

# The obesity paradox in heart failure needs scientific weight

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Obesity paradox is a term for a medical hypothesis which holds that obesity can counterintuitively be protective and associated with greater survival in heart failure (HF) patients [1, 2]. Although obesity is a risk factor for the development of HF and increases the prevalence of classical cardiovascular risk factors (hypertension, insulin resistance, diabetes mellitus and hyperlipidemia), obese patients with HF seem to enjoy a more favorable clinical prognosis [3, 4]. Even more, basic scientific and animal studies identified detrimental effects of adiposity and insulin resistance on the endothelium, cardiac function and remodeling [5, 6]. Thus, it is surprising that obese and overweight HF patients seem to have better prognosis than lean patients.

The Atherosclerosis Risk in Communities (ARIC) study [7] illustrates this phenomenon well. During a decade of retrospective longitudinal data collection, the authors show that even pre-morbid obesity is associated with improved outcome in HF patients [8]. In ARIC, the authors follow-up 1,487 patients with incident HF who had body mass index (BMI) measured at least 6 months prior to diagnosis. The mean interval between BMI assessment and HF diagnosis was 4 years, ensuring that the BMI measurement was not confounded by HF related factors. After adjustment for clinical risk factors, pre-morbid overweight and obesity were associated with 23% and 25% reductions, respectively, in mortality risk during 10-year follow-up.

This improved clinical outcome in obese patients with HF is an epidemiological confounding observation, named “reverse epidemiology”, a confusing term itself [9]. The “obesity paradox”

was coined initially in dialysis patients less than 12 years ago. This concept was discussed only briefly in textbooks [10], and is not mentioned in the European Society of Cardiology (2012) and American Heart Association/American College of Cardiology (2013) Heart Failure Guidelines [11, 12].

As mentioned above, the “obesity paradox” is an observational finding, which has not adhered to scientific validation methods, i.e. active modification of the possible casualties will lead to modification of the observation. In order help clarify the paradox, Zafrir et al. [13] evaluated this issue applying body surface area (BSA) instead BMI because BSA is a more precise metabolic mass index than the BMI and is not influenced by abnormal adipose mass. The author’s findings indicate that BSA is a stronger predictor of mortality than other measures of body habitus, irrespective of height correction. The greater the overall bulk of the body, the better the survival. BSA provides prognostic information similar to BMI in systolic HF. This is concordant with previous studies such as those by Futter et al. [14] and Frankenstein et al. [15].

In order to investigate different confounders, Zafrir et al. [13] performed adjusted analysis from multivariate variables. They concluded that young age was the main bias factor which makes sense being that younger patients have a higher chance of living longer. This finding helps prove that the “obesity paradox” is more of a statistical manipulation than a real occurrence. The U-shaped relationship between body mass and outcome reported from epidemiological studies becomes much flatter with increasing age (Fig. 1) and perhaps with chronic illness it is moved to the right [16].

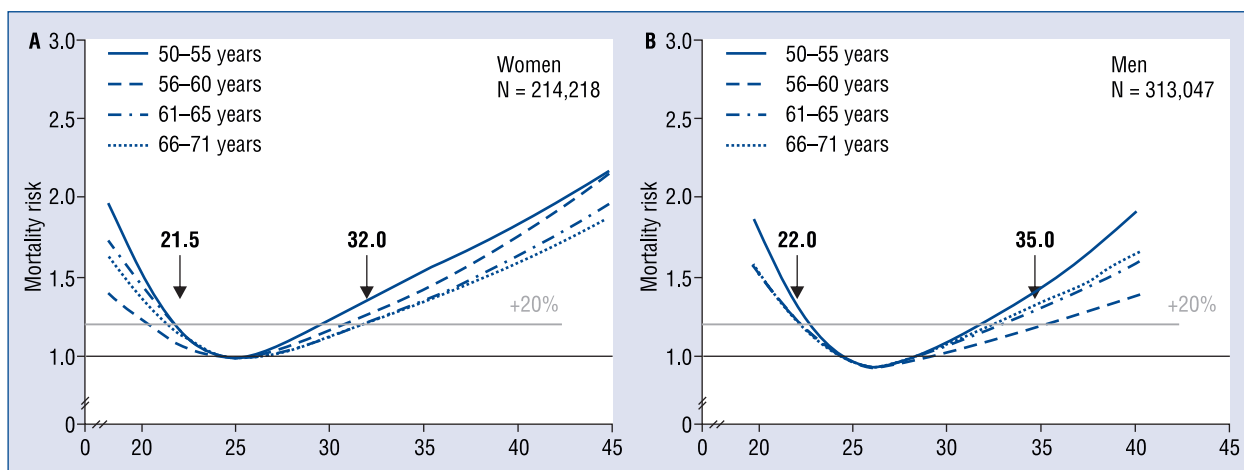
Why do we need to understand this paradox? Does this observation have direct clinical implications? At this point, it is difficult to determine.

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**Figure 1.** Association of body mass index (BMI) and mortality risk in age subgroups in men (A) and women (B). The gray line indicates a 20% increased risk of death, showing a similar risk for men aged over 66 years with a BMI of 22 kg/m<sup>2</sup> and with a BMI 35 of kg/m<sup>2</sup>. Adapted from Adams et al. [16]

Additional studies must be conducted in order to understand this paradox across longer period of time and should focus on other related factors such as metabolic and physiological data, fat distribution, degree of insulin resistance in various HF stages and functional class. If we adopt this paradox as a scientific fact, the weight reduction will be contraindicated in HF patients, which can be a detrimental effect! There is little evidence regarding the impact of weight loss in obese HF and whether or not this is beneficial. There have been small studies regarding the cardiovascular effects of both dietary weight loss and bariatric surgery, but few in HF. This is an important and increasingly relevant clinical question which must be addressed. To understand physiological consequences of obesity in HF, further work is warranted in basic and clinical investigation. Human studies need to include more detailed metabolic and physiological data, fat distribution, degree of insulin resistance in various HF stages and functional class.

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