European Heart Journal (2005) **26**, 5–7
doi:10.1093/eurheartj/ehi055

Editorial

Obesity and heart failure prognosis: paradox or reverse epidemiology?

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Online publish-ahead-of-print 30 November 2004

This editorial refers to 'Effect of obesity and being overweight on long-term mortality in congestive heart failure: influence of left ventricular systolic function'† by F. Gustafsson *et al.*, on page 58

Obesity is a problem reaching epidemic proportions in westernized society and is a major cause of preventable death.[1] Obesity has many adverse effects on coronary artery disease (CAD) risk factors and is probably an independent risk factor for CAD events. Epidemiological studies have clearly shown a strong relationship between obesity and increased risk of cardiovascular disease and mortality in the general population,[1,2] although in some of these studies a 'J-shaped' or 'U-shaped' curve has been present, meaning that those individuals with low body mass index (BMI) also have increased mortality.

Obesity is also known to exert numerous adverse effects on cardiac function. In early obesity, an expanded intravascular volume results in an increase in cardiopulmonary volume or increased pre-load.[1,3] Over time these changes lead to an increased prevalence of eccentric left ventricular hypertrophy and the propensity for more complex ventricular dysrhythmias; we and others have noted these early abnormalities as well as improvements in both diastolic and systolic ventricular function following marked, purposeful weight reduction.[1]

Finding the relationship between obesity and heart failure (HF), however, has been complex. A recent epidemiological study from the Framingham Heart Study clearly indicates that obesity and being overweight are potent predictors of subsequent clinical HF.[4] Although obesity causes abnormalities in diastolic and systolic function and predisposes to clinical HF, obese patients with HF paradoxically seem to have a more favourable clinical prognosis.[1–3,5,6] Kalantar-Zadeh *et al.*[2] have recently reviewed six studies demonstrating that, among patients with HF, obesity appears to be associated with a better overall clinical prognosis and patients with more severe HF tend to have lower BMI than do age- and gender-matched control subjects. Among the studies reviewed, Horwich *et al.*[5] studied 1203 individuals with mostly class IV HF, and found that a higher BMI was associated with a better survival rate (*Figure 1*) and, in multivariate analysis, there was an inverse association between BMI and mortality. We recently studied 209 patients with mostly class II and III HF and a mean ejection fraction of only 23%; we found that higher BMI and higher percentage body fat were associated with better event-free survival during a 2 year follow-up.[6] In fact, in multivariate analysis, a higher percentage body fat was the strongest independent predictor of event-free survival. We have described this as an 'obesity paradox' whereas others have described the relationship between some of the cardiovascular risk factors and chronic HF prognosis as 'reverse epidemiology'.[2] Importantly, only limited information is available on whether this relationship is causal or merely an association. It is postulated that lower body weight may be associated with a heightened catabolic state, which is associated with high levels of tumour necrosis factor and other cytokines and increased cortisol/dihydroepiandrosterone balance.[6] Clearly, in advanced HF, cachexia and wasting appear to be independent predictors of increased mortality.[7] However, in our cohort of patients with HF in the lowest quintile of body composition parameters, the BMI and percentage body fat values were at levels generally considered to be 'healthy' and certainly not at levels consistent with a cachetic state.

In the current issue of the *European Heart Journal*, Gustafsson *et al.*[8] present data which further suggest a protective influence of increasing BMI on subsequent mortality in 4700 patients hospitalized with HF. Moreover, they demonstrated the impact of chronic obstructive

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† doi:10.1093/eurheartj/ehi022

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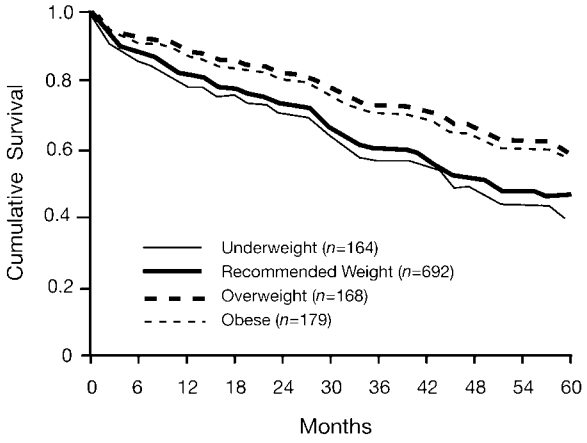

Figure 1 Risk-adjusted survival curves for the four BMI categories at 5 years in a study of 1203 individuals with moderate–severe HF. Survival was significantly better for the overweight and obese categories (from Horwich *et al.*,[5] with permission).

lung disease in these patients, and that obesity seems to be particularly protective in HF patients with more preserved systolic function. Unlike most of the other studies in the literature, however, they did not find a better clinical prognosis in obese patients with more systolic dysfunction, although they did note the considerable differences in their study population compared with the others in the literature, particularly the higher age and their acute hospitalization status. The strength of their study is the very large sample size and the hard endpoint (total mortality). A weakness is that their data may be confounded by presentation with an acutely decompensated HF event requiring hospitalization. There could also be an interaction of co-morbidities in that the patients who died were older and had more renal dysfunction, atrial fibrillation, smoking, and obstructive lung disease, and lower use of angiotensin converting enzyme inhibitors, and many of these factors, including lung disease, are known to be associated with a poor HF prognosis.[9] In addition, medications were not accounted for and there was no description of detailed demographic profiles and co-morbidities in the two distinct HF cohorts with either preserved or reduced systolic function. Finally, their study assessed total mortality but not cardiac events or cause of death, and certainly obesity or body fat status could effect survival from non-cardiac causes. However, despite these potential study limitations, the constellation of findings by Gustafsson *et al.*[8] support the general idea of an 'obesity paradox'.

The reasons for this apparent obesity paradox are uncertain. Several studies have suggested that the natriuretic peptide system and adiposity are closely linked; we recently demonstrated a reduced natriuretic peptide level in obese patients with HF.[3] This lends credence to the explanation that the earlier expression of HF in the presence of obesity could be related to reduced circulating natriuretic peptides. Therefore, obese HF patients may present earlier due to symptoms at a less severe level of HF, therefore promoting discordance between symptoms and prognosis. It is also well recognized that peak oxygen consumption with exercise is a potent predictor of prognosis in advanced HF[1] and, for practical purposes, fat does not consume oxygen or receive substantial perfusion. We have demonstrated that lean adjusted exercise indices (including peak oxygen consumption, anaerobic threshold, and oxygen pulse) all predict prognosis better than non-fat-adjusted variables, which may be particularly applicable to the favourable prognosis in HF patients with a high percentage body fat who generally have relatively high lean-adjusted exercise indices.[10,11] In addition, most of the above HF studies, including the paper by Gustafsson *et al.*,[8] have not accounted for the effects of non-purposeful weight loss, which may be associated with more advanced HF and a poor prognosis.[1,7] Clearly, purposeful weight loss in HF patients with morbid obesity has been associated with improvements in systolic and diastolic function and HF classification,[1] but no large studies have determined the impact of purposeful weight reduction on HF prognosis and mortality in either patients with preserved or abnormal systolic function. Finally, other lines of evidence have suggested enhanced protection with obesity against endotoxin/inflammatory cytokines as well as increased nutritional and metabolic reserve.[3] Certainly, obesity could be associated with a better prognosis in HF and this relationship is not necessarily causal. In this regard, obesity is also associated with better prognosis in other distinct populations, including end-stage renal disease patients undergoing dialysis and the elderly,[2] as well as patients with advanced cancers. Likewise, other conventional cardiovascular risk factors in addition to obesity, including high total cholesterol and higher blood pressure, are associated with better prognosis in chronic HF—hence, the term 'reverse epidemiology'.[2]

Further studies are needed to elucidate the mechanism for this relationship between obesity and improved HF prognosis further. In addition, studies on modalities to improve nutritional/metabolic reserve and purposeful weight reduction, especially in obesity, on HF prognosis are urgently needed.

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