Effect of obesity on intensive care morbidity and mortality: A meta-analysis*

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Objective: To evaluate the effect of obesity on intensive care unit mortality, duration of mechanical ventilation, and intensive care unit length of stay among critically ill medical and surgical patients.

Design: Meta-analysis of studies comparing outcomes in obese (body mass index of ≥30 kg/m^2) and nonobese (body mass index of <30 kg/m^2) critically ill patients in intensive care settings.

Data Source: MEDLINE, BIOSIS Previews, PubMed, Cochrane library, citation review of relevant primary and review articles, and contact with expert informants.

Setting: Not applicable.

Patients: A total of 62,045 critically ill subjects.

Interventions: Descriptive and outcome data regarding intensive care unit mortality and morbidity were extracted by two independent reviewers, according to predetermined criteria. Data were analyzed using a random-effects model.

Measurements and Main Results: Fourteen studies met inclusion criteria, with 15,347 obese patients representing 25% of the pooled study population. Data analysis revealed that obesity was not associated with an increased risk of intensive care unit mortality (relative risk, 1.00; 95% confidence interval, 0.86–1.16; $p = .97$). However, duration of mechanical ventilation and intensive care unit length of stay were significantly longer in the obese group by 1.48 days (95% confidence interval, 0.07–2.89; $p = .04$) and 1.08 days (95% confidence interval, 0.27–1.88; $p = .009$), respectively, compared with the nonobese group. In a subgroup analysis, an improved survival was observed in obese patients with body mass index ranging between 30 and 39.9 kg/m^2 compared with nonobese patients (relative risk, 0.86; 95% confidence interval, 0.81–0.91; $p < .001$).

Conclusion: Obesity in critically ill patients is not associated with excess mortality but is significantly related to prolonged duration of mechanical ventilation and intensive care unit length of stay. Future studies should target this population for intervention studies to reduce their greater resource utilization. (Crit Care Med 2008; 36:151–158)

Key Words: intensive care unit; obesity; body mass index; mortality; length of stay; mechanical ventilation

Obesity is a chronic disease and a major health problem due to its causal relationship with serious medical diseases, increased morbidity and mortality, and substantial economic effect. According to the World Health Organization, the prevalence of obesity has been steadily increasing worldwide (1, 2). The estimated mortality attributable to obesity alone among U.S. adults is approximately 300,000 annually (3), and the direct costs associated with this disease are reported to represent 5.7% of the National Health expenditure in the United States (4).

Obesity is characterized by a series of physiologic changes that may impair the ability to adapt to the stresses of critical illness. The presence of diabetes, cardiovascular strains, and respiratory dysfunction poses significant challenges that may affect intensive care unit (ICU) survival. However, the influence of obesity on outcomes among critically ill patients remains a focus on controversy. Some studies looking at ICU outcome and obesity showed increased mortality and morbidity (5–11), whereas others showed either a decrease (12–17) or no association (18–22). Because of the heterogeneity among these studies, we performed a meta-analysis of published studies to investigate the association between obesity and ICU outcome and to determine whether there is a dose-response effect of elevated body mass index (BMI) on ICU mortality.

MATERIALS AND METHODS

Search Strategy. This study was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (23). We searched MEDLINE (1966 to February 2007), BIOSIS Previews (1990 to February 2007), PubMed (mid 1960s to February 2007), Embase (January 1990 to February 2007), and Cochrane Library, without any language restriction, using relevant text words and search terms to identify articles containing at least one of the following key words: obesity, body mass index, mortality, intensive care unit, or trauma. Close scrutiny and hand searches through cited references of identified articles were undertaken. Abstracts of conference proceedings from meetings of relevant medical societies were perused, and we communicated electronically with some listed authors of studies reviewed, for clarification and retrieval of reported and unreported but presumed relevant data. The Institutional Review Board has waived the need for approval or informed consent.

Study Selection and Data Extraction. Inclusion criteria were studies comparing obese with nonobese critically ill patients admitted to an ICU. Obesity was defined according to

*See also p. 369.

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The authors have not disclosed any potential conflicts of interest.

Supported, in part, by Research for Health in Erie County, Buffalo, NY.

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DOI: 10.1097/01.CCM.0000297885.60037.6E

Table 1. Characteristics of studies included in the meta-analysis

First Author (Reference No.)	Year	Study Design	No. of Obese/Total Patients (%)	Study Population	Obesity Associated with Mortality
El Solh et al. (5)	2001	Retrospective	117/249 (47)	MICU	Y
Bochicchio et al. (11)	2006	Prospective	62/1167 (5)	Trauma ICU	Y
Nasraway et al. (10)	2006	Retrospective	366/1373 (27)	SICU	Y
Brown et al. (9)	2005	Retrospective	283/1153 (25)	Trauma ICU	Y
Bercault et al. (7)	2004	Prospective	170/340 (50)	MICU/SICU	Y
Neville et al. (8)	2004	Retrospective	63/242 (26)	Trauma ICU	Y
Aldawood et al. (17)	2007	Prospective	540/1835 (29)	Mixed ICU	N
Peake et al. (21)	2006	Prospective	129/433 (30)	MICU/SICU	N
Alban et al. (15)	2006	Retrospective	135/918 (15)	Trauma ICU	N
O'Brien et al. (16)	2006	Retrospective	457/1488 (31)	Mixed ICU	N
Garrouste-Orgeas et al. (13)	2003	Prospective	227/1698 (13)	Mixed ICU	N
Ray et al. (18)	2005	Prospective	550/2148 (26)	MICU	N
Morris et al. (22)	2007	Prospective	237/825 (29)	MICU	N
Marik et al. (14)	2003	Retrospective	12011/48176 (25)	Mixed ICU	N

MICU, medical intensive care unit; Y, yes; N, no; ICU, intensive care unit; SICU, surgical intensive care unit.

the National Heart, Blood, and Lung Institute's (NHBLI) published guidelines (24) based on BMI. We excluded noncomparative studies and studies conducted outside an ICU setting. We excluded also studies that utilized the same patient population, including only the study with the most number of patients from the same data set.

The primary outcome was ICU mortality. ICU length of stay (LOS) and duration of mechanical ventilation were included as secondary outcomes when available. We contacted authors of the primary articles with missing data as necessary.

Study Quality. Two reviewers independently rated each study's quality. Because there are no validated tools for quality assessment of outcome studies, we adapted the McMaster criteria for evaluating the validity of studies about prognosis (25). Studies were assessed for presence of five features: description of patient sample characteristics, description of inclusion and exclusion criteria, potential selection bias, definition of outcomes at the start of the study, and objectivity of outcomes. The intraclass correlation coefficient for agreement between the two raters on overall quality rating for all included studies was 0.85. Disagreements were resolved by consensus.

Data Synthesis and Statistical Analysis. Data extracted from the selected studies included: 1) the total number of obese (BMI $\geq$30 kg/m^2) and nonobese patients (BMI $<$30 kg/m^2) in each study, 2) mortality rate, 3) ICU LOS, and 4) duration of mechanical ventilation. Data were analyzed for the various BMI classes whenever reported by investigators. In studies in which only a range for LOS or duration of mechanical ventilation was reported, we calculated estimates of the SD using the Hurlburt's range method (26) to ensure uniformity of data recording.

Meta-analysis was performed using Revman 4.2.9 (Cochrane collaboration, Oxford, UK). Data were pooled using the random-effects model of DerSimonian and Laird (27) to account for both within-study and between-study variations. The pooled effect estimate for ICU mortality was expressed as relative risk (RR) with 95% confidence intervals (CIs), whereas LOS and duration of mechanical ventilation were expressed as mean differences with 95% CIs. Differences in outcomes estimates between the obese and nonobese groups were tested using a two-sided z test with statistical significance set at $p < .05$.

We compared RR estimates of mortality for all subgroups of patients using a two sided z test on the log RRs and expressed as ratio of RRs with its 95% CI. We also derived a curvilinear relationship using a polynomial distribution between BMI strata and RR of mortality (S-Plus 6.1, Insightful Co, Seattle, WA).

Statistical heterogeneity for all variables was assessed by using the I^2 measure (28). To evaluate for potential publication bias, we constructed a funnel plot for the primary outcome, and we carried out the Begg's rank correlation tests as previously reported (29).

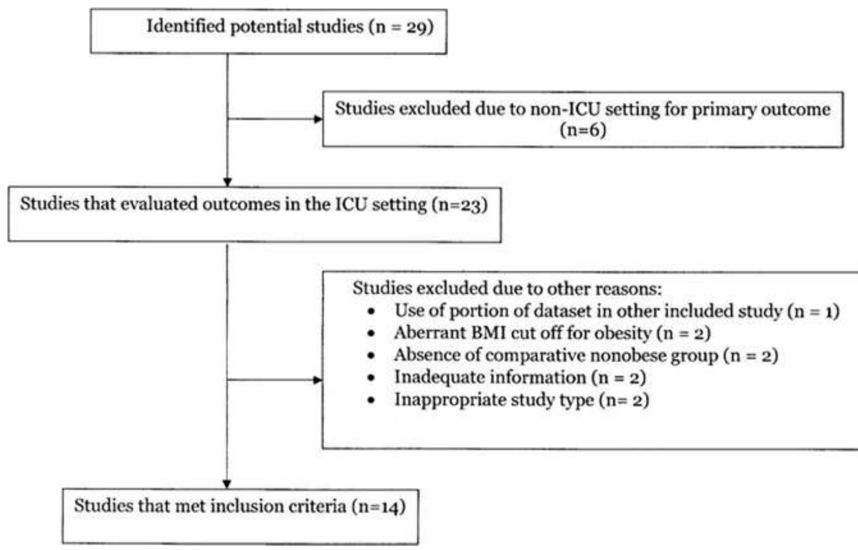

Figure 1. Flow diagram of literature search and study selection process. *ICU*, intensive care unit; *BMI*, body mass index.

RESULTS

The iterative literature search initially retrieved 29 potential relevant studies. Using the prespecified inclusion criteria, an abstract review rejected six references (19, 20, 30–33), yielding 23 studies candidate for possible inclusion in the meta-analysis. Nine studies were subsequently eliminated after a full article review (6, 12, 34–39, 40). Fourteen studies met eligibility criteria established *a priori* (Table 1). Figure 1 depicts our literature search and study selection process. Seven studies were prospective and seven were retrospective in design. Eight studies (10, 13–15, 17, 18, 21, 22) stratified outcomes based on BMI categories of $<$18.5, 18.5–24.9, 25–29.9, 30–34.9, 35–39.9, and $\geq$40 kg/m^2.

Table 2. Quality ratings of included studies

Study, Authors (Reference No.)	Description of Patient Sample Characteristics	Description of Inclusion/Exclusion Criteria	Potential Selection Bias	Definition of Outcomes at the Start of the Study	Objectivity of Outcomes	Total
Alban et al. (15)	1	1	1	0	1	4
Aldawood et al. (17)	1	1	1	1	1	5
Bercault et al. (7)	1	1	0	1	1	4
Bochicchio et al. (11)	1	0	0	1	1	3
Brown et al. (9)	0	0	0	1	1	2
Garrouste-Orgeas et al. (13)	1	0	0	0	1	2
El Solh et al. (5)	1	1	1	1	1	5
Marik et al. (14)	1	0	1	1	1	4
Morris et al. (22)	1	0	1	1	1	4
Nasraway et al. (10)	1	0	0	1	1	3
Neville et al. (8)	1	0	1	1	1	4
O'Brien et al. (16)	1	0	1	1	1	4
Peake et al. (21)	0	0	1	1	1	3
Ray et al. (18)	1	1	0	1	1	4

1, listed; 0, not listed.

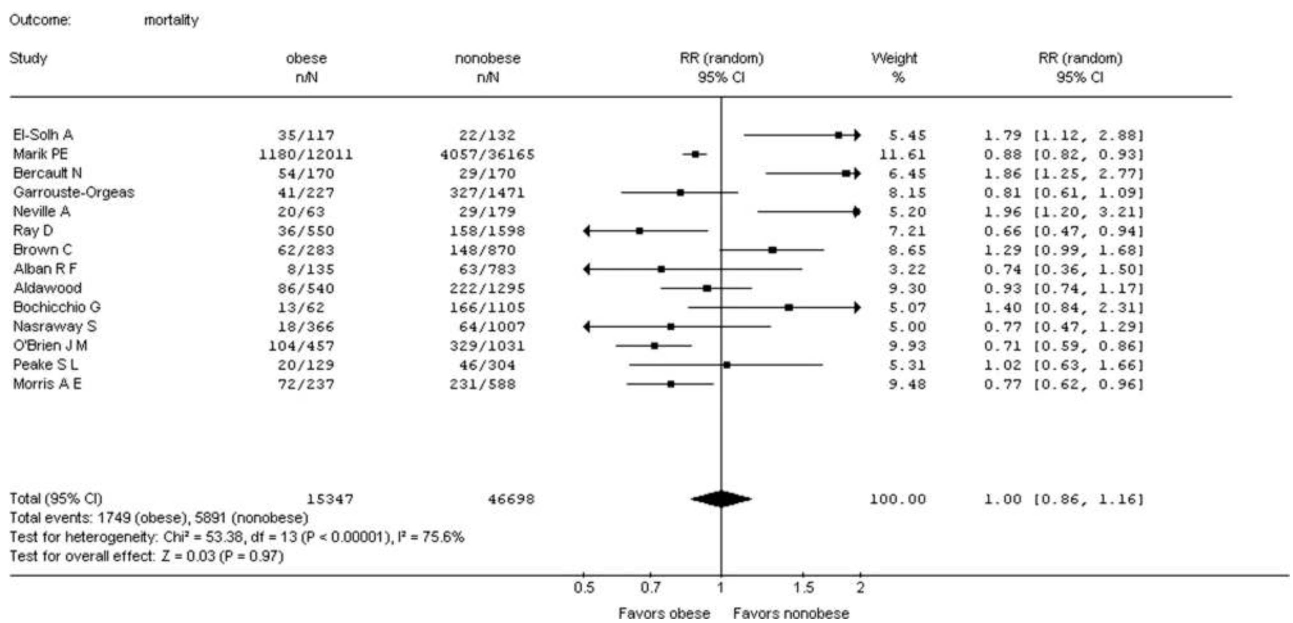

Figure 2. Forest plot examining the risk of intensive care unit mortality among obese vs. nonobese critically ill patients. *Horizontal lines* represent 95% confidence intervals (*CI*); *RR*, relative risk.

Overall quality ratings ranged from 2 to 5 (Table 2). Common quality problems included inadequately clear inclusion and exclusion criteria in nine studies, potential selection bias in eight studies, and problems with definition of outcomes at the start of the study in two studies.

A total of 62,045 unique subjects were included in the analysis. Of these, 15,347 were obese (BMI $\geq$30 kg/m^2) and 46,698 were nonobese (BMI <30 kg/m^2). Study populations included were well-characterized cohorts in the United States, Europe, Australia, and the Middle East. All patients were admitted to either a medical, surgical, or a mixed medical-surgical ICU. Table 1 illustrates the characteristics of the selected studies. The patients ranged in age from 40 $\pm$ 1.4 yrs to 65 $\pm$ 14 yrs. Indications for admission to the medical ICU varied widely, the most common being respiratory disorders: pneumonia, unspecified respiratory failure, and acute respiratory distress syndrome. Surgical ICU admissions were predominantly trauma-related cases. In the selected studies, severity of illness scores (Acute Physiology and Chronic Health Evaluation II [range, 18 $\pm$ 0.8 to 20.6 $\pm$ 12.2], Simplified Acute Physiology Score II [30.2 $\pm$ 17.9 to 43 $\pm$ 14], and Injury Severity Scores [21 $\pm$ 12 to 24.8 $\pm$ 12]) were comparable between the obese (BMI $\geq$30 kg/m^2) and nonobese groups (BMI <30 kg/m^2).

Overall Mortality. ICU mortality data for obese (BMI $\geq$30 kg/m^2) and nonobese patients (BMI <30 kg/m^2) were reported in all selected studies. There were 1,749 (11.4%) and 5,891 (12.6%) primary endpoint events (mortality) in the two groups, respectively. Pooled analysis of data from these 14 studies revealed no mortality difference between the obese and the nonobese group (RR, 1.00; 95% CI, 0.86–1.16; p = .97; I^2 = 75.6%) (Fig. 2). However, the obese group had a higher survival rate than the nonobese group (RR, 0.83; 95% CI, 0.74–0.92; $p < .001$) at time of hospital discharge (Fig. 3).

Duration of Mechanical Ventilation. Six studies reported on duration of mechanical ventilation (5, 9, 11, 17, 18, 22). The mean duration of mechanical ventilation in the obese group (BMI $\geq$30 kg/

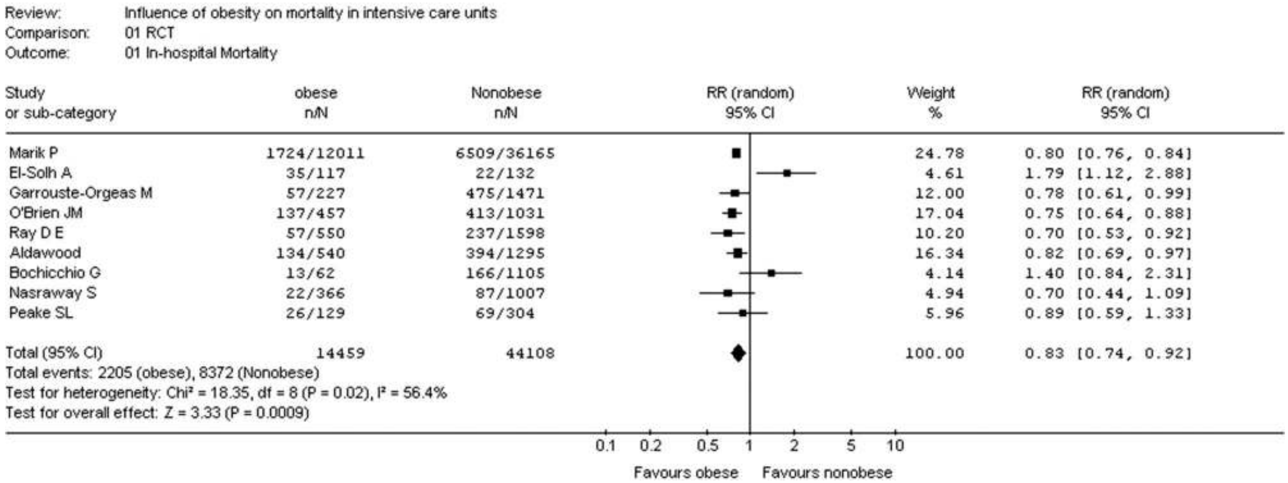

Figure 3. Forest plot examining the risk of hospital mortality among obese vs. nonobese critically ill patients. *Horizontal lines* represent 95% confidence intervals (*CI*). *RCT*, randomized controlled trial; *RR*, relative risk.

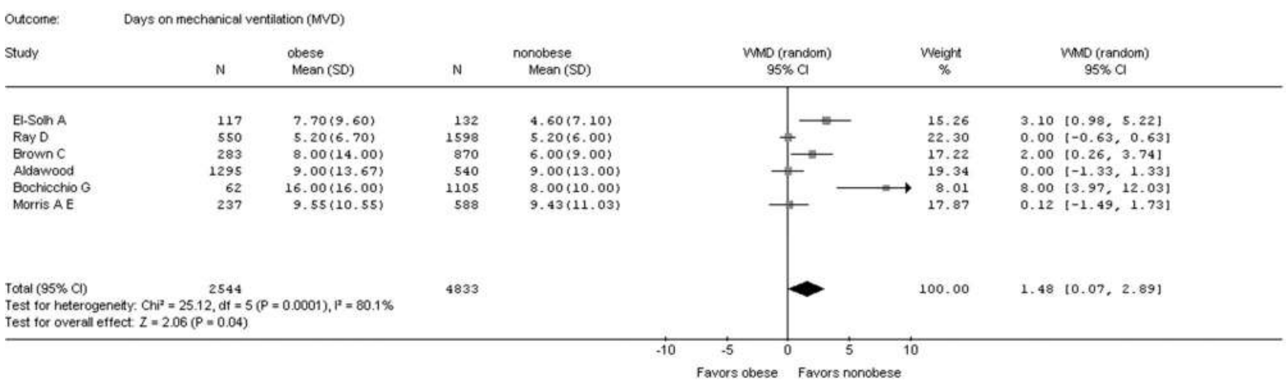

Figure 4. Forest plot depicting the association between obesity and duration of mechanical ventilation (*MVD*). *Horizontal lines* represent 95% confidence intervals (*CI*). *MVD*, days of mechanical ventilation. *WMD*, weighted mean difference.

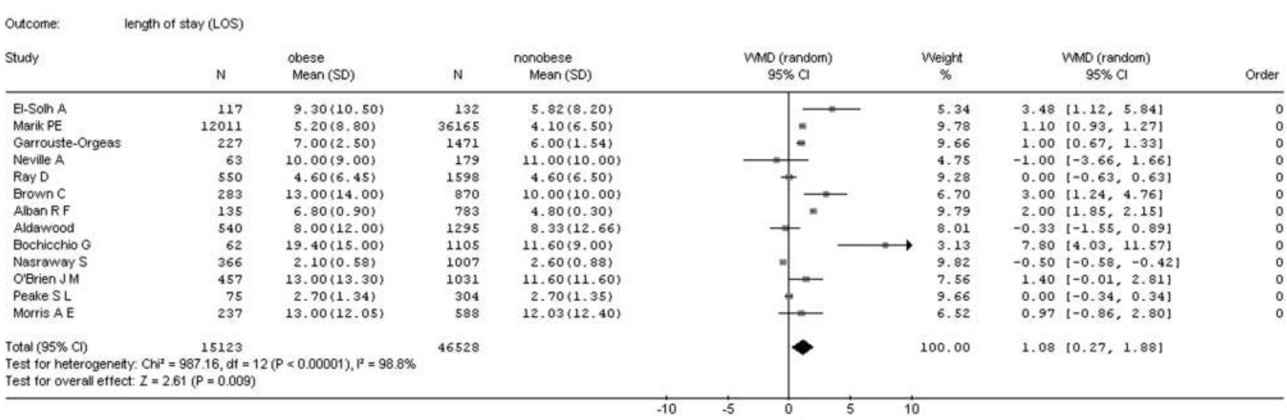

Figure 5. Forest plot depicting the association between obesity and intensive care unit length of stay (*LOS*). *Horizontal lines* represent 95% confidence intervals (*CI*). *WMD*, weighted mean difference.

m^2) ranged from 5.2 to 16.0 days compared with 4.6 to 9.4 days in the nonobese group (BMI <30 kg/m^2). The combined mean difference in duration of mechanical ventilation was lower by 1.48 days (95% CI, 0.07–2.89; $p = .04$; $I^2 = 80.1\%$) in the nonobese compared with the obese group (Fig. 4).

Length of Stay in the Intensive Care Unit. Thirteen studies contributed to the analysis of ICU LOS data (5, 8–11, 13–18, 21, 22). The mean LOS ranged from 2.1 to 19.4 days in the obese group (BMI ≥30 kg/m^2) compared with 2.6 to 12.0 days in the nonobese group (BMI <30 kg/m^2). The combined mean difference in ICU LOS was lower by 1.08 (95% CI, 0.27–1.88; $p = .009$; $I^2 = 98.8\%$) in the nonobese compared with the obese group (Fig. 5).

Subgroup Analysis. Because of significant heterogeneity, we conducted pooled analysis of studies that stratified patients based on different categories of BMI (Fig. 6). The analysis revealed no statistically significant difference in ICU mortality between nonobese (BMI <30 kg/m^2) and morbidly obese patients (BMI ≥ 40 kg/m^2) (RR, 0.97; 95% CI, 0.74–1.26; $p = .8$; $I^2 = 53.8\%$) (Fig. 7). However there was a survival advantage for the obese patients in the BMI range of 30–39.9 kg/m^2 over the nonobese (RR, 0.86; 95% CI, 0.81–0.91; $p < .001$; $I^2 = 0$) (Fig. 8).

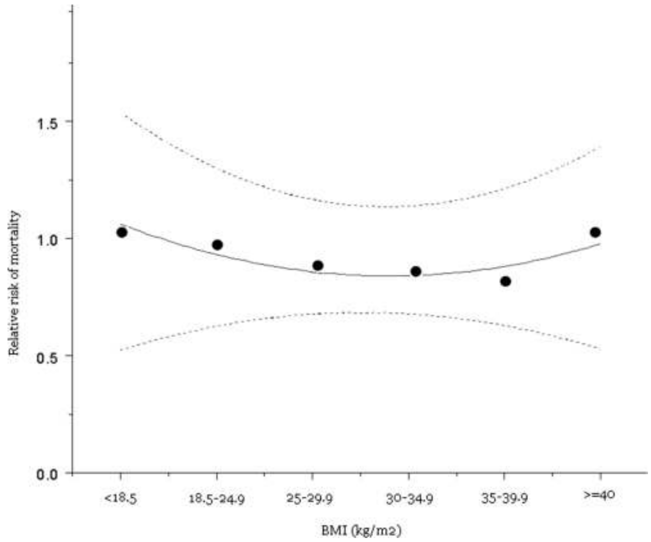

Figure 6. Relative risk of mortality stratified according to body mass index (*BMI*) (95% confidence interval). We obtained the risk trend (*continuous line*) and its 95% confidence band (*dotted line*) by using a polynomial distribution.

Publication Bias. Visual inspection of the funnel plot for ICU mortality denotes asymmetry, indicating underpublication of negative results (Fig. 9). However, formal statistical test using Begg's rank correlation did not support the presence of publication bias (Kendall's τ with continuity correction, -0.18; one-tailed $p = .4$).

DISCUSSION

There are currently no reported aggregate data from ICUs about the proportion of critically ill patients stratified by BMI category. Although a number of clinical investigations reported that obesity contributes to increased ICU mortality, there are other data describing a U-shaped association, with excess mortality in patients who are underweight and in those with severe obesity (41). These conflicting conclusions are the byproducts of clinical and methodologic heterogeneities stemming from variability in participants and outcomes and from trial design and quality. It would not be surprising, therefore, to find that the results of these trials were to some degree

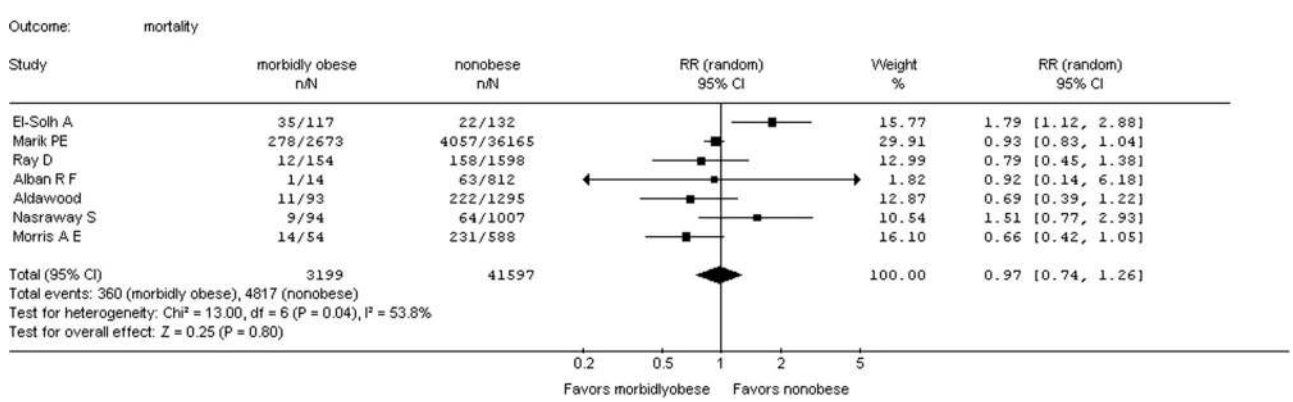

Figure 7. Forest plot examining the risk of mortality among nonobese (body mass index of <30 kg/m^2) vs. morbidly obese (body mass index of ≥ 40 kg/m^2). *Horizontal lines* represent 95% confidence interval (*CI*). *RR,* relative risk.

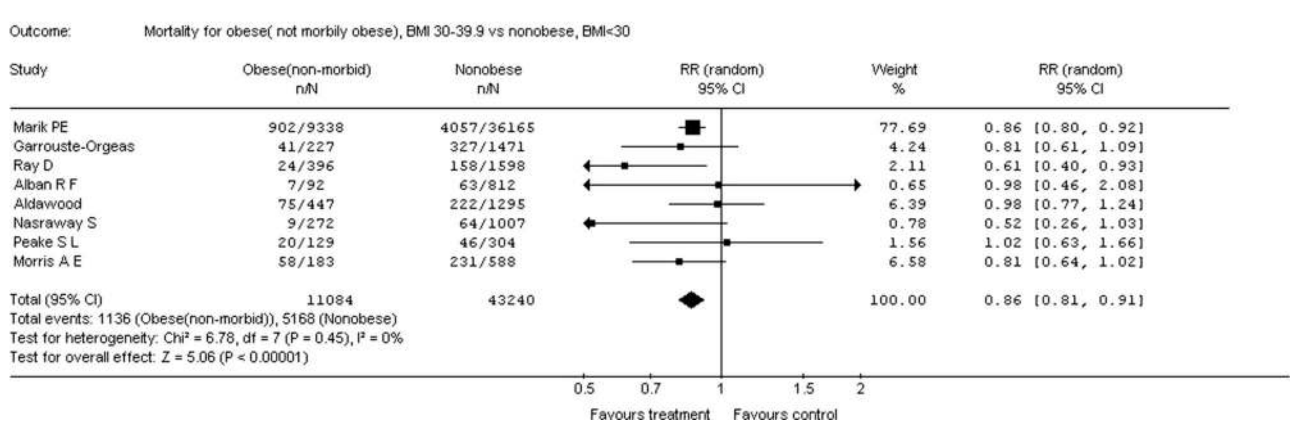

Figure 8. Forest plot examining the risk of mortality among nonobese (body mass index [*BMI*] of <30 kg/m^2) vs. obese with BMI of 30–39.9 kg/m^2. *Horizontal lines* represent 95% confidence interval (*CI*). *RR,* relative risk.

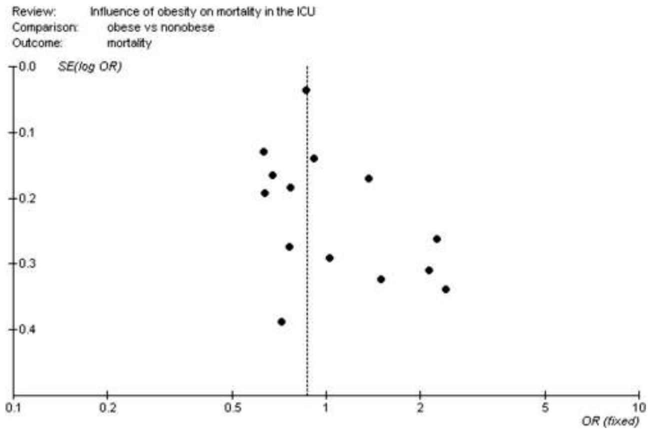

Figure 9. Funnel plot assessing publication bias. The *broken line* represents the combined result of all trials. *ICU,* intensive care unit. *SE (log OR)*, standard error (logarithm of odds ratio); *OR (fixed)*, odds ratio according to "fixed effect model."

incompatible with one another. Indeed, the I^2 test indicated significant degrees of heterogeneity among the selected studies. It has been argued that a meta-analysis should only be considered when a group of trials is sufficiently homogeneous. However heterogeneity will always exist in a meta-analysis, irrespective of whether we are able to detect it using a statistical test (28).

Obesity influences a variety of organ systems, altering the expected physiologic response to injury and illness. The extra burden placed on cardiovascular function and respiratory mechanics has been suspected to confer on obese patients a survival disadvantage when challenged with severe illness. In addition, the distribution, metabolism, protein binding, and clearance of many drugs are altered in the obese, which usually result in underdosing of critical therapeutic agents. Hence, it was not surprising that several studies (5–11) reported a worse outcome in this subset of the population. The most recent investigations, however, seem to suggest that this trend has reversed and others insist that the correlation does not exist (14, 16, 19, 22). Several theories have been advanced to explain this discrepancy. Physiologically, it is plausible that access to the abundant adipose tissue during the highly catabolic state helps to prevent the long-term complications associated with critical illness. There are no clinical data, however, to support this notion at present, but there is increasing evidence that adipocytes-secreting hormones—leptin and interleukin-10—have immunomodulatory properties that might curb the inflammatory response and improve host survival in response to severe illness. Leptin has a notable regulatory effect on T-lymphocytes and interferon-γ production (42). Animal studies have shown that leptin-deficient mice exhibit an impaired host response against Gram-negative pneumonia *in vivo*, and this defect was associated with impaired macrophage and neutrophil phagocytosis of *Klebsiella pneumoniae* and reduced macrophage leukotriene synthesis *in vitro* (43, 44). Clinical studies in humans have also reported higher leptin levels in survivors of severe sepsis and septic shock than nonsurvivors (45). Interleukin-10 is another adipokine that possesses anti-inflammatory properties that help control the initial inflammatory response in critical illness by inhibiting the release of proinflammatory cytokines such as tumor necrosis factor, interleukin-6, and interleukin-8 from macrophages (46). Could it be that adipokines modulation of inflammatory cytokines mitigate the physiologic burden of obesity? A recent investigation in murine model of pulmonary infection suggests that shifting the balance between proinflammatory and anti-inflammatory mediators in favor of the latter by interleukin-10 gene delivery was able to restore normal diaphragmatic force-generating capacity under these conditions (47).

An alternative explanation for the lack of difference in the odds of mortality among critically ill obese and nonobese patients is the increased clinical attention that is being paid to the care of obese patients following the early reports of decreased survival. In addition, the proliferation of therapeutic guidelines in the past few years standardizing the management of hyperglycemia and sepsis could have potentially contributed to a significant decline in the ICU complications of critically ill obese patients compared with the nonobese, yielding effectively a comparable mortality rate between the two groups.

In-hospital mortality findings from our meta-analysis may not be at variance with currently available data in the obesity literature. This is underscored by recent evidence suggesting that the relationship between obesity and hospital mortality is a rather complex one. The obesity paradox was reported in a study of 108,927 patients with acute decompensated heart failure with in-hospital mortality rates of 6.3%, 4.6%, 3.4%, and 2.4% for underweight, healthy weight, overweight, and obese patients, respectively (48). This finding may be explained partly by the effect of chronically ill patients constituting a large proportion of the nonobese group. Similar findings were shown in other studies (16, 49, 50). Lastly, our literature search was directed at studies that primarily addressed ICU mortality. Our analysis of hospital mortality was an extrapolated derivative. Therefore we may have underestimated the effect of excluded data from studies primarily geared toward hospital outcome in obese patients.

One consistent finding across the majority of the combined studies is the longer duration of mechanical ventilation and prolonged ICU length of stay in obese patients compared with nonobese. Only three of 13 studies that reported LOS data failed to show this feature (8, 10, 17). None of the studies showed a shorter duration of mechanical ventilation in obese patients compared with nonobese patients. Duration of mechanical ventilation was at best similar, in two studies (17–18). The mechanical properties of the total respiratory system, the lung, and the chest wall of morbidly obese patients are characterized by marked derangements compared with normal weight subjects (51). Morbidly obese patients dedicate a disproportionately high percentage of total body oxygen consumption to conduct respiratory work, even during quiet breathing. This relative inefficiency suggests a decreased ventilatory reserve and a predisposition to respiratory failure in the setting of even mild pulmonary or systemic insults (52). Moreover, the increase in perioperative complications, particularly wound problems, explains our finding of a longer LOS in postoperative obese patients (40).

Our meta-analysis has several key limitations. First, the vast majority of studies that have addressed the question of obesity and mortality in the ICU are retrospective by design (5, 8–10, 15–16, 34, 37, 39). As such, we cannot confidently exclude the error of selection bias. Second, because this study was based on published reports rather than primary data analysis, the ability to identify patient characteristics associated with greater risks was limited. Different groups of studies reported on similar outcomes, yet each risk estimate may have reflected differences in true effects or biases particular to the studies from which the risk estimate was derived. Third, as the global obesity epidemic continues to amplify and spread, further data will be required on mortality and morbidity for those who are super-obese (BMI >50 kg/m^2).

CONCLUSIONS

This meta-analysis suggests that although mild and moderate obesity may be protective during critical illness, morbid obesity did not have an adverse effect on outcome. However obese patients do have increased morbidity as measured by duration of mechanical ventilation and LOS. As the waistline of the U.S. population continues to enlargen, longer LOS might have significant implications for healthcare costs. Interventional studies are needed to address the causes of and to reduce the greater resource utilization.

ACKNOWLEDGMENT

We thank Dr. Brydon Grant for statistical review of the manuscript.

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