Making Sense of the Obesity Paradox

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Mercedes Carnethon, PhD, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA, discussed the obesity paradox—the tendency for obese individuals, including those with chronic diseases, to survive longer than adults of normal weight as determined by body mass index (BMI).

The data supporting the obesity paradox are strong. A recent meta-analysis based on 89 studies, using normal-weight individuals as the reference, reported a relative risk of all-cause mortality of 0.93 (95% CI, 0.89 to 0.95) for overweight individuals (BMI 25 to < 30 kg/m^2), 1.13 (95% CI, 1.06 to 1.19) for obese individuals (BMI 30 to < 35 kg/m^2), and 1.25 (95% CI, 1.13 to 1.39) for extremely obese individuals (BMI ≥ 35 kg/m^2) [Flegal KM et al. *JAMA*. 2013]. Another meta-analysis of 9 studies that addressed BMI in patients with chronic heart failure reported lower all-cause and cardiovascular mortality rates in overweight (HR, 0.84; 95% CI, 0.79 to 0.90) and obese (HR, 0.67; 95% CI, 0.62 to 0.73) individuals [Oreopoulos A. *Am Heart J.* 2008]. Another meta-analysis involving > 81 000 hemodialysis patients reported a crude hazard ratio for overweight versus normal-weight patients of 0.67 (95% CI, 0.65 to 0.68). Adjustment for age, sex, diabetes, smoking, cholesterol, and chronic kidney disease produced a hazard ratio of 0.94 (95% CI, 0.92 to 0.96) [Jialin W et al. *Nephron Clin Pract.* 2012]. Yet, another meta-analysis exploring weight and acute coronary syndrome that involved > 218 000 patients reported a reduced risk of death in individuals who were overweight (HR, 0.70; 95% CI, 0.64 to 0.76), obese (HR, 0.60; 95% CI, 0.53 to 0.68), and severely obese (HR, 0.70; 95% CI, 0.58 to 0.86) [Niedziela J et al. *Eur J Epidemiol.* 2014].

The list of chronic diseases linked with the obesity paradox is long and includes chronic kidney disease, chronic heart disease, heart failure, stroke, cancer, acquired immunodeficiency syndrome, rheumatoid arthritis, chronic obstructive pulmonary disease, diabetes, and hypertension.

Possible explanations for the obesity paradox include reverse causation (ie, healthier patients with the aforementioned comorbidities may be more overweight or obese) or that weight per se does not fully represent the potential adverse effects of adipose tissue. For instance, the term *metabolically obese normal weight* (MONW) was coined in 1981 to describe individuals who are not considered obese based on their height and weight (BMI < 28 kg/m^2) but who are hyperinsulinemic, insulin resistant, and at risk of type 2 diabetes, hypertriglyceridemia, and premature coronary heart disease [Ruderman NB et al. *Am J Clin Nutr.* 1981]. MONW is prevalent in Americans ≥ 50 years of age, with the prevalence exceeding 50% in those ≥ 65 years of age [Wildman RP et al. *Arch Intern Med.* 2008].

Those affected tend to be nonwhite, less educated, cigarette smokers, and physically inactive, with habitually inadequate sleep and a family history of metabolic diseases. MONW has been linked with increased mortality [Kramer CK et al. *Ann Intern Med.* 2013].

More than 85% of patients with type 2 diabetes are overweight or obese. The diabetes that develops in more normal-weight individuals, however, may be associated with a doubling of the risk of mortality (HR, 2.2; 95% CI, 1.4 to 3.4), including cardiovascular mortality [Carnethon MR et al. *JAMA*. 2012]. In the Look AHEAD study [NCT00017953; The Look AHEAD Research Group. *New Engl J Med.* 2013], 5145 overweight diabetics were randomized to receive intensive modifications in their lifestyle or education. The composite end point after up to 13.7 years of follow-up was fatal or nonfatal cardiovascular disease, stroke, or angina that required hospitalization. Even though the intensive lifestyle intervention focused on weight loss, improved fitness, lowered glycated hemoglobin, and reduced waist circumference, the rate of cardiovascular events was unaffected.

The plausibility of the obesity paradox can be assessed based on several factors. One is nutrition. Obesity, which results from overnutrition, has been linked with longer-term mortality. Wasting, which is due to undernutrition, is associated with short-term mortality. It may be that those with chronic disease do not live long enough to suffer from the adversities of overnutrition

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[Kalantar-Zadeh K et al. *Curr Opin Clin Nutr Metab Care.* 2007]. In this scenario, a leaner body may reflect more advanced disease or increased comorbidities, whereas a heavier body type has greater metabolic wherewithal to withstand illnesses.

A second plausibility factor is age-related loss of muscle mass and strength. Sarcopenia is associated with declining function and higher rate of mortality, and it can be accelerated by factors such as physical inactivity, poor diet, and kidney disease. In older people, increased fat and declining muscle and bone can reduce overall weight. In these people, BMI may be an inappropriate measure because it cannot discriminate the distribution of fat and bone, or body composition (ie, body fat vs muscle mass). Increased abdominal fat is associated with sarcopenia; whether the fat is subcutaneous or visceral is important in determining the risk of mortality.

A third factor is the level of physical activity. Obese individuals who are physically active have a lower risk of mortality than lean individuals who are physically inactive. Fitness, regardless of weight, is associated with lower mortality [Barry VW et al. *Prog Cardiovasc Dis.* 2014].

A fourth factor is smoking. Smokers tend to have a lower BMI, which has been linked with increased mortality, compared to normal-weight individuals [Tobias TK et al. *New Engl J Med.* 2014].

Given the emphasis on BMI in examining the obesity paradox, it is germane to consider that risk factors other than BMI that are difficult to measure, such as genetics and lifestyle, may be operative. If these other factors are associated with higher mortality, then BMI could appear to be inversely related with mortality (ie, a lower BMI would be linked with increased risk of mortality) [Lajous M et al. *Epidemiology.* 2014].

To summarize, the obesity paradox is biologically plausible. In nonobese individuals, factors like diabetes may present a high risk due to underlying factors that cannot be measured. Smoking and physical inactivity may be confounders. On the other hand, the obesity paradox may not be real. Rather, it could reflect a selection bias in studies, with other factors like genetics and lifestyle being the true basis in diabetes and other chronic diseases.

Studies suggesting that obesity is nonproblematic receive prominent coverage in the popular media. With obesity rates rising, there could be a tendency to wish for a normalization of obesity, rather than confront a reality that the present course is undesirable and that a societal change is required. Clearly, more studies are needed.