Disparities in Lung-Protective Ventilation in the United States

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Abstract

Background
The objective of our study was to determine whether disparities exist in the use of lung-protective ventilation for critically ill mechanically ventilated patients in the United States based on gender, race/ethnicity, or insurance status.

Methods
This was a secondary data analysis of a prospective multicenter cohort study conducted from 2010 to 2012. The outcome of interest was the proportion of patients receiving tidal volume > 8 mL/kg predicted body weight (PBW).

Results
There were 1,595 patients in our primary analysis (710 women, 885 men). Women were more likely to receive tidal volumes > 8 mL/kg PBW than men (odds ratio [OR] = 3.42, 95% confidence interval [CI] = 2.67-4.40), a finding largely but not completely explained by gender differences in height. The underinsured were significantly more likely to receive tidal volume > 8 mL/kg PBW than the insured in multivariable analysis (OR = 1.54, 95% CI = 1.16-2.04). The prescription of > 8 mL/kg PBW tidal volume did not differ by racial or ethnic categories.

Conclusions
In this prospective nationwide cohort of critically ill mechanically ventilated patients, women and the underinsured were less likely than their comparators to receive lung-protective ventilation, with no apparent differences based on race/ethnicity alone.

Categories: Pulmonology, Other
Keywords: critical care, sex, insurance coverage, lung injury, respiratory failure, tidal volume, mechanical ventilation

Introduction
Disparities exist in healthcare delivery and clinical outcomes among critically ill patients based on gender, race, and insurance status [1-7].

Lung-protective ventilation is often used for patients with acute respiratory distress syndrome (ARDS) and also for patients without ARDS [8], with several studies indicating lower risk of lung injury and other adverse outcomes in non-ARDS patients [9-11]. Few studies have specifically investigated whether tidal volumes differ based on gender, race, and insurance status among unselected critically ill mechanically ventilated patients [12].

The goal of this study was to explore whether gender, race, and insurance status influenced the use of lung-protective ventilation. To accomplish this goal, we conducted a secondary analysis of The United States Critical Illness and Injury Trials Group-Critical Illness Outcomes Study (USCIITG-CIOS), a multicenter, prospective cohort study designed to evaluate the impact of ICU protocols on patient outcomes [13,14]. We hypothesized that potentially injurious tidal volumes would be differentially applied based on gender, race/ethnicity, and insurance status. Preliminary analyses from this study were previously presented at the American Thoracic Society International Conference on May 23, 2018, and published in abstract form [15].

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Materials And Methods

Study design, setting, and patients

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The details of USCIITG-CIOS have been previously described [13,14]. In brief, this was a prospective cohort study of 6,179 critically ill adult patients from 59 primarily academic intensive care units (ICUs) across the United States. Participating ICUs enrolled newly admitted patients one day per week, with 5-10 days between enrollment days, between July 2010 and March 2012. Data collection elements included demographic characteristics, height, and mechanical ventilation settings abstracted from review of the electronic medical record by trained study personnel at each participating center. Mechanical ventilation parameters were collected from the respiratory flowsheets of the medical record at a single time point at approximately 8:00 am the day of data collection. Patients present in the ICU during the prior data collection day or discharged before the first data collection day were not enrolled. All participating sites received approval from their institutional review boards for data collection with a waiver of informed consent.

**Exposure variables**

The independent variables of interest were gender, race/ethnicity, and insurance status. Race was nominally categorized as White (the base category), African American, Asian-Pacific Islander, and American Indian/Alaskan Native. Ethnicity was binarily categorized as not Hispanic or Latino or Hispanic or Latino. Underinsured patients were those with Medicaid-only coverage, self-pay, or unknown insurance, and insured patients were those with any Medicare or commercial/private insurance [2]. We performed a sensitivity analysis that excluded Medicare patients from the analysis of insurance status to assess the likelihood of confounding by age and comorbid conditions [4].

**Outcome variable**

The outcome variable was prescription of a tidal volume/predicted body weight (VT/PBW) > 8 mL/kg. We chose this outcome because it is a potentially harmful threshold used in prior studies of ventilatory practices [12,16,17] and could be differentially applied in patients based on gender, race/ethnicity, or insurance status. PBW was calculated using the formulas employed by the ARDSnet investigators [18].

**Statistical analysis**

Our primary analysis was a complete case analysis that included patients with non-missing values for race, ethnicity, tidal volume, and height. We also performed a secondary analysis that included patients with missing values for these variables using multiple imputation. The details of the multiple imputation methods are presented in the supplementary methods and Supplementary Tables 5-7.

Descriptive statistics were performed for all dependent and independent variables of interest. Continuous variables with a normal and skewed distribution are reported as mean ± standard deviation or median [interquartile range], respectively. Categorical variables are expressed as proportions. Relationships between dichotomous variables were examined using the chi-square test, and relationships between continuous variables were analyzed using the Kruskal-Wallis test. We used clinical judgment and prior literature to construct directed acyclic graphs conceptualizing covariables that might confound or mediate relationships between the independent and dependent variables of interest [19-21]. These covariables were included together with the predictor variable of interest in multivariable logistic regression models. The outcome variable was VT/PBW > 8 mL/kg. The "cluster" option in Stata was used for estimation of the variance-covariance matrix in all logistic models. This option relaxes the assumption of independent observations within groups, adjusting the standard errors and confidence intervals (CIs) to account for the possibility that care of patients within individual ICUs was correlated [22].

Mediation analysis was conducted according to the methods of Pearl [23] to probe relative contributions of gender and height on tidal volume > 8 mL/kg PBW. Statistical analyses were conducted with Stata version 14.2 (2015, Stata Statistical Software, StataCorp LP, College Station, TX).

**Results**

**Patient characteristics**

We enrolled 6,179 critically ill patients from 59 ICUs, of which 2,513 patients received mechanical ventilation. Race was missing in 193 patients, tidal volume in 689 patients, and height in 147 patients. After exclusion of patients with one or more of these missing variables, 1,595 patients remained for the complete case analysis (Figure 1).
The characteristics of mechanically ventilated patients in the complete case analysis are shown in Tables 1, 2.

**TABLE 1:** Characteristics of mechanically ventilated patients in the complete case analysis.

| Variable             | Total (n = 1,595) | Women (n = 710) | Men (n = 885) | P-value | Underinsured (n = 338) | Insured (n = 1,257) | P-value |
|----------------------|-------------------|-----------------|--------------|---------|------------------------|---------------------|---------|
| Age (years)          | 61 (51 – 71)      | 62 (52 – 73)    | 60 (50 – 70) | 0.001   | 52 (41 – 59)           | 64 (54 – 74)        | <0.001  |
| Height (cm)          | 170 (162 – 178)   | 162 (157 – 167) | 177 (170 – 182) | <0.001 | 170 (162 – 178)        | 170 (160 – 178)     | 0.45    |
| PBW (kg)             | 64 (54 – 73)      | 54 (50 – 59)    | 72 (66 – 77)  | <0.001 | 64 (55 – 87)           | 64 (54 – 92)        | 0.09    |
| Weight (kg)*         | 81 (67 – 98)      | 72 (60 – 93)    | 85 (73 – 102) | <0.001 | 80 (66 – 98)           | 81 (67 – 98)        | 0.28    |
| BMI (cm²/m²)         | 28 (24 – 34)      | 28 (23 – 35)    | 27 (24 – 33)  | 0.10    | 27 (23 – 33)           | 28 (24 – 34)        | 0.07    |
| APACHE II score      | 21 (16 – 26)      | 21 (16 – 25)    | 21 (16 – 26)  | 0.96    | 19 (14 – 24)           | 21 (16 – 26)        | <0.001  |
| SOFA score           | 7 (4 – 10)        | 6 (4 – 9)       | 7 (5 – 10)    | <0.001 | 6 (4 – 10)             | 7 (4 – 10)          | 0.18    |
| Hospital mortality†  | 437 (30%)         | 191 (28%)       | 246 (30%)     | 0.052   | 86 (30%)               | 351 (30%)           | 0.25    |
| Hospital LOS (days)† | 17 (10 – 30)      | 17 (10 – 29)    | 17 (10 – 31)  | 0.49    | 17 (9 – 33)            | 17 (10 – 30)        | 0.62    |
| ICU LOS (days)†      | 10 (5-18)         | 10 (5 – 17)     | 10 (5 – 10)   | 0.24    | 10 (5 – 18)            | 10 (5 – 18)         | 0.28    |

**Comorbid conditions**

- Heart failure 271 (17%) 135 (19%) 136 (15%) 0.054 54 (16%) 217 (17%) 0.58
- COPD 423 (26%) 212 (30%) 211 (24%) 0.007 67 (20%) 356 (28%) 0.002
- Cancer 338 (21%) 139 (20%) 199 (22%) 0.16 43 (12%) 295 (23%) <0.001

**FIGURE 1: Derivation of the study sample.**
**TABLE 1: Patient characteristics by sex and insurance status (complete case analysis)**

*Actual body weight was missing in 11 patients.**Infection types were as follows: pulmonary = 215 (46%), urinary = 47 (10%), abdominal = 45 (9%), central nervous system = 9 (2%), skin/soft tissue = 33 (7%), bloodstream = 73 (15%), other = 19 (4%), unknown = 31 (7%). †Mortality status, ICU length of stay (LOS), and hospital LOS were missing in 114 patients.

Abbreviations: PBW, predicted body weight; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; LOS, length of stay; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome
| Comorbid conditions                      | Heart failure | COPD                     | Cancer                      | Chronic kidney disease | Chronic liver disease | HIV/AIDS                    | Admission diagnosis category |
|------------------------------------------|--------------|-------------------------|-----------------------------|------------------------|-----------------------|---------------------------|------------------------------|
| **Hospital mortality†**                  | 437 (30%)    | 293 (28)                | 120 (30)                   | 22 (43)               | 2 (33)                | 427 (30)                   | 30%                          |
| **Hospital LOS (days)†**                 | 17 (10–30)   | 17 (10–30)              | 18 (9–31)                  | 14 (6–36)             | 16 (15–20)            | 17 (10–30)                 | 30%                          |
| **ICU LOS (days)†**                      | 10 (5–18)    | 10 (5–17)               | 10 (5–18)                  | 10 (4–21)             | 12 (5–20)             | 10 (5–18)                  | 30%                          |
| **Comorbid conditions**                  |              |                         |                             |                        |                       |                           |                              |
| Heart failure                            | 271 (17%)    | 167 (15)                | 99 (24)                    | 4 (8)                 | 1 (14)                | <0.001                     | 266 (17)                     | 5 (10)                      | 0.16                      |
| COPD                                     | 423 (26%)    | 309 (28)                | 104 (24)                   | 9 (18)                | 1 (14)                | 0.23                       | 416 (27)                     | 7 (14)                      | 0.035                     |
| Cancer                                   | 338 (21%)    | 263 (23)                | 62 (15)                    | 11 (22)               | 2 (28)                | 0.002                      | 331 (21)                     | 7 (14)                      | 0.18                       |
| Chronic kidney disease                   | 261 (16%)    | 141 (13)                | 113 (27)                   | 7 (14)                | 0 (0)                 | <0.001                     | 258 (17)                     | 3 (6)                       | 0.040                     |
| Chronic liver disease                    | 183 (11%)    | 121 (11)                | 53 (12)                    | 7 (14)                | 2 (28)                | 0.38                       | 173 (11)                     | 10 (20)                     | 0.064                     |
| HIV/AIDS                                 | 59 (4%)      | 14 (1)                  | 44 (10)                    | 0 (0)                 | 1 (14)                | <0.001                     | 58 (4)                       | 1 (2)                       | 0.50                       |
| Admission diagnosis category             |              |                         |                             |                        |                       |                           |                              |                             |                            |
| Infectious*                              | 472 (30%)    | 291 (26)                | 168 (40)                   | 12 (24)               | 1 (14)                | <0.001                     | 460 (30)                     | 12 (24)                     | 0.34                       |
| Cardiovascular                           | 467 (29%)    | 300 (27)                | 150 (35)                   | 16 (31)               | 1 (14)                | 0.01                       | 462 (30)                     | 5 (10)                      | 0.002                     |
| Gastrointestinal                         | 236 (15%)    | 170 (15)                | 60 (14)                    | 5 (10)                | 1 (14)                | 0.72                       | 231 (15)                     | 5 (10)                      | 0.31                       |
| Trauma                                   | 101 (6%)     | 73 (6)                  | 24 (6)                     | 3 (6)                 | 1 (14)                | 0.76                       | 98 (6)                       | 3 (6)                       | 0.89                       |
| Endocrine                                | 101 (6%)     | 64 (6)                  | 35 (8)                     | 2 (4)                 | 0 (0)                 | 0.24                       | 98 (6)                       | 3 (6)                       | 0.89                       |
| Other                                    | 235 (15%)    | 166 (15)                | 59 (14)                    | 8 (16)                | 2 (28)                | 0.72                       | 230 (15)                     | 5 (10)                      | 0.31                       |
| Admission source                         | <0.001       |                         |                             |                        |                       |                           |                              |                             |                            |
| Emergency department                     | 715 (45%)    | 444 (40)                | 246 (58)                   | 22 (43)               | 3 (43)                | --                        | 685 (44)                     | 30 (59)                     | --                        |
| Hospital floor                           | 315 (20%)    | 215 (19)                | 86 (20)                    | 11 (22)               | 3 (43)                | --                        | 305 (20)                     | 10 (20)                     | --                        |
| Operating room                           | 255 (16%)    | 201 (18)                | 44 (10)                    | 9 (18)                | 1 (14)                | --                        | 249 (16)                     | 6 (12)                      | --                        |
| Outside hospital                         | 252 (16%)    | 212 (19)                | 33 (8)                     | 7 (14)                | 0 (0)                 | --                        | 248 (16)                     | 4 (8)                       | --                        |
| Other                                    | 58 (4%)      | 41 (4)                  | 15 (4)                     | 2 (4)                 | 0 (0)                 | --                        | 57 (4)                       | 1 (2)                       | --                        |

**TABLE 2: Patient characteristics by racial and ethnic categories**

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A total of 26% (n = 411) of the patients in this cohort were diagnosed with ARDS, and 27% (435) of mechanically ventilated patients in this cohort received tidal volumes above 8 mL/kg PBW. There was no difference in hospital mortality in those who received lung-protective ventilation (31%) vs those who received tidal volumes above 8 mL/kg PBW (26%, p = 0.11).

### Complete case analysis

**Relationship Between Gender and Provision of Lung-Protective Ventilation**

Unadjusted tidal volumes were lower in women vs men (400 [360–450] mL vs 500 [450–550] mL, Table 3 and Figure 2).

| Gender | Insurance status | Tidal volume (mL) | P-Value | Tidal volume/PBW (mL/kg) | P-Value | Tidal volume > 8 mL/kg PBW | P-Value | unadjusted odds ratio | P-Value | Height-adjusted odds ratio | P-Value |
|--------|------------------|------------------|---------|--------------------------|---------|----------------------------|---------|----------------------|---------|--------------------------|---------|
| Women (n= 710) | Underinsured (n = 338) | 400 (360 – 450) | <0.001 | 7.6 (6.7 – 8.6) | <0.001 | 3.43 (2.67 – 4.40) | <0.001 | 1.28 (0.91 – 1.60) | 0.15 | 1.28 (0.92 – 1.77)† | 0.14 |
| Men (n = 885) | Insured (n = 1,257) | 500 (450 – 550) | 7.0 (6.2 – 8.0) | 7.1 (6.4 – 8.2) | 1.26 (0.92 – 1.74) | 1 (ref) | 1 (ref) | --- | --- | --- |

**TABLE 3: Relationships of lung-protective ventilation with gender and insurance status**

Note: Values refer to median (interquartile range) or number (percentage)

†Adjusted for age (continuous), height (continuous), total number of comorbidities (0-5). §Adjusted for age (continuous), post-operative from elective surgery status, race, ethnicity, total number of comorbidities (0-5).

Abbreviations: PBW, predicted body weight
However, women received higher tidal volume than men when adjusted for PBW (7.6 [6.7-8.6] mL/kg in women vs 6.7 [6.0-7.6] in men) and were more likely to receive tidal volumes above 8 mL/kg PBW (40% of women vs 17% of men, odds ratio [OR] = 3.43 [2.67-4.40]).

Our hypothesized causal diagram indicated that height may mediate the association between gender and lung-protective ventilation [24] (Figure 3).
When we adjusted for patient height, the association between gender and tidal volume > 8 mL/kg PBW was substantially weakened (OR = 1.28 [0.91-1.80]), demonstrating that height was a strong mediator of the gender and tidal volume relationship. However, to examine whether gender plays a role in tidal volume choice in subgroups of taller and shorter patients, we performed stratified analysis with dichotomous height classification using the median height of 5 feet 7 inches of all patients, as in prior research [17]. We found that gender-based differences in tidal volume > 8 mL/kg PBW occurred both in shorter patients (OR = 1.66, 95% CI = 1.13-2.42) and taller patients (OR = 1.82, 95% CI = 1.14-2.91). This suggests that gender continued to play a role in tidal volume selection despite gender differences in height. Furthermore, the effect estimate for gender was similar across height categories (as above, 1.66 vs 1.82). The lack of heterogeneity between these effect sizes indicates that height is not a significant effect-modifier for the gender-tidal volume relationship, that is, we did not find an interaction between height and gender in predicting tidal volume (see "effect modification (interaction) analysis" in the supplement).

Mediation analysis further explored the relationship between gender and height in predicting tidal volume.
This analysis indicates that a direct effect of female gender on choice of tidal volume was operative in approximately 39% of cases where the provision of tidal volume > 8 mL/kg PBW was related to gender and/or height. Likewise, an indirect mediation pathway, where gender affects height, which, in turn, affects tidal volume choice, was operative in 59% of cases where the provision of tidal volume > 8 mL/kg PBW was related to gender and/or height.

Our hypothesized causal diagram (Figure 3 and Supplementary Table 13) modeled age and comorbidity as variables that could be associated with height (the mediator) and tidal volume choice (the outcome) [25,26]. Multivariable analysis with these covariates demonstrated similar findings to the analysis adjusting for height alone (Table 3). These results indicate minimal influence of age and comorbidity on the gender-height-tidal volume relationship.

**Relationship Between Race/Ethnicity and Lung-Protective Ventilation**

Unadjusted and PBW-adjusted tidal volumes were similar among racial and ethnic categories (Table 4).

| Race/Ethnicity               | Tidal volume (mL) | Tidal volume/PBW (mL/kg) | Tidal volume > 8 mL/kg PBW |
|-----------------------------|-------------------|--------------------------|---------------------------|
| White (n = 1,113)           | 450 (400 – 500)   | 7.1 (6.2 – 8.0)          | 303 (27)                  |
| Black (n = 424)             | 450 (400 – 500)   | 7.07 (6.2 – 8.0)         | 115 (27)                  |
| Asian (n = 51)              | 450 (390 – 500)   | 7.6 (6.4 – 8.3)          | 16 (31)                   |
| American Indian/Alaska      | 350 (300 – 500)   | 6.7 (5.9 – 7.3)          | 1 (14)                    |
| native (n = 7)              |                   |                          |                           |
| Non-Hispanic or Latino      | 450 (400 – 500)   | 7.1 (6.2 – 8.0)          | 419 (27)                  |
| (n = 1,544)                 |                   |                          | 16 (31)                   |
| Hispanic or Latino          | 450 (400 – 500)   | 7.2 (6.4 – 8.2)          |                           |
| (n = 51)                    |                   |                          |                           |

**Table 4:** The relationship of lung-protective ventilation with race/ethnicity

Note: Values refer to median (interquartile range) or number (percentage)

‡ Adjusted for gender, insurance status, and total number of comorbidities (0-5)

Abbreviations: PBW, predicted body weight

These findings were similar after adjustment for gender, insurance status, and comorbidity [27,28] (Table 4; also see Figure 3 illustrating the proposed causal pathway involving these covariates and Supplementary Table 14 detailing relationships between these covariates and race/ethnicity).

**Relationship Between Insurance Status and Lung-Protective Ventilation**

PBW-adjusted tidal volumes were slightly higher in underinsured compared to insured patients (Table 3). There were slightly more underinsured patients receiving tidal volume > 8 mL/kg IBW when compared to insured patients (31% vs 26%, OR = 1.26, 95% CI = 0.92-1.74).

We considered age, race/ethnicity, comorbidity, and ICU admission after elective surgery as potential confounders of the relationship between insurance status and lung-protective ventilation (Figure 3 and Supplementary Table 15) [27,29]. The association between underinsurance and tidal volume above 8 mL/kg PBW was stronger after adjusting for these covariates (OR = 1.55, 95% CI = 1.15-2.07, Table 3). This masking of the true association is explained by the confounding effects of age and ICU admission after elective surgery. These variables were “negatively” associated with the independent variable of interest (underinsurance) and “positively” associated with the outcome of interest (tidal volume above 8 mL/kg PBW).
ICU care, with less aggressive treatment in women vs men, suggesting gender bias in treatment delivery with ARDS and height differences between men and women mediate a large portion of this effect, our analysis suggests that gender also has a direct effect on tidal volume choice. Furthermore, we found that underinsured patients were less likely to receive lung-protective ventilation than insured patients after accounting for other imbalances between these groups.

Discussion

In this multicenter prospective cohort study of critically ill patients with respiratory failure in the United States, we found that women were less likely to receive lung-protective ventilation compared to men. While height differences between men and women mediate a large portion of this effect, our analysis suggests that gender also has a direct effect on tidal volume choice. Furthermore, we found that underinsured patients were less likely to receive lung-protective ventilation than insured patients after accounting for other imbalances between these groups.

The gender disparity we observed in tidal volume is consistent with Han et al.' finding that women with sepsis and ARDS are less likely to receive lung-protective ventilation than men [24], a finding attributed to the shorter height of women. A more recent large study including two U.S. ICU cohorts also demonstrated gender differences in tidal volumes, fully explained by the shorter height of women [12]. Our study reinforces these findings in a separate prospective and multicenter cohort of unselected mechanically ventilated critically ill patients.

Height-based differences in care delivery like the one described here could play a role in the inverse relationship that has been observed between height and mortality in the critically ill [50]. These differences may be exacerbated by overestimating height in shorter patients, thus exposing them to excessive tidal volumes [31]. Our dataset did not specify whether heights were measured or estimated. If estimated, our results may be biased toward underestimating the frequency of high tidal volumes in shorter patients, many of whom are women.

Height may be sufficient to explain gender difference in tidal volume [12]. However, our mediation analysis suggests that a direct effect of female gender on tidal volume choice contributed to 39% of the cases in which high tidal volume was related to gender and/or height. In addition, the gender difference in tidal volume was observed in shorter and taller individuals stratified by the median height > 5 feet 7 inches. Finally, our multiple imputation analysis in the larger sample size indicated that gender was associated with tidal volume > 8 mL/kg PBW even after adjusting for height. These three findings suggest the possibility that gender may influence tidal volume choice, even after accounting for height, as shown previously in patients with ARDS [17]. A number of previous studies have reported gender-based disparities in other aspects of ICU care, with less aggressive treatment in women vs men, suggesting gender bias in treatment delivery [3,7,32].
Sex differences in the PBW formula are an additional factor that could contribute to this gender disparity, providing different PBW-based tidal volumes for women vs men of the sameheight. For example, the 8 mL/kg PBW tidal volume is 493 mL for women 5 feet 7 inches in stature vs 529 mL for men of the same height. If the tidal volume is set at 500 mL for both, only women receive a tidal volume > 8 mL/kg PBW. Although sex-based PBW formulas may be unnecessary for other applications [33], they are appropriate for tidal volume optimization because of sex differences in lung volume [34,35]. Creating ventilator algorithms that calculate and deliver tidal volumes bases on clinician-entered values for sex, measured height, and desired mL/kg PBW tidal volume could more consistently provide lung-protective ventilation than the current practice of ordering absolute unadjusted tidal volume [36].

We found that underinsured patients were less likely than insured patients to receive lung-protective ventilation. To our knowledge, this insurance-based disparity in tidal volume has not been reported previously, though insurance status-based differences in other ICU processes of care are well-known [2,4,27]. Access to acute care probably does not account for this disparity since all patients were receiving critical care at the time of enrollment in our study. Likewise, differences in ICU quality are unlikely to explain our findings since robust variance estimation with ICU-level clustering in our logistic models accounted for the possibility that patients within individual ICUs are correlated. Finally, different treatment preferences or beliefs are unlikely to explain these findings because tidal volume is not a value-sensitive decision and it is improbable that preferences of patient or surrogate decision makers could have influenced tidal volume choice. It is possible that clinicians’ implicit biases influenced their adherence to lung-protective ventilation [37,38], negatively impacting underinsured patients. Prior studies have demonstrated that treatment decisions by clinicians in acute care are influenced by socioeconomic status-based implicit bias [39,40]. Further work is warranted to identify whether insurance-based bias exists in critical care, define its effect on treatment decisions, and test strategies for its elimination.

We did not find racial or ethnic differences in the application of lung-protective ventilation. These results are surprising in the context of numerous studies demonstrating significant racial differences in critical care and outcomes [2,41-43]. Our regression models were clustered by ICU, accounting for potential correlations in processes of care within these ICUs. Prior studies have shown that racial differences in critical care outcomes are attenuated after adjustment for the site (and, by extension, the quality) of care delivery [44,45]. That said, even our unadjusted analyses did not show differences in lung-protective ventilation by race or ethnicity (Table 2).

Our negative findings regarding race and ethnicity may relate to the limitations of our study. Our racial designations were gleaned from the medical records by data abstractors at each site. It is unknown whether these racial designations were consistently recorded in the medical records using the preferred method of self-report [46]. In addition, the medical records frequently contained ambiguous terminology that could not be confidently classified into one of the standard designations [47], contributing to the high number of missing values in our dataset. Even though we did not observe racial/ethnic differences in tidal volume, our analyses demonstrated that minority populations are overrepresented among the underinsured (Supplementary Table 12) and therefore remain at risk of not receiving lung-protective ventilation [27].

Our cohort included all mechanically ventilated patients. Lung-protective ventilation is considered best practice in ARDS, though it is not invariably applied, with average tidal volume of 7.8 mL/kg in ARDS patients across 50 countries [8]. In patients without ARDS, lung-protective ventilation may not be the standard of care, but several studies support its use in these patients as well, showing lower levels of pro-inflammatory cytokines, lower radiographic evidence of lung injury, shorter hospital stays, and less post-operative pulmonary complications [10,11,48-50]. A randomized controlled trial showed no differences in clinical outcomes when patients were randomized to low vs intermediate tidal volume [51], but a large amount of overlap in tidal volume between groups may have biased these results toward the null [52]. Regardless of whether universally accepted in non-ARDS acute respiratory failure, differences in the application of lung-protective ventilation in these demographic groups are an important signal of disparities in ICU care.

Strengths and limitations

Our study has several strengths, particularly the prospective cohort design, manual data abstraction, large sample size, and nationwide ICU representation from 35 medical centers. There are several limitations to our study. First, our observational study design does not permit conclusions about whether there is any causal basis for the associations we observed between tidal volume and gender, height, and insurance status. Likewise, we cannot rule out residual confounding by other unmeasured variables that may explain these associations. Our use of causal models to define potential confounders may be oversimplified and miss important covariates that could be responsible for our findings [19]. For example, we were unable to determine which patients in this dataset had ARDS, and its presence would influence tidal volume. If ARDS were differentially distributed among our demographic groups, this could confound our findings. However, consistent demonstration of disparities in processes of care across different studies increases the likelihood that the similar associations we report are robust [2-4,7,24,39]. Our findings thus add to the evidence suggesting that women, shorter people, and the underinsured are treated differently in U.S. ICUs. Second, our cohort included predominantly academic institutions, and thus its applicability to patients in
community hospital may be limited. Third, we collected each patient’s ventilator data only once, and it may have been on any day from 1 to 10 of their ICU stay. This “snapshot” of tidal volume delivery may not accurately reflect the volume received throughout their treatment with invasive mechanical ventilation. Fourth, height, race, and gender were taken from the medical record without specification about how they were originally ascertained. We are unsure whether race and ethnicity were consistently obtained by the recommended method of self-report [46]. If not, there is risk of non-differential ascertainment bias and possible obscuration of true racial differences [53]. Likewise, heights may have been inaccurate if they were estimated instead of measured, with overestimation particularly likely in women, [51] and accompanying risk of differential ascertainment bias. If so, gender differences in lung-protective ventilation may be even larger than we report here. Fifth, it is important to note that the associations we identify in this study may have changed considerably since 2010-2012 when our data was obtained. In this regard, it is important to note that Swart et al. observed an increase in lung-protective ventilation increased between 2001 and 2015, but gender disparities in lung-protective ventilation persisted through this time interval nevertheless [12]. Determining whether the disparities we observed persist in a more contemporary cohort is an important next step.

Conclusions
This analysis of a large prospective cohort study demonstrates disparities in the provision of lung-protective ventilation in the United States. Women were less likely to receive lung-protective ventilation compared to men, an association largely but not fully explained by the shorter height of women. Furthermore, we find a robust association between underinsurance and non-adherence to lung-protective ventilation especially after accounting for other imbalances between patients with different insurance types. Tidal volume prescription is a clinical management decision. Our findings suggest this decision may be biased by demographic and phenotypic factors such as insurance status, gender, and height. Additional research is required to confirm these findings, evaluate the extent to which implicit bias determines processes of ICU care, and test interventions to eliminate these disparities.

Appendices
Supplement

Multiple Imputation Methods

Race/ethnicity was missing in 96 patients, height was missing in 147 patients, and tidal volume was missing in 738 patients in the full dataset. STATA/SE 14.2 was used for all multiple imputation analyses. The Stata commands for the imputation step, and the completed data analysis/pooling steps are shown in Supplementary Table 5.
We assumed that the mechanism for missingness was not dependent on the unobserved data. For example, a patient’s height was not missing because shorter people tended to have height recorded less frequently, a patient’s race was not missing because black patients were less likely to have their race recorded, and a patient’s tidal volume was not missing because patients receiving higher tidal volumes were less likely to have their tidal volumes recorded in the respiratory flowsheets. This was assumed because the variables with missing values are routinely collected and entered into the medical record by hospital staff. Study investigators used this medical record as the primary source of data abstraction. If hospital personnel did not enter a value for one of these fields, it was recorded as missing by study investigators. It seems unlikely that the missing data for these variables depended on the unobserved data, as in the examples above. Instead, it seems more plausible that these data were missing because of human error in the completeness of medical record keeping by hospital staff and that this did not depend on the missing variables themselves. For these reasons, we considered these data missing at random (MAR) \cite{54}. Finally, we did not make any assumptions about the pattern of missingness and instead assumed that missingness was arbitrary \cite{22}.

We used multiple imputation using chained equations (MICE) with the “augment” option to avoid perfect prediction as the imputation method \cite{22,55,56}. Our imputation model included the primary outcome variable (tidal volume \(> 8 \text{mL/kg PBW}\) [predicted body weight]), our pre-specified covariables from the primary multivariable analyses (Figure 3), and all variables predictive of the missing values (those variables differing \(p < 0.05\) between observations with vs without missing values for race/ethnicity, height, or set tidal volume) \cite{54}. These values included insurance status, APACHE II score, SOFA score, medical history of heart failure, cancer, chronic kidney disease, or HIV infection, a trauma or endocrine admission diagnoses, the source of hospital admission, the ICU type, the hospital type, the presence of nutrition or acute lung injury protocols, or the presence of a daily plan of care (Supplementary Table 6).
|                          | (2,513) | 1,730) | 783) | 61 (50 – 71) | 55 (41 – 67) |
|--------------------------|---------|--------|------|--------------|--------------|
| Age (years)              | 61 (50 – 71) | 60 (50 – 71) | 61 (49 – 72) | 61 (50 – 71) | 55 (41 – 67) |
| Race                     |         |        |      |              |              |
| White                    | 1,620 (67) | 1,113 (70) | 571 (79) | 1.60 (1.30 – 1.99) |  |
| Black                    | 424 (26) | 137 (19) | 0.64 (0.51 – 0.80) |  |
| Asian                    | 51 (3) | 13 (2) | 0.55 (0.27 – 1.04) |  |
| American Indian/Alaskan native | 7 (0.4) | 4 (0.6) | 1.26 (0.27 – 4.97) |  |
| Ethnicity                | 0.52 (0.33 – 0.78) |  |
| Non-Hispanic             | 2,354 (94) | 1,602 (93) | 752 (96) |  |
| Hispanic                 | 159 (6) | 128 (7) | 31 (4) |  |
| Gender                   | 0.94 (0.79 – 1.11) | 0.73 (0.53 – 1.00) |  |
| Men                      | 1,413 (56) | 964 (55) | 449 (57) | 1,291 (56) | 122 (63) |
| Women                    | 1,100 (43) | 766 (44) | 334 (43) | 1,029 (44) | 71 (37) |
| Insurance status         | 0.67 (0.53 – 0.84) |  |
| Insured                  | 1,195 (79) | 1,340 (77) | 655 (84) | 1,865 (80) | 130 (67) |
| Underinsured             | 518 (21) | 390 (23) | 128 (16) | 455 (20) | 63 (33) |
| APACHE II score          | 20 (15 – 25) | 21 (16 – 26) | 18 (13 – 22) | 20 (15 – 25) | 18 (14 – 24) |
| SOFA score               | 6 (4 – 9) | 7 (4 – 10) | 5 (3 – 8) | 6 (4 – 9) | 6 (4 – 9) |
| Hospital mortality†      | 0.76 (0.62 – 0.94) | 1.07 (0.76 – 1.50) |  |
| No                       | 1,687 (72) | 1,136 (70) | 551 (76) | 1,552 (72) | 135 (71) |
| Yes                      | 655 (28) | 478 (30) | 177 (24) | 599 (28) | 56 (29) |
| Hospital length of stay (days)† | 18 (10 – 30) | 17 (10 – 30) | 18 (11 – 30) | 17 (10 – 30) | 19 (12 – 31) |
| ICU length of stay (days)† | 10 (5 – 18) | 10 (5 – 18) | 11 (5 – 19) | 10 (5 – 18) | 13 (6 – 20) |
| Comorbid conditions      |         |        |      |              |              |
| Heart failure            | 378 (15) | 287 (17) | 91 (12) | 0.66 (0.51 – 0.86) | 0.83 (0.51 – 1.29) |
| COPD                     | 639 (25) | 449 (26) | 190 (24) | 0.91 (0.75 – 1.12) | 0.88 (0.61 – 1.26) |
| Condition                      | N1     | N2     | N3     | OR    | 95% CI           | p-value |
|--------------------------------|--------|--------|--------|-------|------------------|---------|
| Cancer                         | 557 (22) | 351 (20) | 206 (26) | 1.40 (1.14 – 1.72) | 0.52 (0.33 – 0.81) |
| Chronic kidney disease         | 375 (15) | 284 (16) | 91 (12)  | 0.67 (0.51 – 0.87) | 0.92 (0.58 – 1.42) |
| Chronic liver disease          | 288 (11) | 208 (12) | 80 (10)  | 0.83 (0.62 – 1.10) | 1.53 (0.99 – 2.32) |
| HIV/AIDS                       | 75 (3)  | 63 (4)  | 12 (2)   | 0.41 (0.20 – 0.78) | 0.67 (0.18 – 1.82) |
| Admission diagnosis category   |        |        |         |       |                  |         |
| Respiratory                    | 1,345 (54) | 937 (54) | 408 (52) | 0.92 (0.77 – 1.09) | 1.24 (0.73 – 1.35) |
| Infectious                     | 723 (29) | 529 (30) | 203 (26) | 0.81 (0.67 – 0.99) | 1.22 (0.88 – 1.68) |
| Cardiovascular                 | 709 (28) | 503 (29) | 206 (26) | 0.87 (0.72 – 1.06) | 0.78 (0.54 – 1.11) |
| Gastrointestinal               | 381 (15) | 264 (15) | 117 (15) | 0.98 (0.76 – 1.24) | 1.46 (0.98 – 2.13) |
| Trauma                         | 207 (8)  | 121 (7)  | 86 (11)  | 1.64 (1.21 – 2.21) | 1.93 (1.20 – 3.01) |
| Endocrine                      | 139 (6)  | 111 (6)  | 28 (4)   | 0.54 (0.34 – 0.83) | 1.04 (0.49 – 1.96) |
| Other                          | 383 (15) | 257 (15) | 126 (16) | 1.10 (0.88 – 1.39) | 0.98 (0.63 – 1.49) |
| Admission source               |        |        |         |       |                  |         |
| Emergency department           | 1,061 (42) | 776 (45) | 285 (36) | 0.70 (0.59 – 0.84) | 0.92 (0.67 – 1.25) |
| Hospital floor                 | 515 (20) | 342 (20) | 173 (22) | 1.15 (0.93 – 1.42) | 1.02 (0.69 – 1.47) |
| Operating room                 | 406 (16) | 267 (15) | 139 (18) | 1.18 (0.94 – 1.49) | 0.61 (0.36 – 0.98) |
| Outside hospital               | 415 (16) | 281 (16) | 134 (17) | 1.06 (0.84 – 1.34) | 1.60 (1.10 – 2.30) |
| Other                          | 116 (5)  | 64 (4)   | 52 (7)   | 1.85 (1.24 – 2.74) | 1.01 (0.44 – 2.04) |
| ICU type                       |        |        |         |       |                  |         |
We handled variables with skewed distributions by using mathematical transformations to approximate normal distributions prior to the imputation step. Once the imputation step was complete, we back-transformed these variables to their original scale [54].

One or more of height, tidal volume, and race/ethnicity was missing in 833 of the 2,513 patients (33%). We used 40 imputations to exceed this 33% frequency of missing values [55,57]. The values from each imputation were similar to each other and to those from the complete cases, indicating that the imputation model was appropriate and suggesting that the MAR assumption was plausible in the context of this model (Supplementary Table 7) [57].

### TABLE 6: Patient characteristics (all mechanically ventilated patients) and comparison of patients with vs without missing values

Note: Values refer to median (interquartile range) or number (percentage).

†Mortality status, ICU length of stay, and hospital length of stay were missing in 171 patients.

Abbreviations: ht, height; vt, tidal volume; OR, odds ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome

| Hospital type | Number of hospital beds | Nutrition protocol | Acute lung injury protocol | Daily plan of care |
|---------------|------------------------|-------------------|------------------------|------------------|
| Medical       | 1,178 (47) 845 (49) 333 (42) | 0.78 (0.65 – 0.92) | 1.081 (46) 97 (50) | 1.16 (0.85 – 1.57) |
| Surgical      | 860 (34) 536 (31) 324 (41) | 1.57 (1.31 – 1.88) | 781 (34) 79 (41) | 1.36 (1.00 – 1.86) |
| Mixed         | 475 (19) 349 (20) 126 (16) | 0.76 (0.60 – 0.95) | 458 (20) 17 (9) | 0.39 (0.22 – 0.66) |
| Hospital type |                        |                   |                        |                  |
| Private (not-for-profit) | 1,637 (65) 1,036 (60) 601 (77) | 2.21 (1.82 – 2.69) | 1,516 (65) 121 (63) | 0.89 (0.65 – 1.22) |
| Private (for profit)       | 153 (6) 121 (7) 32 (4) | 0.57 (0.37 – 0.85) | 149 (6) 4 (2) | 0.31 (0.08 – 0.82) |
| Public (non-federal)       | 708 (28) 562 (32) 146 (19) | 0.48 (0.38 – 0.59) | 640 (28) 68 (35) | 1.43 (1.03 – 1.96) |
| Federal                  | 15 (1) 11 (0.6) 4 (0.5) | 0.80 (0.19 – 2.72) | 15 (1) 0 (0) | --- |
| Number of hospital beds | 687 (496 – 873) 724 (496 – 885) 615 (470 – 845) | 687 (470 – 873) 724 (550 – 800) | 1,515 (60) 980 (57) 535 (68) | 1.65 (1.36 – 1.98) 1,210 (52) 112 (59) | 1.31 (0.96 – 1.80) |
| Nutrition protocol | 2,033 (81) 1,364 (79) 669 (85) | 1.57 (1.24 – 2.0) | 1,919 (83) 114 (59) | 0.30 (0.22 – 0.42) |
| Acute lung injury protocol | 2,138 (85) 1,427 (82) 711 (91) | 2.10 (1.59 – 2.79) | 1,974 (85) 164 (85) | 0.99 (0.65 – 1.55) |
| Height\(\text{inches}\) | Tidal volume\(\text{mL}\) | Race (percent) |
|--------------------------|-------------------|--------------|
| Actual* | 66.5 (4.5) | 458 (88) | 72 | 24 | 3 | 0.5 |
| Imputation 1† | 66.6 (4.5) | 462 (89) | 73 | 23 | 3 | 0.5 |
| Imputation 2 | 66.6 (45) | 462 (89) | 73 | 24 | 3 | 0.6 |
| Imputation 3 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 4 | 66.6 (4.5) | 460 (88) | 73 | 24 | 3 | 0.4 |
| Imputation 5 | 66.6 (4.5) | 461 (89) | 74 | 23 | 3 | 0.4 |
| Imputation 6 | 66.6 (4.5) | 459 (88) | 73 | 23 | 3 | 0.5 |
| Imputation 7 | 66.6 (4.5) | 460 (89) | 73 | 24 | 3 | 0.6 |
| Imputation 8 | 66.6 (4.5) | 461 (87) | 73 | 23 | 3 | 0.5 |
| Imputation 9 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 10 | 66.6 (4.5) | 461 (88) | 72 | 23 | 4 | 0.6 |
| Imputation 11 | 66.6 (4.5) | 459 (87) | 73 | 24 | 3 | 0.7 |
| Imputation 12 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 13 | 66.6 (4.5) | 460 (88) | 73 | 23 | 3 | 0.5 |
| Imputation 14 | 66.6 (4.5) | 460 (89) | 73 | 23 | 3 | 0.5 |
| Imputation 15 | 66.6 (4.5) | 459 (88) | 74 | 23 | 3 | 0.5 |
| Imputation 16 | 66.6 (4.5) | 461 (88) | 73 | 24 | 3 | 0.4 |
| Imputation 17 | 66.6 (4.5) | 460 (88) | 73 | 23 | 3 | 0.5 |
| Imputation 18 | 66.6 (4.5) | 461 (88) | 73 | 24 | 3 | 0.6 |
| Imputation 19 | 66.6 (4.5) | 460 (88) | 73 | 23 | 3 | 0.4 |
| Imputation 20 | 66.6 (4.5) | 459 (88) | 73 | 23 | 3 | 0.6 |
| Imputation 21 | 66.6 (4.5) | 459 (87) | 73 | 24 | 3 | 0.6 |
| Imputation 22 | 66.6 (4.5) | 459 (87) | 73 | 24 | 3 | 0.4 |
| Imputation 23 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.6 |
| Imputation 24 | 66.6 (4.5) | 461 (90) | 73 | 24 | 3 | 0.5 |
| Imputation 25 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.4 |
| Imputation 26 | 66.6 (4.5) | 461 (88) | 74 | 23 | 3 | 0.5 |
| Imputation 27 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.7 |
| Imputation 28 | 66.6 (4.5) | 459 (89) | 73 | 24 | 3 | 0.4 |
| Imputation 29 | 66.6 (4.5) | 460 (89) | 73 | 23 | 3 | 0.8 |
| Imputation 30 | 66.5 (4.5) | 461 (87) | 74 | 23 | 3 | 0.5 |
| Imputation 31 | 66.6 (4.5) | 460 (88) | 73 | 24 | 3 | 0.6 |
| Imputation 32 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.7 |
| Imputation 33 | 66.6 (4.5) | 461 (88) | 74 | 23 | 3 | 0.4 |
| Imputation 34 | 66.5 (4.5) | 460 (88) | 73 | 24 | 3 | 0.5 |
| Imputation 35 | 66.6 (4.5) | 458 (87) | 73 | 24 | 3 | 0.4 |
| Imputation 36 | 66.6 (4.5) | 460 (89) | 73 | 24 | 3 | 0.5 |
We then completed data analysis using the same covariables and logistic regression method as in the complete case analyses for each imputation set, and the results were pooled. Stability of the resulting effect estimates was assessed by varying the number of imputations between 10 and 40.

**Supplementary Results**

Effect modification (interaction) analysis: We used the methods of Matthews et al. [58] to investigate the possibility of heterogeneity in the effect of gender on tidal volume > 8 mL/kg PBW by height categories. The following categories were tabulated:

- Proportion of women of lower height receiving tidal volume > 8 mL/kg PBW (265/604): 0.44
- Proportion of men of lower height receiving tidal volume > 8 mL/kg PBW (51/159): 0.32
- The effect of female gender on tidal volume choice (as a proportion) in shorter patients:
  \[ 0.44 - 0.32 = 0.12 \]
- Proportion of women of higher height receiving tidal volume > 8 mL/kg PBW (23/106): 0.22
- Proportion of men of higher height receiving tidal volume > 8 mL/kg PBW (96/726): 0.13
- The effect of female gender on tidal volume choice (as a proportion) in taller patients:
  \[ 0.22 - 0.13 = 0.09 \]
- The difference in the effect of female gender on tidal volume choice in shorter vs taller individuals:
  \[ 0.12 - 0.09 = 0.03 \]

We then calculated the standard error for this difference in the effect of female gender on tidal volume choice in shorter vs taller individuals to be 0.015 [59].

From here, the 95% CI for the difference in the effect of female gender on tidal volume choice in shorter vs taller individuals is 0.00-0.06. Since this CI included zero, we conclude that there is no significant difference in the effect of female gender on tidal volume choice by category of height.

Mediation analysis: Pearl’s mediation formula [23] was employed to assess the extent to which shorter height mediates the effect of female gender on excessive tidal volume. In this analysis, the exposure (X) is female gender, the mediator (Z) is height < 5’7”, and the outcome (Y) is tidal volume > 8 mL/kg PBW. The mediation formula requires calculation of \( E(Y|x,z) \): the expected proportion of patients with or without the exposure (X) and with or without the mediator (Z) but with the outcome of interest (Y), given by \( g(x,z) \), and \( E(Z|x) \): the expected proportion of patients with or without the exposure (X) but with the mediator (Z), given by \( h(x) \). The formulas for calculating these parameters and the calculations themselves are given in Supplementary Tables 6, 9.
| Number of observations | Exposure (X)* | Mediator (Z)† | Outcome (Y)‡ | E(Y|x,z) = g_{x,z} | E(Z|x) = h_x |
|------------------------|---------------|---------------|--------------|-----------------|-------------|
| n_1                    | 0             | 0             | 0            | \frac{n_2}{n_1+n_2} = g_{0,0} |             |
| n_2                    | 0             | 0             | 1            |                 | (n_3+n_4)/(n_1+n_2+n_3+n_4) = h_{0} |
| n_3                    | 0             | 1             | 0            | n_4/(n_3+n_4) = g_{0,1} |             |
| n_4                    | 0             | 1             | 1            |                 |             |
| n_5                    | 1             | 0             | 0            | n_6/(n_5+n_6) = g_{0,0} |             |
| n_6                    | 1             | 0             | 1            |                 | (n_7+n_8)/(n_5+n_6+n_7+n_8) = h_{0} |
| n_7                    | 1             | 1             | 0            | n_8/(n_7+n_8) = g_{0,1} |             |
| n_8                    | 1             | 1             | 1            |                 |             |

**TABLE 8: Parameters required for mediation analysis: formulas**

\*x = 0 if gender = male, 1 if gender = female. †z = 0 if height ≥ 5'7", z = 1 if height < 5'7". ‡y = 0 if tidal volume ≤ 8 mL/kg PBW, y = 1 if tidal volume > 8 mL/kg PBW.

PBW, predicted body weight

| Number of observations | Exposure (X) | Mediator (Z) | Outcome (Y) | E(Y|x,z) = g_{x,z} | E(Z|x) = h_x |
|------------------------|--------------|--------------|-------------|-----------------|-------------|
| 630                    | 0            | 0            | 0           | g_{0,0} = 0.132 |             |
| 96                     | 0            | 0            | 1           | h_{0} = 0.180   |             |
| 108                    | 0            | 1            | 0           | g_{0,1} = 0.321 |             |
| 51                     | 0            | 1            | 1           |                 |             |
| 83                     | 1            | 0            | 0           | g_{1,0} = 0.217 | h_{1} = 0.851|
| 23                     | 1            | 0            | 1           |                 |             |
| 339                    | 1            | 1            | 0           | g_{1,1} = 0.439 |             |
| 265                    | 1            | 1            | 1           |                 |             |

**TABLE 9: Parameters required for mediation analysis: calculations**

The results are summarized in supplementary Tables 10, 11.
These parameters, in turn, permit calculation of the direct effect of changing X on Y, the indirect effect of changing X on Y via the mediator Z, and the total effect of changing X on Y, accounting for both the direct and indirect pathways. The formulas and results of these calculations are given below:

Direct effect (DE) = (g1,0 - g0,0)(1 - h0) + (g1,1 - g0,1)x h0
DE = (0.22 - 0.13)(1 - 0.18) + (0.44 - 0.32)x 0.18
DE = 0.09 x 0.82 + 0.12 x 0.18
DE = 0.074 + 0.022
DE = 0.096 = 9.6%

Indirect effect (IE) = (h1 - h0)(g0,1 - g0,0)
IE = (0.85 - 0.18)(0.32 - 0.13)
IE = (0.67)(0.19)
IE = 0.127 = 12.7%

Total effect (TE) = [(g1,1 x h1) + g1,0(1 - h1)] - [(g0,1 x h0) + g0,0(1 - h0)]
TE = [(0.44 x 0.85) + 0.22(1 - 0.85)] - [(0.32 x 0.18) + 0.13(1 - 0.18)]
TE = (0.37 + 0.03) - (0.058 + 0.11)
TE = 0.40 - 0.168 = 0.232 = 25%

The analysis and interpretation of these effects are shown in Supplementary Table 12.
Effect calculations | Interpretation
--- | ---
1 - (IE/TE) = 1 - (0.127/0.230) = 0.055 = 55% | 55% of instances of high tidal volume that are related to gender and/or height occur at least in part because female gender is having an effect. This does not exclude concomitant influences of short height on high tidal volume choice in these instances.
1 - (DE/TE) = 1 - (0.096/0.23) = 0.58 = 58% | 58% of instances of high tidal volume that are related to gender and/or height occur at least in part because short height is having an effect. This does not exclude concomitant direct influences of female gender on high tidal volume choice in these instances.

TABLE 12: Interpretation of mediation analysis

| Covariables of interest | Covariables of interest | Covariables of interest |
| --- | --- | --- |
| Age | # of comorbidities | Height (cm) |
| Gender | | | |
| Women (n = 710) | 62 (52 – 73) | 1 (0 – 2) | 162 (157 – 167) |
| Men (n = 885) | 60 (49 – 70) | 1 (0 – 1) | 177 (170 – 182) |
| p-value | 0.01 | 0.38 | <0.001 |
| Tidal volume | | | |
| Tidal volume > 8 mL/kg PBW (n = 466) | 62 (52 – 74) | 1 (0 – 1) | 162 (157 – 170) |
| Tidal volume ≤ 8 mL/kg PBW (n = 1,214) | 60 (50 – 71) | 1 (0 – 2) | 173 (165 – 180) |
| p-value | 0.01 | 0.002 | <0.001 |

TABLE 13: Relationship of gender and tidal volume with covariables of interest

Abbreviations: PBW, predicted body weight
| Covariables of interest | Gender | Insurance status | Number of comorbidities |
|-------------------------|--------|------------------|------------------------|
|                         | Men (n = 885) | Women n = 710 | Insured (n = 1,257) | Underinsured (n = 338) |
| **Race**               |         |                  |                        |                        |
| White (n = 1,113)      | 640 (72) | 473 (67)         | 953 (76)               | 160 (47)               | 1 (0 – 1) |
| Black (n = 424)        | 209 (24) | 215 (30)         | 260 (21)               | 164 (48)               | 1 (0 – 2) |
| Asian (n = 51)         | 33 (4)   | 18 (2)           | 40 (3)                 | 11 (3)                 | 0 (0 – 1) |
| American Indian/Alaska native (n = 7) | 3 (0.3) | 4 (0.6) | 4 (0.3) | 3 (0.9) | 1 (0 – 2) |
| **p-value**            | 0.01    | <0.001           |                        | 0.01                   |
| **Ethnicity**          |         |                  |                        |                        |
| Non-Hispanic or Latino (n = 1,544) | 859 (97) | 685 (96) | 1,224 (97) | 320 (95) | 1 (0 – 2) |
| Hispanic or Latino (n = 51) | 26 (3)   | 25 (4)           | 33 (3)                 | 18 (5)                 | 0 (0 – 1) |
| **p-value**            | 0.51    | 0.01             |                        | 0.02                   |
| **Tidal volume**       |         |                  |                        |                        |
| Tidal volume ≤ 8 mL/kg PBW (n = 1,160) | 738 (83) | 422 (59%) | 927 (74) | 233 (69%) | 1 (0 – 2) |
| Tidal volume > 8 mL/kg PBW (n = 435) | 147 (17) | 288 (40%) | 330 (26) | 105 (31%) | 1 (0 – 1) |
| **p-value**            | <0.001  | 0.08             |                        | 0.002                  |

**TABLE 14: Relationship of race/ethnicity and tidal volume with covariables of interest**

Abbreviations: PBW, predicted body weight
Covariables of interest

| Age | ICU admission after elective surgery | Race | Ethnicity | Comorbidities |
|-----|-------------------------------------|------|----------|---------------|
|     | Years | No (n = 1,414) | Yes (n = 181) | White | Black | Asian | American Indian/Alaskan native | Non-Hispanic or Latino (n = 1,544) | Hispanic or Latino (n = 51) | Number |
|     | Insured (n = 1,257) | 64 (54 – 74) | 1,095 (77) | 162 (80) | 953 (86) | 260 (61) | 40 (78) | 4 (57) | 1,224 (79) | 33 (65) | 1 (0 – 2) |
|     | Underinsured (n = 3,388) | 52 (41 – 59) | 319 (22) | 19 (10) | 160 (14) | 164 (39) | 11 (22) | 3 (43) | 320 (21) | 18 (35) | 1 (0 – 1) |
| p-value | <0.001 | <0.001 | <0.001 | 0.01 | <0.001 |
| Tidal volume | > 8 mL/kg PBW (n = 435) | 62 (52 – 74) | 365 (26) | 70 (39) | 303 (27) | 115 (27) | 16 (31) | 1 (14) | 419 (27) | 16 (31) | 1 (0 – 1) |
|     | ≤ 8 mL/kg PBW (n = 1,160) | 60 (50 – 71) | 1,049 (74) | 111 (81) | 810 (73) | 309 (73) | 35 (69) | 6 (86) | 1,125 (73) | 35 (69) | 1 (0 – 2) |
| p-value | 0.01 | <0.001 | 0.79 | 0.50 | 0.002 |

TABLE 15: Relationship of insurance status and tidal volume with covariables of interest

Abbreviations: PBW, predicted body weight

| Tidal volume (mL)* | Underinsured (n = 338) | Insured (Medicare excluded) (n = 568) |
|-------------------|------------------------|--------------------------------------|
| Tidal volume/PBW (mL/kg)* | 7.1 (6.4 – 8.2) | 7.0 (6.2 – 8.0) |
| Tidal volume > 8 mL/kg PBW (%) | 29 | 27 |
| Unadjusted odds ratio for receiving tidal volume > 8 mL/kg PBW† | 1.47 (1.04 – 2.09) | 1 (ref) |
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW‡ | 1.71 (1.26 – 2.32) | 1 (ref) |

TABLE 16: Relationships between insurance status and tidal volume > 8 mL/kg PBW: sensitivity analysis excluding 689 Medicare patients

*Values refer to median (interquartile range) or number (percentage). †Values refer to odds ratio (95% confidence interval). ‡Adjusted for age (continuous), ICU admission after elective surgery, race, ethnicity, and total # of APACHE II comorbidities (0-5)

Abbreviations: APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight
| Insurance status | Gender       | Race*          | Ethnicity*  |
|------------------|--------------|----------------|-------------|
| Underinsured vs insured† | Women vs men‡ | Black vs white | Hispanic vs non-Hispanic |
| Odds ratio (95% confidence interval) | 1.53 (1.14 – 2.04) | 1.27 (0.91 – 1.75) | 0.86 (0.52 – 1.45) | 1.34 (0.64 – 2.77) | 0.36 (0.06 – 2.30) | 1.07 (0.37 – 3.03) |

**TABLE 17: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW, including adjustment for SOFA score**

*Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and SOFA score. †Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, total # of APACHE II comorbidities (0-5), and SOFA score. ‡ Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and SOFA score.

APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight; SOFA, sequential organ failure assessment

| Insurance status | Gender       | Race*          | Ethnicity*  |
|------------------|--------------|----------------|-------------|
| Underinsured vs insured† | Women vs men‡ | Black vs white | Hispanic vs non-Hispanic |
| Odds ratio (95% confidence interval) | 1.54 (1.14 – 2.07) | 1.26 (0.90 – 1.76) | 0.86 (0.51 – 1.46) | 1.36 (0.66 – 2.79) | 0.35 (0.05 – 2.40) | 0.86 (0.27 – 2.73) |

**TABLE 18: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW, including adjustment for presence or absence of acute lung injury**

Note: The presence or absence of acute lung injury (now termed ARDS) was determined by site investigators by chart review. This was missing in 26 patients, leaving 1,569 patients.

*Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and presence/absence of acute lung injury. †Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, # of APACHE II comorbidities (0-5), and presence/absence of acute lung injury. ‡Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and presence/absence of acute lung injury.

APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight
| Insurance status          | Gender          | Race*                  | Ethnicity*               | Odds ratio (95% confidence interval) |
|---------------------------|-----------------|------------------------|--------------------------|-------------------------------------|
| Underinsured vs insured†  | Women vs men‡   | Black vs white         | Asian vs white           | 1.45 (1.08 – 1.95)                  |
|                           |                 |                        | American Indian/Alaskan native vs white | 1.26 (0.92 – 1.73)                  |
|                           |                 |                        | Hispanic vs non-Hispanic | 0.83 (0.52 – 1.32)                  |
|                           |                 |                        |                          | 1.15 (0.54 – 2.44)                  |
|                           |                 |                        |                          | 0.45 (0.08 – 2.35)                  |
|                           |                 |                        |                          | 1.00 (0.37 – 2.72)                  |

**TABLE 19: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW, including adjustment for mode of mechanical ventilation**

Note: Mechanical ventilation modes were categorized as follows: assist control (n = 845), synchronized intermittent mandatory ventilation (n = 262), pressure support (n = 63), pressure control (n = 6), airway pressure release ventilation (n = 7), high frequency oscillatory ventilation (n = 0), pressure regulated volume control (n = 264), and other (n = 148)

*Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation. †Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation. ‡Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation.

APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight

| Insurance status          | Gender          | Race*                  | Ethnicity*               | Odds ratio (95% confidence interval) |
|---------------------------|-----------------|------------------------|--------------------------|-------------------------------------|
| Underinsured vs insured†  | Women vs men‡   | Black vs white         | Asian vs white           | 1.47 (1.05 – 2.06)                  |
|                           |                 |                        | American Indian/Alaskan native vs white | 1.34 (0.94 – 1.92)                  |
|                           |                 |                        | Hispanic vs non-Hispanic | 0.85 (0.61 – 1.20)                  |
|                           |                 |                        |                          | 1.09 (0.54 – 2.22)                  |
|                           |                 |                        |                          | 0.26 (0.19 – 3.67)                  |
|                           |                 |                        |                          | 1.79 (0.86 – 3.74)                  |

**TABLE 20: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW using hierarchical modeling with patients nested within ICUs**

Note: hierarchical models were generated using the “xtlogit” command in STATA 14 including ICU as a fixed effect. All four patients in one ICU had the same outcome prediction for tidal volume > 8 mL/kg PBW, so these observations were dropped from the model leaving 1,591 patients for analysis.

*Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation. †Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation. ‡Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation.

APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight
TABLE 21: Adjusted odds ratios for association between exposures of interest and tidal volume > 8 mL/kg PBW, all mechanically ventilated patients (n = 2,513)

*Adjusted for sex, insurance status, and total # of APACHE II comorbidities (0-5). †Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, and total # of APACHE II comorbidities (0-5). ‡Adjusted for age (continuous), height (continuous), and total # of APACHE II comorbidities (0-5).

APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight

| Exposures of Interest | Underinsured vs insured† | Women vs men‡ | Black vs white | Asian vs white | American Indian/Alaskan native vs white | Hispanic vs non-Hispanic |
|-----------------------|--------------------------|---------------|---------------|---------------|---------------------------------------|--------------------------|
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW 10 imputations per missing value | 1.40 (1.08 – 1.82) | 1.39 (1.03 – 1.88) | 0.85 (0.56 – 1.30) | 1.34 (0.72 – 2.53) | 0.33 (0.06 – 1.72) | 1.17 (0.61 – 2.27) |
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW 30 imputations per missing value | 1.42 (1.09 – 1.85) | 1.38 (1.03 – 1.84) | 0.85 (0.55 – 1.32) | 1.32 (0.71 – 2.48) | 0.32 (0.05 – 2.27) | 1.25 (0.68 – 2.30) |
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW 40 imputations per missing value | 1.42 (1.06 – 1.89) | 1.37 (1.03 – 1.83) | 0.83 (0.53 – 1.29) | 1.30 (0.70 – 2.44) | 0.31 (0.05 – 2.01) | 1.24 (0.67 – 2.30) |
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW from primary complete case analysis | 1.56 (1.16 – 2.10) | 1.28 (0.92 – 1.77) | 0.86 (0.52 – 1.41) | 1.30 (0.63 – 1.41) | 0.32 (0.05 – 2.00) | 1.08 (0.39 – 2.94) |

TABLE 22: Relationships between insurance status and tidal volume > 8 mL/kg PBW in all ventilated patients, multiple imputation analysis excluding 1,058 Medicare patients (n = 1,455)

†Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, and total # of APACHE II comorbidities (0-5).

APACHE, acute physiology and chronic health evaluation; PBW, predicted body weight

| Exposures of Interest | Underinsured vs insured† |
|-----------------------|--------------------------|
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW 10 imputations per missing value | 1.45 (1.09 – 1.93) |
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW 30 imputations per missing value | 1.49 (1.12 – 1.97) |
| Adjusted odds ratio for receiving tidal volume > 8 mL/kg PBW 40 imputations per missing value | 1.48 (1.09 – 2.02) |

Additional Information

Disclosures

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