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Editorial

Structural Bias in Studies of Cardiovascular Disease: Let's Not Be Fooled by the "Obesity Paradox"

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Peer-reviewed medical journals are publishing an increasing number of articles with conclusions labeled as a paradox. The term "paradox" implies a truth that is surprising and seemingly illogical. However, the results are often not surprising; in fact, they are perfectly logical because of a structural bias within the study design. These so-called paradoxes arise when studies are restricted to only those with a particular disease and then evaluate outcomes of those with a risk factor for that disease, ignoring the role of other risk factors. Since diseases generally have more than 1 cause, this research design means that there will be some causes of disease that appear protective. The problem is that labelling something a paradox can be a source of confusion and implies that more research is required to resolve the mystery. The field of cardiology now has examples in which mislabeled paradoxes are starting to adversely impact clinical recommendations.

The most popular of these so-called paradoxes is the obesity paradox, which appears regularly in cardiology journals.[1-4] Obesity causes a variety of cardiovascular health problems, such as heart failure, hypertension, and atrial fibrillation. The term "obesity paradox" has been coined to describe the phenomenon whereby people with conditions caused by obesity do better if they are obese compared with others who are not obese. Initially, this may seem to be a paradox. How can obesity be both a cause of disease and a protective factor in those with that same disease?

Nonetheless, it is logical. In the case of heart failure, although obesity is a cause, there are other causes that are unrelated to obesity. Thus, the nonobese individuals in a study restricted to those with heart failure are not a random sample of nonobese individuals. Rather, by definition, they are individuals with other causes of heart failure, eg, infectious cardiomyopathy. When studying only those with heart failure, obesity appears protective if the other causes of heart failure are more harmful.

In this design, seemingly protective effects of obesity are expected because of bias, a systematic error that will not correct itself with more participants or more studies performed with a similar design. Various terms have been used to describe this bias. The most general categorization of the bias is "collider stratification,"[5] because uncorrelated causes (eg, obesity and infections) "collide" by each competing to trigger the same outcome (eg, heart failure). Because the studies include only those with the condition, there is "stratification." The "bias" is the spurious inverse correlation that emerges between various causes of the same outcome. Others have demonstrated how this bias is a form of "selection bias,"[6] and the term "index event bias" has also been used because the studies select only those with "index events" such as heart failure.[7] There may be other potential methodological explanations for the so-called paradox acting in concert with selection bias, including but not limited to reverse causation from unintentional weight loss,[8] and misclassification as body mass index is an imperfect measure of adiposity status.[9]

A few decades ago, studies of low birth weight babies found that those born to mothers who smoked did better than those born to mothers who did not smoke. Researchers struggled to try and explain the benefits of smoking during pregnancy.[10] Then, in 2006, Hernández-Díaz et al.[11] explained how collider stratification bias led to the so-called birth weight paradox. There are various reasons why a baby might be born with low birth weight. One reason is maternal smoking; other reasons include more serious problems, such as genetic defects and infections. Babies born with these latter issues do worse, and thus smoking can appear protective when the evaluation is restricted to low birth weight babies. Since the explanation by Hernández-Díaz et al.[11] we are unaware of further articles suggesting that smoking may be beneficial during pregnancy.

Unfortunately, the same has not occurred in the field of cardiology. As shown in Figure 1, there are now > 800 full-text articles about the so-called obesity paradox. Researchers

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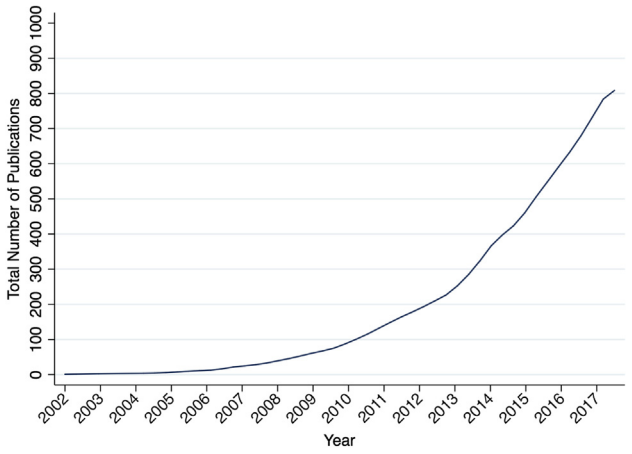

Figure 1. Peer-reviewed publications emphasizing the "obesity paradox." Methods included a search of EMBASE (1947-2017, week 29) for full articles that included the phrase "obesity paradox" in the title, abstract, or keywords. Our search strategy identified 812 articles, with the initial articles appearing in the year 2002.

are now publishing review articles such as a meta-analysis on 124 studies with 22,807 patients finding that among patients with heart failure, the obese do better.[3] Although meta-analyses are considered the highest quality of evidence, a systematic bias will not disappear if studies with a similar design flaw are aggregated. In addition to heart failure, studies with a similar structural bias report that obesity is protective with other obesity-related cardiovascular problems such as stroke,[12] hypertension,[13] and atrial fibrillation.[14]

Aside from wasting resources, these publications are confusing medical professionals. Weight loss through diet and exercise has been a standard recommendation for cardiovascular protection and for the treatment of obesity-related cardiovascular problems such as heart failure, hypertension, and atrial fibrillation. The *Canadian Journal of Cardiology* recently published a study and an accompanying editorial outlining the benefit of adherence to lifestyle recommendations from a study of 3402 randomly selected adults in France.[15,16] However, because of the confusion caused by the structural bias that produces apparently paradoxical results about the effects of obesity, some are starting to question standard recommendations for weight loss. A randomized interventional study published in the *Journal of the American Medical Association* in 2016 found that weight loss for obese individuals with heart failure led to fewer symptoms and objectively improved fitness.[17] However, the authors tempered their conclusions by stating "Because of the reported Heart Failure-Obesity Paradox … before diet can be recommended for obese patients [with heart failure], further studies likely are needed…."[17] A recent review sought to determine whether the paradoxical results are an "impetus to rethink clinical practice?"[18] The authors framed the question as follows: "If I have an obese HF [heart failure] patient, should I strongly advocate weight loss, or should I soft-pedal—perhaps even withhold—such counsel?"[18] Thankfully, the authors did not recommend a "wholesale change in the paradigm of weight loss advocacy." Rather, they offered the following statement, which appears to try and separate counselling for weight loss and actual weight loss: "a clinician who counsels an obese [heart failure] patient to lose weight is not directly inducing weight loss per se; rather the clinician is leading the (compliant) patient to initiate an *attempt* at weight loss."[18]

Why has the obesity paradox persisted, whereas the birth weight paradox ceased after 1 debunking publication? One reason may be the unambiguous perception of smoking as a health hazard. Obesity is a far more complex issue than smoking. Another reason may be that the authors who demonstrated and then debunked the birth weight paradox explained the causal reasoning in their article.[11] Finally, there may be a component of psychological centring. With the birth weight paradox, the focus was on the low birth weight (it was not called the "smoking paradox"), whereas with the obesity paradox, the focus is on the obesity. Were it called the "heart failure paradox," maybe others would see that heart failure can be caused by many things, one of them being obesity.

Unhealthy behaviours and conditions may have isolated health benefits. Smoking causes an increase in hemoglobin and thus greater oxygen carrying capacity. Excessive weight may cause stronger bones. It is rare for things to be universally harmful. Still, the practice of evidence-based medicine obligates us to use the best science when counselling patients; pregnant women should not be encouraged to continue smoking, and obese individuals with obesity-related cardiovascular morbidities should not be encouraged to remain obese. We call on editors and reviewers to start recognizing the structural bias producing these apparently paradoxical results. Further articles reporting a fascination with such results are merely serving to confuse readers and delay advances in health care.

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