Despite the persistence of the obesity epidemic and its contribution to development of metabolic and cardiovascular diseases, a growing number of studies have described a paradoxically longer survival (the obesity paradox) among overweight and obese adults with and without chronic diseases.\(^1\) Whereas the obesity paradox has previously been observed among adults with chronic kidney disease, heart failure, and cancer, a growing number of studies have investigated this question in the setting of diabetes mellitus. Whether the obesity paradox is present in diabetes mellitus is of particular interest given the importance of obesity in the pathogenesis of diabetes mellitus and the development of complications. In this issue of Circulation, Zhao et al\(^2\) report a U-shaped association between weight status and mortality among adults with diabetes mellitus, whereby the lowest mortality rates are observed among adults who are overweight or obese. These findings are consistent with some\(^3,4\) but not all\(^5\) previous findings.

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The present study was carried out using administrative data from the Louisiana State University Health Care Services Division, a healthcare plan that includes 7 public hospitals and affiliated clinics, which cover approximately 35\% of the Louisiana population. Patients were studied as part of the Louisiana State University Hospital–Based Longitudinal Study (LSUHLS). Nearly 35,000 black and white adults with a new diagnosis of type 2 diabetes mellitus between 1999 and 2009 were followed for an average of 9 years for mortality. There are several unique features of the present study, including the use of administrative data, which included multiple measures of body mass index (BMI) captured over time, large samples of both blacks and whites, and adults with a range of health behaviors. These features directly address some of the primary reasons why previous studies may have contrasting results.

Recent investigations of the topic were conducted in cohort studies of adults with incident onset diabetes mellitus.\(^3,5\) Cohort study participants are selected randomly to represent a source population (ie, a representative sample of young adults in a given city or region, or an occupational-based cohort of health professionals). The approach has obvious strengths, namely the standardization of measurements collected at regular intervals. However, a limitation is that adults who join research studies are commonly healthier than their counterparts who do not participate in research studies. In contrast, an administrative database of adults who are seeking healthcare and not participating in a research study may represent the healthcare-seeking population more accurately.

The relevance of overall health status to the obesity paradox may be that adults who are concerned enough about their health to join a research study may be more compliant with diabetes mellitus self-care recommendations. These positive healthcare-seeking characteristics may mitigate the potential adverse influence of overweight and obesity. Although these characteristics should not be differentially present among the overweight or obese, these adults may be more likely to lose weight after diagnosis than their counterparts who are not members of cohort studies. Having repeated measures of BMI available after diagnosis is the only way to capture this effect.

In our review of studies to investigate the obesity paradox in diabetes mellitus,\(^6\) all 18 longitudinal studies relied on a single measure of BMI that was taken at the time of diabetes mellitus identification. Clinical recommendations are to counsel patients with diabetes mellitus to lose weight and to adhere to lifestyle changes, such as increased physical activity and dietary changes, that would lead to weight loss. Although fewer patients are actually able to voluntarily meet these goals than clinicians would prefer, some do. Weight fluctuations cannot be captured with a single BMI measurement. It is also possible that a patient of normal weight at the time of diabetes mellitus diagnosis may gain weight rapidly after diagnosis, which may predispose to higher mortality. In the present study, patients had an average of 15 BMI measurements in between disease identification and death. When the authors tested whether the patterns were similar when a time-dependent BMI measurement was used instead of a single measurement, they observed a similar U-shaped pattern. No previous studies have attempted to characterize this important aspect of the obesity paradox in the setting of diabetes mellitus.

Contrasting findings in 2 recent original investigations of the obesity paradox in diabetes mellitus appear to hinge on whether the lower mortality observed in leaner adults is attributable to the presence of smokers in that group. Both our research group\(^7\) and Tobias et al\(^8\) observed a U-shaped association in the full sample after statistical adjustment for smoking status. However, with the large sample sizes from the combined Nurse’s Health Study and Physicians Health Study, Tobias et al\(^8\) had adequate statistical power to observe a difference when stratified by smoking status. Compared with their...
findings in the full sample, they observed a direct association between weight status and mortality among never smokers with new-onset self-reported diabetes mellitus. Among the nonsmokers in the LSUHLS, the highest mortality rates were still observed among the leanest adults compared with those whose BMI fell between 30 and 34.9 kg/m². No explanation is offered for differences by smoking status in the present study and those from Tobias et al. However, findings by Zhao et al. are consistent with those presented in a comprehensive meta-analysis of studies of the obesity paradox in healthy populations to suggest that smoking status was not an important source of bias.

Finally, the LSUHLS identified 19,478 black and 15,354 white patients with new-onset diabetes mellitus. The study represents the largest sample of blacks to have tested this hypothesis. Although other studies have tested whether the relationship between BMI and mortality varied by race, no previous studies have described a different nadir of mortality for blacks compared with whites. In the LSUHLS, the lowest risk for mortality was observed in the BMI range of 30 to 35 kg/m² in blacks, but at a lower level (25 to 30 kg/m²) in whites. Although the biological plausibility for these differences is not known, the finding is important given that blacks are 1.5 times more likely to be obese than their white counterparts. Rather than using this observation as a rationale not to counsel weight loss in obese blacks who have diabetes mellitus, the findings should be used to justify adherence to recommendations for cardiovascular disease risk factor control in patients who may appear at first glance to be at lower risk because of the absence of obesity.

Zhao et al add important insights to the debate about the presence of an obesity paradox in adults with diabetes mellitus. Unfortunately, their epidemiological study (and others that preceded it) is unable to test hypotheses about the biological underpinnings of higher mortality among leaner persons. Whereas the observations in persons with chronic kidney disease, cancer, and heart failure can be attributed to frailty and muscle wasting secondary to advancing disease, that pathway is not likely with diabetes mellitus, given the contribution of obesity to the pathophysiology of diabetes mellitus. One possible biological explanation is the contribution of sarcopenia, the loss of muscle mass and bone mass that is an independent predictor of frailty and subsequent mortality. There is evidence that sarcopenia is more likely in persons with glucose disorders. Sarcopenia may be prevalent among leaner persons with diabetes mellitus, thus predisposing to higher mortality rates.

In summary, when findings of an obesity paradox in chronic disease are published, inevitable questions arise about whether patients should no longer be counseled to lose weight, or whether leaner patients should be encouraged to gain weight. Cardiovascular diseases remain the leading cause of death in persons with diabetes mellitus. Until convincing evidence is presented from well-designed basic, clinical, and population studies to identify a biological mechanism that could account for the observation of a paradox, clinicians should adhere to the most current recommendations for cardiovascular disease risk prevention. Those recommendations appropriately include weight control and aggressive cardiovascular risk factor management using pharmacotherapy coupled with behavior changes, including adherence to exercise recommendations, particularly strength training. The salient message from the current report should be that all persons with diabetes mellitus, regardless of weight status, should be treated aggressively to mitigate health risks.

Disclosures

None.

References


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Diabetes Mellitus in the Absence of Obesity: A Risky Condition
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