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# The Impact of Obesity on Risk Factors and Prevalence and Prognosis of Coronary Heart Disease—The Obesity Paradox

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ABSTRACT

Obesity is associated with a host of cardiovascular risk factors and its prevalence is rising rapidly. Despite strong evidence that obesity predisposes to the development and progression of coronary heart disease (CHD), numerous studies have shown an inverse relationship between various measures of obesity (most commonly body mass index) and outcomes in established CHD. In this article we review the evidence surrounding the ≪obesity paradox≫ in the secondary care of CHD patients and the CHD presentations where a paradox has been found. Finally we discuss the impact of cardiorespiratory fitness and a number of mechanisms which may offer potential explanations for this puzzling phenomenon.



## Obesity and Coronary Heart Disease (CHD) in primary prevention

Obesity is an increasing public health problem in the United States (US) and much of the developed world. Being overweight is defined by National Institutes of Health as a body mass index (BMI) ≥ 25 kg/m$^2$ and obesity as a BMI ≥ 30 kg/m$^2$. By these criteria, in 1960 approximately one in every ten Americans was obese, a number which has since tripled.[1] At the same time the proportion of the population which was overweight remained constant; currently the majority of the population is overweight or obese. Perhaps most concerning, morbid obesity (defined as ≥40 kg/m$^2$) has increased in prevalence from 1% of the population to 6%. The importance of obesity as a public health problem is difficult to underestimate; by some accounts[2] it is destined to take over smoking as the leading cause of preventable death in the US and it may halt[3] the improvements in life expectancy at a national level.

While in all likelihood obesity is a risk factor for CHD in itself, it is most importantly associated with a cluster of conditions that contribute directly and indirectly to the development and progression of CHD.[4,5] Obesity is associated with insulin resistance and type 2 diabetes mellitus (DM2),[6] through dietary indiscretion and endocrine activity of adipose tissue. This is illustrated by the fact that the increase in prevalence of DM2 has closely followed the rise of obesity.[7] DM2 is possibly the strongest CHD risk factor; it is characterized by the same 10-year risk for cardiovascular (CV) events as the population with known CHD.[8] It is also associated with endothelial dysfunction and dyslipidemias, both crucial to the initial steps in atherogenesis. In addition DM2 is one of the

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**Abbreviations and Acronyms**

**BF** = body fat

**BMI** = body mass index

**CABG** = coronary artery bypass graft

**CHD** = coronary heart disease

**CO** = central obesity

**CRF** = cardiorespiratory fitness

**CV** = cardiovascular

**DM2** = diabetes mellitus type 2

**FFM** = fat-free mass

**HDL-C** = high-density lipoprotein cholesterol

**HF** = heart failure

**HTN** = hypertension

**PCI** = percutaneous coronary intervention

**STEMI** = ST-segment elevation myocardial infarction

**TGs** = triglycerides

**US** = United States

**WC** = waist circumference

**WHR** = waist-to-hip ratio

most common causes of renal dysfunction, which is an independent risk factor for CHD itself. In fact guidelines require cholesterol-lowering treatment to be as aggressive in DM2 as in individuals with known CHD, effectively treating the disease as equivalent to CHD.

Adipose tissue is an endocrine organ,[9] and, especially, central adiposity, has been associated with elevated levels of circulating proinflammatory cytokines, most notably interleukin 6 (produced by adipocytes) which stimulates platelet activity and secretion of C-reactive protein. In addition, elevated levels of tumor necrosis factor alpha in obesity have been implicated in the development of insulin resistance. Angiotensinogen produced by adipose cells is a precursor of the renin–angiotensin–aldosterone system and is likely implicated in the pathogenesis of obesity related hypertension (HTN). Fat cells produce plasminogen activator inhibitor 1, which shifts homeostasis away from physiologic fibrinolysis, increasing thrombosis.

Obesity and, more specifically, central obesity (CO) are essential components of the metabolic syndrome. MS is characterized by central obesity combined with certain diagnoses (including impaired fasting glucose, HTN, dyslipidemias), a combination shown to be strongly associated with early onset CHD, and future events.[10,11] Arterial blood pressure (BP) and prevalence of HTN, yet another risk factor for CHD, are elevated in obesity not only due to the endocrine effect but also due to increased circulating blood volume and total peripheral resistance.[12] Higher BMI and CO are associated with dyslipidemia, including low levels of high density lipoprotein cholesterol (HDL-C) and high levels of triglycerides (TGs) and higher levels of small, dense, atherogenic low density lipoprotein cholesterol.[13] Obesity is associated with poor self esteem and psychological stress, which in itself is an independent risk factor for CHD.[14]

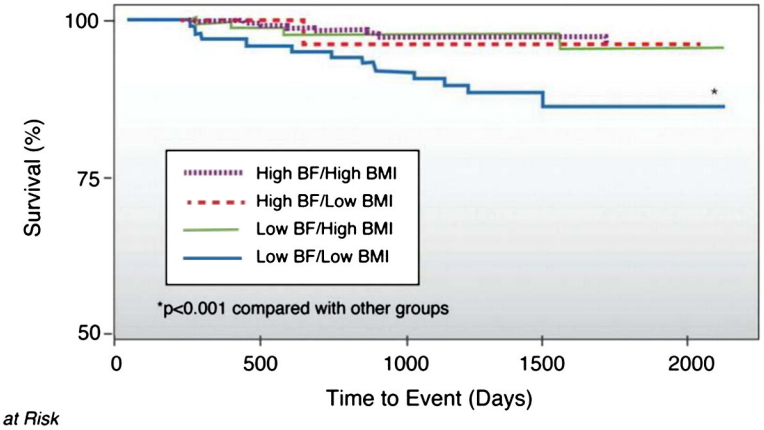
Significant evidence supporting weight loss as a tool to reverse risk factors associated with obesity further underscores the importance of obesity in CHD. In particular, weight loss has been associated with a reduction in BP and TGs. Exercise, a frequently used tool in weight loss programs, has been associated with increased insulin sensitivity, decreases in proinflammatory cytokines and increases in cardioprotective HDL-C. In fact, purposeful weight loss through cardiac rehabilitation and exercise programs has directly been linked to a reduction in CV events and all-cause and CV mortality in randomized clinical trials.[15]

However, despite the evidence of causality between obesity and development of CHD, multiple studies have now indicated that obesity might be associated with a better prognosis in the secondary care of those afflicted with CHD,[16] in stark contrast with primary care.[17] This paradoxical effect has been coined the "obesity paradox". Aside from CHD, similar effects have been shown in many chronic diseases[18] including end stage renal disease,[19] heart failure (HF),[20] chronic obstructive pulmonary disease,[21] DM2,[22] HTN,[23] and atrial fibrillation.[4]

## BMI paradox or obesity paradox

The obesity paradox has been most commonly described defining obesity by BMI, since it is a readily measured parameter in clinical practice. While the presentation of the CHD patient varies, the BMI–mortality curve is typically U-shaped, with increasing mortality at the extremes of obesity.[24] This relationship has been confirmed in many studies from all over the world,[25] with varying results in terms of optimal and most detrimental BMI range. In a large meta-analysis of 40 cohort studies by Romero-Corral[24] and colleagues with 250,000 patients with CHD, the authors noted an optimal adjusted mortality in the overweight (followed by the obese) subgroup. In contrast Das et al.[26] showed a BMI obesity paradox in a cohort of 50,000 patients with ST-segment elevation myocardial infarction (STEMI), favoring class I obesity (BMI 30–35 kg/m$^2$) with the lowest mortality. Dhoot et al.[27] noted an in-hospital, adjusted mortality benefit associated even with morbid obesity (BMI > =40 kg/m$^2$; when compared to <40 kg/m$^2$ aggregated) in 400,000 patients presenting with both STEMI and non-STEMI in 2009. Regardless of what the optimal BMI range is in which population,[28] one consistent result is that the typical National Institutes of Health range of ≪normal≫ BMI (20–25 kg/m$^2$) is not associated with the best outcome.

Despite its widespread use, BMI has received a lot of critique in terms of its accuracy to define obesity[29–32] in the CHD population. In fact it was suggested that its inaccuracy might be the cause of the obesity paradox, given the U shape of the adjusted BMI–mortality curve.[24,33] After all, BMI is an aggregate of varying amounts of fat free mass (FFM) and body fat (BF), each of which contributes in its own way to the metabolic profile of the subject. The overweight range, the nadir of the BMI-mortality curve found by Romero-Corral and colleagues in the meta-analysis, is a range where BMI correlates poorly with BF (r 0.17).[31] In addition, FFM enjoys a widespread acceptance as a positive prognostic factor. It is protective in the general population and by inference in the CHD population through its association with muscle strength,[34,35] nutritional status[36] and cardiorespiratory fitness (CRF). In 2009, researchers in Denmark[37] found an

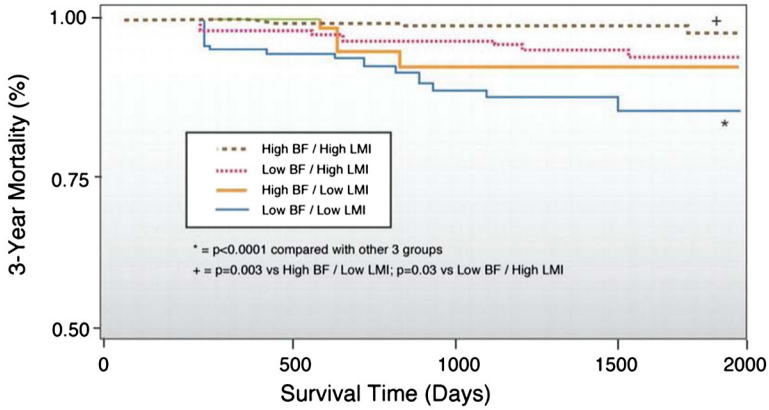



*No. at Risk*

| | | | | | |
|---|---|---|---|---|---|
| High BF/High BMI | 311 | 262 | 186 | 107 | 10 |
| High BF/Low BMI | 125 | 116 | 88 | 51 | 6 |
| Low BF/High BMI | 26 | 23 | 17 | 10 | 2 |
| Low BF/Low BMI | 119 | 110 | 81 | 46 | 12 |

**Fig 1 – Kaplan–Meier survival curves of 581 subjects referred for cardiac rehabilitation by high and low body mass index (BMI) and body fat(BF) followed for 3 years for all cause mortality. The lean, i.e. the subgroup with both low BMI and BF did significantly worse than the other subpopulations. Reproduced with permission from Lavie et al.[38]**

increase of total mortality and CHD associated with low thigh circumference, presumably a surrogate measure for physical activity and muscle mass. This led researchers to examine the impact of body composition on prognosis in CHD. However, surprisingly BF has been shown to have a similar protective effect on all-cause mortality in CHD. In an analysis of nearly 600 patients referred for cardiac rehabilitation after major CHD events and followed for an average of 3.1 years, Lavie et al. was able to illustrate this (Fig 1). Initial observations[38] suggested that specifically the low BMI/low BF subgroup had a particularly high mortality (11% vs. <4% for the other groups), suggesting a lean paradox where the lean do *worse* rather than the obese better. Later the authors expanded on these findings (Fig 2) by proving that FFM and BF were protective independently[39] of each other and major confounders (age, gender, ejection fraction and CRF). Individuals with low BF were 2.6 times less likely to survive at 3-year follow up and low FFM was associated with a 3.1- to 3.9-fold increase in mortality, depending on exactly what was included in the multivariate analysis. This was not the first




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

**Fig 2 – Kaplan–Meier survival curves of 570 subjects referred for cardiac rehabilitation by high and low lean mass index (LMI) and body fat (BF) followed for 3 years for all cause mortality. The subgroups with high LMI and high BF did better than the intermediate groups, and the subgroups with low LMI and low BF did significantly worse, with a mortality of 15%. Reproduced with permission from Lavie et al.[39]**

time that a surprisingly protective effect of BF was shown.[40–42] Interestingly, in the same data the authors noted that the relationship of age- and gender-adjusted BF[43] to mortality followed a U-shaped curve similar to the curve observed in BMI, where those subjects classified as overweight had the lowest mortality (2%), followed by the obese, the normal and finally the underweight with a 3 year mortality of 25% (Fig 3). A notable limitation was the use of the skinfold method to measure BF, which mainly measures subcutaneous fat, which is not consistently associated with the same risk factors as visceral fat.[44] In order to further investigate the role of abdominal adiposity in the obesity paradox other anthropomorphic measurements have been examined, quantifying CO[45] using waist to hip ratio (WHR) or waist circumference (WC). It has been suggested these anthropomorphic measures would do away with the paradox.[46] Although results are inconclusive, thus far the majority of evidence seems to point towards an increased mortality in secondary care associated with visceral fat, similar to primary care. In a recent study of more than 15,000 patients with average 4.7 years of follow up, Coutinho et al.[47] showed the highest adjusted mortality in CO patients (as defined by WHR). Interestingly this detrimental effect of higher WHR was independent of the protective effect of BMI, and those individuals with ≪normal weight CO≫ had a worse prognosis when compared to those with higher BMIs and CO. Of note, independent of WC and BMI, hip circumference has been shown to be protective of CV disease mortality in women (but not in men).[48] A notable exception where WC was found to be protective was a study of McAuley et al.,[49] who found evidence of an obesity paradox by WC in men with low CRF from the Aerobics Center Longitudinal Study (Fig 4).

Despite the mortality benefit of the obese, intentional weight loss remains protective. In 529 consecutive subjects referred for cardiac rehabilitation after major CHD events, Lavie et al.[40] found significantly better improvements in metabolic profiles, exercise capacity and a trend towards lower mortality in overweight/obese individuals with greater weight loss (defined as greater than median −1.5%). Changes in WC have not been shown to have a protective benefit additive to weight loss.[50]

## Impact of presentation

The BMI paradox has repeatedly been shown in registries of hospitalized patients. The above mentioned analysis of Dhoot et al.[27] was done in an in-hospital group of 400,000 patients presenting with both STEMI and non-STEMI in 2009. Fonarow et al.[51] evaluated in-hospital mortality in the Acute Decompensated Heart Failure National Registry and found a decrease of 10% mortality after adjustment for confounders associated with every 5 unit increase in BMI.

In the population referred for revascularization a paradox has also been found.[52] In a meta-analysis of 11 prospective randomized trials, Park et al.[53] found a BMI paradox in nearly 50,000 patients referred for percutaneous intervention (PCI). In fact, despite Asians having a higher percentage BF for the same BMI, the authors noted that the population with BMI over 30 kg/m$^2$ had lower mortality and risk of CV events over mean 2.1 year follow up. Of note, the trials from which the data were pooled all excluded terminal illness and malignancy. Das et al.[26] showed a BMI obesity paradox in a cohort of 50,000 patients with STEMI. The overweight and class I obese had the lowest adjusted mortality, and the highest adjusted mortality was found in class III obese. The normal weight had the highest unadjusted mortality, which decreased significantly relative to the other groups after adjusting for validated mortality predictors (including age). A BMI paradox has also been shown in the CABG population.[54] In a meta-analysis of 22 cohort studies and randomized trials, Oreopoulos et al.[52]

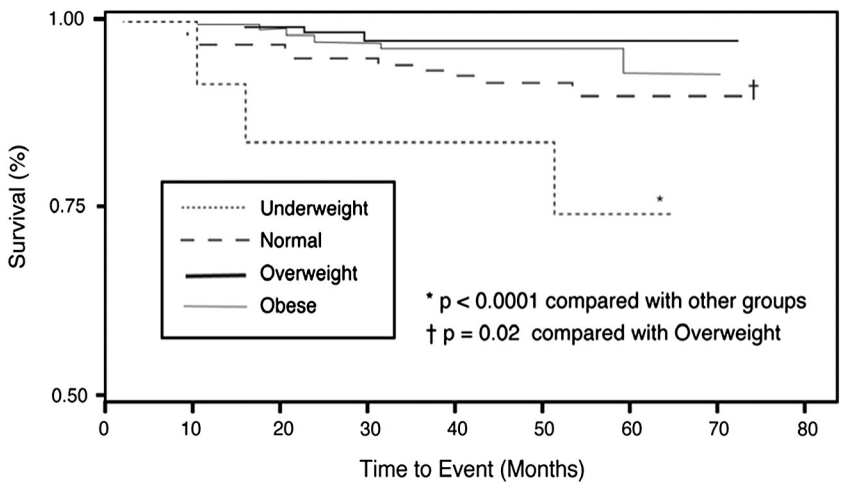



**Fig 3 – Kaplan–Meier survival curves of 581 subjects by age and gender-adjusted body fat category. The underweight and normal body fat categories had significantly worse prognosis than the overweight and obese categories. After adjustment for confounders higher body fat category was associated with lower mortality. Reproduced with permission from De Schutter et al.[43]**

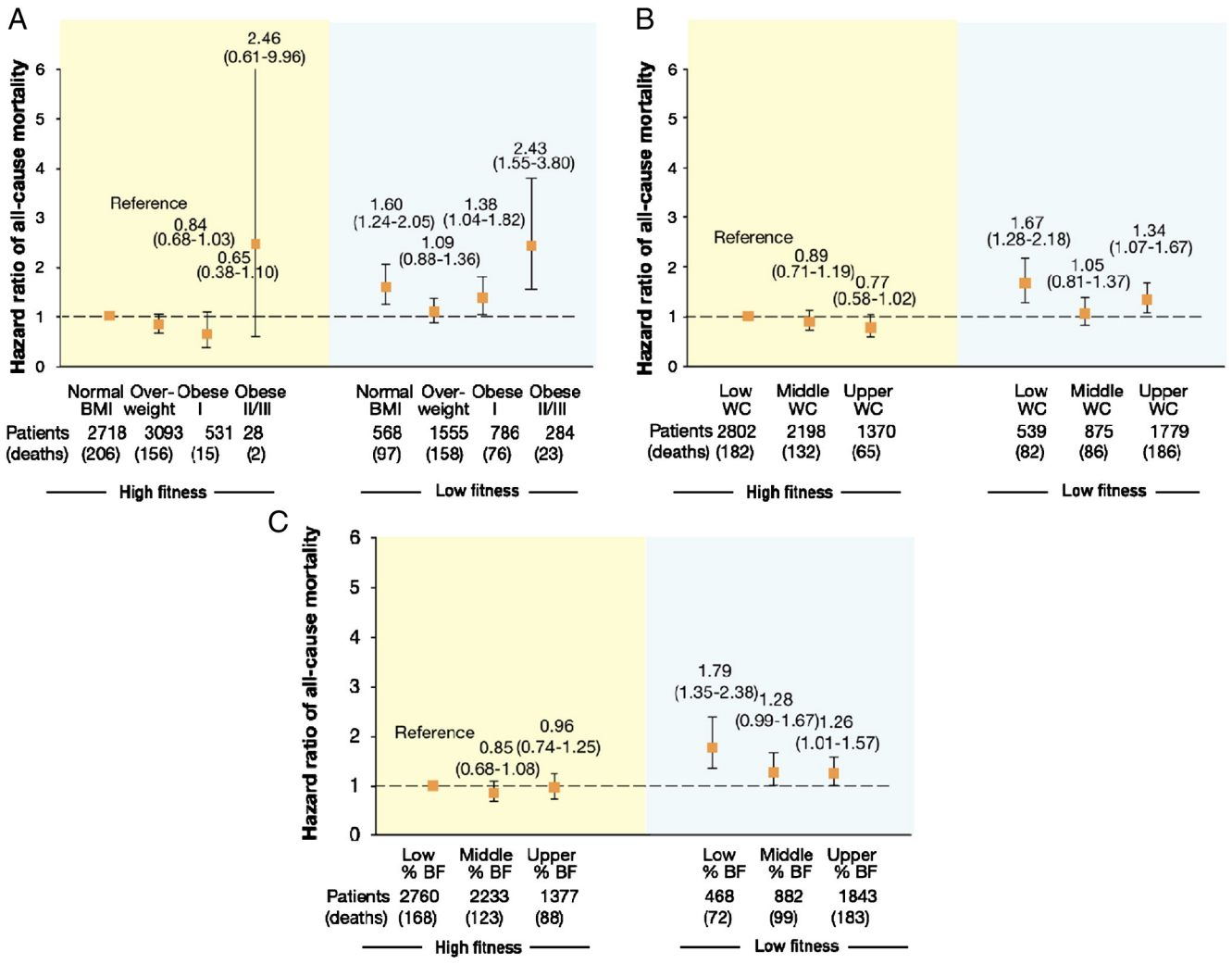



**Fig 4 – 9563 subjects stratified by body mass index (BMI) category (A) and waist circumference (WC) and body fat (BF) tertiles ((B) and (C) respectively) and followed for 13 years for all-cause mortality. Normal BMI, low WC and low BF in the high fitness group were used as reference groups. Boxplot represents hazard ratio and 95% confidence interval after adjustment for age, baseline examination year, physical activity, smoking, hyperlipidemia, diabetes and family history of cardiovascular disease. Reproduced with permission from McAuley et al.[49]**

observed that obese subjects by BMI have a mortality benefit short-term (less than 30 days) but not long-term (up to 5 years) after CABG.

In ambulatory care settings, the paradox has been shown as well. In a recent study from the United Kingdom[55,56] with approximately 4400 patients with a clinical diagnosis of CHD or prior stroke, the obese (BMI > = 30 kg/m$^2$) had a 7 year all-cause mortality benefit despite having more lifestyle risk factors such as low physical activity, self-rated health and higher prevalence of HTN and DM2. Recently the paradox was expanded to individuals without known disease, but with a high suspicion. Uretsky et al.[57,58] found a BMI paradox in individuals referred for cardiac stress testing, with the obese (BMI > 30 kg/m$^2$ as a group) having the lowest all-cause mortality after an average of 8 years of follow-up. Of particular interest was that unlike in other studies, in this population the paradox was noted in all groups, regardless of CRF.

## Impact of CRF

Increasing evidence points towards a significant interaction between CRF and the obesity paradox. CRF is a powerful prognostic factor in CHD and other diseases, and it has even been suggested that its improvement might yield greater health benefits than a change in weight.[59] In several studies now in CHD[60] and HF,[61] the obesity paradox by BMI and other measures of obesity has been shown to be predominantly present in individuals with low CRF. In a recent study of 2066 patients with systolic HF followed for five years, Lavie et al.[61] found an obesity paradox (lowest mortality in the class I obese) in patients with a peak oxygen consumption < 14 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ on cardiopulmonary exercise testing, but no paradox in subjects with higher CRF. McAuley et al.[49] evaluated 9563 subjects with CHD stratified by BMI category as well as by WC and BF tertiles and followed for 13-year all-

cause and CV mortality. After adjustment for age, baseline examination year, physical activity, smoking, dyslipidemia, DM2 and family history of CV disease, they found all-cause and CV mortality benefits associated with higher BMI, WC tertile and BF tertile in the low CRF group, but not in the high CRF group (Fig 4). As mentioned above, a recent study in a nuclear medicine referral population showed an obesity paradox by BMI regardless of CRF, although clinical events were very low in those with high CRF.[57,58]

Having a BMI in the normal range might still be associated with the best prognosis in an individual with normal CRF. Whether there is an intrinsic property to low CRF that is associated with the underlying etiology of the paradox is currently not known. Likely there is a selection bias in testing physically inactive obese subjects earlier for CHD, because of the high pretest probability. In addition CRF is ideally measured using cardiopulmonary stress testing, and severe lung disease might be a limiting factor to CRF, and this may represent an unmeasured confounder of the paradox, given the widespread underdiagnosis of lung disease.[62] However, in several of our studies in patients with CHD, lung disease did not clearly explain the obesity paradox.[38,39,63]

## Mechanisms

The obesity paradox could be associated with several biases such as a lead time bias, confounding bias and publication bias. A lead time bias occurs when earlier detection of the disease is confused with prolonged survival. The increase in pretest probability for CHD in obese individuals could lead to earlier testing, and earlier diagnosis could result in increased survival. In contrast, lean individuals have a lower pretest probability, and consequently present with more advanced disease, and thus a worse subsequent prognosis. There is also the potential for a confounding bias. Smoking is a common precursor for CHD and lung disease, where lower BMIs are known to be associated with mortality.[64] In addition a diet high in red meats, sedentary lifestyle and smoking are all risk factors for CHD and malignancy, a disease known to be associated with cachexia. Some studies have attempted to avoid this bias by excluding malignancy[53] or studying populations in which active malignancy is rare.[38,39] A publication bias arises when positive studies are more likely to be published than negative studies, which could be the case since a survival disadvantage associated with obesity would be considered ≪old news≫ and not contributing to the literature. However, several meta-analysis of prospective randomized trials published for other reasons have now shown a paradox.[52,53]

There are other potential mechanisms through which the paradox could arise. Obesity is associated with modifiable risk factors such as DM2, HTN, dyslipidemia and higher levels of inflammation. At the point of diagnosis, nonobese individuals have less « room for improvement », potentially altering their disease course. Part of the obesity paradox could come from a subset of patients who, with the help of diet and exercise, lose weight, improve CRF and structurally alter their prognosis. Alternatively, obese patients may have earlier, more aggressive intervention for their CHD.[65] In addition, the non-obese population diagnosed with CHD might contain a subset of the population with very poor prognosis due to genetic make-up or may have other risk factors that confer a worse prognosis, such as autoimmune diseases or advanced renal disease.

When evaluating CHD as a systemic disease, one has to consider the potential of CHD to be a cachectic disease, similar to HF. FFM and BF both provide a metabolic buffer and as such could be protective. Poor nutritional status has been shown to be a significant predictor of mortality after cardiac surgery,[66] which a significant proportion of CHD patients will undergo. The CHD population also has significant overlap with the elderly population, a population in which lean mass and nutritional status form a powerful predictor of survival. To our knowledge, none of the studies adjust for non-intentional weight loss.

## Conclusions

Despite the known adverse effects of obesity on the development, severity and progression, it has repeatedly been shown that CHD patients with overweight or obese BMI and even BF have lower mortality, especially in combination with low CRF. Intentional weight loss remains protective and a goal in CHD patients. Above all, higher levels of CRF are associated with better prognosis in all populations of CHD and CV patients, and in most studies, an obesity paradox in not apparent in patients with high, protective levels of CRF. Therefore, improving levels of CRF may be even more important than improving BMI/BF in patients with CHD and CV diseases.

## Statement of Conflict of Interest

The authors declare that there are no conflicts of interest.

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