

The obesity paradox: a statistical outcome or a real effect of clinical relevance?

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Abstract

Obesity is one of the most important risk factors for morbidity and mortality, especially when referring to cardiovascular diseases. Different obesity phenotypes are presented in the medical literature, each one describing a different cardiovascular risk profile. The most important phenotype that is directly linked to the obesity paradox (OP) is the metabolically healthy obese phenotype, characterizing individuals with a BMI ≥ 30 kg/m² and no metabolic abnormalities. This phenotype strengthens the true existence of the OP. In the same time we need to consider all the possible influencers when concluding if the OP is real and worth taking into consideration by clinicians. Analyzing studies that mention the OP, we observed several limitations either of the study itself or of the BMI used to classify obese patients. These limitations are described in the present review and they are of great importance in understanding how the OP is defined and how it should be interpreted.

Keywords: obesity paradox, cardiovascular, BMI, obesity phenotypes.

Introduction

Obesity is currently considered a worldwide epidemic, mainly due to its association with multiple diseases. A recent study that evaluated the correlation of overweight and obesity with morbidity and mortality over a 25-year period and across 195 countries showed

that the obesity prevalence has doubled since 1980, reaching 5% in children and 12% in adults [1].

The relationship between obesity and cardiovascular diseases (CVD) is a complex one [2]. Even though obesity is known to be an important, if not the most important, risk factor for CVD, the “obesity paradox” (OP) debate has arisen in the last years. Several studies have reported a lower risk for developing CVD in a subgroup of obese individuals, uniquely entitled “metabolically healthy obese” phenotype. Thorough analysis is needed in order to better understand the criteria used for defining OP and under what circumstances is the OP present.

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Obesity phenotypes and their association with CVD

Body mass index (BMI) is used in clinical practice as a standard measurement tool for classifying obesity. Recent studies mention the presence of obesity phenotypes with a different cardiovascular (CV) risk profile associated with the same BMI category.

The Metabolically Healthy Obese (MHO) phenotype has various definitions in the literature and a common agreement upon one definition is still needed. A recent systematic review of the prevalence of MHO suggested that MHO phenotype includes obese individuals defined by BMI ≥ 30 kg/m² and lacking the metabolic syndrome characteristics: blood pressure $\geq 130/85$ mmHg, fasting plasma glucose ≥ 6.1 mmol/L, fasting triglyceridaemia 1.5 mmol/L (women) or >2 mmol/L (men), HDL-c <1.03 mmol/L and waist circumference (WC) ≥ 85 cm (women), WC ≥ 90 cm (men) [3].

MHO prevalence ranges between 6% and 75% and is higher in women and younger ages. The important difference between these percentages confirms once again the necessity of a commonly established definition of the metabolic health [3].

When compared to metabolically unhealthy obese (MUO), MHO seem to have a lower risk for CV events, which is comparable to that of normal weight subjects [4, 5]. On a more thorough analysis, MHO may not be such a benign condition. Several studies undergoing a 10-year or more follow-up showed a higher risk for all-cause mortality and/or CVD [6, 7].

A more precise definition of MHO requires information about the degree of visceral adiposity, inflammatory markers, the degree of liver fat and insulin sensitivity [8]. The BMI does not offer information about lean and fat mass separately, this being of great importance in analyzing the obesity pathology.

One more parameter needs to be taken into account for a more precise characterization of the MHO: the cardiorespiratory fitness (CRF). A higher level of CRF in MHO individuals than in MUO individuals suggests that their healthier metabolic profile could be due to a healthier lifestyle. In a recent meta-analysis, the risk factor for all-cause mortality and CVD mortality/morbidity is lower for MHO once physical activity is accounted for [9].

Obesity treatments should focus not only on losing weight, but on improving the CRF level by promoting physical activity and healthier lifestyle habits among patients [9, 10].

The Metabolically Obese Normal Weight (MONW) phenotype is characterized by a normal BMI and the presence of the same CV risk factors as obese patients [11]. A study that used MRI to analyze this phenotype showed a different visceral adipose tissue (VAT) accumulation compared with overweight or obese patients. This new sub-phenotype is called “this-on-the-outside fat-on-the-inside” (TOFI) and is also characterized by high levels of liver and muscle fat [12].

Normal Weight Obese (NWO) subjects are characterized by a high level of body fat percentage (men: $\geq 23.5\%$, women: $\geq 29.2\%$), even though they have a normal BMI. This phenotype lacks metabolic abnormalities, but has a high risk for cardiometabolic disease, directly connected with the high body fat level [11, 13]. Normal weight central obesity subjects have a high mortality rate due to: abdominal visceral fat as a source of inflammation and insulin resistance, the low level of subcutaneous fat in legs and hips known to be protective for CVD and the reduced level of muscle mass [14].

Sarcopenic obesity is characterized by low muscle mass combined with high fat mass, resulting in a limited mobility and muscle weakness. Considering each term by itself, sarcopenia and obesity both relate to the same risk factors. Considering them together, the risk for CVD and mortality increases as compared to each term alone [15, 16]. It is essential to correctly differentiate patients with sarcopenic obesity from patients with only sarcopenia or obesity. This can be achieved by measuring the total body fat mass and the total body lean mass [13]. The treatment for sarcopenic obesity is controversial, the most effective one being a moderate energy restriction diet combined with exercise [17].

Obesity phenotypes and the OP

The obesity phenotypes described above strengthen the idea that obesity classification should have a more complex definition and not just the one based

on BMI. The first article published referring to obesity phenotypes (including the term “MHO” or “MUO” in the title/abstract) was in 2001 and since then there were more than 24000 articles published related to this issue [9].

The notion of OP is currently directly linked to the “BMI paradox” (the association of a high BMI correlated to a better outcome), mainly due to the current obesity classification which is based only on BMI. Among the limitations of using the BMI are the lack of characterization of body composition (the proper distribution of fat mass and lean mass) and the fact that CRF is not accounted for [18] (Table 1).

If other indices are used, the notion of OP is no longer validated [19]: high body fat mass is correlated with a high mortality [20], waist-circumference and waist-hip ratio is also directly associated with mortality in patients with coronary heart disease [21] (Table 2).

The MHO phenotype which best describes the OP involves a high level of CRF which is expected

Table 1. The use of BMI in obesity classification and its limitations (adapted from [18])

Fat distribution	<ul style="list-style-type: none"> • central and visceral obesity provides a higher risk than peripheral and subcutaneous obesity
Body composition	<ul style="list-style-type: none"> • a higher lean mass offers more protection
Cardiorespiratory fitness	<ul style="list-style-type: none"> • physical activity offers more protection for obese individuals than lean mass does
Metabolic reserve	<ul style="list-style-type: none"> • obese patients can rely on a high metabolic reserve when needed
Coronary anatomy	<ul style="list-style-type: none"> • obese patients have larger coronary arteries and a lower risk of restenosis after revascularization
Bleeding complications	<ul style="list-style-type: none"> • leaner patients may have a higher risk of bleeding considering that medication is rarely dose adjusted for weight

Table 2. Tips and trick concerning the obesity paradox (adapted from [19])

<ul style="list-style-type: none"> • Besides BMI, other indices used to define obesity are not linked to the obesity paradox • Studies revealed a “U-shaped” or a “J-shaped” relationship between BMI and CVD risk • Overweight and obese patients with a high BMI and with heart failure or coronary heart disease have a better outcome • The obesity paradox is not supported by all clinical studies • The limitations of BMI and of clinical studies is a possible explanation for the obesity paradox
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taking into consideration the beneficial effect of exercise training on body health, metabolic abnormalities and adipose tissues phenotype. There is a link between MHO and benign adipose tissue starting at a molecular level and continuing with environmental factors, nutritional factors and genetics. Therefore, a more complex analysis is needed to improve diagnosis of the MHO phenotype and to proper associate it with the OP [19].

Possible causes of the OP in CVD

The existence of OP in CVD is currently debatable in the literature, mainly because of the short follow-up period in studies, the use of a poor and non-linear definition of obesity, the existence of reverse causation, the little importance given to the selection and survival bias and also because many studies did not consider the CRF level as a prevention tool for CVD.

In a current follow-up study on patients with coronary artery bypass graft the OP disappeared after 20 years, mainly due to the evolution of the cardiometabolic disease [22]. Another study conducted on 5461 patients, but with only a 6 year follow-up period, showed that in hypertensive population the overweight or the obese status might have a protective effect on all-cause mortality [23].

The BMI alone does not distinguish between the “good fat” and the “bad fat”. The CV health depends

on the type of adiposity, its location, function and inflammation level. The MHO have lower levels of inflammation and higher levels of adiponectin compared to the metabolically unhealthy obese [24].

Reverse causation could be a possible cause of the OP, describing how weight loss or different determinants of low body weight (i.e. several diseases associated with malnutrition) influence the outcome of the patients. It seems that this bias elevates mortality risk and could mislead the results of studies, if not considered properly [25].

A recent sensitivity analysis concluded that selection bias can make an apparently harmful relationship appear protective. This analysis also evaluated the effect of CRF as an unmeasured confounder of the CVD-mortality relationship, describing how it leads the effect of obesity on mortality to the null. If we were to take into account other variables and evaluate their total effect altogether (i.e. CRF, biomarkers, lifestyle factors, depression), we would probably induce an important amount of bias in the study conducted [26].

Conclusions

Our review highlights the importance of considering all the factors in classifying obese patients and afterwards correctly correlate them with the OP. The OP might as well be named the BMI paradox, since in most studies we are simply observing populations poorly characterized only by using the BMI as a measurement tool and without considering other confounders. Bigger cohort studies including all possible influencers of the OP are necessary. At the same time, for a more precise and relevant conclusion concerning the real existence of the OP, the pathophysiology of adiposity should be more thorough analyzed.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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