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To Legitimize the Contentious Obesity Paradox

Obesity is oftentimes quantitatively determined by calculating the body mass index (BMI), ie, weight in kilograms divided height in meters squared, such that BMIs of 30 to 34.9 and 35 to 40 are typically referred to as obesity and morbid obesity, respectively, irrespective of the contributions of higher body fat versus skeletal muscle mass.^{1,2} Whereas a BMI of 25 to 30 is referred to as overweight, a BMI less than 25 is generally considered ideal, although there is less consensus as to what the normal BMI range lower threshold should be. Notwithstanding the many devastating consequences of obesity in health and disease, emerging data suggest that there is an obesity paradox, in that, although obesity is associated with the development of many disease processes (see later herein), after a person has acquired a disease state, a higher BMI may protect against downstream adverse outcomes in acute and chronic disease states.^{3,4}

This seemingly counterintuitive obesity survival advantage (ie, the obesity paradox) in no way undermines the fact that obesity is a risk factor in the development of many acute and chronic disease states with high mortality rates, such as coronary artery disease,^{1,5} heart failure,⁶ chronic kidney disease,⁷ end-stage renal disease,^{8,9} and malignancy.¹⁰ Furthermore, the contributions of obesity to disease also occurs in the setting of advanced age.¹¹ In addition, obesity is clearly associated with poor health-related quality of life.¹²

In the face of an overwhelming association between obesity and disease prevalence, it is even more intriguing that obesity is associated with a survival advantage once an individual acquires the disease. Furthermore, this paradoxical inverse association between obesity and greater survival is also observed with several other cardiovascular (CV) risk factors in certain chronic disease populations, such as patients undergoing dialysis or those with heart failure. These include the lipid and hypertension paradoxes, ie, survival advantages of higher lipid levels and higher blood pressure values.⁶

Although the underlying mechanisms of the obesity paradox and reverse epidemiology remain unclear, the consistency of the data is

remarkable, leaving little doubt that these observational data are beyond statistical constellations and bear biological plausibility. It is not clear, however, what the exact nature of such pathophysiologic mechanisms beyond the obesity paradox are, or which body composition component in obesity is more or less protective in disease states or in advanced age.

In this issue of *Mayo Clinic Proceedings*, Sharma et al¹ and De Schutter et al² examine the pattern and nature of the obesity paradox in people with coronary artery disease and those with preserved left ventricular ejection fraction, respectively. In the meta-analysis of 36 studies by Sharma et al,¹ low BMI (<20) in tens of thousands of people with coronary artery disease who underwent coronary revascularization procedures was associated with a 1.8- to 2.7-fold higher risk of myocardial infarction and all-cause and CV mortality over a mean follow-up of 1.7 years, whereas CV mortality risk was lowest in overweight patients (BMI \geq 25 to <30) compared with normal-weight people (BMI \geq 20 to <25). Indeed, in obese and morbidly obese patients with BMI in the 30 to less than 35 and 35 or greater ranges, all-cause mortality was 27% and 22% lower, respectively, than in people with a normal BMI.¹ Notwithstanding the inherent limitations of the observational study design, this is by far one of the largest meta-analyses related to the reverse epidemiology of obesity and additional proof of the consistency of the obesity paradox in the setting of coronary artery disease. It is highly unlikely that any controlled trials randomizing obese and non-obese people with coronary artery disease to undergo any or no coronary revascularization procedures will be conducted because of the ethical implications of such a study. Hence, observational data remain the main source of obesity paradox investigations.

If obesity truly confers a survival advantage in chronic disease populations, does this counterintuitive reverse epidemiology principle also hold for other so-called CV risk factors or is it limited to obesity or lack thereof? Indeed, in a recent study of more than half a million patients with incident acute myocardial infarction without a previous diagnosis of CV disease, the in-hospital mortality rate was inversely associated with the

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number of preexisting coronary heart disease risk factors, including hypertension, smoking, dyslipidemia, diabetes, and family history of coronary heart disease, such that the greater the number of preexisting CV risk factors that patients had, the more favorable their outcome after the CV event.¹³ How can the very risk factors that lead to the development of coronary artery disease suddenly become protective once the coronary artery disease event has occurred? Metaphorically, we can liken such CV risk factors as obesity to a friend who is a negative influence, causing the two of you to misbehave and be sentenced to jail, but once imprisoned, the friend remains loyal and protects you against poor prison conditions and other inmates. Biologically speaking, there seems to be a time discrepancy between the long-term harmful effects vs short-term survival advantages imparted by CV risk factors, such as the metabolic syndrome and obesity, in that it takes years to decades of exposure to such risk factors to develop CV disease or heart failure, whereas under a diseased state, obesity can confer a short-term advantage against the ravages of these disorders.⁶ Whereas the meta-analysis by Sharma et al,¹ with a relatively short mean follow-up of 1.7 years, is consistent with the time-discrepancy hypothesis and provides further data supporting the obesity paradox, the study provides little information about underlying biological mechanisms.

The study by De Schutter et al² provides incremental knowledge in elucidating the putative mechanisms of the obesity paradox by examining the individual components of large body mass, ie, lean body mass vs fat mass. Using equations based on demographic and BMI data, these investigators estimated body fat and lean mass index in 47,866 people with a preserved left ventricular ejection fraction of 50% or greater and examined the survival advantages of obesity across strata of these body compositions. This study, too, had a relatively short observation period, with a mean follow-up of 3.1 years.² Consistent with previous data on the obesity paradox, this large observational study showed that higher lean body mass was associated with 29% lower mortality. In addition, although higher fat mass also exhibited survival benefits, this advantage disappeared after adjustment for lean body mass, suggesting that nonfat tissue bears the primary role in conferring greater survival.² However, in obese patients, higher

body fat was deleterious with or without adjustment for lean body mass, whereas higher lean body mass was a robust correlate of greater survival. These data suggest that the resilient protection of higher BMI seems to be provided by higher lean body mass, which likely represents larger skeletal muscle mass. Indeed, in similar studies of patients undergoing dialysis, higher muscle mass, represented by a higher serum creatinine level in the setting of minimal residual kidney function, is associated with incrementally greater survival.^{8,14,15} Most individuals with a high BMI are also likely to have higher lean body mass and greater skeletal muscle mass in addition to fat mass.⁹ There are several hypotheses as to how muscle mass is protective, including the protective role of myocytes on vasculature by means of favorable cytokines or myokines.^{8,15} Although the study by De Schutter et al² is an important contribution in defining the primary role of lean body mass, as opposed to body fat, these findings should be qualified by the inherent limitations of observational studies and lack of a more reliable indicator of visceral fat, such as waist circumference or elaborate imaging techniques to assess different types of adipose tissue. Moreover, people who were referred for echocardiography were likely to have higher underlying risk of CV disease and heart failure, and hence, the study cohort should not be considered representative of the healthy general population.² Furthermore, the impact of change in weight or body composition over time on CV events, survival, and other pertinent outcomes remains unclear.

Whereas these^{1,2} and other similar studies underscore the important question of the role of obesity and body composition in disease states, the unfavorable impact of obesity in increasing the risk of de novo CV disease and heart failure should not be forgotten,¹⁶ no matter what favorable impact obesity may have once the CV disease has developed. The findings in these studies^{1,2} should not be considered as an attempt to undermine the legitimacy of the anti-obesity campaign in the best interest of public health. Nonetheless, given the preponderance and consistency of epidemiologic data, there should be little doubt that in certain populations, a higher BMI, which is associated with a higher risk of metabolic syndrome and poor CV outcomes in the long-term, confers short-term survival and CV advantages. Is obesity, indeed, like an

unscrupulous friend who leads you to trouble but remains loyal in protecting you against the hardships he or she has caused you in the first place?¹⁰ Undoubtedly, the impact of obesity in disease and health is much more complicated than one might think. Similarly, the highly provocative discovery of particular advantages of moderate alcohol intake approximately three decades ago showed us that the black-and-white stance on alcohol intake was incorrect. The obesity paradox investigators should continue to be loud and bold, as “we are obliged to say what the real truth is” about survival and other advantages of obesity¹⁷; however, the mainstream anti-obesity investigators should be rest assured that the so-called reverse epidemiology data do not serve to legitimize obesity, just as data about the advantages of moderate alcohol intake never gave legitimacy to alcoholism.

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