Does obesity make it better or worse: insights into cardiovascular illnesses

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This editorial refers to ‘Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry†, by O. Angerås et al., on page 345 and ‘The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness’, by F.B. Ortega et al., on page 389

Oodles of studies have been published with regards to the obesity paradox in chronic disease. Still, researchers remain confused, clinicians unconvinced, and Joe Bloggs does not want to be overweight anyway—mostly because over the last three decades he has been exposed to diverse forms of education saying that ‘obesity makes you ill and kills you’. In the words of the Roman philosopher Seneca (4 BC—65 AD): ‘Every man prefers belief to the exercise of judgement’. Since public belief prefers being slim to being overweight or obese, the prevailing wisdom holds that being slim must be generally good for you. In addition, numerous studies have shown that overweight and obesity confer disadvantages, as their presence is associated with the development of cardiovascular disease, diabetes mellitus, and several other metabolic perturbations. Thus, obesity must be bad.

The question that has arisen over the last 13 years is whether this concept is true, irrespective of a given individual’s circumstances. The original description of the obesity paradox was published in 1999 using data from > 1300 patients with chronic kidney disease undergoing haemodialysis. The authors of that study concluded that ‘nutrition aimed to achieve the high end of normal body mass index (BMI) may help to reduce the high mortality and morbidity in haemodialysis patients’. This conclusion extrapolated far beyond the data obtained in the study, because nutritional intake was not even analysed; however, it paved the way for a vast array of similar studies in patients with chronic obstructive pulmonary disease, chronic heart failure, stroke, and coronary artery disease, as well as in patients with critical illness. For the obesity paradox to take effect, it thus requires a chronic disease in the first place.

Looking at body weight, it should also be considered that there are two extreme ends to the body weight spectrum, underweight and cachexia as well as overweight and obesity. The latter can come in a wide spectrum ranging from a body mass index (BMI) of 30 to well above 45 or 50 when morbid obesity is present. Both extremes can influence the course of the underlying disease. In addition, speaking of body weight requires consideration of body composition, and attention should be directed at whether body weight loss or gain is derived from changes in fat or muscle mass. It is then paramount not to mix up overweight and obesity. In Caucasians, overweight is defined as a BMI between 25 and 30 kg/m², and obesity as a BMI > 30 kg/m². The obesity paradox suggests that a BMI of ~ 25–35 kg/m² carries benefit in patients with chronic disease (Figure 1), possibly because excess fat serves as an energy depot in times of need. Therefore, it would be just as correct to define an ‘obesity paradox’ as we define an ‘obesity paradox’. This statement, however, should not be extrapolated to healthy individuals. In summary, the most obvious seems to be most confusing in understanding the obesity paradox: healthy people and patients with chronic diseases are quite different.

Two recent articles have been published on the association of obesity with outcomes. Angerås et al. analysed data from a prospective registry study of 45 693 patients admitted to Swedish hospitals for suspected acute coronary syndromes. All patients underwent cardiac catheterization, and 92.5% of patients were found to have significant stenosis at coronary angiography. Patients were followed for an mean of 21 months. The authors state that the primary endpoint of the study, i.e. all-cause mortality in patients with significant stenosis of one or more coronary arteries, was highest in patients who were underweight with a BMI < 18.5 kg/m².
followed by patients with normal weight (BMI 18.5 to <25 kg/m²), and lowest in patients who were overweight or obese. This was still true after rigorous multivariable adjustment. Looking at 3-year mortality, however, rates are similar across weight groups from 23.5 to 35 kg/m². The effect appeared to tail off in patients with BMI >35 kg/m², i.e. among those with severe or morbid obesity, although these groups were not further subclassified. Indeed, the 95% confidence intervals were large and crossing 1, suggesting a lack of effect in this group. However, in the study by Angerås et al., only 4.5% (n = 1757) of patients with confirmed acute coronary syndrome fell into this category. This point is worth mentioning as it underscores the striking lack of data in this as in most previous studies for patients with a BMI >35 kg/m². Current data buttress the view that a BMI between 25 and 35 kg/m² may have beneficial effects once chronic illness is present, but they also highlight the fact that we simply do not know whether or not this is still true for patients beyond the upper margin of 35. Even more interesting is the sharp increase in the risk of death in patients with BMI <18.5 kg/m². Unfortunately, the somewhat more clinically relevant cut-off of a BMI <20.0 kg/m² which helps to identify cachexia in chronic illness has not been used.

There are a number of limitations to this study, several of which are duly acknowledged in the manuscript, including the observational nature that should not be regarded as causative. In addition, we do not know whether or not oedema played a role in the significant proportion of patients with heart failure and whether or not there was a selection bias with regards to those who were excluded due to missing data. Since patients were investigated after an acute coronary syndrome, it may also well be that this event prompted some patients to follow a more healthy lifestyle, and such an effect may have influenced outcomes: surprisingly, the difference in survival between BMI groups was only observed after 3 years of follow-up, but not for in-hospital or 30-day outcomes. Apart from that, all patients had a white Caucasian background, and that implies that the findings should not be extrapolated to other ethnic groups such as Asians for whom other cut-offs have been defined to describe obesity. For example, the Cooperative Meta-analysis Group of the Working Group on Obesity in China suggests to define overweight as BMI ≥ 24 kg/m² and obesity as BMI ≥ 28 kg/m².

Since obesity appears to be able to confer survival benefit in patients with chronic disease, it should also be taken into account that obesity is frequently associated with changes in metabolic profiles. Ortega et al. were interested in the fact that some obese subjects remain metabolically healthy, and hypothesized that these subjects have a higher level of cardiovascular fitness than metabolically abnormal obese peers and that such metabolically healthy obese subjects should demonstrate lower mortality rates. A metabolically healthy status was defined using criteria for the definition of the metabolic syndrome, and participants termed metabolically healthy were allowed to fulfilled no more than one such criterion. Obesity was defined as BMI >30 kg/m² or as body fat content ≥ 25% in men and ≥ 30% in women using hydrostatically estimated percentage body fat (underwater weighing). Cardiovascular fitness was defined as the total time of symptom-limited treadmill exercise. The name of the study, the Aerobics Center Longitudinal Study, already suggests that the study predominantly recruited subjects with an interest in a healthy lifestyle and sports activity, and this fact needs to be considered when looking at the data. In addition, the percentage of females was only 24.3% as acknowledged by the authors, and 98% had a Caucasian background.

Data of 43 265 subjects without cardiovascular disease or cancer at baseline were available. The number of obese subjects varied strikingly between the definition criteria: as defined by BMI, 5649 (13.1%) were judged as obese; as defined by body fat content, this was true for 12 829 (29.7%) subjects. A metabolically healthy status was found in 30.8% or 46.3% in the two groups, respectively, and an abnormal metabolic status was strongly associated with increasing BMI, percentage body fat, or waist circumference. Not surprisingly, a metabolically healthy status was associated with better baseline fitness. Interestingly, the authors found that the metabolically healthy phenotype had a 30–50% lower risk of morbidity and mortality than their metabolically abnormal peers. Looking at the hazard ratios for all-cause mortality, we were surprised to see that the smallest group of subjects, i.e. metabolically healthy and obese people, served as a reference group. One may argue that healthy non-obese subjects should be the reference group for risk calculation in this scenario, and in fact this group comprised almost three times as many patients as the other two groups combined. In addition, the authors deliberately left out of their analysis what they call ’middle groups’ of BMI or body fat. This step implies that data of up to 20 000 subjects were left out of the analysis, depending on the diagnostic criteria chosen. Given the relatively small effect differences between the extreme groups, it would have been helpful to see if the ’middle groups’ also follow the same trend. Finally, due to the small effects and the relatively large confidence intervals for the hazard ratios, even for extreme groups, it cannot be ruled out that the subgrouping into metabolically abnormal/healthy and normal weight/obese is far from optimal. As all hazard ratios become insignificant once fitness adjusted, the data suggest that fitness status is the better variable to define prognosis. However, a rigorous statistical
evaluation of fitness status has not been presented. Additionally, an analysis of BMI, percentage body fat, fitness, or the like on a continuous scale would have provided much better insight.

The available studies, together with previously published study data, permit the conclusion that weight loss in patients with chronic illness and a BMI \( \leq 40 \) kg/m\(^2\) is always bad, and in fact not a single study exists to suggest that weight loss in chronic illness makes patients live longer. In this context, fat tissue has several beneficial effects, for example in its action as an endocrine organ, but also, nevertheless, as an aid in protecting against hip fracture. Obesity may carry benefit up to a certain degree, and it should be recognized that obesity is not necessarily associated with abnormal metabolic function.

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**References**