



## ⊗ The Obesity Paradox in Patients in Need of Extracorporeal Membrane Oxygenation

Although the coronavirus disease (COVID-19) pandemic was overwhelming, let us not forget that, in recent decades, another more slumbering pandemic was also raging: the obesity pandemic. The COVID-19 pandemic highlighted the interplay among obesity, adult respiratory distress syndrome (ARDS), and the need for ventilatory support. Early during the COVID-19 pandemic, obesity was recognized as an important risk factor for susceptibility to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as an unfavorable disease course of COVID-19. Consequently, COVID-19 patients with a higher body mass index (BMI) were more likely to need intensive care treatment. Intriguingly, when admitted to the ICU, the prognosis of obese patients was not worse (1) or was even better (2) than the prognosis of patients of normal weight.

### Being Obese Is Not Healthy, but There Is a Paradox

Clearly, obesity leads to multiple health-related problems, including metabolic syndrome, diabetes, cancer, and cardiovascular, respiratory, and infectious diseases, thereby increasing overall mortality (3, 4). However, another intriguing phenomenon is also present, coined the obesity paradox, characterized by the observation that, when a disease is established in a patient, a lower mortality rate is observed in obese patients. This has been demonstrated in patients with heart failure (5), chronic obstructive pulmonary disease, rheumatoid arthritis, AIDS (6), and end-stage renal disease (7), to name a few. The same association is observed in critically ill patients: those with a higher BMI have a better prognosis, even when corrected for other prognostic variables (1, 8, 9). This reverse epidemiology is of relevance because negative attitudes toward obese patients (i.e., the social stigma of obesity) still exist, and this may influence ICU admission decisions, as well as decisions related to the invasiveness of these patients' treatment. The fact that obesity is considered a relative contraindication for extracorporeal membrane oxygenation (ECMO) is an example of such a consequence.

In this issue of the *Journal*, Rudym and colleagues (pp. 685–694) report that a higher BMI is associated with a better, not worse, prognosis in critically ill patients with ARDS who need ECMO (10). This is a well-performed retrospective observational study using data collected in multiple countries. However, there are several issues inherent to the observational nature of studies like this.

### Is this Paradoxical Reverse Association Real?

Obesity may increase the risk of atelectasis, possibly leading to overestimated severity of ARDS. It appears plausible that less sick obese patients may be in need of ECMO because of the unfavorable effects of obesity on pulmonary mechanics. An observed better survival may be the consequence of this collider bias. Also, it appears plausible that obese patients were more likely to be denied ECMO and only those with a higher chance of surviving (young, less organ failure) may have received it, leading to selection bias. The only way to try to correct for these issues is to perform additional analyses with adjustments for baseline characteristics with prognostic value. Indeed, in the study of Rudym and colleagues, obese patients were younger, more likely female, and had a lower disease severity score, which are relevant baseline characteristics related to a more favorable prognosis. Therefore, to state that there is an obesity paradox in patients with ECMO, adjustments are of paramount importance. The authors adequately addressed these issues and performed propensity-matched analyses, after which the observed better outcomes for obese patients remained. Still, one could argue that there will always be unmeasured, residual confounders and possibly reverse causation. Nevertheless, the important lesson from the study is that, overall, the outcome following ECMO is definitely not worse in obese patients. Consequently, obesity should not factor into the decision-making of whether a patient should receive ECMO.

### Can We Assume Causality?

Another limitation of observational association studies is that they are not suited to determine causality, as any clinical association could merely reflect an epiphenomenon. However, several aspects of observed association could point toward causation. These are called the Bradford Hill criteria (11) and consist of 1) strength of the association, 2) consistency, 3) temporality, 4) biological gradient, 5) plausibility, and 6) coherence. For the study by Rudym and colleagues, the association was 1) strong, with an odds ratio for ICU mortality of 0.55 (95% confidence interval: 0.43–0.93) in obese patients; 2) consistent, with the obesity paradox observed in multiple previous studies also performed in critically ill patients (1, 8, 9); 3) temporal, with a higher BMI clearly preceding the described survival benefit; 4) exhibiting a biological gradient, with a higher BMI associated with a more pronounced beneficial effect; and 5) plausible, with various hypotheses that may explain why obesity may be beneficial during critical illness. These include nutritional reserves, as adipose tissue may function as a fuel source during highly catabolic states (12); immunological differences (13); higher cholesterol levels potentially neutralizing endotoxin (14) and providing the precursors for adrenal steroid synthesis (15); obesity-associated neutrophil dysfunction attenuating lung injury (16); and more mechanistic mechanisms such as obesity-induced diaphragmatic remodeling (17) and pulmonary differences. Again, the incidence of ARDS is higher in obese patients (18), but the prognosis is better in these patients (19). Finally, the findings of the study by Rudym and colleagues are 6) coherent, meaning that cause-and-effect interpretation does not

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Originally Published in Press as DOI: 10.1164/rccm.202307-1261ED on August 28, 2023

conflict with the natural history and biology of a disease. After all, from an evolutionary point of view, it may not be counterintuitive that a better nutritional state enables people to overcome periods of physical crisis. Fulfilling these Bradford Hill criteria strengthens the cause-and-effect relationship between obesity and outcome in these patients.

## The Bottom Line

Obesity is a huge and increasing healthcare problem associated with various comorbid conditions, greater susceptibility to diseases, more pronounced physiologic derangements, and physical limitations, complicating acute illness and impeding therapeutic measures. Nevertheless, when obese patients become critically ill, they have better outcomes. The relevant question whether this also holds true for patients who need ECMO is now answered, and therefore the clinically relevant consequence of the results described by Rudym and colleagues is that that obesity is not a reason to withhold ECMO. The mechanism of its potential protective factors and the influence of obesity on acute illnesses are still poorly understood and likely multifactorial, and further research is needed to determine the pathophysiologic mechanisms of this observation. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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