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Obesity, Age, and Cardiac Risk

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Abstract Obesity is a highly prevalent metabolic disorder affecting all sections of society from young children to adults and the elderly. Obesity is a well-established risk factor for several conventional cardiovascular (CV) risk factors such as hypertension (HTN), type 2 diabetes mellitus, and dyslipidemia. Obesity is also a very potent independent risk factor for CV diseases (CVD), including coronary heart disease (CHD), heart failure (HF), peripheral arterial disease (PAD), atrial fibrillation (AF), and sudden cardiac death (SCD), and is also associated with increased CV and all-cause morbidity. Despite this adverse association between obesity and CV risk factors and several CVDs, numerous studies have identified the phenomenon called the "obesity paradox" or "reverse epidemiology", meaning better short- and long-term survival in overweight and obese subjects with HTN, HF, CHD, PAD, and AF. This review summarizes the adverse impact of obesity on CV risk factors and CVDs, effects of obesity and aging in the elderly, and the puzzling phenomenon of the "obesity paradox" in the above-mentioned special populations and the elderly.

Keywords Obesity · Obesity paradox · Age · Cardiac risk · Hypertension · Heart failure · Coronary heart disease · Peripheral arterial disease · Atrial fibrillation · Elderly · Weight loss

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Introduction

Obesity is a highly prevalent metabolic disorder that is increasing in epidemic proportions in both United States (US) and rest of the world [1, 2••]. Currently. obesity is the second leading cause of preventable death and its growth is increasing at a rapid pace [3]. Obesity, with the present increasing trend, may soon overtake cigarette smoking as the leading cause of preventable death [4]. In the US, nearly 70% of adults are classified as being either overweight or obese compared with fewer than 25% some 40 years ago [5]. The World Health Organization statistics show that globally more than 1 billion people are overweight and that number may rise to 1.5 billion by 2,015 if the present trend continues [6]. Each year, an estimated 300,000 deaths and $117 billion in health care costs are attributed to obesity [7]. Recent evidence suggests that obesity is directly related to decreased life expectancy. Because of the pace at which obesity is increasing, Olshansky et al. [8] have predicted that very soon we might witness reversal of the steady increase in life expectancy.

In adults, overweight is defined as a body mass index (BMI) of 25.0–29.9 kg/m^2 and obesity is defined as a BMI ≥30 kg/m^2 [9]. The distribution of BMI in the US has shifted in a skewed fashion such that the proportion of population with extreme obesity has increased to a greater extent compared to overweight and obese cohorts [10]. The dramatic increase in the prevalence of obesity and its adverse consequences on cardiovascular (CV) disease (CVD) and overall health has led to unprecedented interest in learning more about obesity, the underlying mechanisms for adverse health effects, and potential preventive and corrective measures for reducing obesity and its associated risks [11, 12].

Obesity and Cardiovascular and Non-cardiovascular Adverse Effects

Obesity has both a direct and indirect adverse impact on the incidence and prevalence of CVD. Obesity adversely affects the CV risk factors such as hypertension (HTN), dyslipidemia, metabolic syndrome/insulin resistance, type 2 diabetes mellitus (T2DM), and left ventricular (LV) hypertrophy (LVH) (Table 1) [2]. Obesity is also an independent risk factor for heart failure (HF), coronary heart disease (CHD), sudden cardiac death (SCD), and atrial fibrillation (AF) [2••, 13, 14].

Obesity also plays an active role in the pathogenesis of osteoarthritis, chronic kidney disease, asthma, cancers, sleep apnea, and sleep-disordered breathing. In addition, obesity can also lead to reduced confidence, self-esteem, and quality of life [2••, 15••].

Table 1 Adverse effects of obesity

A. Increases in insulin resistance
1) Glucose intolerance
2) Metabolic syndrome
3) Type 2 diabetes mellitus
B. Hypertension
C. Dyslipidemia
1) Elevated total cholesterol
2) Elevated triglycerides
3) Elevated LDL cholesterol
4) Elevated non-HDL cholesterol
5) Elevated apolipoprotein-B
6) Elevated small, dense LDL particles
7) Decreased HDL cholesterol
8) Decreased apolipoprotein-A1
D. Abnormal left ventricular geometry
1) Concentric remodeling
2) Left ventricular hypertrophy
E. Endothelial dysfunction
F. Increased systemic inflammation and prothrombotic state
G. Systolic and diastolic dysfunction
H. Heart failure
I. Coronary heart disease
J. Atrial fibrillation
K. Obstructive sleep apnea/sleep-disordered breathing
L. Albuminuria
M. Osteoarthritis
N. Cancers

HDL high-density lipoprotein; *LDL* low-density lipoprotein

(*From* Lavie CJ, Milani RV, Ventura HO: Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009, 53:1925–1932 [2••]; with permission.)

Although obesity has been implicated as one of the major risk factors for many CV disorders, numerous studies have identified a strong paradox between obesity and subsequent prognosis, whereby overweight and obese subjects with CVD have better prognosis compared with leaner subjects [16–25]. This phenomenon, called the "obesity paradox" or "reverse epidemiology," has been extensively reported in patients with systolic HF [17–20], HTN [21], CHD [25, 26••], peripheral arterial disease (PAD) [27, 28], end-stage renal disease (ESRD)/hemodialysis cohorts [29], AF [30•, 31••], patients referred for outpatient echocardiography [24], and in the elderly [15••, 32, 33] (Table 2).

Some investigators attribute this inconsistent relationship between obesity and clinical events to the inaccurate diagnosis of obesity by conventional BMI, and that defining obesity by other methods, such as waist circumference, waist/hip ratio, and percent body fat may, be more accurate [34–36].

Effects of Obesity on Cardiac Structure and Function

Obesity adversely affects the cardiac structure, function, and its hemodynamics. In obese subjects, to meet the increased metabolic demands of the body, there is an increase in total blood volume, stroke volume, and cardiac output [13]. Most of this increase in cardiac output is due to increase in stroke volume and to some extent due to increase in heart rate from sympathetic activation. The increase in filling pressures and blood volume shifts the Frank-Starling curve to the left, suggesting an increase in CV work. As weight gain is typically associated with an increase in arterial pressure, over a period of time obese subjects invariably end up being hypertensive compared to leaner subjects [2••, 37–39].

In overweight and obese individuals, chronic elevation in filling pressures and volume leads to LV chamber dilatation, called eccentric LV hypertrophy (LVH). Also independent of age and blood pressure, overweight and obesity increase the risk of other LV structural abnormalities, including concentric remodeling and concentric LVH [40]. In addition to LV structural abnormalities, obesity also results in left atrial enlargement secondary to abnormal LV diastolic filling and increase in blood volume. Initially, these structural adaptations are considered to be physiologic in order to meet the increased metabolic demands; however, these changes over a period of time become pathologic, resulting in systolic and diastolic dysfunction, overt clinical HF, with increased risk for benign and malignant atrial and ventricular arrhythmias such as AF and ventricular tachycardia [2••].

Table 2 Obesity paradox[a] in cardiovascular and non-cardiovascular patients

Cardiovascular
A. Hypertension
B. Heart failure
C. Coronary heart disease
1) Percutaneous revascularization
2) Coronary artery bypass graft surgery
3) Treadmill referrals
D. Peripheral arterial disease
E. Echocardiography referrals
Non-cardiovascular
A. Elderly
B. End-stage renal disease and dialysis
C. Advanced cancers
D. Chronic obstructive lung disease
E. Rheumatoid arthritis
F. Human immunodeficiency virus/acquired immune deficiency syndrome

[a] Conditions in which obesity has been associated with a more favorable prognosis compared with that in non-obese patients

(*From* Lavie CJ, Milani RV, Ventura HO: Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009, 53:1925–1932 [2••]; with permission.)

Obesity and Heart Failure

Despite several major advancements in the management of HF, this disease is associated with significant morbidity and mortality. Recent evidence from the Framingham Heart Study implicates overweight and obesity as the potent indicators and predictors of subsequent clinical HF [41]. Kenchaiah et al. [41] analyzed 5,881 participants over a 14-year follow-up and identified a graded increase in the risk of HF with increase in BMI. For every 1-kg/m^2 increase in BMI, the risk of HF increased by 5% in men and 7% in women. In fact, a graded increase in the risk of HF was noted across all categories of BMI, supporting an adverse relationship between excess body weight and increased risk of HF. In a study from Brown et al. [42] in 74 morbidly obese patients, nearly one third had clinical evidence of HF. The other significant finding from this study is the positive association between the duration of obesity and HF risk; at 20 and 25 years of obesity duration, the probability of HF was 66% and 93%, respectively. Despite the vast evidence implicating obesity with future risk of HF, many studies have found that obese patients with HF have a better prognosis compared to leaner patients, suggesting the phenomenon of the "obesity paradox," as discussed below.

Obesity and Hypertension

The majority of obese patients are hypertensive, and hypertensive patients are often found to be overweight or obese. Because these two conditions are closely connected and often co-exist, they exert a dual burden on the cardiac structure, resulting in systolic and diastolic dysfunction. Typically, HTN via increased peripheral vascular resistance leads to LV wall thickening without chamber dilatation, a process referred to as concentric remodeling when LV mass is not increased or concentric LVH when LV mass is increased [2••]. Alternatively, obesity leads to an increase in chamber dilatation without significant increase in wall thickness, a process that is referred to as eccentric LVH. Evidence from National Health and Nutrition Examination Survey III suggests that the prevalence of HTN increases progressively with increasing BMI [42].

In this analysis, the prevalence of HTN increased from 15% in men with BMI <25 kg/m^2 to 42% in men with BMI of 30 kg/m^2; in women the prevalence of HTN increased from 15% at a BMI of <25 kg/m^2 to 38% at a BMI of 30 kg/m^2. Even though a 10-kg higher body weight is associated with only a 3-mm Hg increase in systolic and 2-mm Hg increase in diastolic blood pressure, at the population level this translates in to a 12% and 24% increase in the risk for CHD and stroke, respectively [9].

Analysis of the echocardiographic data in 64 patients from our center indicated a 15% higher prevalence of diastolic dysfunction in hypertensive versus normotensive patients and a 25% higher prevalence in obese versus lean patients, whereas in patients with both HTN and obesity the prevalence of diastolic dysfunction was 40% higher compared to normotensive and normal-weight patients [43].

Obesity and CHD

Obesity is an important risk factor for CHD via its independent adverse effect on individual CHD risk factors such as T2DM, HTN, and dyslipidemia. Other pathophysiologic mechanisms that might confer an increased risk for CHD include obesity-mediated increase in insulin resis-

tance, increase in basal sympathetic activity, high turnover of free fatty acid, and induction and promotion of a hypercoagulable and pro-inflammatory state [16, 25, 26••]. Evidence from multiple long-term prospective studies such as the Manitoba study [44], the Framingham Heart Study [45], and the Nurses' Health Study [46] have suggested that obesity is an independent predictor of CHD. Provocative data in young adults from the Pathological Determinants of Atherosclerosis in Youth study indicate that overweight and obesity accelerate the progression of atherosclerosis decades before the appearance of clinical manifestations [47]. Additionally, obesity has been strongly linked to first non-ST elevation myocardial infarction occurring at a younger age [48].

Obesity and Arrhythmias

Obesity, with its attendant hemodynamic and structural effects on the left atrium and left ventricle, leads to an increase in the incidence and prevalence of AF and ventricular arrhythmias [2••]. Wanahita et al. [30•], in their recent study in 78,602 obese subjects, observed nearly a 50% increase in the risk of developing AF compared to non-obese individuals, and the risk increased linearly with increasing BMI. Each unit increase in BMI has been associated with 4% increase in new-onset AF [49]. Obesity is also implicated as a risk factor in the progression of paroxysmal AF to permanent AF [50]. Also, increased electrical irritability in obese patients may lead to more frequent and complex ventricular arrhythmias [2••].

In the Framingham Heart Study, the annual SCD rate was approximately 40 times higher than in the non-obese cohort [51]. Finally, obesity is associated with abnormal sympathovagal balance, leading to higher basal heart rate and decreased variability in heart rate that might predispose one to increased risk of SCD [12]. Obesity is also associated with increased QT interval, and it is an established fact that prolonged QT interval is a predictor of increased mortality [52].

Obesity and Other Disorders

There is also evidence showing an association between obesity and stroke [1, 53]. In one particular study, for every 1-unit increase in BMI, there was a 4% increase in the risk of ischemic stroke and 6% increase in the risk for hemorrhagic stroke [53]. This is attributed to a higher incidence of HTN, AF, and a prothrombotic state. Additionally, obesity is an important causative risk factor for obstructive sleep apnea (OSA) syndrome [54]. It is a known fact that patients with OSA, especially obese OSA subjects, have increased risk of HTN, arrhythmias, HF, MI, stroke, and pulmonary HTN [55]. Also, obese subjects, due to their increased total body fluid, high-volume lymphatic overload, and physical inactivity, often develop chronic venous insufficiency with edema, deep vein thrombosis, and pulmonary embolism.

Obesity Paradox

Despite the known adverse effects of obesity on cardiac structure and function leading to systolic/diastolic dysfunction and HF, many studies have suggested that obese HF patients have a better short- and long-term prognosis. This phenomenon is termed the "obesity paradox" [2••, 4]. In addition to HF, this paradox is also observed in other patient populations with HTN, CHD, PAD, AF, and ESRD on hemodialysis [15, 17••]. Previous evidence from our lab in a small sample of 209 patients with chronic systolic HF, both higher BMI and percent body fat were independent predictors of better event-free survival [17]. Additional data from our lab regarding 1,000 patients with chronic systolic HF showed a positive impact of increased body fat on total survival [56]. In an analysis of BMI and in-hospital mortality in 108,927 decompensated HF patients, higher BMI was associated with lower mortality. For every 5-U increase in BMI, there was a 10% lower mortality ($P<0.001$) [57]. Oreopoulos et al. [58••], in a recent meta-analysis of nine observational HF studies in 28,209 subjects over 2.7 years of follow-up, noted significant reductions in CV (−19% and −40%) and all-cause (−16% and −33%) mortality in overweight and obese subjects, respectively, in comparison to normal-weight subjects. Additionally, a recent study by Oreopoulos et al. [59] raised the issue that specific assessments of body composition using dual energy X-ray absorptiometry may help explain the obesity paradox, although substantial evidence suggests that both higher BMI and body fat are protective in HF [60]. Most studies reporting the obesity paradox have used BMI to classify obesity. Although BMI is the most common method used to define overweightness and obesity, clearly this method does not necessarily reflect true body fat. Defining obesity by other methods, including waist circumference, waist-hip ratio, and percent body fat, may be more accurate [2••, 60].

Many studies also reported an obesity paradox in revascularized and non-revascularized CHD patients. We assessed the concept of "obesity paradox" in 529 consecutive patients enrolled in a cardiac rehabilitation and exercise training (CRET) program following major CHD events. During 3-year follow-up, total mortality was considerably lower in the overweight/obese patients (BMI $\geq$25 kg/m^2) than in 136 CRET patients with baseline BMI

<25 kg/m^2 (4.1% vs 13.2%; $P<0.001$), as well as in those with higher percent body fat (>25% in men and >35% in women) compared to those with lower percent body fat (3.8% vs 10.6%; $P<0.01$) (Fig. 1) [26••].

Romero-Corral et al. [61••], in their comprehensive analysis of 250,000 patients in 40 cohort studies over 3.8 years of follow-up, determined that overweight and obese patients with CHD had a lower risk of total and CV mortality compared to underweight and normal-weight patients. However, in patients with severe obesity with BMI ≥35 kg/m^2, there was an excess risk for CV mortality without any increase in total mortality.

Gruberg et al. [62], in a large sample of stable CHD patients undergoing percutaneous coronary intervention, found worse clinical outcomes in normal-weight patients compared to overweight and obese patients despite better baseline CV risk profiles and similar angiographic findings among all BMI groups. Another recent study from Buettner et al. [63], looking at the impact of obesity on clinical outcome in patients with acute coronary syndrome subjected to early intervention, found a remarkable decrease in the risk of all-cause mortality from 9.9% in normal BMI subjects, to 7.7% in overweight subjects, to 3.6% in obese subjects, to 0% in severely obese with a BMI >35 kg/m^2. Although the underlying mechanism for this puzzling paradoxical effect is not certain, in summary, all these studies suggest that despite the fact that obesity increases the risk of CHD, at least overweight and mildly obese CHD patients do not seem to have adverse prognosis.

This phenomenon of obesity paradox is also noted in the hypertensive overweight and obese population [2••, 11, 21, 25]. Uretsky et al. [21], in their recent analysis of the International Verapamil SR-Trandolapril study in 22,576 treated hypertensive patients with known CHD, noted a 30% lower risk of all-cause mortality in overweight and obese patients during 2-year follow-up compared to normal-weight group. This incredible benefit was noticed despite less effective blood pressure reduction in these groups compared with the normal-weight group. A similar relationship was noted in another study, the Systolic Hypertension in the Elderly Program, where overweight status was associated with decreased stroke risk and all-cause mortality compared to leaner cohort [64].

Similarly, another major HTN study showed a U-shaped relationship between BMI and all-cause mortality, CV mortality, and non-CV mortality, meaning bad outcomes at both extremes of BMI [65]. In aggregate, these studies suggest that although obesity is a powerful risk factor for HTN and LVH, obese hypertensive patients may have a better prognosis. This could be due to lower peripheral vascular resistance and lower plasma renin levels in obese compared to the normal-weight and leaner cohort.

Although obesity has been associated with increased risk of AF, evidence from the post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management database indicates better clinical outcomes in overweight (BMI 25–30 kg/m^2) and obese (>30 kg/m^2) AF patients compared to normal weight patients with AF. On multivariate analysis, overweight and obese patients had better all-cause (hazard ratio [HR] 0.64 and 0.80, respectively) and CV mortality (HR 0.40 and 0.77, respectively) as compared to normal-weight subjects. This relationship existed even after controlling for the other two most important cohorts (HF and CHD) that are known to be associated with the obesity paradox [31••].

Galal et al. [27], in their recent study in 2,392 high-risk PAD patients undergoing major vascular surgery with 4.4 years of follow-up, observed progressive reductions in mortality in normal BMI, overweight, and obese groups compared with the underweight group. Similar evidence was documented from our echocardiographic database in over 30,000 patients with preserved LV systolic function [24]. Like many previous studies, we found the highest mortality in underweight patients; whereas overweight, mildly obese, and obese patients with BMI ≥35 kg/m^2 had significantly lower mortality than those with ideal BMI

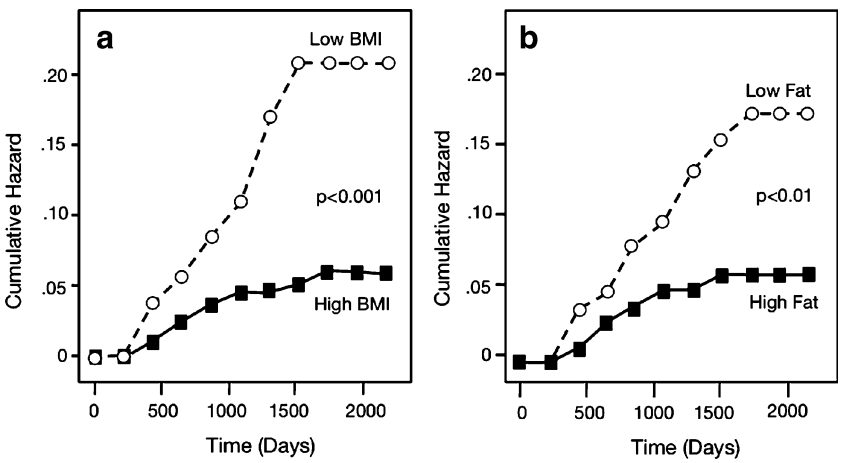

Fig. 1 Actuarial cumulative hazard plot for survival time in 529 coronary patients based on: (**a**) Baseline body mass index (BMI) status (high=BMI ≥25 kg/m^2 vs low=BMI <25 kg/m^2) and (**b**) Baseline percent body fat (high=fat >25% in men and >35% in women vs low fat). Reproduced with permission from Lavie CJ et al., [26••]

of 18.5–25 kg/m^2. In our cohort, although obesity is associated with a higher prevalence of LV structural abnormalities such as concentric remodeling, and concentric and eccentric LVH, which are associated with increased mortality risk, higher BMI was still independently associated with lower mortality.

A very recent study from Kalantar-Zadeh et al. [29] in a national cohort of 121,762 patients receiving hemodialysis 3 times a week has shown that higher BMI (up to 45 kg/m^2) and higher serum creatinine concentration (surrogate for large muscle mass) were incrementally and independently associated with better survival. These findings suggest that, among patients receiving hemodialysis, weight gain with concurrent increase in muscle mass might have a better survival benefit than those with weight gain without concomitant increase in muscle mass.

Another recent study [66••] evaluated the influence of cardiorespiratory fitness (CRF) on the obesity paradox in 12,417 middle-aged male veterans with known or suspected CHD who were referred for exercise stress testing. In multivariate analysis, both CRF and BMI were inversely associated with mortality risk. Within each CRF category (low, moderate, and high was defined as <5, 5–10, and >10 metabolic equivalents, respectively), elevated BMI was associated with reduced mortality risk, and higher levels of CRF within each BMI category decreased the mortality risk. Among all CRF-BMI combinations, highly fit overweight men had the lowest mortality risk, with an HR of 0.43. Overweight and obese men with low CRF were more likely to die than normal-weight men with high CRF. In summary, in this cohort of middle-aged male veterans, both higher BMI and higher CRF were protective for all-cause mortality. Additionally, these data suggest that the "obesity paradox" is not present in men with low CRF and that the obesity paradox can be modified by physical wellness and other un-measured confounding factors that link the presence of chronic disease to outcomes [67].

The underlying mechanisms for this apparent obesity paradox remain elusive. It is postulated that lower body weight is associated with heightened catabolic state, with increasing levels of cytokines and imbalance in cortisol/dehydroepiandrosterone ratio [10, 12]. Our previous research has shown that overweight and obese HF patients have low levels of natriuretic peptides, which result in earlier expression of clinical symptoms, leading to earlier diagnosis and treatment with better long-term clinical outcomes [68]. Other lines of evidence suggest that fatty tissue has tumor necrosis factor-α receptors, which scavenge the interleukin-1 and other cytokines, conferring protective effects against mortality in HF and patients with cancer and other chronic illnesses [10, 21]. Additionally, none of the major studies accounted for non-purposeful weight loss prior to study entry, which would be expected to be associated with a poor prognosis. Finally, because overweight/obesity is a potent risk factor for most CVDs, it is quite likely that many overweight/obese subjects may not have developed CVD in the first place had weight gain been prevented; on the other hand, when lean patients develop the same CVD despite having a "healthy" weight, the cause of their disease is likely different than that in the heavier patient, suggesting genetic predisposition.

Obesity, CV Risk and the Obesity Paradox in the Elderly

The proportion of individuals over the age of 65 years is expected to increase to approximately 18% by the year 2025 [69]. The prevalence of overweight and obesity in the elderly cohort is a growing concern and is increasing at a rapid pace all over the world [15]. In the US, 66% and 74% of women and men aged 60 years and above are either overweight or obese [3]. It is very important to notice the strong association between obesity and CV morbidity and mortality among the elderly, especially among the very old (≥70 years), as the prevalence of obesity in those aged 70 years and above is increasing at an alarming rate, with an estimated prevalence of 35% and over [70].

In 2005, CVD was the underlying cause of death in 864,480 of the approximately 2.5 million total deaths in the US, and the elderly aged ≥65 years accounted for 82% of all deaths attributed to CVD. The incidence and prevalence of CVD increase with increasing age. There is almost a linear increase in the prevalence of CVDs, including HTN, CHD, HF, and stroke from around 40% in those aged 40–59 years, to 70%–75% in persons aged 60–79 years, and to 79%–86% among those aged 80 years and older [71].

Among the elderly, overweight and obese individuals, in addition to their excess CVD risk, are also prone to increased risk for the decline in daily functional activities, such as preparing food, shopping, and traveling. With aging there is an increase in fat accumulation, especially more central/visceral fat around the waist, in combination with a decrease in lean body mass. In a cross-sectional study from Spain in the elderly population, it was found that obesity is associated with weakness, slowness, and the frailty syndrome [15••].

Despite the adverse association between obesity and CV and non-CV morbidity in the elderly population, studies have also indicated better short- and long-term prognosis, as we have recently reviewed [15••]. Flegal et al. [72], in their recent analysis of the association between obesity and death in the US population, observed that being overweight is not related to increased mortality in the elderly. In another study among an elderly cohort aged 80 years and above it, was noted that subjects with a BMI ≥25 kg/m^2

have a lower mortality compared to elders who are underweight with a BMI ≤18.5 kg/m^2. Higher mortality in the underweight was due to excess deaths from cancers and CVDs [73]. Heiat et al. [74], in their analysis of 13 studies examining the relationship between BMI and mortality in subjects aged 65 years and over, observed a U-shaped relationship between BMI and all-cause mortality, with a significant increase in mortality in the group with BMI >30 kg/m^2.

Similarly, Janssen et al. [75], in a systematic review of 32 studies evaluating the relationship between BMI and all-cause mortality in the elderly (≥65 years), found that BMI in the overweight range is not associated with any increase in mortality. However, BMI in the obese range is only associated with a modest (~10%) increase in mortality risk. Some experts are of the opinion that this favorable prognosis in the elderly overweight and obese population is due to the prevailing protective effects of excess fatty tissue/nutritional reserve over its adverse effects. The excess mortality in normal, and underweight subjects can also be explained due to malnutrition, osteoporosis, and traumatic falls, with all the associated morbidity [15••].

In another analysis from our laboratory in 2009, Lavie et al. [76••] assessed the disparate effects of obesity and LV geometry on all-cause mortality in 8,088 elderly patients aged >70 years with preserved LV ejection fraction (≥50%) during a 3-year follow-up. Although abnormal LV geometry progressively increased with increasing obesity, all-cause mortality was strongly and inversely related with BMI (BMI <18.5, 22% mortality; BMI of 18.5–25, 15% mortality; BMI of 25–30, 10% mortality; BMI of 30–35, 9% mortality; and BMI ≥35, 8% mortality). In multivariate analysis, lower BMI was a strong and independent predictor of mortality. Although abnormal LV geometry was strongly related with higher mortality, elevated BMI was protective in every category of LV geometry.

Purposeful Weight Loss in Cohorts with CVD

We have very recently reviewed the topic of weight loss in CVD [77••]. Long-term epidemiologic studies in patients with CVD have shown that weight loss in overweight and obese people is associated with increased mortality, supporting the notion that purposeful weight reduction in overweight and obese CV cohorts might be detrimental [77••]. However, in the non-CV overweight and obese population, the evidence from several studies favoring weight loss is well established, with immense favorable outcomes in metabolic profiles, overall health, functional capacity, and physical and psychological health [78–81].

Studies conducted using lean body mass and body fat as opposed to BMI have shown that subjects losing body fat rather than lean mass have better survival chances. In a retrospective analysis of our CRET data in 529 consecutive patients over 3-year follow-up, we noted a non-significant reduction in total mortality in the higher weight loss group compared to overweight/obese patients who failed to lose weight (3.1% vs 5.1%; P=0.30). Although the baseline overweight/obese cohort did not achieve significant weight loss, there was a marked improvement in multiple CHD risk factors [26••]. In the past, we have demonstrated the beneficial effects of formal CRET in obese CHD patients [82, 83].

In our previous study in a subgroup of 45 obese CHD patients with 5% or greater reduction in body weight following CRET, we noted significant improvements in total cholesterol, high-density and low-density lipoprotein levels, and exercise capacity compared to 81 obese patients who did not lose any weight [82]. In another recent study from the Mayo clinic in 377 consecutive CHD patients, weight loss was associated with marked event-free survival across all BMI ranges [84•]. Despite the obesity paradox, the accumulating evidence still supports the beneficial effects of purposeful weight reduction.

Recently, Ades et al. [85••] evaluated the effects of high-calorie expenditure exercise (3,000–3,500 kcal/wk) compared with standard CRET (700–800 kcal/wk) on weight loss and CV risk factors in 74 overweight CHD patients. After 5 months of CRET, the high-calorie expenditure exercise group achieved a significant reduction in weight loss (8.2±4 kg vs 3.7±5 kg; P<0.001), fat mass loss (5.9±4 kg vs 2.8±3 kg; P<0.001), and waist reduction (−7±5 kg vs −5±5 cm; P=0.02) compared to the standard CRET group. In addition, the high-calorie expenditure exercise group witnessed marked improvements in insulin resistance, total to high-density lipoprotein cholesterol ratio, and individual components of the metabolic syndrome, and their significant weight loss was maintained at 1 year of follow-up. These results suggest that in CRET programs, high-calorie expenditure exercise may be the exercise modality of choice to promote greater weight reduction and CV risk reduction in secondary CHD prevention.

Even though overweight and obese patients with CV diseases seem to have a favorable prognosis compared to leaner patients, the totality of the evidence strongly supports purposeful weight reduction in the prevention and treatment of CV diseases [2••].

Conclusions

As we have discussed, obesity is a highly prevalent CV and non-CV risk factor affecting people across all ages around the world. Although evidence from epidemiologic and cohort studies suggest obesity to be a potent and indepen-

dent risk factor for CVDs such as HTN, CHD, HF, and AF, there are many studies suggesting an intriguing phenomenon called the "obesity paradox." Also, the elderly population faces the double burden of the adverse effects of aging and obesity; however, even in this population, overweight and obesity is found to have a favorable prognosis. The protective nature of obesity in these selected populations does not mean that we should neglect the initiation of active preventive measures to curb the obesity epidemic. In fact, further research and a proactive approach is necessary, searching for novel ideas and strategies to curb this malignant disorder and to learn more about the underlying pathophysiologic mechanisms of the puzzling obesity paradox.

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- • Of importance
- •• Of major importance

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