.1156
	61	67	61	58	56	56	0.0133
	2	1	3	3	3	2	0.1098
Digoxin, %	67	64	61	70	62	64	0.0250
ACE inhibitor/ARB, %	91	91	93	91	92	93	0.7430
Beta blocker, %	64	69	73	62	69	70	0.0037
Diabetes, %	14	28	36	19	26	35	<0.0001
Smoking, %	18	17	22	26	20	21	0.0151
HTN, %	40	45	67	46	56	63	<0.0001
Hyperlipidemia, %	40	56	53	48	60	64	<0.0001
AF, %	9	7	10	13	14	15	0.0027
SBP, mm Hg	108 (96 120)	110 (100 122)	110 (98 126)	104 (94 118)	110 (100 122)	110 (100 124)	<0.0001
Heart rate recovery	12 (7 18)	12 (6 19)	11 (6 19)	10 (5 17)	11 (5 18)	11 (6 18)	0.3535
Max METs	4.6 (3.7 5.6)	4.3 (3.5 5.3)	4.2 (3.4 5.2)	4.6 (3.6 5.8)	4.7 (3.8 6.1)	4.7 (3.7 6)	<0.0001
Peak VO_2, ml/kg/min	16.1 (12.9 19.7)	15.2 (12.2 18.1)	14.8 (11.7 18.4)	16.0 (12.7 20.3)	16.3 (13 21)	16.5 (13.1 20.7)	<0.0001
Peak RER	1.1 (1.0 1.1)	1.1 (1.0 1.1)	1.1 (1.0 1.1)	1.1 (1.1 1.2)	1.1 (1.1 1.2)	1.1 (1 1.2)	<0.0001
Peak Vt, ml	1,108 (909 1,308)	1,168 (1,002 1,419)	1,240 (1,006 1,588)	1,578 (1,256 1,910)	1,740 (1,434 2,106)	1,854 (1,515 2,234)	<0.0001
VE/VCO_2 ratio	38.5 (34 45)	36 (32 42)	35 (31 42)	41 (34 49)	38 (32 45)	35 (31 41)	<0.0001

Values are mean ± SD or median (interquartile range). NW: 18.5 ≤BMI <25; OW: 25 ≤BMI <30; OB: BMI ≥30 kg/m^2.

and CAD, but there was no difference in smoking across BMI categories (Table 2). OB patients had a lower mean age than NW and OW counterparts, raising the possibility of a "healthy survivor" effect. There was also an incremental increase in the proportion of patients tolerating beta-blockers across the BMI categories (63% NW vs. 69% OW vs. 73% OB; p < 0.0001). When stratified by both sex and BMI

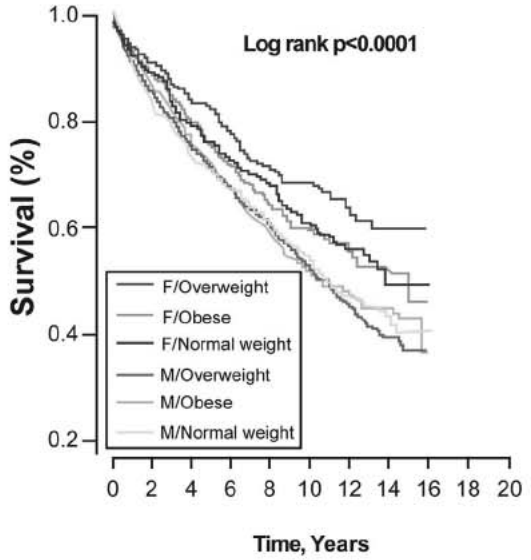
TABLE 4 Mortality Hazard Ratios by Sex and BMI Groups

	NW	OW	OB
All (n 3,811)			
Unadjusted HR	1	0.98 (0.94 1.02); p 0.2717	0.88 (0.85 0.92); p < 0.0001
Adjusted HR	1	1.08 (1.03 1.13); p 0.0005	1.09 (1.04 1.14); p 0.0006
Event rate, %	441/1,044 42.2	576/1,432 40.2	520/1,335 39.0
Female (n 969)			
Unadjusted HR	1	0.85 (0.78 0.93); p 0.0004	0.95 (0.87 1.03); p 0.2011
Adjusted HR	1	0.84 (0.77 0.93); p 0.0005	1.05 (0.94 1.16); p 0.4056
Event rate, %	120/332 36.1	85/303 28.1	114/334 34.1
Male (n 2,842)			
Unadjusted HR	1	0.98 (0.93 1.02); p 0.314	0.85 (0.81 0.89); p < 0.0001
Adjusted HR	1	1.15 (1.10 1.21); p < 0.0001	1.12 (1.06 1.18); p 0.0001
Event rate, %	321/712 45.1	491/1,129 43.5	406/1,001 40.6

Adjusted for age, race, ischemic etiology, NYHA, digoxin, ACE inhibitor/ARB, beta-blocker, diabetes, smoking, HTN, hypercholesterolemia, AF, resting SBP, HRR, peak VO_2, peak RER, peak Vt, subsequent transplant or LVAD. NW: 18.5 ≤BMI <25; OW: 25 ≤BMI <30; OB:BMI ≥30 kg/m^2.

HR hazard ratio; other abbreviations as in Tables 1 and 2.

FIGURE 1 Kaplan-Meier Unadjusted Survival Curves for All-Cause Mortality Stratified by Sex and BMI Category



category, it can be seen that the 6 groups are dissimilar by many characteristics, including OW and OB females attaining lower median peak VO_2 levels than their male counterparts (Table 3).

UNADJUSTED AND ADJUSTED HRs. Over a median 6.2-year follow-up period, females had a lower crude mortality rate than males (32.9% vs. 42.9%). The crude mortality hazard ratio for male sex was 1.42 (95% confidence interval [CI]: 1.25 to 1.60, $p < 0.0001$). Compared with NW subjects, the unadjusted all-cause mortality was significantly lower in the OB group (HR: 0.88; 95% CI: 0.85 to 0.92; $p < 0.0001$), supporting the presence of an overall unadjusted "obesity survival paradox" (Table 4). When examined by sex, the unadjusted survival paradox was evident in both females and males, although the risk was distributed differently; the OW group was associated with lower mortality in females, whereas the OB group was associated with lower mortality in males (Figure 1). After adjustment for all relevant confounders, the only BMI subgroup to retain a survival benefit was the OW female group (adjusted HR: 0.84; 95% CI: 0.77 to 0.93; p 0.0005 compared with NW females). Conversely, the OW and OB males showed increased adjusted mortality compared with NW males. A subgroup analysis was conducted to confirm this pattern was consistent when restricted to subjects with RER ≥1.05, indicating attainment of anaerobic threshold and a VO_2 representing peak oxygen consumption (Table 5).

COX MODEL WITH RESTRICTED CUBIC SPLINE. Female sex was a significant predictor of survival on multivariable Cox modeling using the restricted cubic spline (Table 6) ($p < 0.0001$). There was a statistically significant interaction between BMI and sex ($p < 0.0001$), supporting the previous observation of a differential impact of BMI on all-cause mortality in males versus females with HF. Figures 2A and 2B illustrate the adjusted mortality HR along the continuum of BMI for males and females. A nadir in mortality hazard was seen just below 30 kg/m² in females with both ischemic and nonischemic HF etiologies. This relationship also persisted regardless of diabetes status (data not shown). Conversely, males demonstrated the highest mortality hazard around a BMI of 30 kg/m². When peak VO_2 was substituted by LBM-adjusted peak VO_2 in the model, the significant

TABLE 5 Mortality HRs by Sex and BMI Groups, Subjects With Peak RER ≥1.05 Only

	NW	OW	OB
All (n 2,805)			
Unadjusted HR	1	1.02 (0.97 1.07); p 0.4871	0.91 (0.87 0.96); p 0.0003
Adjusted HR	1	1.13 (1.08 1.19); p < 0.0001	1.17 (1.10 1.23); p < 0.0001
Event rate, %	321/782 41	444/1,092 40.7	365/931 39.2
Female (n 629)			
Unadjusted HR	1	0.89 (0.8 1.00); p 0.0475	0.99 (0.89 1.10); p 0.8487
Adjusted HR	1	0.89 (0.79 1.00); p 0.0506	1.11 (0.98 1.26); p 0.1066
Event rate, %	72/218 33	54/201 26.9	69/210 32.9
Male (n 2,176)			
Unadjusted HR	1	1.01 (0.96 1.06); p 0.6967	0.88 (0.83 0.93); p < 0.0001
Adjusted HR	1	1.19 (1.13 1.26); p < 0.0001	1.19 (1.12 1.27); p < 0.0001
Event rate, %	249/564 44.1	390/891 43.8	296/721 41.1

Adjusted for age race, ischemic etiology, NYHA, digoxin, ACE inhibitor/ARB, beta-blocker, diabetes, smoking, HTN, hypercholesterolemia, AF, resting SBP, HRR, peak VO_2, peak RER, peak Vt, subsequent transplant, or LVAD. NW: 18.5 ≤BMI <25; OW: 25 ≤BMI <30; OB: BMI ≥30 kg/m².

Abbreviations as in Tables 1, 2, and 4.

TABLE 6 Wald Statistics for the Multivariable Cox Model Using Restricted Cubic Spline for All-Cause Mortality (n 3,811)

	Chi-Square	Degrees of Freedom	p Value
Age	722.87	2	<0.0001
Nonlinear	2.39	1	0.1217
Sex (factor + higher order factors)	138.20	5	<0.0001
All interactions	41.11	4	<0.0001
Caucasian	0.64	1	0.4252
LVEF	27.01	2	<0.0001
Nonlinear	1.03	1	0.3096
BMI (factor + higher order factors)	41.37	4	<0.0001
All interactions	31.67	2	<0.0001
Nonlinear (factor + higher order factors)	31.37	2	<0.0001
Ischemic etiology	25.83	1	<0.0001
NYHA functional class	47.04	3	<0.0001
Digoxin	474.62	1	<0.0001
ACE inhibitor/ARB	7.35	1	0.0067
Beta blocker	744.35	1	<0.0001
Diabetes	76.87	1	<0.0001
Smoker	25.68	1	<0.0001
HTN	42.37	1	<0.0001
Hyperlipidemia	156.16	1	<0.0001
AF	91.25	1	<0.0001
Resting SBP	67.29	2	<0.0001
Nonlinear	0.12	1	0.7283
Heart rate recovery	34.58	2	<0.0001
Nonlinear	9.72	1	0.0018
Peak VO_2 (factor + higher order factors)	314.06	4	<0.0001
All interactions	10.73	2	0.0047
Nonlinear (factor + higher order factors)	43.55	2	<0.0001
Peak RER	30.85	2	<0.0001
Nonlinear	16.23	1	<0.0001
Peak Vt	3.26	2	0.1961
Nonlinear	3.00	1	0.0831
Heart transplantation	334.05	1	<0.0001
Left ventricular assist device	125.29	1	<0.0001
Total nonlinear	98.67	10	<0.0001
Total interaction	41.11	4	<0.0001
Total nonlinear + interaction	114.93	12	<0.0001
Total	6,052.09	36	<0.0001

Abbreviations as in Table 1.

interaction between BMI and sex remained unchanged. The interaction also persisted when the VE/VCO_2 ratio replaced peak VO_2 in the model and when the analysis was restricted to subjects who attained an RER ≥1.05. The correlation between peak VO_2 and $VE/VECO_2$ was -0.54 ($p < 0.0001$) and so both parameters were not added to the model concurrently; the overall model chi-square value was greatest using peak VO_2 rather than $VE/VECO_2$ (6,052 vs. 5,999) and hence this is the model reported.

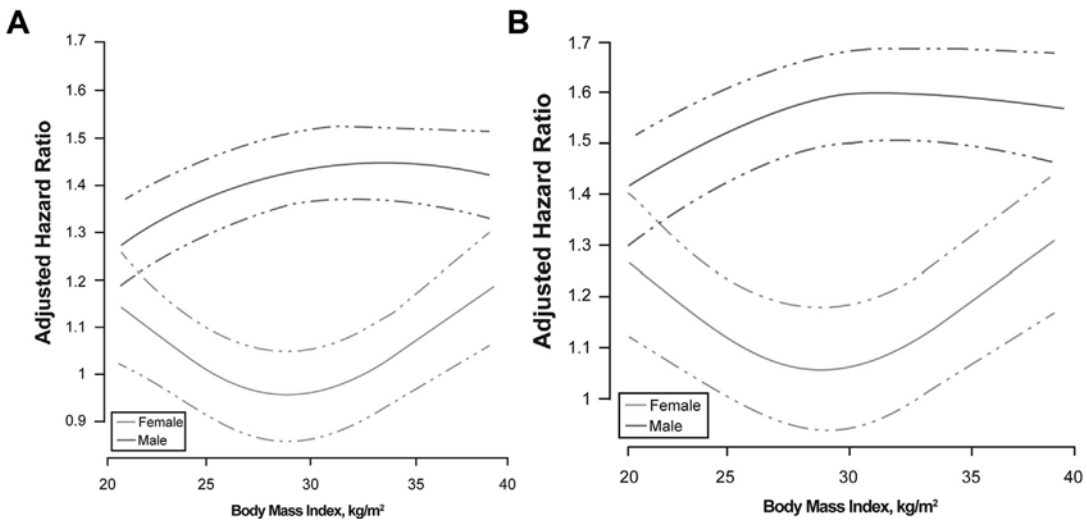
DISCUSSION

There are basic science observations that support our clinical finding of a differential response to the overweight/obese state in females versus males with systolic HF. Peterson et al. identified that female sex is independently associated with greater myocardial fatty acid uptake and lower myocardial glucose utilization (14). This may be an effect of estrogen, which reduces glucose oxidation, gluconeogenesis, and glycogenolysis in other organs and inhibits glucose uptake. Chronic estrogen replacement in healthy post-menopausal women enhances myocardial fatty acid uptake and oxidation (18). Nonhormonal mechanisms are also likely involved, such as in the higher turnover of fatty acids in females (19). This raises the possibility that female hearts are more dependent on fatty acids for energy production than male hearts, potentially explaining the survival advantage of females with some excess adiposity. The availability of fatty acids for myocardial utilization would only be beneficial if sufficient oxygen is delivered to the myocardium, because upregulation of fatty acid oxidation and downregulation of glucose utilization reduces myocardial efficiency. Interestingly, this hypothesis may be upheld by the observation in a cohort overlapping with our study in which females with ischemic HF had disproportionately poorer survival than nonischemics (20). Sexual dimorphism has also been recognized in the relationship between adiponectin and cardiovascular mortality, with high circulating adiponectin being associated with increased cardiovascular mortality in males, but not females, with type 2 diabetes (21).

A relationship between excess adiposity and favorable survival in females is plausible given that females have a higher percentage of body fat, and percent body fat has proven protective from mortality in HF (22). A few prior HF publications have divided their cohorts by sex, but do not have the sensitivity to observe differential sex effects along the full spectrum of BMI. An HF cohort containing 680 females was stratified by sex and BMI (dichotomized BMI into normal, 18.5 to 24.9 kg/m^2, vs. high, ≥25 kg/m^2). The higher BMI category was associated with improved adjusted 2-year survival in both sexes (23). However, there was no statistical comparison between the sexes and no presentation of mortality trends along the BMI continuum >25 kg/m^2.

One recent publication did formally compare the mortality risk conferred by increasing BMI in males versus females with acutely decompensated HF. This international analysis supported an obesity survival paradox: there was an 11% decrease in 30-day

FIGURE 2 Interaction Plot Between BMI and Sex for Nonischemic Etiology and Ischemic Etiology



(A) Nonischemic etiology; **(B)** ischemic etiology. Model adjusted for age, race, left ventricular ejection fraction, etiology, New York Heart Association, digoxin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta blocker, diabetes, smoking, hypertension, hyperlipidemia, atrial fibrillation, rest systolic blood pressure, heart rate recovery, peak oxygen uptake, respiratory exchange rate, peak tidal volume, heart transplantation, or left ventricular assist device placement. The nonparallel lines confirm a differing relationship between BMI as a continuous value (x axis) and adjusted mortality HR (y axis) in females versus males. For females, the lowest mortality hazard was seen just below BMI 30 kg/m^2, with higher HRs in the NW (<25 kg/m^2) and stage II/III obesity (>35 kg/m^2) regions of the x axis. Males had a higher mortality hazard overall and showed an increased mortality hazard in the OW and OB ranges as compared with the NW range. BMI body mass index; NW normal weight; OW overweight.

mortality and 9% decrease in 1-year mortality per 5 kg/m^2 BMI increase, $p < 0.05$ (24). No interaction between sex and BMI was detected, with a hazard ratio for all-cause mortality per 5 kg/m^2 BMI of 0.87 (0.79 to 0.96) in males and 0.92 (0.85 to 0.99) in females, p for interaction 0.92. However, unlike our study, the follow-up period was short, there was no risk adjustment for cardiorespiratory fitness (CRF), and the relationship between BMI and mortality was found to be log-linear.

It is notable that the unadjusted HRs in this analysis suggested an obesity survival paradox in both males and females, but that this disappeared with risk adjustment. This highlights the critical importance of careful covariate selection when constructing a model that aims to determine the "pure" effect of baseline BMI on subsequent outcomes. As demonstrated by Güder and colleagues, adjustment by incrementally more complete models can attenuate the strength of the inverse relationship between BMI and mortality (25). Measures of CRF have been also been shown to attenuate the obesity paradox, in cohorts with and without HF (26-30). There is a danger that adding a wide range of potential confounders may unknowingly insert a factor on the biological pathway between BMI and mortality and negate a true relationship. That the OW females continued to show a significantly lower adjusted HR makes this explanation unlikely. The absence of an overall-adjusted HF obesity survival paradox in this study is not unique (8,29). It may be relevant to note that these prior studies reporting no survival advantage for obese HF patients had some similarities to our current study in terms of their younger HF populations and risks adjustments for CRF.

The contribution of this sex-BMI analysis to the study of the obesity paradox is 3-fold. First, this analysis highlights the importance of recognizing a nonlinear relationship between BMI and mortality to permit detection of the differential effects of BMI on survival within different regions of the BMI spectrum. We propose that the linearity of the BMI-mortality relationship should always be examined and more complex nonlinear modeling options pursued if indicated. Second, it highlights the importance of adequate covariate adjustment given that the 6 sex/BMI subgroups were quite dissimilar in their baseline characteristics and an apparent obesity paradox was replaced by a more nuanced relationship between BMI and survival after covariate adjustment. Third, the observation of a HF survival paradox that is limited to overweight females

merits further clinical and basic science investigation. Greater understanding of why modest excess adiposity may have a more favorable biological impact in females may reveal new therapeutic opportunities in advanced HF and also permit accurate counseling of HF patients regarding weight management.

STUDY LIMITATIONS. Although the baseline and CRF data were prospectively collected, the findings of this study should be viewed in the context of a retrospectively analyzed cohort study design. There are other data parameters, such as biomarkers of nutritional status and invasive hemodynamics, which were unavailable and may have improved risk adjustment. Importantly, body habitus was represented only by BMI, with no available anthropomorphic measurements (31). In HF, weight may partly reflect fluid congestion, although a higher BMI resulting from a greater volume overload would be expected to increase mortality, which was not uniformly seen across sex groups. In studies involving obesity, CRF, and sex, body fat assessment by skinfold thickness should ideally be used to calculate lean body mass adjusted peak VO_2 (32), although a recent study using estimated LBM did support the validity of such methods (33). An additional limitation is that this is a study of systolic HF patients who were well enough to perform exercise testing, but sick enough to require advanced disease evaluation; therefore, the results may not apply to the full systolic HF population.

CONCLUSIONS

In this large advanced systolic HF cohort, an unadjusted obesity survival paradox was ameliorated by adjustment for confounders. Overweight or obese males showed higher adjusted mortality than normal weight males; the only group to retain an adjusted survival benefit was overweight females. A more favorable response to modest excess adiposity may partially explain the female HF survival advantage.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A female survival advantage has consistently been observed in outpatient systolic heart failure cohorts, the reasons for which are unclear.

TRANSLATIONAL OUTLOOK: Preliminary research suggests female hearts have greater myocardial fatty acid uptake and lesser myocardial glucose utilization, which could be protective in the advanced heart failure state. The next step is to better characterize the sex differences in adipokine hormones (adiponectin, resistin, leptin, tumor necrosis factor-alpha) that are thought to signal between adipose tissue and the myocardium. Understanding sex-specific effects of the systemic metabolism on the myocardium may facilitate development of novel pharmacological therapies for heart failure.

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