



# Addressing Reverse Causation Bias in the Obesity Paradox Is Not “One Size Fits All”

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The obesity epidemic is a global crisis, extending well beyond the U.S. and Western countries. Korea is no exception, with the prevalence of overweight/obesity (BMI  $\geq 23$  kg/m<sup>2</sup>) escalating in recent decades to 61.3% for men and 45.3% for women in 2014 (1).

Despite the overwhelming evidence implicating excess adiposity in the development of several chronic diseases, there has been a prolonged debate surrounding the association between BMI and all-cause mortality. The public health implications of this relationship are not trivial and contribute to the ongoing attention given to this topic.

In this issue of *Diabetes Care*, Lee et al. (2) report their analysis of 12.8 million adults aged 18–99 years in the National Health Insurance Service of Korea at baseline examinations in 2001, with follow-up through 2013. BMI was evaluated in relation to all-cause mortality, demonstrating a U-shaped association between BMI and all-cause mortality. The authors concluded that the optimal BMI for survival after 10.5 years was 25.0–30.9 kg/m<sup>2</sup> for men and 23.5–29.4 kg/m<sup>2</sup> for women; thus, maintaining a body weight in the range of overweight and obesity appears ideal for longevity. This controversial finding has been observed by many, but not all, prior studies of BMI and mortality in those with and without diabetes. Novel to this publication by Lee et al. (2) is the additional observation that the optimal

BMI increases with worsening state of glycemia.

The methodological challenges in quantifying the association between body weight and mortality are complex and have been exhaustively described in detail elsewhere (3). Reverse causation emerges as a prevailing explanation of the bias underlying the paradoxical association, although other potential biases likely coexist (4). This broad term includes confounding by antecedent weight loss or other determinants of low body weight (e.g., chronic illness, malnutrition, infectious disease, smoking duration and intensity) that in turn elevate mortality risk.

Sources of reverse causation bias depend on patterns of cultural and lifestyle factors, prevailing infectious and chronic illnesses, variability in socioeconomic status, and many other factors. I commend Lee et al. (2) for conducting extensive sensitivity analyses to address potential sources of reverse causation bias that have been identified in other previous populations. However, it is not surprising that exclusions for smoking status and baseline cancer, heart disease, or stroke had minimal effect on altering the paradoxical U-shaped association in their analysis, given these factors were not positively associated with low BMI in the Korean population (Supplementary Table 2 in Lee et al. [2]). It is likely that other characteristics were more pertinent confounders in this study population.

Lack of information on cause-specific mortality is another major limitation in the interpretation of these findings. In an analysis of 220,000 Chinese men with 15 years of follow-up, Chen et al. (5) observed that an inverse relationship between BMI and mortality persisted for deaths due to respiratory diseases and cancers of the lung and stomach. However, overweight and obesity were positively related to deaths from vascular diseases and diabetes or renal causes. Similarly, an analysis of nearly 11 million adults worldwide illustrated that the elevated mortality at lower BMIs predominantly included deaths from respiratory causes (6). In Korea, respiratory deaths due to pneumonia have risen alarmingly to the fifth leading cause of death in 2014, and deaths from chronic lower respiratory disease rank ninth (7). Malignancies have remained the leading cause of death for both men and women in Korea for more than a decade, and cancers of the lung, liver, and stomach rank the highest. Collectively, these trends support the high potential for confounding in this analysis by Lee et al. (2) by unmeasured infectious and chronic diseases at baseline, as well as lifestyle and socioeconomic factors, which might have been elucidated with information on cause-specific mortality. Further, by evaluating only all-cause mortality, this analysis obscures important relationships between BMI and cardiovascular mortality and

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thus masks critical areas of opportunity for prevention.

Attributing a survival advantage to excess body weight in the absence of biological evidence is misleading and potentially hazardous. The authors, as have others before them, propose that accumulating excess adipose tissue may causally benefit mortality risk by acting as a “metabolic reservoir” of fat, protecting other tissues from overexposure. Evidence now overwhelmingly indicates that adipose tissue is not simply a benign storage area for excess calories but rather a metabolically active endocrine organ (8). Adipocytes become dysfunctional when enlarged, and the cascade of hormonal and cardiometabolic consequences that follows is likely what implicates excess adiposity as an established risk factor of so many health outcomes.

Patient body weight and mortality are two readily available statistics in increasingly larger health records databases; therefore, analyses of this relationship will no doubt continue to be published. The effectiveness of various methodological approaches to address sources of bias will differ widely based on populations’ underlying health status, determinants

and distribution of major confounding factors, and prevalence of competing risk factors across BMI strata. Analyzing individuals’ historical highest body weight to address unintentional weight loss from illness and aging may provide another solution (9). In most cases, the paradoxical association between BMI and mortality is resolved with these strategies (6), including among subjects with type 2 diabetes (10), demonstrating a positive dose-response, with elevated body weight incurring a higher mortality risk. Overall advice should remain to maintain a healthy body weight for the prevention and management of related chronic diseases, including type 2 diabetes.

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