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The Obesity Paradox and Cardiovascular Disease

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Abstract Obesity is increasingly recognized as a global pandemic that threatens the health of millions of people. Obesity is considered to be an important cardiovascular risk factor, but there is increasing evidence that patients with elevated body mass index may be better off than others if they develop cardiovascular or renal disease. This phenomenon has been described as the "obesity paradox" or "reverse epidemiology." This article reviews some recent publications that have studied this phenomenon as it relates to heart failure, coronary artery disease, peripheral arterial disease, kidney disease, and a cohort of patients undergoing nonbariatric surgery.

Keywords BMI · CVD · Hypertension · Heart failure · Coronary heart disease · Dyslipidemia · Metabolic syndrome · Reverse epidemiology

Clinical Trial Acronyms

CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines Quality Improvement Initiative
INVEST	International Verapamil
SR	Trandolapril study.

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Introduction

Over the past decade, obesity in adults and in children has been increasingly recognized as a growing problem, and some have suggested that we have a pandemic of obesity that continues to trend upward, especially in Western countries. Obesity has been recognized as a major risk factor for the development of cardiovascular disease (CVD), hypertension, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, and the development of the metabolic syndrome. Despite the adverse associations with cardiovascular risk factors, numerous studies have now been published documenting an obesity paradox, in which overweight and obese people have a better prognosis than normal-weight or thin individuals [1]. Death from coronary artery disease has been declining, perhaps owing to better control of risk factors such as cholesterol levels and smoking, as well as improved treatments [2, 3]. This article reviews some of the most recent studies published concerning the obesity paradox.

Heart Failure and the Obesity Paradox

Habbu et al. [4] reviewed data from eight studies published between 2001 and 2005 regarding obesity and mortality in heart failure patients. Their thorough review pointed towards a U-shaped relationship between body mass index (BMI, expressed in kg/m^2) and survival in heart failure patients, with poor survival in both cachectic patients (BMI <21.5) and patients with severe obesity (BMI >34.1). They also suggested that the very concept of the obesity paradox may be driven by deleterious effects of cachexia, not salutary effects of obesity. They pointed out that the diagnosis of heart failure in some studies was based on clinical variables

and may not be completely accurate; the obese patients in these studies may actually have been healthier than the nonobese groups [4].

Fonarow et al. [5••] reviewed data from 108,927 hospitalizations in the Acute Decompensated Heart Failure National Registry to assess the relationship of BMI to inhospital mortality. Patients with BMI between 16 and 23.6 had the highest inpatient mortality. Furthermore, the mortality in patients with a BMI of 27.8 to 33.3 was significantly lower than the mortality in patients with a BMI between 23.7 and 27.7. The study is particularly interesting in that an obesity advantage was observed even in acutely decompensated heart failure patients during a short period of hospitalization. It was worth noting that the patients with higher BMI were younger and had more comorbidities, including diabetes.

As a possible explanation for these findings, Fonarow et al. [5••] proposed that heavier patients may be presenting earlier with worse symptoms but less advanced disease state than patients with lower BMI. Patients with higher BMI were less likely to have systolic failure than patients with lower BMI. Patients with healthy weight may not have adequate nutritional stores or metabolic reserves to overcome the metabolic demands and catabolic stress resulting from an acute exacerbation of heart failure. But, because obese patients were at an even lower risk than overweight patients, adequate nutritional stores may not explain the survival advantage of obese patients. It was suggested that increased adiposity and serum cholesterol levels serve as scavengers to bind and neutralize circulating lipopolysaccharides and bacterial endotoxin. Other questions need further study: Do elevated adiponectin levels in patients with decreased BMI play a role in the process? Is there a role for increased catecholamine response to stress in lean individuals that puts them at higher risk than the decreased catecholamine response seen in overweight and obese individuals? Could there be differences in pharmacokinetics between lean and obese patients that put lean patients at a disadvantage? Are there other conventional risk factors that have a paradoxical association with clinical outcomes? Can a therapeutic approach in providing acute nutritional and metabolic support for patients have a favorable impact on inhospital mortality of patients with acute decompensated heart failure?

In a recent meta-analysis of nine observational studies including heart failure patients, Oreopoulos et al. [6] compared all-cause mortality with BMI and found that overweight (BMI 25–29.9) and obese (BMI >30) patients had a more favorable prognosis than those who were either underweight or normal weight. Both overweight and obese patients were found to have lower all-cause and cardiovascular mortality than patients with BMI < 25.

Arena et al. [7] observed 1160 patients after cardiopulmonary exercise testing for a mean period of 30 months to assess the influence of heart failure etiology on the prognostic ability of BMI categories. These authors were interested in comparing patients with ischemic and nonischemic heart failure according to body weight to see whether weight contributed to the long-term prognosis. Patients were divided into three groups according to BMI: obese (BMI >30), overweight (BMI 25–29.9) and normal weight (BMI 18.5–24.9). Patients classified as obese had dramatically better survival regardless of heart failure etiology. Survival characteristics were similarly poor for both overweight and normal-weight patients in the ischemic subgroup. In contrast, both the obese and overweight patients fared better in the nonischemic subgroup. The study demonstrated that although heart failure risk and development increases with BMI, patients with increased BMI have much better survival once they have been diagnosed with heart failure regardless of etiology and differences in age, gender, and pharmacologic management.

The authors postulate that several physiologic mechanisms may explain the protective effect of a greater BMI in the presence of heart failure. They suggest that adipose tissue itself may counteract greater levels of circulating inflammatory markers such as tumor necrosis factor (TNF). Could lower adipose tissue levels in normal-weight and overweight patients be inadequate to provide favorable conditions in ischemic heart failure patients who have higher levels of inflammatory markers and oxidative stress? Is there a role for B-type natriuretic peptide, which is decreased in nonischemic heart failure patients compared with ischemic heart failure patients and which is decreased as BMI increases in patients with heart failure? It is uncertain whether favorable trends in prognosis with increasing BMI extend into the morbidly obese group, because they were underrepresented in this study. The authors suggest that exercise-induced weight loss, which has been shown to favorably affect inflammatory cytokines and neurohormonal levels, may be beneficial and may result in optimal outcomes in patients with heart failure.

All of these studies in patients with heart failure confirm an improved prognosis in overweight and obese patients as compared with normal-weight and underweight patients. The issue of cardiac cachexia in the worse-off patients is seen as a confounder, but even when this is factored into the analysis, there seems to be a survival advantage for patients with increased BMI.

Hypertension and the Obesity Paradox

Uretsky et al. [8••] assessed 22,576 vigorously treated hypertensive patients with coronary artery disease (CAD)

over a 2.7-year follow-up for the risk of all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke in the INVEST study cohort. They classified patients into five groups according to their baseline BMI: less than 20 (thin), 20 to less than 25 (normal weight), 25 to 30 (overweight), 30 to 35 (class I obesity), and 35 or more (class II–III obesity). They found that overweight and obese patients had lower risk of all three major cardiovascular events, although it was noted that blood pressure reduction in obese patients was less than in normal-weight patients. The authors suggest that obesity may confer protective benefits in patients with known cardiovascular disease.

The study was a post hoc analysis limited by short-term follow-up, inadequate sample size in some of the age groups, and the younger age of obese patients compared with normal-weight patients. It raises many questions that need further elucidation. Is there a cardioprotective role of soluble TNF-α "antagonist" receptors produced by adipose tissue, which may neutralize the deleterious effects of TNF-α? Could the patients with higher BMI be seeking medical care earlier than their leaner counterparts because of their phenotype, leading to diagnosis of heart failure at an earlier stage? Could the hemodynamics of obesity play a role in their better outcomes by lowering systemic vascular resistance? What is the role of proinflammatory cytokines and inflammatory mediators released by adipose tissue? Because BMI is not a direct measure of body composition and does not reflect the body muscle content, which is reduced in patients with chronic diseases, would more accurate measures of body composition help to further stratify patients at greater risk? Would intentional weight loss and exercise programs help improve outcomes? Is waist-to-hip ratio a better predictor of outcomes? Are there racial and ethnic disparities in regard to the obesity paradox?

Lavie et al. [9] have suggested the possibility that obese, hypertensive patients have lower systemic vascular resistance as well as plasma renin activity, which may contribute to their better prognosis.

End-Stage Renal Disease and the Obesity Paradox

Kalantar-Zadeh et al. [10] examined a 2-year cohort of 54,535 maintenance hemodialysis patients using data collected by DaVita, Inc, one of the largest dialysis care providers in the United States. They were able to show that weight gain and elevated BMI were associated with reduced cardiovascular mortality in these patients, describing a reverse epidemiology in which obesity is paradoxically associated with improved survival.

Lea et al. [11] looked retrospectively at data regarding 74,167 Medicare patients treated for acute MI in terms of their risk of developing end-stage renal disease (ESRD) based on race and BMI class. Subsequently, patients who developed ESRD were reevaluated for race/mortality interaction. The study concluded that obesity does not independently increase risk of developing ESRD among blacks or whites in an elderly cohort with cardiovascular disease. However, both black and white obese patients with ESRD had better survival than their normal-weight counterparts. This study also questioned the validity of the use of BMI as an index of obesity, especially because BMI is not a good measure of fat; lean body mass is reduced in the elderly and in patients with chronic kidney disease.

Peripheral Arterial Disease and the Obesity Paradox

Galal et al. [12] reviewed 2392 patients who underwent major vascular surgery for peripheral arterial disease (PAD) and were at high risk for mortality during the follow-up period. At a mean follow-up of 4.37 years, they reported significantly better survival among the patients in the normal-BMI, overweight, and obese quartiles compared with an underweight quartile of patients. However, the prevalence of chronic obstructive pulmonary disease (COPD) was 46.4% in this cohort of patients, and when the severity of COPD was added to the multivariate analysis, the relationship between low BMI and mortality was almost completely explained by a high prevalence of moderate to severe COPD. The inverse relationship between BMI and mortality stayed statistically significant in the overweight and obese groups, however.

This study is important in that it demonstrated that the obesity paradox occurs in patients with PAD but also showed that COPD may be an important contributing factor for increased mortality, especially in the underweight PAD patient. These authors also pointed out that smoking is a significant cause of PAD, as well as of COPD. It is noteworthy, however, that correction for smoking and COPD did not explain why the overweight and obese patients did better than the underweight group.

Obesity and Cardiovascular Risk

Strandberg et al. [13••] followed the longitudinal cohort from the Helsinki Businessmen Study, consisting of 1114 patients from age 25 to old age and looked at BMI changes and their trajectory in relationship to all-cause mortality during midlife and old age. Patients who were overweight were found to have higher mortality during midlife than normal-weight patients. However, when the patients were evaluated in their old age, men who were overweight during midlife but became normal-weight in old age had

twofold increased mortality risk compared with the constantly normal-weight group. They found overall that lean men had better prognosis than overweight men when mortality before later life (midlife) is taken into account. Their study suggests that overweight or obesity in late life may be protective and beneficial, further supporting the concept of the obesity paradox.

In their excellent review, Lavie et al. [1] recognize the important role of obesity in the pathogenesis and progression of cardiovascular disease. They pointed out that, despite the obesity paradox, purposeful weight loss should be considered to prevent and treat cardiovascular disease.

Coronary Artery Disease and the Obesity Paradox

Hastie et al. [14] studied 4880 patients who underwent percutaneous coronary intervention (PCI) for CAD to investigate the impact of BMI on long-term all-cause mortality. The patients were observed for 5 years after the PCI. Patients with BMI of 27.5 to 30.0 were reported to have lower 5-year mortality than patients with BMI of 20 to 25, but there was no difference in mortality rates for patients with BMI of 25 to 27.5 and BMI greater than 30. The results of the study supported an obesity paradox: an inverse relationship was noted between BMI and mortality in patients undergoing elective PCI for established CAD. The association was U-shaped, with poorer survival in underweight patients.

The authors attribute this association to reverse causation, as underweight patients tend to be more malnourished and cachectic and have a higher prevalence of comorbid conditions such as malignancy and heart failure. In addition, underweight patients tend to be older. They also suggest that there may be a lead-time bias, in that patients with elevated BMI are investigated and treated at an earlier stage in the disease process. Although they found an increased prevalence of other cardiovascular risk factors such as diabetes and hypertension in patients with elevated BMI, the reduced risk was independent of these comorbid conditions, and its association with increased BMI was not attenuated by their inclusion in the model. It was also noted that periprocedural complications and mortality occurred more frequently in lean patients than in overweight or obese patients. It was suggested that waist-hip ratio may be a better measure to assess obesity than BMI. They point out that there could be a causal link between obesity and improved prognosis because low-density lipoproteins scavenge unbound circulating lipopolysaccharides and consequently have an anti-inflammatory effect. In addition, obese subjects have lower levels of TNF and other inflammatory cytokines.

Diercks et al. [15] looked at data from the CRUSADE initiative involving over 80,000 patients who were treated for non-ST-segment elevation (NSTE) acute coronary syndrome and found that overweight and obese patients were less likely to have adverse outcomes than normal-weight and underweight patients. These authors separated patients into six groups based on BMI: underweight (<18.5), normal-weight (18.5–24.9), overweight (25–29.9), obese I (30–34.9), obese II (35–39.9), and extreme obesity (>40). They also found that obesity seemed to be a risk factor for developing acute coronary syndrome at a younger age, which in turn was associated with more aggressive management, which may have been a factor in the improved outcomes of the overweight and obese groups.

Cardiac Rehabilitation and the Obesity Paradox

Most recently, Lavie et al. [16••] retrospectively studied 529 patients with preserved systolic function who were enrolled in a cardiac rehabilitation and exercise training (CRET) program following major coronary events. During their 3-year follow-up, overall mortality trended only slightly lower in patients who were overweight or obese at baseline and had more weight loss. However, total mortality on follow-up was considerably lower in baseline overweight/obese patients (1.8% in those with baseline BMI >35) than in 136 CRET patients with baseline BMI less than 25 (13.2%), as well as in those with higher baseline fat content. An obesity paradox was noted regardless of whether patients were classified as obese by BMI categories or by percentage of body fat determined by skinfold measurements (>25% in men and >35% in women). The study results demonstrated the safety and potential long-term benefits of purposeful weight loss and exercise training in overweight and obese patients with CVD.

Nonpurposeful weight loss before study entry was not accounted for or specifically measured. The study was not controlled for COPD, but few patients were actively smoking. Lower circulating B-type natriuretic peptide associated with obesity may cause obese patients to present earlier with dyspnea and less severe disease as a result of sodium and fluid retention.

Nonbariatric Surgery and the Obesity Paradox

Mullen et al. [17] prospectively conducted a multi-institutional study of 118,707 patients undergoing nonbariatric surgery. Looking at all-cause mortality over a 30-day postoperative period, the study concluded that after adjusting for all perioperative risk factors, the extremes of underweight status (BMI <18.5) or morbid obesity remained important risk factors for 30-day mortality, whereas overweight status

(BMI 25.1–30.0) and obesity class II were protective. A reverse J-shaped relationship was observed for the risk of complications and death, with the highest rates in the two extremes of BMI and the lowest rates in the overweight and moderately obese groups. The study confirmed the existence of an "obesity paradox" in the short term in patients undergoing nonbariatric general surgery.

The study is both significant and generalizable to the population at large in that it is well powered: of the more than 110,000 patients, more than 41,000 were obese and more than 9000 were morbidly obese. The reverse J-shaped relationship between BMI and 30-day mortality persisted even after adjustments were made for risk factors such as diabetes, hypertension, COPD, and cancer-related variables. In light of the poor outcome of underweight patients, the authors suggest that underweight patients with low albumin and recent weight loss should receive perioperative nutritional supplementation in an effort to build up nutritional reserves and reduce postoperative mortality. Other than increased minor wound infections, obesity was not found to have any impact on complications (eg, MI, pneumonia, thromboembolic phenomena).

Mullen et al. [17] suggest that because the obese state is characterized by low-grade, chronic inflammation in which the white adipose tissue and adipose tissue–derived macrophages secrete a whole host of "adipokines" and cytokines such as TNF-α, interleukin (IL)-1, and IL-6, that the patient is "primed" and adapted for responding appropriately to injury and tissue repair subsequent to major surgery. In addition, patients with elevated BMI have sufficient nutritional reserves, so they function in a more efficient metabolic state and can mount the appropriate inflammatory (immune) response to the stress of surgery. On the other hand, these authors point out that individuals at the extremes of the weight spectrum are inefficient in their use of energy or lack thereof, leading to inadequate and inappropriate responses to the inflammatory and oxidative stress, resulting in further metabolic dysfunction and immunosuppression and more adverse outcomes.

Mortality and the Obesity Paradox

The Prospective Studies Collaboration [18••] pooled data from 57 studies to analyze outcomes relating BMI to mortality and causes of mortality in nearly 900,000 people. In contrast to the many reports of an obesity paradox, this study found that overall mortality was lowest in individuals with a BMI between 22.5 and 25 kg/m^2 in both sexes and at all ages. They also noted that for each 5 kg/m^2 increase above the ideal range, mortality risk increased by 20% to 120%, depending on the specific disease. This large study does put into question reports of the obesity paradox. Could it be that many of the studies reporting an obesity paradox are not adequately powered because of small sample size or short follow-up periods? The study also noted that the inverse association between COPD and BMI may be due to reverse causality, in that low BMI was an indicator of worsening COPD.

In 2005, Thomas et al. [19] evaluated a large cohort of French patients (139,562 men and 104,236 women) in terms of cardiovascular mortality and obesity and followed them for an average of 14 years. In age-adjusted analyses, increasing BMI was strongly associated with increased cardiovascular mortality, but after adjusting for cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes, the association became nonsignificant. The study found that the presence of hypertension was the most important determinant that led to increased mortality from CVD among overweight men and women. Their study also showed that cardiovascular mortality dramatically increased in overweight subjects if the hypertensive patients also had hypercholesterolemia and diabetes, but it did not increase if hypertension was not involved. A J-shaped curve between BMI and all-cause mortality was observed, particularly in men. The study did not negate the existence of the obesity paradox in the French population but reaffirmed that hypertension associated with increasing BMI was a strong predictor of increased cardiovascular mortality.

These two population studies are adequately powered and seem to affirm the traditional view that obesity is associated with increased morbidity and mortality. It is not clear to us why the Prospective Studies Collaboration was not able to detect evidence of the obesity paradox.

Conclusions

The studies discussed offer several possible explanations for the phenomenon of the obesity paradox:

- TNF-α receptors are increased in adipose tissue, which in turn may help to neutralize increased circulating levels of TNF-α during periods of stress and inflammation, which have deleterious effects on the myocardium; on the other hand, TNF-α levels are elevated in lean patients.
- Obese individuals generally present earlier, so disease states may be recognized and treated earlier.
- The hemodynamics of obesity hypertension are characterized by higher cardiac output, increased blood volume, and decreased systemic vascular resistance, factors that may contribute to decreased mortality in obese patients with cardiovascular disease. Anatomically obese patients have higher coronary calcium scores,

whereas normal-weight patients have a significantly higher percentage of high-risk coronary anatomy.
- BMI may not be the most accurate index for obesity.

Several pitfalls should be noted:

- In most of the studies, patients with higher BMI were much younger than their normal-weight counterparts.
- Obese patients may have benefited from lead-time bias, as they tend to present earlier and thus are investigated and treated earlier.
- Clinical criteria for diagnosing heart failure in obese patients may not be accurate.
- Increased use of standard therapy—β-blockers, renin-angiotensin aldosterone system (RAAS) inhibitors, and lipid-lowering agents—were found among higher-BMI patients.
- Increased incidence of hypotension, pulmonary edema, renal impairment, and vascular complications was found in lean patients.
- BMI may not be the most accurate index for obesity, and subcutaneous fat measurement by means of skin-fold thickness may not be an accurate index of fat.
- Data and results reported regarding patients with BMI greater than 35 kg/m^2 have been minimal.
- The obesity paradox may just be an overrepresentation of cachexia.
- Obese patients have higher baseline blood pressure, lesser reduction in blood pressure, and more use of medications.
- No randomized, controlled trial is yet available.

Most of the studies we have reviewed confirm the existence of an obesity paradox across diverse populations in cohorts of heart failure, hypertension, CAD, chronic kidney disease, and PAD, and obesity appears to improve outcome in patients undergoing general surgery. How should we proceed? Is purposeful weight loss to be recommended to our patients in light of survival benefits of increased BMI? On the other hand, purposeful weight loss is associated with favorable cardiovascular prognosis; it has been shown to improve left ventricular systolic and diastolic function and to reduce risk factors for coronary heart disease. As underlying mechanisms for the obesity paradox or reverse epidemiology are further investigated, purposeful weight loss with caloric restriction and exercise training, which does not reduce lean body mass, should be encouraged for the primary and secondary prevention of cardiovascular disease [20].

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