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## Women, obesity, and the incidence of heart failure: an uncertainty that has begun to be solved

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The epidemiological importance of heart failure<sup>1</sup> (HF) in any of its manifestations is evident and constitutes a challenge for public health in our times. Likewise, obesity, one of the main manifestations of the lifestyle of “developed” countries, has also reached epidemic proportions, and major associations between the two have been described, with the so-called “obesity paradox”<sup>2-3</sup> denoting patients who present HF and are in the overweight/obese range (mainly measured using the body mass index (BMI)) as having a better prognosis than patients who do not present it.

There are many physiopathological mechanisms involved in the “HF obesity paradox”, which could also be present in obese patients with later development of HF. Among these are the hemodynamic alterations obesity produces (increase in central blood volume and cardiac output), which predispose to eccentric or concentric left ventricle (LV) hypertrophy depending on the LV loading conditions. However, hemodynamics may only be part of the story. Neurohormonal and metabolic variables<sup>2-4</sup> may also play a role in altering LV morphology in obesity. Such variables include hyperinsulinemia associated with insulin resistance, hyperleptinemia associated with leptin resistance, and activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system. All of these mechanisms occur with obesity and may contribute to alterations in LV mass, LV wall thickness, and LV chamber size. Purposeful weight loss is the most effective long-term measure to combat all of these mechanisms, reverse the abnormalities of cardiac performance and morphology associated with obesity, and to improve the clinical manifestations of HF in patients with obesity cardiomyopathy, as Alpert et al. have highlighted<sup>4</sup>.

Nevertheless, we do not know whether these mechanisms could influence the incidence of HF in an “apparently” healthy population and the later development of the clinical syndrome of HF with its associated complications. Although, given the epidemic characteristics of obesity in our society, this matter seems essential, there are still many unknown aspects. This is particularly true for women, who are always underrepresented in clinical studies and about whom there was practically no evidence available until the recent study presented by Björck et al. in this issue of our journal<sup>5</sup>.

In brief, the work of Björck et al. describes a uniquely large (1,374,031 females) prospective cohort of young women in their first or second pregnancy (from the Swedish Birth Register 1982–2014), and the association, through the Swedish National Inpatient Register (considering International Classification of Diseases (ICD)-8, ICD-9, and ICD-10), with risk of hospitalization for HF or of death in a median follow-up of 15.3 years (7.3–23). The authors found that the risk of early HF in women was strongly associated with increasing body weight. Compared with lean women (BMI 20–22.5 as a reference at the time of the first prenatal visit), the risk of HF started to increase at high-normal risk BMI levels, and was nearly five-fold in women with a BMI  $\geq 35$  kg/m<sup>2</sup>.

### **What are the main strengths (and limitations) of the study that can help us in our daily clinical practice?**

Firstly, it provides information that we did not have until now. Although the deleterious effects of obesity on health in general have been well described, we were faced with uncertainty about its relationship with the incidence of HF, which remained even more uncertain after the establishment of the “obesity paradox” for previously diagnosed patients. This same group had already described<sup>6,7</sup> the connection between overweight (BMI 25–30 kg/m<sup>2</sup>) and obese (BMI  $\geq 30$  kg/m<sup>2</sup>) compared to normal weight (BMI  $< 25$  kg/m<sup>2</sup>) women, and the risk of developing HF in a population other than the one that is the subject of this research. Unlike women over the age of 65 adjusted by number of important variables, only women between 26 and 65 years presented an association with the incidence of HF. This research by Björck et al. is in consonance with previous research, and analyses only women between the ages of 18 and 45 years, establishing a causal relationship that increases with the different BMI ranges, which makes this relationship stronger and more evident. However, as the authors themselves indicate, one limitation could be that among this population group the incidence of HF is low, and the number of new cases is very small, both globally and by range.

Secondly, it is well known that the relationship between obesity and HF is not simple. There are many comorbidity situations that may interact, such as age considered as a continuous variable, diabetes mellitus, arterial hypertension, and even educational level. In addition, in situations of obesity, the differential diagnosis of HF to assess the main symptom such as dyspnea is difficult. Although this work excludes the outpatient diagnosis of HF and takes into account three models of multivariate analysis to maintain the relationship between BMI and new cases of HF, this relationship is restricted, as the authors acknowledge, by the quality of the information in the administrative databases that were used. As has recently been described in our publication,<sup>8,9</sup> the relationship with diabetes mellitus is particularly strong; while in this series of young women it has little prevalence, it may, however, be more relevant for other population series

Thirdly, as the authors show, they find a J-curve relationship between BMI and the events analyzed. This type of curve does not seem to be any different to the situation found among male patients, although they present some well-known differentiating characteristics to those of women: lower age of onset, a different association to classic risk factors such as diabetes, and high blood pressure. We would like to highlight the divergence of the studies in two points we consider critical: 1) the cut-off point for considering a person as normal weight, overweight, or obese – although it is true that almost all are based on the BMI (kg/m<sup>2</sup>), other, more specific, indexes such as the percentage, type, and distribution of fat, or the number of subsets used to establish the relationships, are omitted; and 2) weight at a given time in a person’s life is not a fixed variable, but subject to fluctuations that may alter the relationship between the variables analyzed – artificial intelligence could, without a doubt, help with as well as establish relationships that fluctuate over time and depend on three or more variables.<sup>10</sup>

Finally, we would like to congratulate the authors on this elegant article that helps us begin to shed light on this grey area of clinical practice. We likewise express our admiration for the deeply rooted tradition of Swedish registers, particularly in the area of cardiology, of which the authors are participants, which have, to date, contributed excellent in-depth knowledge and will doubtlessly continue to do so.

In short, the first step we should take after reading this paper seems obvious: reduce body weight among obese young women by reason of the multiple health benefits, including the incidence of HF.

It is difficult to establish unequivocal causal relationships in medicine; they do not arise from a single study, and require concordant studies among different populations with designs that show us a relationship. In the meantime, we have two options in clinical practice: either wait until this relationship becomes clear, or begin to act by adopting therapeutic measures – for instance, against obesity – that will improve the health of the population we attend. Without a shadow of a doubt, we will choose the latter option.

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