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The obesity paradox in secondary prevention: a weighty intervention or a wait for more evidence?

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If you were to ask the average cardiologist how much effort they expend on helping their patients with CVD lose weight, most would admit to "very little". In defence of this approach, they could point to many proven treatments that lessen risks for patients with CVD. Why bother therefore with obesity when evidence for the benefits of weight loss in this group remains sparse? Furthermore, prior observational studies suggest weight loss in people with existing disease such as those with heart failure is associated with higher risk of adverse outcome including all-cause mortality.[1] Such evidence has led some researchers to propose (somewhat controversially) that there exists an obesity paradox, whereby being obese in some scenarios may be "protective".[2]

In this issue of EHJ, Doehner et al sought to examine this issue further.[3] To do so, they took a closer look at BMI, weight change and outcome data from the excellent ORIGIN trial, conducted in predominantly diabetes patients, many of whom had prior history of CVD.[4] Whilst this paper represents an observational analyses of trial data of a selected patient group, the benefits of trials for such work includes robust ascertainment of hard outcomes and extensive and near complete ascertainment of exposure measurements. Furthermore, trials often contain a wealth of serial data on key measures, allowing better tracking of risk factor changes over time.

What did the authors find? Compared to the reference group of participants with BMI of between 22-24.9kg/m^2, all cause and CVD specific mortality risks were lower in those with a BMI of 25-39.9kg/m^2, whereas risks were higher (by around 29 to 35%) in those with baseline BMIs under 22kg/m^2. Moreover, they showed that patients who lost weight after baseline had higher total and CVD mortality risks (by 32 and 18%, respectively), compared to those who did not, whereas risks were not elevated in those who gained weight.

Associations were adjusted for a range of potential confounding variables. The authors are to be commended on noting several caveats to their analyses but even so, in the end, they concluded that "further research is needed to clarify if recommendations on weight management should differentiate more clearly between primary prevention and patients with established disease and advanced cardiovascular risk profiles."

The notion of a paradox in these findings arises because if one considers the primary prevention setting, there is now excellent and consistent evidence, as reviewed[5] from epidemiology, genetics[6] and trials demonstrating that BMI is a strong causal risk factor for diabetes. Indeed, substantial weight loss has been shown to lead to remission of early diabetes in a randomised trial recently conducted in the UK.[7] Furthermore, strong observational data[8] and very compelling genetic evidence suggest higher BMI is causally related to a range of cardiovascular outcomes, including but not limited to CHD, heart failure and atrial fibrillation.[9] Whilst trials of weight loss on hard outcomes are lacking, trial evidence shows weight loss lowers blood pressure, improve lipids and reverses diabetes, all causal risk factors for CVD (Figure). For these reasons, there is no reason to doubt that intentional weight loss, which results in loss of greater loss of body fat than muscle mass, is beneficial in primary prevention.

Why then the somewhat apparently paradoxical association of BMI with CVD mortality in those with established cardiometabolic disease? One view could be that these findings could represent a true causal association, so that high BMI confers some survival capacity to those with established cardiometabolic disease (Figure). However, there are also alternative non-causal potential mechanisms, including residual confounding, as indicated by a few observations in this new study. Firstly, those in the lowest BMI group had lowest prescription

of a range of blood pressure medications, were modestly older, and had the longest duration of diabetes. Those in the highest BMI group had the lowest prevalence of prior CVD, were far more likely to be female, and had the youngest age and lowest duration of diabetes. Despite adjustments for such confounders, it is clear patients with low BMI were systematically different from other groups and so potentially more at risk of mortality for reasons other than adiposity. Secondly, whilst having ever smoked was adjusted for, the authors discuss that current or historical smoking is self-reported and it was not reported how many were actively smoking and how much they were smoking, factors we know are related to higher risk of death, and casually associated with lower BMI.[10] Also, alcohol consumption or diet were not adjusted for. The common theme with these points is that even when observational analyses are adjusted for many potential confounding factors (as the authors carefully did), the potential for residual confounding can never be fully excluded, especially in studies where hazard ratios are generally modest.

Another potential issue in considering non-causal associations is the issue of reverse causality.[11] Essentially, this refers to a situation where the outcome (or factors leading to the outcome) influences the exposure, rather than the implied pathway. It should be noted that weight is exquisitely sensitive to the effects of disease with subtle or major shifts in weight trajectory occurring at different stages of disease. It is well known that the sickest patients lose weight unintentionally anywhere between three to 10 years before the end of life (particularly those that die of CVD and cancer[12]) due to diminished appetite, diminished physical activity, and other factors such as systemic inflammation. With these facts in mind, it is notable that the average BMI in cohorts of diabetes patients is usually around 30kg/m^2 yet the "normal" BMI reference category for this analyses in the ORIGIN study was 22 to 24.9kg/m^2 i.e. 5 to 8 BMI units *lower* than the BMI patients with diabetes are typically

diagnosed at, at least in whites aged around 55 to 60 years of age. This means the referent group was around 15 to 25kg lighter than their expected average weight status at diabetes diagnosis around 6 years earlier, with even greater weight difference in the subgroup with BMIs less the 22kg/m^2. Whilst ethnic variations may be a factor in lower BMI groups (something not adjusted for), it is more plausible that many people in the two lowest BMI groups had already lost considerable weight – perhaps well beyond the amount expected from intentional weight loss efforts – after their diabetes diagnosis and before they entered the ORIGIN trial. In other words, those in the two lowest BMI groups at the start of the study may already have been experiencing unintentional weight loss for several prior years.

Unintentional weight loss often represents proportionally greater loss of muscle than fat,[13] something that would be reflected in a decline in BMI over time. To measure these body compositional changes would require some form of imaging, and of course most large outcome trials are unable to perform such tests. Regardless, unintentional weight loss could be one alternative explanation for the associations of both low baseline BMI and subsequent weight loss trajectories with excess mortality risks seen in this study (Figure). It is also possible that unintentional weight loss in some groups can make other groups that are weight stable or gaining weight look as if they have lower risks i.e. are "protected". However, these features perhaps only identify the group of patients with a lower relative burden of comorbidities, or less severe disease.

All the caveats aside, Doehner and colleagues have nicely highlighted the complexity of this area and correctly suggest that robust evidence for the benefits for intentional weight loss in the secondary prevention setting is lacking but needed. We fully agree. Trials to settle whether intentional weight loss is beneficial or harmful in patients with existing CVD would

resolve any uncertainty, and these should look not only to investigate cardiovascular outcomes, but also quality of life. They should also consider parallel designs with resistance exercise to help maintain muscle mass. As we also discussed, weight loss trials could extend beyond those with CHD to include people with obesity and heart failure. We accept trials such as these may be difficult to do and that it is important to prove people with CVD or HF who are overweight or obese and wish to lose weight, can do so in a sustainable manner. That noted, the appetite for such work is increasing. For now, however, for all individuals who wish to lose weight, whether in primary or secondary prevention, guidelines should promote a range of differing evidenced based options to lose weight, and explain these in simple and empathetic manner.[14] Until data from trials are in, and the BMI paradox becomes a verified BMI paradigm, we hope cardiologists likewise continue to offer (or signpost) helpful dietary advice to any overweight or obese patients with or without CVD who wish to lose weight.

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Conflicts of interest

NS reports personal fees from Amgen, AstraZeneca, Eli Lilly, Novo Nordisk, Pfizer, and Sanofi, and grants and personal fees from Boehringer Ingelheim, outside the submitted work. PW reports no conflicts of interest.

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Figure Legend

This figure depicts the differences in levels of evidence for weight loss in the primary and secondary prevention settings, using a life course model. There is clear and consistent evidence from a variety of sources for a causal role of obesity in primary prevention of CVD and of diabetes, as well as evidence for diabetes remission with weight loss. By contrast, multiple observational studies suggest people losing weight in the secondary prevention setting may be at greater risks of total and CVD mortality, as seems the case in the ORIGIN trial. However, the interpretation of such findings may be complicated by residual confounding and reverse causality. Future trials in this space would help improve the evidence base and help resolve the obesity paradox conundrum.