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Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999-2013
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Running Head: ARDS Mortality Trends in the US, 1999-2013

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Abstract

Rationale: Acute Respiratory Distress Syndrome (ARDS) is an acute hypoxemic respiratory failure seen in critically ill patients following an inciting injury. The burden of ARDS mortality in the United States (US) in recent years is not well characterized.

Objectives: In this study we aim to describe trends in the annual incidence of ARDS mortality in the United States from 1999 to 2013. We also describe demographic characteristics, geographic and seasonal trends, and other associated underlying causes of death in this population.

Methods: Data on all deceased US residents is available through the Multiple Cause of Death (MCOD) database of the National Center for Health Statistics. ARDS-related deaths were identified in MCOD using International Classification of Diseases, 10th Revision.

Measurements and Main Results: Aggregate annual crude and age-adjusted mortality rates and mortality rate ratios were used to compare various demographic sub-populations. Over the fifteen-year period, the national ARDS-related age-adjusted mortality rate demonstrated an annual seasonal variation peaking in winter and overall decreased in a non-linear fashion with a plateau from 2010 to 2013. The ARDS-related age-adjusted mortality rate was 5.01 per 100,000 persons (95% Confidence Interval (CI) 4.92 – 5.09) in 1999 and 2.82 per 100,000 persons (95% CI 2.76 – 2.88) in 2013. Males had a higher average ARDS-related mortality rate than females. Asian/Pacific Islanders had the lowest average age-adjusted ARDS-related mortality rate and Black/African Americans the highest.

Conclusions: National age-adjusted ARDS-related mortality rates have decreased from 1999 to 2013 in the US yet still show relative racial and gender disparities. However, death certificates
largely underestimate the overall mortality burden from ARDS when compared to studies of clinically-ascertained cases.

Abstract Word Count: 265
Acute Respiratory Distress Syndrome (ARDS) is a critical illness characterized by an acute, inciting inflammatory event followed by hypoxemic respiratory failure. The inciting injury, commonly pneumonia, sepsis or trauma, is not necessarily anatomically located within the respiratory system but leads to diffuse inflammatory pulmonary infiltrates, hypoxemic respiratory failure and an associated high probability of mortality (1-3). The syndrome has been described in the literature since 1967, with the first consensus definition introduced by the American European Consensus Conference in 1994 (4, 5). In 2012, this definition was revised and validated by an international panel of experts to produce the Berlin Definition, a clinical tool that endeavors to maintain diagnostic and prognostic utility as well as compatibility with previous research (1, 6).

Despite significant advances in the understanding of the pathophysiology and treatment of ARDS, the burden of ARDS mortality in the United States (US) in recent years is not well characterized, with the majority of published work from single hospital systems in restricted geographic regions (7-15). One study from a 16-month period in 1999 in King County, Washington estimated an ARDS incidence of 79 cases per 100,000 person-years with a 38.5% case-fatality rate (9). Another report from Olmsted County, Minnesota showed a decline in ARDS incidence from 82 to 39 cases per 100,000 person-years from 2001 to 2008 with the case-fatality rate remaining largely unchanged (21% to 19% over the time period) (8).

Moss et al. examined US national trends in ARDS mortality from 1979-1996, showing an increase in ARDS-related deaths from 1979 to 1993 (5 to 8 per 100,000 persons) that subsequently decreased towards the end of the study period in 1996 (7 deaths per 100,000 persons) (11). Another study examining US national trends from 1992 to 2007 demonstrated
an increase in incidence from 36 cases per 100,000 to 106 cases per 100,000 with a steady decline in case-fatality rates (7).

In this study, we aim to describe the temporal and geographic trends in the annual incidence of ARDS mortality in the US from 1999 to 2013 using a complete national sample. We also aim to describe demographic characteristics and other associated causes of death in this population.

**Methods**

**Data Source and Definitions**

All data for these analyses were collected from the National Center for Health Statistics’ Multiple Cause of Death (MCOD) database. The MCOD is derived from the National Death Index and contains information from death certificates of every US resident who died within the fifty states and District of Columbia, and is publicly available through the Centers for Disease Control and Prevention (CDC) WONDER web site as aggregated, not individual-level data (16). MCOD data designates one underlying cause of death and up to 20 additional contributing causes of death. The multiple sequential human and then computer systems developed by the National Center for Health Statistics to extract text diagnoses from the death certificate, convert them into numeric codes and then process and organize them are described in documentation from the CDC (17).

All deaths in the US from 1999-2013 were eligible for inclusion in this study. We excluded deaths of individuals with an age less than 1 year-old or whose age was missing. We
narrowed the study time period to 1999-2013 for uniformity in the outcome definition, since 1999 was the year that cause of death coding transitioned to the International Classification of Diseases, 10th Revision (ICD-10).

We defined ARDS-related mortality as a death with the ICD-10 code J80 (Adult Respiratory Distress Syndrome) listed among any of the 20 causes of death. Other variables reported included age category, race, ethnicity, sex, other associated causes of death and the urban-rural designation and US Census Bureau geographic division of the legal residence at time of death. We included deaths with race coded as Asian or Pacific Islander, Black or African American, and White; those coded as American Indian or Alaska Native were excluded due to small numbers.

Geographic information was based on location of legal residence at time of death as indicated on the death certificate and if not provided, residence was assigned to the place where the death occurred. Urbanization classification was determined by county per the 2006 NCHS Urban-Rural Classification Scheme (18).

To characterize other acute injuries associated with ARDS-related mortality, we further categorized cases as associated with septicemia, influenza and pneumonia, trauma or pneumonitis due to food and vomit by the other ICD-10 codes listed on the death record. We used a previously published ICD-10 definition of septicemia-associated cases (supplementary Table E1) (19). Trauma-associated deaths were defined by modifying the National Trauma Data Standard inclusion criteria (Supplementary Table E2) (20). Influenza and pneumonia-associated deaths were defined by ICD-10 codes J09 through J18 (Supplementary Table E3). Pneumonitis due to food and vomit-associated deaths were defined by ICD-10 code J69.0. Of note, these
sub-categorizations of ARDS associated with other specified causes of death are not mutually exclusive. For example, a hypothetical death record listing ARDS, a trauma diagnosis and a septicemia diagnosis would be counted twice as both an ARDS associated with trauma death and an ARDS associated with septicemia death for this particular part of the analysis.

**Sensitivity Analyses**

In responding to scientific review and revising this work, several *post hoc* sensitivity analyses were performed. We re-performed analyses of ARDS trends in the US with ARDS death defined only as the underlying causes of death, i.e. when it is listed in the first position on the death record. Of note, since this predictably produces smaller death counts, not all analyses could be performed as CDC WONDER suppresses output of any estimates based on death counts below a certain cutoff (generally either 10 or 20 depending on the geographic substrata of analysis). Furthermore, we graphed temporal mortality trends of other respiratory failure diagnoses that may mimic or be recorded in place of ARDS including acute pulmonary edema (J81.0); acute respiratory failure, unspecified (J96.0); respiratory failure, unspecified (J96.9).

While we attempted to include transfusion-related lung injury (J95.84) in this list, the MCOD databases does not delineate the J95.8 group to the hundredth decimal position, Therefore we could not isolate this diagnosis from the others in the group which include other post-operative pulmonary complications. Finally, we graphed published results of death counts from clinically determined ARDS in Olmsted County, Minnesota from 2001-2008 alongside death counts from various acute respiratory diagnoses within this same county as determined
by MCOD in order to highlight the disparity between clinical diagnosis of ARDS-related deaths and that determined by death certificate records (8).

**Statistical Analysis**

Age-adjusted mortality incidences were generated by the direct method using the 2000 US Census Bureau’s population estimates. Incident rate ratios were calculated using quasi-Poisson regression, allowing for possible over-dispersion. Effect modification of time on incident rate ratios was assessed using $\chi^2$ test. Details on preparing WONDER aggregate age-adjusted rates for quasi-Poisson regression is provided in the Appendix. All data analysis was done using R 3.1.2 ([http://www.R-project.org)]).

This study was submitted to the Emory University Institutional Review Board and deemed exempt from requiring full review for approval.

**Results**

**Trends in ARDS-Related Mortality in the United States**

In the 15 year time period 1999-2013, there were 36,424,223 total deaths in the US with 156,357 entries listing ARDS as any cause of death, meeting our study definition of ARDS-related mortality. The proportion of ARDS-related mortality where ARDS was listed as the principal underlying cause of death was 15.6% in 1999 and 16.5% in 2013. The majority of deaths (94.9%) occurred in an inpatient medical facility with small proportions occurring before
arrival to the hospital (0.1%), in the emergency room (1.2%), in the decedent’s home (1.0%), a hospice facility (0.3%), a long term care facility (1.5%), or location unknown (1.0%).

The overall number of ARDS-related deaths in the US as determined by MCOD records decreased over the study period, from 13,612 in 1999 to 9,762 in 2013. The corresponding ARDS-related age-adjusted mortality rates also decreased from 5.01 per 100,000 persons (95% Confidence Interval (CI) 4.92 – 5.09) to 2.82 per 100,000 persons (95% CI 2.76 – 2.88) for 1999 and 2013 respectively (Figure 1, Supplementary Table 4).

Demographic Characteristics

Table 1 describes the ARDS-related mortality in the US over the 1999-2013 study period by demographic characteristics. The crude ARDS-related mortality rate was lower in the 5-14 year-old age group compared to the 1-4 year-old age group then increasing in nearly every subsequent older age group. When adjusted for age, males had a higher average ARDS-related mortality rate than females (IRR 1.33, 95% CI 1.26 – 1.41). Asian/Pacific Islanders had the lowest average age-adjusted ARDS-related mortality rate at 3.04 per 100,000 person years, 95% CI 2.95 – 3.13), then Whites at 3.33 per 100,000 person years, with Black/African Americans having the highest mortality rate (4.07 per 100,000, 95% CI 4.01-4.12) (Supplementary Figure E1).

There was no effect modification of time in years on the relative age-adjusted mortality rates by race ($\chi^2$ test for interaction P=0.24) as exemplified by the observation that the rate ratio between Black/African Americans and Asian/Pacific Islanders did not grossly change from 1999 to 2013 (IRRs 1.30 and 1.27, respectively) Furthermore, the differences in mortality rates
by race depended on age and were the most pronounced in the 45-64 year-old age groups with a changing pattern after an age of approximately 70 years (Figure 2). There were no significant differences in the average age-adjusted mortality rates between Hispanics and non-Hispanics (IRR 1.05, 95% CI 0.97 – 1.14).

**Geographic Distributions**

There was variation in average annual age-adjusted ARDS-related mortality rates by US Census Region (maximum 3.39, minimum 2.96, and absolute difference 0.43 deaths per 100,000) and US Census Division (maximum 4.50, minimum 2.95, and absolute difference 1.55 deaths per 100,000) (Table 2). There was even more variation among states with Alabama having the highest annual average mortality rate (5.47 per 100,000) and New York having the lowest (2.55 per 100,000) (Supplementary Table 5, Figure 3). In addition to a geographic distribution with higher risk concentrated in the Southeastern states, the pattern of ARDS-related deaths also demonstrates a seasonal periodicity over the course of each calendar year with higher death counts in the winter months and a nadir in the summer months (Supplementary Figures E2 and E3).

**Other Causes of Death Associated with ARDS-Related Deaths**

Averaged over the study period, influenza and pneumonia diagnoses were listed as another underlying cause of death in 35.1% of ARDS-related deaths. Septicemia diagnoses, trauma diagnoses and the pneumonitis due to food and vomit diagnosis were each listed as other diagnoses in ARDS-related deaths in 28.1%, 2.5% and 6.4% of death records respectively (these
are potentially overlapping categories). Figure 4 displays the annual percentages of ARDS-related deaths with these diagnostic categories also listed on the death record. Influenza and pneumonia had an average 0.4% increase per year with a notable spike in 2009, septicemia had 0.3% increase per year, and pneumonitis due to food and vomit had 0.2% increase per year while trauma had 0.1% decrease (Supplementary Table 6).

**Post-hoc Sensitivity Analyses**

Figure 5 demonstrates temporal trends of ARDS-related mortality alongside the rates of deaths with codes for other respiratory diagnoses that maybe be assigned in the stead of an ARDS diagnosis on a death certificate. While the majority of the temporal trends are similarly declining, “Acute respiratory failure” is the exception with a non-linear increasing rate starting around 2004.

Since the MCOD database can provide data at the county-level, we graphed temporal trends of ARDS-related death counts alongside death counts from other respiratory diagnoses in Olmsted County, Minnesota (Figure 6). We then superimposed the annual ARDS death counts provided in the results from the Li et al. clinical study of ARDS incidence that captured all of Olmsted County from 2001-2008 (8). Given the dataset’s rules regarding suppression of data with counts below 10 at the county-level, ARDS-related deaths and ‘Acute respiratory failure’ do not appear on the graph while the counts from ‘Respiratory failure, unspecified’ and ‘Pneumonitis due to food and vomit’ lie above the clinically determined counts from Li et al. (8).

Finally, the primary analyses were re-performed using an alternative case definition, with an ARDS death defined as the ARDS diagnosis listed as the principle underlying cause of
death (UCOD) rather than among any of the potentially 20 diagnoses listed on the death record (MCOD). Figure 1 includes the temporal trends of ARDS mortality as UCOD in the US, showing a decreased magnitude of cases when compared to ARDS as MCOD, but with a similar nonlinear, downward trend with a slight increase in 2009 and then a plateau. More specifically, the age-adjusted mortality from ARDS as UCOD decreased from 0.79 per 100,000 (95% CI 0.76 - 0.83) in 1999 to 0.45 per 100,000 in 2013 (95%CI 0.43 – 0.47). In regards to the relative risks calculated using the UCOD and MCOD definitions, the directions of the IRRs are consistent with some differences in magnitude (Supplementary Table E7). Some of the geographic comparisons of ARDS-related mortality do change depending on case definition, particularly in the Northeast and West Census Regions and Middle Atlantic, South Atlantic and Pacific Census Divisions (Supplementary Table E8, Supplementary Figure E4).

**Discussion**

This study represents an important examination of the national epidemiology of ARDS-related mortality in the US from 1999 to 2013, addressing temporal, seasonal, geographic and demographic trends as well as highlighting inconsistencies between administrative and clinical data in the US. The national ARDS-related mortality generally decreased from 1999 to 2007, increased in 2009 when the US was afflicted by the H1N1 influenza pandemic and has been relatively stable from 2010 to 2013. The current observed trend is a consistent continuation of the trends noted by a prior US study spanning 1979-1996, which employed the same dataset but used ICD-9-CM codes to define ARDS (where we used the ICD-10 codes that were
implemented in this dataset in 1999). That study demonstrated an increase in ARDS mortality from 1979-1993 from 5.0 to 8.1 deaths per 100,000 persons with a subsequent decrease from 1993-1996 to 7.4 per 100,000 persons, identifying a nearly continuous decline of ARDS-related deaths that are coded on death certificates from 1993 to 2013 (11).

Data Set

Given that this study utilized a dataset accounting for every recorded death certificate within the US, its results are representative only of the trends and burden of ARDS-related deaths captured by ICD-10 coding practices. While its strength is that it includes the entire US population without any sampling performed, a limitation of this study is that it cannot address the specific reasons for these trends. The decline in ARDS-related mortality from 1999-2007 could be due to decreases in: 1) the incidence of ARDS, 2) the case-fatality rate from ARDS, 3) both of these metrics and/or 4) death certificate coding.

Comparison to Other Studies

In trying to disentangle these mechanisms using results of other studies that clinically define ARDS cases, we discover conflicting results. We find similar absolute numbers in several European studies, much higher numbers in US studies and at least two different patterns of the case incidence/case fatality trends. An incidence study using a sample of hospitals in Spain in 2008 estimated 7.2 cases per 100,000 persons with 47.8% in-hospital mortality (21). With an assumption that most fatalities are not occurring outside of the hospital, this estimates 3.4 ARDS-related deaths per 100,000 persons, similar to our 2008 estimate of 3.0. Similarly, a
longitudinal study of hospitals in Iceland from 1988-2010 demonstrated an average of 7.2 cases per 100,000 with a 37.0% in-hospital fatality, estimating an average of 2.6 ARDS-related deaths per 100,000 (22). This Icelandic study also demonstrated increasing ARDS case incidence with a concurrently decreasing ARDS case-fatality (22).

In the US, one study examining a large representative sample of national hospital discharges from 1992-2007 demonstrated a similar longitudinal pattern of an increase in the incidence of ARDS with an overall decline in case-fatality yet with significantly larger incidences ranging from 36.1 to 106.1 per 100,000 persons (7). Another study of patients participating in clinical trials of ARDS, while unable to estimate a population incidence, demonstrated decreases in case-fatality from ARDS from 1996-2005 (23). In contrast, a study of Olmsted County, Minnesota from 2001-2008 showed a declining incidence of ARDS (ranging from 82.4 to 38.9 cases per 100,000) without a change in case-fatality (8). Finally, in a 16-month study spanning 1999-2000 in King County, Washington there was an estimated 86.2 cases per 100,000 with an in-hospital mortality of 38.5%, estimating 33.2 ARDS-related deaths per 100,000 (estimate plotted in Figure 7 for comparisons) (9). Therefore, there is not a completely uniform pattern of trends in case incidence and case-fatality across these studies that determined ARDS cases using clinical data.

**Coding Practices**

In regards to the confounding of coding practices on the results, our data suggest several key points. Changing our case definition from ARDS as a diagnosis listed among any on the death record to ARDS listed as the principle underlying cause of death did not greatly effect estimates
of relative risk of ARDS-related death across demographic characteristics but did reveal different relative risk estimates based on geographic characteristics. This suggests regional differences in ARDS death certificate coding practices. Additionally, the low estimates of ARDS deaths observed in this study when compared to results from clinical studies suggests that a majority of ARDS-related deaths are not being coded for on death certificates.

Figure 5 leads us to hypothesize that other codes, such as ‘Respiratory failure, unspecified’ may be coded in death certificates instead of ARDS. Furthermore, when we compared the data from a clinical study encompassing all of Olmsted County and data from the MCOD in this county over the same time period, there were fewer than 10 cases per year of deaths with ARDS recorded on death certificates while the clinical study determined 16-20 ARDS deaths per year (Figure 6)(8).

In further regard to the other causes of death associated with ARDS-related mortality, trauma as an additional cause of death comprised only 2.5% of ARDS-related deaths. This may be due the fact that ARDS secondary to trauma seems to have a lower incidence and a lower case fatality or that surgeons may be less likely to code for this diagnosis than internists (9, 22, 24). Septicemia diagnoses listed as another cause of death comprises a major portion of ARDS-related deaths at 28.1%. The limitations of this dataset unfortunately, did not allow us to calculate precisely how many ARDS-related deaths were recorded on death records without an accompanying causal diagnosis.

These are troubling findings since ARDS and the severe respiratory and commonly associated multi-organ failure should be sentinel clinical events proximate to the time of death. Given that the listing of diagnoses on a death certificate has no financial incentives, the
conceivable hypotheses as to why ARDS is under-coded on death certificates are numerous. We hypothesize that these findings result from a combination of the following: 1) physicians not confidently recognizing the diagnosis; 2) the decreasing use of routine chest radiographs and arterial blood gases needed to make the diagnosis; 3) physicians erroneously filling out the document; 4) ARDS cases surviving longer until time of death, leading to the diagnosis being less salient; and 5) increases in transfers to palliative care facilities where the diagnosis may be less commonly utilized.

**Demographics**

This study does reveal relative disparities in ARDS-related mortality. Of note, it does not distinguish that these disparities are necessarily specific to ARDS and therefore, the observed disparities may be a reflection of overall trends for all-cause mortality. With this in mind, males had an approximately 30% higher age-adjusted mortality rate over the study period. In regards to race, Black/African Americans suffer an approximately 30% higher mortality rate than Whites or Asian/Pacific Islanders. However, given that the overall mortality rates from ARDS have been decreasing over time, the absolute mortality difference between racial groups may be decreasing.

In regards to geographic trends, it is not surprising that more variation in ARDS-related mortality is revealed the smaller the geographic unit analysis and at the state-level there are states that have ARDS-related mortality rates outside of the 95% CI of the national average rate. In general, there seems to be higher rates of ARDS-related mortality in the southeastern states as well as in Washington State. Since the granularity of the data source does not allow further
investigation as to the causes of this geographical distribution, explanations remain purely speculative but include: differences in underlying all-cause mortality rates, differences in underlying comorbidity and severity of illness, differences in recognition and coding, and potentially true differences in underlying ARDS-inciting events.

A further important implication of this geographical variation may be that it advises caution in generalizing the results of epidemiological studies drawn from a specific geographic area (8, 9). In regards to the seasonal variation of ARDS-related mortality, there is a peak in the winter months that we speculate is likely due to the fact that the influenza and pneumonia diagnoses are associated with 35.1% of ARDS-related deaths and these respiratory illnesses cluster in the fall and winter seasons in the northern hemisphere.

Conclusions

The national ARDS-related mortality rates as recorded on US death certificates likely largely underestimates the true number of ARDS deaths, yet shows patterns of seasonal periodicity with increases in fall and winter, relative racial and gender disparities, and an overall decrease from 1999 to 2013 with stabilization of the age-adjusted mortality rates in recent years.
References


Table 1. Average Annual Age-Adjusted Rates of Acute Respiratory Distress Syndrome-Related Mortality by Demographic Characteristic in the United States, 1999-2013

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deaths (%)</th>
<th>Age-Adjusted Rate Per 100,000 (95% CI)</th>
<th>Incident Rate Ratio (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>76,029 (48.6)</td>
<td>3.03 (3.01-3.05)</td>
<td>referent</td>
<td></td>
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<tr>
<td>Male</td>
<td>80,328 (51.4)</td>
<td>4.00 (3.97-4.03)</td>
<td>1.33 (1.26-1.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>**Race ***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>130,216 (83.3)</td>
<td>3.33 (3.31-3.35)</td>
<td>1.06 (0.94-1.19)</td>
<td>0.34</td>
</tr>
<tr>
<td>Black or African American</td>
<td>19,504 (12.5)</td>
<td>4.07 (4.01-4.12)</td>
<td>1.30 (1.14-1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>4,895 (3.1)</td>
<td>3.04 (2.95-3.13)</td>
<td>referent</td>
<td></td>
</tr>
<tr>
<td><strong>Hispanic Origin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>13,101 (8.4)</td>
<td>3.46 (3.39-3.52)</td>
<td>1.05 (0.97-1.14)</td>
<td>0.23</td>
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<tr>
<td>Not Hispanic or Latino</td>
<td>142,894 (91.4)</td>
<td>3.43 (3.41-3.45)</td>
<td>referent</td>
<td></td>
</tr>
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<td><strong>Urbanization (2006)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NonCore (non-metro)</td>
<td>13,395 (8.6)</td>
<td>3.79 (3.72 – 3.85)</td>
<td>1.25 (1.16-1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Micropolitan (non-metro)</td>
<td>19,829 (12.7)</td>
<td>3.87 (3.81 – 3.92)</td>
<td>1.28 (1.19-1.37)</td>
<td>&lt;0.001</td>
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<tr>
<td>Small Metro</td>
<td>16,328 (10.4)</td>
<td>3.69 (3.63 – 3.74)</td>
<td>1.23 (1.14-1.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medium Metro</td>
<td>31,224 (20.0)</td>
<td>3.38 (3.35 – 3.42)</td>
<td>1.13 (1.07-1.20)</td>
<td>&lt;0.001</td>
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<tr>
<td>Large Fringe Metro</td>
<td>32,131 (20.6)</td>
<td>2.99 (2.96 – 3.02)</td>
<td>referent</td>
<td></td>
</tr>
<tr>
<td>Large Central Metro</td>
<td>43,450 (27.8)</td>
<td>3.49 (3.46 – 3.52)</td>
<td>1.15 (1.09-1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ten-year Age Groups †</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 years</td>
<td>868 (0.5)</td>
<td>0.37 (0.34-0.39)</td>
<td>2.05 (1.50-2.81)</td>
<td>&lt;0.001</td>
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<td>5-14 years</td>
<td>1,095 (0.7)</td>
<td>0.18 (0.17-0.19)</td>
<td>referent</td>
<td></td>
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<td>15-24 years</td>
<td>2,926 (1.8)</td>
<td>0.46 (0.45-0.48)</td>
<td>2.61 (2.05-3.34)</td>
<td>&lt;0.001</td>
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<td>25-34 years</td>
<td>4,838 (3.1)</td>
<td>0.80 (0.78-0.82)</td>
<td>4.49 (3.57-5.66)</td>
<td>&lt;0.001</td>
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<td>35-44 years</td>
<td>9,980 (6.4)</td>
<td>1.55 (1.52-1.58)</td>
<td>8.60 (6.91-10.72)</td>
<td>&lt;0.001</td>
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<td>45-54 years</td>
<td>20,177 (12.9)</td>
<td>3.19 (3.14-3.23)</td>
<td>18.04 (14.56-22.35)</td>
<td>&lt;0.001</td>
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<tr>
<td>55-64 years</td>
<td>27,835 (17.8)</td>
<td>5.86 (5.79-5.93)</td>
<td>33.85 (27.36-41.87)</td>
<td>&lt;0.001</td>
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<td>65-74 years</td>
<td>34,569 (22.1)</td>
<td>11.38 (11.26-11.50)</td>
<td>64.86 (52.47-80.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>75-84 years</td>
<td>37,872 (24.2)</td>
<td>19.51 (19.31-19.70)</td>
<td>109.61 (88.71-135.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>85+ years</td>
<td>16,197 (10.4)</td>
<td>21.77 (21.43-22.10)</td>
<td>124.66 (100.49-154.65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Race group “American Indian or Alaska Native” excluded due to small population size and large variance making rate estimates unreliable.
† Unable to calculate age-adjusted rates for age groups so these numbers represent crude rates and confidence interval.
Table 2. Average Annual Age-Adjusted Rates of Acute Respiratory Distress Syndrome-Related Mortality by Census Geographic Distributions in the United States, 1999-2013

<table>
<thead>
<tr>
<th>Geographic Designation</th>
<th>Average Age-Adjusted Rate Per 100,000 (95% CI)</th>
<th>Incidence Rate Ratio (95% CI) †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Census Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>2.96 (2.93-3.00)</td>
<td>0.86 (0.81-0.92)</td>
</tr>
<tr>
<td>Midwest</td>
<td>3.27 (3.24-3.31)</td>
<td>0.95 (0.90-1.01)</td>
</tr>
<tr>
<td>South</td>
<td>3.80 (3.77-3.83)</td>
<td>1.11 (1.06-1.16)</td>
</tr>
<tr>
<td>West</td>
<td>3.39 (3.35-3.42)</td>
<td>1.00 (0.94-1.06)</td>
</tr>
<tr>
<td><strong>Census Division</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New England</td>
<td>3.00 (2.93-3.07)</td>
<td>0.88 (0.80-0.96)</td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>2.95 (2.91-2.99)</td>
<td>0.86 (0.81-0.91)</td>
</tr>
<tr>
<td>East North Central</td>
<td>3.32 (3.28-3.37)</td>
<td>0.96 (0.91-1.01)</td>
</tr>
<tr>
<td>West North Central</td>
<td>3.17 (3.11-3.23)</td>
<td>0.92 (0.85-0.99)</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>3.49 (3.45-3.53)</td>
<td>1.02 (0.98-1.07)</td>
</tr>
<tr>
<td>East South Central</td>
<td>4.50 (4.42-4.58)</td>
<td>1.31 (1.22-1.41)</td>
</tr>
<tr>
<td>West South Central</td>
<td>3.94 (3.89-4.00)</td>
<td>1.16 (1.10-1.23)</td>
</tr>
<tr>
<td>Mountain</td>
<td>3.19 (3.12-3.25)</td>
<td>0.94 (0.87-1.01)</td>
</tr>
<tr>
<td>Pacific</td>
<td>3.50 (3.45-3.54)</td>
<td>1.02 (0.97-1.07)</td>
</tr>
</tbody>
</table>

† Rate ratios are calculated using the US national annual average age-adjusted rate of 3.45 per 100,000 as the referent as there is no inherent order of interest in geography.
Figure Legends

**Figure 1.** Age-Adjusted Rates of Acute Respiratory Distress Syndrome-Related Mortality in the United States, 1999-2013. The red line displays mortality rates determined by a case definition of ARDS listed among any of the potentially 20 causes of death listed on a death record. The blue line displays mortality rates determined by ARDS listed as the principle underlying cause of death on a death record. The ribbons represent the 95% confidence limits of the estimates.

**Figure 2.** Average Annual Crude Rates of Acute Respiratory Distress Syndrome-Related Mortality by Age Group and Race in the United States, 1999-2013. The ribbons represent the 95% confidence limits of the estimates.

**Figure 3.** Average Annual Age-Adjusted Rates of Acute Respiratory Distress Syndrome-Related Mortality by State in the United States, 1999-2013.

**Figure 4.** Annual Proportions of Acute Respiratory Syndrome-Related Deaths with Other Accompanying Diagnoses in the United States, 1999-2013. The categories for associated diagnoses are not mutually exclusive and may be counted in multiple categories. For example, a death record with ARDS, a septicemia diagnosis and a pneumonia diagnosis would be counted in both the Septicemia and Influenza & Pneumonia groups.
Figure 5. Age-Adjusted Mortality Rates from Acute Respiratory Causes in the United States, 1999-2013. The superimposed data point is extrapolated from published study results (Rubenfeld GD et al. Incidence and outcomes of acute lung injury. The New England journal of medicine 2005; 353: 1685-1693). It represents 33.2 deaths per 100,000 which was calculated by multiplying the 86.2 ARDS cases per 100,000 by the 38.5% in-hospital case fatality reported in the study.

Figure 6. Comparison of Crude Death Counts from Acute Respiratory Causes as Determined by Death Certificates and a Clinical Study in Olmsted County, Minnesota, 1999-2013. The red line represents in-hospital death counts of ARDS as reported in published study results (Li G et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. American journal of respiratory and critical care medicine 2011; 183: 59-66). The other data was extracted for Olmsted County, Minnesota using the CDC WONDER Multiple Cause of Death (MCOD) dataset. While ARDS defined in the MCOD was included in the data request, the data did not meet the CDC’s minimum requirements of >10 counts to be reported.
Results from Rubenfeld et al. study

- Acute respiratory failure
- Adult respiratory distress syndrome
- Other postprocedural respiratory disorders
- Pneumonitis due to food and vomit
- Pulmonary oedema
- Respiratory failure, unspecified

Age-Adjusted Mortality (per 100,000)
Death counts between 0 and 10 are suppressed in the dataset, therefore data for ARDS−related deaths from MCOD are not available.
Online Data Supplement

Mortality Trends of Acute Respiratory Distress Syndrome in the United States from 1999-2013

Shea E. Cochi, BS, Jordan A. Kempker, MD, MSc, Srinadh Annangi, MD, Michael R. Kramer, PhD, Greg S. Martin, MD, MSc
Supplementary Appendix

Supplementary Methods

To perform the Quasi-Poisson regression to calculate age-adjusted incidence rate ratios (IRR) from the aggregate data supplied by CDC WONDER, the following methodology was used. CDC WONDER supplies age-adjusted incident rates by category, such as the Race category in the below table. While simple IRRs can be hand-calculated from this data, there is no simple way to calculate the confidence intervals of the IRRs. Therefore we transformed the age-adjusted incidence rates into age-adjusted death counts for each group in order to perform the Quasi-Poisson regression to calculate age-adjusted IRRs with 95% confidence intervals. The age-adjusted death counts were calculated by the following formula:

\[
\text{(Age-adjusted incidence rate)}_{ij} \times \text{(Total population count)}_{ij} = \text{(Age-adjusted death count)}_{ij}
\]

Where \( i \) and \( j \) subscripts refer to the Race and Year, respectively.

### Sample of calculated Age-adjusted Death Counts

<table>
<thead>
<tr>
<th>Race</th>
<th>Year</th>
<th>Death Count</th>
<th>Total Population</th>
<th>Crude Rate</th>
<th>Age-Adjusted Rate</th>
<th>Age-Adjusted Death Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian or Pacific Islander</td>
<td>1999</td>
<td>352</td>
<td>11185711</td>
<td>3.15</td>
<td>4.99</td>
<td>558</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1999</td>
<td>1751</td>
<td>35567736</td>
<td>4.92</td>
<td>6.47</td>
<td>2301</td>
</tr>
<tr>
<td>White</td>
<td>1999</td>
<td>11383</td>
<td>225707013</td>
<td>5.04</td>
<td>4.81</td>
<td>10857</td>
</tr>
</tbody>
</table>

These counts (labeled \textit{pseudopop} in the below code) were analyzed using the \textit{glm} function of the \textit{stats} package in R 3.1.2 (© 2014 The R Foundation for Statistical Computing). Below is a sample of the code utilized.

```r
glm(pseudopop ~ year + race, family="quasipoisson", data=race_clean, offset = log(population))
```
<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A40.0</td>
<td>Septicemia due to streptococcus, group A</td>
</tr>
<tr>
<td>A40.1</td>
<td>Septicemia due to streptococcus, group B</td>
</tr>
<tr>
<td>A40.2</td>
<td>Septicemia due to streptococcus, group C</td>
</tr>
<tr>
<td>A40.3</td>
<td>Septicemia due to streptococcal pneumonia</td>
</tr>
<tr>
<td>A40.8</td>
<td>Other streptococcal septicemia</td>
</tr>
<tr>
<td>A40.9</td>
<td>Streptococcal septicemia, unspecified</td>
</tr>
<tr>
<td>A41.0</td>
<td>Septicemia due to Staphylococcus aureus</td>
</tr>
<tr>
<td>A41.1</td>
<td>Septicemia due to other specified Staphylococcus</td>
</tr>
<tr>
<td>A41.2</td>
<td>Septicemia due to other unspecified Staphylococcus</td>
</tr>
<tr>
<td>A41.3</td>
<td>Septicemia due to Haemophilus influenza</td>
</tr>
<tr>
<td>A41.4</td>
<td>Septicemia due to anaerobes</td>
</tr>
<tr>
<td>A41.5</td>
<td>Septicemia due to other Gram-negative organisms</td>
</tr>
<tr>
<td>A41.8</td>
<td>Other specified septicemia</td>
</tr>
<tr>
<td>A41.9</td>
<td>Septicemia, unspecified</td>
</tr>
<tr>
<td>A02.1</td>
<td>Salmonella septicemia</td>
</tr>
<tr>
<td>A22.7</td>
<td>Anthrax septicemia</td>
</tr>
<tr>
<td>A26.7</td>
<td>Erysipelothrix septicemia</td>
</tr>
<tr>
<td>A32.7</td>
<td>Listerial septicemia</td>
</tr>
<tr>
<td>A42.7</td>
<td>Actinomycotic septicemia</td>
</tr>
<tr>
<td>B00.7</td>
<td>Herpesviral septicemia</td>
</tr>
<tr>
<td>B37.7</td>
<td>Candidal septicemia</td>
</tr>
</tbody>
</table>

Melamed et al. originally used this coding schema in 2005 (1).
Table E2. ICD-10 Codes Used to Define Trauma-Associated Deaths

1. Include the following ICD-10 sub-chapters and groups:

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S00-S09*</td>
<td>Injuries to the head</td>
</tr>
<tr>
<td>S10-S19*</td>
<td>Injuries to the neck</td>
</tr>
<tr>
<td>S20-S29*</td>
<td>Injuries to the thorax</td>
</tr>
<tr>
<td>S30-S39*</td>
<td>Injuries to the abdomen, lower back, lumbar spine, and pelvis</td>
</tr>
<tr>
<td>S40-S49*</td>
<td>Injuries to the shoulder and upper arm</td>
</tr>
<tr>
<td>S50-S59*</td>
<td>Injuries to the elbow and forearm</td>
</tr>
<tr>
<td>S60-S69*</td>
<td>Injuries to the wrist and hand</td>
</tr>
<tr>
<td>S70-S79*</td>
<td>Injuries to the hip and thigh</td>
</tr>
<tr>
<td>S80-S89*</td>
<td>Injuries to the knee and lower leg</td>
</tr>
<tr>
<td>S90-S99*</td>
<td>Injuries to the ankle and foot</td>
</tr>
<tr>
<td>T07</td>
<td>Unspecified multiple injuries</td>
</tr>
<tr>
<td>T14</td>
<td>Injury of unspecified body region</td>
</tr>
<tr>
<td>T20-T25*</td>
<td>Burns and corrosions of external body surface, specified by site</td>
</tr>
<tr>
<td>T26-T28*</td>
<td>Burns and corrosions confined to eye and internal organs</td>
</tr>
<tr>
<td>T30</td>
<td>Burn and corrosion, body region unspecified</td>
</tr>
<tr>
<td>T31</td>
<td>Burns classified according to extent of body surface involved</td>
</tr>
<tr>
<td>T32</td>
<td>Corrosions classified according to extent of body surface involved</td>
</tr>
<tr>
<td>T79*</td>
<td>Certain early complications of trauma, not elsewhere classified</td>
</tr>
</tbody>
</table>

*For these diagnoses, National Trauma Data Standard (NTDS) inclusion requires 7th character modifiers A, B, or C to indicate initial encounter. Per NTDS, 7th character modifiers D through S are excluded as they represent late effects of traumatic injury (2). MCOD provides ICD codes only up to 4 characters in length. Therefore, all codes in categories indicated by the asterisk were included.

2. Exclude the following isolated injuries:

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S00</td>
<td>Superficial injuries to the head</td>
</tr>
<tr>
<td>S10</td>
<td>Superficial injuries to the neck</td>
</tr>
<tr>
<td>S20</td>
<td>Superficial injuries to the thorax</td>
</tr>
<tr>
<td>S30</td>
<td>Superficial injuries to the abdomen, lower back, and external genitals</td>
</tr>
<tr>
<td>S40</td>
<td>Superficial injuries to the shoulder and upper arm</td>
</tr>
<tr>
<td>S50</td>
<td>Superficial injuries to the elbow and forearm</td>
</tr>
<tr>
<td>S60</td>
<td>Superficial injuries to the wrist, hand, and fingers</td>
</tr>
<tr>
<td>S70</td>
<td>Superficial injuries to the hip and thigh</td>
</tr>
<tr>
<td>S80</td>
<td>Superficial injuries to the knee and lower leg</td>
</tr>
<tr>
<td>S90</td>
<td>Superficial injuries to the ankle, foot, and toes</td>
</tr>
</tbody>
</table>
**Table E3. ICD-10 Codes Used to Define Influenza and Pneumonia-associated Deaths**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J09.0</td>
<td>Influenza due to identified avian influenza virus</td>
</tr>
<tr>
<td>J10.0</td>
<td>Influenza with pneumonia, influenza virus identified</td>
</tr>
<tr>
<td>J10.1</td>
<td>Influenza with other respiratory manifestations, influenza virus identified</td>
</tr>
<tr>
<td>J10.8</td>
<td>Influenza with other manifestations, influenza virus identified</td>
</tr>
<tr>
<td>J11.0</td>
<td>Influenza with pneumonia, virus not identified</td>
</tr>
<tr>
<td>J11.1</td>
<td>Influenza with other respiratory manifestations, virus not identified</td>
</tr>
<tr>
<td>J11.8</td>
<td>Influenza with other manifestations, virus not identified</td>
</tr>
<tr>
<td>J12.0</td>
<td>Adenoviral pneumonia</td>
</tr>
<tr>
<td>J12.1</td>
<td>Respiratory syncytial virus pneumonia</td>
</tr>
<tr>
<td>J12.2</td>
<td>Parainfluenza virus pneumonia</td>
</tr>
<tr>
<td>J12.3</td>
<td>Human metapneumovirus pneumonia</td>
</tr>
<tr>
<td>J12.8</td>
<td>Other viral pneumonia</td>
</tr>
<tr>
<td>J12.9</td>
<td>Viral pneumonia, unspecified</td>
</tr>
<tr>
<td>J13.0</td>
<td>Pneumonia due to Streptococcus pneumoniae</td>
</tr>
<tr>
<td>J14.0</td>
<td>Pneumonia due to Hemophilus influenzae</td>
</tr>
<tr>
<td>J15.0</td>
<td>Pneumonia due to Klebsiella pneumoniae</td>
</tr>
<tr>
<td>J15.1</td>
<td>Pneumonia due to Pseudomonas</td>
</tr>
<tr>
<td>J15.2</td>
<td>Pneumonia due to staphylococcus, unspecified</td>
</tr>
<tr>
<td>J15.3</td>
<td>Pneumonia due to streptococcus, group B</td>
</tr>
<tr>
<td>J15.4</td>
<td>Pneumonia due to other streptococci</td>
</tr>
<tr>
<td>J15.5</td>
<td>Pneumonia due to Escherichia coli</td>
</tr>
<tr>
<td>J15.6</td>
<td>Pneumonia due to other aerobic Gram-negative bacteria</td>
</tr>
<tr>
<td>J15.7</td>
<td>Pneumonia due to Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>J15.8</td>
<td>Pneumonia due to other specified bacteria</td>
</tr>
<tr>
<td>J16.0</td>
<td>Chlamydial pneumonia</td>
</tr>
<tr>
<td>J16.8</td>
<td>Pneumonia due to other specified infectious organisms</td>
</tr>
<tr>
<td>J18.0</td>
<td>Bronchopneumonia, unspecified organism</td>
</tr>
<tr>
<td>J18.1</td>
<td>Lobar pneumonia, unspecified organism</td>
</tr>
<tr>
<td>J18.8</td>
<td>Other pneumonia, organism unspecified</td>
</tr>
<tr>
<td>J18.9</td>
<td>Pneumonia, unspecified</td>
</tr>
</tbody>
</table>
**Table E4. Acute Respiratory Syndrome-Related Mortality in the United States by Year, 1999-2013.**

<table>
<thead>
<tr>
<th>Year</th>
<th>Deaths</th>
<th>Population</th>
<th>Crude Rate (95% CI)</th>
<th>Age Adjusted Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>13612</td>
<td>275244406</td>
<td>4.95 (4.86-5.03)</td>
<td>5.01 (4.92-5.09)</td>
</tr>
<tr>
<td>2000</td>
<td>12971</td>
<td>277616258</td>
<td>4.67 (4.59-4.75)</td>
<td>4.75 (4.67-4.83)</td>
</tr>
<tr>
<td>2001</td>
<td>12361</td>
<td>280956297</td>
<td>4.4 (4.32-4.48)</td>
<td>4.44 (4.36-4.52)</td>
</tr>
<tr>
<td>2002</td>
<td>12041</td>
<td>283673732</td>
<td>4.24 (4.17-4.32)</td>
<td>4.27 (4.19-4.34)</td>
</tr>
<tr>
<td>2003</td>
<td>10552</td>
<td>286132062</td>
<td>3.69 (3.62-3.76)</td>
<td>3.67 (3.60-3.74)</td>
</tr>
<tr>
<td>2004</td>
<td>10163</td>
<td>288791040</td>
<td>3.52 (3.45-3.59)</td>
<td>3.46 (3.39-3.53)</td>
</tr>
<tr>
<td>2005</td>
<td>9718</td>
<td>291512206</td>
<td>3.33 (3.27-3.40)</td>
<td>3.28 (3.22-3.35)</td>
</tr>
<tr>
<td>2006</td>
<td>9250</td>
<td>294338174</td>
<td>3.14 (3.08-3.21)</td>
<td>3.05 (2.99-3.11)</td>
</tr>
<tr>
<td>2007</td>
<td>8898</td>
<td>297083210</td>
<td>3.00 (2.93-3.06)</td>
<td>2.89 (2.83-2.95)</td>
</tr>
<tr>
<td>2008</td>
<td>9092</td>
<td>299961231</td>
<td>3.03 (2.97-3.09)</td>
<td>2.89 (2.83-2.95)</td>
</tr>
<tr>
<td>2009</td>
<td>10322</td>
<td>302767942</td>
<td>3.41 (3.34-3.47)</td>
<td>3.22 (3.16-3.28)</td>
</tr>
<tr>
<td>2010</td>
<td>9204</td>
<td>304801385</td>
<td>3.02 (2.96-3.08)</td>
<td>2.81 (2.75-2.87)</td>
</tr>
<tr>
<td>2011</td>
<td>9287</td>
<td>307595380</td>
<td>3.02 (2.96-3.08)</td>
<td>2.80 (2.74-2.86)</td>
</tr>
<tr>
<td>2012</td>
<td>9124</td>
<td>309970963</td>
<td>2.94 (2.88-3.00)</td>
<td>2.67 (2.62-2.73)</td>
</tr>
<tr>
<td>2013</td>
<td>9762</td>
<td>312187056</td>
<td>3.13 (3.06-3.19)</td>
<td>2.82 (2.76-2.88)</td>
</tr>
<tr>
<td>Total</td>
<td>156357</td>
<td>4412631342</td>
<td>3.54 (3.53-3.56)</td>
<td>3.45 (3.43-3.47)</td>
</tr>
</tbody>
</table>
Table E5. Average Annual Age-Adjusted Acute Respiratory Distress Syndrome-Related Mortality by State, United States 1999-2013

<table>
<thead>
<tr>
<th>State</th>
<th>Age-Adjusted Rate per 100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama</td>
<td>5.47 (5.30-5.64)</td>
</tr>
<tr>
<td>District of Columbia</td>
<td>4.91 (4.44-5.39)</td>
</tr>
<tr>
<td>Tennessee</td>
<td>4.45 (4.31-4.58)</td>
</tr>
<tr>
<td>Arkansas</td>
<td>4.39 (4.20-4.59)</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>4.38 (4.07-4.69)</td>
</tr>
<tr>
<td>Mississippi</td>
<td>4.26 (4.07-4.46)</td>
</tr>
<tr>
<td>Delaware</td>
<td>4.11 (3.76-4.45)</td>
</tr>
<tr>
<td>North Carolina</td>
<td>4.05 (3.94-4.16)</td>
</tr>
<tr>
<td>South Carolina</td>
<td>4.01 (3.86-4.16)</td>
</tr>
<tr>
<td>Washington</td>
<td>4.01 (3.88-4.14)</td>
</tr>
<tr>
<td>West Virginia</td>
<td>4.00 (3.78-4.22)</td>
</tr>
<tr>
<td>Texas</td>
<td>3.97 (3.90-4.04)</td>
</tr>
<tr>
<td>Wyoming</td>
<td>3.95 (3.51-4.39)</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>3.90 (3.74-4.07)</td>
</tr>
<tr>
<td>Louisiana</td>
<td>3.82 (3.67-3.97)</td>
</tr>
<tr>
<td>Maryland</td>
<td>3.82 (3.69-3.95)</td>
</tr>
<tr>
<td>Georgia</td>
<td>3.70 (3.59-3.81)</td>
</tr>
<tr>
<td>Utah</td>
<td>3.67 (3.45-3.90)</td>
</tr>
<tr>
<td>Missouri</td>
<td>3.66 (3.53-3.78)</td>
</tr>
<tr>
<td>Kentucky</td>
<td>3.64 (3.50-3.79)</td>
</tr>
<tr>
<td>Ohio</td>
<td>3.64 (3.55-3.73)</td>
</tr>
<tr>
<td>Idaho</td>
<td>3.56 (3.31-3.82)</td>
</tr>
<tr>
<td>Indiana</td>
<td>3.53 (3.41-3.65)</td>
</tr>
<tr>
<td>California</td>
<td>3.48 (3.43-3.53)</td>
</tr>
<tr>
<td>Kansas</td>
<td>3.48 (3.31-3.66)</td>
</tr>
<tr>
<td>New Mexico</td>
<td>3.47 (3.26-3.68)</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>3.45 (3.37-3.53)</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td><strong>3.45 (3.43-3.47)</strong></td>
</tr>
<tr>
<td>Michigan</td>
<td>3.35 (3.26-3.44)</td>
</tr>
<tr>
<td>Connecticut</td>
<td>3.31 (3.16-3.45)</td>
</tr>
<tr>
<td>Hawaii</td>
<td>3.29 (3.04-3.53)</td>
</tr>
<tr>
<td>Nebraska</td>
<td>3.27 (3.06-3.48)</td>
</tr>
<tr>
<td>Alaska</td>
<td>3.26 (2.82-3.70)</td>
</tr>
<tr>
<td>Arizona</td>
<td>3.20 (3.08-3.32)</td>
</tr>
<tr>
<td>North Dakota</td>
<td>3.20 (2.87-3.54)</td>
</tr>
<tr>
<td>Nevada</td>
<td>3.16 (2.97-3.35)</td>
</tr>
<tr>
<td>Illinois</td>
<td>3.13 (3.05-3.21)</td>
</tr>
<tr>
<td>State</td>
<td>Value (95% CI)</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Maine</td>
<td>3.10 (2.87-3.33)</td>
</tr>
<tr>
<td>Florida</td>
<td>3.09 (3.03-3.15)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>3.08 (2.98-3.17)</td>
</tr>
<tr>
<td>Vermont</td>
<td>2.98 (2.64-3.32)</td>
</tr>
<tr>
<td>Virginia</td>
<td>2.92 (2.82-3.02)</td>
</tr>
<tr>
<td>Oregon</td>
<td>2.84 (2.70-2.97)</td>
</tr>
<tr>
<td>Colorado</td>
<td>2.79 (2.66-2.92)</td>
</tr>
<tr>
<td>Minnesota</td>
<td>2.79 (2.67-2.91)</td>
</tr>
<tr>
<td>Montana</td>
<td>2.73 (2.47-2.99)</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>2.70 (2.48-2.93)</td>
</tr>
<tr>
<td>South Dakota</td>
<td>2.68 (2.39-2.96)</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>2.65 (2.55-2.76)</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>2.64 (2.54-2.74)</td>
</tr>
<tr>
<td>Iowa</td>
<td>2.63 (2.49-2.77)</td>
</tr>
<tr>
<td>New York</td>
<td>2.55 (2.49-2.60)</td>
</tr>
</tbody>
</table>
### Table E6. Proportions of Acute Respiratory Distress Syndrome-Related Deaths by Other Multiple Causes of Death, United States 1999-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza and Pneumonia</th>
<th>Septicemia</th>
<th>Pneumonitis due to Food and Vomit</th>
<th>Trauma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>4,450 (32.7)</td>
<td>3,543 (26.0)</td>
<td>746 (5.5)</td>
<td>465 (3.4)</td>
<td>13,612</td>
</tr>
<tr>
<td>2000</td>
<td>4,114 (31.7)</td>
<td>3,484 (26.9)</td>
<td>742 (5.7)</td>
<td>413 (3.2)</td>
<td>12,971</td>
</tr>
<tr>
<td>2001</td>
<td>3,911 (31.6)</td>
<td>3,174 (25.7)</td>
<td>698 (5.7)</td>
<td>399 (3.2)</td>
<td>12,361</td>
</tr>
<tr>
<td>2002</td>
<td>3,911 (32.5)</td>
<td>3,244 (26.9)</td>
<td>709 (5.9)</td>
<td>382 (3.2)</td>
<td>12,041</td>
</tr>
<tr>
<td>2003</td>
<td>3,595 (34.1)</td>
<td>2,918 (27.7)</td>
<td>613 (5.8)</td>
<td>274 (2.6)</td>
<td>10,552</td>
</tr>
<tr>
<td>2004</td>
<td>3,457 (34.0)</td>
<td>2,824 (27.8)</td>
<td>587 (5.8)</td>
<td>290 (2.9)</td>
<td>10,163</td>
</tr>
<tr>
<td>2005</td>
<td>3,560 (36.6)</td>
<td>2,739 (28.2)</td>
<td>596 (6.1)</td>
<td>245 (2.5)</td>
<td>9,718</td>
</tr>
<tr>
<td>2006</td>
<td>3,297 (35.6)</td>
<td>2,558 (27.7)</td>
<td>598 (6.5)</td>
<td>215 (2.3)</td>
<td>9,250</td>
</tr>
<tr>
<td>2007</td>
<td>3,212 (36.1)</td>
<td>2,552 (28.7)</td>
<td>592 (6.7)</td>
<td>235 (2.6)</td>
<td>8,898</td>
</tr>
<tr>
<td>2008</td>
<td>3,131 (34.4)</td>
<td>2,736 (30.1)</td>
<td>572 (6.3)</td>
<td>194 (2.1)</td>
<td>9,092</td>
</tr>
<tr>
<td>2009</td>
<td>4,212 (40.8)</td>
<td>2,828 (27.4)</td>
<td>637 (6.2)</td>
<td>201 (1.9)</td>
<td>10,322</td>
</tr>
<tr>
<td>2010</td>
<td>3,243 (35.2)</td>
<td>2,685 (29.2)</td>
<td>625 (6.8)</td>
<td>180 (2.0)</td>
<td>9,204</td>
</tr>
<tr>
<td>2011</td>
<td>3,551 (38.2)</td>
<td>2,745 (29.6)</td>
<td>688 (7.4)</td>
<td>178 (1.9)</td>
<td>9,287</td>
</tr>
<tr>
<td>2012</td>
<td>3,116 (34.2)</td>
<td>2,715 (29.8)</td>
<td>753 (8.3)</td>
<td>179 (2.0)</td>
<td>9,124</td>
</tr>
<tr>
<td>2013</td>
<td>3,739 (38.3)</td>
<td>2,951 (30.2)</td>
<td>793 (8.1)</td>
<td>154 (1.6)</td>
<td>9,762</td>
</tr>
</tbody>
</table>
Figure E1. Age-Adjusted Rates of Acute Respiratory Distress Syndrome-Related Mortality by Race in the United States, 1999-2013

The ribbons represent the 95% confidence limits of the estimates.
**Figure E2.** Periodicity of Acute Respiratory Syndrome-Related Deaths by Month and Year in the United States, 1999-2013

Vertical red lines mark the September 22 (Autumn Equinox) date of each corresponding year.
Figure E3. Acute Respiratory Syndrome-Related Deaths by Month in the United States, 1999-2013
Table E7. Comparison of Mortality Rate Ratios by Demographic Characteristic between Acute Respiratory Distress Syndrome Listed as Any Underlying Cause of Death versus the Principle Underlying Cause of Death in the United States, 1999-2013

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARDS as Principle Cause of Death Incident Rate Ratio (95%CI)</th>
<th>ARDS as Any Cause of Death Incident Rate Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td>Male</td>
<td>1.25 (1.18-1.33)</td>
<td>1.33 (1.26-1.41)</td>
</tr>
<tr>
<td>**Race *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.36 (1.20-1.55)</td>
<td>1.06 (0.94-1.19)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1.79 (1.56-2.06)</td>
<td>1.30 (1.14-1.48)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td><strong>Hispanic Origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>1.13 (1.03-1.24)</td>
<td>1.05 (0.97-1.14)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td><strong>Urbanization (2006)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NonCore (non-metro)</td>
<td>1.20 (1.10-1.31)</td>
<td>1.25 (1.16-1.36)</td>
</tr>
<tr>
<td>Micropolitan (non-metro)</td>
<td>1.24 (1.15-1.34)</td>
<td>1.28 (1.19-1.37)</td>
</tr>
<tr>
<td>Small Metro</td>
<td>1.16 (1.07-1.26)</td>
<td>1.23 (1.14-1.32)</td>
</tr>
<tr>
<td>Medium Metro</td>
<td>1.06 (0.99-1.13)</td>
<td>1.13 (1.07-1.20)</td>
</tr>
<tr>
<td>Large Fringe Metro</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td>Large Central Metro</td>
<td>0.94 (0.95-0.96)</td>
<td>1.15 (1.09-1.21)</td>
</tr>
<tr>
<td><strong>Ten-year Age Groups †</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4 years</td>
<td>0.88 (0.68-1.15)</td>
<td>2.05 (1.50-2.81)</td>
</tr>
<tr>
<td>5-14 years</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td>15-24 years</td>
<td>3.18 (2.58-3.91)</td>
<td>2.61 (2.05-3.34)</td>
</tr>
<tr>
<td>25-34 years</td>
<td>6.21 (5.11-7.55)</td>
<td>4.49 (3.57-5.66)</td>
</tr>
<tr>
<td>35-44 years</td>
<td>12.24 (10.14-14.78)</td>
<td>8.60 (6.91-10.72)</td>
</tr>
<tr>
<td>45-54 years</td>
<td>25.04 (20.82-30.13)</td>
<td>18.04 (14.56-22.35)</td>
</tr>
<tr>
<td>55-64 years</td>
<td>37.80 (31.46-45.41)</td>
<td>33.85 (27.36-41.87)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>51.51 (42.90-61.85)</td>
<td>64.86 (52.47-80.16)</td>
</tr>
<tr>
<td>75-84 years</td>
<td>58.76 (48.95-70.54)</td>
<td>109.61 (88.71-135.44)</td>
</tr>
<tr>
<td>85+ years</td>
<td>25.00 (20.78-30.07)</td>
<td>124.66 (100.49-154.65)</td>
</tr>
</tbody>
</table>

* Race group “American Indian or Alaska Native” excluded due to small population size and large variance making rate estimates unreliable.
† Unable to calculate age-adjusted for age groups so these numbers represent crude rate and confidence interval.
Table E8. Average Annual Age-Adjusted Mortality Rates of Acute Respiratory Distress Syndrome Listed as the Principle Underlying Cause of Death by Census Geographic Distributions in the United States, 1999-2013

<table>
<thead>
<tr>
<th>Geographic Designation</th>
<th>Principle Underlying Cause of Death Incident Rate Ratio (95%CI) *</th>
<th>As Any Cause of Death Incident Rate Ratio (95%CI) †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Census Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>1.00 (0.93-1.07)</td>
<td>0.86 (0.81-0.92)</td>
</tr>
<tr>
<td>Midwest</td>
<td>1.03 (0.97-1.10)</td>
<td>0.95 (0.90-1.01)</td>
</tr>
<tr>
<td>South</td>
<td>1.20 (1.14-1.26)</td>
<td>1.11 (1.06-1.16)</td>
</tr>
<tr>
<td>West</td>
<td>0.66 (0.61-0.71)</td>
<td>1.00 (0.94-1.06)</td>
</tr>
<tr>
<td><strong>Census Division</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New England</td>
<td>0.89 (0.80-1.00)</td>
<td>0.88 (0.80-0.96)</td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>1.03 (0.97-1.10)</td>
<td>0.86 (0.81-0.91)</td>
</tr>
<tr>
<td>East North Central</td>
<td>1.06 (0.99-1.12)</td>
<td>0.96 (0.91-1.01)</td>
</tr>
<tr>
<td>West North Central</td>
<td>0.96 (0.87-1.05)</td>
<td>0.92 (0.85-0.99)</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>1.13 (1.07-1.19)</td>
<td>1.02 (0.98-1.07)</td>
</tr>
<tr>
<td>East South Central</td>
<td>1.44 (1.33-1.56)</td>
<td>1.31 (1.22-1.41)</td>
</tr>
<tr>
<td>West South Central</td>
<td>1.20 (1.12-1.28)</td>
<td>1.16 (1.10-1.23)</td>
</tr>
<tr>
<td>Mountain</td>
<td>0.93 (0.84-1.02)</td>
<td>0.94 (0.87-1.01)</td>
</tr>
<tr>
<td>Pacific</td>
<td>0.54 (0.50-0.59)</td>
<td>1.02 (0.97-1.07)</td>
</tr>
</tbody>
</table>

* Rate ratios are calculated using the US national annual average age-adjusted rates of 0.56 per 100,000 for ARDS as the principle underlying cause of death
† Rate ratios are calculated using the US national annual average age-adjusted rates of 3.45 per 100,000 for ARDS defined as listed among any of the underlying causes of death
**Figure E4.** Average Annual Age-Adjusted Mortality with Acute Respiratory Distress Syndrome Listed as the Principle Underlying Cause of Death by State in the United States, 1999-2013.
References