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To Legitimize the Illegitimate Obesity Paradox

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Obesity is oftentimes quantitatively determined by calculating the body mass index (BMI), i.e., weight in kg divided height squared in m^2, such that a BMI of ≥30 kg/m^2 and ≥35 to 40 kg/m^2 are typically referred to as obesity and morbid obesity, respectively, irrespective of the contributions of higher body fat vs. skeletal muscle mass.[1, 2] Whereas a BMI >25 kg/m^2 and up to 30 kg/m^2 are referred to as being overweight, a BMI <25 kg/m^2 is generally considered ideal, although there is less consensus as to what the lower threshold of the normal BMI range should be. Notwithstanding many devastating consequences of obesity in health and disease, emerging data suggest that there is existence of an obesity paradox, in that higher BMI counterintuitively protects against adverse outcomes in many acute and chronic disease states.[3, 4] This seemingly counterintuitive obesity survival advantage has been observed despite prior data showing that obesity is a risk factor in the development of many acute and chronic disease states conferring high mortality such as coronary artery disease,[1, 5] heart failure,[6] chronic kidney disease,[7] end-stage renal disease,[8, 9] and malignancy,[10] as well as advanced age,[11] and despite the consistent association of obesity with poor health-related quality of life.[12] These provocative observations of an inverse association between obesity and greater survival are also one of several cardiovascular (CV) risk factors that demonstrate a “reverse epidemiology” pattern among certain chronic disease populations such as dialysis or heart failure patients, and also include the lipid paradox and hypertension paradox, i.e., survival advantages of higher lipid level concentrations 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 studies are beyond statistical constellations and bear biologic 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.

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In this issue of the *Mayo Clinic Proceedings*, Sharma *et al*[1] and De Shutter *et al*[2] have examined 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 kg/m^2 in tens of thousands of people with coronary artery disease who underwent coronary revascularization procedures was associated with 1.8 to 2.7-fold higher risk of myocardial infarction and all-cause and cardiovascular (CV) mortality over a mean follow up period of 1.7 years, while CV mortality risk was lowest among overweight patients (BMI 25–<30 kg/m^2) compared to normal weight people (BMI 20–<25 kg/m^2). Indeed, in obese and morbidly obese patients with BMI in the 30–<35 and ≥35 kg/m^2 range, all-cause mortality was 27% and 22% lower than people with 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 trial randomizing obese and non-obese people with coronary artery disease to undergo any or no coronary revascularization procedure will be conducted given the unethical nature 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 among over half a million patients with incident acute myocardial infarction without prior cardiovascular disease, in-hospital mortality was inversely associated with the number of pre-existing coronary heart disease risk factors including hypertension, smoking, dyslipidemia, diabetes, and family history of coronary heart disease, such that the greater the number of pre-existing CV risk factors patients had, the more favorable their outcome following 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 CV risk factors to a friend who is a negative influence, causing 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 appears to be a time-discrepancy between the long-term harmful effects vs. short-term survival advantage imparted by CV risk factors such as 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 period 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 biologic mechanisms.

The study by de Schutter *et al*[2] provides incremental knowledge in elucidating the putative mechanisms of the obesity paradox by examining the individual components of large body mass, i.e., lean body mass vs. fat mass. Using equations based on demographics and BMI data, these investigators estimated body fat and lean mass index in 47,866 people with a preserved left ventricular ejection fraction ≥50% 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 prior data on the obesity paradox, this large observational study showed that higher lean body mass was associated with 29% lower mortality, and while higher fat mass also exhibited survival benefits, this advantage disappeared after adjustment for lean body mass, suggesting that non-fat 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 appears to be provided by higher lean body mass, which likely represents larger skeletal muscle mass. Indeed, in similar studies of dialysis patients, higher muscle mass, represented by higher serum creatinine level in the setting of minimal residual kidney function, is associated with incrementally greater survival.[8, 14, 15] Most individuals with 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 upon vasculature by means of favorable cytokines or myokines.[8, 15] Whereas the study by De Schutter *et al*[2] 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 upon 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 higher BMI, which is associated with 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/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 upon 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 obesity;[17] however, the mainstream anti-obesity investigators should be rest assured that the so-called reverse epidemiology data do not serve to legitimize obesity, as data about advantages of moderate alcohol intake never gave any legitimacy to alcoholism.

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