Obesity and mortality: summary of best evidence with explanations for the obesity paradox

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Abstract

The link between obesity and increased risk of mortality is well established. However, those who are obese have greater survival when they have chronic diseases such as rheumatoid arthritis or cardiac failure; this is known as the ''obesity paradox''. The obesity paradox is most probably attributable to obese individuals being more susceptible to milder forms of disease than normal-weight individuals, although other mechanisms may also operate. The benefits of weight loss in the general population are also unclear, as some study participants also lose weight through disease. Further work is required to help guide weight recommendations in both healthy individuals and those with chronic diseases.
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The patterns of association between adiposity and increased risk of death in the general population are now well established and exemplified by two recent powerful studies. A meta-analysis of 57 studies involving 894 576 participants, the Prospective Studies Collaboration [1], recently showed that all-cause mortality is lowest at body mass index (BMI)* 22.5–25 kg/m^2, after adjustment is made for age, sex, and smoking status, and excluding deaths in the first 5 years of follow-up. For each 5 kg/m^2 increase above BMI 25 kg/m^2, there was a 39% greater mortality from ischemic heart disease, 39% from stroke, 116% from diabetes, 59% from renal disease, and 82% from liver disease. These results were broadly similar to results from the European Prospective Investigation into Cancer and Nutrition [2], which followed 359 387 participants for approximately 10 years and adjusted for key potential confounders of educational attainment, smoking, alcohol, physical activity, and height. They found the lowest risk of death to be at BMI 25.3 kg/m^2, with a 28% increase in mortality at BMI 30–34.9 kg/m^2 and 106% at BMI >35 kg/m^2, compared with BMI 23.5–25 kg/m^2.

The obesity paradox

The link between obesity and mortality in the general population is well established; however, there is conflicting evidence in disease states, with obesity seemingly having a protective effect against mortality; this is known as the ''obesity paradox''. For example, in a meta-analysis of studies with a total of 28 209 patients with cardiac failure [3], patients with a BMI in the overweight and obese categories had 16% and 27%, respectively, lower all-cause mortality during 2.7 years of follow-up than patients in the normal weight (BMI 18.5–24.9 kg/m^2) category. A similar pattern was observed for patients with coronary artery disease [4]: in the follow-up of 250 152 such patients, even after adjustment for confounding factors, the

overweight category had a 13% lower mortality over 3.8 years than the normal-weight group, with no differences in mortality seen in the obese (BMI 30–34.9 kg/m^2) and severely obese (BMI $\geq$35 kg/m^2) categories compared with normal-weight.

In rheumatoid arthritis, a near-linear relationship exists between increasing BMI and lower mortality, with the effect existing even in severe obesity. In a prospective cohort of 779 patients, the mortality rate over 4.4 years associated with a BMI >30 kg/m^2 was 66% lower than that in patients with BMI 20–24.9 kg/m^2, even after adjustment for smoking, duration of disease, and medication [5]. Survival after non bariatric general surgery was also increased in the obese: a prospective cohort of 118 707 patients showed a 31% lower mortality for those with BMI 30.1–35 kg/m^2 and 41% lower mortality with BMI >35 kg/m^2 compared with individuals of normal weight [6].

The two main explanations for the obesity paradox are residual confounding or ''selection'' bias, and a possible protective effect of obesity against the complications of cachexic states. Selection bias/residual confounding is probably the major factor in all the studies reviewed above. This is shown most clearly in the rheumatoid arthritis study, in which the positive association between baseline BMI and improved survival disappeared on adjustment for severity of disease and comorbidity [5].

In the heart failure meta-analysis, there were many differences between obese and non obese groups that would bias survival in the obese group; these included younger age (6.4 years), greater left ventricular ejection fraction, 11% fewer current smokers, 10% fewer with a previous myocardial infarction indicating a possible alternative pathophysiology, and 15% more who were prescribed β-blockers [3]. In the general surgery cohort, obese categories were also younger, less likely to smoke, less likely to have had an emergency procedure, more likely to be receiving antihypertensive drugs that may have a cardioprotective effect during and after surgery, and had far less preoperative non intentional weight loss [6]. In other words, although obesity can lead to earlier development of diseases, it is of a different characteristic (often more benign) than that in a leaner individual. For lean individuals to develop major diseases such as heart failure, major pathophysiological factors that are more aggressive in nature must be prevalent, in turn explaining earlier death in such individuals. Attempts are being made to adjust for some of these factors in epidemiological studies, but it is not possible to do so completely.

A possible protective effect of obesity against the complications of cachexic states is, of course, another possible explanation for the obesity paradox in certain conditions, but there are currently no data to prove this direct link. It is well known that disease states, severity, and cachexia are all linked, with cardiac cachexia in heart failure [7], rheumatoid cachexia [5], and cancer cachexia [8] being prime examples. It seems plausible that having access to large adipose stores during acute or chronic illness helps avoid the complications of cachexia. There is also some early in-vitro evidence that adipose tissue itself may have an effect on the immune system [9] that may be beneficial during severe illness; however, that has not been borne out in-vivo, and is beyond the scope of this review.

Obesity treatment and mortality

The evidence for the effect of weight-loss treatments on mortality is surprisingly poor, given the importance of this topic and the current recommendations for weight loss [10]; this is because of the considerable difficulties associated with study design. Most obesity treatments only produce modest weight loss – in the region of 5 kg – and thus large sample sizes and long-term follow-up would be required. To be able to attribute any differences in mortality to weight loss would require a pure obesity treatment; obesity drugs may have effects on mortality that are independent of weight loss [11]. Simply looking at weight change in large cohort studies has produced results that are in disagreement with current recommendations: they show that weight loss is associated with increased mortality [12,13]. However, these non interventional studies dealing with small amounts of weight change are heavily confounded by the effects of non intentional weight loss in disease states.

Studies involving bariatric surgery have the benefit of large weight loss that would far exceed any disease-related non intentional weight loss (>20 kg); however, large randomized trials are not financially viable, and the resulting studies have the bias of those in the cohort who elected to have surgery, versus those that chose not to. Nevertheless, two large studies have been published showing a beneficial effect on mortality of weight loss from bariatric surgery. The Swedish Obese Subjects study, a prospective cohort study of 2010 patients having a variety of bariatric surgery operations compared with 2017 patients having non surgical obesity management, showed a 29% reduction in mortality in the operated group over 10.9 years of follow-up [14]. A similar retrospective cohort study matched, for weight, 9949 patients having gastric bypass with a control group from among driving license applicants, and showed a 40% reduction in mortality among the operated group over 7 years, with 49% fewer cardiovascular deaths and 60% fewer cancer deaths [15]; however, weight was self-reported by driving license applicants, and the death data were from death certification, so the accuracy of the data used could not be guaranteed.

Key points

- In the general population, risk of death increases with a body mass index >25 kg/m^2.
- In studies of patients with disease such as heart failure and rheumatoid arthritis, increasing body mass appeared to be associated with decreased mortality – the ''obesity paradox''.
- The obesity paradox may be explained by overweight and obese individuals getting symptomatic, but less severe, forms of disease at an earlier age than normal-weight individuals, biasing their survival.
- The effects of intentional weight loss on risk of death are not clear, as studies have been confounded by non intentional disease-related weight loss.
- Large-scale weight loss with bariatric surgery does appear to have a beneficial effect on mortality, with a reduction in mortality of between 27 and 40% compared with similarly obese individuals choosing not to have surgery.

Summary

The best available evidence supports an adverse effect of obesity on mortality. However, there is little evidence available, other than in bariatric surgery, that reducing weight with obesity treatments decreases mortality rates. Until there is an improvement in data about the long-term benefits or otherwise of weight loss in those already obese, efforts should continue to focus on the prevention of obesity, and on the weight maintenance of those already overweight and obese.

*see glossary for definition of this term. ■

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