

Obesity Paradox in Asian Population: the Protective Effects of Excessive Body Mass

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Received: May 20, 2015

Revised: June 15, 2015

Accepted: June 20, 2015

Published online: August 10, 2015

ABSTRACT

The link between central obesity and cardiovascular diseases has been firmly established in recent years. On the other hand, numerous studies have observed that excessive body mass may be associated with a relatively favorable prognosis in advanced heart diseases. In this review article, we will summarize the findings from recent Asian and worldwide studies. We will also discuss the underlying mechanisms and other contributing factors of the obesity paradox.

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Key words: Obesity paradox; Heart failure; Cardiorespiratory fitness; Adiponectin; Metabolic syndrome

Lai YH, Kuo JY. Obesity Paradox in Asian Population: the Protective Effects of Excessive Body Mass. *Journal of Cardiology and Therapy* 2015; 2(4): 360-364 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/1315>

INTRODUCTION

Obesity has been well-established as an independent factor in the pathogenesis of heart failure (HF) and cardiovascular diseases (CVD). The term “obesity cardiomyopathy” refers to a clinical syndrome characterized by adverse cardiac structural and hemodynamic changes as a direct result of excessive adiposity^[1]. On the other hand, numerous observational studies and meta-analyses have demonstrated that an obesity paradox may exist in advanced heart diseases. Namely, patients who are overweight (BMI 25 to 29.9 kg/m²) or obese (Class I: BMI 30 to 34.9 kg/m², Class II: BMI 35 to 39.9 kg/m², Class III: BMI ≥40 kg/m²) may have more favorable clinical outcome and long-term survival, especially with chronic HF patients.

We reviewed the adverse effects of obesity on cardiac structure and function in a previous article^[2]. In brief, excessive adiposity and body weight leads to increased total blood volume and cardiac output. Systemic vascular resistance then decreases to accommodate the increase in cardiac output^[3,4]. This results in adverse changes in hemodynamic status including volume and pressure overload, structural alterations such as left ventricular (LV) hypertrophy and dilation accompanied by increased LV wall stress^[5,6]. These effects had been widely observed, including a large Taiwanese retrospective study published by our group^[7]. Central obesity is also independently associated with LV diastolic dysfunction, which is closely connected to LV hypertrophy^[8-10]. As the remodeling progresses, LV hypertrophy fails to compensate for dilation and wall stress, gradually developing a combined state of systolic and diastolic heart failure, which then produces pulmonary venous hypertension and eventually pulmonary arterial hypertension. In severely obese patients, sleep apnea syndrome may also contribute to pulmonary arterial hypertension. Finally, right ventricular dilation and hypertrophy ensues, leading to concurrent right ventricular failure. Other pathways linking obesity with cardiac disorders include systemic inflammation^[11-13], and neurohormonal activities such as insulin resistance, leptin resistance, and activation of the renin-angiotensin-aldosterone system (RAAS)^[14,15].

OBSESITY PARADOX IN CARDIOVASCULAR DISEASE

The paradoxical protective effect of obesity has been widely explored in current literature for more than a decade^[16-18], and this observation is not solely limited to severe HF. For example, one prospective study on diabetic patients from Taiwan showed lower noncancer mortality in obese people^[19]. The first large-scale meta-analysis performed a database search of more than 28000 HF patients with an average span of 2.7 years^[20]. After adjusting for baseline variables, both overweight [adjusted hazard ratio (HR) 0.93, confidence interval (CI) 0.89-0.97] and obesity (adjusted HR 0.88, CI 0.83-0.93) remained protective against mortality. No significant change in these results was observed after excluding underweight individuals. In other words, overweight and obesity patients still had survival advantage even when compared with normal-BMI people. A recent meta-analysis on more than 21000 patients with history of acute coronary syndrome and 5 years of follow-up also showed that overweight (RR 0.70, CI 0.64-0.76), obese (RR 0.60, CI 0.53-0.68) and severely obese (RR 0.70, CI 0.58-0.86) patients had lower mortality compared with normal BMI group^[21].

The U- or J-shaped association between weight status and mortality has been well-documented^[22], with highest mortality appearing in the lowest and highest BMI groups. Most recently, a systematic review on 97 prospective studies representing more than 2.88 million individuals in the general population showed that overweight was associated with decreased all-cause mortality, whereas increased mortality was present in Class II and III obesity^[23]. In a Taiwanese study on coronary artery disease (CAD) patients with 10-year follow-up^[24], the obesity paradox was more pronounced in underweight subjects during the first 5 years. The aforementioned J-curve developed after the 5-year mark (Figure 1). Further meta-analysis confirmed that a J-shaped relationship exists between BMI and total mortality beyond 5-year follow-up^[25].

ROLE OF BODY FAT COMPOSITION

Although BMI is a very simplistic and cost-effective method, it has often been criticized for not reflecting real adipose tissue burden, and could be confounded by several clinical variables. Furthermore, it provides no information on fat distribution at specific sites, hence failing to describe the anatomy of visceral adipose depots^[26]. As a result, there had been investigations on whether fat mass or lean mass plays a stronger role in the obesity paradox^[27,28]. So far, more evidence has been in favor of the combined effects of body fat percentage coupled with BMI. In other words, patients with simultaneously low body fat and BMI seem to have particularly high long-term mortality. In a three-year observational study by Lavie *et al.*^[27], combination of low body fat and low BMI translated to a 4.24-fold increase in mortality rate (CI 1.76-10.23, $p=0.001$).

ROLE OF CARDIORESPIRATORY FITNESS

There had also been discussions on whether exercise function should be factored into the prognosis of heart failure patients. It stands to reason that people with higher fat mass also has more sufficient muscle strength and higher cardiac reserve. Several recent studies have demonstrated an inverse relationship between BMI and plasma B-type natriuretic peptide (BNP) concentration in subjects with^[29] and without^[30] heart failure. There is evidence that lower BNP level

was associated with increased muscle mass^[31]. It is believed that the obesity paradox is actually limited to only people with low exercise function in terms of cardiorespiratory fitness^[32-34]. For example, a study by McAuley *et al.*^[33] showed no difference in cumulative survival across any anthropometric parameter (including BMI and body fat) in people with normal or high fitness (Figure 2). Lavie *et al.*^[34] also demonstrated that the obesity paradox was masked by the presence of higher aerobic capacity in terms of peak VO₂ (oxygen uptake). In another large study with 11-year follow-up, men who lost fitness had higher all-cause and CVD mortality risks regardless of BMI change after multivariate analysis. Every 1-MET improvement was associated with 15% and 19% decreases in all-cause and CVD mortality, respectively^[35]. These findings implied that cardiorespiratory fitness, especially when assessed by aerobic exercise performance, may have a larger impact than obesity on the prognosis of chronic heart failure patients.

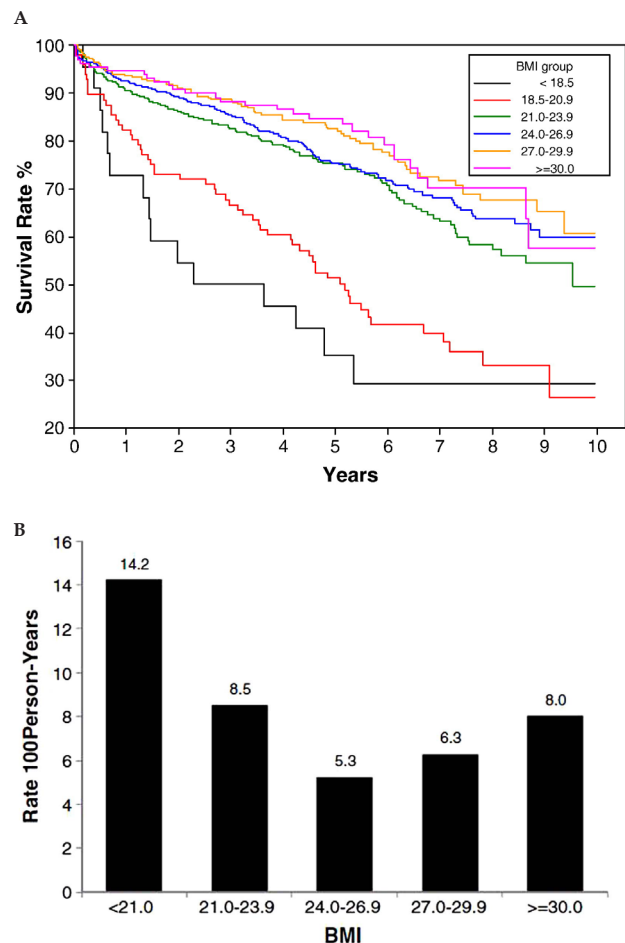


Figure 1 A: Kaplan-Meier survival curves for overall mortality by BMI subgroups in 1258 patients with CAD. Underweight patients had highest mortality (black line), followed by patients with normal-low BMI (red line). During the first 5 years, obese patients (pink line) had the best survival rate, but gradually fell behind their counterparts after 5 years. B: 5-to-10 year mortality rate per 100 person-years by BMI group in 718 CAD patients who survived beyond 5 years. Although the underweight and normal-low weight group (BMI<21) still had highest mortality, there's a J-curve distribution with the obese group. Reprinted with permission from Lin *et al.*^[24].

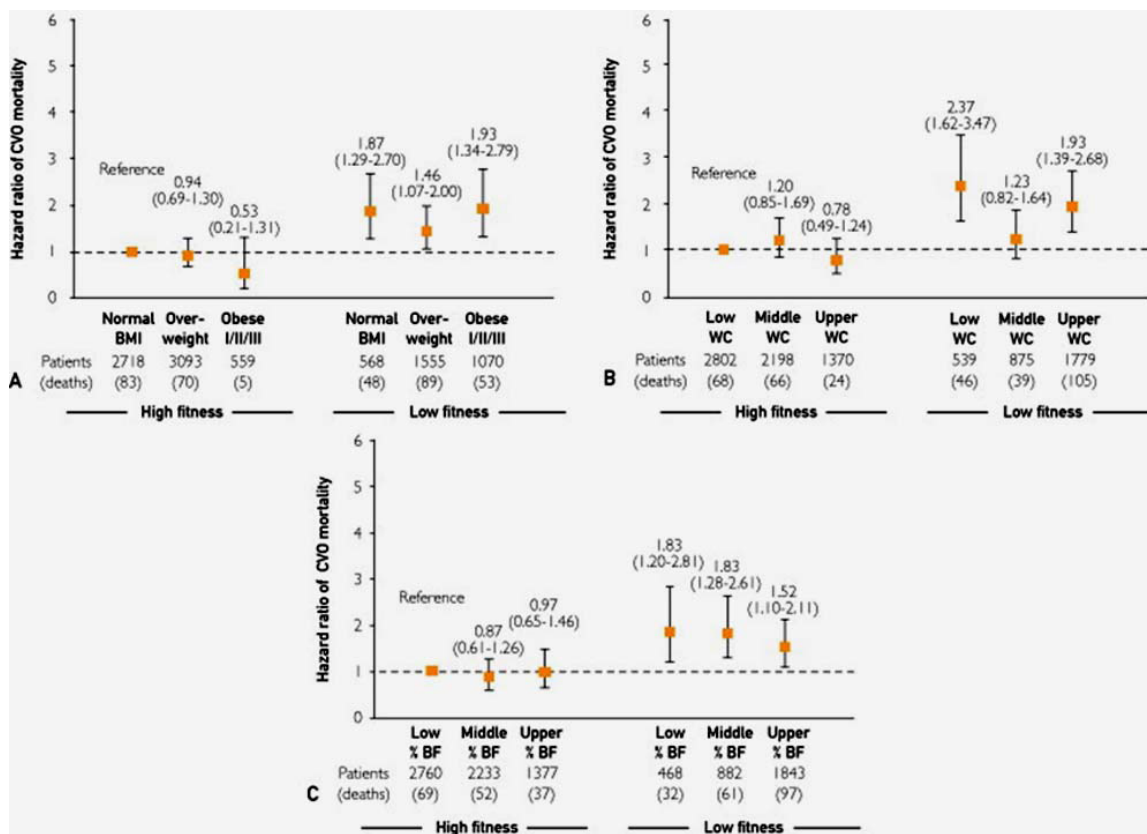


Figure 2 Joint effects of cardiorespiratory fitness and body mass index (BMI) (A), waist circumference (WC) (B), and body fat (BF) (C), on cardiovascular disease (CVD) mortality. Obesity paradox was observed in the low fitness groups, while no significant difference in mortality was seen in the high fitness groups. Reprinted with permission from McAuley *et al*^[33].

ROLE OF CYTOKINES

The adipose tissue secretes various cytokines that regulate energy balance in the human body. One of them is adiponectin, which can protect healthy individuals from developing CVD^[36,37], due to its anti-inflammatory and anti-atherogenic properties^[38]. Although adiponectin is secreted only from fat tissue, plasma adiponectin level is paradoxically decreased in obese subjects^[39]. However, in patients with HF, higher adiponectin level was instead associated with increased mortality independent of other clinical variables^[40]. This phenomenon also exists in patients with history of acute coronary syndrome (ACS)^[41]. In a two-year follow-up of post-ACS patients in the PROVE IT-TIMI 22 trial^[41], adiponectin was inversely related to BMI but was independently associated with an increased risk of death or myocardial infarction (HR 1.58, CI 1.10-2.28) and heart failure (HR 2.17, CI 1.21-3.89). Therefore, adiponectin has been suggested as a possible mediator of the obesity paradox. One possible explanation is the increased energy expenditure and muscle wasting process, which may be detrimental to heart failure.

In a recent Taiwanese study on the prognosis of patients who underwent coronary artery bypass grafting (CABG)^[42], higher BMI was associated with less cardiovascular mortality even after multivariate adjustment (HR 0.912 per 1kg/m² BMI increase, CI 0.833-0.998). However, additional adjustment for preoperative adiponectin, hs-CRP or NT-proBNP levels attenuated this inverse relationship, suggesting that these cytokines might play a stronger role in the obesity paradox. Further supporting this notion was that all three cytokines predicted mortality in patients with normal weight, rather than in overweight or obese patients. This finding was in

concordance with international large studies such as the AtheroGene Study^[43], in which increased adiponectin levels were predictive of adverse cardiovascular outcome in patients with documented CAD (either chronic stable angina or ACS).

ROLE OF METABOLIC STATUS

Recent interest has focused on the term “metabolically healthy overweight/obese” (MHO), namely individuals with isolated high BMI yet relatively normal metabolic status that doesn’t fit the metabolic syndrome criteria. In contrast, people with metabolic syndrome but normal BMI are termed “metabolically obese normal weight” (MONW). There are distinctive characteristics between these two phenotypes. Generally, MHO subjects tend to be younger and have a shorter duration of obesity and healthier lifestyle. MONW mostly develops at an older age and has a more malicious presentation with unintentional weight loss and cachexia. It remains controversial how much advantage the former group really has in terms of cardiovascular morbidity and mortality^[44,45].

In a meta-analysis that included eight studies and more than 61000 patients, MONW patients (RR 3.14, CI 2.36-3.93) had the highest risk for all-cause mortality and cardiovascular events compared to overweight (RR 2.70, CI 2.08-3.30) and obese patients with metabolic syndrome (RR 2.65, CI 2.18-3.12). This is partially compatible with the obesity paradox. However, when compared with metabolically healthy normal-weight people, MHO still had increased risk for adverse events after more than 10 years of follow-up (RR 1.24, CI 1.02-1.55)^[46]. This implies that obesity cannot be regarded as a purely benign condition even in the absence of

metabolic derangements. Furthermore, the weight of metabolic status seems to overwhelm any protective effect that obesity may have in the diseased population.

CONCLUSION

In conclusion, overwhelming evidence supports the importance of obesity in the pathogenesis of cardiovascular disease. Excessive weight is associated with the development of subclinical metabolic and vascular dysfunction that ultimately leads to increased incidence of adverse cardiovascular events and long-term mortality. On the other hand, the obesity paradox does exist in certain populations, most notably in heart failure. Possible mechanisms include preservation of energy and muscle strength, protective cytokines. The interaction between other factors such as body fat composition, distribution, cardiorespiratory fitness and metabolic status should also be considered.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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