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RESEARCH ARTICLE

Is body mass index associated with outcomes of mechanically ventilated adult patients in intensive critical units? A systematic review and meta-analysis

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Abstract

Background

Obesity paradox refers to lower mortality in subjects with higher body mass index (BMI), and has been documented under a variety of condition. However, whether obesity paradox exists in adults requiring mechanical ventilation in intensive critical units (ICU) remains controversial.

Methods

MEDLINE, EMBASE, China Biology Medicine disc (CBM) and CINAHL electronic databases were searched from the earliest available date to July 2017, using the following search terms: "body weight", "body mass index", "overweight" or "obesity" and "ventilator", "mechanically ventilated", "mechanical ventilation", without language restriction. Subjects were divided into the following categories based on BMI (kg/m²): underweight, < 18.5 kg/m²; normal, 18.5–24.9 kg/m²; overweight, BMI 25–29.9 kg/m²; obese, 30–39.9 kg/m²; and severely obese > 40 kg/m². The primary outcome was mortality, and included ICU mortality, hospital mortality, short-term mortality (<6 months), and long-term mortality (6 months or beyond). Secondary outcomes included duration of mechanical ventilation, length of stay (LOS) in ICU and hospital. A random-effects model was used for data analyses. Risk of bias was assessed using the Newcastle-Ottawa quality assessment scale.

Results

A total of 15,729 articles were screened. The final analysis included 23 articles (199,421 subjects). In comparison to non-obese patients, obese patients had lower ICU mortality (odds ratio (OR) 0.88, 95% CI 0.0.84–0.92, $I^2 = 0\%$), hospital mortality (OR 0.83, 95% CI 0.74–0.93, $I^2 = 52\%$), short-term mortality (OR 0.81, 95% CI 0.74–0.88, $I^2 = 0\%$) as well as long-term mortality (OR 0.69, 95% CI 0.60–0.79, $I^2 = 0\%$). In comparison to subjects with

normal BMI, obese patients had lower ICU mortality (OR 0.88, 95% CI 0.82–0.93, $I^2 = 5\%$). Hospital mortality was lower in severely obese and obese subjects (OR 0.71, 95% CI 0.53–0.94, $I^2 = 74\%$, and OR 0.80, 95% CI 0.73–0.89, $I^2 = 30\%$). Short-term mortality was lower in overweight and obese subjects (OR 0.82, 95% CI 0.75–0.90, $I^2 = 0\%$, and, OR 0.75, 95% CI 0.66–0.84, $I^2 = 8\%$, respectively). Long-term mortality was lower in severely obese, obese and overweight subjects (OR 0.39, 95% CI 0.18–0.83, and OR 0.63, 95% CI 0.46–0.86, $I^2 = 56\%$, and OR 0.66, 95% CI 0.57–0.77, $I^2 = 0\%$). All 4 mortality measures were higher in underweight subjects than in subjects with normal BMI. Obese subjects had significantly longer duration on mechanical ventilation than non-obese group (mean difference (MD) 0.48, 95% CI 0.16–0.80, $I^2 = 37\%$), In comparison to subjects with normal BMI, severely obese BMI had significantly longer time in mechanical ventilation (MD 1.10, 95% CI 0.38–1.83, $I^2 = 47\%$). Hospital LOS did not differ between obese and non-obese patients (MD 0.38, 95% CI 0.17–0.59, $I^2 = 70\%$). Hospital LOS and ICU LOS than non-obese patients (MD 0.38, 95% CI 0.17–0.59, $I^2 = 70\%$). Hospital LOS did not differ significantly in subjects with different BMI status.

Conclusions

In ICU patients receiving mechanical ventilation, higher BMI is associated with lower mortality and longer duration on mechanical ventilation.

Introduction

Obesity, typically defined as BMI of \geq 30 kg/m², is an increasing public concern [1]. It is one of the top 10 risk factors of chronic diseases [2–4]. Nearly 300,000 Americans die from a range of diseases related to obesity each year, and the economic burden exceeds more than 5% of the national health expenditure [5, 6]. Consistently with the trend in the general population, the number of obese patients admitted to ICUs is rapidly rising [7].

Obesity has been associated with increasing mortality in critically ill patients [8–10]. A variety of factors contribute to the association between obesity and mortality, including a series of physiological changes that result in poor stresses related to acute inflammatory and immune responses, or in many comorbidities including diabetes, cardiovascular events, respiratory diseases and cancer [11]. However, "obesity paradox" (namely, lower mortality in obese subjects) has also been reported in ICU patients in other studies [12–13]. The relationship between obesity and mortality of ICU patients thus remain largely unclear [14]. In the current study, we conducted a systematic review and meta-analysis of published studies to investigate the relationship between BMI and ICU outcomes in patients received mechanical ventilation.

Materials and methods

Literature search and study selection

We conducted a comprehensive electronic search of MEDLINE, EMBASE, CBM and Cochrane Central Register of Controlled Trials databases (CENTRAL) from the earliest available date to July 2017. The search strategy is described in <u>S1 Text</u>. Two authors (Yonghua Zhao, Zhiqiang Li) manually searched the references listed in each identified article and other relevant articles to identify all eligible studies. The search was not restricted in publication type or languages.

Inclusion and exclusion criteria

For inclusion in data analysis, studies must meet all following criteria: 1) cohort studies in patients receiving mechanical ventilation in ICU; 2) patients across two or more BMI categories; 3) outcomes include all-cause mortality, including ICU mortality, long-term mortality, short-term mortality, hospital mortality, or duration of mechanical ventilation, hospital and ICU LOS. The exclusion criteria included: patients under 18 years of age, review articles, case reports or animal experiment.

Data extraction and outcomes

Data extraction was carried out as recommended by the *Cochrane* handbook, and included authors, year of publication, study design, participants, BMI categories, demographic characteristics, severity of illness, measurement of BMI. BMI was classified into 5 categories using the National Institutes of Health (NIH) criteria [15]: 1) underweight: BMI <18.5 kg/m²; 2) normal weight: BMI 18.5–24.9 kg/m²; 3) overweight: BMI 25–29.9 kg/m²; 4) obese: BMI 30–39.9 kg/m²; 5) severely obese: BMI \geq 40 kg/m². Both review of full texts and extraction of data were independently performed by two reviewers (Yonghua Zhao, Zhiqiang Li). Duplicate reports were discarded by screening titles and abstracts. Any disagreement between the two primary reviewers was resolved by discussion with the third party (Xiuming Xi).

Quality assessment

Risk of bias of individual studies at the outcome level was assessed using the Newcastle-Ottawa quality assessment scale: 4 for selection, 2 for comparability and 3 for outcome. Study quality was rated based on the score: 1 (very poor) to 9 (very high) (S1 Table).

Statistical analysis

Statistical analysis was performed using the Cochrane systematic review software Review Manager (RevMan; Version 5.3.5). Data analysis was performed using a random-effects model developed by DerSimonian and Laird [16]. Dichotomous variables are presented as odds ratio (OR) with 95% confidence intervals (CI). Continuous variables are presented as mean difference (MD) with 95% confidence intervals. Significant heterogeneity was defined as P < 0.1 in χ 2 test and I² > 50%. If the literature reported the median or range of continuous variables, we used the median as the mean and the method provided by the Cochrane handbook [17] to calculate the standard deviation, and carried out sensitivity analysis. Publication bias was assessed with a funnel plot when there were 10 or more eligible studies.

Results

The search identified a total of 15,729 articles. After screening the titles and abstracts and removal of duplicates, 23 articles (199, 421 subjects) were included in the meta-analysis (Fig 1).

Study description

All eligible studies were approved by their corresponding institutional ethics committee. A total of 199,421 subjects participated in the 23 studies, which consisted of 14 prospective [8, 13, 18–29] and 9 retrospective cohort studies [9–12, 30–35]. Fourteen studies were from North



Fig 1. Flow diagram of study selection process.

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America [9, 10, 12, 13, 19, 20, 21, 25, 27, 28, 30, 32–34], one from South America [31], five from Europe [8, 18, 22, 23, 24, 29], and two from Australia [26, 35]. In seven studies [8, 9, 18, 19, 22, 31, 32], BMIs was classified only into obese versus non-obese (Table 1). Five studies reported short-term mortality [20, 23, 26, 28, 30]. Four studies reported long-term mortality [14, 19, 26, 28].

Publication bias

Since there were more than ten studies comparing the obese patients, it was possible to assess for publication bias, Funnel plot did not reveal significant publication bias on duration of mechanical ventilation (S1A Fig), ICU and hospital LOS (S1B and S1C Fig).

Mortality

In comparison to non-obese subjects, obese patients had lower ICU mortality (OR 0.88, 95% CI 0.84–0.92, Z = 6.22, P<0.00001 I² = 0%), hospital mortality (OR 0.83, 95% CI 0.74–0.93, Z = 3.11, P<0.002, I² = 52%), short-term mortality (OR 0.81, 95% CI 0.74–0.88, Z = 5.00, P<0.00001, I² = 0%), as well as long-term mortality (OR 0.69, 95% CI 0.60–0.79, Z = 5.41, P<0.00001, I² = 0%, Fig 2). In comparison to subjects with normal BMI, The results are as follows: obese patients had lower ICU mortality (OR 0.88, 95% CI 0.82–0.93, Z = 4.11, P<0.00001, I² = 5%, Fig 3A), a trend for lower ICU morality (not statistically significant) was also observed in severely obese subjects (OR 0.82, 95% CI 0.66–1.00, Z = 1.92, P = 0.06, I² = 35%, Fig 3A). Overweight and obese patients had lower long-term mortality (OR 0.66, 95% CI 0.57–0.77, Z = 5.38,

Table 1.	Study characteris	tics by body mas	s index category.
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References	Country	Study design	Study period	ICU type	BMI categories(kg/	Sample	Age	Male	Severity of illness
					m ²⁾	size	Mean ± SD or median	%	Mean ± SD or median
Wardell S[19]	Canada	Prospective	Jan 2008 to Mar	Mixed ICU					APACHE II
			2009		Nonobese: < 30.0	202	51.8(18.9)	34.7	20.8(8.5)
					Obese: ≥ 30.0	146	57.7(16.4)	42.5	23.5(8.1)
Lee CK[<u>30</u>]	USA	Retrospective	Jan to Dec 2009	Medical ICU					APACHE II
					Nonobese: < 30.0	306	63.0(16.5)	48.4	24.7(8.1)
					obese: \geq 30.0	85	59.6(16.2)	59.6	23.4(8.0)
					severely obese: > 35.0	113	NR	NR	NR
O'Brien JM	USA	Prospective	Feb 2006 to Jan	Medical ICU					NR
[13]			2008		Normal: < 25.0	213	58.3(17.1)	56.8	
					Overweight: 25.0 to 30.0	129	57.2(15.5)	54.3	
					Obese: ≥ 30.0	238	56.2(13.8)	52.9	
Martino JL	33	Prospective	2007 to 2009	ICU		¢			APACHE II
[20]	countries				Normal:18.5 to 24.9	3490	58.6(18.9)	61	22.2(8.0)
					Overweight:25 to 29.9	2604	60.2(17.4)	66.4	22.4(8.1)
					Obese: 30 to 39.9	1772	60.8(15.2)	57.7	22.9(8.0)
					Extremely obese: \geq 40.0	524	NR	44.8	NR
Anzueto A	USA	Prospective	Apr 2004	ICU					SAPS II
[21]					Underweight: < 18.5	184	55(19)	54.4	43(19)
					Normal: 18.5 to 24.9	1995	57(19)	58.8	43(18)
					Overweight: 25.0 to 29.9	1781	61(17)	67.1	43(17)
					Obese: 30 to 39.9	792	61(14)	55	44(17)
					Severely obese: > 40.0	216	55(14)	45.9	42(17)
Diaz E[22]	Spain	Prospective	Jan 2010	ICU					APACHE II
					Nonobese:< 30.0	265	43(15.4)	59.6	13.3(7.4)
					Obese: ≥ 30.0	150	43.9(12.3)	55.3	13.5(6.5)
Moock M[31]	Brazil	Retrospective	Apr 2005 to Nov	ICU					APACHE II
			2008		Nonobese:< 30.0	146	49.1 (57.5-69.6)	72	8 (12–16)
					Obese: \geq 30.0	73	49.7 (59.4-69.7)	33	8 (16-20)
Morris AE	USA	Prospective	Apr 1999 to Jul	ICU					APACHE II
[25]			2000		Underweight : < 18.5	50	64.7(18.4)	56	82.3(31.5)
					Normal: 18.5 to 24.9	301	61.5(18.1)	64.8	74.9(29.2)
					Overweight: 25.0 to 34.9	237	58.9(17.4)	66.2	74.9(30.0)
					Obese : 35.0 to 39.9	183	57.0(15.9)	63.4	70.3(29.8)
					Severely obese: \geq 40.0	54	54.7(13.9)	48.1	75.0(35.1)
Peake SL[26]	Australia	Prospective	2001	ICU					APACHE II
					Underweight : < 18.5	24	62.0(16.5)	58.3	20.8(8.0)
					Normal: 18.5 to 24.9	129	61.3(20.4)	60.5	19.9(7.9)

(Continued)

Table 1. (Continued)

References	Country	Study design	Study period	ICU type	BMI categories(kg/	Sample	Age	Male	Severity of illness
					m ²⁾	size	Mean ± SD or median	%	Mean ± SD or median
					Overweight: 25.0 to 29.9	151	64.1(16.1)	58.3	19.9(7.9)
					Obese : 30.0 to 34.9	75	62.9(14.4)	57.3	19.9(8.7)
					Severely obese: \geq 35.0	54	61.0(15.7)	50	19.4(8.0)
Brown CVR	USA	Retrospective	1998 to 2003	ICU					ISS
[9]					Nonobese:< 30.0	870	45(20)	71	21(12)
					Obese: \geq 30.0	283	46(18)	70	21(13)
Ray DE[27]	USA	Prospective	Jan 1997 to Aug	Medical ICU					APACHE II
			2001		Underweight: < 20.0	350	62.2(20.2)	47.4	18.2(8.3)
					Normal:20.0 to 24.9	663	65.2(18.6)	54.6	18.4(8.9)
					Overweight:25.0 to 29.9	585	64.8(16.3)	54	18.3(9.3)
					Obese:30 to 39.9	396	61.7(16.7)	46.2	17.0(8.7)
					Severely obese: \geq 40.0	154	57.4(16.0)	34.4	18.2(9.0)
Goulenok C	France	Prospective	Jan 1999 to Jan	Medical ICU					APACHE II
[8]			2000		Nonobese: < 27.0	598	48 (34-65)	41	32 (19-48)
					Obese: ≥ 27.0	215	58 (47-71)	42	36 (27–56)
El-Solh A [10]	USA	retrospective	January 1994 to	Medical and					APACHE II
			June 2000	surgical ICU	nonobese: < 30.0	132	46.2(21.7)	55.3	20.6(12.2)
					Morbidly obese: \geq 40.0	117	44.4(18.2)	43.59	19.1(7.6)
Frat J[24]	France	Prospective	Sep 2002 to Jun	ICU					SAPS II
			2004		Nonobese: < 30.0	124	65(11)	64.52	45(14)
					Severely obese: \geq 35.0	82	64(11)	59.76	45(16)
Alberda C[23]	37	Prospective	Jan 2007	ICU					APACHE II
	countries				Underweight: < 20.0	289	58.7(19.0)	50.9	22.04(7.71)
					Normal: 20.0 to 25.0	937	58.3(19.0)	59.8	21.40(8.15)
					Overweight: 25 to 30.0	818	60.0(17.8)	65.6	21.43(7.96)
					Obese: 30.0 to 35.0	395	62.2(15.3)	57.5	22.41(7.40)
					Severely obese: 35.0 to 40.0	162	62.3(13.7)	50.6	21.62(8.36)
					$\begin{array}{l} \text{Morbidly obese:} \geq \\ 40.0 \end{array}$	171	56.9(13.3)	45	22.21(8.53)
Duane TM [<u>32</u>]	USA	Retrospective	Jan 2004 to Dec 2005	ICU	Nonobese: < 30.0	51	NR	NR	NR
					Obese: > 30.0	10			
O'Brien JM Jr [33]	USA	Retrospective	Dec 1995 to Sep 2001	ICU	Underweight < 185	88	62 4(16 2)	16.6	NR
-					Normal: 18 5 to 24 9	544	61.0(17.8)	56.4	
					Overweight: 25.0 to	399	59.4(16.7)	55.9	
					Obese : 30.0 to 39.9	326	58.0(16.3)	46.6	
					severely obese: \geq 40.0	131	53.6(14.9)	33.6	

(Continued)

Table 1. (Continued)

References	Country	Study design	Study period	ICU type	BMI categories(kg/	Sample	Age	Male	Severity of illness
					m ²⁾	size	Mean ± SD or median	%	Mean ± SD or median
Tafelski S[18]	Germany	Prospective	Aug 2009 to Apr	Surgical ICU					SAPS II
			2010		Nonobese: < 30.0	451	63 (50–72)	57	36 (24-48)
					Obese: ≥ 30.0	130	64 (53–72)	53	35 (25–53)
Dennis, DM	Australia	Retrospective	Nov 2012 to Jun	ICU					APACHE II
[35]			2014		Underweight : < 18.5	18	56(39)	NR	19(12.0)
					Normal: 18.5 to 24.9	200	57(24)		18(10.0)
					Overweight: 25.0 to 29.9	249	55(25)		18(10.0)
					Obese : 30.0 to 39.9	216	60(19)		18(9.0)
					severely obese: \geq 40.0	52	60(15)		19(9.5)
Lewis O[34]	USA	Retrospective	2012	Medical ICU					mortality prediction model II
					Underweight : < 18.5	61	59.62(18.73)	62.3	37.19(27.80)
					Normal: 18.5 to 24.9	206	58.06(16.08)	59.22	39.61(28.54)
					Overweight: 25.0 to 29.9	127	58.57(16.74)	49.61	36.28(28.76)
					Obese(class1) : 30.0 to 34.9	90	59.48(15.72)	41.11	33.04(27.7)
					Obese(class2): 35 to 39.9	57	59.07(16.51)	28.07	38.21(29359)
					severely obese: \geq 40.0	64	54.64(17.41)	29.69	34.09(27.63)
Trivedi V[12]	USA	Retrospective	Jan 2010 to May	Medical ICU					APACHE II
			2011		Underweight : < 18.5	41	61.8(18.2)	56.1	20.3(9.7)
					Normal: 18.5 to 24.9	259	61.3(19.8)	59.1	18.7(8.3)
					Overweight: 25.0 to 29.9	194	60.4(17.3)	59.3	18.0(8.9)
					Obese : 30.0 to 39.9	205	61.3(15.3)	44.9	18.7(9.6)
					severely obese: \geq 40.0	59	NR	NR	NR
Pickkers P	Dutch	Prospective	January 1,1999, to	ICU					SAPS II
[29]			January 1,2010		Underweight : < 18.5	5343	60.0 (46-74)	38.6	36.4(19.6)
					Normal: 18.5 to 24.9	74883	65.0 (50-75)	58.6	35.1 (19.2)
					Overweight: 25.0 to 29.9	52141	67.0 (55–75)	62.5	35.7(19.4)
					Obese(class1) : 30.0 to 34.9	14660	65.0 (54–74)	53.1	34.7(19.1)
					Obese(class2): 35 to 39.9	4339	62.0(51–71)	42.4	34.6(19.9)
					severely obese: \geq 40.0	2992	57.0 (45-67)	34.6	31.6(20.8)

(Continued)

Table 1. (Continued)

References	Country	Study design	Study period	ICU type	BMI categories(kg/	Sample	Age	Male	Severity of illness
					m ²⁾	size	Mean ± SD or median	%	Mean ± SD or median
Abhyankar S	USA	Prospective	from 2001 to 2008	Mixed ICU					SAPS
[28]					Underweight : < 18.5	786	70.6(53.0-81.8)	56.4	12.3 (5.3)
					Normal: 18.5 to 24.9	5463	69.4(51.7-80.4)	45.2	12.2 (5.4)
					Overweight: 25.0 to 29.9	5276	67.2(53.6-77.8)	36	12.0 (5.3)
					Obese: \geq 30.0	5287	62.3(51.7-3.2)	44.6	12.0 (5.3)

BMI body mass index; ICU intensive care unit; NR no report; SAPSII simplified acute physiology score II; APS acute physiology score; APACHEII Acute Physiology and Chronic Health Evaluation II; ISS Injury Severity Score.

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P<0.00001, I² = 0% and OR 0.63, 95% CI 0.46–0.86, Z = 2.88, P = 0.004, I² = 56%, Fig 3B), only 1 of 23 studies reported long-term mortality in severely obese patients (lower than subjects with normal BMI) (Fig 3B). Obese and overweight patients had lower short-term mortality (OR 0.75, 95% CI 0.66–0.84, Z = 4.89, P<0.00001, I² = 8% and OR 0.91, 95% CI 0.67–1.24, Z = 0.59, P = 0.55, I² = 45%, Fig 3C). Obese and severely obese patients had lower hospital mortality (OR 0.80, 95% CI 0.73–0.89, Z = 4.22, P<0.0001, I² = 30% and OR 0.71, 95% CI 0.53–0.94, Z = 2.40, P = 0.02, I² = 74%, Fig 3D). In contrast, underweight subjects had higher mortality than normal BMI (ICU mortality in Fig 3A, long-term mortality in Fig 3B, short-term mortality in Fig 3D).

Duration of mechanical ventilation

The mean duration of mechanical ventilation in the included studies ranged from 2.17 to 15.2 days in the obese subjects and 1.86 to 13.2 days in the non-obese subjects. In a sensitivity analysis that excluded the studies that did not report mean and standard deviation, the outcome did not significantly change. In comparison with non-obese subjects, the combined mean difference in duration of mechanical ventilation was longer by 0.48 days in obese patients (95% CI, 0.16–0.80, Z = 2.92, P = 0.003, $I^2 = 37\%$, S2A Fig). In comparison to the subjects with the normal BMI, severely obese patients had significantly longer duration on mechanical ventilation (MD 1.10, 95% CI 0.38–1.83, Z = 2.99, P = 0.003, $I^2 = 47\%$, S2B Fig). No significant differences were found between the normal BMI and underweight subjects (MD -0.26, 95% CI -0.89 to 0.38, Z = 0.79, P = 0.43, $I^2 = 11\%$, S2B Fig), overweight (MD 0.18, 95% CI -0.33 to 0.70, Z = 0.70, P = 0.48 $I^2 = 62\%$, S2B Fig) or obese patients (MD 0.23, 95% CI -0.03 to 0.48, Z = 1.75, P = 0.08, $I^2 = 0\%$, S2B Fig).

ICU and hospital LOS

Non-obese patients had shorter ICU LOS than obese patients (MD 0.38, 95% CI 0.17–0.59, Z = 3.58, P = 0.0003, $I^2 = 70\%$, S2C Fig). A sensitivity analysis that excluded studies that did not report mean and standard deviation did not change these findings. In comparison to subjects with normal BMI, no significant differences in ICU LOS were found in underweight (MD -0.31, 95% CI -1.22 to 0.60, Z = 0.67, P = 0.50, $I^2 = 0\%$, S2D Fig), obese (MD 0.25, 95% CI -0.02 to 0.52, Z = 1.84, P = 0.07 $I^2 = 85\%$, S2D Fig), overweight (MD 0.09, 95% CI -0.04 to 0.21, Z = 1.37, P = 0.17, $I^2 = 48\%$, S2D Fig) and severely obese patients (MD 0.72, 95% CI -0.07 to 1.52, Z = 1.78, P = 0.08, $I^2 = 61\%$, S2D Fig). Hospital LOS did not differ between obese and

	obes	se	non-o	bese		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 ICU mortality					•		
Anzueto A. 2011	285	1008	1188	3776	6.9%	0.86 [0.74, 1.00]	
Diane M.D.2016	21	268	31	449	0.5%	1.15 [0.64, 2.04]	
Duane TM, 2006	4	28	19	110	0.1%	0.80 [0.25, 2.57]	
Frat JP, 2008	20	82	31	124	0.4%	0.97 [0.51, 1.85]	
O'Brien JM Jr. 2012	88	238	124	342	1.4%	1.03 [0.73, 1.45]	.
O'Brien, JM, 2006	104	457	295	943	2.4%	0.65 [0.50, 0.84]	
Peake SL, 2007	20	129	40	280	0.5%	1.10 [0.61, 1.97]	
Peter Pickkers.2013	2714	21990	17454	127024	87.2%	0.88 [0.85, 0.92]	
Wardell S. 2015	26	146	39	202	0.5%	0.91 [0.52, 1.57]	——————————————————————————————————————
Subtotal (95% CI)		24346		133250	100.0%	0.88 [0.84, 0.92]	♦
Total events	3282		19221				
Heterogeneity: $Tau^2 = 0.00$:	Chi ² = 7.	89. df = 8	B(P = 0.4)	$(44): ^2 = 0^{\circ}$	%		
Test for overall effect: $Z = 6$	22 (P < 0	0,00001)		,,			
	(
1.1.2 long-term mortality							
O'Brien JM Jr. 2012	134	238	229	342	15.6%	0 64 [0 45 0 89]	_ _
Peake SL 2007	42	129	117	280	9.5%	0.67 [0.43, 1.04]	
Swanna Abhyankar 2012	231	1106	816	2923	65.9%	0.68 [0.58, 0.80]	
Wardell S 2015	48	146	72	2020	9.0%	0.88 [0.56, 1.39]	
Subtotal (95% CI)	10	1619	12	3747	100.0%	0.69 [0.60, 0.79]	•
Total events	455		1234				
Heterogeneity: $Tau^2 = 0.00^{\circ}$	$Chi^2 = 1$	42 df = 3	3(P = 0.7)	70)· l² = 0º	2/2		
Test for overall effect: $7 = 5$	41 (P < 0	12, 01 - 1 00001)	5 (i = 0.1	0), 1 = 0	/0		
	.+1(1 < 0						
1.1.3 short-term mortality							
Alberda C. 2009	193	728	511	1755	18 7%	0.88 [0.72 1.07]	
	60	198	113	306	4.8%	0.74 [0.51 1.09]	— • –+
Martino II 2011	653	2820	1666	6004	65.2%	0.80 [0.72, 0.80]	-
Peake SL 2007	26	129	64	280	2.7%	0.85 [0.51, 1.42]	
Swanna Abhyankar 2012	68	600	231	1554	8.5%	0.73 [0.55, 0.98]	
Subtotal (95% CI)	00	4475	201	9989	100.0%	0.81 [0.74, 0.88]	•
Total events	1000		2585				
Heterogeneity: $Tau^2 = 0.00$	$Chi^2 = 1$	41 df =	1 (P = 0)	$(34) \cdot 1^2 = 0^0$	2/2		
Test for overall effect: $7 = 5$	00 (P < 0)	00001	+ (i = 0.0	, r = 0	/0		
1000000000000000000000000000000000000	.00 (1 < 0						
1.1.4 hospital mortality							
Anzueto A 2011	326	1008	1363	3776	19.9%	0 85 [0 73 0 98]	
Diane M D 2016	36	268	58	1/0	5.5%	1 05 [0.73, 0.30]	
	35	117	20	132	3.3%	2 13 [1 17 3 01]	
Erot ID 2008	24	82	30	102	3.3%	2.13 [1.17, 3.91]	
Morrie AE 2007	24 70	227	200	529	0.270 0.00/		
O'Brian IM Ir 2012	104	237	209	242	0.0 %	0.09 [0.50, 0.95]	_ _
O'Brien IM 2006	104	250	275	042	0.0 %	0.61 [0.56, 1.15]	_ _
O Brieff, JW, 2000 Botor Bickkors 2012	2052	21001	25052	107004	10.170 20.40/		
Swanna Abbyankar 2012	5955	21391 E10	20902	121024	20.4%		
Swapna Abriyankar,2012 Subtotal (95% CI)	57	049 24047	1/4	134679	9.2% 100.0%	0.70 [0.37, 1.08]	
Total overta	1714	2734/	20250	1340/0	100.0%	0.03 [0.74, 0.93]	▼
Hotorogonoiti :: Tou2 = 0.04	4/44	. CO 4	20309	021.12 - 1	- 20/		
Therefore every $Tau^2 = 0.01$;	-11 (D - 0)	0.09, at =	0 (2 = 0	$(03); 1^2 = 3$	JZ70		
Test for overall effect: $Z = 3$	(P=(1.002)					
							0.2 0.5 1 2 5
							obese non-obese

Fig 2. Obese and non-obese patients mortality.

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٨	E:	xperimental	Contro	 Totol M	Voight N	Odds Ratio	Odds Ratio	-		Experimental	Control	Odds	Ratio	Odds Ratio	
A	1.1.1 obese vs normal	vents rotar	Events	I Otal W	veight iv	I-H. Random. 95% CI	M-H. Random. 95% Ci	— C	Study or Subgroup	Events Total	Events Total Wei	ght M-H, Ran	idom, 95% Cl	M-H, Random, 95% Cl	
	Anzueto A, 2011	227 792	630	1995	11.1%	0.87 [0.73, 1.04]			Alberdo C. 2000	142 557	200 027 22	70/ 0.0	1 10 64 1 021	-	
	Diane M.D,2016	14 216	14	200	0.7%	0.92 [0.43, 1.98]			Martino II 2011	409 1772	1015 3490 60	2% 0.0	3 [0.64, 1.03]		
	Denen, JM, 2006 Peake SL, 2007	20 151	20	544 129	3.8% 0.9%	0.83 [0.47, 0.88]			Peake SL, 2007	20 75	31 129 3.	.2% 1.15	5 [0.60, 2.21]	<u> </u>	
	Peter Pickkers,2013	2355 18999	10259 7	4883 8	83.5%	0.89 [0.85, 0.94]			Swapna Abhyankar,2012	68 600	152 910 13.	.9% 0.64	4 [0.47, 0.87]		
	Subtotal (95% CI)	20484	7	7751 1	00.0%	0.88 [0.82, 0.93]	•		Subtotal (95% CI)	3004	5466 100	.0% 0.75	5 [0.66, 0.84]	♦	
	Total events	2691 0: Chi² = 4 20 d	11096 f = 4 (P = 0	38)-12 =	- 5%				Total events	640	1478				
	Test for overall effect: Z =	4.11 (P < 0.000	1)		- 578				Heterogeneity: Tau ² = 0.00); Chi ² = 3.25, df = 3	(P = 0.35); I ² = 8%				
									Test for overall effect: Z =	4.89 (P < 0.00001)					
	1.1.2 overweight vs norn	nal 559 1791	620	1005	5 2%	0.00 0.00 0.1 121	4		132 avanualisht ve norm	al.					
	Diane M.D.2016	17 249	14	200	0.2%	0.97 [0.47, 2.03]			Alberda C 2000	231 818	280 037 20	5% 0.0	2 (0 75 1 1/1	+	
	O'Brien JM Jr, 2012	41 129	83	213	0.5%	0.73 [0.46, 1.16]			Martino JL. 2011	651 2604	1015 3490 66.	.4% 0.8	1 [0.72, 0.91]		
	O'Brien, JM, 2006 Reake SL 2007	122 399 20 151	173	544 120	1.3%	0.94 [0.71, 1.25]			Peake SL, 2007	33 151	31 129 2.	.8% 0.8	B [0.51, 1.55]		
	Peter Pickkers,2013	7195 52141	10259 7	4883 9	92.7%	1.01 [0.98, 1.04]			Swapna Abhyankar,2012	79 644	152 910 10.	.2% 0.70	0 [0.52, 0.93]		
	Subtotal (95% CI)	54850	7	7964 1	00.0%	1.00 [0.97, 1.04]	t		Subtotal (95% CI)	4217	5466 100	.0% 0.82	2 [0.75, 0.90]	•	
	I otal events Heterogeneity: Tau ² = 0.0	7953 0: Chi² = 2.44 d	111/9 f = 5 (P = 0	78)· 1² =	= 0%				I otal events	994 N CHR - 3 53 - 4 - 3	14/8 /D = 0.47); 12 = 00/				
	Test for overall effect: Z =	0.29 (P = 0.78)	(0,0				Test for overall effect: 7 =	J; UIIF = 2.55, UI = 5 4 07 (D < 0.0001)	(P = 0.47), P = 0%				
	4.4.2								163(10) 0/6/8/ 6/160(.2 -	4.07 (1 < 0.0001)					
	Anzueto A. 2011	58 216	630	1995	25.2%	0.80 [0.58, 1.09]			1.3.3 severe obesity vs n	ormal					
	Diane M.D,2016	7 52	14	200	4.3%	2.07 [0.79, 5.42]			Alberda C, 2009	50 171	280 937 37.	.5% 0.97	7 [0.68, 1.39]		
	O'Brien, JM, 2006	29 131	173	544	15.8%	0.61 [0.39, 0.96]			Martino JL, 2011	122 524	409 1772 53.	.0% 1.0	1 [0.80, 1.27]		
	Peter Pickkers.2013	359 2992	10259 7	4883 5	3.8% 50.8%	0.86 [0.20, 1.57]	=		Peake SL, 2007 Subtotal (95% CI)	6 54 749	31 129 9.	.5% 0.40	D [0.15, 1.01]		
	Subtotal (95% CI)	3445	7	7751 1	00.0%	0.82 [0.66, 1.00]	◆		Total events	178	720	.070 0.01	[0.07, 1.24]		
	Total events	458 2: Chi2 = 6 17 d	11096 f = 4 (P = 0	10)-12 -	- 25%				Heterogeneity: Tau ² = 0.03	3: Chi ² = 3.63. df = 2	(P = 0.16); I ² = 45%				
	Test for overall effect: Z =	1.92 (P = 0.06)	1 - 4 (F - 0	. 19), 1* =	- 33%				Test for overall effect: Z =	0.59 (P = 0.55)	,, <i>p</i>				
	1.1.4 underweight vs noi Anzueto A 2011	60 184	630	1995	18.0%	1 05 (0 76 1 45)	_ _		1.3.5 underweight vs nor	mal					
	Diane M.D,2016	4 18	14	200	1.5%	3.80 [1.10, 13.08]		→	Alberda C, 2009 Rooko SL 2007	103 289	280 937 62.	.6% 1.30 20 0.91	0 [0.98, 1.72]		
	O'Brien, JM, 2006	34 88	173	544	9.7%	1.35 [0.85, 2.15]			Swanna Ahhvankar 2012	43 185	152 910 33	.3% 0.6. 1% 1.5	3 [0.29, 2.41] 1 [1 03 2 21]		
	Peake SL, 2007 Peter Pickkers 2013	6 24 855 5343	20	129 4883 (2.1% 68.7%	1.82 [0.64, 5.14]			Subtotal (95% CI)	498	1976 100	.0% 1.34	[1.07, 1.67]	•	
	Subtotal (95% CI)	5657	7	7751 1	00.0%	1.22 [1.04, 1.42]	◆		Total events	151	463				
	Total events	959 1: Chi2 = 4.96	11096	201-12 -	- 100/				Heterogeneity: Tau ² = 0.00); Chi ² = 1.19, df = 2	(P = 0.55); I ² = 0%				
	Test for overall effect: Z =	2.49 (P = 0.01)	1 – 4 (P – U	.30); 1	- 10%				Test for overall effect: Z =	2.60 (P = 0.009)					
						_							+		-+
							0.2 0.5 1 2 5						0.	1 0.2 0.5 1 2 5	10
							Favours (experimental) Favours (control)							Favouis (cyperimental) Favouis (control)	
		Experimenta	Con	trol		Odds Ratio	Odds Ratio			Experimental	Control	Od	ds Ratio	Odds Ratio	
B	Study or Subgroup	Experimenta Events To	l Cont tal Events	trol 5 Total	Weight	Odds Ratio M-H. Random, 95% CI	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup	Experimental Events Tota	Control Events Total W	Od Veight M-H. R	ds Ratio andom. 95% CI	Odds Ratio M-H. Random. 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal	Experimenta Events To	I Cont tal Events	trol <u>5 Total</u>	Weight	Odds Ratio M-H. Random. 95% CI	Odds Ratio M-H. Random, 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011	Experimental Events Tota 263 792	Control <u>Events Total W</u> 708 1995 2	Od <u>Veight M-H. R</u> 21.2% 0	ds Ratio andom. 95% Cl	Odds Ratio M-H, Random, 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012	Experimenta Events To 134 2	I Cont t <u>al Events</u> 38 151	trol <u>5 Total</u> 213	Weight 30.7%	Odds Ratio M-H. Random, 95% CI 0.53 [0.36, 0.78]	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011 Diane M.D,2016 Morris 6, 2007	Experimental Events Tota 263 792 25 216	Control Events Total W 708 1995 : 27 200 122 201	Od Veight M-H. R 21.2% 0 2.9% 0	ds Ratio andom. 95% Cl .90 [0.76, 1.08] .84 [0.47, 1.50] .88 [0.47, 1.50]	Odds Ratio M-H. Random. 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007	Experimenta Events To 134 2 31	I Coni tal Events 38 151 75 51	trol <u>5 Total</u> 213 129	Weight 30.7% 19.4%	Odds Ratio M-H, Random, 95% CI 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 (0.40 0.681	Odds Ratio M-H, Random, 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011 Diane M.D.2016 Morris AE, 2007 O'Brien, JM, 2006	Experimental Events Tota 263 793 25 216 58 18 99 326	Control Events Total W 708 1995 2 27 200 122 301 223 544	Odi Veight M-H. R 21.2% 0 2.9% 0 6.1% 0 9.9% 0	ds Ratio andom, 95% CI .90 [0.76, 1.08] .84 [0.47, 1.50] .68 [0.46, 1.00] .63 [0.47, 0.84]	Odds Ratio M-H. Random. 35% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtratal (PSK CI)	Experimenta Events To 134 2 31 231 11 14	I Coni tal Events 38 151 75 51 06 542	trol <u>5 Total</u> 213 129 1720 2062	Weight 30.7% 19.4% 49.9% 100.0%	Odds Ratio M-H, Random, 95% Cl 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.65 [0.46, 0.68]	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011 Diane M.D.2016 Morris AE, 2007 O'Brien, J.M. 2006 Peter Pickkers, 2013	Experimental Events Tota 263 790 25 216 58 180 99 326 3432 18999	Control Events Total W 708 1995 2 27 200 122 301 223 544 15576 74883 2 200	Odi Veight M-H. R 21.2% 0 2.9% 0 6.1% 0 9.9% 0 52.1% 0	ds Ratio andom. 95% CI .90 [0.76, 1.08] .84 [0.47, 1.50] .68 [0.46, 1.00] .63 [0.47, 0.84] .84 [0.81, 0.87]	Odds Ratio	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (95% Cl) Total events	Experimenta Events To 134 2 31 231 11 14 396	I Cont tal Events 38 151 75 51 06 542 19 744	trol 213 129 1720 2062	Weight 30.7% 19.4% 49.9% 100.0%	Odds Ratio <u>M-H, Random, 95% Cl</u> 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.63 [0.46, 0.86]	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011 Diane M.D, 2016 Morris AE, 2007 O'Brien, JM, 2006 Peter Fickkers, 2013 Swapna Abhyankar, 2013 Subtotal (9%, CI)	Experimental Events Tota 263 793 25 216 58 183 99 321 3432 18996 2 57 543 21065 21065	Control Events Total W 708 1995 : 27 200 122 301 223 544 15576 74883 ! 15576 74883 ! 78722 10	Odi 21.2% 0 2.9% 0 6.1% 0 9.9% 0 9.9% 0 7.8% 0 00.0% 0.	ds Ratio andom. 95% Cl .90 [0.76, 1.08] .84 [0.47, 1.50] .68 [0.46, 1.00] .63 [0.47, 0.84] .64 [0.81, 0.87] .68 [0.48, 0.95] .80 [0.73, 0.89]	Odds Ratio M-H. Random, 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (95% Cl) Total events Heteropreneity: Tair ² = 0.04	Experimenta <u>Events</u> To 134 2 31 231 11 14 396 Chi ² = 4.54 df	I Cont tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0	trol 213 129 1720 2062	Weight 30.7% 19.4% 49.9% 100.0%	Odds Ratio M-H. Random. <u>95% Cl</u> 0.53 (0.36, 0.78) 1.08 (0.60, 1.92) 0.57 (0.48, 0.68) 0.63 (0.46, 0.86)	Odds Ratio M-H. Random, 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011 Diane M. Q2016 Morris AE, 2007 O'Brien, JM, 2006 Peter Pickkers, 2013 Swapna Abhyankar, 2013 Subtotal (95% CI) Total evvents Materconsecht: Total = 0.	Experimental Events Tota 263 793 25 214 58 183 99 324 3432 1899 2 57 544 21065 3934 0 0 ba 7 13 df =	Control Events Total W 708 1995 1 27 200 122 301 223 544 15576 74883 2 117 789 78722 11 16773 16773	Od <u>Veight M-H. R</u> 21.2% 0 2.9% 0 6.1% 0 9.9% 0 9.9% 0 0.7.8% 0 00.0% 0.	ds Ratio andom, <u>95% Cl</u> .90 [0.76, 1.08] .84 [0.47, 1.50] .68 [0.46, 1.00] .63 [0.47, 0.84] .84 [0.81, 0.84] .68 [0.48, 0.95] .80 [0.73, 0.89]	Odds Ratio M-H. Random, 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar, 2012 Subtotal (95% Cl) Total events Heterogeneily: Tau ² = 0.04 Test for overall effect. Z = 1	Experimenta <u>Events</u> To 134 2 31 231 11 14 396 ; Chi ² = 4.54, df 2.88 (P = 0.004)	I Cont tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0.1	trol 213 129 1720 2062 10); ² = 5	Weight 30.7% 19.4% 49.9% 100.0%	Odds Ratio M-H. Random. 95% CI 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.63 [0.46, 0.86]	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup 1.4.1 obese vs normal Anzueto A, 2011 Diane ML, 2016 Morris AE, 2007 O'Brien, JM, 2006 Peter Pickders, 2013 Swapna Abhyankar, 2013 Subtotal (95% CI) Total events Heterogeneity: Tau ^a = 0. Test for overall effect Z	Experimental Events Tota 263 792 25 211 58 183 99 324 3432 1899 2 57 544 21065 3934 00: ChP = 7.13, df = 4.22 (P < 0.0001)	Control Events Total W 708 1995 : 27 200 122 301 122 301 122 301 122 301 125 7483 ! 1577 7483 ! 1577 7483 ! 16773 5 (P = 0.21); P = 30%	Odi <u>/eight M-H. R</u> 21.2% 0 2.9% 0 6.1% 0 59.9% 0 52.1% 0 7.8% 0 00.0% 0. 5	ds Ratio andom. <u>95% Cl</u> .90 (0.76, 1.08] .84 (0.47, 1.50) .68 (0.46, 1.00] .63 (0.47, 0.84] .63 (0.47, 0.84] .84 (0.81, 0.87] .68 (0.48, 0.95] .80 [0.73, 0.89]	Odds Ratio	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (95% Cl) Total events Heterogeneily: Tau ² = 0.04 Test for overall effect: Z = 2	Experimenta <u>Events</u> To 134 2 31 231 11 14 396 4; Chi ² = 4.54, df 2.88 (P = 0.004)	I Coni tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0.	trol 213 129 1720 2062 10); I ² = 5	Weight 30.7% 19.4% 49.9% 100.0%	Odds Ratio M-H. Random. 95% Cl 0.53 (0.36, 0.78) 1.08 (0.60, 1.92) 0.57 (0.48, 0.68) 0.63 (0.46, 0.86)	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup 1.4.1 obese vs. normal Anzusto A, 2011 Diane M.D.2016 Morris AE, 2007 O'Brien, JM, 2006 Peter Pickkers, 2013 Subtotal (95% CI) Total event Heterogeneity: Tau ² = 0. Test for overall effect. Z 1.4.2 overweicht vs. no	Experimental <u>Events</u> Tota 263 79; 25 211 58 18; 99 32; 3432 1899 2 57 54; 3934 00; ChP = 7, 13, df = 4,22 (P < 0.0001) rmal	Control Events Total W 708 1995 : 27 200 122 301 223 544 15576 74883 ! 16773 5 (P = 0.21); P = 30%	Odi 21.2% 0 2.9% 0 6.1% 0 9.9% 0 52.1% 0 00.0% 0. 6	ds Ratio andom, <u>95% C1</u> .90 [0.76, 1.08] .84 [0.47, 1.50] .68 [0.46, 1.00] .63 [0.47, 0.84] .84 [0.81, 0.87] .88 [0.48, 0.95] .80 [0.73, 0.89]	Odds Ratio M-H. Random. 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (9% C(1) Total events Heterogeneity: Tau ² = 0.04 Test for overall effect: Z = 7 1.2.2 overweight vs norm	Experimenta Events To 134 2 31 231 11 14 396 I; Chi ² = 4.54, df 2.88 (P = 0.004) tal	I Coni tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0.	trol 213 129 1720 2062 10); I ² = 5	Weight 30.7% 19.4% 49.9% 100.0%	Odds Ratio M-H. Random. <u>95% C1</u> 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.63 [0.46, 0.86]	Odds Ratio M-H, Random, 95% Cl	— D	Study or Subgroup 1.4.1 obses vs normal Arzueto A. 2011 Dane M.2016 Morra AE.2007 O'Brien, M.2006 Peter Picksms,2013 Subbral (95%, CI) Todal events Heterogeneity: Tau'= 0 1.4.2 overweight vs no Arzueto A. 2011	Experimental <u>Events</u> Tota 263 79; 25 211 58 18; 99 32; 3432 1899 2 57 54; 3934 00 ChP = 7.13, df = = 4.22 (P < 0.0001) rmal 655 178°	Control Events Total W 708 1995 : 27 200 122 301 122 301 15576 7483 5 (P = 0.21); P = 30% 708 1995 :	Odd <u>Veight M-H.R</u> 2.1.2% 0 2.9% 0 2.9% 0 6.1% 0 9.9% 0 5.21% 0 0.0% 0. 5 24.7% 1	ds Ratio andom. 95% C1 90 (0.76, 1.06) 84 (0.47, 1.50) 68 (0.46, 1.00) 63 (0.47, 0.84) 84 (0.47, 0.84) 84 (0.47, 0.85) 80 (0.73, 0.89) 0.6 (0.93, 1.21)	Odds Ratio M-H Random 95% Cl	
B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04 Test for overall effect: Z = ; 1.2.2 overweight vs norm O'Brien JM Jr, 2012	Experimenta Events To 134 2 31 231 11 14 396 1; Chi ² = 4.54, df 2.88 (P = 0.004) nal 78 1	I Coni tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0. 29 151	trol 213 129 1720 2062 10); ² = 5 213	Weight 30.7% 19.4% 49.9% 100.0% 56%	Odds Ratio <u>M-H, Random, 95% C1</u> 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.63 [0.46, 0.86] 0.63 [0.40, 1.00]	Odds Ratio M-H. Random. 95% Cl	— D	Study or Subgroup 1.4.1 obses vs normal Anzueto A, 2011 Dane MD, 2016 Morris AE, 2007 O'Bien, MJ, 2006 Peter Pickers, 2013 Swapan, Abhyaniaz, 2013 Subtotal (BYC, Tauli * C) Total events Heteropeneing Tsuli * C) Total events Heteropeneing the single state Anzueto A, 2017 Dane MD, 2016 Merris AE, 2007	Experimental Events Tota 263 79; 25 21; 58 18; 99 32; 3432 1899; 2 57 54; 2 1065 3934 00; Chi ^a = 7.13, df = 4.22 (P < 0.0001) rmal 655 178; 31 24; 87 23;	Control Events Total W 708 1995 : 27 200 122 301 122 301 15576 7484 9 117 789 78722 11 16773 5 (P = 0.21); P = 30% 708 1995 : 27 200	Od 21.2% 0 2.9% 0 6.1% 0 9.9% 0 52.1% 0 52.1% 0 0.00% 0 6 24.7% 1 2.2% 0 66% 0	ds Ratio andom. <u>95% C1</u> .90 (0.76, 1.08) .84 (0.47, 1.50) .68 (0.46, 1.00) .68 (0.48, 0.87) .68 (0.48, 0.87) .68 (0.48, 0.95) .68 (0.48, 0.95) .06 (0.93, 1.21) .91 (0.52, 1.58) .85 (0.61, 21)	Odds Ratio M-H. Random 35% Cl	
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B	Study or Subgroup 1.2.1 obese vs normal O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.04 O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar,2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 3	Experimentat Events To 134 2 31 231 11 231 11 44 396 ; Chi ² = 4.54, of 2.88 (P = 0.004) 14 78 1 274 12 14 408 ; Chi ² = 1.76, of 5.38 (P < 0.0000)	I Cont tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0. 29 151 51 51 03 542 83 744 = 2 (P = 0. 1)	trol 213 129 2162 2062 10); l ² = { 213 129 213 129 213 2062 213 2062 213 2062 213 209 2062 213 209 2062 213 209 2062 213 209 2002 20	Weight 30.7% 19.4% 49.9% 100.0% 56% 10.7% 9.7% 79.6% 100.0% 0%	Odds Ratio <u>M-H. Random. 95% CI</u> 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.63 [0.46, 0.86] 0.63 [0.40, 1.00] 0.90 [0.56, 1.46] 0.64 [0.54, 0.76] 0.66 [0.57, 0.77]	Odds Ratio M-H. Random. 95% CI	— D	Study or Subgroup 1.4.1 obses vs normal Arzuto A, 2011 Dane M. 2016 Morris AE. 2007 O'Bien, M. 2006 Pater Pickers 2013 Swappa Achymatriz 2013 Dane M. 2016 Morris AE. 2007 O'Bien, M. 2016 Morris AE. 2007 Morris AE. 2007 Morr	Experimental Events Tota 283 79; 25 21; 99 32; 432 1999 200, CNF = 71, dir 2105 3034 2105 300, CNF = 71, dir 210, CNF = 71, dir 665 176; 31 244 29; 10376 11036 55, dir 11047 = 58, dir = 1, 79 (P = 0.07)	Control Events Total W 2 708 1995 ; 122 201 122 201 122 201 123 544 117 799 7677 3722 11 16773 7822 11 16773 7822 21 16773 7822 21 16773 782 20 16773 782 20 16576 7483 25 102 23 544 115576 7483 545 115576 7483 545 115576 7483 545 115776 7485 115776 7485 115776 115776 7485 115776 115776 115776 115776 1157776 1157776 11577777777777 1157777777777777777777	Odd Keight M-H R 21.2% 0 2.2% 0 2.9% 0 5.2% 0 5.2% 0 5.2% 0 7.8% 0 000.0% 0. 5 24.7% 1 2.9% 0 6.5% 0 24.7% 1 2.9% 0 6.5% 0 0.0% 0 6.5% 0 6.5% 0 0.0% 0 6.5% 0 0.0% 0 6.5% 0 0.0% 0 0.	da Ratio andom. 95% CI .90 [0.76, 1.08] .48 (0.47, 1.50) .68 [0.48 (1.07) .68 [0.48, 1.08] .68 [0.48, 0.98] .68 [0.48, 0.48] .58 [0.69, 1.21] .58 [0.69, 1.21] .58 [0.61, 1.04] .59 [0.48, 0.54] .57 [0.48, 0.54] .57 [0.48, 1.17]	Odds Ratio	
B	Study or Subgroup 1.2.1 obese vs normal O'Bien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar, 2012 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.04 Test for overall effect: Z = 1 1.2.2 overweight vs norm O'Brien JM Jr, 2012 Peake SL, 2007 Swapna Abhyankar, 2012 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1	Experimenta Events To 134 2 31 231 11 14 396 ; Chi ^p = 4.54, df 2.88 (P = 0.004) al 78 1 56 1 274 12 14 408 ; Chi ^p = 1.76, df 5.38 (P < 0.0000	I Coni tal Events 38 151 75 51 06 542 19 744 = 2 (P = 0. 29 151 51 51 03 542 83 744 = 2 (P = 0. 1)	trol 213 129 2162 2062 10); l ² = { 213 129 2062 10); l ² = { 213 129 2062 213 209 2062 213 209 209 209 209 209 209 209 209	Weight 30.7% 19.4% 49.9% 100.0% 56% 10.7% 9.7% 79.6% 100.0% 0%	Odds Ratio M-H. Random. <u>95% C1</u> 0.53 [0.36, 0.78] 1.08 [0.60, 1.92] 0.57 [0.48, 0.68] 0.63 [0.46, 0.86] 0.63 [0.40, 1.00] 0.90 [0.56, 1.46] 0.64 [0.54, 0.76] 0.66 [0.57, 0.77]	Odds Ratio M-H. Random, 95% Cl	— D	Study or Subgroup. 1.4.1 obses vs normal Anzuto A, 2011 Dane MD, 2016 Morris AE, 2007 O'Brin, M, 2006 Subpara Advantaz, 2013 Subpara Advantaz, 2013 Subpara Advantaz, 2013 Todal oversits Todal oversits Test for oversital effect. 2 1.4.2 overweight vs no Dane MD, 2016 Morris AE, 2007 O'Brin, M, 2016 Morris AE, 2007 O'Brin, M, 2016 Morris AE, 2007 O'Brin, M, 2012 O'Brin, M, 2013 Morris AE, 2007 O'Brin, M, 2014 Morris AE, 2007 O'Brin, M, 2015 Todal oversits Heterogeneing), Tau ² = 0 Test for overall effect. 2 1.4 Servere obesity vs	Experimental Events Tota Events Tota 283 79; 25 21; 381 42; 393 432 1959; 3934 21965; 3934 221965; 3934 221965; 3934 22196; 3934 2219; 3934 2219; 393	Control Events Total W For the second	Odd Keight M-H R 21.2% 0 2.2% 0 2.2% 0 6.1% 0 0.5% 0 5.21% 0 7.8% 0 0.0% 0 5.4% 0 10.3% 0 4.4% 0 10.3% 0 4.4% 0 0.0% 0 5.4% 0	ds Ratio andom, 95% CI 90 (0.76, 1.60) 84 (0.47, 1.50) 63 (0.47, 0.48) 84 (0.81, 0.87) 63 (0.48, 0.88) 86 (0.48, 0.36) 86 (0.48, 0.36) 80 (0.73, 0.88) 90 (0.73, 0.88) 91 (0.52, 1.58) 88 (0.60, 1.21) 7.7 (0.48, 1.51) 89 (0.92, 1.74) 89 (0.92, 1.64) 91 (0.48, 0.94) 91 (0.48, 1.04)	Odds Ratio	
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Fig 3. Association of obesity and mortality in in mechanical ventilation patients in ICU. (A) ICU mortality. (B) long-term mortality. (C) short-term mortality. (D) hospital mortality.

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non-obese patients (MD -0.06, 95% CI -0.52 0.63, Z = 0.19, P = 0.85, $I^2 = 80\%$, <u>S2E Fig</u>). A sensitivity analysis eliminating the studies that did not report mean and standard deviation did not change the findings. Hospital LOS did not differ among different BMI categories (S2F Fig).

Discussion

Obesity is a risk factor of death in the general population [36]. The current meta-analysis showed that, in comparison to subjects with normal BMI, obese ICU patients receiving mechanical ventilation had lower measures of mortality rate (ICU, hospital, short-term as well as long-term). Several factors may have attributed to the "obesity paradox" in this population. First, adipose tissue is considered to be an ancestral immune organ [37], and could secrete leptin, adiponectin and many other biological response modifiers [38]. Leptin is a critical component of the host defense in the lungs [39]. Adiponectin produces anti-inflammatory effects through acting on inflammatory cells, NF- κ B, and TNF- α , and could regulate inflammatory response, improve glucose tolerance and reduced vasopressor requirement in obese patients [40]. A recent study found that obese patients have lower levels of proinflammatory cytokines (IL-6, IL-8) and surfactant protein D, The lack of reduced mortality related to obesity might be due to low grade inflammatory response [41]. Second, both animal and human studies showed that adipocytes are infiltrated by activated macrophages under critical illnesses[41, 42]; these macrophages have important immune and scavenger functions, and produce an anti-inflammatory response. Third, obese patients have higher energy reservoir to counteract the influence by increased catabolic stress of disease [43]. Lastly, obese patients might have a lower threshold for ICU admission due to heightened perception of by doctors and nurses [20].

In the current study, underweight subjects had higher hospital mortality than those with normal BMI. Contributing factors may include insufficient energy stores to maintain organ function during times of critical illness and weak immune response to challenges due to poor nutritional status. A previous prospective study suggested low BMI as a potential marker for the underlying chronic diseases, such as cancer [44]. However, the increased risk of mortality reported in patients with a low BMI could also reflect illness-related weight loss or other serious illnesses before hospitalization [45].

Consistent with a previous study [46], duration on mechanical ventilation was longer in obese patients than in non-obese patients in the current study. Several reasons might have contributed to this finding. First, obese patients have decreased lung and chest wall compliance, and are more susceptible to atelectasis or increased alveolar tension [47]. Obese patients also tend to have ventilation flow imbalance, and lower functional residual and lung volume [48]. Second, obese patients consume more oxygen and produce more carbon dioxide production [49,50], and thus have increased respiratory work. Abdominal visceral fat accumulation could also increase abdominal pressure and thus increased respiratory work [51,52]. which were easy to cause respiratory muscle fatigue and difficult weaning. Third, clinicians often overestimate lung size for obese patients, and tend to use higher tidal volumes, thus placing patients on risk to develop ventilator-associated lung injury [21].

We also found significantly longer ICU LOS in obese patients than in non-obese patients. This could have been due to prolonged duration of mechanical ventilation in ICU, or higher rate of ICU complications, especially sepsis and pneumonia [14]. Also, nursing is particularly difficult in obese patients, and could lead to increased risks of skin laceration and other complications [53].

The current study has several limitations. First, assessment of BMI in the included studies could have been biased by resuscitation fluids given prior to ICU admission. Also, the height

and weight of patients admitted into ICU typically estimated by physician rather than actually measured. Second, statistical heterogeneity in our analysis showed that the differences in outcomes might be explained by other characteristics not BMI, especially for length of stay (LOS) in hospital. Third, many confounding factors, including age, sex, and complications, could not be accurately extracted from the original studies. It must be emphasized that the results from the current study are based on ICU patients receiving mechanical ventilation. Similar results also occurred in obesity patients in ICU, Hogue [54] reported that obesity in ICU was associated with lower hospital mortality, but not associated with increased risk for ICU mortality. Extrapolation into other population must be cautious. Previous studies by Calle in the US [55] and Faeh in Switzerland [56] showed that obesity is associated with excess risk of mortality in adults, mainly due to complications, such as cardiovascular diseases and cancer. The existence of "obesity paradox" remains debated, and further studies are needed to determine whether adding BMI would decrease risk of mortality.

Conclusion

In summary, compared to subjects with normal BMI, obese ICU subjects receiving mechanical ventilation had lower ICU and hospital mortality. There were also some evidence for lower short or long-term mortality. Obese patients had longer duration of mechanical ventilation and ICU LOS than non-obese patients.

Supporting information

S1 Text. MEDLINE search strategy. (PDF)

S1 Fig. Funnel plots. (A) duration of mechanical ventilation.(B) ICU length of stay. (C) hospital length of stay. (PDF)

S2 Fig. Figures of duration of mechanical ventilation, ICU LOS and hospital LOS. (A) duration of mechanical ventilation in the obese vs non-obese patients.(B) duration of mechanical ventilation of different BMI classification.(C) ICU LOS of obese vs non-obese patients.(D) ICU LOS of different BMI classification.(E) hospital LOS of obese vs non-obese patients.(F) hospital LOS of different BMI classification. (PDF)

S1 Table. Quality assessment scale of included articles. (PDF)

S2 Table. PRISMA checklist. (PDF)

Author Contributions

Conceptualization: Yonghua Zhao, Zhiqiang Li. Data curation: Yonghua Zhao, Zhiqiang Li. Formal analysis: Yonghua Zhao, Zhiqiang Li. Funding acquisition: Xiuming Xi. Investigation: Yonghua Zhao, Zhiqiang Li, Xiuming Xi. Methodology: Yonghua Zhao, Zhiqiang Li, Xiuming Xi.

Project administration: Xiuming Xi.

Resources: Tao Yang, Meiping Wang.

Software: Tao Yang, Meiping Wang.

Supervision: Xiuming Xi.

Validation: Yonghua Zhao, Zhiqiang Li, Tao Yang, Meiping Wang, Xiuming Xi.

Visualization: Yonghua Zhao, Zhiqiang Li, Tao Yang, Meiping Wang, Xiuming Xi.

Writing - original draft: Yonghua Zhao, Zhiqiang Li, Xiuming Xi.

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