Protective overweight in cardiovascular disease: moving from ‘paradox’ to ‘paradigm’

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This editorial refers to ‘Cardiovascular risk in relation to body mass index and use of evidence-based preventive medications in patients with or at risk of atherothrombosis’1, by B. Hansel et al., on page 2716.

By denying scientific principles, one may maintain any paradox. Galileo Galilei

Obesity is an ever-growing health burden to our society. The report on the global burden of disease sees obesity within the top 10 of 67 global risk factors and even moving from rank 10 up to rank 6 between 1990 and 2010. Consequently, weight reduction is a unanimously propagated recommendation by healthcare providers. In fact, there has rarely been any healthcare advice—perhaps with the exception of the recommendation for smoking cessation—that has been more rigorously implanted in the public consciousness than to consider weight loss a benefit for population health.

Without doubt, maintaining a normal body weight is desirable for healthy middle-aged subjects and is beneficial for public health on a population level. Weight loss in moderate obesity is undoubtly acceptable in the presence of cancer, where an active weight loss regimen would hardly be recommended by anyone. The opposite is, however, usually the case in the cardiovascular (CV) disease continuum where obesity is understood to be a major risk factor ‘no matter what’.

The transformation of obesity in cardiovascular disease from a basic risk factor into something else

Over the last decade, a debate has gained momentum to challenge this role of high body weight as an unidirectional risk factor in affected subjects. Increasing evidence emerged that in the setting of established chronic disease, overweight patients and those with mild obesity may, in fact, often have a better survival. Even for patients with moderate obesity, no significant increase in mortality was observed. Low body weight and reported weight loss, on the other hand, were associated with higher mortality, and this effect was even independent of whether the weight loss was deemed intentional or not.

To address this unexpected and, for many, counter-intuitive finding, the term ‘obesity paradox’ was coined, and a controversial and at times heated discussion about the acceptance or refusal of these findings fuelled the scientific debate. Arguments to account for this seemingly paradoxical finding included unaccounted for confounders, lack of age adjustment, inappropriateness of body mass index (BMI) as a global measure of body composition, or distorted interpretations and limitations of the data themselves. Meanwhile, the finding of a survival benefit in overweight and mildly obese patients and at least no increase in mortality in obese patients (up to a BMI of 35 or 40 kg/m²) was repeatedly confirmed not only in patients with heart failure, whether acute or chronic, systolic or diastolic in kind, and regardless of disease severity and aetiology, but also in just about every other CV disease or condition that was scrutinized for the impact of body weight on outcome (Table 1).

In this issue of the journal, an article by Hansel et al. provides further evidence in support of the more complex interaction between body weight and mortality in patients with CV conditions. They report an analysis from the REACH population, an international prospectively collected cohort including outpatients with documented
A differentiation according to the individual health condition should be considered when weight management recommendations are to be made. Healthy subjects aiming to maintain absence of disease should be looked at differently from a patient with existing CV disease aiming to survive with it. For patients with systolic heart failure this has indeed been implemented in several validated risk score calculators where higher body weight is considered as an indicator of lower mortality.7,8

Different therapy across body mass index groups does not hold true as a confounder

There are two reasons why the current study by Hansel et al. is not just a confirmatory study, but adds new evidence to the ongoing discussion. First, the authors address the argument of better medical therapy in heavier patients. Indeed, more rigorous adherence to full guideline-recommended therapy and higher doses of medications are often observed in relation to higher body weight. This is one key argument to discount reports on improved outcomes in overweight patients as being confounded by differences in adequate therapy. In the current study, as expected, larger patients received better therapy and, in turn, patients who received more stringent medical therapy had better outcomes. Notably, the reverse J-shaped relationship between BMI and outcome persisted when only patients on optimum medical therapy were studied. Hence, better therapy does not explain away the obesity paradox.

Table 1  Cardiovascular diseases and conditions that were reported with an inverse association of higher body weight with lower mortality.5

<table>
<thead>
<tr>
<th>CV disease</th>
<th>Chronic heart failure</th>
<th>Acute heart failure</th>
<th>Heart failure with preserved ejection fraction</th>
<th>Coronary artery disease + cardiovascular risk profile</th>
<th>Acute coronary syndrome</th>
<th>Unstable angina/NSTEMI</th>
<th>Acute myocardial infarction</th>
<th>Acute cerebral stroke or transient ischaemic attack</th>
<th>Diabetes + cardiovascular risk profile</th>
<th>Cardiovascular rehabilitation</th>
<th>Atrial fibrillation</th>
</tr>
</thead>
</table>

CV interventions

- Percutaneous coronary intervention
- Acute percutaneous coronary intervention
- Trans-catheter aortic valve implantation
- Carotid endarterectomy
- Bypass surgery
- Valvular surgery
- Vascular surgery
- Heart transplantation

CV disease or advanced risk for atherosclerosis (defined by ≥3 clinically established risk factors such as diabetes, hypertension, hyperlipidaemia, current smoking, and others). In this large cohort of 54,285 patients who were followed for up to 4 years, the authors observed what they described as an inverse ‘J-shaped’ relationship of body weight with the main outcomes (all-cause mortality, CV mortality, and CV events). Patients who were underweight (BMI < 18 kg/m²) had the highest risk for all outcomes; however, overweight and obese patients had lower risks of death and CV events when compared with patients with BMI 18–25 kg/m². The latter served as the reference group in accordance with the World Health Organization’s definition of this BMI range as normal or ‘ideal’ body weight.

If one looks—at the significantly better survival of overweight patients as compared with the patients with ‘ideal body weight’, this might lead to some reflection on the meaning of the word ‘ideal’ in this context. For most people, longer survival is more ideal than shorter survival: life, simple as that! Common sense and science should dictate nomenclature, not opinions and beliefs. The life insurance industry gets this one right—ideal weight is the weight at which one lives the longest. Moreover, choosing the subgroup with the lowest risk as reference would document the survival disadvantage of certain body weight groups more clearly, as a risk ratio which is calculated not by comparison with the best or worst group by survival but with an intermediate risk group will never reflect the full extent of the advantage or disadvantage that certain patient and body weight groups have.

J-shaped relationship already seen in patients at risk of cardiovascular disease

Secondly, the relationship between body weight and outcomes also works in the primary prevention setting of the current study. In patients at high risk of CV disease—as indicated by the presence of ≥3 risk factors or pre-disposing co-morbidities (including diabetes, diabetic nephropathy, hypertension, hyperlipoproteinaemia, or smoking)—those who were overweight or had mild to moderate obesity were found to have a significantly lower total mortality and CV events.

Before this finding further shakes our belief in obesity as a worldwide disease-causing burden for healthy subjects, we should be reminded that the REACH registry included subjects with advanced CV risk profiles. The study cohort is therefore not a completely healthy population, where the term primary prevention may be more fully applicable. The REACH cohort conforms, however, to the INVEST study, a prospective interventional trial in 22,576 patients with hypertension and documented coronary artery disease, with and without previous CV events.9 In line with the REACH analysis, overweight and obesity were predictive of lower mortality and morbidity (i.e. non-fatal CV events) in the INVEST cohort.

A call to move from paradox to paradigm

While further data are constantly emerging to support the existence of the obesity paradox, it may be the time to challenge the view of...
this phenomenon as a ‘paradox’. The term paradox is of Greek origin (‘para’ means ‘beside’ and ‘doxa’ means ‘opinion’) and is used to indicate self-contradictory situations. The observation of an inverse association of body weight with outcome has been confirmed multiple times and in numerous patient cohorts over a wide spectrum of CV diseases and disease severities and using various methods. The results are also implemented in risk assessment scores we use on a daily basis. So why would this still be considered an unexpected and contradictory or ‘paradoxical’ finding?

Of course, this inverse association is still in total contrast to the deeply internalized wisdom of obesity as a trigger for many illnesses and a burden to society. In healthy and young(ish) people, this view appears to be correct. However, in anyone else, it may not be. It may be the time to propagate a more differentiated position on weight management that distinguishes more carefully between healthy and young subjects and those with an established CV disease (Figure 1). Avoiding overweight and obesity may doubtless benefit one’s long-term health in the absence of any disease. The metabolic imbalance in chronic disease (as is also the case in CV diseases) may, however, be far too complex to be reduced to the unisono clinical recommendation of weight reduction in all cases of overweight and obesity. Weight gain and weight loss are frequently observed in many chronic illnesses and affect all body compartments, and this has various consequences besides survival per se.

It appears clear from all the research available that the optimum (or ideal) body weight is shifting to a higher BMI range, once a chronic disease of some kind is present. This view acknowledges a cardio-clinical recommendation of weight reduction in all cases of overweight and obesity. The metabolic and obesity paradigm’ (or overweight paradigm) may be proposed, to appreciate more positively the shifting association of higher body weight and outcome in CV disease.

Lifestyle recommendations for those patients who are overweight should be made, with more careful consideration of the often catabolic condition of chronic CV disease, and may be more focused on encouraging exercise and a healthy diet that may not necessarily include caloric restriction. Weight recommendations should be made with the clear understanding of the different metabolic conditions in healthy subjects and those with established CV disease.

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**References**


Three sea anemones sitting on the aortic valve

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A 72-year-old woman underwent a transesophageal echocardiographic examination to exclude cardiac causes of recurrent transient ischaemic attacks (TIAs). All cardiac structures were shown to be normal except of three vegetation-like structures affecting the three leaflets of the aortic valve (Panel A). On questioning, she reported neither cardiac symptoms nor recent history of fever. Laboratory investigations showed normal inflammatory parameters. At surgery, the structures were affecting the three leaflets of the aortic valve and decision made to replace it using tissue prosthesis. Macroscopically, they had a characteristic frond-like structure and, immersed in water, they looked like sea anemones (Panels B and C) with tiny streaks of clotted blood (arrow). Histological examination confirmed the diagnosis of multiple papillary fibroelastoma having a core consisting of mucopolysaccharides and covered with CD34-positive endothelial cells (Panel D). The patient had an uneventful course after the operation.

Panel A: 3D echocardiograph of aortic valve showing the vegetation-like structures.
Panel B: The excised affected leaflets immersed in water.
Panel C: Frond-like structure of the fibroelastoma with streaks of clotted blood on it.
Panel D: Microscopic image of the fibroelastoma.