Diabetes, body mass and mortality: Is there really an obesity paradox?

There have been a number of recent high-profile publications on the link between type 2 diabetes, body mass at time of diagnosis and subsequent mortality (Carnethon et al, 2012; Logue et al, 2013; Tobias et al, 2014). It may seem fairly obvious that increased body mass at the time of diagnosis of type 2 diabetes would be associated with an increased risk of death compared to lower body mass, as it is in the general population (Berrington de Gonzalez et al, 2010). However, the body mass at which a person develops diabetes is a function of age and genetics (Logue et al, 2011); that is, older people need less adiposity to develop diabetes and those who develop diabetes at lower body mass must, therefore, have a higher genetic component or another pathophysiological process at play, perhaps age-related beta-cell dysfunction? If obese individuals reach their own personal threshold for the development of diabetes, will metabolic derangement and, therefore, subsequent cardiovascular risk be equal across all levels of body mass?

What is currently known about the obesity paradox?

The answer to this question is less than simple. Both our study (Logue et al, 2013) and that of Tobias et al (2014) agree that risk of mortality increases in individuals diagnosed with type 2 diabetes when their BMI is 35 kg/m^2 or greater. However, in our study of 106 640 participants in Scotland, the lowest risk of mortality was in those diagnosed with type 2 diabetes and a BMI of around 30 kg/m^2, and those with a BMI between 20 and 25 kg/m^2 at time of diagnosis had a 20–30% increased risk of death during the follow-up period. Tobias et al (2014) did not find an increased risk of mortality in people with a BMI between 22.5 and 25 kg/m^2 at time of diabetes diagnosis: they found there was equal risk in diabetes development from a BMI of 22.5 up to 30 kg/m^2.

This effect is known as the obesity paradox, that is that obesity can appear to have a protective effect against death and other adverse outcomes and is seen in a variety of conditions in patients with established disease including coronary heart disease (Romero-Corral et al, 2006), heart failure (Oreopoulos et al, 2008) and rheumatoid arthritis (Escalante et al, 2005). There can be many reasons for these findings: disease severity is linked to weight loss through cachexia; symptoms may be more prominent in obese individuals despite less severe disease (e.g. breathlessness in heart failure); and obese people may be targeted for earlier primary prevention or more stringent risk factor management.

The higher risk of diabetes seen in those with lower BMI may be due to a more severe underlying disease – diabetes related or arising from other conditions. For example, it may be that those with lower BMI have more insulin insufficiency than insulin resistance, or it may be that they have a higher prevalence of coexistent conditions. These residual confounding factors may explain some of the differences between the Tobias et al (2014) results and our own (Logue et al, 2013), as the Tobias analysis was able to exclude people with pre-existing cancer or cardiovascular disease, though both papers excluded the first few years of deaths to avoid the effects of pre-existing, weight-losing, terminal conditions. The difference may also be related to the timing of the studies; our data were mainly from 2000 onwards, whereas Tobias et al (2014) have analysed data from the 1970s onwards. Not only have there been substantial increases in body mass since then, but there have also been improvements in the management of diabetes and the life expectancy of people with the condition, which may have been disproportionate across the range of BMI categories.

Interpreting the relationship between diabetes, body mass and mortality

The complexity of the relationship between

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diabetes, BMI and mortality can lead to its misinterpretation both by the authors of papers and by the media and lay public. This was the case after the publication on the Carnethon paper (2012), which described their pooled analysis of five longitudinal studies. A small sample size of people with incident diabetes only allowed comparisons to be drawn between those with a BMI between 18.5 and 25 kg/m^2, and more than 25 kg/m^2. A high risk of death among those with a very low BMI confounded the results and the authors, therefore, concluded that a high BMI was safer in diabetes and that current advice that obese individuals should lose weight when they have type 2 diabetes should be revised.

The study by Carnethon et al (2012) had no relevance to weight loss advice as only intervention studies with long-term endpoint measurements would possibly be able to provide evidence to guide this. Endpoint obesity intervention trials may be near impossible to conduct now; the LookAHEAD study (Wing et al, 2013), a weight management intervention trial for people with type 2 diabetes, failed to meet its primary outcome of a reduction in cardiovascular events after nearly 10 years follow-up. This study recruited 5145 people with type 2 diabetes and randomised them to receive usual care or a very intensive lifestyle intervention, including free meal replacements, personal trainers and fortnightly contact for 4 years. As this large study of a very intensive, expensive intervention and the subsequent weight loss difference between groups failed to show a benefit as a result of the intervention in participants (who were receiving exemplary diabetes care and risk factor management) for cardiovascular endpoints, the size and scale of trial that would be required to try and show a difference is almost certainly unfeasible. However, it did not hint at any adverse effect of the intervention and did show a reduction in medication required to meet treatment targets. Therefore, in the absence of evidence to the contrary, we should still actively encourage people with type 2 diabetes to lose weight. ■

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