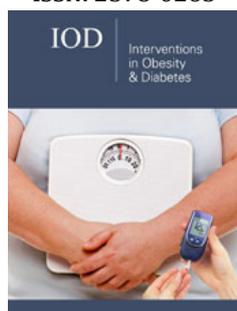


# Obesity Paradox in Cardiovascular Diseases and Research Progress

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## Abstract

In recent years, clinical evidence suggests that obese and overweight people with established cardiovascular diseases (CVDs) seem to have a better prognosis compared with lean patients. This phenomenon has been described as the 'obesity paradox', but there are also those who disagree with this seemingly deviant view, its existence remains a point of debate. This review tries to summarize the latest research progress of obesity paradox in CVDs and concludes with some explanations for this puzzling phenomenon.

**Keywords:** Overweight; Cardiovascular diseases; Hypertension; Obese patients

**Abbreviations:** CVDs: Cardiovascular Diseases; BMI: Body Mass Index; DBP: Diastolic Blood Pressure; WHR: Waist-to-Hip Ratio; CAD: Coronary Artery Disease; ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation

## Introduction

The World Health Organization has defined overweight and obesity based on body mass index (BMI; weight in kilograms/height in meters squared,  $\text{kg}/\text{m}^2$ ). The prevalence of overweight and obesity as defined by BMI is rapidly increasing, particularly in children and adolescents, and associated with significantly increased risk of CVDs at an earlier age [1]. There is scientific consensus that obesity increases the risk of CVDs, excessive body weight associated with negative effects on hemodynamics, cardiac morphology and ventricular function, even metabolically healthy obese individuals had a higher risk for coronary heart disease [2,3]. It seems different from what we imagined, despite this negative correlation, recent epidemiological data and numerous studies found that overweight and obese people with established CVDs appear to have a better clinical prognosis. It is necessary for us to face up to this problem, because it may affect our diagnosis and treatment of patients. Is patients with CVDs fatter really fitter?

## Obesity paradox and hypertension

Many epidemiological studies have confirmed the relationship between obesity and hypertension (HTN). Higher BMI were associated with higher risk of HTN in adults [4]. Barrett et al. [5] first reported the obesity paradox and HTN in 1985 in 1727 patients with systolic HTN, observing that obese patients with systolic blood pressure (SBP)  $\geq 160\text{mmHg}$  had lower cardiovascular and ischemic heart disease mortality than nonobese patients with HTN. Subsequently, other scholars reported similar observations. Agarwal et al. [6] assessed 281,560 HTN emergency hospitalizations finding that overall mortality was significantly lower in-hospital mortality in those with obesity. In-hospital mortality has also been demonstrated to be lower in patients with pulmonary arterial HTN (PAH) and obesity (3.5%) compared to the non-obese (8.1%) from a 9-year nationwide study [7]. And found the combination of early marked weight loss and rapid blood pressure reduction seems to be harmful in obese elderly cardiovascular disease population [8]. Obesity, as defined by BMI, seems to have a positive effect in patients with hypertension. Whether the obesity paradox can be explained by a causal mechanism involving blood pressure (BP), Dorresteyn et al. [9] found each  $5\text{kg}/\text{m}^2$  BMI was associated with  $+3.8\text{mmHg}$  (95% CI 3.0-4.6) SBP difference and  $+2.3\text{mmHg}$  (95% CI 1.9-2.8) diastolic blood pressure (DBP) difference in both men and women. Measures of centralized adiposity compared with BMI were equally related with BP. In contrast, subcutaneous adipose tissue was only weakly related with DBP and not related with SBP and

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pulse pressure. Furthermore, 5kg/m<sup>2</sup> BMI change during follow-up was associated with +8.1/5.1mmHg BP change. In a meta-analysis, Coutinho et al. [10] found that central obesity was associated with mortality (HR: 1.70, 95% CI 1.58-1.83), whereas BMI was inversely associated with mortality (HR: 0.64, 95% CI 0.59-0.69). Central obesity was also associated with higher mortality in the subset of subjects with normal BMI [11].

As stated above, more recent studies using a mix of more appropriate obesity indices, in particular central obesity, such as waist circumference (WC) and waist-to-hip ratio (WHR), skinfold thickness, and bioelectrical impedance, raise some doubt about the real significance of obesity paradox. And there are several studies that show either no protective effect of obesity or even worse effect [12]. Therefore, it is uncertain whether the obesity paradox is due to a real causal effect or to a statistical bias.

### Obesity paradox and coronary artery disease (CAD)

Obesity is an independent risk factor for the development and progression of CAD. Obesity is associated with accelerated coronary atherosclerosis in adolescent and young adult men, atherosclerotic vascular lesions of patients with higher BMI values are more frequent and advanced compared to subjects with normal body weight [13]. Studies in the past few years have found the obesity paradox in CAD, excess weight and obesity are associated with a favorable prognosis. A systematic review of 40 studies with 250,152 patients show that patients with a low BMI had an increased relative risk (RR) for total mortality (RR=1.37 [95% CI 1.32-1.43]), and cardiovascular mortality (1.45 [1.16-1.81]) compared with those for people with a normal BMI [14]. If so, is fatter healthier? One research studied 3,307 individuals (1,038 women) with CAD, after adjusted for age, smoking, blood pressure, diabetes, alcohol, and self-reported health, observed that no mortality risk reductions associated with weight loss in individuals with CAD, and reduced mortality risk associated with weight gain in individuals who were normal weight at baseline [15]. The result seems optimistic. The latest research seems to offer different views, a large meta-analysis of 89 studies including 1.3 million CHD patients also confirmed an obesity paradox, which was evident during early follow-up even in patients with severe obesity. Such protective effects, however, seemed to disappear after approximately 5 years [16]. Younis et al. [17] studied 15,357 patients with stable CAD, Kaplan-Meier survival analysis showed that at 20 years of follow-up the rate of all-cause mortality was significantly higher among obese patients (67%) compared to overweight (61%) and normal weight (61%). Data from other research shows that there is no obesity paradox when measuring body fat percentage (BF%) instead of BMI [18,19].

The author think underweight patients tend to be more malnourished and cachectic and have a higher prevalence of comorbid conditions such as malignancy and heart failure. In addition, underweight patients tend to be older. They also suggest that there may be a lead-time bias, in that patients with elevated BMI are investigated and treated at an earlier stage in the disease process. Although they found an increased prevalence of other

cardiovascular risk factors such as diabetes and hypertension in patients with elevated BMI, the reduced risk was independent of these comorbid conditions, and its association with increased BMI was not attenuated by their inclusion in the model.

### Obesity paradox and acute coronary syndrome(ACS)

A meta-analysis of 26 observational studies, including nearly 218,532 patients by Niedziela et al. [20] showed that the highest risk of mortality was found in low BMI patients (RR 1.47[95 % CI 1.24-1.74]), while overweight, obese and severely obese patients had lower mortality compared with those with normal BMI. In one study, Kouvari et al. [21] have demonstrated that BMI status and 10-year ACS prognosis followed a J-shape association (p=0.009). Overweight patients had significantly better ACS prognosis than their normal-weight counterparts (OR=0.45, 95% CI (0.23, 0.90)). The aforementioned paradoxical association was retained only in patients with specific conditions. In a large and unselected group of patients with ACS, the relation between BMI and mortality was U-shaped and was also observed in patients with type 2 diabetes mellitus and ACS, the protective effect of obesity disappeared in patients treated with insulin [22,23]. Migaj et al. [24] reported that obesity seems to have a different influence on outcomes in both genders, only male patients seem to contribute to the obesity paradox observed in patients with ACS. Diercks et al. [25] showed that overweight or obese were younger and more likely to present with comorbid conditions, including diabetes mellitus, hypertension, and hyperlipidemia. Although obesity appears to be a risk factor for developing ACS at a younger age, it also appears to be associated with more aggressive ACS management and, ultimately, improved outcomes. Age, lifestyle, and fitness are also variables that must be considered, as well as preexisting diseases. Sex differences could also be important, as observed in a study from the Cleveland Clinic, in which BMI has a different impact on mortality in males versus females and obesity paradox disappears in males after adjustment for potential confounders [26]. The protective role of overweight and obesity against all-cause mortality seems to be linked to a condition of high fitness. Also in older subjects (60 or over), physical fitness may be a more important determinant of survival than overweight [27].

In patients presenting with ST-segment elevation myocardial infarction (STEMI) and left ventricle dysfunction, with worse outcomes for those with normal weight, when compared to overweight or obese individuals [28]. These findings are consistent with the obesity-paradox. In AMI patients with primary percutaneous coronary intervention (PCI), but the obesity paradox was recognized only in patients in the elderly age group and not in the younger age group, which means the prognostic impact of BMI may differ by age in AMI patients [29,30].

With regards to the impact of BMI on survival after coronary artery bypass graft (CABG), the results are also inconsistent. Takagi et al. [31] reported that overweight, but not obesity, may be associated with better short-term and mid-to-long-term post-CABG survival compared to normal weight. A 2014 analysis of

12 CABG studies in 60,000 patients found worst survival rates in underweight patients, who had a 2.7-fold higher mortality than patients with normal BMI [32]. But there was a tendency to lower survival among patients with BMI > 35kg/m<sup>2</sup> [33]. Another study observed that there is no significant difference in hospital or follow-up mortality among patients undergoing CABG surgery when modified by BMI, obese patients gained less benefit in terms of QoL dimension, and there was no significant difference in overall mortality in the long-term follow-up [34].

### **Obesity paradox and atrial fibrillation(AF)**

Obesity is an independent risk factor for AF and may also be a risk factor for progression of paroxysmal to persistent AF, which carries higher morbidity and mortality [35,36]. In 2009, Lavic et al. [37] found obesity paradox exists in patients with AF with overweight and obese patients have a better prognosis than leaner patients with the same degree of severity of cardiovascular disease/AF. In patients with CHD and heart failure, overweight and obese patients with AF have a considerably better prognosis than do those patients with normal BMI. In a study of 431, 734 hospitalizations for AF, Agarwal et al. [38] found obese patients had lower risk-adjusted odds of in-hospital mortality and stroke events. In contrast, the obese group had a better prognosis in major adverse events compared with the normal weight group (HR 0.34, 95% CI 0.13-0.89, p=0.029). This paradox also exists in the elderly AF patients and in patients with AF treated with oral anticoagulants [39,40].

But the evidence from the INTERHEART study, which assessed 2,540 patients enrolled in the EORP-AF Registry with 1 year follow-up, finding all-cause mortality was significantly different according to BMI among female patients (9.3% normal BMI, 5.3% overweight, and 4.3% obese, P=0.023), but not among male patients (P=0.748). The composite outcome of thromboembolic events and death was also significantly different, being lower in obese females (P=0.035). Among male patients, bleeding events were significantly more frequent in obese subjects (P=0.035) [41]. A meta-analysis of 6 observational studies, including nearly 2358 patients by Guijian et al. [42] showed that elevated BMI increased the risk of AF recurrence compared to normal BMI by 31%.

### **Obesity paradox and heart failure(HF)**

Previous research found that obesity may result in HF by inducing changes in cardiac hemodynamics, structure, function and conduction. Recent years, there is a large amount of evidence which suggests there is obesity paradox in patients with heart failure, risk for total mortality and cardiovascular mortality and hospitalization was highest in patients with chronic HF who were underweight as defined by low BMI, whereas risk for cardiovascular mortality and hospitalization was lowest in overweight subjects [43]. In a recent meta-analysis of nine observational studies including heart failure patients, Oreopoulos et al. [44] compared all-cause mortality with BMI and found that overweight and obese patients had a more favorable prognosis than those who were either underweight or normal weight. Weight loss ≥5% in patients with chronic HF was

associated with high long-term mortality, particularly among obese patients with HF [45]. In a study of 6,142 patients with acute decompensated HF, Shah et al. [46] also found the obesity paradox, but the “protective” association of BMI with mortality was confined to persons with older age, decreased cardiac function, no diabetes and de novo HF. Habbu et al. [47] pointed towards a U-shaped relationship between BMI, and survival in heart failure patients, with poor survival in both cachectic patients and patients with severe obesity.

The author think heavier patients may be presenting earlier with worse symptoms but less advanced disease state than patients with lower BMI. Patients with higher BMI were less likely to have systolic failure than patients with lower BMI. Patients with healthy weight may not have adequate nutritional stores or metabolic reserves to overcome the metabolic demands and catabolic stress resulting from an acute exacerbation of heart failure. The obesity paradox may be driven by deleterious effects of cachexia, not salutary effects of obesity. Furthermore, the survival paradox of BMI disappears also in diabetic patients with heart failure [48] or when peak oxygen consumption (VO<sub>2</sub>) was used for multivariate analysis [49]. These results support the superior prognostic power of peak oxygen consumption and diabetes compared to obesity, which attenuates the “obesity paradox” phenomenon [50].

### **Obesity paradox and stroke**

Many research found that overweight and obesity were associated with progressively increasing risk of ischemic stroke [51]. What is surprising that most observational data indicate a survival benefit of obese patients after stroke [52,53]. In a Korean observational study, including 34,132 patients with acute ischemic stroke by Kim et al. showed that compare to normal body weight, mortality risk was lowest in overweight (HR 0.77 95% CI 0.63–0.93) followed by the obese (HR 0.83, 95% CI 0.74–0.92), whereas highest in under-weight patients (HR 1.36, 95% CI 1.25–1.48) [54]. This is supported by evidence from the Andersen et al. [55] which assessed 45 615 acute first-ever stroke patients, finding that mortality was significantly lower in overweight (HR 0.72; 95% CI 0.68–0.78) and obese (HR 0.80; 95% CI 0.73–0.88) patients while significantly higher in underweight patients (HR 1.66; 95% CI 1.49–1.84) compared with normal weight patients. Subsequently, Wohlfahrt et al. [56] found normal weight at hospital admission and weight loss after ischemic stroke are independently associated with increased mortality. Though more observational data indicate a survival benefit of obese patients after stroke, but methodological concerns still exist. Among which no obesity paradox was observed in patients after intravenous thrombolysis [57].

The author think there is a need for well-designed randomized controlled trials assessing the effects of weight reduction on stroke risk in obese patients. In summary, most observational data indicate a survival benefit of obese patients after stroke, but a number of methodological concerns exist. Available data support obesity as an independent risk factor for occurrence of stroke, and weight reduction in overweight or obese patients is still recommended for primary stroke prevention.

## Other Issues

### When assessing obesity in different ways

Previous studies have relied predominantly on the BMI to assess the association of adiposity with the risk of death, but few have examined whether the other methods for evaluating obesity contributes to the prediction of death. More recent studies have investigated obesity paradox in patients not only on the basis of body weight, but also with the use of other measures of body fat, such as WC, WHR, skinfold thickness, and bioelectrical impedance, and the results show a picture much less clear [58]. In the study by Pischon et al. [59], BMI remained significantly associated with the risk of death in models that included WC or WHR ( $P < 0.001$ ). This supports that both general adiposity and abdominal adiposity are associated with the risk of death and support the use of WC or WHR in addition to BMI in assessing the risk of death. Another opinion is that the obesity paradox is mainly due to the effect of confounding on BMI and disappears on other adiposity measures as waist, WHR and BF% [60].

### When considering metabolism

Metabolically healthy obese phenotype (MHO) refers to obese individuals without metabolic abnormalities such as dyslipidemia, insulin resistance or hypertension. A meta-analysis aiming to assess the risks of cardiovascular events and all-cause mortality for MHO individuals and confirms a positive association between MHO and the risk of cardiovascular events [61]. The latest study used non-targeted metabolomics and whole-genome sequencing to identify metabolic and genetic signatures of obesity. An abnormal metabolome associated with a 2- to 5-fold increase in cardiovascular events when comparing individuals who were matched for BMI but had opposing metabolome signatures. The health consequences observed across the various BMI groups indicate that there is a durable benefit of maintaining a healthy metabolome signature and point to an ongoing risk for the individuals that have an unhealthy metabolome despite stability of BMI [62]. A recent study of 54 089 men and women from five cohort studies found that obesity may not be associated with higher risk for all-cause mortality compared to lean healthy individuals in the absence of metabolic abnormalities [63].

### When rethinking the BMI

BMI is sometimes criticized for not distinguishing fat from lean mass and ignoring fat distribution, leaving its ability to detect health effects unclear [64,65]. Obesity defined by BMI alone is a remarkably heterogeneous condition with varying cardiovascular and metabolic manifestations among individuals. Although it is clear that the accumulation of visceral/ectopic fat is a major contributor to cardiovascular and metabolic risk above and beyond BMI, implementation of fat distribution assessment into clinical practice remains a challenge. This paradox may also arise from BMI failing to measure fat redistribution to a centralized position in later life. The claimed BMI-defined overweight risk paradox may result in part from failing to account for central adiposity, rather than reflecting a protective physiologic effect of higher body-fat

content in later life [66]. At present, the definition of obesity is not ideal. BMI is not as good as body fat, fat distribution, body weight and body fluid components. These controversial effects of obesity are mostly due to the use of different indices of obesity in various studies.

### The other possible explanations for this phenomenon

It is well known that excess weight and obesity, as phenomenon of the metabolic syndrome, lead to enhanced cardiovascular risk, endothelial dysfunction, inflammation, and atherosclerosis. The analyses show that in the case of 2% of thin patients, comorbid conditions, mostly malignant diseases, heart failure, malnutrition or multiple organ dysfunction could be observed. Moreover, these patients were much older than their normal weight or obese counterparts [67]. Adiponectin, a secretory protein produced by adipocytes and inversely proportional to BMI, is a possible mediator for the so-called "obesity paradox" [68].

### Conclusion

Obesity has reached epidemic dimensions worldwide as a major risk factor for the metabolic syndrome, diabetes mellitus, dyslipidemia and hypertension, all significant causes of CVDs. When comes to the 'obesity paradox', inherent limitations of BMI as an index of adiposity, as well as methodological biases and the presence of confounding factors, may account for the observed findings of clinical studies, but also may distort the true relationship between obesity and mortality. Obese individuals generally present earlier, so disease states may be recognized and treated earlier. The obesity paradox may just be an over representation of cachexia. Therefore, it is possible that observations supporting the existence of an obesity paradox could be driven by both the limitations of BMI as an obesity index and clinical studies per se and may represent an epiphenomenon rather than a true causal relationship.

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