Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 63, No. 14, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.01.022

STATE-OF-THE-ART PAPERS

Obesity and Cardiovascular Diseases

Implications Regarding Fitness, Fatness, and Severity in the Obesity Paradox

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Obesity has been increasing in epidemic proportions, with a disproportionately higher increase in morbid or class III obesity, and obesity adversely affects cardiovascular (CV) hemodynamics, structure, and function, as well as increases the prevalence of most CV diseases. Progressive declines in physical activity over 5 decades have occurred and have primarily caused the obesity epidemic. Despite the potential adverse impact of overweight and obesity, recent epidemiological data have demonstrated an association of mild obesity and, particularly, overweight on improved survival. We review in detail the obesity paradox in CV diseases where overweight and at least mildly obese patients with most CV diseases seem to have a better prognosis than do their leaner counterparts. The implications of cardiorespiratory fitness with prognosis are discussed, along with the joint impact of fitness and adiposity on the obesity paradox. Finally, in light of the obesity paradox, the potential value of purposeful weight loss and increased physical activity to affect levels of fitness is reviewed. (J Am Coll Cardiol 2014;63:1345–54)

Obesity has been increasing in epidemic proportions in both adults and children over many decades, and recently, the proportion of the population with more severe, or morbid, obesity has increased to a greater extent than has overweight and mild obesity (1–3). Currently, nearly 70% of adults are classified as either overweight or obese as compared with fewer than 40% just 40 years ago (3). One can argue about the impact of overweight and mild obesity on overall prognosis particularly without accounting for levels of cardiorespiratory fitness (fitness). Nevertheless, very recent high-profile data have suggested obesity may account for nearly 20% of overall mortality (4).

There are numerous adverse effects of overweight and obesity on general and cardiovascular (CV) health (3). Clearly, obesity worsens most of the major CV risk factors, including plasma lipids, blood pressure, glucose, inflammation, and places a "heavy" burden on the heart, negatively affecting ventricular structure and systolic and diastolic ventricular function (3,5,6). Not surprisingly, obesity is associated with the prevalence of most CV diseases, including hypertension, coronary heart disease (CHD), heart failure (HF), and atrial fibrillation (AF) (3,5). Nevertheless, substantial data, mostly published during the last decade, have demonstrated an "obesity paradox," where obese patients generally have a better short- and long-term prognosis than do their leaner counterparts with the same CV diseases (3,5).

This state-of-the-art paper briefly reviews the pathophysiology/hemodynamics of obesity, discusses possible causes of the obesity epidemic, and reviews the changing landscape of obesity on survival in the general population and in those with CV diseases, including hypertension, CHD, HF, and AF. Additionally, we discuss the impact of severe or morbid obesity on prognosis, especially in light of the obesity paradox noted at least in overweight and mildly obese patients with CV diseases. We also discuss the role of cardiorespiratory fitness (fitness) compared with fatness, and implications of fitness in the obesity paradox. Finally, we briefly review the impact of purposeful weight reduction on prognosis, especially considering the obesity paradox.

CV Pathophysiology/Hemodynamics

Overweight and obesity have many adverse effects on hemodynamics and CV structure and function (Fig. 1, Table 1) (5), which have been reviewed in detail elsewhere

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Manuscript received October 9, 2013; revised manuscript received December 17, 2013, accepted January 6, 2014.

JACC Vol. 63, No. 14, 2014
April 15, 2014:1345–54

Abbreviations and Acronyms

AF = atrial fibrillation
BF = body fat
BMI = body mass index
CHD = coronary heart disease
CV = cardiovascular
HF = heart failure
LV = left ventricle/ventricular
MET = metabolic equivalent

(3,5). Obesity certainly increases total blood volume, stroke volume, and cardiac output, so typically, systemic vascular resistance in obesity is reduced for any given level of blood pressure. Although most of the increases in cardiac output in obesity are due to high stroke volume (because heart rate is typically not increased), occasionally, heart rate may be slightly increased as a result of increased activation of the sympathetic nervous system. The Frank-Starling curve in obesity is often shifted to the left as a result of increases in filling pressure and volume, which increases CV work, also leading to left ventricular (LV) changes with dilation and LV hypertrophy. Additionally, obesity can lead to enlargement of the left atrium, not only from the increased circulating blood volume, but also from alterations in LV diastolic filling (5,7). From multiple mechanisms, obesity has adverse effects on both systolic and, especially, diastolic ventricular function (8).

Etiologies of Obesity and Energy Balance

During recent years, the origins of the obesity epidemic have been in considerable dispute (9,10). Regardless of this debate, it is widely accepted that increments in body weight and overall adiposity, at the most fundamental level, are the result of chronic positive energy balance (i.e., energy expenditure < energy intake) (11,12). There has been a number of studies suggesting that energy or food intake is largely, if not completely, responsible for the obesity epidemic, essentially blaming much of the obesity epidemic in the Westernized world on poor dietary choices (13–15). One of the arguments to support this theory is that time spent in leisure-time physical activity has remained essentially unchanged in recent decades, thus leading to the conclusion that obesity is solely due to excessive energy or caloric intake (11). However, leisure-time physical activity represents a relatively small portion of total time per week, which is much more affected by occupation-related activity and household management energy expenditure.

Recently, we have demonstrated very marked declines in occupation-related physical activity during the last 5 decades (Fig. 2) (11), with similar declines in household management energy expenditure in women during this same time (Fig. 3) (12,16). In fact, the typical woman now has an energy expenditure that is more than 1,800 calories/week less than that of 5 decades ago (12). Considering the fact that generally 100 calories are burned for every mile traveled by foot, the typical woman would have to walk or run over 18 miles/week to make up for this loss of household management energy expenditure. This suggests that reductions in occupation-related activity and energy expenditure, similar to household management energy expenditure in women, largely explain the marked increased prevalence in obesity noted during recent decades (Fig. 4) (11).

Importantly, because voluntary physical activity (e.g., housework, exercise) is the only major modifiable component of total daily energy expenditure, these significant reductions are independent of the relatively nonmodifiable components of total daily energy expenditure such as resting metabolic rate (17), thermic effect of food (18), and non-exercise activity thermogenesis (19,20).

Table 1 Effects of Obesity on Cardiac Performance

Hemodynamics
Increased blood volume
Increased stroke volume
Increased arterial pressure
Increased LV wall stress
Pulmonary artery hypertension
Cardiac structure
LV concentric remodeling
LV hypertrophy (eccentric and concentric)
Left atrial enlargement
RV hypertrophy
Cardiac function
LV diastolic dysfunction
LV systolic dysfunction
RV failure
Inflammation
Increased C-reactive protein
Overexpression of tumor necrosis factor
Neurohumoral
Insulin resistance and hyperinsulinemia
Leptin insensitivity and hyperleptinemia
Reduced adiponectin
Sympathetic nervous system activation
Activation of renin-angiotensin-aldosterone system
Overexpression of peroxisome proliferator-activator receptor
Cellular
Hypertrophy
Apoptosis
Fibrosis

Adapted with permission from Lavie et al. (5).
LV = left ventricular; RV = right ventricular.

The Changing Landscape of Obesity

Recently, scientists have debated the impact of overweight and obesity on overall chronic disease, including all-cause mortality (21). In fact, it has been recently argued that obesity is accounting for almost 1 in 5 deaths worldwide. (4) On the other hand, Flegal and colleagues (21) have performed a large meta-analysis of 97 studies in nearly 2.9 million people. They demonstrated that obesity, defined by standard body mass index (BMI) criteria ($\geq$30 kg/m^2), when considering all grades, was associated with a significantly increased risk of mortality compared with normal BMI (18.5 to 25 kg/m^2). However, the optimal survival occurred at the

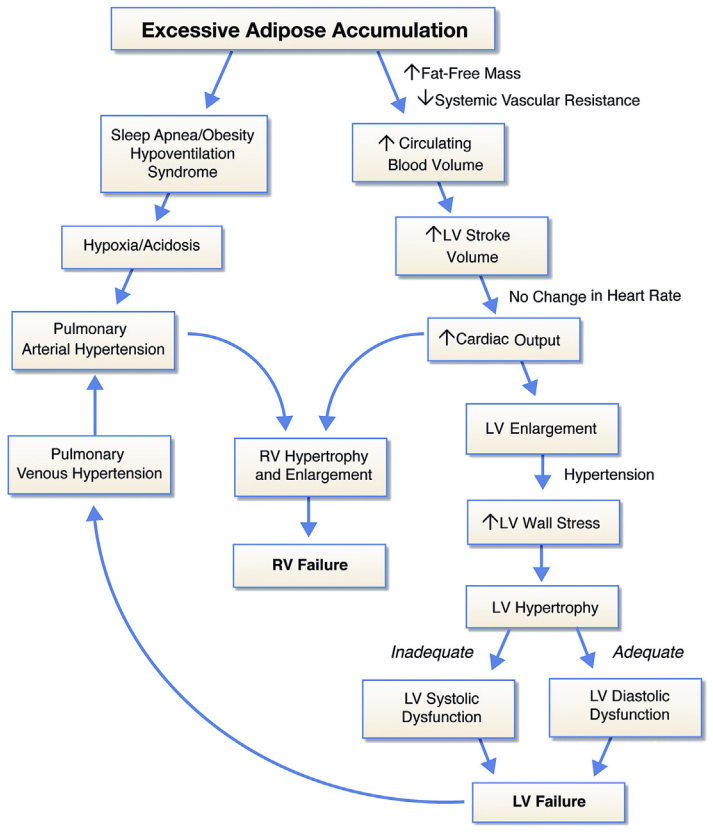


Figure 1 **Pathophysiology of Obesity Cardiomyopathy**

This diagram shows the central hemodynamic, cardiac structural abnormalities, and alterations in ventricular function that may occur in severely obese patients and predispose to heart failure. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. In uncomplicated (normotensive) severe obesity, eccentric LV hypertrophy predominates. In severely obese patients with long-standing systemic hypertension, concentric LV hypertrophy is frequently observed and may occur more commonly than eccentric LV hypertrophy. Whether and to what extent metabolic disturbances such as lipotoxicity, insulin resistance, leptin resistance, and alterations of the renin-angiotensin-aldosterone system contribute to obesity cardiomyopathy in humans is uncertain. RV = right ventricular. Adapted with permission from Lavie et al. (5).

overweight BMI (25 to 30 kg/m^2); these patients had a statistically significant 6% lower mortality than did the normal BMI cohort. Additionally, the mildly obese or class I obese (BMI: 30 to 35 kg/m^2) patients, had a 5% lower mortality than did the normal BMI group, although this did not reach statistical significance. The adverse effects of higher BMI on mortality are particularly noted in younger cohorts, whereas higher BMI appears to be more protective in older cohorts (22). Nevertheless, as mentioned previously, the prevalence of more extreme degrees of obesity seem to be increasing more so than is the prevalence of overweight and mild obesity (1,2). In the Flegal et al. meta-analysis (21), the contribution of class II obesity (BMI: 35 to 40 kg/m^2) and class III obesity (BMI: $\geq$40 kg/m^2) exists and appears particularly ominous, especially considering the fact that class III or "morbid" obesity has been markedly increasing, now approaching 3% prevalence in the United States (1–3). Clearly, efforts to prevent and reverse these severe degrees of obesity are needed, whereas the data to support intervention in overweight and mild obesity are less evident.

Obesity Paradox

Despite the adverse impact of overweight and obesity on most of the CV risk factors, as well as increasing the prevalence of most CV diseases, numerous studies during the past decade demonstrate a clear obesity paradox, where overweight and obese patients with CV diseases have a better prognosis than do their leaner counterparts (3). The mechanisms for this paradox are difficult to reconcile, but several potential mechanisms are listed in Table 2. Additionally, it has been argued that BMI, the typical method used to assess obesity, has a poor diagnostic performance to identify obesity in the general population and also in cohorts with CHD (23–26), which may explain some, although not all, of the paradoxes listed in this review. Therefore, we also briefly review the impact of other assessments of obesity, including waist circumference and body fat (BF).

Hypertension. Obese patients have a higher prevalence of hypertension compared with lean subjects, and obesity adversely affects CHD risk factors and leads to increased prevalence of LV hypertrophy, independent of arterial

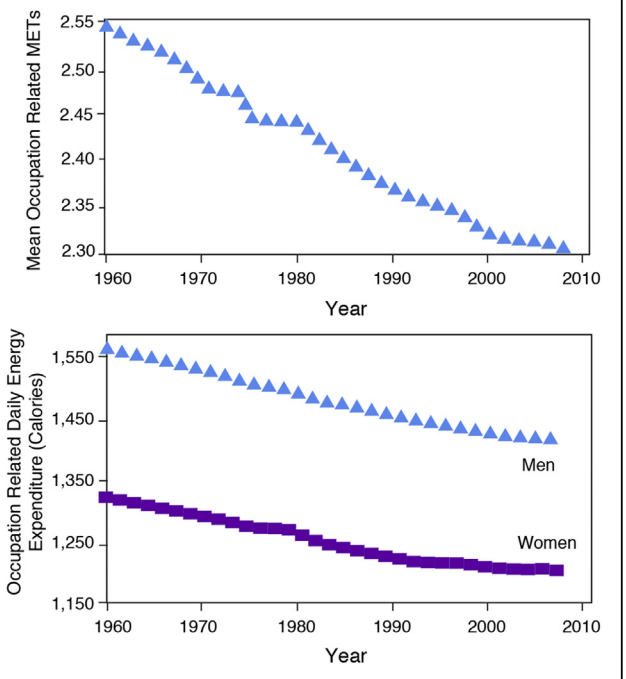


Figure 2 Occupational METs and Energy Expenditure Since 1960

The **upper panel** plots the mean occupation-related metabolic equivalents (METs) since 1960, and the **lower panel** presents the mean occupational daily energy expenditure in men and women since 1960. Reproduced with permission from Church et al. (11).

pressure. However, several studies demonstrate an obesity paradox in hypertensive subjects. The largest of such studies is from Uretsky et al. (27), who investigated the effects of obesity on outcomes in 22,576 patients with treated hypertension and with known CHD. Despite an overall worse control of blood pressure during a 2-year follow-up, all-cause mortality was 30% lower in overweight and obese hypertensive patients compared with their lean counterparts. Other studies have either demonstrated the same finding or demonstrated a U-shaped relationship between BMI and all-cause, CV, and non-CV mortality, being that excess mortality was noted at both extremes of BMI (3). Certainly, overweight and mildly obese hypertensive patients seem to have a better prognosis than their leaner counterparts.

Coronary heart disease. Obesity plays a major role in adversely affecting CHD risk factors and increasing the prevalence of CHD (3), although some studies indicate that CHD may not be increased in "metabolically healthy" obesity (28–31). Nevertheless, as with hypertension, many studies using various measures of adiposity, including BMI (32–41), % BF (33–35), and some even with central obesity or waist circumference (34), have demonstrated an obesity paradox in CHD. Romero-Corral et al. (32) performed a meta-analysis of 40 cohort studies in more than 250,000 patients with CHD and reported that overweight and obese CHD patients have a lower risk of total and CV mortality compared with underweight and normal-weight CHD patients. However, those authors demonstrated that in patients with class II obesity (BMI: 35 to 40 kg/m^2), there was an

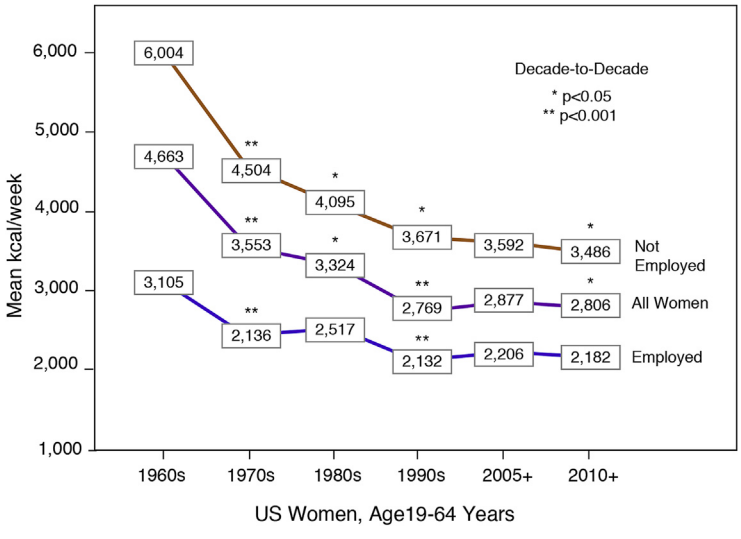


Figure 3 Household Management Energy Expenditure per Week

This figure depicts the decade-to-decade change in household management energy expenditure per week for all women and by employment status. Reproduced with permission from Archer et al. (12).

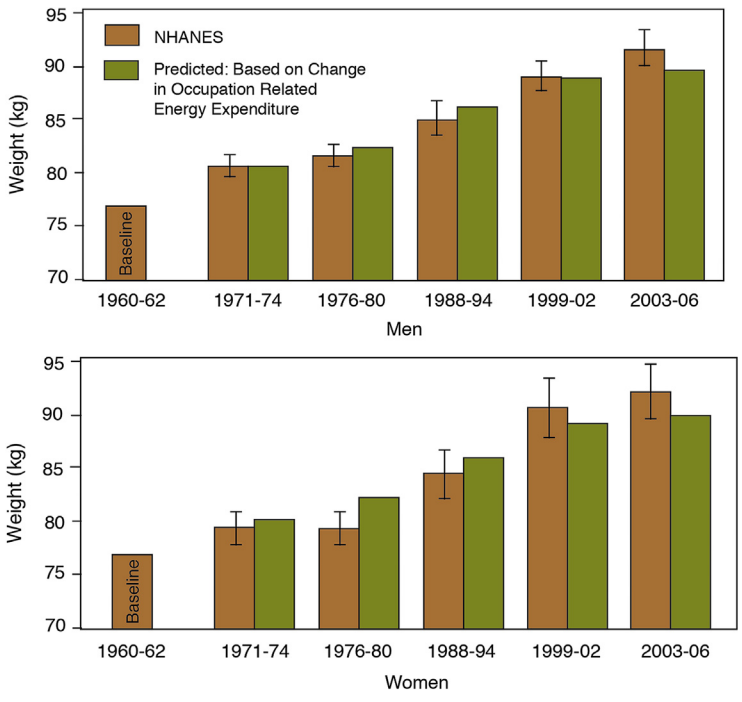


Figure 4 **Predicted Weights and NHANES Weights**

This figure presents the energy balance model–predicted mean U.S. bodyweight based on change in occupation-related daily energy expenditure since 1960 compared with mean U.S. weight gain based on the National Health and Nutrition Examination Survey (NHANES) examination periods for 40- to 50-year-old men **(top)** and women **(bottom)**. Reproduced with permission from Church et al. (11).

excess risk of CV mortality without any increase in total mortality. Recently, some studies have demonstrated an increased risk in CHD patients with "normal weight obesity" and "normal weight central obesity", in which % BF or waist circumference, respectively, is high, although BMI is in the normal range (31,36,37), whereas others have only demonstrated this finding in those with low fitness (discussed in the following text) (34).

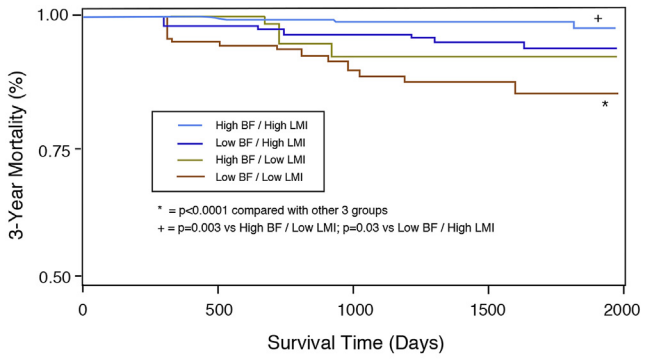
Several recent studies have raised the possibility that the association with lower adiposity and worse outcomes in CHD may represent as much as a "lean paradox" as an obesity paradox (33,35,38,39). We have demonstrated this obesity paradox with low BF (defined as <25% in men and <35% in women) and low BMI (33,40), and both low BF and low BMI are independent predictors of worse outcomes. However, in a study of 581 patients with CHD, we demonstrated that only those with low BMI (<25 kg/m^2) and low BF had a high mortality rate compared with the other groups (33). Most recently, we demonstrated that both low BF and low lean mass (or nonfat mass) is associated with the worst survival, patients with both high lean mass and BF had the best survival, whereas intermediate survival rates were noted in the other groups (Fig. 5) (35). Other studies demonstrate that this may represent more of an "overweight paradox," where overweight CHD patients do particularly well compared with lean (38,39).

Therefore, in CHD, it appears that there is a strong obesity paradox, particularly with BMI, but also with BF and central obesity, with the best prognosis noted in overweight CHD patients, as opposed to those with more severe obesity (41).

Heart failure. Because obesity causes marked abnormalities in LV structure and function (3,5), the increase in the prevalence of HF with obesity is not surprising. Kenchaiah et al. (42) studied 5,881 Framingham Heart Study participants and demonstrated a 5% increase in HF prevalence in

Table 2 **Potential Reasons for the Obesity Paradox in Cardiovascular Diseases**

1.	Nonpurposeful weight loss
2.	Younger age at presentation
3.	Lower prevalence of smoking
4.	Greater metabolic reserves
5.	Less cachexia
6.	Lower atrial natriuretic peptides
7.	Attenuated response to renin-angiotensin-aldosterone system
8.	High blood pressure, allowing for more cardiac medications
9.	Differing etiology, associated with a better prognosis
10.	Increased muscle mass and muscular strength
11.	Implications regarding cardiorespiratory fitness
12.	Unmeasured confounding factors



High %BF High LMI	276	234	167	96	7
Low %BF High LMI	179	165	128	71	11
High %BF Low LMI	53	44	33	21	5
Low %BF Low LMI	62	58	40	25	7

Figure 5 **Body Composition and CHD Survival**

Three-year survival based on body composition: low and high body fat (BF) and low and high lean mass index (LMI). Mortality was highest in the low BF/low LMI group (15%, or 9 of 62), followed by the high BF/low LMI group (5.7%, or 3 of 53), low BF/high LMI group (4.5%, or 8 of 179), and high BF/high LMI group (2.2%, or 6 of 270). CHD = coronary heart disease. Reproduced with permission from Lavie et al. (35).

men and a 7% increase in women for every 1 kg/m^2 increase in BMI, with the risk of HF increasing across the entire spectrum of BMI. However, in a study of 550 subjects without diabetes, increased BMI was not associated with increased risks of HF, whereas metabolic syndrome increased the risk of HF by 2.5-fold. (43) In this study, in contrast to normal weight patients with metabolic syndrome, metabolically healthy obese subjects had a decreased HF risk in a 6-year follow-up. However, a recent study from Norway demonstrated that in contrast to CHD, metabolically healthy obese patients still had an increased risk of HF (29). Alpert et al. (44) demonstrated a very strong relationship between morbid obesity and HF prevalence.

The obesity paradox in HF has recently been reviewed in detail (5). In a meta-analysis of observational HF studies (N = 28,209), Oreopoulous et al. (45) demonstrated that compared with patients with normal BMI, overweight and obese HF patients had reductions in CV (−19% and −40%, respectively) and total mortality (−16% and −33%, respectively) during an average 2.7-year follow-up. The obesity paradox in HF has been demonstrated with BMI, % BF, and with waist circumference or central obesity (5,46–48).

Atrial fibrillation. As with obesity, the prevalence of AF has been increasing and is expected to increase by 2.5-fold during the next 30 years (3). The increase in AF may be partly due to the obesity epidemic, with its adverse hemodynamic effects and the impact on LV and left atrial structure and function (3,7). In a meta-analysis of 16 studies of more than 120,000 patients, Wanahita et al. (49) demonstrate that obese patients had a 50% increased risk of developing AF. However, as in patients with hypertension, CHD, and HF, overweight and obese patients with AF have a considerably better prognosis than do those patients with normal BMI (3).

Impact of Morbid Obesity

The prevalence of morbid or class III obesity (BMI ≥40 kg/m^2) has been dramatically increasing, and is now present in close to 3% of the United States population (1,2). Although an obesity paradox exists, recent evidence suggests that this does not typically apply to more morbid obesity, where prognosis is adversely affected in acute CHD (50,51), CHD patients undergoing revascularization (52,53), including percutaneous intervention and coronary artery bypass grafting, as well as in patients with HF (54,55). This level of severe obesity is a major risk factor for development of CV diseases and is associated with poor prognosis when CV diseases become manifest. Therefore, efforts to prevent and treat morbid obesity are urgently needed.

Impact of Cardiorespiratory Fitness

Fitness versus fatness. Body fatness and fitness are strong predictors of CV disease risk factors, as well as CV morbidity and mortality (3,56–58). The relative and combined contributions of fitness and fatness to health are controversial, but substantial evidence suggests that fitness remains very predictive and largely negates the adverse effects of body fatness, as well as other traditional CV risk factors, including overweight/obesity, metabolic syndrome/type II diabetes mellitus, and hypertension (59–64). In most of these CV disorders, patients with high fitness have lower mortality than do patients without these disorders, but with low levels of fitness. In a recent meta-analysis of 33 studies of more than 100,000 participants, Kodama et al. (58) demonstrated that for every 1 metabolic equivalent (MET) increase in fitness, all-cause mortality and CHD/CV events are reduced by 13% and 15%, respectively. In 66,371 subjects without prior CV disease from the Cooper Center Longitudinal

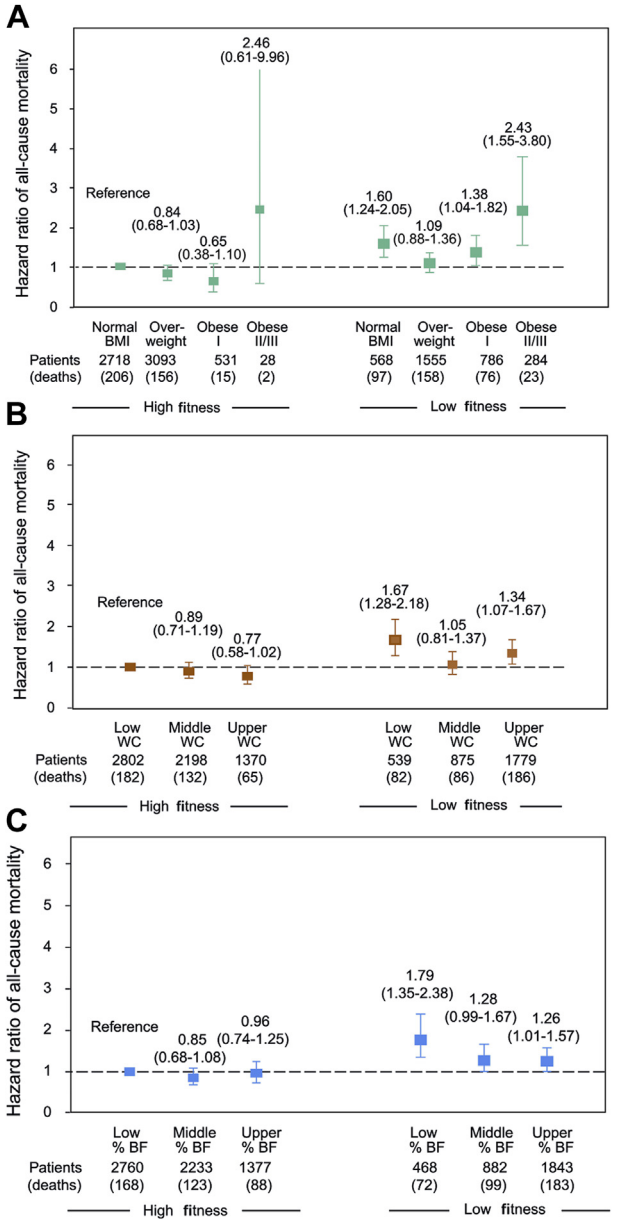


Figure 6 **Obesity Paradox and Fitness in CHD**

Joint effects of cardiorespiratory fitness and BMI **(A)**, waist circumference (WC) **(B)**, and % BF **(C)**, on all-cause mortality. Hazard ratios **(boxes)** and 95% confidence intervals (error bars represent values) after adjusting for age, baseline examination year, physical activity (active or inactive), smoking (current smoker or not), alcohol intake (>14 drinks/week or not), hypercholesterolemia, hypertension, and diabetes (present or not for each), and family history of cardiovascular disease. Abbreviations as in Figure 5. Reproduced with permission from McAuley et al. (34).

Study, a single measure of fitness significantly improved classification of both 10-year and 25-year risks for CV mortality when added to traditional CV risk factors (65). In a study of 3,148 healthy adults, changes over time in both adiposity (BMI and % BF) and fitness predicted the development of hypertension, metabolic syndrome, and hypercholesterolemia, but the impact of fitness appears somewhat better than did adiposity for future risk of these CV disorders (66). In addition, a 1-MET increase in fitness on 2 maximal exercise stress tests separated by an average of 6.3 years in 14,345 men was associated with reductions in all-cause and CV mortality of 15% and 19%, respectively; BMI change was not associated with all-cause and CV mortality after adjusting for possible confounders and changes in fitness (67). The constellation of these data suggests that although ideal prevention of both age-associated loss in fitness and increase in adiposity may be useful, maintaining or improving fitness is more important than preventing increased adiposity with regard to long-term health outcomes.

Obesity paradox and fitness. Several studies have suggested that fitness markedly alters the relationship between adiposity and prognosis in both CHD and HF (34,68–70). In a recent study of nearly 10,000 patients with CHD, only those in the bottom 33rd percentile for age- and sex-related levels of fitness demonstrated an obesity paradox, which was present by BMI, %BF, and even by waist circumference or central obesity (Fig. 6) (34). On the other hand, CHD patients without low fitness had a good prognosis regardless of their level of adiposity, so no obesity paradox was apparent, which has been described elsewhere (71). We recently demonstrated the same finding in 2,066 patients with systolic HF; in fact, HF patients with peak oxygen consumption <14 ml/kg/min had a poor prognosis, and a strong obesity paradox was present, with obese (BMI: >30 kg/m^2) having a better prognosis, lean (BMI: 18.5 to 25 kg/m^2) having a particularly poor prognosis, and overweight (BMI: 25 to 30 kg/m^2) having an intermediate prognosis. On the other hand, HF patients with relatively preserved fitness (peak oxygen consumption >14 ml/kg/min) had a good overall prognosis regardless of BMI, and again no obesity paradox was apparent (Fig. 7) (69). A recent study by Uretsky et al. (72), however, of more than 5,000 patients with normal nuclear perfusion stress tests, demonstrated that an obesity paradox was maintained regardless of the level of fitness. Nevertheless, those with relatively preserved fitness (≥6 estimated METs) had an extremely low mortality rate of <1% per year, although the normal BMI group had a higher mortality rate (1.4%/year) compared with the overweight and obese groups (0.9%/year and 0.6%/year, respectively) (72,73). None of these studies, however, have adequately accessed the impact of fitness on prognosis of patients with severe obesity, particularly with class II and class III obesity (BMI: 35 to 40 and >40 kg/m^2, respectively). It is noteworthy that in this latter group of patients, assessing levels of fitness can be challenging.

Role of Purposeful Weight Reduction

The role of purposeful weight reduction, except in the morbidly obese patient, where obesity is particularly detrimental to health outcomes, continues to be controversial

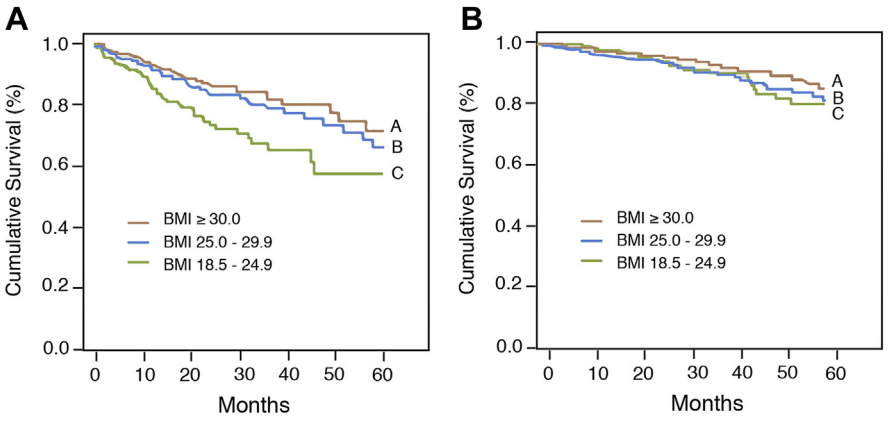


Figure 7 **Obesity Paradox and Fitness in HF**

Kaplan-Meier analyses according to BMI with the low CRF group (O_2 consumption <14 ml O_2 kg^{-1} min^{-1}, log rank 11.7, p = 0.003) and high CRF group (O_2 consumption ≥14 ml O_2 kg^{-1} min^{-1}, log rank 1.72, p = 0.42) on the left and right, respectively. BMI = body mass index; CRF = cardiorespiratory fitness; HF = heart failure. Adapted from data in Lavie et al. (69) and reproduced with permission from Lavie et al. (73).

(3,5,74,75). Some long-term studies have suggested that weight loss may be associated with increased mortality (3,76), and coupled with the obesity paradox discussed in the preceding text, it has been suggested that purposeful weight loss can be detrimental. Clearly, however, lifestyle interventions with diet and exercise training and at least mild weight reduction have markedly reduced the prevalence of metabolic syndrome and type II diabetes mellitus (77–79), although a recent large study on diabetes did not demonstrate survival benefits from small amounts of weight loss in diabetic subjects (80). In a CHD study of 530 patients that demonstrated an obesity paradox, overweight and obese patients who were successful with purposeful weight reduction had a trend of lower mortality (40). In a study of 1,500 CHD patients, intentional weight loss produced a lower incidence of CHD events over 4-year follow-up (81). A small study of 377 CHD patients showed the benefits of weight loss on major CV events even in patients with BMI <25 kg/m^2 (82).

In hypertension, purposeful weight loss has resulted in marked improvements in arterial pressure and LV geometry (83). In HF, weight loss, especially with bariatric surgery, has improved LV geometry, systolic and diastolic function, and clinical symptoms (5). Currently, many severely obese patients are being referred for bariatric surgery. Although 30-day mortality may be higher than ideal as a result of surgeon inexperience (84), most studies in severely obese and diabetic patients are showing improvements in short- and long-term prognosis (3,85–89).

Although better large-scale weight loss intervention trials are needed, the constellation of data still supports purposeful weight reduction in patients with CV diseases, especially in the more severely obesity (probably BMI >35 kg/m^2 and especially BMI >40 kg/m^2). Considering the importance of fitness to improve prognosis in almost every patient group studied, including overweight and obese patients, as well as the clear evidence that improvements in fitness are associated with reductions in mortality in both CHD (33,90,91) and HF (69,92), incorporating exercise training and efforts to improve fitness into weight loss programs appears to be particularly beneficial (93,94).

Conclusions

Although obesity adversely affects CV risk factors and LV structure and function, and is associated with increased risk of most CV diseases, an obesity paradox exists showing that overweight and obese patients with CV diseases have a better prognosis than do their leaner counterparts. This obesity paradox seems largely apparent in patients with low fitness, whereas those with better fitness have a good prognosis, and no clear obesity paradox is apparent. Although better long-term intervention studies are needed, purposeful weight reduction, and especially incorporating exercise training and improvements in fitness, seems to be beneficial.

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Key Words: cardiovascular disease ■ fitness ■ obesity.