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The *obesity paradox* in murine sepsis models: a systematic review and meta-analysis

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Abstract

The *obesity paradox*, suggesting improved survival in obese individuals compared to those with normal weight, remains debated, particularly in sepsis. While it has been explored in clinical and experimental settings, conclusive evidence is lacking. This study systematically reviews and meta-analyses the relationship between obesity and survival in murine sepsis models. This systematic review and meta-analysis following PRISMA guidelines included studies from PubMed/Medline (up to January 31, 2025) comparing sepsis survival in obese and non-obese mice. All eligible murine studies were systematically reviewed, whereas only those employing diet induced obesity (DIO) and cecal ligation and puncture (CLP) were pooled in the meta-analysis and meta-regression. Twenty-one studies (38 survival experiments) met the criteria: CLP ($n = 14$), intraperitoneal lipopolysaccharide ($n = 7$), and other bacterial inoculation models ($n = 17$). Across all models, obesity increased survival in 10, decreased it in 9, and had no effect in 19 experiments. Quantitative synthesis of 10 CLP-DIO experiments (159 obese vs. 149 lean mice) showed no overall mortality difference ($P = 0.391$). Meta-regression explained 86% of heterogeneity: later highfat diet (HFD) initiation and longer feeding reduced mortality, whereas older age at sepsis induction increased mortality (all $P < 0.001$). Across the studies, obesity exerted mixed effects; pooled analysis of CLP-DIO experiments showed no survival benefit. Variability among studies was associated with time-related factors: age at HFD initiation, feeding duration, and age at sepsis induction, highlighting the need to investigate these relationships and to develop a time-point-standardized CLP-DIO sepsis model.

Key words: obesity, *obesity paradox*, sepsis, mouse, animal model.

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For the past 25 years [1], the *obesity paradox* has been documented in the medical literature. It describes the phenomenon of higher survival rates among obese and overweight patients in comparison to normal- and underweight counterparts, with underweight patients often showing the highest mortality rates. This paradox has been mainly investigated in sepsis for nearly 15 years and has been the focus of multiple systematic reviews and meta-analyses [2–8].

Despite extensive research in clinical settings, a definitive conclusion regarding the validity of the *obesity paradox* remains elusive [2–8]. Evaluating this phenomenon in preclinical models offers a controlled environment to study the complex interactions between obesity and sepsis outcomes, potentially reducing the heterogeneity of the study group. However, the results of individual studies can vary due to differences in design-related variables, which can significantly influence survival outcomes [9]. Furthermore, the physiological differences between humans and mice, particularly in immune system function and metabolism, add another layer of complexity to interpreting these findings [10, 11]. Nevertheless, given the significant heterogeneity and multimorbidity among sepsis patients [12, 13], the murine sepsis-obesity model offers a promising approach to investigate the validity of the *obesity paradox* in sepsis.

Sepsis in humans is defined as *life-threatening organ dysfunction caused by a dysregulated host response to infection* [14]. In animal studies, sepsis is typically modelled using three main approaches: injection of a toxic agent, injection of live pathogens, and impairment of barrier tissue integrity. The first two methods are generally minimally invasive and non-surgical, while the third often requires surgical intervention [15–17]. Overweight and obesity are classified as abnormal or excessive fat accumulation that poses a health risk, with a body mass in-

dex (BMI) over 25 kg m^{-2} considered overweight and over 30 kg m^{-2} classified as obese [18]. Animal models of obesity can be broadly divided into two categories: those based on genetic mutations or manipulations, and those based on exposure to obesity-promoting factors, such as a high-fat diet (HFD) [19, 20].

METHODS

Aim of the study

The aim of the study was to systematically review and meta-analyze published research on the *obesity paradox* in murine sepsis models, specifically focusing on the relationship between obesity and survival outcomes.

Literature search

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. A PRISMA flow diagram detailing the study selection process is presented in Figure 1. Articles were searched for in the PubMed/Medline database. The search included articles available until January 31, 2025 (inclusive). The following search criteria were used: ((sepsis[Title/Abstract]) OR (septic[Title/Abstract])) AND ((obesity[Title/Abstract]) OR (obese[Title/Abstract]) OR (fat[Title/Abstract]) OR (adipose[Title/Abstract]) OR (body mass[Title/Abstract])) AND ((animal[Title/Abstract]) OR (mouse[Title/Abstract]) OR (mice[Title/Abstract]) OR (murine[Title/Abstract])).

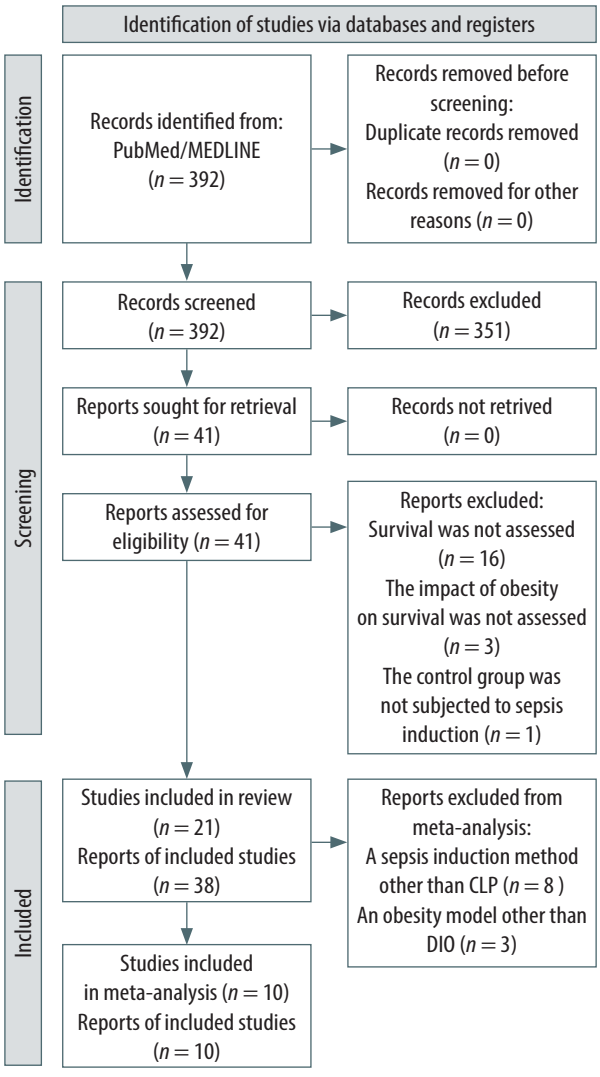

FIGURE 1. PRISMA flow diagram of the literature review process [21]

The screening and selection of studies were performed by three researchers. Two team members independently screened titles and abstracts for eligibility, and full texts of potentially relevant studies were assessed against predefined inclusion criteria. A third investigator supervised the process, resolved discrepancies, and ensured methodological consistency. Studies were included if they met the following eligibility criteria: (1) murine model of sepsis, (2) septic mice without obesity as a control group, and (3) available mortality data for both groups. All studies meeting these criteria were included in the systematic review, regardless of the specific sepsis or obesity model used. Each distinct survival assessment – defined by a unique pairing of obesity-induction method, HFD variant, and sepsis model – was counted as an individual experiment, even when reported within the same publication, to capture within-study heterogeneity.

For the meta-analysis, only studies in which sepsis was induced using the cecal ligation and puncture (CLP) method and obesity was obtained using the diet-induced obesity (DIO) model were included. These models were the most frequently used, allowing for standardization of the analysis in terms of sepsis and obesity induction. To comprehensively assess the impact of HFD duration on survival in sepsis, studies involving short-term HFD administration were also included in both the systematic review and meta-analysis.

Data extraction

Data extraction was performed independently by two researchers using a predefined extraction form. A third investigator oversaw the process, verified the extracted data, and resolved any discrepancies. For each survival experiment, the primary outcome was mortality, assessed as the number of individuals reported dead by the end of the investigator-defined period.

Additionally, data related to the obesity model used, sepsis model, sex, age at the start of HFD administration (in the case of DIO), duration of HFD administration, age at sepsis induction, observation time, and diet composition were extracted. When necessary, corresponding authors of the included

studies were contacted to clarify or obtain missing data.

Statistical analysis

Meta-analysis and meta-regression were performed using Statistica software (v13.3, StatSoft, Tulsa, USA). Results were considered statistically significant at $P < 0.05$. For each study included in the meta-analysis, the odds ratio (OR) based on mortality data was calculated to assess the effect of obesity and other covariates. A random-effects model was used, and heterogeneity was evaluated using Cochran's Q test ($P < 0.05$) and the I^2 statistic. Potential publication bias was examined via funnel plots, Egger's test ($P < 0.05$), and the trim-and-fill method. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was applied to assess the overall certainty of evidence, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias [22].

RESULTS

A total of 392 records were identified via a systematic search of the database for articles published before January 31, 2025, and screened for inclusion based on eligibility criteria. Titles and abstracts of all articles were reviewed, and 41 potentially eligible articles were retrieved. The full text was then reviewed, and 21 studies were selected that met the inclusion criteria for the systematic review. Ten of them used the CLP method to induce sepsis and HFD for the induction of obesity (CLP-DIO sepsis-obesity model) and were included in the meta-analysis. The study selection process is presented in Figure 1.

SYSTEMATIC REVIEW

Study characteristics and quality assessment

The systematic review included 21 studies that assessed survival in the murine model of sepsis in a total of 38 experiments [23–43]. CLP was used to induce sepsis in 14 experiments (13 studies). In the remaining experiments, sepsis was induced by intraperitoneal administration of lipopolysaccharide (LPS) (7 experiments/5 studies), intravenous administration of *Staphylococcus aureus* LS-1 (8/2), intraperitoneal administration of *Pseudomonas aeruginosa* (4/1), intraperitoneal administration of *Salmonella typhimurium* (4/1), and intraperitoneal administration of cecal slurry (CS) (1/1).

In 33 experiments (18 studies), HFD was used; in 3 experiments (3 studies), obesity was achieved by subcutaneous injection of monosodium glutamate (MSG) in the neonatal period; and in 2 experiments (2 studies), obesity was induced through genetic modification (leptin-deficient). Two studies used more than one obesity model. The HFD used in the studies differed in composition, fat content, and percentage of energy from fat depending on the study (39.1–61.1%). The diets used in the control group also differed regarding the above parameters (percentage of energy from fat 9.0–18.0%). Some studies assessed the impact of HFDs with various compositions on survival, primarily focusing on the type of fat used. Moreover, in individual studies, the animals differed in age at the initiation of the HFD (42–112 weeks), duration of its use (3–172 days), and age of sepsis induction (58–224 weeks). Depending on the study, the observation period to assess survival ranged from 30 to 672 hours. Detailed information for the studies included in the systematic review is summarized in Table 1.

Impact of obesity on survival

In the evaluated studies, mortality in the group with obesity (or short-term HFD use) was higher than in the control group in 18 experiments, equal in 4 experiments, and lower in 16 experiments.

Two studies examined the effect of HFD composition on survival in sepsis. Svahn *et al*. [39] assessed the impact of a research diet administered for eight weeks and found that the difference in fat composition influenced survival. Mice fed a polyunsaturated HFD had increased survival during sepsis compared with mice fed a saturated HFD, while differences in the proportion of dietary protein and carbohydrates did not affect septic survival. Clouva-Molyvdas *et al*. [43] used two models of sepsis (one with *Pseudomonas aeruginosa* and the other with *Salmonella typhimurium*), in which the animals were fed an HFD for 2 and 3 weeks, respectively, before infection. In both models, four different HFDs differing in the source of fat and a control diet were used. No significant differences were observed in survival among groups fed various levels and fat sources.

Two studies assessed sepsis survival in the DIO model and the genetic (leptin-deficient) model. In the study by Vankrunkelsven *et al*. [29], after five days of sepsis, mortality was highest in leptin-deficient mice ($P = 0.03$ vs. DIO) but not significantly different between control and DIO mice. Moreover, in this study, despite similar body masses (DIO mice 43.9 ± 4.7 g, leptin-deficient mice 44.4 ± 2.8 g, $P = 0.5$), leptin-deficient mice had higher fat mass but lower lean body mass than obese DIO mice ($P < 0.0001$ for both). Strandberg *et al*. [42] reported that C57BL/6 mice on an HFD for eight weeks, like genetically obese mice on a low-fat diet (LFD), had increased mortality during *Staphylococcus aureus*-induced sepsis compared with LFD-fed C57BL/6 controls. They also found that the mortality in C57BL/6 mice fed an HFD throughout the entire

TABLE 1. Characteristics of studies included in the systematic review.

Ref.	Experimental group (obese)						Control group (lean)					Sepsis model	Start feeding age (days)	Feeding duration (days)	Sepsis induction age (days)	Observation duration (hours)
	Strain	Sex	Obesity model	kcal % FAT	*n*	Mortality %	Strain	Sex	kcal % FAT	*n*	Mortality %					
Berto-Pereira *et al.*, 2024 [23]	Swiss mice	F	MSG	n/d	16	81.3	Swiss mice	F	n/d	21	100.0	CLP	n/a	n/a	75	168
Nakama *et al.*, 2024 [24][a]	Swiss mice	M	MSG	11.5	22	~40.0	Swiss mice	M	11.5	48	~80.0	CLP	n/a	n/a	75	168
Nishimura *et al.*, 2023 [25][a]	KCASP1Tg	F	DIO	60.0	5	60.0	KCASP1Tg	F	n/d	5	100.0	LPS (500 µg i.p.)	112	56	168	36
	C57BL/6N	n/d	DIO	60.0	5	0.0	C57BL/6N	n/d	n/d	5	0.0	LPS (500 µg i.p.)	n/d	56	n/d	36
Bodilly *et al.*, 2023 [26]	C57BL/6	M	DIO	61.1	16	100.0	C57BL/6	M	16.5	16	100.0	CLP	42	49	91	96
Gomes *et al.*, 2023 [27]	C57BL/6	F	DIO	39.2	24	41.7	C57BL/6	F	9.5	21	13.1	CLP	21-28	98	119–126	168
Petroni *et al.*, 2022 [28]	C57BL/6	M	DIO	60.0	15	93.3	C57BL/6	M	11.5	15	86.7	LPS (10 mg/kg i.p.)	56	42	98	72
Vankrunkelsven *et al.*, 2022 [29]	B6.V-Lepob/ob/JRj	M	leptin KO	10.0	30	53.3	C57BL/6J	M	9.0	18	38.9	CLP	42	77–84	119–126	125
	C57BL/6J	M	DIO	60.0	26	23.1										
Lewis *et al.*, 2022 [30]	C57BL/6	M	DIO	60.0	18	33.3	C57BL/6	M	10.0	20	75.0	CS (500 µl CS i.p.)	42	140–147	182–189	336
Martins *et al.*, 2021 [31]	Swiss mice	M	DIO	60.2	6	100.0	Swiss mice	M	11.5	5	0.0	CLP	56	3	59	96
Nakama *et al.*, 2021 [32]	Swiss mice	M	MSG	11.5	20	5.0	Swiss mice	M	11.5	20	45.0	CLP	n/a	n/a	75	168
Wang *et al.*, 2021 [33][a]	C57BL/6	M	DIO	60.0	11	100.0	C57BL/6	M	10.0	11	90.9	LPS (10 mg/kg i.p.)	28	105	133	72
Souza *et al.*, 2019 [34][b]	Swiss mice	M	DIO	60.0	5	100.0	Swiss mice	M	10.0	7	100.0	LPS (30 mg/kg i.p.)	56	3	59	54
	Swiss mice	M	DIO	60.0	6	100.0	Swiss mice	M	10.0	6	50.0	CLP	56	3	59	150
Napier *et al.*, 2019 [35][a]	BALB/c	F	DIO	42.0	n/d	100.0	BALB/c	F	18.0	n/d	~17.0	LPS (6 mg/kg i.p.)	42-56	16	58–72	100
	BALB/c	F	DIO	42.0	n/d	100.0	BALB/c	F	18.0	n/d	100.0	LPS (8 mg/kg i.p.)	42-56	16	58–72	80
Frydrych *et al.*, 2019 [36]	C57BL/6 C57BL/6J	M	DIO	60.0	20	60.0	C57BL/6	M	13.0	20	20.0	CLP	42	154–172	196–224	672
Kaplan *et al.*, 2016 [37][a]	C57BL/6	M	DIO	61.1	12	83.3	C57BL/6	M	16.5	12	66.7	CLP	42	42–49	84–91	30

TABLE 1. Cont.

Ref.	Experimental group (obese)						Control group (lean)					Sepsis model	Start feeding age (days)	Feeding duration (days)	Sepsis induction age (days)	Observation duration (hours)
	Strain	Sex	Obesity model	kcal % FAT	*n*	Mortality %	Strain	Sex	kcal % FAT	*n*	Mortality %					
Siegl *et al.*, 2015 [38]	C57BL/6J	M	DIO	54.0	24	0.0	C57BL/6J	M	11.0	30	20.0	CLP	49	84	133	48
Svahn *et al.*, 2015 [39]	C57BL/6	M	DIO	60.0 S P : C -1 : 1	20	80.0	C57BL/6	M	10.0	20	35.0	*Staphylococcus aureus* LS-1 (0.2 ml *i.v.*)	49	56	105	408
	C57BL/6	M	DIO	60.0 P P : C-1 : 1	20	15.0										
	C57BL/6	M	DIO	60.0 S P : C -3 : 1	20	60.0										
	C57BL/6	M	DIO	60.0 P P : C-3 : 1	20	20.0										
	C57BL/6	M	DIO	60.0 S P : C-1 : 3	20	60.0										
	C57BL/6	M	DIO	60.0 P P : C-1 : 3	20	15.0										
Siegl *et al.*, 2014 [40]	C57BL/6J	M	DIO	54.0	14	28.6	C57BL/6J	M	11.0	10	90.0	CLP	49	84	133	240
Kaplan *et al.*, 2012 [41][a]	C57BL/6	M	DIO	61.1	12	91.7	C57BL/6	M	16.5	12	50.0	CLP	42	21	63	30
Strandberg *et al.*, 2009 [42][a]	C57BL/6	M	DIO	58.0 and 60.0	18	55.6	C57BL/6	M	10.8 and 10.0	21	14.3	*Staphylococcus aureus* LS-1 (0.2 ml *i.v.*)	42–56	56	98–112	408
	Ob/Ob	M	leptin KO	10.8 and 10.0	18	72.2	C57BL/6	M	10.8 and 10.0	15	20.0	*Staphylococcus aureus* LS-1 (0.2 ml *i.v.*)	42–56	56	98–112	408

TABLE 1. Cont.

Ref.	Experimental group (obese)						Control group (lean)					Sepsis model	Start feeding age (days)	Feeding duration (days)	Sepsis induction age (days)	Observation duration (hours)
	Strain	Sex	Obesity model	kcal % FAT	*n*	Mortality %	Strain	Sex	kcal % FAT	*n*	Mortality %					
Clouva-Molyvdas *et al.*, 1992 [43]	CF1	F	DIO	39.1 coconut oil	30	26.7	CF1	F	11.7	20	30.0	*Pseudomonas aeruginosa* (*i.p.*)	n/d	14	n/d	168
	CF1	F	DIO	39.1 safflower oil	30	20.0										
	CF1	F	DIO	39.1 oleic acid	30	26.7										
	CF1	F	DIO	39.1 MaxEPA oil	30	20.0										
	CF1	F	DIO	39.1 coconut oil	31	71.0	CF1	F	11.7	31	58.1	*Salmonella typhimurium* (*i.p.*)	n/d	21	n/d	336
	CF1	F	DIO	39.1 safflower oil	31	61.3										
	CF1	F	DIO	39.1 oleic acid	30	66.7										
	CF1	F	DIO	39.1 MaxEPA oil	31	54.8										

M – male, F – female, DIO – diet-induced obesity, S – saturated, P – polyunsaturated, P : C – ratio of calories from protein to calories from carbohydrates, KO – knockout, MSG – monosodium glutamate, CLP – cecal ligation and puncture, LPS – lipopolysaccharide, CS – cecal slurry, *i.v.* – intravenous, *i.p.* – intraperitoneal, *n* – sample size, n/a – not applicable, n/d – no data.

[a]Mortality data were not explicitly provided in the text or tables but were presented in graphical form. In these cases, values were estimated by extracting data from the corresponding figures.

[b]The source article mistakenly reported $n = 5$ with 50% mortality; following email correspondence with its authors, the true group size was confirmed as $n = 6$, and all analyses herein use the corrected value.

experiment was higher than in mice on an LFD throughout the whole period ($P = 0.02$). There was no increase in mortality when comparing mice that had been switched from LFD to HFD on the day of staphylococcal inoculation with mice that had been fed an LFD throughout. Moreover, there was no significant difference in mortality between mice fed an HFD before inoculation and switched to an LFD on the day of inoculation and mice on an HFD throughout [42].

Rationale for performing a meta-analysis and for model selection

Differences in mortality between obese and control groups across various studies suggest that additional factors may influence outcomes. As noted earlier, the range of mouse age at the start of HFD feeding, the duration of feeding, the age at sepsis induction, and the observation period varied considerably among the reviewed studies. Moreover, the systematic review revealed that CLP was the most frequently used sepsis model, whereas HFD was the most common approach to inducing obesity. Hence, a meta-analysis was carried out exclusively on studies employing this combination of the most frequently used models (CLP-DIO) to reduce variability and reveal additional factors affecting mortality. By selecting the most widely utilized sepsis and obesity induction methods, the intention was to minimize discrepancies arising from differing obesity mechanisms and sepsis induction protocols.

Meta-analysis and meta-regression

Meta-analysis

To obtain a homogeneous group for the meta-analysis, studies were selected in which sepsis was induced by CLP and obesity by the DIO model. Ten studies met these criteria, involving 159 DIO mice and 149 control mice. They are summarized in Table 2. Eight studies used C57BL/6 mice, including four C57BL/6J mice. The remaining two studies used Swiss mice. In nine studies, the mice were male. Six experiments used commercial high-fat formulas with publicly available fatty-acid profiles (58Y1 $n = 3$, E15186-34 $n = 2$, E15742-34 $n = 1$); three employed modified high-fat versions of AIN-93 (AIN-93M $n = 2$, AIN-93G $n = 1$), and one used an unnamed HFD without further compositional details, precluding analysis of fat-type effects. Figure 2 presents, for each study, the age at HFD initiation, the duration of HFD feeding, and the age at sepsis induction.

There was no statistically significant difference between animals receiving an HFD and those receiving a control diet (OR = 1.65, 95% CI: 0.53–5.19; $P = 0.391$), as illustrated in the forest plot presented in Figure 3.

To assess the robustness of this result, a leave-one-out sensitivity analysis was performed. In this analysis, each study was sequentially excluded and the pooled effect size was recalculated. The resulting ORs ranged from 1.29 (when excluding Martins *et al*., 2021 [32]) to 2.35 (when excluding Siegl *et al*., 2014 [41]). In all cases, the direction and statistical significance of the pooled estimate remained unchanged (OR = 1.65, 95% CI: 0.53–5.19; $P = 0.391$), indicating that no individual study unduly influenced the overall result.

Meta-regression

The statistical meta-regression analysis showed that a higher age at the time of introduction of an HFD ($P < 0.001$) and a longer duration of feeding with an HFD ($P < 0.001$) reduce mortality. A higher age ($P < 0.001$) at sepsis induction increases mortality. In the above model, the regression coefficient R^2 is 0.86 ($P < 0.001$). Figure 4 presents univariate analyses that illustrate the individual impact of these factors. In addition, the percentage of dietary energy from fat was evaluated as a potential predictor of survival; however, it was not significantly associated with mortality ($P = 0.1016$).

Heterogeneity and publication bias

A moderate-to-high level of heterogeneity was observed (Cochran's Q $P = 0.0007$, $I^2 = 68.6\%$), supporting the use of a random-effects model. A funnel plot was constructed to assess potential small-study effects (Figure 5). Although a few studies appear outside the main funnel boundary and may be considered outliers, overall visual inspection did not indicate substantial asymmetry, and Egger's regression test ($P = 0.7896$) confirmed the absence of statistically significant publication bias. The trim-and-fill method ($P = 0.3906$) further indicated that no additional "missing" studies needed to be imputed, supporting the robustness of the meta-analytic findings.

GRADE assessment

The overall certainty of the evidence from the included studies was evaluated using the GRADE framework. As summarized in Table 3, the risk of bias was judged as moderate, heterogeneity as low, indirectness as low, imprecision as high (due to wide confidence intervals including 1), and publication bias as moderate. These ratings underscore both the variability in study designs and the relatively wide confidence intervals observed in the pooled analyses.

TABLE 2. Characteristics of studies included in the meta-analysis

Ref.	Experimental group (obese)								Control group (lean)								Start feeding age (days)	Feeding duration (days)	Sepsis induction age (days)	Observation duration (hours)	Needle gauge [G]	Punctures (*n*)
	Strain	Sex	Energy [kcal/g]	Kcal % FAT	Kcal % PRO	Kcal % CHO	Total (*n*)	Mortality %	Strain	Sex	Energy [kcal/g]	Kcal % FAT	Kcal % PRO	Kcal % CHO	Total (*n*)	Mortality %						
Bodilly *et al.*, 2023 [26]	C57BL/6	M	5.10	61.1	18.1	20.3	16	100.0	C57BL/6	M	3.54	16.5	26.6	56.8	16	100.0	42	49	91	96	21	2
Gomes *et al.*, 2023 [27]	C57BL/6	F	4.59	39.2	13.5	47.3	24	41.7	C57BL/6	F	3.79	9.5	16.3	74.2	21	13.1	21–28	98	119–126	168	21	1
Vankrunkelsven *et al.*, 2022 [29]	C57BL/6J	M	5.15	60.0	20.0	20.0	26	23.1	C57BL/6J	M	3.23	9.0	24.0	67.0	18	38.9	42	77–84	119–126	125	18	2
Martins *et al.*, 2021 [31]	Swiss mice	M	5.20	60.2	19.9	19.9	6	100.0	Swiss mice	M	3.50	11.5	25.7	62.8	5	0.0	56	3	59	96	18	1
Souza *et al.*, 2019 [34][a]	Swiss mice	M	5.20	60.2	19.9	19.9	6	100.0	Swiss mice	M	3.50	11.5	25.7	62.8	6	50.0	56	3	59	150	n/d	n/d
Frydrych *et al.*, 2019 [36]	C57BL/6 and C57BL/6J	M	n/d	60.0	n/d	n/d	20	60.0	C57BL/6	M	n/d	13.0	n/d	n/d	20	20.0	42	154–172	196–224	672	20	2
Kaplan *et al.*, 2016 [37][b]	C57BL/6	M	5.10	61.1	18.1	20.3	12	83.3	C57BL/6	M	3.54	16.5	26.6	56.8	12	66.7	42	42–49	84–91	30	22	2
Siegl *et al.*, 2015 [38]	C57BL/6J	M	4.97	54.0	17.0	29.0	24	0.0	C57BL/6J	M	n/d	11.0	23.0	65.0	30	20.0	49	84	133	48	23	1
Siegl *et al.*, 2014 [40]	C57BL/6J	M	4.97	54.0	17.0	29.0	14	28.6	C57BL/6J	M	n/d	11.0	23.0	65.0	10	90.0	49	84	133	240	23	1
Kaplan *et al.*, 2012 [41][b]	C57BL/6	M	5.10	61.1	18.1	20.3	12	91.7	C57BL/6	M	3.54	16.5	26.6	56.8	12	50.0	42	21	63	30	21	2

M – male, F – female, n/d – no data, Kcal% FAT – percentage of total calories derived from fat, Kcal% PRO – percentage of total calories derived from protein, Kcal% CHO – percentage of total calories derived from carbohydrates.

[a]The source article mistakenly reported $n = 5$ with 50% mortality; following email correspondence with its authors, the true group size was confirmed as $n = 6$, and all analyses herein use the corrected value.

[b]Mortality data were not explicitly provided in the text or tables but were presented in graphical form. In these cases, values were estimated by extracting data from the corresponding figures.

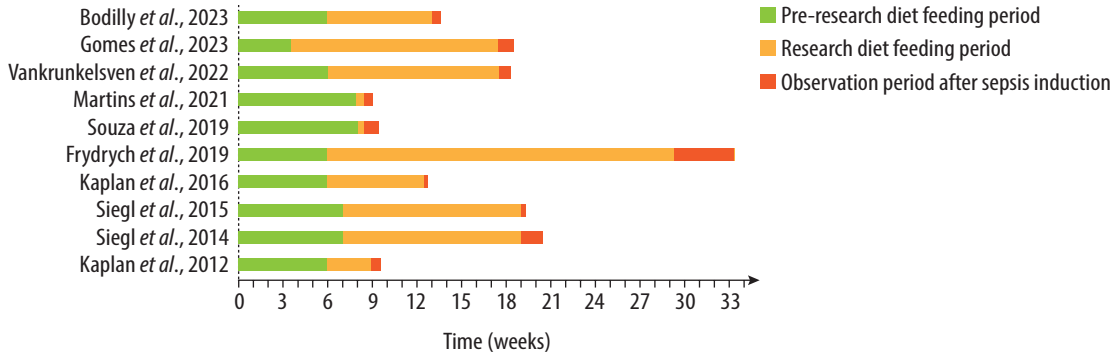

FIGURE 2. Comparison of the duration of individual periods (pre-research diet feeding period, research diet feeding period, and observation period after sepsis induction) in the studies included in the meta-analysis

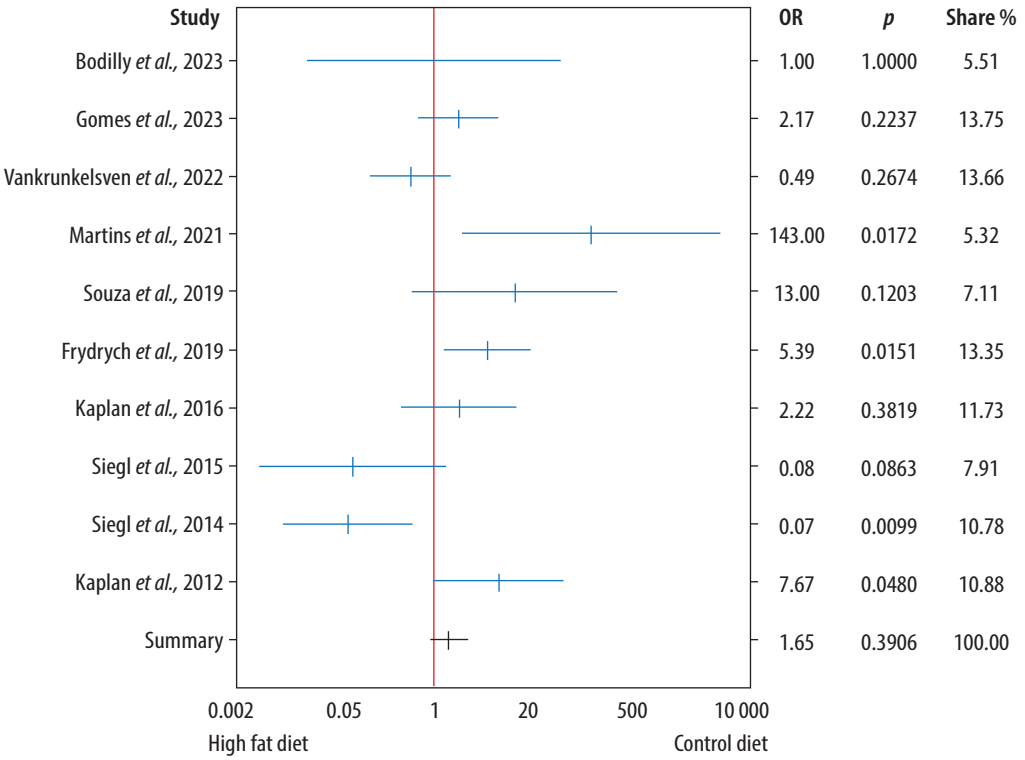

FIGURE 3. Forest plot displaying the odds ratios (OR) and 95% confidence intervals for survival in mice fed a high-fat diet (HFD) compared to a control diet in the murine model of sepsis across the studies included in the meta-analysis. There was no statistically significant difference between the groups ($P = 0.391$)

DISCUSSION

The *obesity paradox* remains a complex and intriguing phenomenon within medical research. Our systematic review and meta-analysis aimed to elucidate the relationship between obesity and survival outcomes in murine models of sepsis. The findings demonstrate significant variability in mortality outcomes, with some studies showing a survival benefit in obese mice while others do not.

The studies evaluated revealed mixed results, with obesity associated with higher mortality in 18 experiments, equal mortality in 4, and lower mortality in 16 experiments. This variability suggests that factors beyond obesity may be crucial in determining outcomes. The research by Svahn *et al*. [39] and Clouva-Molyvdas *et al*. [43] highlights the significant impact of dietary composition on survival outcomes. Mice fed polyunsaturated fats exhibited improved survival rates compared to those on saturated fats, underscoring the importance of nutritional components beyond caloric content. The comparison of DIO and genetic (leptin-deficient) models by Vankrunkelsven *et al*. [29] emphasizes the complexity of obesity as a phenotype. Despite similar body masses, leptin-deficient mice demonstrated differences in fat and lean mass composition, affecting survival outcomes. Obesity's impact on the immune response, as shown in studies by Lewis *et al*. [30] and Strandberg *et al*. [42], further

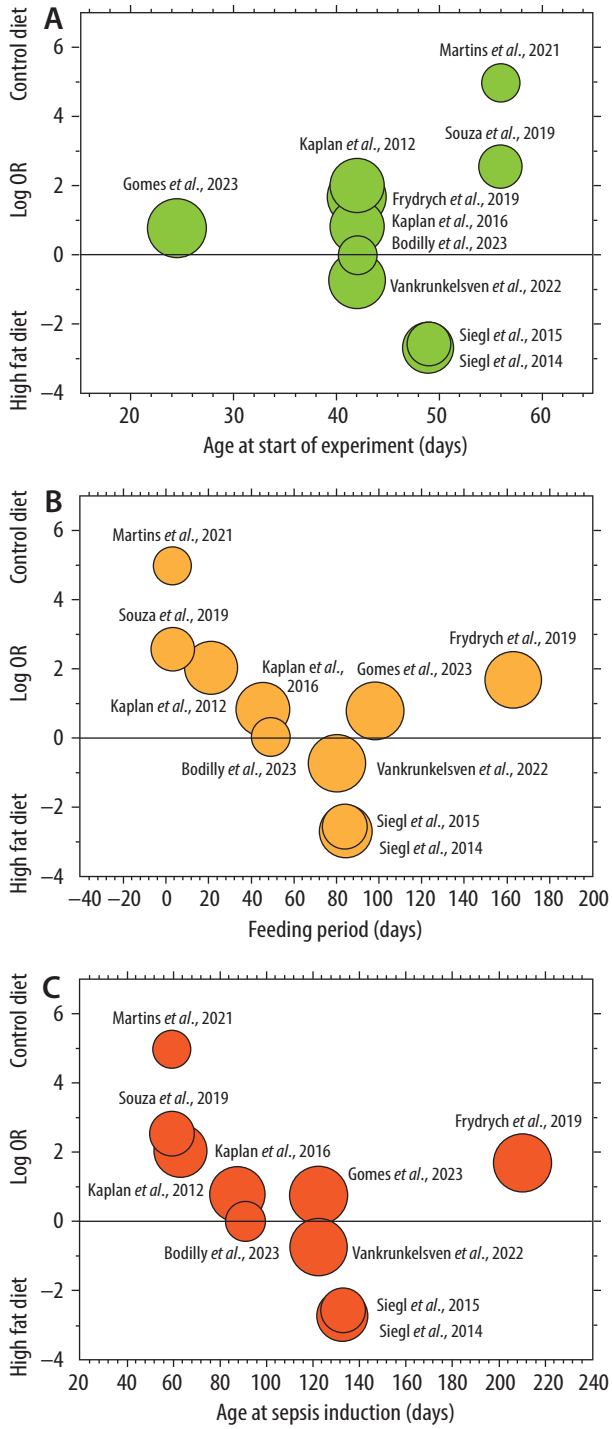

FIGURE 4. Univariate meta-regression analyses illustrate the individual impact of age at the initiation of a high-fat diet (HFD) (**A**), duration of HFD (**B**), and age at sepsis induction (**C**) on survival in murine sepsis models. These analyses demonstrate the independent influence of each factor. In the multivariate analysis presented in the Results section, these effects are moderated by the interactions between variables, leading to different outcomes when all factors are considered simultaneously

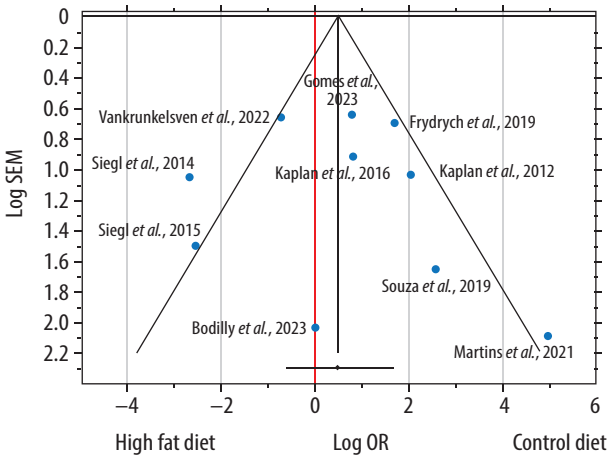

FIGURE 5. Funnel plot of the studies included in the meta-analysis, assessing the association between a high-fat diet and mortality in murine sepsis models. The x-axis shows the log odds ratio (OR), with negative values favoring the high-fat diet group, and the y-axis shows the standard error of the mean (SEM). The vertical red line represents the pooled effect estimate, and the diagonal lines correspond to the pseudo 95% confidence intervals around this estimate. Although a few studies appear outside these boundaries and may be considered outliers, the overall distribution is relatively symmetrical, suggesting no definitive evidence of publication bias

complicates the relationship between obesity and sepsis survival. Altered cytokine profiles and immune cell functions in obese mice may contribute to differential survival outcomes [30, 42].

The results of the meta-analysis provide essential insights into the relationship between obesity and survival in murine models of sepsis, specifically those utilizing the CLP-DIO model. The lack of a statistically significant difference in mortality between the HFD and control groups ($P = 0.391$) suggests that obesity, as induced by an HFD, does not uniformly affect survival in sepsis. However, the statistical regression analysis identified critical variables influencing outcomes: higher age at the start of the HFD and longer duration of diet administration were associated with reduced mortality, while higher age at sepsis induction was linked to increased mortality. These findings underscore the importance of time-dependent factors in modulating the effects of obesity on sepsis outcomes and suggest that the *obesity paradox* may be context-dependent, varying with the timing of dietary intervention and the age at which sepsis is induced.

Despite observing a substantial degree of heterogeneity ($I^2 = 68.6\%$), our analyses did not reveal significant publication bias. The funnel plot showed no marked asymmetry, and Egger's test ($P = 0.7896$), together with the trim-and-fill method ($P = 0.3906$), indicated that no additional "missing" studies were necessary to adjust the pooled estimate. These findings suggest that, despite variability in study protocols, the overall conclusions from our meta-analysis remain robust to small-study effects. Furthermore, the GRADE framework highlighted both the strengths and limitations of the current evidence. Although the risk of bias was rated as moderate and indirectness as low, imprecision was high due to wide confidence intervals that frequently

TABLE 3. GRADE assessment of the certainty of evidence

Domain	GRADE rating	Explanation
Risk of bias	Moderate	The included studies may have a moderate risk of systematic error.
Inconsistency	Low	$I^2 = 68.6\%$ suggests moderate-to-high heterogeneity. However, since the overall conclusions were not substantially altered, the concern for inconsistency was rated as low.
Indirectness	Low	The outcomes directly address the research question, and no major applicability issues were identified.
Imprecision	High	Wide confidence intervals and ORs crossing 1 indicate inconclusive results, diminishing precision.
Publication bias	Moderate	Possible constraints in the availability of full study data.

crossed the line of no effect. This underscores that the pooled result from the meta-analysis may be less conclusive on its own. Indeed, meta-regression – pinpointing the importance of the age at HFD initiation, HFD duration, and the timing of sepsis induction – proved more revealing than the overall forest plot estimate. Such findings underscore the complexity of the *obesity paradox* in murine sepsis models and emphasize the need to consider time-dependent factors both when designing experiments and when interpreting the impact of obesity on survival in these experimental conditions.

The impact of obesity on outcomes in preclinical animal models of sepsis has already been the subject of comprehensive reviews, with detailed analyses provided by Xu *et al*. [44], and Eng *et al*. [9]. Xu *et al*. [44], in a systematic review and meta-analysis published in 2020, evaluated 21 studies comparing survival in obese versus non-obese animals (mice or rats) following exposure to bacteria, lipopolysaccharide, or influenza virus. The studies included in the comparison utilized various models of sepsis, infection, and obesity. Their analysis demonstrated that obesity consistently reduced survival in both single-strain bacteria- and lipopolysaccharide-exposed studies, not significantly in CLP models, and significantly in influenza models, albeit with high heterogeneity. Eng *et al*. [9], in a scoping review published in 2024, provided critical insights by analyzing the diversity of diet-induced sepsis-obesity murine models, focusing on differences in sepsis induction (such as variable induction protocols, needle gauge, number of punctures), fluid resuscitation, antibiotic therapy, and analgesic administration, as well as variations in obesity models, particularly concerning the composition of HFDs [9]. These reviews have significantly advanced the understanding of the complexities of modelling sepsis and obesity in preclinical settings. To date, this paper is the first meta-analysis to assess the impact of time points and specific interventions, such as the age at the start of HFD, the duration of HFD, and the age at the time of sepsis induction, on survival in the CLP-DIO (sepsis-obesity) model.

The current body of research on the *obesity paradox* in murine models of sepsis is characterized by significant heterogeneity in experimental design. The most commonly used approach appears to be the CLP-DIO sepsis-obesity model; however, the composition of the HFD and the CLP procedures varies across studies. Our study and others addressing the sepsis-obesity murine model underscore the need for standardization. Additionally, our meta-analysis suggests that factors such as the age of the animals at the start of HFD, the duration of HFD, and the age at sepsis induction may significantly influence the observed impact of obesity on sepsis survival. Further research in this area would not only provide valuable insights into the effects of these variables and offer a clearer understanding of the mechanisms driving the *obesity paradox* but also contribute to the standardization of the sepsis-obesity model.

This study has several limitations. The heterogeneity in experimental designs across the included studies, particularly regarding HFD composition, sepsis induction methods, and animal strains, may have introduced variability that could affect the comparability of results. Although our meta-analysis attempted to standardize some of these variables by focusing on the CLP-DIO model, differences in experimental protocols across studies still make it challenging to draw definitive conclusions. Additionally, the relatively small sample sizes in some of the included studies may have limited the statistical power to detect subtle effects of obesity on sepsis outcomes. Moreover, previous research has indicated that sex may also influence survival in sepsis-obesity models [23]. In this meta-analysis, only one study included female mice, thereby precluding any meaningful subgroup analysis based on sex. Similarly, although the majority of studies used C57BL/6 or C57BL/6J mice, the limited diversity and unequal distribution of strains, including a mixed-strain cohort in one study, prevented reliable analysis of strain-specific effects. Furthermore, the included studies exhibited considerable methodological heterogeneity, not only in the parameters assessed in the meta-regression but also in technical aspects of the CLP procedure, such as needle

gauge and the number of punctures (Table 2). While these factors may have influenced the overall severity of peritonitis, systemic inflammation, and survival outcomes across studies, they were consistent within each experiment and therefore did not affect the comparison between obese and lean groups. Taken together, these limitations further highlight the need for standardization in experimental designs to enhance the reproducibility and comparability of findings in the sepsis-obesity model.

Developing a universally accepted CLP-DIO protocol will require dedicated studies that vary key parameters in a factorial manner. In addition to the temporal factors highlighted by our meta-regression (age at HFD initiation, HFD duration, and age at sepsis induction), future optimization should address the composition of the HFD – including macronutrient ratios and a detailed fatty-acid profile – as well as strain and sex of the mice, anesthetic regimen, number of cecal punctures and needle gauge, type and volume of fluid resuscitation, and adjunct therapies such as antibiotics or analgesics. Systematically quantifying the impact of each variable on survival and inflammatory end-points will allow the field to converge on a time-point-standardized, clinically relevant CLP-DIO protocol.

In parallel with standardizing survival protocols, future CLP-DIO studies should incorporate immunometabolic endpoints to link phenotypic outcomes with underlying mechanisms and strengthen translational relevance. These endpoints ought to capture systemic inflammation, adipose-tissue signaling, oxidative stress, whole-body metabolic status, and host–microbiome interactions – for example, comprehensive cytokine and adipokine panels, markers of oxidative damage, dynamic glucose–insulin measurements, metabolomic profiling, and characterization of intestinal microbiota.

Although the current meta-analysis was limited to studies using the CLP-DIO model to ensure methodological consistency, this approach inherently restricts generalizability. Other models, such as LPS-induced sepsis in DIO mice, may yield different results; however, substantial variability in experimental design, LPS dosing, and animal characteristics, along with missing data in some reports, precluded a robust meta-analysis of these alternatives. A broader meta-analysis may become feasible in the future as more studies with appropriate methodological details and consistency become available.

CONCLUSIONS

The findings from this systematic review and meta-analysis highlight the complexity of the *obesity paradox* in murine models of sepsis. Although some studies suggest a survival advantage for obese mice, our meta-analysis found no statistically significant difference in mortality between mice on an HFD and those on a standard diet. These observations indicate that factors beyond obesity per se shape survival in the sepsis-obesity model. Notably, our meta-analysis is the first to quantify how specific time-related variables – age at HFD initiation, HFD duration, and age at sepsis induction – influence survival.

Developing a universally accepted CLP-DIO protocol will require experimental designs that systematically vary key parameters. In addition to the temporal factors identified here, future work must define HFD composition (macronutrient ratios and fatty acid profile), include both sexes and relevant strains, standardize anesthesia, and harmonize CLP technique and adjunct therapies. Moreover, integrating immunometabolic endpoints – comprehensive cytokine and adipokine panels, markers of oxidative stress, metabolic profiling, and microbiome characterization – will link survival outcomes to underlying pathways. A deeper understanding of these factors may help clarify the mechanisms behind the .

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5. Graphical abstract is included as a Supplementary File.

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