Title: Obesity and heart failure – when “epidemics” collide

Short title: Obesity and heart failure

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Keywords: heart failure, obesity, epidemiology, incidence, body mass index, myocardial infarction, stroke

Word count: 1180

The growing burden of obesity has been referred to as an "epidemic". The World Health Organisation estimates that 50% of adults living in Europe are overweight or obese [1], a population approximately equivalent to that of Germany, France, the United Kingdom and Italy together. This concerning statistic is made more terrifying by the data presented by Rosengren *et al* [2] in this issue of the *European Heart Journal*. They examined the association between body weight and the development of heart failure in over 1.5 million young men (mean age 18.6 years). They report that the incidence of heart failure in these young men, who had their body mass index (BMI) calculated as part of the physical examination for national service, was 5-7 per 100,000 person years of follow up in those of normal weight, rising to 12 to 40 per 100,000 person years of follow up in those who were overweight or obese as defined by their BMI. The risk of developing heart failure was 9 times higher in the highest BMI category (≥35 kg/m^2) compared to those with normal BMI even after adjustment. Behind this relatively simple (and perhaps unsurprising) message lies a complex story that underscores the difficulty we have in dealing with the obesity epidemic.

Compared to those who were normal weight, in those who were obese, the relative risk of developing heart failure was higher than the risk of experiencing a myocardial infarction (MI) or stroke. This suggests there may be a closer association between BMI and heart failure than either stroke or MI. Given that heart failure is commonly caused by ischaemic heart disease this finding is somewhat counterintuitive. We might expect BMI to be more strongly linked to the commonest precursor of heart failure, atherosclerotic heart disease, than heart failure itself. Obesity is associated with diabetes, high cholesterol and inflammation, all risk factors for the development of atherosclerosis. However, there is evidence linking obesity directly to heart failure. Obesity has a number of effects on the

cardiovascular system (Figure). Many of these are direct effects on the myocardium and are linked to the development of heart failure. Left ventricular mass and left atrial volume increase with increasing BMI, as does the degree of diastolic and systolic dysfunction [3] and ongoing myocardial injury may be detectable with newer high sensitivity troponin assays [4]. Higher BMI is also associated with higher cardiac output, increased blood volume and alterations in pressure volume relationships in the heart that deal with these changes [5]. Activation of various inflammatory pathways may explain some of the relationship between obesity and heart failure [6]. Finally, cardiac steatosis is a recognised complication of obesity. Deposition of fat in the myocardium leads to progressive fibrosis further altering cardiac function [7]. Contrast this to the associations between obesity and ischaemic heart disease which are less direct (Figure). Although not all atherosclerotic disease culminates in a myocardial infarction, autopsy findings of military personnel confirm that increasing BMI is associated with a greater burden of atherosclerosis [8]. Therefore, despite the evidence linking obesity directly to the development of heart failure, could the association between obesity and heart failure simply be confounded by ischaemic heart disease?

In the analysis by Rosengren *et al* [2], subgroup and secondary analyses were used to explore this issue. The association between BMI and heart failure was examined according to the aetiology of heart failure. The risk of heart failure with a secondary diagnosis of coronary heart disease, hypertension or diabetes mellitus was higher than the risk of heart failure without any of these diagnoses. For every one unit increase in BMI the risk of heart failure with coronary heart disease, diabetes or hypertension was 1.21 (95%CI 1.19- 1.22). Although this was stronger than the association between BMI and heart failure due to cardiomyopathy i.e. heart failure without an obvious aetiology (HR 1.11 95%CI 1.08-1.14)

the the population attributable fraction for obesity and heart failure due to cardiomyopathy was 15.4%, suggesting that the direct link between obesity and the development of heart failure is a substantial issue at a population level.

However, we must be careful when trying to draw conclusions from these data, no matter how careful the analyses. The competing risk of death was not taken into account nor was the occurrence of MI or other risk factors for heart failure occurring in the intervening period. Other findings from the analyses also merit consideration when interpreting these data. The mean age at diagnosis of heart failure (which was defined as a hospitalisation for heart failure) was only 46 years. This may be a function of the length of follow up of this young cohort, but it is much younger than in other cohorts that report the mean age at diagnosis [9-11]. Furthermore, the aetiology of heart failure in the young tends to be very different to the old [12]. There were no data on other metrics of obesity such as waist and hip circumference. The distribution of body fat may be important in determining risk [13]. This may be especially important in women whose body fat distribution is different to men. Similarly, there may be ethnic differences in body composition and the response to obesity that are important. Despite these limitations, how can we translate these epidemiological analyses into practice?

Perhaps the most difficult and most important issue raised by the analyses is what is the ideal BMI? Although a number of interventions, at an individual and population level, are being explored as potential treatments for the obesity epidemic, what BMI should these interventions aim for? At a population level the answer would seem to be a BMI of less than 22.5 kg/m^2 in young men. Even a BMI in the range of 22.5 to <25 kg/m^2, which is classed as

normal, was associated with a 58% higher risk of heart failure. Given that this group constituted nearly a quarter of the population studied, the absolute numbers of heart failure events in this group was one of the largest. The same was observed for MI (and to a lesser extent for stroke). The burden of heart failure, MI and stroke was greatest in the group with a BMI in the higher range of normal. Given these observations, should the "normal" range be redefined? Do BMI targets for weight loss interventions need to be lowered? Being underweight (BMI <18.5 kg/m^2) was associated with a higher risk of events. Therefore, what happens to a person's risk if they lose too much weight? Without further studies, on more heterogeneous populations, who are more fully characterised (allowing for more complete multivariable adjustment of potential confounders), these questions remain difficult to answer.

While Rosengren *et al* [2] have presented a salutary warning, as with all good research they raise more questions than they have answered. We must gain a better understanding of how the population level changes in the distribution of body mass are likely to influence rates of cardiovascular disease in the future. Otherwise we are in danger of finding ourselves dealing with both an obesity epidemic, and, the resurrection of epidemics of cardiovascular diseases that we had thought had begun to subside [9-11, 14].

Conflict of interest

None

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Figure Legend

Figure. Pathways linking obesity to the development of heart failure.