

Excess Body Weight Is Not Independently Associated with Outcome in Mechanically Ventilated Patients with Acute Lung Injury

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Background: Despite an epidemic of obesity among adults, the effect of excess body weight on outcome from critical illness is not well studied.

Objective: To examine the association between excess body weight and outcome in mechanically ventilated patients with acute lung injury.

Design: Secondary analysis of participants in trials of therapy for acute lung injury.

Setting: 10 U.S. medical centers that participate in the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network.

Patients: 902 mechanically ventilated patients who were enrolled in randomized, controlled trials of therapy for acute lung injury.

Intervention: Assignment to higher (12 mL/kg of predicted weight) or lower (6 mL/kg of predicted weight) tidal volume ventilation strategies with specified weaning protocols. Some patients also received ketoconazole, lisofylline, or placebo by factorial design.

Measurements: Mortality rate, rate of unassisted ventilation by day 28, and number of ventilator-free days.

Results: Indirect causes of lung injury, including trauma, were more common in obese patients. Overweight and obese patients had higher peak and plateau airway pressures before enrollment because of higher set tidal volumes. After risk adjustment, excess body weight was not associated with death, achievement of unassisted ventilation, or number of ventilator-free days. This lack of effect persisted with categorical or continuous measures of body mass index (BMI). We found no significant interaction between ventilator protocol assignment and BMI category.

Conclusions: After risk adjustment, overweight and obese patients with acute lung injury have outcomes similar to those of patients with normal BMI. The lack of interaction between ventilator protocol assignment and BMI suggests that patients with normal, overweight, or obese BMI benefit from lower tidal volume ventilation for acute lung injury.

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Sixty-four percent of U.S. adults are overweight or obese, and this trend is accelerating (1, 2). Despite the well-described chronic health consequences of excess weight (3), we know little about the effect of obesity on outcomes from acute illnesses, particularly those requiring admission to the intensive care unit. Obese patients have a greater prevalence of comorbid conditions that may affect outcome (3), and they experience physiologic changes (4, 5) that may impair their ability to compensate for the stresses of critical illness. Because of these findings, conventional wisdom holds that obesity increases mortality and morbidity for patients in the intensive care unit. However, an independent effect of obesity on outcome from critical illness has never been conclusively demonstrated. If, in fact, obese persons are at risk, investigators should determine the mechanism of this increased risk and target interventions to this group.

Acute lung injury is an inflammatory pulmonary condition associated with a variety of initiating insults. Acute lung injury is a frequent cause of respiratory failure requiring mechanical ventilation and a common indication for admission to the intensive care unit. The reported mortality rate is 40% to 60% (6). We performed a secondary analysis of a randomized trial of ventilator management in patients with acute lung injury (7) to better describe the influence of excess body weight on the outcome of critical illness. In that trial, patients randomly assigned to low tidal

volume had better outcomes than patients assigned to high tidal volume. The experimental protocols for this trial required measurement of height to determine assigned tidal volume. This measurement also allowed calculation of body mass index (BMI) for each patient, a variable not often recorded for critically ill patients. Some argue that larger tidal volumes are beneficial for obese patients requiring mechanical ventilation (8). This raises concern that patients with different BMIs may require different ventilator strategies. By evaluating the interaction between the assigned ventilator protocol and BMI, we were able to determine whether the beneficial effect of lower tidal volume extends to obese patients with acute lung injury.

METHODS

Setting and Sample

We examined data on patients who participated in the National Heart, Lung, and Blood Institute's multicenter, randomized trials of the Acute Respiratory Distress Syndrome Network (7, 9, 10). Of the 902 patients in these studies, the first 861 participated in a randomized trial of mechanical ventilation that compared lower tidal volume with higher tidal volume (6 mL/kg of predicted body weight vs. 12 mL/kg, respectively). In a factorial design, 2 other trials evaluated ketoconazole versus placebo (234 patients) or lisofylline versus placebo (194 patients). After the

ventilator trial ended because it showed a significant benefit associated with lower tidal volumes, an additional 41 patients received lisofylline or placebo plus the lower tidal volume strategy. Neither lisofylline (9) nor ketoconazole (10) affected outcomes of acute lung injury.

Details of these studies and inclusion and exclusion criteria are described elsewhere (7, 9, 10). In brief, patients were eligible if they required mechanical ventilation and met diagnostic criteria for acute lung injury. Patients with a weight-to-height ratio (kilograms divided by centimeters) of 1.0 or greater were excluded. Analysis was done on an intention-to-treat basis.

Measures of Excess Body Weight

We used BMI as a measure of the degree of excess body weight. We calculated BMI from data in enrollment documents by dividing the patient's body weight in kilograms by the square of his or her height in meters.

Ventilator and Weaning Protocols

The protocol for mechanical ventilator management is described elsewhere (7). The major difference between the two study groups was the selected tidal volume. Investigators calculated predicted body weight from the patient's height and sex and used this predicted weight to determine the initial tidal volume for each patient. In the group assigned to higher tidal volumes, the initial tidal volume was 12 mL/kg of predicted body weight. In the group treated with lower tidal volumes, the initial tidal volume was 6 mL/kg. Investigators performed a daily "weaning screen" on every patient in an attempt to standardize the process of liberation from mechanical ventilation.

Outcome Measures

The primary outcome measure was survival to 28 days after study enrollment. Secondary dependent variables included achievement of unassisted ventilation by day 28, survival to discharge to home or to 180 days (the duration of follow-up in the primary studies), and the number of ventilator-free days. Unassisted ventilation was defined as liberation from mechanical ventilation for 48 or more consecutive hours. The number of ventilator-free days is the number of days of unassisted ventilation from day 1 to day 28.

Statistical Analysis

We performed unadjusted analyses by comparing values for patients across the 3 BMI categories (normal vs. overweight vs. obese) for outcome variables of interest and for other predictors. Unadjusted associations between other predictors and the outcomes were also explored. We used a 2-sided Fisher exact test for dichotomous variables; a 2-sided likelihood ratio chi-square test for nondichotomous categorical variables; and a Kruskal–Wallis test, analysis of variance, or Wilcoxon rank-sum test for continuous variables, as appropriate. We constructed correlation matrices to guide regression estimation.

We used logistic regression for the dichotomous outcome variables and linear regression for the continuous

Context

Although obesity poses many health risks, clinicians have been uncertain whether excess body weight adversely affects the outcomes of severe illnesses such as acute lung injury requiring mechanical ventilation.

Contribution

Among patients in a trial of mechanical ventilation strategies, obese patients and lean patients had similar mortality and ventilation outcomes.

Implications

Physicians should not assume that intubated obese patients fare worse than those who are of normal weight. Whether excess body weight puts patients at risk for poor outcomes in other types of critical illness is a subject for future study.

—The Editors

outcome variables. To estimate the base regressions, we selected variables for inclusion on the basis of several considerations, including significant differences in unadjusted analyses and clinical relevance. Among variables with a correlation greater than 0.50, only 1 was considered for inclusion to minimize multicollinearity. Variables that were thought to be strongly clinically relevant to the outcome and those found to have a statistically significant unadjusted effect ($P < 0.05$) were ultimately included in the base model. Variables in addition to those in Table 1 that were evaluated for inclusion were study site, ethnicity, diagnosis of diabetes, peak glucose level within 24 hours of enrollment, nonpulmonary organ failures, use of vasopressors, fluid balance in the 24 hours before study entry, and pneumonia as primary cause of lung injury. Unless otherwise stated, variables reflected the patient's clinical state at the time of study enrollment.

After estimation of the base regressions, we forced the indicators of excess body weight into the model and determined their predictive values. We performed analyses in several different ways. We used the National Heart, Lung, and Blood Institute divisions of BMI to categorize patients as normal weight (BMI of 18.5 to 24.9 kg/m²), overweight (BMI of 25.0 to 29.9 kg/m²), or obese (BMI \geq 30 kg/m²). To test any effect across BMI category, we used a categorical variable with 2 degrees of freedom in the regression. Because of concern that we would not be able to detect an effect that was nonincremental, we compared the overweight BMI group with the normal BMI group and the obese BMI group with the normal BMI group.

To examine whether the efficacy of lower tidal volume ventilation varied by degree of excess body weight, we estimated the interaction effects between BMI group and assignment to the higher tidal volume protocol. Because

Table 1. Characteristics of the Sample*

Characteristic	Records with Complete Data†	All Patients	Patients with Normal BMI	Patients with Overweight BMI	Patients with Obese BMI	P Value
Participants, n (%)	807 (100)	807 (100)	334 (41.4)	254 (31.5)	219 (27.1)	
Descriptive data						
BMI, kg/m ²	807 (100)	27.6 ± 6.5	22.2 ± 1.8	27.3 ± 1.4	36.1 ± 5.6	<0.001
Age, y	807 (100)	51.5 ± 17.4	51.9 ± 18.0	52.7 ± 17.6	49.4 ± 15.9	0.1191
Male sex, n (%)	807 (100)	478 (59.2)	194 (58.1)	165 (65.0)	119 (54.3)	0.0543
APACHE III score	802 (99.4)	76.4 ± 27.7	78.2 ± 27.4	76.8 ± 27.4	73.0 ± 28.2	0.0899
Type of lung injury, n (%)						
Direct	807 (100)	411 (50.9)	186 (55.7)	134 (52.8)	91 (41.6)	0.0039
Trauma	805 (99.8)	84 (10.4)	23 (6.9)	32 (12.6)	29 (13.2)	0.0189
Baseline ventilator variables						
Tidal volume, mL	556 (68.9)	670 ± 126	644 ± 112	698 ± 128	680 ± 137	<0.001
Tidal volume per kg of predicted body weight, mL/kg	556 (68.9)	10.38 ± 1.86	10.05 ± 1.60	10.56 ± 1.85	10.76 ± 2.22	0.0012
PaO ₂ :Fio ₂ ratio	746 (92.4)	149 ± 71	150 ± 68	149 ± 75	150 ± 69	>0.2
Static compliance, mL/cm H ₂ O	489 (60.6)	35.1 ± 15.8	34.9 ± 13.3	35.5 ± 13.7	34.8 ± 22.0	>0.2
Plateau airway pressure, cm H ₂ O	625 (77.4)	30.2 ± 7.9	28.9 ± 7.9	30.4 ± 7.4	31.8 ± 8.1	<0.001
Peak airway pressure, cm H ₂ O	739 (91.6)	37.0 ± 9.4	35.5 ± 9.5	36.7 ± 8.6	39.5 ± 9.5	<0.001
Treatment assignment, n (%)						
Lower tidal volume	807 (100)	424 (52.5)	174 (52.1)	132 (52.0)	118 (53.9)	>0.2
Factorial assignment to study drug						
No study drug	807 (100)	377 (46.7)	147 (44.0)	121 (47.6)	109 (49.8)	<0.001
Ketoconazole study						
Placebo		105 (13.0)	61 (18.3)	27 (10.3)	17 (7.8)	
Ketoconazole		105 (13.0)	48 (14.4)	37 (14.6)	20 (9.1)	
Lisofylline study						
Placebo		111 (13.8)	31 (9.3)	39 (15.4)	41 (18.7)	
Lisofylline		109 (13.5)	47 (14.1)	30 (11.8)	32 (14.6)	

* Data presented with a plus/minus sign are the mean ± SD. APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index.

† Data in this column are the number (percentage) of patients.

the interaction effects between BMI category and treatment assignment were not significant (as tested by using a likelihood ratio test with 2 degrees of freedom), a main effects model was fit. This likelihood-ratio test was also used to test the significance of the 3-category BMI variable. To examine the patients with extreme excess body weight, patients were divided into 4 BMI categories (normal, overweight, obese [BMI of 30 to 39.9 kg/m²], and severely obese [BMI ≥ 40 kg/m²]). This categorical variable with 3 degrees of freedom was also tested in the regression. In addition to these analyses, we also used BMI as a continuous variable. Because critically ill patients often receive fluid resuscitation or diuresis, we recalculated BMI as adjusted for the net fluid balance for each patient over the 24 hours before study entry (fluid-adjusted BMI). Negative fluid balances were added to the patient's body weight and positive fluid balances were subtracted from his or her weight to calculate BMI. We substituted the median fluid balance for the patient's study site if the individual fluid balance was unavailable (51 records). We used a Mantel-Haenszel chi-square test for the ordinally categorical variables and a Wilcoxon rank-sum test for continuous variables. Pearson chi-square test produced results similar ($P > 0.2$) to those of the Mantel-Haenszel test.

We used SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina), for all analyses. A P value less than 0.05 was considered statistically significant.

Protection of Human Subjects

The institutional review boards of each participating center approved the primary studies. Patients or their surrogates provided informed consent before enrollment. The Acute Respiratory Distress Syndrome Network stripped patient data of all identifying information before providing it to us. The Colorado Multiple Institution Review Board approved a waiver of additional consent for performance of this study.

Role of the Funding Source

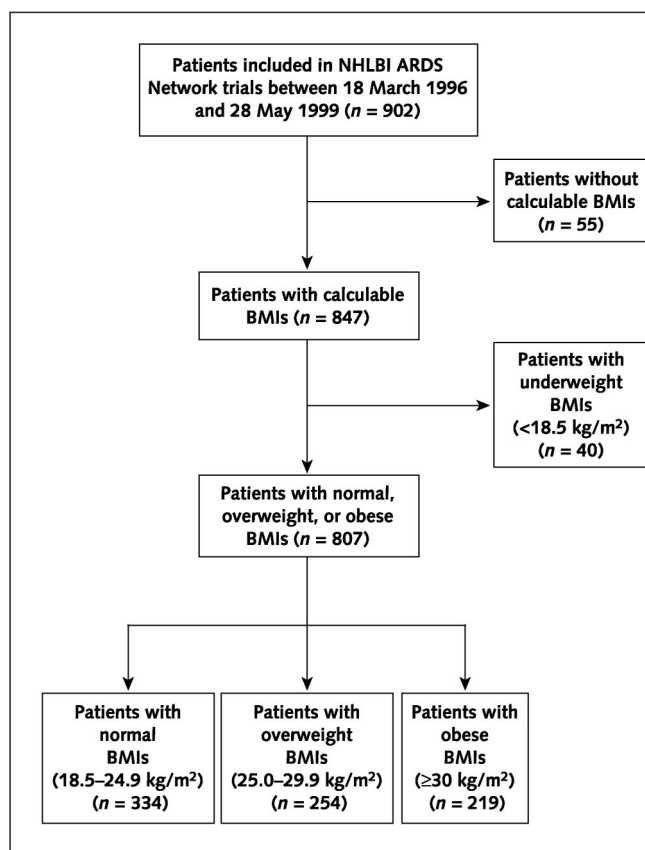
The National Heart, Lung, and Blood Institute oversaw the study, including data and safety monitoring. Representatives of the Acute Respiratory Distress Syndrome Network reviewed and approved the manuscript before publication.

RESULTS

Study Sample

For 847 patients (93.9%), information was adequate to determine BMI (Figure 1). Body mass index could not be calculated for 55 patients because body weight was missing; we excluded these records. Patients whose records lacked this information were more likely than patients with calculable BMIs to have an ethnicity classification of white, non-Hispanic (85.5% vs. 72.5% [$P = 0.040$]) and to have had fewer pre-enrollment nonpulmonary organ failures

Figure 1. Inclusion and exclusion criteria.



ARDS = acute respiratory distress syndrome; BMI = body mass index; NHLBI = National Heart, Lung, and Blood Institute.

(0.764 vs. 0.962 [$P = 0.025$]). There were no other statistically significant differences between patients without calculable BMI and those with calculable BMI. Of the 847 patients with calculable BMI, 40 patients (4.7%) were underweight (BMI < 18.5 kg/m²). Because the focus of our investigation was the effect of excess body weight, we ex-

cluded these patients. Eight hundred seven patients (89.5% of the initial cohort) therefore underwent analysis.

Baseline Characteristics

Table 1 shows patient characteristics by BMI group. The distribution of BMI approximated that of the general population at the time of the study (1–3). Obese and overweight patients were more likely than patients with normal BMI to have an indirect cause of lung injury, including trauma, and had higher pre-enrollment peak and plateau airway pressures and higher set tidal volumes.

Unadjusted Outcomes across BMI Groups

The BMI groups did not differ significantly for any of the dependent variables (Figure 2). Assignment to a tidal volume of 6 mL/kg of predicted body weight resulted in better outcomes in all groups (Table 2).

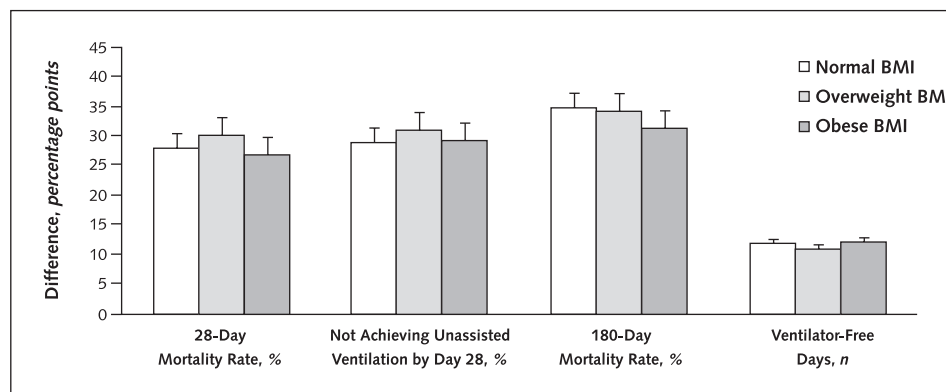
Unadjusted Analyses

Table 3 shows markers of excess body weight in the patients who survived and those who did not survive to day 28. All measures were equally distributed between the groups. Results of analyses for the other dependent variables were similar to those for the primary outcome measure (data not shown). This finding was predicted by the high correlation between day 28 mortality rate and death by 180 days ($r = 0.884$), achievement of unassisted ventilation ($r = -0.848$), and number of ventilator-free days ($r = -0.655$).

Regression Models

Because values were missing for at least 1 variable, 127 records (15.7% of records with calculable BMIs) were excluded from the regression models. Patients whose information was excluded from regression models were more likely than those whose records were included to have an ethnicity designation of black, non-Hispanic (23.6% vs. 15.6% [$P = 0.038$]), a higher ratio of PaO₂ to FiO₂ (182.4 ± 78.8 vs. 146.2 ± 69.0 [$P < 0.001$]), lower pre-enrollment plateau airway pressures (27.6 ± 7.1 vs. 30.4 ± 7.9 [$P = 0.010$]), and fewer average failed nonpul-

Figure 2. Unadjusted differences in outcomes across body mass index (BMI) categories.



Mortality rate and ventilation variables are shown as the proportion of patients with the outcome (\pm SE). Ventilator-free days are shown as the mean for the BMI category. No statistically significant differences across BMI category were observed for any dependent variable.

Table 2. Unadjusted Differences in Clinical Outcomes across Body Mass Index Categories, Stratified by Treatment Assignment*

Outcome	All Patients	Patients with Normal BMI	Patients with Overweight BMI	Patients with Obese BMI	P Value
28-day mortality rate, <i>n</i> (%)					
6-mL/kg tidal volume group	100 (23.6)	36 (20.7)	34 (25.8)	30 (25.4)	>0.2
12-mL/kg tidal volume group	130 (33.9)	58 (36.3)	43 (35.2)	29 (28.7)	>0.2
Unassisted ventilation by day 28, <i>n</i> (%)					
6-mL/kg tidal volume group	318 (75.0)	136 (78.2)	96 (72.7)	86 (72.9)	>0.2
12-mL/kg tidal volume group	249 (65.0)	101 (63.1)	79 (64.8)	69 (68.3)	>0.2
180-day mortality rate, <i>n</i> (%)					
6-mL/kg tidal volume group	124 (29.2)	51 (29.4)	39 (29.6)	34 (28.8)	>0.2
12-mL/kg tidal volume group	148 (38.6)	65 (40.6)	48 (39.4)	35 (34.7)	>0.2
Mean ventilator-free days (95% CI)					
6-mL/kg tidal volume group	12.7 (11.7–13.7)	13.5 (12.0–15.1)	11.6 (9.8–13.4)	12.7 (10.8–14.6)	>0.2
12-mL/kg tidal volume group	10.7 (9.6–11.7)	10.3 (8.6–12.0)	10.2 (8.4–12.1)	11.8 (9.6–13.9)	>0.2

* BMI = body mass index.

monary organ systems (0.78 ± 0.90 vs. 0.99 ± 0.93 [$P = 0.010$]). No other significant differences were observed between these 2 groups. We included the remaining 680 records in the model for 28-day mortality rate.

We initially tested the 3-category BMI variable and the 2 interaction effects for significance (the interaction effects between the 3-category BMI variable and assignment to the higher tidal volume protocol). Because the interactions were not significant ($P = 0.1682$), a main-effects model was fit without these terms. Table 4 shows the variables included in the main-effects model. We included peak airway pressure because this variable correlates highly with other, more clinically relevant variables (such as plateau airway pressure [$\rho = 0.738$]) and because this information was available in a greater number of records, thereby allowing us to include more records in the regression. The base model had very good predictive value (*c* statistic, 0.760). We included age, Acute Physiology and Chronic Health Evaluation III score, ratio of PaO_2 to FiO_2 , and peak airway pressure as continuous variables because there was no obvious point of division into categories.

Compared with normal BMI, an overweight or obese BMI was not associated with death by 28 days. In the model with 4 BMI categories, severe obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) also was not associated with higher odds of death by day 28 (adjusted odds ratio, 0.804 [CI, 0.303 to 2.131]; $P > 0.2$). When BMI was used as a continuous variable in

the main-effects model, no significant association with outcome was observed (adjusted odds ratio, 0.994 [CI, 0.964 to 1.025]; $P > 0.2$).

In determining fluid-adjusted BMIs, we observed a wide range in net fluid balance (mean balance, 2591 mL gained [CI, 5527 mL lost to 10 709 mL gained]). The BMI category of 116 patients changed because of this adjustment. However, unadjusted and fluid-adjusted BMIs were closely correlated ($r = 0.978$), and fluid-adjusted BMI was not associated with death by 28 days (adjusted odds ratio, 0.990 [CI, 0.960 to 1.020]; $P > 0.2$).

We included the variables from the 28-day mortality regression analysis in the base effects models for the other outcome variables. Each of these models had good predictive ability (for achieving unassisted ventilation, $c = 0.756$; for death by 180 days, $c = 0.754$; for ventilator-free days, adjusted $r^2 = 0.1690$). We forced indicators of excess weight into each model in the same manner as for death by 28 days. After risk adjustment, excess body weight was not associated with the response variables in any of the analyses (data not shown).

DISCUSSION

In this secondary analysis of a randomized trial of ventilator management in patients with acute lung injury, excess body weight was not independently associated with clinical outcomes. Factors that were independently associated with poorer outcomes were older age, higher Acute Physiology and Chronic Health Evaluation III scores, assignment to the 12-mL/kg tidal volume protocol, a lower baseline ratio of PaO_2 to FiO_2 , and higher pre-enrollment peak airway pressure. Patients with trauma as the primary risk factor for acute lung injury had improved outcomes. Lack of interaction between BMI group and ventilator protocol assignment indicates that the benefit of lower tidal volume in the primary study was similar for patients with normal, overweight, or obese BMI.

Obese persons have a higher prevalence of comorbid conditions, such as cardiovascular disease and diabetes (3),

Table 3. Measures of Excess Body Weight at 28 Days in Patients Who Survived and Those Who Died*

Measure of Excess Body Weight	Alive at 28 Days (<i>n</i> = 577)	Death by 28 Days (<i>n</i> = 230)	P Value
Categorical			
Normal BMI, <i>n</i> (%)	240 (41.6)	94 (40.9)	
Overweight BMI, <i>n</i> (%)	177 (30.7)	77 (33.5)	
Obese BMI, <i>n</i> (%)	160 (27.7)	59 (25.7)	>0.2
Continuous			
Mean BMI \pm SD, kg/m^2	27.7 \pm 6.7	27.2 \pm 5.8	>0.2
Mean fluid-adjusted BMI, kg/m^2	27.0 \pm 6.8	26.1 \pm 6.1	>0.2

* BMI = body mass index.

and experience physiologic changes, particularly in the cardiovascular and pulmonary systems (4, 5), that may affect the outcome of acute illnesses. However, few studies have examined the influence of excess weight on outcomes of critical illness. A retrospective study of 184 persons who experienced blunt abdominal trauma in the 1980s reported that obese patients had a higher risk-adjusted mortality rate than did nonobese patients (11). However, considering the advances in critical care in the decades since completion of this study, it is difficult to apply these findings to current patients. Of note, the majority of obese patients in the study by Choban and colleagues (11) died of hypoxemic respiratory failure, implying that these patients had experienced acute lung injury. We found that acute lung injury was more likely to have been caused by trauma in overweight and obese patients than in normal-weight patients, suggesting a link among obesity, trauma, and acute lung injury. Further study is needed to determine whether excess weight is truly a risk factor for lung injury in persons who experience trauma.

Study limitations and contradictory results hamper the interpretation of other studies of the obese critically ill patients. A report on patients with severe burns determined that obese persons have poorer outcome (12), but multivariate analysis was not performed. One study found that the large neck of obese patients was a risk factor for problematic endotracheal intubation (13), whereas another report failed to demonstrate such an association (14). Some studies (15, 16), but not others (17, 18), described a higher incidence of postoperative complications in obese patients.

Two published studies have examined outcomes in medical intensive care units. One was a retrospective case-control study at 2 university-affiliated hospitals that compared 117 severely obese patients (BMI ≥ 40 kg/m²; mean BMI, 51.1 ± 25.9 kg/m²) with nonobese patients (BMI < 30 kg/m²; mean BMI, 27.6 ± 3.1 kg/m²) (19). Despite matching, the prevalence of comorbid conditions differed significantly between obese and nonobese patients. Obese patients had higher rates of cardiac, pulmonary, and endocrine diseases, whereas nonobese patients were more likely to have hepatic diseases and immunosuppression. On the basis of unadjusted mortality rates, the investigators concluded that obese patients had significantly worse outcomes. However, multivariate analysis indicated that obesity was not associated with death in the hospital. The second, more recent study included patients from an observational database of critically ill patients (20). In regression models, overweight and obese patients did not have poorer risk-adjusted outcomes than did patients with normal BMI. However, it was unclear whether the obese patients were similar to the referent group. For example, the primary indication for admission to the intensive care unit was not evaluated and may have differed for obese and nonobese patients.

Our finding that excess body weight does not affect outcomes of acute lung injury contradicts conventional

Table 4. Main-Effects Model for Death at 28 Days, Including Indicators of Excess Body Weight*

Variable	Odds Ratio (95% CI)	P Value
Covariates		
Age	1.037 (1.025–1.050)	<0.001
APACHE III score	1.020 (1.013–1.027)	<0.001
Pao ₂ :Fio ₂ ratio	0.996 (0.993–0.999)	0.0044
Assignment to higher tidal volume	1.688 (1.166–2.444)	0.0055
Peak airway pressure at study enrollment	1.025 (1.003–1.048)	0.0237
Trauma as primary lung injury category	0.322 (0.120–0.863)	0.0243
Female sex	1.168 (0.802–1.700)	>0.2
Assignment to ketoconazole or lisofylline	0.944 (0.619–1.441)	>0.2
Excess body weight variables		
BMI category		>0.2
Overweight BMI versus normal BMI	1.096 (0.711–1.690)	
Obese BMI versus normal BMI	1.111 (0.693–1.782)	

* APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index.

wisdom. We suspected that the cardiopulmonary changes and excess comorbid conditions associated with excess body weight would impair the ability of obese patients to compensate for the stress of acute lung injury. We found higher rates of diabetes among the obese patients (data not shown), suggesting that they had more weight-associated comorbid conditions. However, although the obese patients almost certainly had physiologic abnormalities and comorbid conditions due to their excess weight, these factors were not sufficient to lead to detectable differences. The processes of care provided to the patients in our study may have compensated for these abnormalities. For instance, if sleep apnea was more common in the obese patients and confers risk, bypassing the upper airway with an endotracheal tube may have masked its influence on outcome.

Unlike observational reports, the study from the Acute Respiratory Distress Syndrome Network included explicit clinical protocols, including automatic weaning trials and tidal volumes based on predicted body weight. Standardized procedures for weaning are associated with better outcomes in mechanically ventilated patients (21, 22). A possible explanation for the benefits of such protocols is the removal of provider bias and practice variation. Because clinicians commonly have negative opinions of overweight and obese patients (23–26) and these prejudices can affect practice (27, 28), standardized care may be particularly important for obese persons. For example, obese patients in our study had significantly higher tidal volumes than did those with normal BMI at the time of study entry. This finding suggests that clinicians overestimated lung size for obese persons and chose tidal volumes on the basis of actual body weight rather than ideal weight. These inappropriately high tidal volumes may place overweight and obese patients at risk for ventilator-associated lung injury (29). The lack of effect of excess weight on outcome in our study

may be due to standardization of tidal volume based on predicted body weight.

Our study had limitations. We performed a secondary analysis of an existing data set that was not initially designed to test the influence of obesity on outcome of acute lung injury. Confounding due to an important unmeasured covariate associated with BMI may have occurred. As with all retrospective studies, our conclusions are dependent on the completeness of data collected. For the regression models, we excluded 55 records because BMI could not be calculated and removed another 127 records before regression analysis because explanatory variables were missing. Differences between the records included in the models and those excluded for missing data were minimal. However, censoring these records may have affected our results. In addition, our results may be weaker because obese and overweight persons at high risk of death because of reasons other than BMI but associated with excess body weight (for example, cancer) may have been excluded from the primary study. It is reassuring that the distribution of patients within BMI categories paralleled that of the general public at the time of the study (1–3).

For the primary study, a weight-to-height ratio of 1.0 or greater was an exclusion criterion. These very obese persons may have different outcomes than our study cohort. However, only 0.74% of patients who met the inclusion criteria were excluded for this reason. We analyzed a subgroup of patients with severe obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) and did not find an independent influence on outcome. In fact, these patients showed a nonsignificant trend toward improved risk-adjusted mortality rates. The prevalence of extreme obesity in our study (4.7%) was higher than that reported in the most recent epidemiologic study (2.2%) (30).

Although BMI does not specifically quantify the percentage or distribution of body fat, it is a valid measure that has been associated with the increase in excess all-cause mortality due to excess weight (31–33) and is highly correlated with more complicated methods of determining excess body weight (34, 35). Other physical measures (such as waist circumference) or determinations of body composition (such as electrical impedance) might detect an influence of excess body weight that BMI does not. However, these measures are rarely used in critically ill patients and are therefore unlikely to be of clinical utility.

As with all subgroup analyses that were not defined a priori, type 2 errors may have occurred. The rate of cardiovascular mortality is increased by 50% to 100% in obese patients (3). With a sample of 807 patients, a 2-sided α value of 0.05, and 80% power, we could detect an increase in relative risk for death by 28 days of 37.4% for obese patients, compared with patients who had normal BMI. For patients with acute lung injury, we demonstrated a 7.8% increase in the unadjusted relative risk for death at 28 days above that seen for patients with normal BMI (28-day mortality rates, 28.1% in the normal BMI group,

30.3% in the overweight BMI group, and 26.9% in the obese BMI group). These observed differences in mortality rates are unlikely to be clinically significant. We also expect that an effect of excess weight would become more pronounced with increasing BMI. The decrease in unadjusted mortality rate for patients in the obese BMI group relative to the overweight and normal BMI group provides further evidence that a true effect is lacking.

In conclusion, BMI was not independently associated with outcome from acute lung injury in our study. Furthermore, the benefit of ventilation with a lower tidal volume (for example, 6 mL/kg of predicted body weight) in patients with acute lung injury appears to be similar for those with a normal, overweight, or obese BMI. A prospective investigation that focuses on the influence of excess body weight on the outcome from critical illness is needed to confirm our findings and to extend the results to patients with other severe illnesses. Because the obesity epidemic shows no signs of reversing, clinicians must appreciate the effect of excess weight on outcome of acute illness. In the intensive care unit environment, understanding the risks to obese patients is the first step to develop new therapeutic approaches for this growing group of critically ill patients.

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