Obesity Paradox Does Exist

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Adipose tissue has been shown to be a pivotal organ in the aging process and in the determination of life span. Owing to the rising prevalence of obesity, especially at younger ages, a potential decline in life expectancy is expected in the U.S. in the 21st century. Obesity, and mainly its abdominal form, is considered a major risk factor not only for type 2 diabetes, lipid disorders, and hypertension but also for coronary heart disease and certain cancers. In epidemiological studies, BMI, an indicator of relative weight for height (weight in kilograms divided by the square of height in meters) is frequently used as a surrogate for assessment of excess body fat. For characterization of the relative risks (RRs) of mortality and morbidity, the rates in underweight (BMI <18.5 kg/m^2), overweight (25 to <30 kg/m^2), class I obesity (30 to <35 kg/m^2), class II obesity (35 to <40 kg/m^2), and class III obesity (BMI >40 kg/m^2) are compared with those in normal-weight subjects (18.5 to <25 kg/m^2). A plot of the RR of mortality against BMI follows a U-shaped, or J-shaped, curve with the minimum mortality close to a BMI of 25 kg/m^2. Mortality increases as BMI increases above 25 kg/m^2 and as BMI decreases below 25 kg/m^2 (1). During the past decade, there is increasing evidence that patients, especially elderly, with several chronic diseases and elevated BMI may demonstrate lower all-cause and cardiovascular mortality compared with patients of normal weight. This article summarizes some of these paradoxical findings known as the "obesity paradox" and discusses potential causes of its manifestation.

Obesity paradox in overweight and obese patients with coronary heart disease

Ten years ago, Gruberg and coworkers observed better outcomes in overweight and obese patients with coronary heart disease undergoing percutaneous coronary intervention compared with their normal-weight counterparts. This unexpected phenomenon was described as "an obesity paradox" (2). Normal-weight patients had higher incidence of major in-hospital complications, including cardiac death. Moreover, at 1-year follow-up significantly higher mortality rates were observed in low- and normal-weight patients compared with obese and overweight. A systematic review of 40 cohort studies with 250,152 patients found significantly lower risks for total mortality (RR 0.87) and cardiovascular mortality (RR 0.88) in overweight patients (3). These mortality risks were not increased in obese patients (BMI 30–35 kg/m^2) compared with normal-weight subjects. However, severely obese patients (BMI $\geq$35 kg/m^2) exhibited the highest risk (RR 1.88) for cardiovascular mortality (3). The obesity paradox was also confirmed in patients with hypertension and coronary heart disease (4). In hypertensive patients, the occurrence of death, nonfatal myocardial infarction, or nonfatal stroke was lower in overweight patients (RR 0.77), class I obese patients (RR 0.68), and class II and III obese patients (RR 0.76) than in patients of normal weight. In this large cohort of hypertensive patients (n = 22,576), an obesity paradox was driven primarily by a decreased risk of all-cause mortality. Furthermore, in a recent Dutch study with a 7-year follow-up, overweight, but not obesity, was associated with a lower risk (RR 0.60) for all-cause mortality after percutaneous coronary intervention (5). This is in line with the previous study of Hastie et al. (6), who also found the best prognosis after percutaneous coronary intervention in overweight patients. Those with a BMI $\geq$27.5 and <30 kg/m^2 were at reduced risk of dying during 5-year follow-up (RR 0.59). A recent study on an association of BMI with mortality in patients with acute myocardial infarction requires special attention (7). BMI was inversely associated with a crude 1-year mortality rate: normal weight 9.2%, overweight 6.1%, obese 4.7%, and morbidly obese 4.6% ($P < 0.001$). This protective effect of overweight and obesity was not modified by age, sex, or the presence of diabetes. However, the mortality hazard in patients with myocardial infarction increased in subjects with BMI >40 kg/m^2. The manifestation of this obesity paradox was also shown in older patients with coronary artery calcification (8). In 9,993 patients (mean age 66.6 years) with clinically significant coronary lesions who had undergone percutaneous coronary intervention, an inverse relationship between BMI and coronary artery calcification was observed. This finding supports a "calcification paradox," whereby reduced bone mineral density in the elderly is related to increased vascular calcification (9).

Obesity paradox in patients with chronic heart failure

Investigations carried out in patients with chronic heart failure show a paradoxical decrease in mortality in those with higher BMI. This observation has been referred to as a "reverse epidemiology" (10). Consequently, several other studies in patients with both chronic and acute heart failure confirmed lower mortality in those with higher BMI (11–16). In the Digitalis Investigation Group Trial, data from 7,767 outpatients with stable heart failure were analyzed after a mean follow-up of 37 months (11). The risk of death was

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lower for both overweight (RR 0.88) and obese (RR 0.81) patients compared with normal-weight patients. On the other hand, underweight patients (BMI <18.5 kg/m^2) were at increased risk of death (RR 1.21). An association between BMI and in-hospital mortality was analyzed in 108,927 patients enrolled from the Acute Decompensated Heart Failure National Registry over a 3-year period. In-hospital mortality rates decreased in a near-linear fashion across successively higher BMI quartiles (12). For every increase in BMI of 5 kg/m^2, the mortality risk was 10% lower. A recent study of Voulgari and collaborators demonstrated a decreased risk (RR 0.44) of heart failure among metabolically healthy obese subjects (BMI ≥30 kg/m^2) compared with normal-weight individuals (<25 kg/m^2) with metabolic syndrome (RR 2.33) (13). It is not surprising, though, that better outcomes were observed among metabolically healthy obese individuals. However, another study found that not only elevated BMI (≥25 kg/m^2) but also abdominal obesity (defined as waist circumference ≥88 cm in women and ≥102 cm in men) was associated with better primary outcomes (mortality, urgent heart transplantation, and ventricular assist device placement) in men and women with advanced systolic heart failure (mean left ventricular fraction 22.9%) who had been followed for 2 years (16). Controversies, however, remain as to whether the obesity paradox is related to all patients with heart failure. Zamora et al. (17) confirmed this obesity paradox in patients with non-ischemic heart failure but failed to observe it in patients with ischemic heart failure.

Other manifestations of obesity paradox

Further studies over the past decade documented that the obesity paradox or reverse epidemiology is not specific for coronary heart disease, hypertension, and heart failure. Protective effects of overweight and obesity in other chronic diseases have recently been reviewed (18). The following diseases and health states were shown to be protected by increased body weight:

1. Peripheral arterial disease: The overall mortality rates in patients with peripheral arterial disease decreased with increasing BMI, reaching 54% in underweight, 50% in normal weight, 40% in overweight, and 31% in obese subjects (19). This paradoxical association was partly explained by the increasing prevalence of chronic obstructive pulmonary disease among individuals with a lower BMI. Later on, an inverse correlation between BMI and cardiovascular mortality was confirmed in patients with peripheral or coronary artery disease but not in those with cerebrovascular disease (20).
2. Stroke: Overweight and obese patients have significantly better survival rates after stroke than their normal-weight counterparts (21). In another study, class I obesity was associated with decreased risk of postoperative stroke after carotid endarterectomy (22).
3. Thromboembolism (23,24): Obese patients with acute venous thromboembolism have less than one-half the mortality in normal-weight subjects (24). In addition, in this cohort an incidence of major nonfatal bleeding complications was more frequent among underweight patients.
4. Postoperative complications in patients after cardiac surgery: Obese and severely obese patients after coronary artery bypass grafting are at lower risk of postoperative complications (reintubation, reexploration, prolonged stay in the intensive care unit, and 30-day mortality) than patients with low BMI (25).
5. Complications during catheter ablation for atrial fibrillation: Patients with less robust stature were more prone to complications during catheter ablation for atrial fibrillation with the use of intracardiac echocardiograhy. Low body weight was a significant risk factor (P = 0.013), with 0.8% increase of complication rate/10 kg body wt decrease (26).
6. In-hospital mortality in surgical intensive care unit (27).
7. Mortality in patients undergoing nonbariatric general surgery: Lower risk of death was observed in overweight and moderately obese patients undergoing nonbariatric general surgery than in those with normal weight (28).
8. Type 2 diabetes: Among patients with type 2 diabetes and cardiovascular comorbidity, overweight and obese patients had a lower mortality compared with normal-weight subjects. Moreover, weight loss and not weight gain was associated with increased morbidity and mortality during the mean follow-up of 34.5 months (29).
9. Amputation risk among nonelderly diabetic men: Amputation risk decreased in diabetic men with increasing BMI (30).
10. Chronic obstructive pulmonary disease (31,32) and its acute exacerbation (33).
11. Hemodialysis patients: Higher mortality rates were observed in hemodialysis patients who exhibited lower BMI and weight loss (34). In this case, the obesity paradox is likely explained by a loss of muscle mass with the concomitant decline in serum creatinine level.
12. Critically ill patients: Unadjusted analyses found that extremely obese critically ill patients in intensive care units had lower mortality (RR 0.77). However, this association was not significant when controlled for confounders (35). Severely obese patients (BMI ≥40 kg/m^2) spent longer time on mechanical ventilation and in the intensive care unit.
13. Osteoporosis: Until 10 years ago, only osteoporosis had been recognized as a disease, which is beneficially affected by obesity. This is due to the obesity-related increased levels of leptin, insulin, and estrogens that stimulate bone growth and inhibit bone remodelling. Recently, it has been shown that not only general obesity but also central obesity was negatively associated with osteoporosis in elderly women (36).

How to explain obesity paradox?

Gruberg et al. (2) have suggested several mechanisms to explain a better outcome, including lower mortality rates, after percutaneous coronary interventions in obese patients. Among the factors responsible for worse prognosis in lean patients, excessive anticoagulation and the presence of severe, noncardiovascular, underlying diseases in very thin individuals should be considered. However, health status at baseline, evaluated by the 36-item short-form health survey (SF-36), did not seem to explain the obesity paradox in overweight patients who had undergone percutaneous coronary intervention (5).

Role of age and less risky obesity

It is apparent that most of the studies that confirmed the obesity paradox were in cohorts of patients who had been recruited from elderly subjects. Lainscak with collaborators evaluated nine large-scale

studies about obesity paradox in chronic diseases (18). Eight of the studies included subjects at mean age >62 years. Only the Copenhagen City Heart Study evaluated younger patients, with a mean age 56 ± 11 years (31). Aging is associated with a significant decline in energy expenditure and fat oxidation, loss of skeletal muscle mass, and increased muscular lipid infiltration as well as increased visceral fat accumulation. The accumulation of visceral fat in abdominal obesity is associated with low-grade inflammation, blood lipid disorders, and increased risk of developing type 2 diabetes and cardiovascular diseases. Abdominal adiposity is associated with higher mortality; the RR of death among men and women in the highest quintile of waist circumference reached 2.05 in a cohort of 359,387 participants recruited in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study and followed over 9.7 years (37). On the other hand, the EPIC study revealed that hip circumference was not significantly associated with the risk of death after adjustment for BMI. These results may evoke the following hypothesis for explaining the obesity paradox: obese patients with risky abdominal obesity die earlier, and thus, among obese in the higher age categories, those with less risky lower-body obesity survive. It should be taken into account that many elderly obese exhibit late-onset obesity and, because of its short duration, health risks and comorbidities have not been able to manifest. No relevant data on the prevalence of less risky (metabolically healthy) obesity in the elderly have been available. In the Cremona Study, however, metabolically healthy, insulin-sensitive subjects represented only 11% of the obese middle-aged population (38). Obese insulin-sensitive subjects had similar BMI but lower waist circumference, blood pressure, fasting glucose, triglycerides, and fibrinogen and higher HDL cholesterol than obese insulin-resistant subjects. Due to the favorable metabolic profile, these subjects, in contrast to insulin-resistant individuals, did not show an increased all-cause, cardiovascular, or cancer mortality in a 15-year follow-up study (38). A review published recently by Mathus-Vliegen and collaborators reported that in the elderly, the prevalence of abdominal obesity defined by waist circumference is higher than the prevalence of obesity defined by BMI (39). However, studies evaluating visceral adipose tissue (VAT) by computed tomography demonstrated that the amount of gained visceral fat decreases with age. A prospective cohort study conducted in nondiabetic Japanese American men and women aged 34–74 years revealed that an accumulation of intra-abdominal fat over 10–11 years was significantly greater (52.1%) at younger ages (34–43 years) compared with older ages (54–63 years: 7.0% increase; ≥64 years: 11.2%) (40). Sex did not affect these associations between adiposity change and age. Similar slopes for these associations between age and adiposity change were demonstrated if Sansei (third generation of immigrants) and Nisei (second generation of immigrants) Japanese were evaluated separately. Data in Japanese American are in line with previously reported data for African Americans and Hispanics aged 20–69 years (41). The rate of increments in the VAT area in these cohorts followed over a 5-year period was greatest in young adulthood and declined with advancing age-group in both men and women, regardless of race. Moreover, except for Hispanic men, a decrease in the VAT area was demonstrated in all cohorts in the oldest age category (60–69 years old). If the rate of accumulation in VAT decreases with age, then the accumulation of peripheral fat stores may predominate and may be responsible for the obesity paradox. It has been shown that large accumulations of subcutaneous fat in the lower body in adults is associated with a lesser likelihood of insulin resistance and type 2 diabetes than when the adipose tissue is centrally distributed in the upper body (42). Lower-body obesity also prevents the progression of carotid atherosclerosis. Not only larger waist circumference (>83 cm) but also smaller hip circumference (≤ 98 cm) was associated with the greatest progression of carotid atherosclerosis quantified by intima-media thickness in a 12-year follow-up study carried out in elderly women aged 60–70 years at baseline (43). Debette et al. (44) found an inverse association of calf circumference with carotid plaques. The calf circumference itself does not differentiate between the fat and muscle mass but is among the strongest correlates of total body skeletal muscle volume and also provides surrogate estimates of both total and subcutaneous body fat but not of visceral fat (45). Thus, the observed protective effect of calf circumference on carotid atherosclerosis may be due either to an enlargement of peripheral fat stores in the lower body obesity or to an increased volume of skeletal muscles. Adipose tissue deposits accumulated in the lower body have relatively high lipoprotein lipase activity and low rates of basal and stimulated lipolysis. These deposits can protect the liver and skeletal muscle from high exposure to free fatty acids and their uptake with subsequent fatty infiltration.

Medical treatment

Schenkeveld et al. (46) compared medical treatment in patients treated with percutaneous coronary intervention. They found more optimal medical treatment in patients with a high BMI than in those with a normal BMI. This fact may explain a lower mortality in obese patients. However, our clinical experience is that polymorbid obese patients referred to our obesity unit are usually lacking comprehensive medical treatment.

Body composition

There are several explanations why higher BMI paradoxically improves prognosis in patients with heart failure. Oreopoulos et al. (47) directly measured body composition using dual-energy X-ray absorptiometry in patients with chronic heart failure and revealed that BMI misclassified body fat status in 41% of examined patients. In the cohorts of normal-weight, overweight, and obese patients at mean age of 62–66 years, BMI was a better indicator of lean body mass than of adiposity. Lean body mass but not body fat was associated with favorable changes in prognostic factors such as better handgrip strength and lower NH_2-terminal pro–B-type natriuretic peptide, a predictor of mortality among patients with acute and chronic coronary heart disease. Other researchers hypothesized that a decreased BMI could be a surrogate of the "malnutrition-inflammation complex syndrome" that may cause a worse prognosis in patients with chronic heart failure as well as in patients in maintenance dialysis (10).

Enlarged muscle mass and better nutritional status

The obesity paradox may be partly explained by the lack of the discriminatory power of BMI to differentiate between lean body mass and fat mass. Higher mortality in the low BMI categories may be due to the sarcopenic obesity that is characterized by low muscle mass (48). Sacropenia exacerbates insulin resistance and dysglycemia in both nonobese and

obese individuals. Many obese patients demonstrate not only increased fat mass but also increased muscle mass. Elderly patients with heart failure, who exhibited high BMI and had improved survival, had a better nutritional status than those with lower BMI (49). BMI and triceps skinfold thickness did not predict mortality, while a larger mid-arm muscle area, as a protective factor, did. A composite measure of mid-arm muscle mass and waist circumference was proposed as the most effective predictor of mortality in older men (50). Men aged 60–79 years with low waist circumference (≤102 cm) and above-median muscle mass demonstrated the lowest mortality rate.

Cardiorespiratory fitness

During recent decades, many studies provided evidence that obese subjects with an increased cardiorespiratory fitness have lower all-cause mortality and lower risk of cardiovascular and metabolic diseases and certain cancers (51). Thus, the obesity paradox may be partly explained by the level of cardiorespiratory fitness. Cardiorespiratory fitness may result in a healthy obesity that suppresses metabolic consequences of aging and is therefore associated with a better life expectancy. It has recently been shown that in men with known or suspected coronary heart disease, cardiorespiratory fitness greatly modified the relation of adiposity to cardiovascular and all-cause mortality (52).

Increased muscle strength

Muscle mass need not reflect muscle function, which largely differs and is dependent on the size, number, and contractility of fibers; fat infiltration; collagen content; etc. (48). Recent studies emphasize that a major factor influencing the mortality risk is not muscle mass but muscle strength as a marker of muscle quality (48,52). Muscle strength is negatively associated with metabolic risks independent of cardiorespiratory fitness. Grip strength is easily measured with isometric dynamometry. Grip strength provides risk estimates similar to those of quadriceps strength that is measured with isokinetic dynamometry (53). Handgrip strength has been recommended as a predictor of prognosis in patients with congestive heart failure in Japan (54). Thus, greater handgrip strength, reflecting better nutrition and physical fitness in some obese patients, may be a simple marker of a better outcome of congestive heart failure.

Endothelial progenitor cells

Less coronary atherosclerosis demonstrated in autopsies of severely obese subjects is another example of the obesity paradox (55). Biasucci and collaborators reported paradoxical preservation of vascular function in severely obese individuals (56). In these patients, both the higher flow-mediated dilation and the lower intima-media thickness were observed in comparison with obese and normal-weight subjects. The authors hypothesized that severely obese patients, despite higher levels of C-reactive protein and leptin, may be partially protected from atherogenesis through a greater mobilization of endothelial progenitor cells. A reduction of circulating bone marrow–derived endothelial progenitor cells has been proposed as a novel mechanism of vascular disease in type 2 diabetes (57). A greater mobilization of endothelial progenitor cells may protect severely obese patients from the development of diabetic vasculopathy.

Thromboxane production

Cardiovascular protection of severely obese subjects may also be mediated by a decreased production of thromboxane (58). Thromboxane A2 represents a marker of platelet activation that substantially contributes to increased cardiovascular morbidity and mortality. Levels of thromboxane B2, a stable metabolite of thromboxane A2, were lower in morbidly obese subjects than in lean and obese subjects (58). Thromboxane B2 negatively correlated with BMI and leptin. Graziani suggested that the decreased thromboxane production in severely obese subjects may be due to the resistance to proaggregatory action of leptin (58). However, the decreased thromboxane production in the severely obese may also be influenced by their paradoxically better endothelial function compared with obese and lean individuals (56).

Ghrelin sensitivity

Ghrelin is a gastric peptide hormone, initially described as the endogenous ligand for the growth hormone secretagogue receptor. Ghrelin stimulates growth hormone release and food intake, promotes positive energy balance/weight gain, and improves cardiac contractility (59). Ghrelin receptors have been found in both heart and blood vessels. The administration of ghrelin improved left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. A recently described positive association of plasma acylated ghrelin with blood pressure and left ventricular mass may represent a compensatory mechanism to overcome the development of heart failure in patients with metabolic syndrome (60). Lund et al. (61) suggested a role of ghrelin resistance in the development of cardiac cachexia. They demonstrated an association of heart failure with resistance to the appetite-stimulating effects of ghrelin. Resolved ghrelin sensitivity after heart transplantation resulted in an increase in caloric intake and weight gain (9.6 ± 6.2 kg) accompanied by a decline in ghrelin levels (61). We hypothesize that appropriate ghrelin sensitivity in the hypothalamus and myocardium associated with increased caloric intake and weight gain may be a protective factor against both heart failure and cardiac cachexia and thus could contribute to explanation of the obesity paradox in patients with heart failure.

Soluble tumor necrosis factor receptor

An increased production of inflammatory cytokines as tumor necrosis factor (TNF)-α plays an important role in the development of cardiometabolic risks in obese patients. The healthy heart does not express TNF, while the failing heart produces enormous quantities of TNF. Among patients with heart failure, obese subjects exhibit lower concentrations of TNF (62). Lower concentrations of TNF-α may cause a better outcome in obese patients with heart failure. Decreased TNF levels in obese patients with heart failure are related to the production of soluble TNF receptor by subcutaneous adipose tissue. It is assumed that these receptors bind TNF-α and neutralize its adverse effects on the myocardium. Venous concentrations of both isoforms of soluble TNF receptor, I and II, significantly correlate with BMI and percent body fat. On the other hand, no relationship between TNF-α and adiposity indexes has been demonstrated.

Conclusions

Despite the fact that obesity is recognized as a major risk factor in the development of cardiovascular diseases and diabetes, a higher BMI may be associated with a lower mortality and a better outcome in several chronic diseases and health circumstances. This protective effect of obesity has been described as the "obesity paradox" or "reverse epidemiology."

However, it should be emphasized that the BMI is a crude and flawed anthropometric biomarker that does not take into account fat mass/fat-free mass ratio, nutritional status, cardiorespiratory fitness, body fat distribution, or other factors affecting health risks and the patient's mortality (63). This review summarizes manifestations of the obesity paradox in different diseases such as coronary heart disease, heart failure, hypertension, peripheral artery disease, stroke, thromboembolism, kidney and pulmonary diseases, and type 2 diabetes. Obese individuals may also demonstrate better outcome in response to certain therapeutic procedures. The obesity paradox was mostly reported in elderly. Therefore, the protective effect of nutritional status in overweight and obese elderly individuals and the health-deteriorating effect of undernutrition in nonoverweight subjects probably contribute to this paradox. Besides the age and nutritional status, other factors such as less risky lower-body obesity, favorable body composition, and cardiorespiratory fitness are discussed as potential contributors to the obesity paradox. We may discuss the appropriateness of this term rather than its existence. A more relevant term that reflects individual health protective agent/s in each specific condition should be considered. Nevertheless, the discussion over the existence of the obesity paradox cannot lead to an underestimation of obesity as a crucial risk factor for the development of cardiovascular and metabolic diseases that requires comprehensive prevention and management strategies.

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References

1. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861–1867
2. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? J Am Coll Cardiol 2002; 39:578–584
3. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666–678
4. Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med 2007;120:863–870
5. Younge JO, Damen NL, van Domburg RT, Pedersen SS. Obesity, health status, and 7-year mortality in percutaneous coronary intervention: In search of an explanation for the obesity paradox. Int J Cardiol. 2 April 2012 [Epub ahead of print]
6. Hastie CE, Padmanabhan S, Slack R, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. Eur Heart J 2010;31:222–226
7. Buchholz EM, Rathore SS, Reid KJ, et al. Body mass index and mortality in acute myocardial infarction patients. Am J Med 2012;125:796–803
8. Kovacic JC, Lee P, Baber U, et al. Inverse relationship between body mass index and coronary artery calcification in patients with clinically significant coronary lesions. Atherosclerosis 2012;221:176–182
9. Persy V, D'Haese P. Vascular calcification and bone disease: the calcification paradox. Trends Mol Med 2009;15:405–416
10. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;43:1439–1444
11. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med 2005;165:55–61
12. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. Am Heart J 2007; 153:74–81
13. Voulgari C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. J Am Coll Cardiol 2011;58:1343–1350
14. Zapatero A, Barba R, Gonzalez N, et al. Influence of obesity and malnutrition on acute heart failure. Rev Esp Cardiol (Engl Ed) 2012;65:421–426
15. Komukai K, Minai K, Arase S, et al. Impact of body mass index on clinical outcome in patients hospitalized with congestive heart failure. Circ J 2012;76:145–151
16. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. Am J Cardiol 2012; 110:77–82
17. Zamora E, Lupón J, de Antonio M, et al. The obesity paradox in heart failure: Is etiology a key factor? Int J Cardiol 2013; 166:601–605
18. Lainscak M, von Haehling S, Doehner W, Anker SD. The obesity paradox in chronic disease: facts and numbers. J Cachexia Sarcopenia Muscle 2012;3:1–4
19. Galal W, van Gestel YR, Hoeks SE, et al. The obesity paradox in patients with peripheral arterial disease. Chest 2008;134: 925–930
20. Barba R, Bisbe J, Pedrajas JN, et al.; FRENA Investigators. Body mass index and outcome in patients with coronary, cerebrovascular, or peripheral artery disease: findings from the FRENA registry. Eur J Cardiovasc Prev Rehabil 2009;16: 457–463
21. Vemmos K, Ntaios G, Spengos K, et al. Association between obesity and mortality after acute first-ever stroke: the obesity-stroke paradox. Stroke 2011;42:30–36
22. Jackson RS, Black JH 3rd, Lum YW, et al. Class I obesity is paradoxically associated with decreased risk of postoperative stroke after carotid endarterectomy. J Vasc Surg 2012;55:1306–1312
23. Barba R, Zapatero A, Losa JE, et al.; Riete Investigators. Body mass index and mortality in patients with acute venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2008; 6:595–600
24. Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: the mounting evidence of risk and the mortality paradox. Thromb Res 2011;128:518–523
25. Potapov EV, Loebe M, Anker S, et al. Impact of body mass index on outcome in patients after coronary artery bypass grafting with and without valve surgery. Eur Heart J 2003;24:1933–1941
26. Aldhoon B, Wichterle D, Peichl P, Čihák R, Kautzner J. Complications of catheter ablation for atrial fibrillation in a high-volume centre with the use of intracardiac echocardiography. Europace 2013;15: 24–32
27. Hutagalung R, Marques J, Kobylka K, et al. The obesity paradox in surgical intensive care unit patients. Intensive Care Med 2011;37:1793–1799
28. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. Ann Surg 2009;250:166–172
29. Doehner W, Erdmann E, Cairns R, et al. Inverse relation of body weight and

weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. Int J Cardiol 2012;162:20–26
30. Sohn M-W, Budiman-Mak E, Oh EH, et al. Obesity paradox in amputation risk among nonelderly diabetic men. Obesity (Silver Spring) 2012;20:460–462
31. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 160:1856–1861
32. Blum A, Simsolo C, Sirchan R, Haiek S. "Obesity paradox" in chronic obstructive pulmonary disease. Isr Med Assoc J 2011; 13:672–675
33. Lainscak M, von Haehling S, Doehner W, et al. Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. J Cachexia Sarcopenia Muscle 2011;2:81–86
34. Kalantar-Zadeh K, Streja E, Molnar MZ, et al. Mortality prediction by surrogates of body composition: an examination of the obesity paradox in hemodialysis patients using composite ranking score analysis. Am J Epidemiol 2012;175:793–803
35. Martino JL, Stapleton RD, Wang M, et al. Extreme obesity and outcomes in critically ill patients. Chest 2011;140:1198–1206
36. Chang CS, Chang YF, Wang MW, et al. Inverse Relationship Between Central Obesity and Osteoporosis in Osteoporotic Drug Naive Elderly Females: The Tianliao Old People (TOP) Study. J Clin Densitom 2013;16:204–211
37. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008; 359:2105–2120
38. Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. Diabetes Care 2011;34:210–215
39. Mathus-Vliegen EMH, Basdevant A, Finer N, et al.; Obesity Management Task Force of the European Association for the Study of Obesity. Prevalence, pathophysiology, health consequences and treatment options of obesity in the elderly: a guideline. Obes Facts 2012;5:460–483
40. Lee CG, Fujimoto WY, Brunzell JD, et al. Intra-abdominal fat accumulation is greatest at younger ages in Japanese-American adults. Diabetes Res Clin Pract 2010;89:58–64
41. Hairston KG, Scherzinger A, Foy C, et al. Five-year change in visceral adipose tissue quantity in a minority cohort: the Insulin Resistance Atherosclerosis Study (IRAS) family study. Diabetes Care 2009;32: 1553–1555
42. Snijder MB, Dekker JM, Visser M, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. Am J Clin Nutr 2003; 77:1192–1197
43. Hassinen M, Lakka TA, Komulainen P, Haapala I, Nissinen A, Rauramaa R. Association of waist and hip circumference with 12-year progression of carotid intima-media thickness in elderly women. Int J Obes (Lond) 2007;31:1406–1411
44. Debette S, Leone N, Courbon D, et al. Calf circumference is inversely associated with carotid plaques. Stroke 2008;39:2958–2965
45. Heymsfield SB, Martin-Nguyen A, Fong TM, Gallagher D, Pietrobelli A. Body circumferences: clinical implications emerging from a new geometric model. Nutr Metab (Lond) 2008;5:24
46. Schenkeveld L, Magro M, Oemrawsingh RM, et al. The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study. BMJ Open 2012;2:e000535
47. Oreopoulos A, Ezekowitz JA, McAlister FA, et al. Association between direct measures of body composition and prognostic factors in chronic heart failure. Mayo Clin Proc 2010;85:609–617
48. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. Curr Opin Nutr Metab Care 2008;11:693–700
49. Casas-Vara A, Santolaria F, Fernández-Bereciartúa A, González-Reimers E, García-Ochoa A, Martínez-Riera A. The obesity paradox in elderly patients with heart failure: analysis of nutritional status. Nutrition 2012;28:616–622
50. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. Am J Clin Nutr 2007;86:1339–1346
51. Hainer V, Toplak H, Stich V. Fat or fit: what is more important? Diabetes Care 2009;32(Suppl 2):S392–S397
52. McAuley PA, Artero EG, Sui X, et al. The obesity paradox, cardiorespiratory fitness, and coronary heart disease. Mayo Clin Proc 2012;87:443–451
53. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006;61:72–77
54. Izawa KP, Watanabe S, Osada N, et al. Handgrip strength as a predictor of prognosis in Japanese patients with congestive heart failure. Eur J Cardiovasc Prev Rehabil 2009;16:21–27
55. Kortelainen ML, Porvari K. Extreme obesity and associated cardiovascular disease verified at autopsy: time trends over 3 decades. Am J Forensic Med Pathol 2011; 32:372–377
56. Biasucci LM, Graziani F, Rizzello V, et al. Paradoxical preservation of vascular function in severe obesity. Am J Med 2010;123: 727–734
57. Fadini GP, Boscaro E, de Kreutzenberg S, et al. Time course and mechanisms of circulating progenitor cell reduction in the natural history of type 2 diabetes. Diabetes Care 2010;33:1097–1102
58. Graziani F, Biasucci LM, Cialdella P, et al. Thromboxane production in morbidly obese subjects. Am J Cardiol 2011;107: 1656–1661
59. Ledderose C, Kreth S, Beiras-Fernandez A. Ghrelin, a novel peptide hormone in the regulation of energy balance and cardiovascular function. Recent Pat Endocr Metab Immune Drug Discov 2011;5:1–6
60. Rodríguez A, Gómez-Ambrosi J, Catalán V, et al. Association of plasma acylated ghrelin with blood pressure and left ventricular mass in patients with metabolic syndrome. J Hypertens 2010;28:560–567
61. Lund LH, Williams JJ, Freda P, LaManca JJ, LeJemtel TH, Mancini DM. Ghrelin resistance occurs in severe heart failure and resolves after heart transplantation. Eur J Heart Fail 2009;11:789–794
62. Feldman AM, Combes A, Wagner D, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol 2000;35:537–544
63. Heymsfield SB, Cefalu WT. Does body mass index adequately convey a patient's mortality risk? JAMA 2013;309:87–88