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Review Article

Role of obesity in lower mortality risk in sepsis: a meta-analysis of observational studies

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Abstract: This meta-analysis aims to explore the correlation between obesity and mortality in patients with sepsis. Data were gathered from various sources, including PubMed, the Cochrane Library, and Embase (no language restrictions). Clinical studies, both retrospective and prospective ones, were selected to analyze mortality due to sepsis in patients with or without obesity. The Newcastle-Ottawa Scale was used to assess the quality of the studies included. In data synthesis, odds ratio (OR) and 95% confidence interval (CI) were meta-analyzed using the DerSimonian-Laird random-effects model, followed by sensitivity and heterogeneity analyses. Two cohort studies were included to investigate survival in inpatients with obesity and sepsis, with pooled analysis indicating a lowered mortality rate (OR=0.88; 95% CI: 0.81-0.95; I^2=0.00%; P=0.000). This meta-analysis lends support to the obesity paradox, suggesting a reduced mortality from sepsis in obese patients. However, further prospective trials and research on mechanisms are needed to test this hypothesis.

Keywords: Obesity, mortality, sepsis, meta-analysis, obesity paradox

Introduction

Obesity is characterized by an excessive body mass index (BMI) [1], a metric directly linked to the risk of long-term complications and inversely correlated with life expectancy [2]. Over the past three decades, there has been a steady rise in global obesity prevalence [3], making it a significant public health concern associated with escalating healthcare costs and adverse effects on both physical and mental well-being, as well as increasing the susceptibility to other illnesses [4]. In recent years, there has been increasing focus on the relationship between obesity and mortality, including meta-analyses of more than 2.3 million subjects [5, 6]. Findings reveal that obesity and being overweight are associated with increased mortality risk across various diseases [7].

Despite the conventional understanding that higher BMI correlates with increased mortality, some studies have shown an association between higher BMI and higher survival rate, a phenomenon known as the obesity paradox [8]. This paradox has been extensively observed in cardiovascular diseases [9], cancers [10, 11], and metabolic disorders [12]. A higher survival rate has also been found in patients with severe obesity by large-scale meta-analysis and recent experimental results [13, 14]. In other words, this obesity conflict may occur in some serious chronic illness [15]. However, the underlying causes of the obesity paradox remain unclear, and explanations are subject to controversy [16, 17].

Sepsis arises from an imbalanced host response to infection, manifesting as severe organ dysfunction and serving as a significant global cause of acute illness and death [18]. Recently, the number of sepsis cases and associated deaths has surpassed 48.9 million, accounting for 19.7% of all global deaths [19].

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Among the severe global public health challenges, sepsis is marked by high morbidity, mortality, economic burden, and challenging treatment [20]. The existence of an obesity paradox in sepsis mortality remains unclear. A comprehensive analysis of seven studies [21], revealed conflicting evidence regarding the relationship between obesity and sepsis mortality. Subsequently, a meta-analysis [22] including six observational studies showed that among adults admitted to the ICU for sepsis-related conditions, high BMIs were associated with reduced adjusted mortality. Additionally, meta-analysis of Wang et al. indicated that individuals who are overweight, rather than obese or morbidly obese exhibited lower mortality rates in cases of sepsis [23]. These studies suggest that in patients with sepsis, those with normal BMIs exhibit significantly worse outcomes compared to obese patients. Nonetheless, the correlation of sepsis with obesity-related diseases remains poorly understood [22, 23]. Recently, several studies, with a collective patient count exceeding 100,000 [24, 25], have linked obesity to sepsis survival. Hence, the objective of this recent meta-analysis is to identify factors contributing to obesity in sepsis patients and assess the correlation of obesity with survival and mortality. The innovation and necessity of this study lie in its incorporation of the latest two clinical studies on obesity and sepsis, thereby updating the current evidence on obesity and sepsis mortality. Based on the latest evidence, we believe that there is a reduction in mortality in patients with sepsis and obesity. In addition, the correlation of obesity with study outcomes may be confounded [26]. However, previous meta-analyses have not conducted unbiased analyses due to insufficient inclusion of studies, leaving bias unresolved to date. Thus, an up-to-date meta-analysis, incorporating currently available prospective or retrospective studies, is conducted to summarize the most recent and comprehensive evidence.

Methods

This meta-analysis adheres to the guidelines outlined in the latest issue for the preparation of systematic reviews (PRISMA 2020) [27]. It has been registered on the PROSPERO platform under the registration number CRD4202-2342547.

Data sources

Thorough searches were conducted in the Cochrane Library, EMBASE, and PubMed databases, covering all records from inception to April 10, 2024, without any restrictions. Subject headings (Emtree in EMBASE and MeSH in PubMed) and corresponding keywords were utilized. These keywords included terms such as obesity, sepsis, risk factors, and their variants. Additionally, a review of the retrieved literature and previous meta-analyses was conducted to identify additional studies meeting the selection criteria. The search strategies employed are detailed in **Tables 1**-**3**.

Eligibility criteria

Studies were considered eligible if they met the following criteria: (a) Subjects: adult patients diagnosed with sepsis, irrespective of its cause; (b) Exposure: inclusion of individuals classified as overweight or obese based on BMI measurements; (c) Comparison: comparison with a population of normal or low weight; (d) Study design: inclusion of cohort (both prospective and retrospective), case-control, and cross-sectional studies; (e) Outcome: primary outcome focused on mortality among patients diagnosed with sepsis.

Exclusion criteria

(1) Review articles, or conference abstracts; (2) Duplicate publications; (3) Studies focused on diseases other than sepsis; (4) Studies lacking relevant outcome measures; (5) Studies involving non-septic infections; (6) Studies with incomplete data.

Research selection

Two reviewers (DJ and YL) separately reviewed the test. First of all, repetitive and irrelevant literature was removed from the title and abstract. Two reviewers carried out independent data extraction; in case of disagreement, a third reviewer (JM) participated in the discussion for decision-making.

Data extraction

Two reviewers (JM and DJ) independently performed data extraction using pre-designed forms, which included the following informa-

Table 1. PubMed

No.	Content	Result
#1	Search: ("Adiposity"[Mesh]) OR "Obesity"[Mesh] Sort by: Most Recent	253,217
#2	Search: ((Obesity[Title/Abstract]) OR (Adiposity[Title/Abstract])) OR (Obese[Title/Abstract]) Sort by: Most Recent	368,310
#3	Search: (("Adiposity"[Mesh]) OR "Obesity"[Mesh]) OR (((Obesity[Title/Abstract]) OR (Adiposity[Title/Abstract])) OR (Obese[Title/Abstract])) Sort by: Most Recent	420,236
#4	Search: "Sepsis"[Mesh] Sort by: Most Recent	136,303
#5	Search: ((((sepsis*[Title/Abstract]) OR (septicemia*[Title/Abstract])) OR (septic*[Title/Abstract])) OR (systemic inflammatory response syndrome[Title/Abstract])) OR (SIRS[Title/Abstract]) Sort by: Most Recent	177,070
#6	Search: ("Sepsis"[Mesh]) OR (((((sepsis*[Title/Abstract]) OR (septicemia*[Title/Abstract])) OR (septic*[Title/Abstract])) OR (systemic inflammatory response syndrome[Title/Abstract])) OR (SIRS[Title/Abstract])) Sort by: Most Recent	245,365
#7	Search: ((("Adiposity"[Mesh]) OR "Obesity"[Mesh]) OR (((Obesity[Title/Abstract]) OR (Adiposity[Title/Abstract])) OR (Obese[Title/Abstract]))) AND (("Sepsis"[Mesh]) OR (((((sepsis*[Title/Abstract]) OR (septicemia*[Title/Abstract])) OR (septic*[Title/Abstract])) OR (systemic inflammatory response syndrome[Title/Abstract])) OR (SIRS[Title/Abstract]))) Sort by: Most Recent	1,823
#8	Search: "Risk"[Mesh] Sort by: Most Recent	1,345,064
#9	Search: (risk[Title/Abstract]) OR ("Risk"[Mesh]) Sort by: Most Recent	3,026,429
#10	Search: ((((("Adiposity"[Mesh]) OR "Obesity"[Mesh]) OR (((Obesity[Title/Abstract]) OR (Adiposity[Title/Abstract])) OR (Obese[Title/Abstract]))) AND (("Sepsis"[Mesh]) OR (((((sepsis*[Title/Abstract]) OR (septicemia*[Title/Abstract])) OR (septic*[Title/Abstract])) OR (systemic inflammatory response syndrome[Title/Abstract])) OR (SIRS[Title/Abstract])))) AND ((risk[Title/Abstract]) OR ("Risk"[Mesh])) Sort by: Most Recent	774

Table 2. Embase

No.	Content	Result
#1	'obesity'/exp	610,573
#2	'obesity'/exp OR obesity OR adiposity:ab,ti OR obese:ab,ti	757,801
#3	#1 OR #2	757,801
#4	'sepsis'/exp	315,859
#5	sepsis:ab,ti OR septicemia*:ab,ti OR septic*:ab,ti	249,760
#6	#4 OR #5	390,402
#7	#3 AND #6	6,310
#8	'risk'/exp	2,837,731
#9	risk:ab,ti	3,613,620
#10	#8 OR #9	4,444,319
#11	#7 AND #10	2,834

tion: first author, year of publication, country, sample size; BMI, average baseline age, follow-up time, criteria for diagnosing sepsis, and adjusted confounding factors. The primary outcome was mortality, with preference given to intensive care unit (ICU), in-hospital, 30-day, and 1-year mortality rates, in that order. Various statistical methods were employed to assess mortality in the included studies. The secondary outcome was the prevalence of obesity.

Literature quality assessment

The Newcastle-Ottawa Clinical Trial Quality Assessment questionnaire available at (www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was utilized to assess the selected studies across three dimensions. For cohort and case-control studies, scores ranged from 0 to 9, with higher scores indicating better research quality. The grading of research quality and corresponding scores were categorized as follows: excellent (7-9 points), good (4-6 points), and moderate (0-3 points). Studies assessed as moderate quality were excluded from the analysis.

Statistical analyses

The data were analyzed using STATA (version 15.1). Chi-square tests were employed for com-

Table 3. Cochran library

No.	Content
#1	MeSH descriptor: [Adiposity] explode all trees
#2	MeSH descriptor: [Obesity] explode all trees
#3	(Obesity):ti,ab,kw OR (Adiposity):ti,ab,kw OR (Obese):ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Sepsis] explode all trees
#6	(sepsis*):ti,ab,kw OR (septicemia*):ti,ab,kw OR (septic*):ti,ab,kw
#7	#5 OR #6
#8	#4 AND #7
#9	MeSH descriptor: [Risk] explode all trees
#10	(risk):ti,ab,kw
#11	#9 OR #10
#12	#8 AND #11

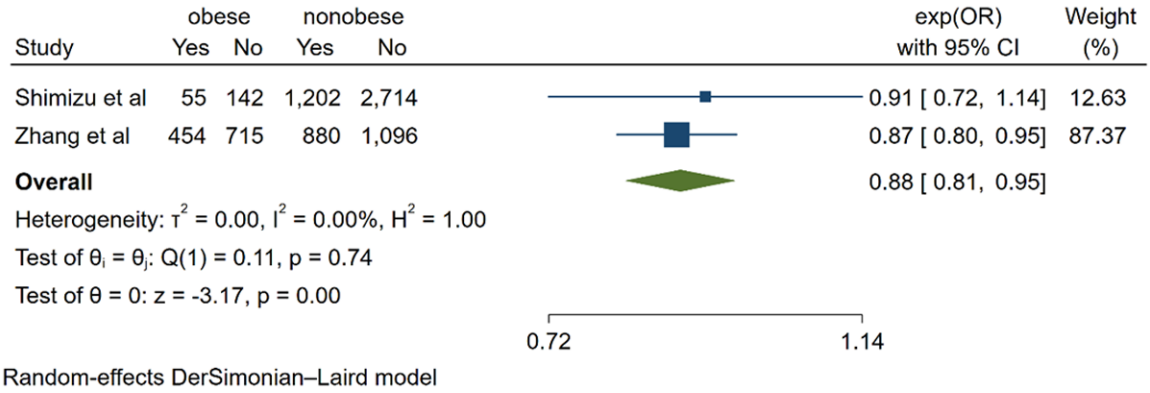

Figure 1. The mortality in sepsis patients with obesity.

parisons between two groups. Heterogeneity was assessed using I-squared (I^2) statistics. Random-effects models were utilized in instances of high heterogeneity (I^2>50%), while fixed-effects models were applied otherwise [28, 29]. Odds ratios (ORs) with 95% confidence intervals (CIs) were obtained using random-effects or fixed-effects models for meta-analyses.

Results

Identification of studies

A total of 3,682 studies were initially retrieved through electronic and manual searches, with 567 duplicates removed. Following screening of titles and abstracts, 3,086 studies were excluded. After a full-text review, 29 studies were excluded based on the predefined inclusion and exclusion criteria. Ultimately, 12 studies [24, 25, 30-39] met the criteria and were included in this review. Please refer to **Figure 1** for the study selection process.

Study characteristics

The selected papers varied in sample size, ranging from 149 to 55,038, and were published between 2007 and 2024. All studies employed clear diagnostic criteria for sepsis and included patients with sepsis, severe sepsis, and septic shock. The World Health Organization's BMI classification was utilized as a measure of obesity across most studies. These studies were conducted in 5 countries, including 2 from China, 7 from the USA, 1 from Finland, 1 from Austria, and 1 from Japan. Although there were slight variations in the modified covariates, the revised estimates remained applicable across all studies. The characteristics of the surveys included in this article are summarized in **Table 4**. Additionally, we focused on studies published within the

Table 4. Characteristics of studies included in this review

Author	Year	Country	Study type	Sample size	Study period	Age (years)	ICU	Diagnosis of sepsis	Diagnosis of obese	Sepsis type	Confounders adjusted
Shan Lin	2020	China	Retrospective cohort	Total: 7,967, obese: 2,664, no obese: 5,303	2002-2012	65.92 ± 15.98	Yes	Sepsis-3	World Health Organization BMI classification	Sepsis	Age, sex, SOFA, mechanical ventilation on the first day, renal replacement therapy on the first day, fluid and electrolyte disorders, alcohol abuse, drug abuse, and depression.
Dominique J	2019	USA	Retrospective cohort	Total: 55,038, obese: 18,161, no obese: 36,877	2009-2015	/	/	Sepsis-3	World Health Organization BMI classification	Sepsis/Septic shock	Demographic factors, admission year, hospital level factors, infection factors, and severity of illness.
Yun Ji	2017	China	Retrospective cohort	Total: 236, obese: 110, no obese: 126	2012.8.1-2016.7.31	/	Yes	American College of Chest Physicians/Society of Critical Care Medicine	Visceral obesity was defined as a visceral adipose tissue area exceeding 100 cm^2 in both sexes	Severe sepsis/Septic shock	Age, use of vasopressor, mixed organism, and Acute Physiology and Chronic Health Evaluation II score.
Shuhe Li	2019	USA	Retrospective cohort	Total: 5,563, obese: 1,910, no obese: 3,653	2001-2012	66.3 (16.2)	Yes	ICD9 codes: 99591, 99592, 78552	World Health Organization BMI classification	Sepsis/Severe sepsis/Septic shock	/
Hallie C Prescott	2014	USA	Retrospective cohort study	Total: 1,404, obese: 334, no obese: 1,070	1999-2005	/	Yes	Commonly employed, validated claims-based definition of severe sepsis	World Health Organization BMI classification	Severe sepsis	Age, race, gender, marital status, wealth, acute organ dysfunctions, ICU use, mechanical ventilation use, diabetes, other co-morbidities, baseline cognitive status, and functional limitations.
Reetta Huttunen	2007	Finland	Retrospective cohort	Total: 149, obese: 27, no obese: 122	1999.6-2004.1	Mean 59	No	Blood microbiological culture finding	World Health Organization BMI classification	Bacteraemia	Alcohol abuse, age, sex and causative organism.
E Tay-Lasso	2022	USA	Retrospective cohort	Total: 1,246, obese: 680, no obese: 566	2017	/	/	Sepsis plus organ dysfunction, hypotension (low blood pressure), or hypoperfusion (insufficient blood flow) to 1 or more organs	World Health Organization BMI classification	Severe sepsis	Age, alcohol use, hypertension, congestive heart failure, diabetes mellitus, injury severity score, respiratory rate, pulse rate, systolic blood pressure, intensive care unit days, Glasgow coma scale.
Bettina Wurzinger	2010	Austria	Retrospective cohort	Total: 301, obese: 66, no obese: 235	2003.1-2008.12	/	Yes	The presence of arterial hypotension requiring norepinephrine infusion despite adequate fluid resuscitation in patients with infection and two or more signs of systemic inflammation	World Health Organization BMI classification	Septic shock	Admission year, sex, age, presence of heart disease or chronic renal insufficiency, the number of pre-morbidities, origin of sepsis and the simplified acute physiology score II.

Timothy Glen Gaulton	2014	USA	Retrospective cohort	Total: 1,779, obese: 573, no obese: 1,206	2007.3.1-2011.6.30	/	No	ICD-9	World Health Organization BMI classification	Sepsis	Sepsis severity.
Ethan F Kuperman	2013	USA	Retrospective cohort	Total: 792, obese: 233, no obese: 559	2007.7.1-2010.6.30	60.8 ± 14.2	No	ICD-9 codes: 38.0-38.9	World Health Organization BMI classification	Sepsis	Age, gender, race, severity of illness, length of stay, and comorbid conditions.
Zhang	2023	USA	Retrospective cohort	Total: 3,145, obese: 1,169, no obese: 1,976	2002.1.1-2011.12.30	65.3 ± 16.6	Yes	Sepsis-3	World Health Organization BMI classification	Sepsis	Age, sex, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS).
Shimizu	2024	Japan	Retrospective cohort	Total: 3,145, obese: 1,169, no obese: 1,976	2014.4 to 2018.3	73 (64-81)	Yes	Sepsis-3	World Health Organization BMI classification	Sepsis	Age, sex, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS).

Table 5. Newcastle-Ottawa Scale for quality assessment

First author	Year	Selection	Comparability	Outcome	Overall quality score
Shimizu	2024	★★★★	★★★	★★	9
Zhang	2023	★★★★	★★	★★	8

Table 6. Gender distribution and statistics of the patients

Study	Obese	No obese	Male	Female
Zhang et al. [38]	1,169	1,976	1,674	1,471
Shimizu et al. [39]	197	3,719	2,399	1,517

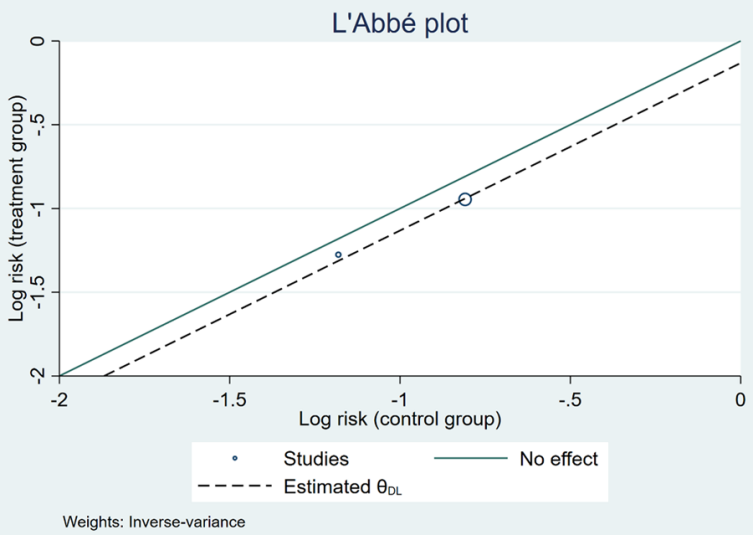

Figure 2. Heterogeneity analysis.

past two years, specifically one conducted by Shimizu et al. [39] and one by Zhang et al. [40].

Quality assessment

NOS assessment results regarding the quality of the studies are presented in **Table 5**. All included studies achieved a score of ≥8, indicating a high level of quality. Specifically, the study conducted by Shimizu et al. received a score of 9, and the study by Zhang et al. obtained a score of 8.

Gender distribution and statistics of obese patients

Table 6 provides detailed information on the gender distribution and the number of obese patients in both studies. In the study by Shimizu et al., there were 2,399 males and 1,517 females, resulting in a total of 197 obese patients. In the research conducted by Zhang et al., there were 1,674 males and 1,471 females, with a total of 1,169 obese patients.

Mortality risk in patients with sepsis and obesity

As illustrated in **Figures 1**, **2** cohort studies examined survival among hospitalized patients with both obesity and sepsis. The pooled analysis revealed a decrease in mortality among obese patients with sepsis (OR=0.88; 95% CI: 0.81-0.95). The analysis indicated an I^2-value of 0.00% and a *P*-value of 0.74, suggesting no significant heterogeneity between the two studies. Additionally, a test for heterogeneity was conducted, the results of which are presented in **Figure 2**. Sensitivity analysis was performed by systematically excluding individual studies, showing consistent and stable conclusions (**Figure 3**). Consequently, these findings are considered robust.

Publication bias

Funnel plots were employed to assess the presence of publication bias. Visual inspection of the funnel plots revealed symmetry. Additionally, the absence of publication bias was confirmed by Egger's test (P=0.770).

Discussion

Principal findings

Overall, patients with sepsis and obesity exhibit a mortality rate of approximately 22%. Our meta-analysis indicates a lower fatality rate among patients with sepsis and obesity compared to controls. This finding aligns with the results of the meta-analysis conducted by Pepper et al. [22], which also suggests a correlation between having an overweight and obese BMI and reduced mortality. Sepsis is a hypercatabolic acute disease wherein excess body

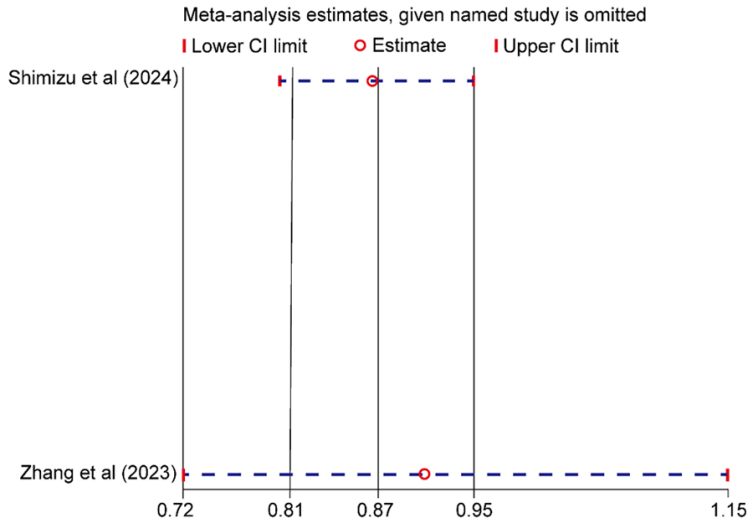

Figure 3. Sensitivity analysis.

fat serves as a source of fuel and energy [40]. Specifically, higher body weight provides a reservoir of nutrients crucial for survival during acute and life-threatening conditions. Adipose tissue stores surplus energy in the form of triglycerides and releases fuel substrates such as fatty acids and glycerol to meet the metabolic demands of other organs when necessary [23, 41]. Additionally, adipose tissue plays a role in modulating immunity by secreting proteins like leptin, an anti-inflammatory adipocytokine [42]. Moreover, obese individuals typically exhibit elevated baseline levels of leptin [43].

Comparison with existing studies

Two meta-analyses addressing similar topics were published in 2016 and 2017 [14, 15]. Wang et al.'s meta-analysis [23] included studies on sepsis patients but did not specifically focus on obese or morbidly obese individuals. Among the eight studies included in Wang et al.'s analysis, only four were complete cohort studies, while the remaining four were conference abstracts. Conference abstracts often lack comprehensive information due to space limitations, thus providing an incomplete picture. In contrast, our meta-analysis exclusively incorporated full-text cohort studies to minimize bias and furnish stronger evidence. Pepper et al.'s recent meta-analysis [22] concluded that for adults admitted with sepsis, severe sepsis, or septic shock, both underweight and overweight BMI categories were associated with reduced adjusted mortality. Our analysis, comprising 2 retrospective cohort studies [38, 39] involving 7,061 individuals is the most recent and comprehensive compared to previous meta-analyses. Furthermore, our meta-analysis specifically examined mortality among patients with sepsis and obesity, thereby offering more extensive data and credible evidence.

Possible biological and physiological findings from this study

Previous studies have suggested several potential biological and physiological mechanisms, although further research is required to fully elucidate the underlying mechanisms. One possible explanation is that adipose tissue can be mobilized to provide additional energy reserves, supporting patients with sepsis during times of metabolic stress. Second, the increase in adipose tissue may be associated with heightened activity of the renin-angiotensin system [44], which could confer hemodynamic protection during sepsis, potentially reducing the need for fluid or vasopressor support [45]. Third, elevated levels of blood lipids and adipose tissue in patients with elevated BMIs may inhibit the production of lipopolysaccharide or other harmful microbial products associated with sepsis [46]. Fourth, obesity may enhance immune function, attributed to increased levels of tumor necrosis factor-alpha (TNF-α) [47]. Soluble TNF receptor levels may counteract the deleterious effects of excessive TNF-α production during sepsis. Moreover, studies have indicated that obesity could mitigate the release of harmful inflammatory mediators in sepsis and sepsis-related lung injury [48].

Study limitations

While this meta-analysis adheres to PROSPERO registration and PRISMA guidelines, thereby enhancing transparency and comprehensibility, several limitations should be acknowledged. Firstly, the inclusion of patients with heterogeneous disease-induced extensive sepsis may

introduce variability into the results, potentially affecting the reliability of comparisons across different sepsis populations. Secondly, although obesity was assessed using BMI, variations in obesity grading and classification criteria among the original studies may contribute to clinical heterogeneity. Moreover, BMI may not accurately reflect fat mass, muscle-to-fat ratio, or body composition, thus limiting its effectiveness as an obesity indicator [49]. Lastly, despite conducting comprehensive literature searches excluding conference abstracts, the possibility of overlooking relevant studies cannot be entirely ruled out.

Conclusion

The concept of the obesity paradox appears to hold merit in patients with sepsis; however, further validation through additional prospective trials and research on mechanisms is warranted.

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Disclosure of conflict of interest

The authors claim no business or financial links that could be interpreted as a potential conflict of interest.

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