Obesity Paradox and Stroke
Noticing the (Fat) Man Behind the Curtain

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See related articles, pages 3397 and 3646.

Obesity has a well-known association with initial incidence of cardiovascular disease, stroke, cancer, and early death. However, a growing number of studies have found that overweight and frankly obese patients who survive the first event tend to have improved subsequent cardiovascular (CVD)†,‡ and cerebrovascular disease burden,§,¶ morbidity, and mortality. The idea that a known risk factor somehow transforms into a “protective” agent after an occurrence of a vascular clinical event—the obesity paradox—is both surreal and troubling. Should we conclude that our advice of weight loss as the yellow brick road of secondary prevention (for those with above-normal body mass index [BMI]) causes actual harm? First, the definition and measurement of obesity, techniques of statistical analysis, and the various effects of the initial cerebrovascular event on the patients’ weight all deserve a closer look.

The article by Ovibagele et al5 is the latest study in assessing the link between obesity and recurrent vascular events in stroke survivors. The data from the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes Trial) was reviewed with 20,246 subjects being stratified by their BMI measurements and waist circumference. The groups had some important differences: the obese subjects were younger and had a higher proportion of women but a smaller percentage of smokers. They were also more likely to have a lacunar stroke and a greater likelihood of carrying a diagnosis of diabetes, hyperlipidemia, or hypertension, and of taking antihypertensive drugs. Despite differences in the diagnosis of hypertension, the baseline median blood pressure levels were comparable between obese and nonobese subjects. After adjusting for common confounders, the authors found no statistically significant difference in the recurrence of stroke for lean (9.06%), overweight (8.82%), and obese (8.89%) groups over 2.5-year follow-up. The secondary outcome (time to stroke, myocardial infarction, or vascular death), however, was “paradoxical”: being obese (hazard ratio, 0.86; 95% CI, 0.77–0.96) or overweight (hazard ratio, 0.84; 95% CI, 0.77–0.92) was protective when compared with the lean group.

The study is a post hoc analysis of a clinical trial and the interpretation of results has its inherent limitations. PROFESS excluded patients with a severely disabling stroke, for instance, introducing a selection bias. Obese patients tended to have more lacunar strokes, which generally carry a more favorable prognosis, and may foreshadow a faster recovery and overall better subsequent health, thus lessening the chance of meeting a secondary outcome. More aggressive or frequent follow-up care may have been bestowed on corpulent stroke survivors simply due to them “looking” like they were more at risk.

Neither the BMI nor the waist circumference was systematically validated in the study, but the problem may be more fundamental. Although easy to measure, these metrics may be too simplistic; they do not account for the proportion and distribution of muscle, bone, and adipose tissue or how that proportion of weight to height was accomplished. Adipose tissue has evolved from a proverbial spare tire around the waist to an endocrine organ; its effects on the inflammatory cascades, endothelial function, regulation of glucose, and cerebrovascular disease are intricate and our knowledge of these constructs primitive but evolving. With so little known about the molecular pathways of obesity in disease, and only a single number (BMI) to hold its place, are we even analyzing the real variables of interest?

An argument can be made that many “paradoxical” studies may not be adequately controlling for confounders and accurately accounting for risk factors and may suffer from an index event bias.7 Obesity paradox studies have a recurrence risk design: their selection of patients for enrollment and their outcomes analysis depend on the recurrence of the same or a very similar event. They are selecting for and conditioning on the outcome, which may lead to the dependence of varied and normally independent risk factors, resulting in minimization (favoring the null hypothesis) or even reversal (paradoxical findings) of their contribution to the variable of interest.8

Other paradoxes exist (an “aspirin paradox,” a “thrombophilia paradox,” and a “smoker’s paradox”), but let us use Ovibagele et al as an example. Obese subjects were younger with proportionally more women and nonsmokers; these characteristics represent a lesser risk–burden and would be expected to produce fewer strokes, with obesity likely being the final step in the cascade of producing a clinical event.
Nevertheless, despite having more lacunar strokes (which produce less morbidity), the obese subgroup reached the primary end point of the study at the same statistical rate as their sicker and leaner counterparts. It can be argued that obesity again filled in the gap between a lesser degree of other stroke risk factors and the amount needed to produce a recurrent event. So, in reality, it remains a significant risk factor for both the initial and recurrent strokes.

A similar argument can be made for the study’s secondary end points. Obesity, although correlated with many other stroke risk factors, does not account for them all. By selecting for obese patients with the initial event, the burden of their other stroke risk factors by definition must be less compared with those who are not obese. (The study’s data show the obese patients to be younger, more likely to be female, and to smoke less.) The same cluster of risk factors also predisposes to subsequent vascular events, the study’s measured outcome. Because we just implicitly selected our obese group to have a smaller nonadipose stroke risk burden by conditioning on the initial stroke, it seems reasonable that this lesser risk will lead to a smaller ensuing event rate. This leads to a surprising and paradoxical “protective” effect of obesity and serves as a good example of an index event bias. The direction and degree of the bias is difficult to determine, especially if there are numerous factors and confounding variables, which are difficult or impossible to measure directly. More advanced statistical techniques such as causal-directed acyclic graphs and counterfactuals accurately tally these interrelationships may be needed. Of note, a recent study using propensity score matching design in patients with chronic heart failure and diabetes mellitus has not encountered the “obesity paradox” at all.11

This is not to say that interactions among stroke, obesity, and weight are all statistical slights of hand and cannot be known or studied. Scherbakov et al12 present an interesting overview of some of the latest studies exploring the interface between obesity and cerebrovascular disease. The patients acutely recovering from a stroke exist in a catabolic state: with fever, sympathetic activation, endothelial, and insulin sensitivity dysfunction leading to muscle wasting and overall weight loss. The authors review several population studies in which long-term survival was decreased in those with normal and underweight BMI after a stroke. Besides the aforementioned statistical concerns, it is unclear if lower BMI was a result of healthy living, medical or psychiatric illness, malnutrition, neglect, lower socioeconomic status, or drug abuse. Of note, two Asian population studies13,14 did not demonstrate the obesity paradox; the differences in incidence of obesity, lifestyle, and diet may lessen the contribution of corpulence as a risk factor for initial strokes and hence its subsequent “protective” effect. Immobilized limbs after an infarct lose bone mineral density, muscle area, and gain in intramuscular fat with changes possibly accelerating with age. Frequent infections, high fevers, and swallowing difficulties in people with stroke only compound the weight loss problem. Systemic neuroendocrine activation and lipolytic signaling also take place with increased release of catecholamines, natriuretic peptides, and inflammatory and catabolic chemokines, whereas damage to the hypothalamus disrupts the hypothalamic–pituitary–adrenal axis.16 It may very well be that having a higher BMI (ie, a higher amount of muscle, bone, and adipose tissue) can indeed be advantageous in surviving and recovering from this disabling and devastating disease.

In exploring the “obesity paradox,” these 2 publications serve an important role: they challenge us to explain and clarify these counterintuitive findings through future randomized and prospective clinical trials. These efforts will lead us to a more nuanced definition of obesity and ideal weight (and weight loss), advanced and novel statistical techniques, and new clinical studies exploring the interactions between obesity and stroke. They may produce less wondrous but more accurate results.

Until then, our recommendations to all our overweight and obese patients with stroke should be of no surprise: a balanced diet and a regular exercise regimen to lose the extra pounds—even if they happen to be the wonderful Wizard of Oz.

Disclosures
None.

References


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