

Asad Khan, MD

Department of Internal Medicine, Cleveland Clinic, Cleveland, OH; Clinical Instructor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Erik H. Van Iterson, PhD

Director, Cardiac Rehabilitation, Section of Preventive Cardiology and Rehabilitation, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH

Luke J. Laffin, MD

Co-director, Center for Blood Pressure Disorders, Section of Preventive Cardiology and Rehabilitation, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH

The obesity paradox in heart failure: What is the role of cardiorespiratory fitness?

ABSTRACT

The obesity paradox describes a survival benefit for higher body mass index in patients with heart failure. But other factors like cardiorespiratory fitness may play a role in heart failure development, severity, and survival. Although more research is needed to better understand the relationships between body mass index and fitness in patients with heart failure, evidence indicates that recommending weight loss and an exercise program is appropriate for most patients.

KEY POINTS

Obesity increases the risk of developing heart failure regardless of fitness level, but better fitness attenuates the risk.

Weight appears to be only part of the obesity paradox story. Evidence indicates that cardiorespiratory fitness is a major factor influencing the paradox.

Fitness modifies the obesity paradox in patients with heart failure and reduced ejection fraction, with the paradox remaining strongest in patients who are less fit.

Although more research is needed on risk reduction for heart failure, evidence indicates that intentional weight loss and increased fitness are advisable for select patients.

OBESITY IS A WELL-ESTABLISHED and important predictor of morbidity and mortality in patients with cardiovascular (CV) disease and other conditions, including chronic kidney disease and chronic obstructive pulmonary disease. Yet some studies report obesity is associated with lower mortality in patients with heart failure—a finding known as the obesity paradox.

Though not fully understood, several possible reasons for the obesity paradox have been proposed (Table 1).^{1–9}

Understanding the obesity paradox has important clinical implications given the high prevalence of obesity in patients with heart failure (42% of those with preserved ejection fraction [HFpEF] and 36% of those with reduced ejection fraction [HFrEF]).¹⁰ What should patients be advised about weight management? What should patients be advised about cardiorespiratory fitness, a major factor influencing the paradox?

This review summarizes current understanding of the roles of cardiorespiratory fitness and body mass index (BMI) in patients with heart failure and its development. It also discusses how to advise patients about fitness and body mass in light of the obesity paradox.

BENEFIT OF FITNESS IN CARDIOVASCULAR DISEASE

The effect of cardiorespiratory fitness on CV outcomes is an active area of clinical research. The standard for measuring cardiorespiratory fitness is cardiopulmonary exercise testing, using

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TABLE 1

Select theoretical mechanisms of the obesity paradox

Greater metabolic reserves
 Less cardiac cachexia
 Increased concentration of tumor necrosis factor receptors
 Earlier presentation owing to greater functional impairment
 Attenuated response to renin-angiotensin-aldosterone system
 Higher blood pressure leading to greater use of cardioprotective medications

Adapted from reference 6.

an incremental treadmill or upright cycle protocol. Numerous studies have found associations between poor CV disease outcomes and low peak exercise oxygen uptake (peak Vo_2).^{11,12}

Low fitness predicts poor outcomes

In 1996, Blair et al¹³ were among the first to quantify the effects of cardiorespiratory fitness on cardiovascular disease outcomes. After following 25,341 men and 7,080 women in a preventive medicine clinic for about 9 years, they found that low fitness was independently associated with increased all-cause mortality in both men (relative risk [RR] 1.52, 95% confidence interval [CI] 1.28–1.82) and women (RR 2.10, 95% CI 1.36–3.21). Low fitness was associated with statistically significant increased cardiovascular disease mortality risk in men (RR 1.70, 95% CI 1.28–2.25), although the difference was not statistically significant in women. In both sexes, low fitness was a more significant prognostic factor than other traditional cardiac risk factors. Interestingly, elevated BMI ($> 27 \text{ kg/m}^2$) was not found to be significantly associated with increased mortality in either sex.

Fitness may be more important than weight

A 1999 prospective observational study by Wei et al¹⁴ also found that low cardiorespiratory fitness is a strong independent predictor of cardiovascular disease mortality in the general population, and perhaps more so than BMI. The study assessed nearly 26,000 men for cardiorespiratory fitness, cardiovascular disease,

and risk factors for cardiovascular disease development, with follow-up for about 10 years. Cardiorespiratory fitness was determined using maximal treadmill exercise testing with age-based metabolic equivalent (MET) values for fitness levels. Participants also were stratified by BMI using standard thresholds for normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), and obesity ($> 30 \text{ kg/m}^2$).¹⁴

Results showed that cardiovascular disease mortality increased with increasing BMI levels.¹⁴ Expectedly, the lowest risk for cardiovascular disease mortality was a combination of normal weight and high fitness. However, the relative risk of cardiovascular disease mortality in the obese high-fitness cohort was half that in the low-fitness normal-weight cohort, suggesting that fitness is a more important predictor of cardiovascular disease mortality than body weight. The effect of low cardiorespiratory fitness on cardiovascular disease mortality was also higher than the presence of diabetes, dyslipidemia, hypertension, or current smoking across all BMI levels.¹⁴

HEART FAILURE DEVELOPMENT: CARDIORESPIRATORY FITNESS AND BMI

The mechanisms related to obesity that contribute to the development of HFpEF and HFrEF include hemodynamic alterations that may predispose the patient to changes in cardiac morphology and ventricular function.¹⁰

Possible mechanisms

The mechanisms related to low cardiorespiratory fitness that contribute to the development of heart failure are not well understood. Low cardiorespiratory fitness may indirectly affect development of cardiovascular risk factors (ie, reduced cardiorespiratory fitness is associated with a low level of physical activity),¹⁵ which may accelerate the development of heart failure risk factors including diabetes, hypertension, and coronary artery disease. Alternatively, cardiovascular symptoms such as angina or dyspnea on exertion may limit habitual physical activity, in turn leading to reduced cardiorespiratory fitness.

Even in the absence of traditional cardiovascular disease risk factors, studies demonstrate that sedentary aging leads to increased stiffness of the left ventricular myocardium, a potential substrate for heart failure.¹⁶ Higher

Low fitness is a strong independent predictor of cardiovascular disease mortality

TABLE 2

Studies assessing BMI and cardiorespiratory fitness: Effect on heart failure development

Study	N	Design ^a	End point	Main findings
Pandey et al ¹⁹ Cooper Center Longitudinal Study	19,485	Patients stratified by BMI and peak METs into quintiles	Long-term risk of hospitalization for HF	Higher midlife BMI was significantly associated with greater risk of hospitalization for HF in older age. This association was attenuated after adjusting for cardiorespiratory fitness.
Kenchaiah et al ²⁰ Physicians' Health Study	21,094	Patients stratified by BMI and vigorous physical activity	New onset HF	Compared with lean participants, overweight and obese participants had increased HF risk. Vigorous physical activity conferred decreased HF risk. No interaction was found between BMI, vigorous physical activity, and HF risk.
Hu et al ²¹	59,178	Patients stratified by physical activity and indicators of adiposity (eg, BMI, waist circumference, waist-to-hip ratio)	New onset HF	Higher BMI, waist circumference, or waist-to-hip ratio was associated with increased HF incidence in men and women. The protective effect of physical activity on HF risk was consistent in participants at all levels of BMI.
Kokkinos et al ²²	20,254	Patients stratified by BMI and cardiorespiratory fitness in quartiles	New onset HF	Increased cardiorespiratory fitness was associated with progressively lower HF risk regardless of BMI. After adjusting for fitness, BMI was not a significant predictor of HF risk.
Pandey et al ²³ Look AHEAD trial	5,109 (with DM)	Patients stratified by BMI and cardiorespiratory fitness into tertiles	New onset HF	High cardiorespiratory fitness was associated with lower risk of developing HFpEF. Sustained long-term improvement in fitness was associated with lower risk of HF after 4 years.

^a All studies are retrospective.

AHEAD = Action for Health in Diabetes; BMI = body mass index; DM = diabetes mellitus; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; METs = metabolic equivalents

levels of physical activity are associated with beneficial effects on cardiovascular measures, including improved early diastolic filling time and favorable cardiac remodeling.¹⁷ In addition, an animal study showed a direct and favorable effect of exercise training on cardiac structure and function, leading to a delayed onset of heart failure.¹⁸

Study comparing fitness and BMI

The combined impact of cardiorespiratory fitness and BMI on heart failure development is gaining increasing attention, and many studies have been conducted (Table 2).^{19–23}

Data from the Cooper Center Longitudinal study¹⁹ indicated that cardiorespiratory fitness may be at least as important as BMI for developing heart failure. The study stratified

nearly 20,000 participants by standard BMI thresholds and cardiorespiratory fitness levels (low, moderate, and high as determined by calculated METs achieved with treadmill exercise testing). A higher BMI during midlife was associated with a significantly greater risk of heart failure hospitalization in older patients (age 65 and older), even after adjusting for other established heart failure risk factors. When adjusted for cardiorespiratory fitness, this association was attenuated, such that cardiorespiratory fitness accounted for 47% of the heart failure risk associated with BMI. Furthermore, the BMI-associated risk of hospitalization for heart failure was more pronounced in participants who had low fitness or were moderately fit.

Cardio-respiratory fitness may be at least as important as BMI for developing heart failure

A subgroup of about 9,000 participants underwent repeat measurements of cardiorespiratory fitness and BMI at a median follow-up of 4.2 years. Increased cardiorespiratory fitness, but not BMI, was significantly associated with decreased risk of heart failure hospitalization in older patients (hazard ratio [HR] 0.91, 95% CI 0.84–0.98 per 1 MET increase).¹⁹

Data from the Physicians' Health Study showed that participation in self-reported vigorous activity (defined as "working up a sweat") 1 to 3 times a month conferred a 26% decrease in new-onset heart failure development.²⁰ In contrast, a 1-kg/m² increase in BMI increased the risk of heart failure by 13%. Adjusting for vigorous physical activity did not alter the risk of heart failure associated with elevated BMI.

Hu et al²¹ studied the relationship between physical activity, heart failure risk, and indicators of adiposity (ie, BMI, waist circumference, and waist-to-hip ratio) in nearly 60,000 Finnish participants who were free of heart failure at enrollment. During a mean follow-up of 18.4 years, the risk of developing heart failure directly increased with BMI and other measures of adiposity for men and women. Moderate or high levels of physical activity were associated with a reduced risk of heart failure in both sexes at all levels of BMI and waist-to-hip ratio.

In a study published in 2019, Kokkinos et al²² stratified 20,000 US men by standard BMI thresholds and cardiorespiratory fitness. Fitness thresholds were based on quartiles following age and sex-specific MET adjustments. After a mean follow-up of 13.4 years, they found that heart failure risk increased progressively with decreasing fitness in each BMI category. Although age, BMI, and cardiorespiratory fitness were strong independent predictors of heart failure risk, the association between BMI and heart failure risk was no longer statistically significant after adjusting for fitness. Each increase of 1 MET was associated with a 16% lower risk of heart failure (HR 0.84; 95% CI 0.83–0.86; *P* < .001).

Clues from patients with diabetes

A recent post hoc analysis of the Look AHEAD (Action for Health in Diabetes) trial²³ also examined the impact of fitness and BMI on heart failure development. It found that intensive life-

style modification did not lower the risk of heart failure more than diabetes support and education groups (HR 0.96, 95% CI 0.75–1.23).

However, a pooled multivariate analysis found a statistically significant, graded, inverse association between baseline cardiorespiratory fitness and heart failure incidence in participants who were moderately or highly fit. Interestingly, this association was only observed for heart failure with preserved but not reduced ejection fraction. Also, the association of BMI with heart failure was not statistically significant after adjusting for baseline cardiorespiratory fitness and traditional risk factors. In a subset of patients who underwent repeat assessment of cardiorespiratory fitness and BMI at 1 and 4 years, there was a statistically significant association between improved fitness and lower risk of overall heart failure at 4 years (HR 0.86, 95% CI 0.79–0.94).²³

More information needed on women and type of heart failure

Other than in a study by Hu et al,²¹ which included comparable numbers of men (1,921) and women (1,693), women are vastly underrepresented in the studies. The Physicians' Health Study²⁰ consisted entirely of men, and in the Cooper Center Longitudinal Study,¹⁹ women accounted for less than 10% of participants in the overweight category and less than 11% in the obese category. Given the known differences between men and women, especially body fat distribution, more studies that include women are essential.

Another criticism is that only the Look AHEAD trial²³ determined the risk for specific heart failure phenotypes (ie, HF_rEF vs HF_pEF). In most studies, the primary outcome was defined by a combination of International Classification of Diseases codes, limiting overall interpretation.

Bottom line

Despite limitations, these studies, taken as a whole, have two important implications for heart failure prevention:

- BMI and cardiorespiratory fitness both affect heart failure development, but fitness is likely the more significant factor
- Increased fitness is associated with a reduced risk of heart failure hospitalization as one ages.

TABLE 3

Studies assessing BMI and cardiorespiratory fitness: Effect on heart failure prognosis

Study	N ^a	Average LVEF of target groups	Design ^b	End point	Main findings
Lavie et al ²⁴	2,066	High fit = 30.1% Low fit = 26.0%	Patients stratified by BMI and peak Vo ₂	Overall mortality	In patients with low cardiorespiratory fitness, BMI ≥ 30 kg/m ² was a significant predictor of better survival. No obesity paradox seen at the high fitness level.
Clark et al ⁷	1,675	High fit = 23.4% Low fit = 23.2%	Patients stratified by BMI and peak Vo ₂	Death, urgent status 1A heart transplant, or VAD placement.	BMI of obesity class was associated with a significantly lower risk of death, urgent transplant, or device placement than with normal BMI in the group with low peak Vo ₂ . In the high peak Vo ₂ group, no difference was seen for BMI and survival.
Piepoli et al ²⁷ MECKI Score Research Group	4,623	BMI (kg/m ²) < 25 = 31% 25 to 30 = 33% > 30 to ≤ 35 = 33% > 35 = 33%	Patients stratified by BMI and peak Vo ₂	All-cause mortality and CV death	Higher BMI and peak Vo ₂ were significant positive predictors of longer survival. When patients in a BMI category were matched according to age, sex, LVEF, and peak Vo ₂ , the protective role of BMI disappeared.
McAuley et al ²⁶ FIT Project	774	High fit = 41% Low fit = 40%	Patients stratified by BMI and peak METs	Overall mortality	Significant positive association between BMI category and survival for exercise capacity < 4 METs, but not ≥ 4 METs.

^a All patients had established heart failure.^b All studies were retrospective.

BMI = body mass index; CV = cardiovascular; FIT = Henry Ford Exercise Testing; LVEF = left ventricular ejection fraction; MECKI = Metabolic Exercise test data combined with Cardiac and Kidney Indexes; METs = metabolic equivalents; VAD = ventricular assist device; Vo₂ = exercise oxygen uptake

HEART FAILURE PROGNOSIS: CARDIORESPIRATORY FITNESS AND BMI

Studies have been conducted in patients with heart failure to determine the impacts of fitness and BMI, and whether fitness affects the obesity paradox (Table 3).^{7,24–27}

Clark et al⁷ also found that higher fitness levels likely mitigate the obesity paradox in patients with heart failure. They assessed almost 2,000 patients referred for heart transplant evaluation. Participants were stratified by BMI and fitness, as determined by cardiopulmonary exercise testing. After 2 years of follow-up, a high BMI (≥ 30 kg/m²) was a significant predictor of improved survival in the low-fitness group but not in the high-fitness group.

The Henry Ford Exercise Testing (FIT) Project²⁶ followed nearly 800 participants with heart failure and a BMI of at least 18.5 kg/m². Participants were grouped into standard BMI categories and then stratified by fitness (< 4 or ≥ 4 METs) based on treadmill stress test-

ing. After a mean follow-up of 10 years, the authors concluded that the higher the BMI, the lower the mortality in those with a low level of fitness, but not in those with a high level of fitness. Thus, exercise capacity should be considered when stratifying risk.

HFrEF: Higher fitness may negate the obesity paradox

In the MECKI Score Research Group study,²⁷ 4,623 patients with HFrEF underwent maximum cardiopulmonary exercise testing at enrollment and were followed for a median of 3 years. The population was divided according to BMI and peak Vo₂. On univariate analysis, groups with higher BMI and peak Vo₂ had lower mortality. However, when groups were matched for age, sex, left ventricular ejection fraction (LVEF), and predicted peak Vo₂, the protective role of BMI disappeared.

Fitness: An obesity paradox modifier

The above studies support an obesity paradox-

cardiorespiratory fitness dichotomy in established heart failure: obesity is predominantly protective in patients with low fitness but not in highly fit patients. Hence, high fitness can be thought of as a modifier of the obesity paradox.

A strength of the data is the wide range in the mean age of each low-fitness obese cohort (50.8–63 years),^{8,27} indicating that the protective effect of obesity is not limited to younger patients. Studies also have included a range of mean LVEF (23.6%–40%),^{2,7,27} suggesting that cardiorespiratory fitness is likely an obesity paradox modifier in patients with reduced LVEF (< 40%), mid-range LVEF (40%–50%), and preserved LVEF (> 50%).

HFpEF: Does the obesity paradox hold?

The obesity paradox is not as consistently reported for heart failure patients with preserved ejection fraction as it is for those with reduced ejection fraction. Aerobic exercise capacity has been examined in patients with preserved ejection fraction in relation to indices of obesity and adiposity.^{28,29} In those trials, BMI predicted lower exercise capacity but did not correlate with cardiac-specific functional and prognostic parameters, including measures of left ventricular function.

A retrospective analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial³⁰ indicated that the obesity paradox may not hold for HFpEF. It found that a higher baseline level of physical activity was associated with lower risk of adverse cardiovascular events through the duration of the trial (median follow-up 2.4 years), independent of BMI and other risk factors.

It is possible that the apparent lack of an obesity paradox in HFpEF may be because obesity itself is a risk factor for HFpEF. Also, patients with HFpEF and obesity are more likely to have other cardiovascular risk factors such as hypertension, diabetes, and obstructive sleep apnea that may attenuate any protective effect of obesity.³¹

What about heart failure with mid-range ejection fraction?

Heart failure with mid-range ejection fraction (LVEF 40%–50%) is a more recently characterized group that is not well defined or understood.^{32,33} It is possible that the mechanisms

underlying fitness as an obesity-paradox modifier in these patients are similar to those with reduced ejection fraction, but that is not well established. It is unclear if beneficial interventions in one group are relevant to the other.

Obesity definitions vary by study

Most of the above studies defined obesity broadly as a BMI greater than 30 kg/m², limiting the generalizability of conclusions. Only the MECKI Score study²⁷ subdivided patients based on obesity classes. Certain BMI thresholds may exist for which protective effects of obesity become deleterious.

IMPACT OF WEIGHT LOSS

A meta-analysis by Mahajan et al⁴ found that weight loss induced by bariatric surgery resulted in significantly improved measures of cardiac function and morphology (diastolic function, left ventricular mass index, and left atrial size). However, clinical outcomes (eg, heart failure incidence) were not assessed. Furthermore, patients did not have a diagnosis of heart failure at baseline, so the effect of bariatric surgery in established heart failure was uncertain.

Other studies have not found improved cardiac function with weight loss. Kitzman et al³⁴ found that left ventricular mass and relative wall thickness decreased after diet-induced weight loss, but resting cardiac function did not improve.

A Swedish registry study with nearly 40,000 participants without heart failure at baseline evaluated the effects of weight loss from either intensive lifestyle intervention or bariatric surgery.³⁵ Baseline weight and BMI did not differ between the cohorts. Surgery led to 18.8 kg more weight loss than lifestyle interventions at 1-year follow-up and 22.6 kg more at 2 years. After a median follow-up of 4.1 years, surgery was associated with lower heart failure incidence than lifestyle modification (4.1% vs 7.6% per 10,000 person-years; HR 0.54, 95% CI 0.26–0.81). A 10-kg weight loss from both cohorts combined resulted in decreased heart failure incidence (HR 0.77, 95% CI 0.60–0.97).

Bariatric surgery may also help mitigate established heart failure. In a population-based study,³⁶ 524 patients with heart failure were followed after bariatric surgery, with a

Vigorous activity 1 to 3 times a month conferred a 26% decrease in new-onset heart failure development

composite of emergency department visits or hospitalizations for heart failure exacerbation as the primary outcome measure. In the 13 to 24 months after surgery, heart failure exacerbations were significantly reduced (odds ratio 0.57, 95% CI 0.39–0.82). There were 184 heart failure events (43% systolic and 57% diastolic). No information on body weight reduction was reported, so it is unclear if more weight loss correlated with fewer events.

In contrast, a study by Zamora et al³⁷ of 1,000 patients with ambulatory chronic HFrEF were followed for 3 years to determine the impact of significant weight loss (defined as more than 5% of body weight over 1 year) on the mortality rate. Mortality was higher in patients who lost significant weight (27.6%) than in patients without significant weight loss (15.3%). Among obese patients, significant weight loss was associated with a higher risk of all-cause death (adjusted HR 2.38, 95% CI 1.31–4.32) than in nonobese patients (adjusted HR 1.83, 95% CI 1.16–2.89).

Does unintentional weight loss explain the obesity paradox?

Intentional vs unintentional weight loss likely explains the different heart failure outcomes following weight loss, particularly in patients with HFrEF.

When evaluating candidates for intentional weight loss via bariatric surgery or lifestyle modifications, medical clearance for participation requires a certain level of baseline functional status. However, unintentional weight loss in patients with advanced HFrEF may be the result of sarcopenia and cardiac cachexia, leading to poor baseline metabolic reserves and adverse clinical outcomes. Thus, the obesity paradox may simply reflect the severity of heart failure, with lower BMI occurring in end-stage heart failure and obesity, indicating a better baseline metabolic reserve.

Body composition is also important

Patients with HFpEF and obesity also have sarcopenia and adipose infiltration of muscle,³¹ indicating a highly inflamed and catabolic state. This highlights one of the limitations of using BMI as a surrogate of adiposity, and it demonstrates the need to further describe body composition when evaluating heart failure outcomes.

More attention is being focused on the ef-

fect of lean mass on cardiorespiratory fitness. Lean mass is used as a surrogate for skeletal muscle mass, which is independently associated with cardiorespiratory fitness, possibly via endothelial and mitochondrial dysfunction and respiratory muscle abnormalities.^{28,38} In a 2017 review, reduced lean mass contributed to impaired cardiorespiratory fitness, independent of cardiac function.³⁹ BMI reductions occur with loss of lean mass, which may partially account for the obesity paradox in heart failure.⁴⁰

Osman et al⁴¹ prospectively studied 225 consecutive ambulatory patients with chronic systolic heart failure who were referred for cardiopulmonary exercise testing. They found that adjusting peak Vo_2 to lean mass provided greater prognostic strength than adjusting by body weight, particularly in people with obesity.

The pattern of regional tissue deposition, especially increased proportions of intra-abdominal fat, may play a key role in exercise intolerance in patients with HFpEF. Haykowsky et al⁴² found that patients with HFpEF had higher ratios of intermuscular fat to skeletal muscle mass than healthy controls, and this was significantly related to reduced peak Vo_2 . This evidence suggests that body composition indices such as lean mass play an important role in cardiorespiratory fitness regardless of BMI.

Drug-induced weight loss: The evidence is unclear

There is little evidence to demonstrate the safety and efficacy of pharmacologic weight loss in patients with heart failure. A recent post hoc analysis of the Functional Impact of GLP-1 (glucagon-like peptide-1) for Heart Failure Treatment (FIGHT) trial⁴³ found that in patients with reduced ejection fraction, there was a treatment-related 4.1-lb weight loss for liraglutide vs placebo (95% CI –7.94 to –0.25; $P < .04$), but no effect was found in worsening heart failure, making the clinical implications unclear. More research is needed to determine whether pharmacologic weight loss is an effective strategy to improve clinical outcomes in this patient population.

■ WHAT TO ADVISE PATIENTS?

Studies support 2 major themes:

- Obesity and low cardiorespiratory fitness are risk factors for the development of heart failure

In patients with established heart failure, obesity is predominantly protective in patients with low fitness

TABLE 4

The obesity paradox: What we know and what we don't

Setting	Established study findings	Current limitations	Research questions
Patients with heart failure	BMI appears to be protective predominantly in patients with low fitness.	Different obesity classes have not been specifically evaluated. No separate evaluation of patients with either preserved or mid-range ejection fraction; they are largely grouped with reduced ejection fraction.	Is cardiorespiratory fitness an obesity paradox modifier in specific classes of obesity? Is cardiorespiratory fitness an obesity paradox modifier in HFpEF and HFmrEF?
Heart failure prevention	Improving cardiorespiratory fitness may be more important for risk reduction than lowering BMI. In patients with established diabetes, improved fitness may decrease the risk of developing HFpEF. Increasing BMI and specific measures of adiposity correlate with increased risk of developing heart failure. Even small amounts of physical activity decrease risk of developing heart failure. Physical activity appears to have a dose-dependent effect on heart failure risk, with the lowest risk associated with highest frequency of physical activity.	No differentiation between types or duration of physical activity. Limited specificity of type of heart failure as end point (ie, HFpEF, HFmrEF, or HFrEF). Women underrepresented.	What type of physical activity leads to the lowest risk of heart failure development? How do BMI and cardiorespiratory fitness (and interventions) affect development of different types of heart failure? Are findings relevant for women?
Weight loss	Either surgical or lifestyle-based weight loss may reduce morbidity from heart failure. Unintentional weight loss indicates acute illness and contributes to poor metabolic reserve, leading to worse outcomes.	Lack of clinical outcomes data after intentional weight loss for patients with heart failure and obesity. Limited data on specific exercise training programs in heart failure outcomes or prevention.	How does medical vs surgical weight loss affect heart failure morbidity and mortality rates, particularly with newer medical therapies for obesity? How does supervised exercise for patients with heart failure and obesity affect fitness, weight loss, and outcomes?

BMI = body mass index; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction

- Obesity in people with low fitness is protective for those with established heart failure.

How can clinicians use this knowledge to advise patients regarding weight loss and exercise training? The answer is unclear. The most recent American and European heart failure guidelines give only limited guidance on obesity management in patients with established

heart failure.^{44,45} A 2018 position paper from the Heart Failure Association of the European Society of Cardiology advocates cardiopulmonary exercise testing only for assessing the risk of heart failure.⁴⁶

Bottom line: Advise to increase fitness and consider weight loss

Although large-scale clinical trials are needed to better assess and define the risks and ben-

efits of weight loss in patients with heart failure, particularly in those with reduced ejection fraction, recommending moderate weight loss may be appropriate. Lifestyle interventions aimed at weight loss and improving cardiorespiratory fitness—such as with a phase 2 (outpatient) cardiac rehabilitation program—should be considered, as studies suggest they reduce heart failure risk by improving fitness in patients with obesity and heart failure. And no data suggest harm.

For heart failure prevention, weight loss through dietary and lifestyle changes can be recommended, given that evidence shows a lower BMI predicts reduced risk of heart failure development. In patients with established heart failure and reduced ejection fraction, it appears that intentional weight loss through lifestyle modification or bariatric surgery may be beneficial,³⁵ although unintentional weight loss appears to be detrimental.³⁶ Thus, when advising weight loss to obese patients with heart failure, it is important to consider the individual's clinical profile.

FUTURE DIRECTIONS FOR RESEARCH

Understanding the overlapping impact of obesity and cardiorespiratory fitness in heart failure is important to identify gaps in evidence and assess future research directions (Table 4).

A high priority for future studies is to better evaluate the impact of obesity on different heart failure phenotypes. Distinct pathophysiologic differences exist between heart failure with reduced, mid-range, or preserved ejec-

tion fraction, with each responding differently to therapeutic interventions. Grouping all patients with heart failure together in analyses may blur results. Current literature has consistent findings in reduced ejection fraction, but dedicated analyses of preserved and mid-range ejection fraction are needed.

Similarly, it is likely that there are certain BMI thresholds where the protective effects of obesity become deleterious, but different obesity classes are commonly considered together in studies. Future research should examine if fitness modifies the obesity paradox in heart failure when assessing individuals with class II (BMI 35–39.9 kg/m²) or class III (> 40 kg/m²) obesity.

Other major gaps in evidence include the specific weight reduction interventions that result in better heart failure outcomes in patients with obesity. Metabolic surgery has been studied the most. How do pharmacological therapies compare? How do supervised exercise programs (particularly cardiac rehabilitation) impact risk in patients with established heart failure? Which is more important, weight loss or increased cardiorespiratory fitness? Future studies should assess relative risk reduction of specific exercise training combined with metabolic surgery or pharmacotherapy-induced weight loss in patients with heart failure.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: Luke J. Laffin, MD, Section of Preventive Cardiology and Rehabilitation, JB-1, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; laffinl@ccf.org