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METABOLISM (M DALAMAGA, SECTION EDITOR)

Is There an Obesity Paradox in Critical Illness? Epidemiologic and Metabolic Considerations

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Abstract

Purpose of Review Obesity represents a global epidemic with serious implications in public health due to its increasing prevalence and its known association with a high morbidity and mortality burden. However, a growing number of data support a survival benefit of obesity in critical illness. This review summarizes current evidence regarding the obesity paradox in critical illness, discusses methodological issues and metabolic implications, and presents potential pathophysiologic mechanisms.

Recent Findings Data from meta-analyses and recent studies corroborate the obesity-related survival benefit in critically ill patients as well as in selected populations such as patients with sepsis and acute respiratory distress syndrome, but not trauma. However, this finding warrants a cautious interpretation due to certain methodological limitations of these studies, such as the retrospective design, possible selection bias, the use of BMI as an obesity index, and inadequate adjustment for confounding variables. Main pathophysiologic mechanisms related to obesity that could explain this phenomenon include higher energy reserves, inflammatory preconditioning, anti-inflammatory immune profile, endotoxin neutralization, adrenal steroid synthesis, renin-angiotensin system activation, cardioprotective metabolic effects, and prevention of muscle wasting.

Summary The survival benefit of obesity in critical illness is supported from large meta-analyses and recent studies. Due to important methodological limitations, more prospective studies are needed to further elucidate this finding, while future research should focus on the pathophysiologic role of adipose tissue in critical illness.

Keywords Body mass index · Critically ill · Mortality · Obese · Obesity paradox · Overweight · Sepsis · Survival

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Introduction

Obesity, which represents the increase of body weight due to expansion of adipose tissue, has become a global epidemic with important implications in public health. Epidemiologic studies have shown that obesity exhibits an overtly increasing prevalence in both economically developed and developing countries during the last four decades [1–4]. According to the World Health Organization (WHO), obesity has tripled since 1975, with 1.9 billion adults being overweight and 650 million of them being obese in 2016. This comprises a worldwide prevalence rate of 39% for overweight and 13% for obesity in adults [5]. Furthermore, if these increasing trends continue, it has been estimated that overweight and obesity prevalence will exceed 57% by 2030 [6].

WHO defines overweight and obesity as abnormal or excessive fat accumulation that may impair health. Epidemiological

studies have widely adopted the WHO classification of obesity for adults of both sexes and all ages, based on BMI, an index calculated as the ratio of body weight to squared height (kg/m^2). According to this classification, overweight is defined as a BMI greater than or equal to 25 kg/m^2 and obesity as a BMI greater than or equal to 30 kg/m^2 [5]. Further classification of the severity of adulthood obesity comprises 3 classes: class I (moderate) with BMI 30–34.9 kg/m^2, class II (severe) with BMI 35–39.9 kg/m^2, and class III (very severe) with BMI greater or equal to 40 kg/m^2. Normal weight is considered a BMI of 18.5–24.9 kg/m^2, while a BMI below 18.5 kg/m^2 defines underweight. Although BMI is not the most reliable measure of body fat, needing appropriate adjustments for race and body fat distribution, it is a simple and useful epidemiological tool based on large population studies [4]. Thus, it is currently the most widely accepted measure of overweight and obesity in adults.

Obesity is an established risk factor for metabolic and cardiovascular diseases; certain malignancies; and respiratory, musculoskeletal, and mental disorders [5, 7]. Overweight and obesity are associated with a high mortality burden, contributing to 4 million deaths globally in 2015, which comprise approximately 7.1% of total deaths [3, 8]. Additionally, the economic burden of health care costs along with indirect costs attributed to obesity is substantially high [9].

At the same time, as obesity rises in the general population, overweight and patients with obesity comprise a significant proportion of the critically ill population, estimated to be around 34% for overweight and 15–20% for obesity [10, 11]. Treating critically ill patients with obesity is challenging due to difficulties in airway management and oxygenation, nutritional support with underlying metabolic syndrome and diabetes, altered pharmacokinetics, high risk of acute kidney injury, and higher risk of serious complications [12]. Thus, one would expect that obesity would inadvertently influence the already poor outcome of critical illness. However, many observational studies have shown a decreased mortality in overweight and moderate obesity compared to normal weight critically ill patients [13–14, 15••]. This unexpected phenomenon has been termed "obesity paradox," and it has also been observed in various acute and chronic diseases, like sepsis, acute respiratory distress syndrome (ARDS), heart failure, coronary artery disease, and chronic renal failure [16•, 17, 18•, 19–21]. The "obesity paradox" in critical illness has raised great consideration in the scientific community, and numerous cohort studies were carried out aiming at elucidating this phenomenon.

In this review, we analyze the epidemiologic data regarding the "obesity paradox" or survival benefit in critical illness, including meta-analyses and recent clinical studies: we discuss methodological issues and metabolic implications of obesity in critical illness; we highlight potential pathophysiologic mechanisms explaining this phenomenon; and finally, we present the clinical implications and future perspectives.

The Obesity Paradox in Critical Illness: Epidemiologic Data

Data from Meta-analyses

Meta-analyses of observational studies investigating the association of obesity with mortality in critically ill patients are summarized in Table 1. Studies regarding mixed critically ill populations were analyzed in 4 meta-analyses, one of them being recent [13–14, 15••, 22], while 5 meta-analyses investigated selected critically ill patients: sepsis (2), ARDS (2), and trauma (1) [17, 18•, 23••, 24–25].

In a large meta-analysis of 23 observational studies and 76,737 critically ill patients, Oliveros et al. demonstrated a significantly decreased mortality risk in overweight and patients with obesity, but not those with severe obesity, compared to normal weight patients, despite a longer length of intensive care unit (ICU) stay and an increased risk of multiple organ dysfunction [13]. These studies reported BMI upon ICU admission and various outcome measures including ICU, hospital, and 28-day mortality. They were highly heterogeneous, while mortality risk was not adjusted in 9 studies. In a concurrent meta-analysis, Akinnusi et al. analyzed 14 studies (included in the previous meta-analysis) aiming to explore the association of obesity with ICU mortality [22]. The authors reported that although obesity (BMI ≥ 30 kg/m^2) was not associated with crude ICU mortality, hospital mortality was lower in patients with obesity compared to those without (BMI < 30 kg/m^2). Moreover, in a subgroup analysis, they showed that patients with obesity and BMI 30–39.9 kg/m^2 had lower ICU mortality than those with BMI < 30 kg/m^2. In this meta-analysis, comparisons were made with patients without obesity as a reference group. Thus, considering underweight, normal weight, and overweight as one group may have resulted in missed opportunities to identify any association of overweight with ICU mortality. In a subsequent analysis, Hogue et al. included 8 studies reporting ICU mortality after risk adjustment, stratified by BMI category, and found no difference in ICU mortality of all BMI classes compared to normal BMI, while patients with obesity had lower hospital mortality [14]. However, included studies were extremely heterogeneous. Finally, a more recent meta-analysis of 199,421 adult critically ill patients receiving mechanical ventilation (MV) investigating the impact of obesity on ICU, hospital, short-term, and long-term mortality showed that those with obesity (BMI ≥ 30 kg/m^2) had lower mortality compared to those without (BMI < 30 kg/m^2) regarding all measures of mortality [15••]. Subgroup analysis further showed that patients with obesity (BMI 30–39.9 kg/m^2) had lower ICU mortality compared to normal weight patients (BMI 18.5–24.9 kg/m^2). Overall, the abovementioned meta-analyses are in agreement regarding the survival benefit of obesity in critical illness compared to normal weight, while overweight was also

Table 1 Meta-analyses of epidemiologic studies regarding obesity and mortality in critically ill patients

Author/ year	Study selection	Studies (*N*)	Population (*N*)	Main findings	Comments
Oliveros et al., 2008 [13]	Observational studies in English 1966–2007 BMI: on ICU admission Obesity definition according to WHO Mortality: ICU, hospital or at 28 days	23 Study design not reported	76,737 Adult (> 18 years old) critically ill patients (medical, surgical, trauma and patients with ALI)	Mortality was decreased in overweight and critically ill patients with obesity, but not in patients with severe obesity compared to normal weight BMI 25–29.9: OR 0.91 ($p = 0.01$) BMI 30–39.9: OR 0.82 ($p = 0.03$) BMI ≥ 40: OR 0.94 ($p = 0.26$) (reference group: BMI 18.5–24.9)	Extremely heterogeneous studies regarding: • Mixed population • Outcome • BMI categories • Adjustment of OR (not adjusted in 9 studies) Additional findings • Longer LOS in the ICU for underweight, overweight and patients with severe obesity • Increased risk of MOD associated with overweight and obesity
Akinnusi et al., 2008 [22]	Observational studies without language restrictions 1966–2007 Obesity definition according to NIH Mortality: ICU	14 Prospective: 7 Retrospect: 7	62,045 Adult medical, surgical, and trauma ICU patients 25% were obese (BMI ≥ 30)	Obesity (BMI ≥ 30) was not associated with crude ICU mortality RR 1.00; 95% CI 0.86–1.16; $p = 0.97$ (reference group: BMI < 30) Obesity (BMI ≥ 30) was associated with lower in-hospital mortality than BMI < 30 RR 0.83; 95% CI 0.74–0.92; $p < 0.001$ In subgroup analysis, BMI 30–39.9 had lower ICU mortality than BMI < 30 RR 0.86; 95% CI 0.81–0.91; $p < 0.001$	Heterogeneous studies regarding design, outcome and BMI categories (only 8 studies stratified outcomes based on BMI categories) Severity of critical illness (APACHE II, SAPS II, ISS) was comparable between patients with or without obesity Subgroup analysis considered underweight, normal weight, and overweight as one group Additional findings • Longer LOS and duration of MV for patients with obesity
Hogue et al. 2009 [14]	English-language studies through March 10, 2008 Obesity definition according to WHO Mortality: ICU and hospital	22 Prospective: 6 Retrospect: 13 Case control: 3	88,051 Medical, surgical, and trauma ICU patients, aged ≥ 16 years	ICU mortality of underweight, overweight, patients with obesity, and morbid obesity did not significantly differ compared to normal weight (data from 8 studies) Obesity was associated with lower hospital mortality compared to normal weight (data from 9 studies) RR 0.76; 95% CI 0.59–0.92 (p value not reported) (reference group: BMI 18.5–24.9)	Analysis included studies reporting mortality after risk adjustment High heterogeneity in studies for all BMI categories except underweight and morbid obesity Additional findings • Overweight and morbid obesity were associated with a non-significant trend towards lower and underweight towards higher hospital mortality compared to normal weight • No association of BMI with duration of MV • Patients with morbid obesity had longer ICU and hospital LOS than patients with normal weight
Liu et al. 2013 [25]	English-language studies through June 2012 Obesity definition according to WHO Mortality: not specified	18 Prospective: 5 Retrospect: 13	51,501 Critically ill trauma patients, aged > 13 years 17% were obese (BMI ≥ 30)	Patients with BMI ≥ 30 presented higher mortality compared to those with BMI < 30 (7.7% vs. 4.7%) Obesity was associated with a significant increase in mortality risk compared to patients without obesity (OR 1.45) Subgroup analysis showed that patients with BMI ≥ 30 had higher mortality risk compared to patients with normal weight (BMI 18.5–24.9). OR 1.45; 95% CI 1.22–1.64; $p < 0.001$	Mixed age (children-adult) population Unspecified mortality rate, not adjusted for major confounding factors in some studies ISS did not differ between patients with or without obesity Additional findings • Obesity was associated with longer ICU LOS and higher rates of complications

Table 1 (continued)

Author/ year	Study selection	Studies (*N*)	Population (*N*)	Main findings	Comments
Pepper et al., 2016 [17]	Studies with no language restrictions through November 18, 2015 Obesity definition according to WHO Sepsis definition according to SEPSIS-2 Mortality: ICU, hospital, 28, 30, or 60 days	6 Prospective: 2 Retrospect: 4	7165 Critically ill patients with sepsis, severe sepsis and septic shock, aged ≥ 16 years (excluded trauma and surgical patients)	Overweight and obesity had a lower adjusted mortality risk compared to normal weight BMI 25–29.9 aOR 0.83; 95% CI 0.75–0.91; $p = 0.0002$ BMI 30–39.9 aOR 0.82; 95% CI 0.67–0.99; $p = 0.04$ (reference group: BMI 18.5–24.9) Morbid obesity and underweight were not associated with mortality BMI ≥ 40 aOR 0.90; 95% CI 0.59–1.39; $p = 0.64$ BMI < 18.5 aOR 1.24; 95% CI 0.79–1.95; $p = 0.35$	Moderate heterogeneity of studies Three studies used measured weight and height for BMI calculation All studies adjusted mortality for severity of disease while adjustment for multiple baseline variables varied between studies Outcome considered combined mortality rate Small number of patients with morbid obesity
Zhi et al., 2016 [24]	Studies with no language restrictions through April 2016 Obesity definition according to NIH Mortality: 28, 60, or 90 days	24 Prospective: 8 Retrospect: 16	9,187,248 Critically ill patients with ARDS/ALI	Overweight and obesity had a lower mortality risk compared to normal weight, while morbid obesity was not associated with mortality (data from 9 studies) BMI 25–29.9 OR 0.88; 95% CI 0.78–1.00; $p = 0.05$ BMI 30–39.9 OR 0.74; 95% CI 0.64–0.84; $p < 0.0001$ BMI ≥ 40 OR 0.87; 95% CI 0.69–1.08; $p = 0.21$ (reference group: BMI 18.5–24.9)	Obesity definition varied between studies ARDS/ALI definition was not reported in some studies Mortality risk not adjusted for confounding factors (age, gender, underlying disease) High heterogeneity Additional findings • Obesity and morbid obesity (but not overweight) were associated with increased risk of ARDS/ALI compared to normal weight (OR 1.89)
Ni et al., 2017 [18•]	Studies with no language restrictions 1946–July, 2016 Obesity definition according to NIH Mortality: ICU, hospital or 90 days	5 Prospective: 1 Retrospect: 3 Cohort study:1	6268 Critically ill patients with ARDS, aged ≥ 18 years	Patients with obesity and morbid obesity had lower mortality compared to normal weight BMI 30–39.9 OR 0.68; 95% CI 0.57–0.80; $p < 0.00001$ BMI > 40 OR 0.72; 95% CI 0.56–0.93; $p = 0.01$ (reference group: BMI 18.5–24.9)	Studies without classification of patients according to NIH were excluded All studies included were multicenter studies from the USA with no significant heterogeneity regarding mortality BMI was recorded upon ICU or hospital admission Outcome considered combined mortality rate with no adjustment for age, gender, severity of disease, and comorbidities Additional findings • Morbid obesity was associated with decreased duration of MV compared to normal weight • ICU and hospital LOS did not significantly differ between BMI classes
Wang et al., 2017 [23••]	Observational studies with no language restrictions through December 1, 2016	8 Prospective: 2 Retrospect: 6	9696 Adults with sepsis, severe sepsis or septic shock	Overweight and patients with BMI ≥ 25 exhibited lower mortality compared to normal weight patients BMI 25–29.9 OR 0.87; 95% CI 0.77–0.97; $p = 0.02$ BMI ≥ 25	High-quality studies Analysis and reporting of adjusted mortality Only 4 studies reported ICU hospitalization and outcome, but these studies represented the majority of participants (71%) Additional findings

Table 1 (continued)

Author/ year	Study selection	Studies (*N*)	Population (*N*)	Main findings	Comments
	Obesity definition according to NIH Mortality: ICU, hospital, 28, or 60 days			OR 0.81; 95% CI 0.74–0.89; $p < 0.0001$ (reference group: BMI 18.5–24.9) Patients with obesity and morbid obesity had a non-significant trend of decreased mortality compared to normal weight patients BMI 30–39.9 OR 0.89; 95% CI 0.72–1.10; $p = 0.29$ BMI > 40 OR 0.64; 95% CI 0.38–1.08; $p = 0.09$ (reference group: BMI 18.5–24.9)	• Obesity was associated with shorter ICU LOS than normal weight patients, but with no significant difference between those with obesity and morbid obesity • Hospital LOS of overweight patients and patients with obesity and morbid obesity did not significantly differ from normal weight patients
Zhao et al., 2018 [15••]	Studies with no language restrictions through July, 2017 Obesity definition according to NIH Mortality: ICU, hospital, short term (< 6 months), and long term (> 6 months)	23 Prospective:14 Retrospect: 9	199,421 Critically ill patients on MV, aged ≥ 18 years	Patients with obesity (BMI ≥ 30) had lower mortality compared to those with BMI < 30 ICU mortality OR 0.88; 95% CI 0.84–0.92; $p < 0.00001$ Hospital mortality OR 0.83; 95% CI 0.74–0.93; $p < 0.002$ Short-term mortality OR 0.81; 95% CI 0.74–0.88; $p < 0.00001$ Long-term mortality OR 0.69; 95% CI 0.60–0.79; $p < 0.00001$ Patients with obesity (BMI 30–39.9) had lower ICU mortality compared to normal weight patients OR 0.88; 95% CI 0.82–0.93; $p < 0.00001$ (reference group: BMI 18.5–24.9) Patients with obesity and severe obesity had lower hospital mortality compared to normal weight patients BMI 30–39.9 OR 0.80; 95% CI 0.73–0.89; $p < 0.0001$ BMI ≥ 40 OR 0.71; 95% CI 0.53–0.94; $p = 0.02$ (reference group: BMI 18.5–24.9) Overweight and patients with obesity had lower short- and long-term mortality compared to normal weight patients	Studies were from 4 continents and included mixed (medical, surgical) ICU population In seven studies, patients were classified in patients with obesity versus without obesity Additional findings • Obesity associated with longer duration of MV than non-obese patients • Severe obesity (BMI > 40) associated with longer duration of MV than normal weight patients • Obesity associated with longer ICU (but not hospital) LOS • ICU and hospital LOS did not significantly differ between BMI classes

ALI, acute lung injury; *aOR*, adjusted odds ratio; *APACHE*, acute physiology and chronic health evaluation; *ARDS*, acute respiratory distress syndrome; *BMI*, body mass index; *CI*, confidence interval; *ICU*, intensive care unit; *ISS*, injury severity score; *LOS*, length of stay; *MOD*, multiple organ dysfunction; *MV*, mechanical ventilation; *NIH*, National Institutes of Health; *OR*, odds ratio; *RR*, relative risk; *SAPS*, simplified acute physiology score; *WHO*, World Health Organization

associated with lower mortality risk in one meta-analysis [13] and patients with obesity and severe obesity had a lower in-hospital mortality as shown in the largest and most recent meta-analysis [15••].

Two recent meta-analyses analyzed collectively 11 studies regarding the impact of obesity in the outcome of critically ill patients with sepsis, severe sepsis, or septic shock [17, 23••]. Pepper et al. found that overweight and patients with obesity had a lower adjusted mortality risk compared to normal weight, while they could not demonstrate an association with mortality in patients with severe obesity and in underweight subjects [17]. The researchers combined data for mortality at various time points (ICU; hospital; 28, 30, and 60 days) while studies were moderately heterogeneous. However, all studies adjusted mortality for severity of disease as well as multiple baseline parameters. In a larger meta-analysis of high quality studies including 3 studies of the previous meta-analysis with 5 additional studies, Wang et al. confirmed the findings of Pepper et al. for overweight but not patients with obesity [23••]. Again, researchers reported adjusted mortality estimates.

Zhi et al. conducted a meta-analysis of 24 studies including a large number of study participants ($N = 9{,}187{,}248$) to investigate the obesity paradox in critically ill patients with acute lung injury (ALI) and ARDS [24]. Although they demonstrated that obesity and morbid obesity were associated with an increased risk of ARDS/ALI (based on data from 16 studies), overweight and obesity presented a lower mortality risk compared to normal weight, while morbid obesity was not associated with mortality (based on data from 9 studies). Nevertheless, certain methodological issues such as the high heterogeneity of studies, the inconsistent obesity, and ARDS definitions employed across studies as well as failure to adjust for major confounding factors may limit the value of this finding. Another meta-analysis including 5 studies from the USA further showed that critically ill patients with obesity or morbid obesity and ARDS presented lower mortality compared to normal weight patients [18•]. This analysis considered combined mortality measures while there was no adjustment for age, gender, severity of disease, and comorbid illness. Additionally, patients with obesity had lower severity scores and were younger than the reference group.

The association of obesity with the outcome of critically ill patients with trauma was evaluated by Liu et al. in a meta-analysis of 18 studies [25]. They reported a higher mortality in patients with BMI ≥ 30 kg/m^2 compared to those with BMI < 30 kg/m^2 and a significantly increased mortality risk of those with obesity compared to normal weight patients. The comparison was made between groups with a similar injury severity score (ISS). However, their analysis included highly heterogeneous studies with regard to study design and quality, inclusion criteria, BMI classification, and mortality at various time points, not adjusted for key confounding variables in all studies.

Overall, despite methodological limitations, all meta-analyses are in agreement regarding the lower mortality risk associated with obesity in critically ill patients, either considered as a group, or in selected populations like patients with sepsis and ARDS, but not in critically ill patients with trauma, who present a higher mortality risk associated with obesity. Moreover, 4 meta-analyses (1 in critically ill, 2 in septic, and 1 in ARDS patients) showed that overweight was also associated with decreased mortality compared to normal weight.

Data from Recent Studies

While the meta-analyses presented herein have evaluated studies through 2017, there are a number of relevant studies, published in the last 3 years, not included in these meta-analyses. Two retrospective observational studies confirmed a survival benefit of overweight and obesity in critically ill patients in the USA ($N = 1{,}042{,}710$) and in Asia ($N = 273$) [26, 27]. Furthermore, in an interesting retrospective review of a large USA single-center database of critically ill patients, Acharya et al. evaluated the effect of comorbidity burden in critically ill patients of all BMI classes [28••]. The authors studied 11,433 adult patients admitted to the ICU during a 12-year period and classified them according to 30 comorbid diseases. They found that overweight and obesity were associated with decreased risk for hospital and 30-day mortality compared to normal weight, regardless of the comorbidity burden. They also showed a consistent trend towards lower mortality with higher BMI regardless of comorbidities, refuting the hypothesis that a difference in comorbid diseases is responsible for the obesity paradox in critical illness. This finding is also in line with a recently published large study from the UK including more than 0.5 million ICU patients that showed that the optimal weight associated with the lowest hospital mortality was in the range of class I obesity (BMI 34.3 kg/m^2) [29••]. Finally, a recent retrospective review on 373 medical ICU patients with obesity failed to demonstrate an increased mortality in the higher BMI groups reporting similar mortality rates between patients with obesity (BMI 30–40 kg/m^2), severe obesity (BMI 40–50 kg/m^2), and very severe obesity (BMI > 50 kg/m^2) [30].

Studies regarding selected critically ill populations such as patients with sepsis, acute and chronic renal failure, post-operative, and patients receiving extracorporeal membrane oxygenation (ECMO) have also explored the obesity-related survival benefit. Two retrospective cohort analyses in 5563 and 55,038 adult critically ill patients with sepsis from US hospitals reported that overweight and obesity was associated with a lower short- and long-term mortality, after adjustment for multiple confounding factors including age, gender, race, weight loss, severity of disease, site of infection, and comorbidities [31•, 32••]. Furthermore, a retrospective study regarding acute kidney injury (AKI) in critically patients with sepsis

showed that although obesity was a risk factor for the development of AKI during sepsis, it was not associated with hospital mortality [33]. However, a retrospective analysis of 12,206 with chronic renal disease found that, among those who did not require renal replacement therapy, overweight and those with obesity had the lowest mortality, while patients with BMI < 20 kg/m^2 and ≥ 40 kg/m^2 had the highest mortality rate, after adjustment for age, gender, and comorbidities [34]. Finally, a study of 194 patients with acute respiratory failure requiring ECMO in a dedicated ICU could not demonstrate any association of obesity with increased mortality [35]. In conclusion, evidence from recent studies confirms the survival benefit of overweight/obesity in critical illness, being in line with previous meta-analyses.

Epidemiologic and Methodological Considerations

Studies regarding the mortality risk in critical illness with regard to body weight present considerable methodological limitations. A major argument is that critical illness is not a homogenous disease but rather represents an acute stress state characterized by life-threatening multiple organ dysfunction or failure. Therefore, critical ill patients comprise a heterogeneous population per se. Most relevant studies include mixed (medical and surgical) populations. Previous clinical studies have shown that surgical critically ill patients have a better outcome than medical patients [11, 36]. These differences in the outcome between medical and surgical patients have also been shown in critically ill patients with obesity [11, 31•], while evidence suggest a survival benefit of obesity in surgical patients [37, 38].

A retrospective cohort study investigated medical and surgical critically ill patients separately and found that surgical patients with BMI 30–40 kg/m^2 had a lower mortality risk, while medical patients with a BMI > 30 kg/m^2 showed a non-significant trend towards lower mortality risk compared to normal weight patients [39]. However, other studies in surgical populations failed to demonstrate an association of BMI with mortality, while studies in medical critically ill patients have been contradicting [40–43]. As most meta-analyses have evaluated studies with either medical, surgical, or mixed populations as a whole, a possible favorable effect of obesity on mortality risk due to the better outcome of the surgical patients cannot be excluded. However, the meta-analyses also included studies on trauma patients, who present worse outcomes with increasing BMI [25]. According to recent observational data, an inverse association between BMI and in-hospital mortality has also been demonstrated in non-critically ill hospitalized adults in internal medicine, surgical, and other specialty departments, suggesting a broader protective effect of obesity in various acute disease states requiring hospitalization [44].

On the other hand, evidence regarding the obesity related survival benefit in selected critically ill populations like patients with sepsis or ARDS has been more consistent. Two recent meta-analyses of 11 studies in total regarding critically ill patients with sepsis have reported that adjusted mortality was significantly lower in overweight compared to normal weight patients, while a lower mortality in patients with obesity was found in one of them [17, 23••]. This finding is further supported by a more recent retrospective analysis based on clinical data of a large cohort of 5563 critically ill patients with sepsis reporting a significant protective effect in overweight as well as in the whole range of obesity including morbid obesity, with significantly better short- and long-term outcomes [31•]. Regarding ARDS, two meta-analyses of 24 studies in total agree on the favorable outcome associated with higher than normal BMI [18•, 24]. However, there are some important methodological issues since adjustment for major confounding factors such as age, gender, severity of disease, and comorbidities was not considered, and BMI classification was not consistent in the studies included in the meta-analyses.

An important source of bias is the use of self-reported instead of measured weight and height values used to calculate BMI, resulting in possible misclassification of patients, producing systematic errors and heterogeneity in the results. However, a meta-analysis of all-cause mortality in the general population including studies using measured or self-reported weight and height reported that the association of overweight with lower mortality persisted even when the studies based on self-reported values were excluded from the analysis [45]. Moreover, a recent study exploring the impact of measured or estimated weight and height values on the association of BMI with mortality in 690,405 critically ill patients in the UK showed that this association was independent of measurement or estimation of weight and height and also confirmed the *J*-shaped association with the "optimal" range well above the normal BMI values and the nadir of this curve at BMI 34.3 kg/m^2 [29••].

Nevertheless, even when studies use measured weight and height, there is a strong argument regarding the appropriate timing of measurements. The actual weight upon admission to the ICU may vary substantially from the weight before aggressive treatment such as fluid replacement and transfusion of blood products and drugs that have been applied in the first hours of critical illness in the emergency room or the ward. It seems that the most appropriate measure of weight should be the one before the onset of the acute illness leading to hospitalization. Furthermore, it has been shown that recent weight loss is an independent predictor of 30-day mortality in hospitalized patients, regardless of BMI [46]. Additionally, another possible confounder regarding the implications of obesity in critical illness outcomes is the effect of nutritional status, which is not well represented by BMI. Lower BMI values could result from a chronic devastating disease such as cancer, and therefore previously overweight or patients with obesity

with a poor outcome may present with a "normal" weight on ICU admission. A large cohort study in a mixed critically ill population showed that the obesity associated survival benefit was attenuated after adjustment for nutritional status [47].

The issue of reliable reporting of overweight and obesity in epidemiologic studies is further complicated by the view that BMI is a poor index of body fat mass and fat distribution (visceral versus subcutaneous). Waist circumference and waist to hip ratio represent more reliable tools for assessment of fat distribution, which are useful to estimate additional risks related to expansion of visceral fat, after adjustment for BMI [48]. A subcutaneous distribution of fat is not associated with the same risk for metabolic and cardiovascular diseases as the visceral fat accumulation in subjects with similar BMI [49]. It is possible that better outcomes may reflect the influence of mixed population with obesity, with different metabolic profiles, not carrying the same risk. This issue was addressed by Acharya et al. in their recent study, showing that the survival benefit associated with obesity was independent from comorbidities [28••]. However, defining the metabolic derangements and phenotypes of obesity could be more helpful for a proper classification of obesity regarding cardiometabolic risks, than BMI alone.

It is noteworthy that researchers have questioned the optimal BMI in the general population as well, triggering a long-standing debate about the BMI range associated with the lowest mortality risk. Population studies have indicated that overweight is associated with the lowest mortality risk from all causes [50]. In particular, a previous meta-analysis of 26 observational studies and 388,622 individuals failed to confirm an increased mortality risk in overweight, questioning the current classification of overweight [51]. Furthermore, a more recent systematic review of 97 studies and a sample size of more than 2.88 million individuals investigating the association of all-cause mortality with overweight and obesity in the general population have shown that overweight is associated with significantly lower all-cause mortality, while class I obesity was not associated with mortality and only classes II and III obesity presented a significantly higher mortality [45]. However, a subsequent meta-analysis of 239 prospective studies and 10,625,411 participants from four continents found a gradual increase of all-cause mortality associated with both overweight and obesity in the general population [52]. Despite the conflicting data on this issue, more recent evidence from a cohort study of 3.6 million adults seems to unravel the association of BMI with overall mortality, demonstrating a *J*-shaped association, with the nadir of the association curve at BMI 25 kg/m^2 and most of the mortality burden distributed to BMI ≥ 30 kg/m^2 [8]. Another interesting finding of this study was that the association of BMI with mortality attenuated with age, shifting the nadir of the respective curve to the right for adults older than 70 years, and also differed by gender being stronger in men than in women [8]. Finally, in a recent study from Denmark regarding three cohorts from the same general population enrolled at different times from 1976 to 2013, it was demonstrated that the BMI associated with the lowest all-cause mortality has increased over time from 23.7 to 27 kg/m^2, having moved to the overweight range [53].

Other important methodological issues that may limit the value of the meta-analyses presented herein are the inadequate adjustment for relevant confounding factors regarding the severity of critical illness and pre-existing diseases as well as the effects of treatment on outcomes. Some authors argue that there may be a selection bias for subjects with obesity who may receive better care. As obesity is known to increase morbidity and is associated with serious complications, patients with obesity and less severe illness may be admitted to the ICU earlier and receive better care, due to the anticipation of worse outcomes [12].

Overall, the epidemiologic finding of obesity-related survival benefit in critically ill patients should be interpreted with caution, mainly due to the inherent limitations of the observational studies supporting this finding, such as the retrospective design, the inadequate adjustment for confounding variables, the possibility of selection bias, and the use of BMI as an obesity index.

Metabolic Considerations

Obesity is associated with various metabolic, endocrine, and immune alterations, while in the context of critical illness, further structural and functional changes of adipose tissue may possibly reflect adaptive responses to stress and altered physiology. Adipose tissue is an active endocrine organ producing a plethora of bioactive molecules, collectively referred to as adipokines, which exert endocrine, paracrine, and autocrine actions [54]. Considering total body fat mass, adipose tissue is actually the larger endocrine organ in the body, consisting of various types of cells beside adipocytes: preadipocytes, stroma cells, fibroblasts, endothelial cells, and numerous immune cells such as macrophages, lymphocytes, and eosinophils, while it is also highly vascularized and innervated [54–56]. Amid adipose tissue secretome, there are hormones, cytokines, chemokines, complement, coagulation and fibrinolysis system proteins, growth factors, and enzymes involved in steroid synthesis. Through these secreted molecules, adipose tissue regulates body metabolism, endocrine, and immune functions, while it also interacts with other body systems (neural, endocrine, and immune), expressing alterations in cell synthesis and function during disease [57, 58].

Obesity is not only the result of a simple expansion and accumulation of fat. Adipose tissue undergoes various cellular and structural changes while it expands. This process is called remodeling and comprises a range of specific alterations: adipocyte hypertrophy and hyperplasia, extracellular matrix adaptation, expansion of the vasculature, and inflammatory cell

infiltration [59]. Once obesity is established, it results in adipose tissue dysfunction characterized by limited ability to store lipids, altered adipokine expression, chronic inflammation, and fibrosis [60]. The dysfunctional adipose tissue is responsible for the metabolic dysregulation such as insulin resistance [61–64].

Critical illness also results in morphological and functional changes of adipose tissue. Despite severe muscle wasting in critical illness, adipose tissue is preserved and it is characterized by an increased number of newly differentiated smaller adipocytes, while infiltration by macrophages is prominent [65]. The enhanced ability of the increased numbers of the adipocytes to uptake and metabolize glucose and to store triglycerides during critical illness has been postulated to exert beneficial metabolic effects, by reducing the circulating concentrations of these potentially toxic molecules, thus attenuating their detrimental metabolic effects [65]. Additionally, adipose tissue macrophages exhibit a phenotype switch from M1 inflammatory state to M2 anti-inflammatory type [66, 67]. M2-type macrophages have been shown to exert protective and healing actions such as enhanced phagocytic ability, attenuation of inflammation, insulin-sensitizing properties, and tissue remodeling [68]. Whether these changes contribute to a better outcome in patients with obesity has yet to be proven. However, they may suggest a potential adaptive process in response to critical illness with immunometabolically protective implications.

Other pathophysiologic mechanisms which are postulated to be beneficial and may result in a favorable outcome in critically ill patients with obesity are summarized below (Fig. 1):

- Higher energy reserves: Critical illness is a hypercatabolic state characterized by increased energy demands. Overweight and patients with obesity are able to provide substrates, due to high lipid depots, meeting the higher demands of the activated immune system in the context of critical illness, while liver and muscle energy consumption is diminished [69]. This mechanism is supported by a large cohort study in over 1 million critically ill patients that demonstrated that early enteral nutrition may increase survival in patients with BMI < 25 kg/m^2 [26].
- Anti-inflammatory immune profile: During the acute phase of critical illness, inflammatory adipokines and cytokines increase while M1-type macrophages predominate in adipose tissue [70]. However, the chronic phase of critical illness is characterized by an anti-inflammatory adipokine profile and an M2-type macrophage accumulation [67]. Obesity has been shown to exhibit a blunted inflammatory response [71]. An attenuated pro-inflammatory cytokine profile has been shown in patients with obesity and ARDS as well as in animal studies [72, 73]. Leptin, the classic adipokine, exerts immunomodulatory actions which may be related to favorable outcomes in sepsis [74–76], while adiponectin, an anti-inflammatory adipokine, has been shown to be protective in post-operative and critically ill patients with sepsis [77–79].
- Inflammatory preconditioning: Obesity is associated with a chronic low-grade inflammation. It is postulated that this chronic inflammatory state triggers multiple anti-inflammatory and anti-oxidant endogenous pathways as an adaptive response to counteract the chronic inflammation of obesity. In the context of critical illness, new onset acute inflammatory reactions may be blunted due to a protective environment created by preconditioning. This hypothesis is supported by research findings including impaired neutrophil chemotaxis and M2-type macrophage switching [80].
- Endotoxin neutralization: Adipose tissue is the source of lipoproteins, which act as scavengers for lipopolysaccharide (LPS). High-density lipoprotein (HDL) has been shown to attenuate LPS-induced cytokine production [81].

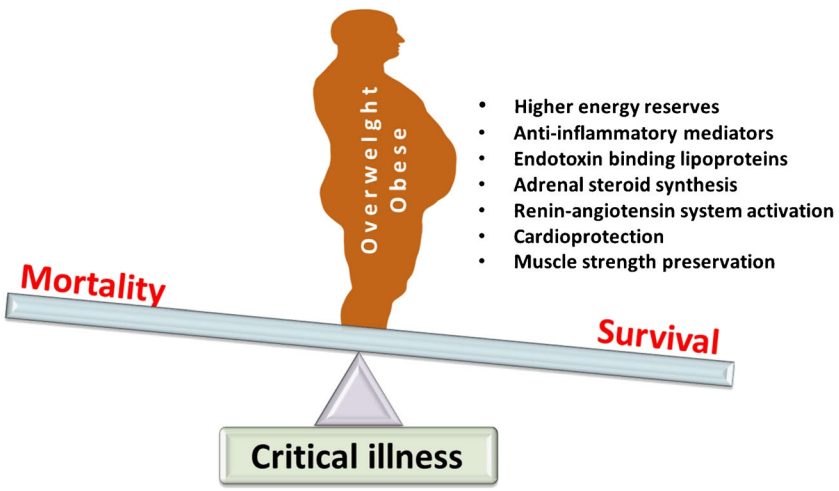

Fig. 1 Pathophysiologic mechanisms linking obesity to survival benefit in critical illness include higher energy reserves, anti-inflammatory mediators, endotoxin-binding lipoproteins, adrenal steroid synthesis, renin-angiotensin system activation, and cardioprotection and muscle strength preservation

- Adrenal steroid synthesis: Critical illness may cause adrenal insufficiency resulting in hemodynamic suppression. Cholesterol derived from adipose tissue is a substrate for steroid synthesis. Restoring natural steroids may have beneficial hemodynamic effects [82].
- Renin-angiotensin system activation: Adipose tissue produces angiotensinogen and activates rennin-angiotensin system, which normally exerts mainly paracrine actions. However, in obesity, angiotensinogen production is increased with systemic implications in blood pressure regulation. Thus, increased activity of the renin-angiotensin system may be protective against circulatory failure, which is common in critical illness [83, 84].
- Cardioprotective metabolic effects: Studies have shown that obesity confers a protection against death in patients with established coronary artery disease, possibly through favorable vascular anti-inflammatory actions [85].
- Prevention of muscle wasting and weakness: In animal and human studies, obesity has been linked to reduced muscle wasting during critical illness compared to normal weight subjects [86]. Obesity attenuates the activity of the ubiquitin-proteasome and the autophagy-lysosome pathways, which are associated with muscle wasting in critical illness [87]. Moreover, a different metabolic response has been shown in animals with obesity during prolonged critical illness, characterized by the preferential use of fat from adipose tissue rather than ectopically stored lipids and proteins as energy substrates along with an increased fatty acid and glycerol turnover rate due to more efficient hepatic breakdown of these substrates [88].

Is There an "Obesity Paradox" in Critical Illness?

The "obesity paradox" in critical illness represents an intriguing and challenging finding. Many researchers have investigated this phenomenon and reported lower mortality rates in overweight and patients with moderate obesity compared to critically ill patients with normal weight, while others have questioned it arguing that a flawed methodology may be responsible for the "unexpected" survival benefit [89]. Nevertheless, most meta-analyses, including the most recent ones evaluating data from a large number of participants, have confirmed the survival benefit of obesity in critical illness [13, 15••, 17, 18•, 24]. Furthermore, subsequent studies have addressed some of the methodological issues successfully, putting into question the paradoxical nature of this phenomenon [28••, 32]. Consequently, it has been proposed that the term "paradox" is inaccurate and misleading [90] and an intriguing concept that optimal weight varies between health and disease and between different disease states is gaining ground [50].

Although obesity is a major risk factor for cardiovascular, metabolic, and other diseases with known detrimental effects on health in the long term, studies have consistently shown that once a chronic disease such as coronary artery disease, heart failure, or chronic renal failure is established, overweight and moderate obesity is no longer a risk factor for mortality as one would expect [19]. The "obesity paradox" has also been consistently shown in acute disease states such as pneumonia, ARDS, and sepsis [17, 18•, 91]. All the above diseases or syndromes are critical disease states characterized by life-threatening organ dysfunction and share common pathophysiologic mechanisms. Critical illness, although not an individual disease, is actually an acute stress state of diverse etiologies, involving complex biological processes and affecting multiple organ systems. Thus, as the optimal weight associated to a lower mortality risk varies with age, gender, and disease, critical illness may also present a different mortality risk—BMI association curve presenting a nadir moving to the right compared to healthy state [8].

There are multiple possible explanations of the "obesity paradox" in critical illness comprising a range of immune, metabolic, and endocrine alterations of adipose tissue in critically ill patients with obesity (Fig. 1). These postulated mechanisms are mostly based in experimental studies, although some of them are supported by clinical studies as well. However, current evidence cannot fully explain the "obesity paradox".

Clinical Implications and Future Perspectives

As obesity is an established risk factor for many chronic diseases and cancer, a global strategy to reduce obesity in the general population is an important primary prevention measure. However, overweight/obesity may also be protective in the context of specific acute and chronic disease states. Therefore, aiming at a normal weight is a good strategy for preventing a wide range of diseases, but once specific diseases have been developed, obesity may no longer be harmful but rather protective. Since critical illness often occurs in patients at risk due to pre-existing diseases, strategies to reduce body weight may actually result in higher mortality risk in specific patient groups suffering from chronic illness.

More epidemiologic data are needed to define the optimal weight in critical illness including specific critically ill patient groups such as sepsis, ARDS, and surgical and trauma patients. Future prospective studies, specifically designed to investigate the association of obesity with mortality as the primary outcome, should take special care in avoiding known selection bias and adjusting for important confounding factors including recent weight changes, smoking, chronic diseases, severity of critical illness, and therapeutic interventions. Moreover, more accurate measures of obesity better

characterizing body composition (body fat and lean mass) and fat distribution (waist circumference and waist to hip ratio) should be used, preferably before the onset of critical illness. Thus, future research may produce more robust evidence regarding the obesity-related survival benefit in critical illness and may clarify any causal association.

Finally, as epidemiologic studies investigating the effect of obesity on mortality are observational, by nature they cannot explain the mechanisms behind the reported results. Therefore, research should also focus on explaining this phenomenon, by investigating the pathophysiological processes that are observed in obesity in the context of critical illness. To this end, unraveling the multifaceted functions of adipose tissue is a promising research field that may help us understand the role and clinical implications of obesity in critical illness.

Conclusions

Meta-analyses as well as recently published studies regarding the obesity associated survival benefit in critical illness support the finding that overweight and obesity are associated with a significantly decreased mortality compared to normal weight. Moreover, this finding is in line with the lower mortality associated with obesity in selected critically ill populations such as patients with sepsis and ARDS. However, as most studies are retrospective in design, they present important methodological limitations. Larger prospective studies are needed to further clarify the impact of obesity in outcomes of critically ill patients. Future research focused on elucidating the pathophysiologic mechanisms lying behind the survival benefit of obesity could offer new evidence for a more individualized approach to the critically ill patient.

Compliance with Ethical Standards

Conflict of Interest Irene Karampela, Evangelia Chrysanthopoulou, Gerasimos Socrates Christodoulatos, and Maria Dalamaga declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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