

“The obesity paradox” in disease – is the protective effect of obesity true?

Nina Braun^{a,b}, Filomena Gomes^a, Philipp Schuetz^{a,c}

^a University Department of Internal Medicine, Kantonsspital Aarau, Switzerland

^b Department of Internal Medicine, Kantonsspital Mönsterlingen, Switzerland

^c Medical Faculty of the University of Basel, Switzerland

Summary

Although obesity and the associated metabolic syndrome negatively impact on health outcomes, a paradoxical relationship between obesity and mortality has been reported for specific patient populations – the “obesity paradox”. However, underlying mechanisms remain unclear and several possible explanations are being discussed. First, a true protective effect of obesity is possible, mediated through differences in the immune response and more metabolic reserves. Although there is a growing body of evidence supporting this hypothesis, the influence of obesity on immune function is complex and not completely understood. Second, a statistical bias is possible, owing to confounding, selection bias, performance bias and measurement bias of most observational studies reporting the obesity paradox. Within this article, we summarise current concepts regarding the underlying pathophysiology and possible explanation for the obesity paradox, and discuss open questions such as whether age is an effect modifier on the relationship of obesity and mortality.

Key words: obesity; pneumonia; inflammation; biomarker

What is the obesity paradox?

Imagine two patients presenting at the emergency room, both suffering from a community-acquired pneumonia and with similar age, ethnicity and comorbidities. However, one of them has a normal body mass index (BMI) of 18.5–25 kg/m², while the other one meets the criteria for mild obesity (BMI 30–35 kg/m²). Which patient is at higher risk for mortality over the next few years? Most people would choose the mildly obese patient. Empirical evidence, however, shows that the mildly obese patient with pneumonia, compared with the normal weight patient, has a more favourable prognosis in regard to mortality – a phenomenon that has been named the “obesity paradox”. Similar data are available for patients suffering from heart failure [1], acute coronary syndrome [2], diabetes type 2 [3], cancer [4], kidney disease [5], stroke [6], chronic obstructive lung

disease [7] or community-acquired pneumonia [8] and the elderly population [9].

Obesity and the metabolic syndrome are associated with negative health outcomes. Obesity is a risk factor for diabetes type 2, hypertension, dyslipidaemia, cardiovascular diseases and several malignancies. In a healthy population, the BMI-associated mortality curve is U-shaped with lowest mortality at a BMI between 22.5–25 kg/m² [10]. Thus, it seems paradoxical that epidemiological studies in the above-mentioned patient populations reported a survival benefit for overweight and obese patients. Several reasons have been discussed that could explain these paradoxical associations, which are outlined in more detail below. Furthermore, several open questions remain regarding the obesity paradox. Whether the obesity paradox is only true for mild obesity (BMI 30–35 kg/m²) or if patients with more severe obesity also have survival benefits is unclear, and findings of the existing studies are inconsistent. The type of obesity (i.e., hedonic or metabolic) may also play an important role. A recent study looking at >15 000 adults from the National Health and Nutrition Examination Survey (NHANES) found central obesity to be a risk factor for mortality even among individuals with a normal BMI [11]. Multivariate analyses demonstrated that normal-weight men and women with central obesity were more likely to die during a mean follow-up of 14 years than were other participants. In their analysis waist-to-hip ratio was the better outcome predictor compared with BMI. Also, from the “SOS study” we have learned that weight loss caused by bariatric surgery improves survival in morbidly obese patients (≥ 34 kg/m² in men and ≥ 38 kg/m² in women) [12].

Are there true protective factors of obesity?

Although clinical data have repeatedly shown improved survival in obese patients, underlying pathophysiological mechanisms remain largely unclear. One often discussed argument for a survival advantage in obesity is the increased metabolic reserve during cachectic states – such as disease-associated cachexia [13, 14]. Loss of appetite and the consequent unintentional weight loss is a frequent find-

ing associated with acute disease and may lead to malnutrition with negative impact on immune function. In this context, the fat reserves of obese patients may make them more resistant to the catabolic progression of wasting diseases [15]. Aquilani and colleagues found that, in patients with chronic heart failure, only obese individuals had balanced muscle protein catabolism, and it is known that an unbalanced protein catabolism is associated with reduced immunological capacity and tissue integrity [16]. Fat tissue also has other relevant beneficial effects, for instance, in the protection against bone fractures [17], infectious complications and pressure sores [18].

Another argument is a possible difference in immune and inflammatory response. Obesity is known to be a state of chronic inflammation and proinflammatory adipokines, released by adipocytes, are thought to play a crucial role in the pathogenesis of obesity and related adverse outcomes [19–21]. A more pronounced inflammatory response, evidenced by higher body temperature and a higher increase in C-reactive protein levels was associated with favourable long-term prognosis in one study looking at a large cohort of patients with community-acquired pneumonia [22]. Thus, one may speculate that a stronger inflammatory and immune response may help the body to overcome an infectious episode with favourable long-term effects. A recent study investigated associations of obesity and inflammation biomarkers in a cohort of 763 patients with community-acquired pneumonia [23]. In this cohort, we observed that obese patients had higher survival rates when compared with the nonobese population, providing again empirical evidence in favour of the obesity paradox (fig. 1). However, there was no evidence of a different immune response in obese patients, which could explain these findings [23]. Inflammation was measured by means of different biomarkers (C-reactive protein, white cell count, procalcitonin, proadrenomedullin), but other markers such as cytokines and interleukins were not available in this cohort [24]. Thus the study still does not preclude inflammation from being the missing link in the obesity paradox.

There are several pro- and anti-inflammatory adipokines, which play an important role in immune function. For ex-

ample the proinflammatory tumour necrosis factor- α (TNF- α) and its soluble anti-inflammatory antibodies are both produced by adipocytes [25, 26]. The latter are supposed to be beneficial in the overwhelming TNF α production observed in lethal sepsis [25]. Leptin is another adipokine, which is important for host response by modulating T-cell response [27]. Adiponectin has anti-inflammatory effects and may suppress inflammation in the lungs [21]. Also, the inflammatory response *per se* has in turn effects on lipids and obesity [28]. Clearly, further studies are needed to investigate the relation of immune-biomarkers and outcome in the obese population.

Is it all about bias?

There are important methodological shortcomings in epidemiological studies that have analysed the association between BMI and mortality, which could explain the “obesity paradox” (fig. 2). First, because all studies were observational, they do not prove causality and are prone to confounding. Smoking and heavy alcohol consumption is more frequent in lean persons and is associated with increased mortality [29, 30]. Cancer and other severe chronic illnesses cause unintentional weight loss and cachexia. Mild obesity may therefore rather be mirror of a good health condition with absence of chronic diseases. This effect is called “reverse causation” because obesity is rather a consequence than a cause of a good health condition with absence of chronic diseases [31]. Although many studies used statistical techniques such as multivariable adjustment to overcome this bias, residual confounding is possible [32]. Stokes and Preston recently published a study in which the obesity paradox disappeared after restricting the reference group to patients who never experienced weight loss. Mortality was even increased in the overweight/obese group after limiting the analysis to never-smokers [33]. Importantly, not only unintentional weight loss is a possible confounder, but also intentional weight loss or diet. Two individuals may have the same BMI, one without a history of dieting and the other with multiple attempts to lose weight. This difference could have an impact on the immune system and consequently on the ability to handle any illness. Another recently discussed methodological issue similar to confounding is the “collider stratification bias” [31, 32, 34–36]. This bias occurs if several medical conditions, which interact with each other, are risk factors for the disease under investigation. For example, obese people have a higher risk of acquiring pneumonia and thus obesity is a pneumonia risk factor [8]. Other risk factors include alcoholism [37] or smoking, which are negatively associated

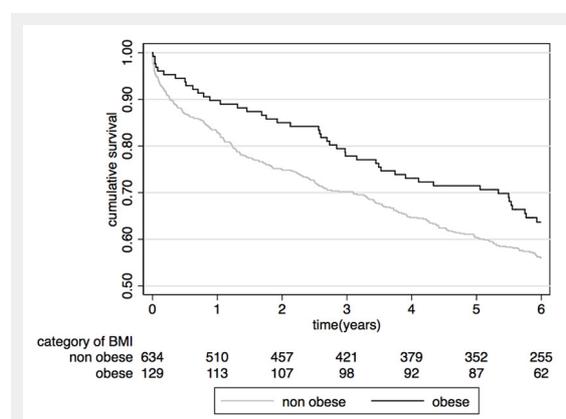


Figure 1

Association between obesity and survival in a cohort of patients with community-acquired pneumonia.
nonobese = body mass index (BMI) <30 kg/m²; obese = BMI ≥30 kg/m²

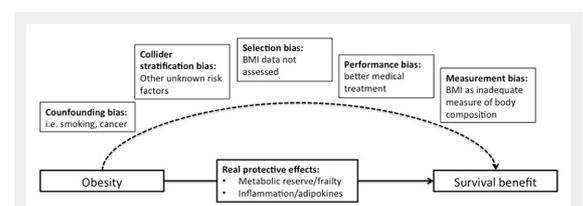


Figure 2

Possible explanations of the obesity paradox.

with mortality. Yet when the impact of weight on pneumonia outcomes is investigated, the proportion of patients with pneumonia due to alcoholism or smoking may be less in the obese group because obesity itself is a risk factor. This results in a biased group of patients in regard to their BMI.

Also, selection bias may be an important issue in previous studies. For example, the obesity paradox has been described in multiple studies with stroke patients, conducted in different countries, including first and recurrent strokes, ischaemic and haemorrhagic strokes. The results are consistent and show a protective effect of being overweight and/or obese (when compared with the lean counterparts) on short- and long-term mortality, functional outcomes and even recurrent strokes. These results were proved to be independent of age, cause of death and severity of stroke [6, 38]. However, it should be noted that the majority of these studies are either a subanalysis of clinical trials or a retrospective analysis of observational studies, where a significant proportion of patients was not included in the analysis because of lack of a record of BMI (e.g. 45% [39]). This may represent an important selection bias and it is not possible to determine whether the study represents a rather selected stroke population.

Also, it is possible that obese individuals receive better medical treatment (e.g. statins), which could have a favourable impact on outcomes [8]. This phenomenon is called “performance bias”. Nonetheless, a recent large cohort of patients with cardiovascular disease showed that the paradoxical association between BMI and outcome persisted when only patients with optimal medical therapy were studied, suggesting that the obesity paradox is independent of the intensity of the medical therapy received [40].

Finally, there is also the possibility of a “measurement bias”. The use of BMI for body composition assessment is controversial because it does not differentiate between adipose tissue and lean muscle mass. The results in trials with other body composition measures (waist-to-hip ratio or waist circumference) are not consistent [41].

Outlook and future direction

Current evidence suggests that the optimal BMI for the healthy population is different from the optimal BMI for the population with chronic/wasting diseases and the elderly population. If the obesity paradox is true and a higher BMI has beneficial effects on long-term survival, the concept of optimal BMI may need to be revised and individualised, where factors such as quality of the diet (vs pure calorie restriction), general fitness and metabolic state should be taken in consideration. In the population of chronic heart failure patients, the obesity paradox was only prevalent in the patients with low fitness, while patients with high fitness had a better survival independent of their BMI [42]. Also a differentiation between “unhealthy” and “healthy” metabolic states (defined by parameters of the metabolic syndrome) in the obese population has been suggested [43]. Padwal et al. proposed the Edmonton obesity staging system for better classification of obesity; obesity-related comorbidities and functional status are part of this staging system, which shows a high correlation with mor-

ality [44]. However, this assessment is more complex and time consuming, questioning its applicability in daily routine.

Another unresolved issue is whether age is an effect modifier on the relationship of obesity and mortality, i.e. if obesity is protective in older age, but less so in younger persons. Most studies including patients with chronic medical diseases had a high mean age of participants – and data on younger patients are lacking. Even though most studies adjusted their results for age, the question of effect modification cannot be answered conclusively. One study that stratified patients by age found the obesity paradox only in patients >65 years of age [45].

Because the underlying mechanisms of the obesity paradox remain unclear, further good quality studies are warranted to understand this paradoxical relationship and to define the optimal BMI for populations with chronic and wasting diseases. Whenever possible, the design of observational studies should take into consideration the limitations and biases described above. It is also important to analyse more patient-centred outcomes other than mortality, such as quality of life, infectious complications and functional capacity. Ideally, randomised trials should assess the long-term effect of intentional weight loss of obese patients in these patient populations.

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Correspondence: Professor Philipp Schuetz, M.D., MPH, Department of Endocrinology, Diabetes and Clinical Nutrition, University Department of Internal Medicine, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, [Philipp.Schuetz\[at\]unibas.ch](mailto:Philipp.Schuetz[at]unibas.ch)

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Figures (large format)

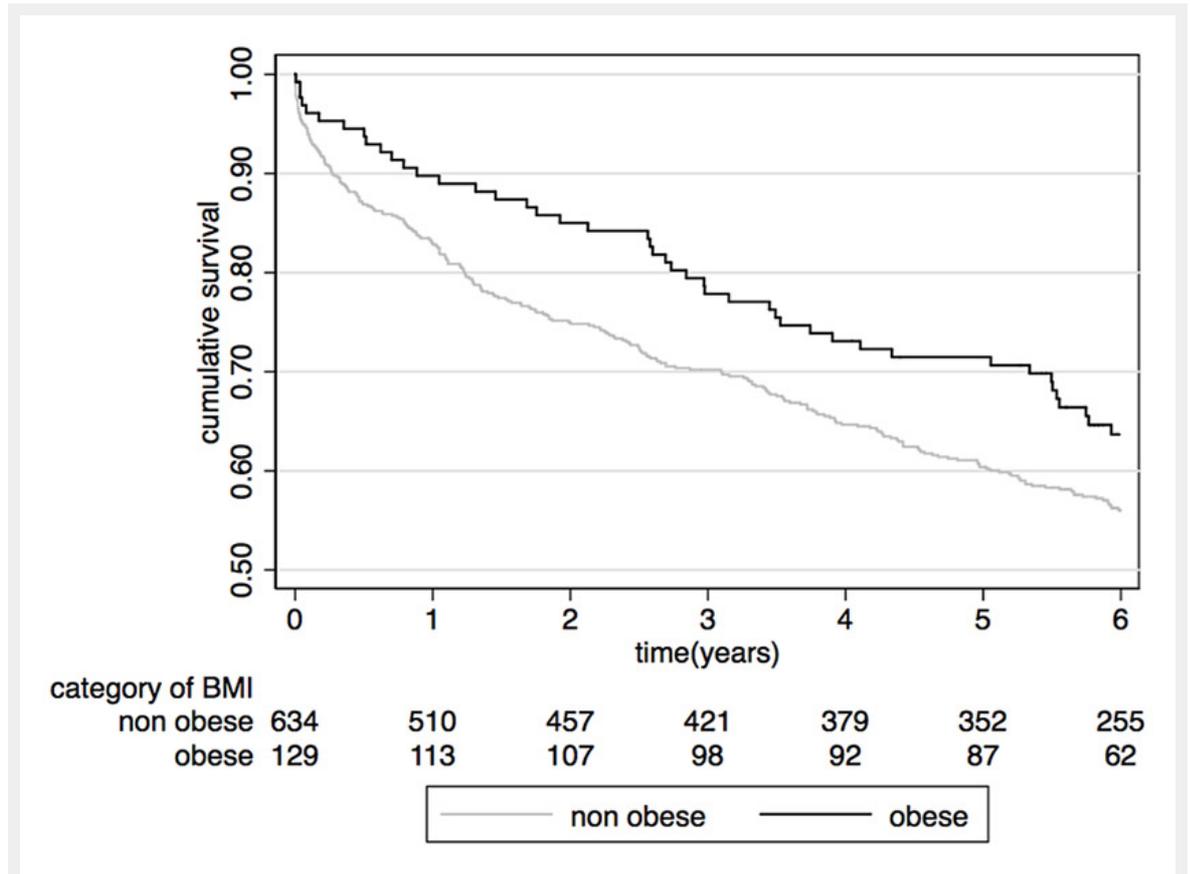


Figure 1

Association between obesity and survival in a cohort of patients with community-acquired pneumonia. nonobese = body mass index (BMI) <30 kg/m²; obese = BMI ≥30 kg/m²

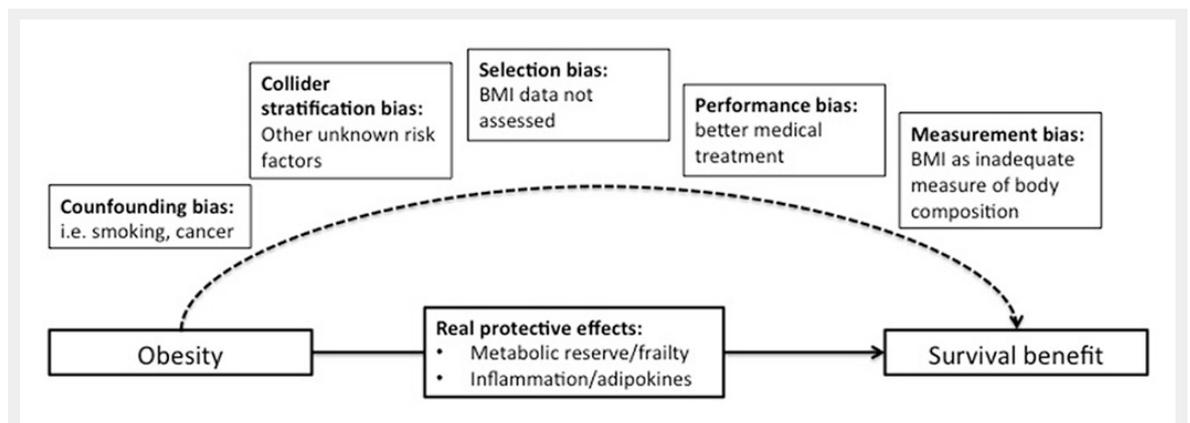


Figure 2

Possible explanations of the obesity paradox.