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EDITORIAL

The 'obesity paradox' may not be a paradox at all

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Take a moment to imagine the following situation:

> *You're a researcher seeking to understand the effect of exposure X on outcome Y in disease group Z. Hundreds, if not thousands, of articles have been published reporting a harmful effect of X on Y in the general population. Large public health programs are in place to prevent X from occurring in an effort to minimize the risk of Y. To answer this question, you use data from a large cohort study of individuals with disease Z. You analyze the data using standard techniques. While reading the output from your statistical software, you notice a surprising finding. Both the point estimate and 95% confidence intervals indicate a protective effect of X (RR < 1.0). You check and re-check your analysis.*
>
> *At this point you are faced with two options: (A) you think to yourself, 'oh no, I must have done something wrong along the way to cause this unexpected finding or there must be some bias I have overlooked, I'd better go look seriously at what could be causing this unexpected and contradictory result' or option (B) label the result a 'paradox' and write up the manuscript for publication in an academic journal.*

In this Editorial we argue that the many articles in the obesity literature reporting evidence of an obesity paradox indicates that often researchers are too quick to opt for option B rather than option A. There is a growing body of literature on potential methodological explanations for the obesity paradox, such as misclassification bias caused by using BMI as a measure of obesity,[1,2] reverse causation,[3] or a form of selection bias called collider stratification bias.[3–7]

Over the past several years there has been substantial interest in the so-called 'obesity paradox'. Despite the known association between obesity and mortality in the general population,[8] numerous studies have reported that obesity confers a survival advantage among patients with cardiovascular disease, cancer, diabetes, respiratory disease, and renal disease, among other conditions.[2,9–12] Meta-analyses have also been published on the obesity paradox,[9,13–15] leading some researchers to conclude that 'the consistency of the data are remarkable, leaving little doubt that these observational data are beyond statistical constellations and bear biological plausibility'[16] (p.1033).

Papers by Bagheri *et al.*[10] and Mazimba *et al.* that appear in this issue of the *Journal* both report apparently paradoxical findings. On the basis of the results of a meta-analysis, Bagheri *et al.* found evidence of a 'paradox within a paradox' in survival after renal cell carcinoma (RCC). They concluded that cancer specific survival was *higher* in obese patients with RCC (the typical obesity paradox), but overall survival was *lower* in obese patients with RCC (a paradoxical finding within the typical obesity paradox).[10] The idea of a paradox within a paradox is curious and presents a logical fallacy. The reverse of a paradoxical finding is not a 'paradox within a paradox', in fact, it is not a paradox at all. The apparent protective effect of obesity among individuals with chronic disease is a so-called 'paradox' because it conflicts with the well-known harmful effect of obesity in the general population. If the authors found evidence that overall survival was lower among obese individuals with RCC, it means they did not find evidence of an obesity paradox. The article by Mazimba and colleagues[17] reports a different type of paradox, an 'overweight paradox' among individuals with group 1 pulmonary hypertension. They found the highest 5-year survival probability among normal and underweight individuals with PH and the lowest among overweight individuals with PH.

Although both Bagheri *et al.*[10] and Mazimba *et al.*[17] give several hypothesized explanations for their findings, they fail to mention collider stratification bias as a possible explanation.[3–5,7] For an in depth introduction of collider stratification bias, we refer readers to Hernán *et al.*[6] It is well-documented that collider stratification bias can potentially reverse the direction of an effect, making a harmful exposure appear protective.[4,18,19] Figure 1 presents a causal diagram for the obesity paradox scenario in renal cell carcinoma (RCC). Smoking is a known risk factor for RCC and mortality; in epidemiologic terms, it is a strong confounder of this relationship. Only one of the studies included in the meta-analysis by Bagheri *et al.* adjusted for smoking in the multivariate analysis.[20] The explanation for why collider stratification bias occurs is as follows: obese individuals may have developed RCC because they are obese or because they smoke, while non-obese individuals must have developed RCC due to smoking since in our simplified example, there are only two causes of RCC. Among individuals with RCC, obese individuals are less likely to be smokers while non-obese individuals are more likely to be smokers. Smoking is a much stronger risk factor for RCC than obesity and is much more deadly, therefore among individuals with RCC, obesity may appear protective because its presence indicates the absence of a more harmful risk factor, like smoking.[21]

Another possible explanation that is not addressed in either article is the potential for bias due to illness related weight loss.[22] This bias may serve to increase mortality risk in the normal weight group, creating the appearance that overweight is protective.[7] The causal diagram in Figure 2 describes the bias created by illness related weight loss. This scenario is sometimes referred to as reverse causality but is more appropriately characterized as confounding by pre-existing disease, because disease-related weight loss affects both exposure and outcome. Additionally, the authors failed to control for smoking status, a known confounder of the obesity-mortality and PH-mortality relationships.

Careful consideration of methodological problems and bias is essential in observational research studies examining the link between obesity and health outcomes. Before beginning any analysis, it is important to ask oneself whether the data in hand

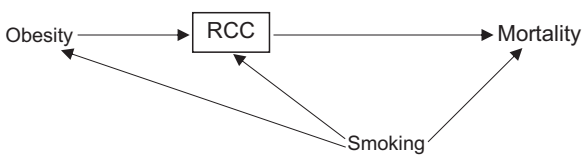

Figure 1. Causal diagram depicting the relationship between obesity, renal cell carcinoma (RCC) and mortality. Obesity is a known risk factor for RCC and RCC is associated with mortality. Smoking is associated with an increased risk of RCC and mortality. In this diagram, RCC is a collider (indicated by the black box) and conditioning on RCC through adjustment, stratification or restriction will induce collider stratification bias.

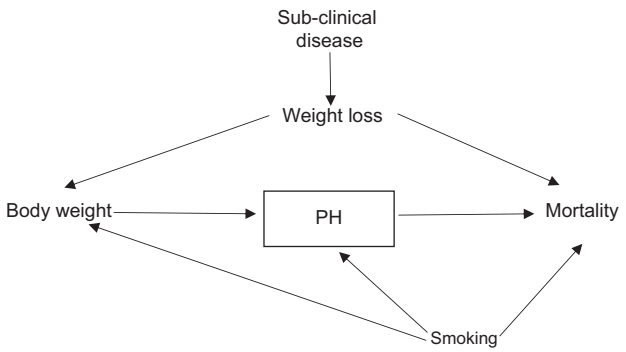

Figure 2. Causal diagram depicting the relationship between body weight, pulmonary hypertension (PH), and mortality. Sub-clinical disease often results in weight loss, possibly due to loss of appetite or increased metabolic demands. Body weight (defined by BMI category) measured at time of PH diagnosis is affected by weight loss due to sub-clinical disease prior to disease diagnosis. Weight loss due to subclinical illness is also associated with increased mortality risk. Additionally, pulmonary hypertension (PH) is a collider; conditioning on PH will induce collider stratification bias.

can answer the research question of interest. Trying to obtain an unbiased estimate of the effect of obesity among individuals with prevalent disease is a challenging task; to avoid collider stratification bias one would need longitudinal data in which the measurement of body weight temporally precedes disease incidence and in which there is an additional measurement of body weight after disease was diagnosed.[4,21] Alternatively, if the relevant question concerns weight change among individuals with prevalent disease, a randomized controlled trial would be the natural study design to choose.[21] One strategy to minimize bias due to illness related weight loss is to use weight history data in place of using baseline weight.[7]

Fortunately, to the best of our knowledge, there has been no call to change clinical guidelines based on findings of an obesity paradox.[21] We want to emphasize, however, that this is the implicit message contained in studies supporting the existence of an obesity paradox. Authors must understand that this is what they are arguing for when claiming to have uncovered evidence of a true obesity paradox. Our concluding message is simple: paradoxes should be met with skepticism; counterintuitive results should be discussed with colleagues and collaborators with different areas of expertise. The only 'paradox' we can see here is why researchers continue to claim to have evidence of a paradox without careful consideration of potential methodological explanations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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