

Long-Term Ozone Exposure Increases the Risk of Developing the Acute Respiratory Distress Syndrome

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At a Glance Commentary

Scientific Knowledge on the Subject. Ozone induces lung inflammation and oxidative stress in humans and experimental models. In population-based studies, ozone exposure has been implicated in hospital admissions and mortality related to heart and lung disease. Recent evidence suggests that environmental exposures such as tobacco smoke and alcohol abuse may enhance the risk of developing ARDS, but the effect of exposure to ambient levels of environmental pollutants such as ozone on risk of ARDS has not been investigated.

What this Study Adds to the Field. We found that long-term ozone exposure, even at relatively low levels, is associated with development of ARDS in at-risk critically ill patients. These findings suggest that ozone exposure, like other environmental exposures such as alcohol and tobacco, may represent an important and previously unrecognized risk factor for development of ARDS.

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

ABSTRACT

Rationale: The contribution of air pollution to the risk of ARDS is unknown.

Methods: We studied 1558 critically ill patients enrolled in a prospective observational study at a tertiary medical center who lived <50 km from an air quality monitor and had an ARDS risk factor. Pollutant exposures (ozone, NO₂, SO₂, PM_{2.5}, PM₁₀) were assessed by weighted average of daily levels from the closest monitors for the prior 3 years.

Associations between pollutant exposure and ARDS risk were evaluated by logistic regression controlling for age, race, sex, smoking, alcohol, insurance status, rural vs. urban residence, distance to study hospital and APACHEII.

Main Results: The incidence of ARDS increased with increasing ozone exposure: 28% in the lowest exposure quartile vs. 32%, 40% and 42% in the 2nd, 3rd and 4th quartiles, P<0.001. In a logistic regression model controlling for potential confounders, ozone exposure was associated with risk of ARDS in the entire cohort (OR 1.58 [95% CI 1.27, 1.96]) and more strongly associated in the subgroup with trauma as their ARDS risk factor (OR 2.26 [1.46, 3.50]). There was a strong interaction between ozone exposure and current smoking status (p = 0.007). NO₂ exposure was also associated with ARDS but not independently of ozone exposure. SO₂, PM_{2.5}, and PM₁₀ were not associated with ARDS.

Conclusions: Long-term ozone exposure is associated with development of ARDS in at-risk critically ill patients, particularly in trauma patients and current smokers. Ozone exposure may represent a previously unrecognized environmental risk factor for ARDS.

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INTRODUCTION

The Acute Respiratory Distress Syndrome (ARDS) is a common syndrome of acute lung inflammation, non-cardiogenic pulmonary edema and acute respiratory failure (1). With a U.S. incidence of 190,000 cases per year and mortality of 30–40% (2), ARDS is an important and costly public health problem. The most common clinical risk factors for ARDS are sepsis, pneumonia, severe trauma, aspiration of gastric contents, and multiple transfusions (3). However, ARDS develops in only a subset of patients with these risk factors. The mechanisms that predispose to ARDS in some, but not all, at-risk patients are not understood.

Recent evidence suggests that environmental exposures such as tobacco smoke (4-6) and alcohol abuse (7) may enhance the risk of developing ARDS, but the effect of exposure to ambient levels of environmental pollutants on risk of ARDS has not been investigated. We hypothesized that long-term exposure to high levels of ambient pollutants primes the lung to develop ARDS in the setting of another clinical risk factor. To test this hypothesis, we analyzed the association between ARDS and long-term exposure to air pollutants including ozone, NO₂, particulate matter (PM)_{2.5}, PM₁₀, and SO₂ in a large cohort of critically ill patients at risk for ARDS.

Some of the results of these studies have been previously reported in the form of an abstract (8).

METHODS

A complete description of methods is in the online supplement.

Patients. We studied patients from Validating Acute Lung Injury biomarkers for Diagnosis, a prospective observational cohort of critically ill medical, surgical and trauma patients admitted to Vanderbilt University Medical Center (VUMC) (9-12). Subjects enrolled 2006-2012 were included if a residential address was available, they lived within 50 km of at least one U.S. Environmental Protection Agency (EPA)-approved air quality monitor and had an ARDS risk factor.

Clinical Data. Clinical data included demographics, insurance status, current smoking, alcohol use, medical history, medications, APACHE II (13), hemodynamics, ventilator settings, laboratory values and outcomes. Patients were coded as metro or non-metro dwellers using USDA 2003 and 2013 Rural-Urban Continuum Codes. Patients were phenotyped at enrollment and on subsequent 3 days for sepsis (14), organ dysfunction (15) and ARDS. Patients were classified as having ARDS if they met American European Consensus Conference (16) criteria for acute lung injury (ALI) or ARDS on two or more consecutive days and as having no ARDS if they did not meet criteria on any day. Patients meeting criteria on a single or on two non-consecutive days were deemed “indeterminate” ARDS status and were included only in a sensitivity analysis.

Air pollutant exposure estimates. Daily measurements of ozone, NO₂, SO₂, PM_{2.5}, and PM₁₀ were obtained from the EPA’s Aerometric Information Retrieval System. The 24-hour average was computed for each pollutant except for ozone. Because ozone levels are typically elevated only during daylight hours, the highest 8-hour average was used. Since ozone levels are monitored only in warmer months in Tennessee, ozone data were restricted to April through September.

Patient addresses were geocoded and distances to all monitors calculated (Haversine formula). Daily pollutant exposures were estimated by the inverse-distance-squared weighted average of daily levels from monitors within 50km (17). Long-term exposures were estimated using average pollutant levels for the 1-, 3-, and 5-year periods prior to ICU admission and short-term exposures using levels for the prior 3 days and 6 weeks. Findings for 1-, 3- and 5-year ozone exposures were similar; 3-year data are presented. Because no significant associations between long-term exposures to SO₂, PM_{2.5} and PM₁₀ and risk of ARDS were observed, these are presented in the Supplement. As there were no associations between any short-term air pollutant exposure and ARDS, these data are not shown. For reference, correlations between pollutant levels are shown in **Supplementary Table E1**.

Statistical Analysis. Demographic and clinical data were compared between ARDS and non-ARDS patients using Pearson's chi-squared tests and Wilcoxon rank-sum tests. Missing values of regression covariates were multiply imputed with predictive mean matching (18) to avoid case-wise deletion of patient records. We fit logistic regression models to examine the relationship between ARDS and pollutant levels controlling for pre-specified confounders including age, race, sex, enrollment month (to control for season), current smoking, alcohol use, insurance status (as a proxy for socioeconomic status), median household income, metro vs. non-metro residence, distance to VUMC, APACHE-II, injury severity score (ISS, trauma subset only) and blunt vs. penetrating trauma. A restricted cubic spline with 3 knots was used for age, month, and APACHE-II to permit nonlinear associations. Data analyses were performed using R Version 3 (R Core Team).

RESULTS

Patients. Differences between patients who were eligible for inclusion in the study compared to those who were not eligible related to the requirement for living within 50km of an air pollution monitor, leading to more non-metro dwellers and a farther distance to Vanderbilt among excluded patients (**Supplemental Table E2**). There were 1558 patients who met the inclusion criteria for the ozone analysis and 1257 who met the inclusion criteria for the NO₂ analysis (**Figure 1**). There were 1350, 1355, and 1130 patients available for the SO₂, PM_{2.5}, and PM₁₀ analyses, respectively; levels of the individual air pollutants were only moderately correlated (**Table E1** in the Online Supplement).

Patient characteristics for the ozone analysis are in **Table E3** in the Online Supplement. Of the 1558 patients, 563 met criteria for ARDS. Patients with ARDS were older, were more likely to have sepsis as their ARDS risk factor and had a higher severity of illness compared to patients who did not develop ARDS.

Ozone exposure and ARDS. The geographic distribution of the ozone monitors that were included in the study is shown in **Figure 2**. The median distance from a patient's residence to the nearest air quality monitor was 19 km. Three-year average ozone exposure levels were lower than current EPA standards (19) (median 51.5 ppb, range 41.5 to 58.2). Despite these low levels of exposure, the incidence of ARDS increased significantly with increasing long-term ozone exposure (**Table 1** and **Figure 3A**). In a logistic regression model that controlled for potential confounders, long-term ozone

exposure was independently associated with risk of ARDS (**Table 2 and Figure 4A**). The findings were not different if 24-hour average levels of ozone were utilized rather than the highest daily 8-hour average (**Table E4** in the Online Supplement)

The association between ARDS and ozone exposure was strongest in the subgroup of patients (n = 552) with trauma as their ARDS risk factor (**Figure 3B**). In a logistic regression model that controlled for potential confounders, long-term ozone exposure was independently associated with risk of ARDS in trauma patients (**Table E5** in the Online Supplement). The interaction between trauma and ozone exposure was statistically significant (P=0.039).

NO₂ exposure and ARDS. Patient characteristics for the NO₂ analysis are in **Table E6** in the Online Supplement. NO₂ exposure levels were relatively low (median 15.4 ppb, range 1.7 to 17.7). Although overall rates of ARDS across quartiles of NO₂ exposure were not significantly different in an unadjusted analysis (**Table E7** in the Online Supplement), NO₂ exposure was associated with risk of ARDS in a logistic regression model that controlled for potential confounders (**Table E8** in the Online Supplement). As with ozone, the effect was strongest in trauma patients (n = 419, OR per 5 ppb increase 1.92 [95% CI 1.25, 2.94]). When 3-year ozone and NO₂ exposure were included in the same model, only ozone exposure remained significantly associated with ARDS (**Table E9** in the Online Supplement).

Interaction with smoking and alcohol. Since exposure of the lung to cigarette smoke could be synergistic with ozone for increasing the risk of ARDS, we tested for an interaction between current smoking and ozone exposure. The interaction term was

highly significant ($p = 0.007$). Ozone was significantly associated with ARDS only in current smokers and not in non-smokers (**Figure 4B**). There was no association between alcohol and ARDS in this study and no interaction between alcohol and ozone (p -value for interaction: 0.60) or any other pollutant.

Sensitivity analyses. To determine if accuracy of exposure estimates affected the findings, we restricted analysis to patients living within 15 km of a monitor. None of the analyses were substantively changed (not shown). In a second sensitivity analysis, we included the 80 patients with “indeterminate” ARDS status as controls. Ozone exposure was still associated with ARDS (OR 1.56, 95% CI 1.25, 1.94) especially in trauma patients (OR 2.27, 95% CI 1.46, 3.51). The interaction of ozone exposure with smoking was unchanged ($p < 0.001$).

DISCUSSION

In critically ill patients at risk for ARDS, long-term exposure estimates for ozone based on residential address were associated with development of ARDS. Importantly, this association was independent of other known risk factors for ARDS such as age and severity of illness. In addition, this association persisted after adjustment for potential confounders including metro versus non-metro dwelling, source of insurance and median household income as indicators of socioeconomic status, and distance of residence from the study hospital, which was included to control for possible unmeasured differences in severity of illness that could lead to transfer to VUMC of sicker patients from remote hospitals with different levels of pollutant exposure. We also found an association of long-term exposure to NO_2 and risk of ARDS; however, in two pollutant models with

ozone and NO₂, only ozone remained significant. There was no association between exposure estimates for other pollutants (SO₂, PM_{2.5} and PM₁₀) and ARDS. To our knowledge, this is the first report of an association between ambient air pollution and risk of ARDS. Furthermore, the observed association occurred at relatively low levels of exposure that fall within current EPA standards, suggesting that these observations, if reproduced, could be relevant even in areas with low levels of ambient ozone. Based on these findings, long-term exposure to ozone could represent a previously unrecognized risk factor for development of ARDS.

Although ozone exposure has not previously been associated with ARDS, both acute and chronic ozone exposure have been associated with respiratory disease in experimental and clinical studies. Acute ozone exposure induces acute lung injury in animals, primarily by producing an oxidant-mediated injury to the lung epithelium that leads to increased permeability and lung inflammation (20). Controlled short-term exposure to ozone (at doses that are much higher than ambient pollutant levels) in humans also causes airway inflammation and oxidant injury (21-23). In epidemiologic studies, acute exposure to high ozone levels has been associated with asthma exacerbations (24). Both ozone and NO₂ exposure over the preceding 6 weeks were associated with acute exacerbation of idiopathic pulmonary fibrosis (25), a syndrome that shares pathologic features with ARDS. Chronic ozone exposure has been associated with decreased lung growth in children (26, 27) and decreased small airways function in young adults (28). In a study of over 400,000 subjects, chronic ozone exposure was associated with mortality from respiratory causes (29); data on ARDS as a cause of respiratory mortality were not available in that study.

In the current study, the association between ARDS and ozone exposure was strongest in patients at risk for ARDS from severe trauma. Since it is well established that trauma-associated ARDS is clinically and pathophysiologically different from ARDS from other causes (30), ambient ozone exposure may uniquely prime the lung to develop ARDS in the setting of severe trauma. The higher rate of smoking in the trauma group (54%) compared to the non-trauma group (34%, $P < 0.0001$) may have potentiated the effects of ambient ozone exposure. Since the incidence of ARDS in the trauma group was lower (32%) than in the non-trauma patients (40%), another potential explanation is that other ARDS risk factors such as sepsis represent such a potent and overwhelming stimulus for acute lung injury that the contribution of chronic ozone exposure to risk of ARDS is less apparent. Finally, it is possible that patients who develop ARDS as a result of trauma spend more time outdoors than patients with other ARDS risk factors leading to higher exposure levels to ambient pollutants.

Smoking has only recently been recognized to be an independent risk factor for ARDS. Prospective studies report a strong association between cigarette smoking and risk of ARDS in severe trauma (4), non-pulmonary sepsis (6), lung transplant recipients (31) and patients receiving blood transfusions (5). Indeed, given the low levels of ambient ozone exposure in the VALID cohort, it is somewhat surprising that the effect of smoking on development of ARDS does not overwhelm the signal from ozone exposure. Potential mechanisms for potentiation of ARDS by smoking have considerable overlap with mechanisms of ozone-induced lung injury (32). These include harmful effects on lung epithelial and endothelial permeability and function (33, 34), pro-inflammatory effects due to changes in neutrophil alveolar macrophage trafficking and function, and effects on

cell-mediated and humoral immunity (35, 36). Smoking and air pollutant exposure have previously been shown to have synergistic effects on risk of obesity, pulmonary function deficits and lung cancer (37-39). The strong interaction between smoking and ozone exposure in the current study suggests that ozone exposure may also potentiate the harmful effects of tobacco smoke on the lung with regard to ARDS risk. This observation is important since both smoking and air pollution exposure are potentially modifiable environmental risk factors for developing ARDS.

Although we found an association between long-term NO₂ exposure and ARDS, this association was not significant after controlling for ozone levels. There are several potential explanations. First, since nitrogen oxides are the most prevalent ambient reactant for ozone formation, the association between NO₂ and risk of ARDS may only be indicative of ozone exposure. Second, since nitrogen oxides are predominantly traffic-related pollutants, exposure estimates based on regional monitors may not be accurate. Studies that analyze distance to roadway might be better suited to determine the relationship between NO₂ or other traffic-related pollutants such as PM_{2.5} and PM₁₀ and development of ARDS. Finally, since there were fewer monitoring stations for NO₂ than for ozone, this analysis had less power.

This study has several strengths. First, we studied a large heterogeneous cohort of critically ill medical, surgical, and trauma patients, enhancing the potential generalizability of the findings. Second, the patients were rigorously phenotyped prospectively for both ARDS risk factors and development of ARDS by physician investigators. This is in sharp contrast to many epidemiologic studies that have relied on inherently less reliable death certificate data or administrative coding for patient

phenotyping. Third, residential addresses and dates of admissions were used for exposure estimates, allowing for individualized rather than population or neighborhood-based exposure estimates. Finally, the extensive prospective data collection in the VALID study allowed us to control for a large number of potential confounders, decreasing but not eliminating the possibility of residual confounding.

This study has some limitations. First, patients were drawn from only one geographic region, and air pollutant effects may differ by geographic region. Second, as in any study that does not directly measure air pollutant levels, there is the possibility of exposure misclassification. To mitigate the concern of exposure misclassification, a sensitivity analysis included only patients who lived within 15 km of a monitor with similar results. Exposure misclassification could also be caused by reliance on the address provided at hospital admission; information about prior addresses during the exposure period was not available. Exposure misclassification may also arise from exposures that occur away from the residence including at the place of occupation. Number of hours spent outdoors versus indoors could also affect total exposure and would not be captured in our estimates. Third, the possibility of residual confounding and in particular residual spatial confounding remains. We attempted to mitigate this concern by including socioeconomic status (measured by insurance source and zip code-based median household income), metro versus non-metro residence and distance to the study hospital in the regression models. However, given the concern for potential unmeasured confounders, it will be important to confirm these findings in geographically diverse patient groups with both higher and lower levels of ozone exposure. Fourth, in this exploratory study, we did not aim to strictly control the type I error rate. In order to minimize the likelihood of

identifying false positive associations, we pre-specified the variables and interaction terms to include in the primary models prior to data examination. Subgroup analyses such as trauma/non-trauma were also pre-specified. Although we did not adjust for multiple comparisons, our primary finding of ozone-ARDS association has a p-value of <0.001 , which would be significant with post-hoc significance adjustment using a conservative Bonferroni method. Finally, because this was an observational study, causality cannot be inferred.

In summary, in a large group of rigorously phenotyped critically ill patients, we report an association between long-term ozone exposure levels and risk of developing ARDS. This risk was potentiated by cigarette smoking and was strongest in patients with severe trauma as their ARDS risk factor. These findings indicate that ozone exposure may be a previously unrecognized environmental risk factor for ARDS.

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FIGURE LEGENDS

Figure 1. Flow diagram summarizing patient selection for the ozone and NO₂ analyses.

Figure 2. Geographic distribution of the 163 ozone monitors that contributed exposure data for the ozone analysis.

Figure 3. Relationship between quartile of ozone exposure and development of ARDS.

In an unadjusted analysis of (A) all patients and of (B) the subset with trauma as their ARDS risk factor, patients in the 2nd, 3rd and 4th quartiles of 3-year ozone exposure estimates were significantly more likely to develop ARDS ($P < 0.001$). For 3A, the incidence of ARDS was 28.0%, (95% CI 23.4 - 32.7%) in quartile 1, 30.8% (95% CI 26.0% - 35.6%) in quartile 2, 41.0% (95% CI 36.0% - 46.1%) in quartile 3 and 41.8% (95% CI 36.7% - 46.9%). For 3B, the incidence of ARDS was 13.8% (95% CI 7.5% - 20.1%) in quartile 1, 22.9% (95% CI 15.9% - 29.8%) in quartile 2, 38.9% (95% CI 30.9% - 46.9%) in quartile 3 and 41.3% (95% CI 33.2% - 49.3%) in quartile 4.

Figure 4. Relationship between 3-year average ozone exposure level and predicted risk of ARDS in a logistic regression model controlling for age, race, sex, enrollment month, smoking, alcohol use, insurance status, zip-code based median household income, metro vs. non-metro residence, distance to the VUMC, and APACHE-II in (A) all patients in the ozone analysis and (B) in the same patients segregated by smoking status. The association between 3-year average ozone exposure level and predicted risk of ARDS differed between smokers and non-smokers and was only significant in the smokers.

Table 1. Comparison of patients by quartile of ozone exposure

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
Ozone (ppb-3 year avg)	41.5 – 49.0	49.0 – 51.5	51.5 – 53.5	53.5 – 58.2	
Age (y, median, IQR)	53 (40, 64)	54 (37, 65)	52 (36, 62)	52 (40, 63)	0.64
Male (n, %)	214 (60%)	214 (61%)	202 (57%)	219 (62%)	0.56
Caucasian (n, %)	239 (67%)	289 (82%)	319 (90%)	314 (89%)	< 0.001
Current smoker (n, %)	138 (42%)	119 (38%)	132 (41%)	139 (41%)	0.74
Alcohol abuse (n, %)	74 (21%)	60 (17%)	67 (19%)	64 (18%)	0.62
Insurance (Group 1*)	205 (58%)	243 (69%)	250 (71%)	231 (66%)	0.001
APACHE II (median, IQR)	25 (20, 30)	25 (20, 31)	25 (20, 31)	26 (21, 31)	0.34
Distance to VUMC (km, median, IQR)	11 (6, 51)	49 (17, 100)	70 (31, 102)	73 (52, 120)	< 0.001
Metro (vs. non-metro) residence county (n, %)	293 (82%)	249 (70%)	260 (73%)	222 (63%)	< 0.001
ARDS risk factor (n, %)					
Trauma	116 (33%)	140 (40%)	144 (40%)	143 (40%)	0.19
Sepsis	194 (54%)	182 (51%)	177 (50%)	178 (50%)	
Other	47 (13%)	32 (9%)	35 (10%)	33 (9%)	
Zip code based median household income (\$1000)	39.2 (30.4, 47.8)	44.8 (38.2, 57.0)	45.2 (38.1, 56.0)	43.0 (36.8, 51.5)	< 0.001
ARDS (n, %)	100 (28%)	109 (31%)	146 (41%)	148 (42%)	< 0.001

* Group 1 = Private, Medicare, Federal

Table 2. Logistic regression analysis for ARDS in ozone cohort

Variable	Comparator	Odds Ratio	95% Confidence Interval
Ozone	5ppb increment (49 to 54)	1.58	1.27 – 1.96
Age	Q3 : Q1 ¹	0.95	0.79 – 1.14
Gender	Female : Male	1.05	0.84 – 1.31
Race	Non-Caucasian : Caucasian	0.70	0.50 – 0.98
Current smoker	Smoker : Non-smoker	0.98	0.75 – 1.28
Alcohol abuse	Yes : No	0.94	0.70 – 1.28
Insurance Status	Group 2 : Group 1 ²	0.93	0.71 – 1.22
APACHE II	Q3 : Q1 ³	1.83	1.55 – 2.16
Distance to VUMC	Q3 : Q1 ⁴	0.89	0.62 – 1.28
Residence County	Non-Metro : Metro	0.92	0.67 – 1.26
Enrollment month	September : March	0.92	0.75 – 1.12
Median household income	Q3 : Q1 ⁵	0.88	0.72 – 1.08

¹ Lower quartile is 39, and upper quartile is 64.

² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

³ Lower quartile is 20, and upper quartile is 31.

⁴ Lower quartile is 19, and upper quartile is 109.

⁵ Lower quartile is 35.8k, and upper quartile is 51.5k.

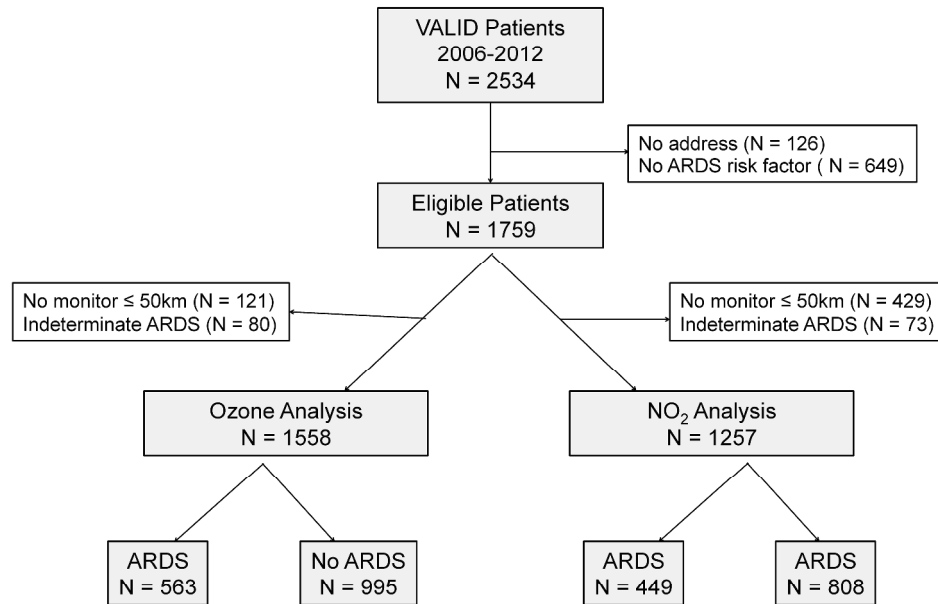


Figure 1

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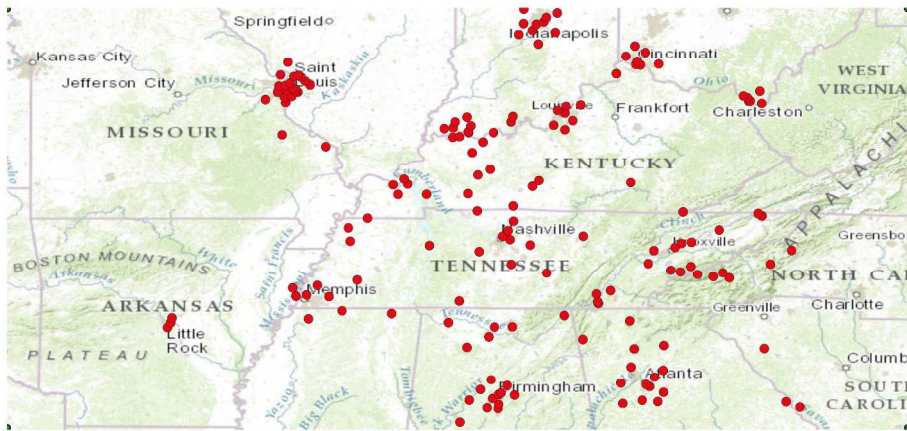


Figure 2

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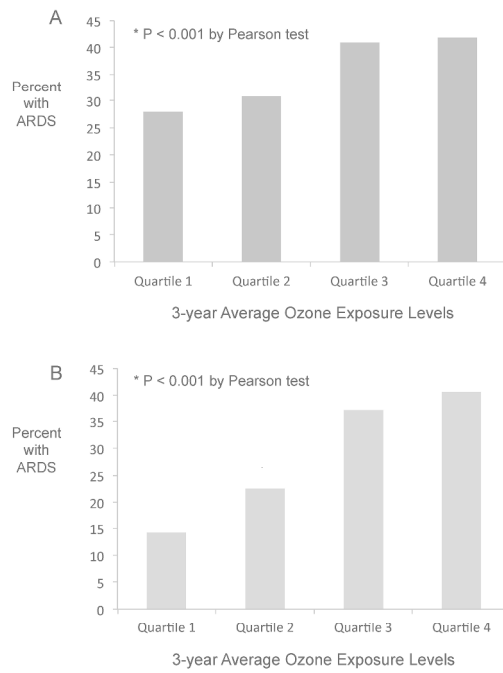


Figure 3

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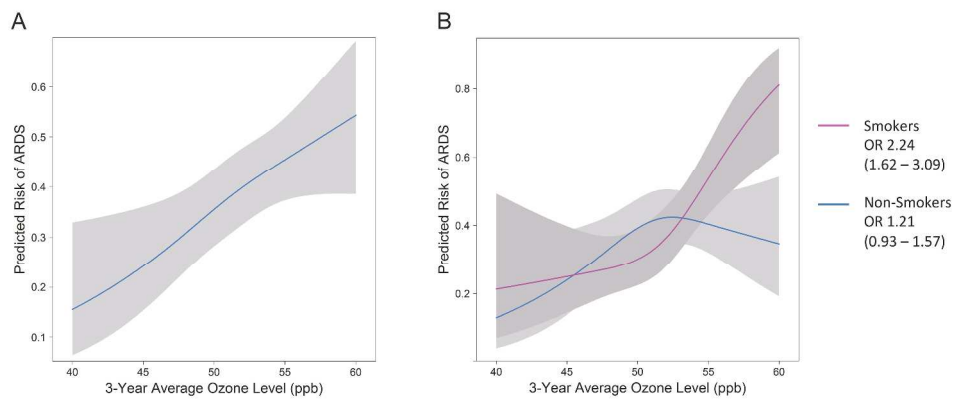


Figure 4
651x302mm (278 x 278 DPI)

Online Supplement to “Long-Term Ozone Exposure Increases the Risk of Developing the Acute Respiratory Distress Syndrome” by Ware et al.**Table of Contents**

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DETAILED METHODS

Patients. We studied patients from the Validating Acute Lung Injury biomarkers for Diagnosis study (VALID, Vanderbilt IRB #051065), a prospective observational cohort of critically ill medical, surgical and trauma patients admitted to Vanderbilt University Medical Center (VUMC), a tertiary medical center in Nashville, TN. Detailed inclusion and exclusion criteria and informed consent procedures have been published (E1-E4). Briefly, patients are eligible for enrollment into VALID if they are admitted to the Vanderbilt Medical, Surgical, Trauma or Cardiovascular ICUs at Vanderbilt and are still in the ICU on the morning of ICU day 2 with no plans to transfer out of the ICU on that day. Patients with uncomplicated overdose, cardiothoracic surgery or chronic lung disease requiring supplemental oxygen are excluded. VALID subjects enrolled between 2006 and 2012 were included if a residential address was available, they lived within 50 km of at least one U.S. Environmental Protection Agency (EPA)-approved air quality monitor and had a risk factor for ARDS such as sepsis, pneumonia, aspiration of gastric contents or severe trauma. We excluded patients if they lived outside a pre-specified geographic area bounded by latitude and longitude 33-40° N and 80-95° W because very few patients lived outside this area.

Clinical Data. Clinical data included demographics, insurance status, smoking, alcohol use, medical history, medications, APACHE II (E5), hemodynamic parameters, ventilator settings, laboratory values and clinical outcomes. Patients were coded as metro or non-metro dwellers using USDA 2003 Rural-Urban Continuum Codes (Codes 1-3 were classified as metro, and codes 4-9 were classified non-metro). The distance from a patient's address of residence to VUMC was defined as the great-circle distance between

the place of residence and VUMC, calculated with the Haversine formula. Health insurance status was collected at the time of admission as a surrogate for socioeconomic status. Due to small numbers in some categories, private, federal and Medicare insurance were grouped as indicative of higher socioeconomic status (Group 1), and all others (ie TennCare which is Tennessee Medicaid, other Medicaid and no insurance) were grouped together as indicative of lower socioeconomic status (Group 2). Each patient in VALID was phenotyped at enrollment and for the subsequent 3 days for sepsis, severe sepsis (E6), organ dysfunction (E7) and ARDS. Phenotyping for ARDS was done using American European Consensus Conference (AECC) definitions (E8) by two-physician review of the chest radiograph, clinical history and blood gases. ARDS criteria could also be met using the SpO_2/FiO_2 if PaO_2/FiO_2 was not available (E9). For the current study, patients were classified as having ARDS if they met AECC criteria for acute lung injury (ALI) or ARDS on two or more consecutive days during the four study days and as having no ARDS if they did not meet AECC ALI or ARDS criteria on any day. Patients meeting criteria on a single or on two non-consecutive days were deemed to have indeterminate ARDS status and were excluded from the primary analysis but included in a sensitivity analysis.

Air pollutant exposure estimates. Daily measurements of ozone, NO_2 , SO_2 , $PM_{2.5}$, and PM_{10} were obtained from the EPA's Aerometric Information Retrieval System for monitors located within the study region for 2001-12. The 24-hour average was computed for each pollutant except for ozone. Concentrations of ozone are generally higher in the day than night because it is formed in sunlight. We used the 8-hour daily maximum for ozone which is consistent with the metric used in the National Ambient Air

Quality Standard for ozone. If a monitor used more than one instrument then the average of the daily summaries for each was used. Since ozone levels are usually only monitored in warmer months in the study region, data were restricted to April through September; data from all months were used for other pollutants.

Patient addresses were geocoded (Google Maps Application Programming Interface) and the distances to all monitors calculated using the Haversine formula. Each patient's daily exposure to a pollutant was estimated by the inverse-distance-squared weighted average of daily levels from all monitors within 50km of the patient's address, based on the assumption that local levels of ambient pollutants reasonably estimate an individual's exposure (E10). We investigated both long-term exposures using the averages of 1-, 3-, and 5-year periods prior to ICU admission and short-term exposures using the average pollutant levels for the 3 days and 6 weeks prior to ICU admission. Findings for 1-, 3- and 5-year ozone exposures were similar; only 3-year data are presented. Because no significant associations between long-term exposures to SO₂, PM_{2.5} and PM₁₀ and risk of ARDS were observed, these analyses are presented in the Online Supplement. As there were no associations between any short-term air pollutant exposure and ARDS, these data are not shown.

Statistical Analysis. Demographic and clinical data were compared between ARDS and non-ARDS patients using Pearson's chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous ones. Similar univariate analyses were conducted for groups defined by quartiles of exposure. Missing values of regression covariates were multiply imputed with predictive mean matching (E11) to avoid case-wise deletion of patient records. First, missing values were initialized using a random

sample of observed values. A flexible additive model was then fit with each variable with missing data as the outcome. The process was repeated 10 times, each time initialized using the previous step's results. The standard error estimates in the final model were adjusted to account for variability associated with the imputation procedure. We fit logistic regression models to examine the relationship between ARDS and pollutant levels controlling for prespecified confounders including age, race, sex, enrollment month (to control for season), smoking, alcohol use, insurance status (as a proxy for socioeconomic status), zip code based median household income (from the 2006 – 2010 American Community Survey of the U.S. Census Bureau), metro vs. non-metro residence, distance to the VUMC, APACHE-II, injury severity score (ISS, trauma subset only) and blunt vs. penetrating trauma. A restricted cubic spline with 3 knots was used for age, month, and APACHE-II to permit nonlinear associations. To investigate the effect of ozone exposure in trauma patients and in smokers, prespecified subgroup analyses and models with interactions were utilized. Data preparation and analyses were performed by Drs. Zhao and Koyama using R Version 3 (R Core Team).

Table E1. Spearman's correlation coefficients for associations between exposure estimates for the five pollutants in each patient

	NO₂	PM₁₀	PM_{2.5}	SO₂
Ozone	-0.096 n = 987 p = 0.003	0.089 n = 1024 p = 0.005	0.292 n = 1294 p < 0.001	0.228 n = 1123 p < 0.001
NO₂		0.639 n = 877 p < 0.001	0.191 n = 930 p < 0.001	0.172 n = 985 p < 0.001
PM₁₀			0.559 n = 1036 p < 0.001	0.378 n = 983 p < 0.001
PM_{2.5}				0.393 n = 1060 p < 0.001

Table E2. Comparison of included and excluded patients for the ozone analysis

	Included in Ozone Analysis (n = 1558)	Excluded from Ozone Analysis (n = 201)	P Value
Age (y, median, IQR)	53 (39, 64)	51 (33, 65)	0.287
Male (n, %)	942 (60%)	136 (68%)	0.058
Caucasian (n, %)	1294 (83%)	164 (82%)	0.675
Current smoker (n, %)	573 (40%)	79 (45%)	0.233
Alcohol abuse (n, %)	279 (18%)	32 (16%)	0.551
Insurance (Group 1*) (n %)	1029 (67%)	133 (67%)	1.000
APACHEII (median IQR)	26 (20, 31)	25 (20, 32)	0.991
Distance to VUMC (km)	65 (19, 109)	152 (78,630)	<0.001
Metro (vs Non-Metro) (n %)	1041 (67%)	114 (57%)	0.006
ARDS Risk Factor (n, %)			
Trauma	585 (37%)	90 (45%)	0.117
Sepsis	810 (52%)	95 (47%)	
Other	163 (10%)	16 (8%)	
Zip code-based median household income (\$1000)	41.4 (35.8, 51.5)	41.1 (34.5, 50.9)	0.204
ARDS (n, %)	564 (36%)	39 (34%)	0.705

Table E3. Clinical characteristics of patients included in the ozone analysis

	N	Included in Ozone Analysis (n = 1558)	ARDS (N = 563)	No ARDS (N = 995)	P Value*
Age (y, median, IQR)	1558	53 (39, 64)	54 (40, 64)	52 (38, 64)	0.1
Male (n, %)	1558	942 (60%)	334 (59%)	608 (61%)	0.49
Caucasian (n, %)	1558	1294 (83%)	488 (87%)	806 (81%)	0.004
Current smoker (n, %)	1428	573 (40%)	206 (39%)	367 (41%)	0.456
Alcohol abuse (n, %)	1558	279 (18%)	95 (17%)	184 (19%)	0.423
Insurance Status (Group 1**) (n, %)	1537	1029 (67%)	387 (70%)	642 (65%)	0.081
APACHE II (median, IQR)	1558	26 (20, 31)	28 (23, 33)	24 (19, 30)	< 0.001
Distance to VUMC (km, median, IQR)	1558	65 (19, 109)	70 (24,115)	63 (18,106)	0.058
Metro (vs Non-Metro) (n, %)	1558	1041 (67%)	369 (66%)	672 (68%)	0.422
ARDS Risk Factor (n, %)	1558				< 0.001
Trauma		585 (37%)	178 (32%)	407 (41%)	
Sepsis		810 (52%)	348 (62%)	462 (46%)	
Other		163 (10%)	37 (6%)	126 (13%)	
Zip code-based median household income (\$1000)	1540	41.4 (35.8, 51.5)	42.3 (35.4, 53.5)	41.7 (35.9, 50.9)	0.74
Ozone (ppb, 3-year average)	1421	51.5 (49.0, 53.5)	52.1 (49.5, 54.0)	51.2 (48.5, 53.2)	< 0.001

N is patients with non-missing data; * comparison between ARDS and no ARDS groups, ** Private, Medicare and Federal insurance

Table E4. Logistic regression analysis for ARDS in ozone cohort using 24-hour average ozone levels instead of highest 8-hour daily maximum levels.

	Comparator	Odds Ratio	95% CI
Ozone¹	5ppb increment	1.61	1.27 – 2.03
Age	Q3 : Q1 ¹	0.94	0.79 – 1.13
Gender	Female : Male	1.05	0.85 – 1.32
Race	Non-Caucasian : Caucasian	0.70	0.50 – 0.97
Current smoker	Smoker : Non-smoker	0.97	0.76 -- 1.25
Alcohol abuse	Yes : No	0.95	0.70 – 1.29
Insurance	Group 2 : Group 1 ²	0.97	0.74 – 1.26
APACHE II	Q3 : Q1 ³	1.83	1.55 – 2.17
Distance to VUMC	Q3 : Q1 ⁴	0.72	0.47 – 1.10
Residence county	Non-Metro : Metro	0.87	0.64 – 1.18
Enrollment month	September : March	0.91	0.75 – 1.12
Household income	Q3 : Q1 ⁵	0.85	0.69 – 1.05

¹ Lower quartile is 39, and upper quartile is 64.

² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

³ Lower quartile is 20, and upper quartile is 31.

⁴ Lower quartile is 19, and upper quartile is 109.

⁵ Lower quartile is 35.8k, and upper quartile is 51.5k.

Table E5. Logistic regression analysis for ARDS in ozone cohort (with ozone-smoking interaction)

	Comparator	Odds Ratio	95% CI
Ozone¹	5ppb increment (49 to 54)	2.22 (smoker)	1.59 – 3.10
		1.27 (non-smoker)	0.96 – 1.69
Age	Q3 : Q1 ²	0.94	0.79 – 1.13
Gender	Female : Male	1.07	0.86 – 1.34
Race	Non-Caucasian : Caucasian	0.68	0.49 – 0.96
Current smoker	Smoker : Non-smoker	---	---
Alcohol abuse	Yes : No	0.95	0.70 – 1.30
Insurance	Group 2 : Group 1 ³	0.92	0.70 – 1.21
APACHE II	Q3 : Q1 ⁴	1.83	1.55 – 2.17
Distance to VUMC	Q3 : Q1 ⁵	0.89	0.62 – 1.28
Residence county	Non-Metro : Metro	0.91	0.67 – 1.24
Enrollment month	September : March	0.91	0.74 – 1.11
Household income	Q3 : Q1 ⁶	0.87	0.71 – 1.07

¹ P-value for ozone-smoking interaction is 0.007.

² Lower quartile is 39, and upper quartile is 64.

³ Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

⁴ Lower quartile is 20, and upper quartile is 31.

⁵ Lower quartile is 19, and upper quartile is 109.

⁶ Lower quartile is 35.8k, and upper quartile is 51.5k.

Table E6. Logistic regression analysis for ARDS in the subgroup of patients at risk for ARDS due to severe trauma

Variable	Comparator	Odds Ratio	95% Confidence Interval
Ozone	5ppb increment (49 to 54)	2.26	1.46 – 3.50
Age	Q3 : Q1 ¹	1.07	0.79 – 1.46
Gender	Female: Male	0.74	0.47 – 1.18
Race	Non-Caucasian: Caucasian	1.57	0.84 – 2.91
Current smoker	Smoker: Non-Smoker	1.18	0.74 – 1.87
Alcohol abuse	Yes: No	0.64	0.38 – 1.08
Insurance Status	Group 2 : Group 1 ²	0.83	0.51 – 1.35
APACHE II	Q3 : Q1 ¹	1.95	1.37 – 2.78
Distance to VUMC	Q3 : Q1 ¹	1.06	0.51 – 2.19
Residence county	Non-Metro: Metro	0.81	0.48 – 1.37
Enrollment month	September: March	0.72	0.51 – 1.03
Zip code-based median household income (\$1000)	Q3 : Q1 ¹	1.05	0.81 – 1.37
Injury severity score	Q3 : Q1 ¹	1.71	1.25 – 2.35
Type of trauma	Penetrating: Blunt	0.66	0.31 – 1.37

¹ Lower quartile is 39, and upper quartile is 64; ² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None; ³ Lower quartile is 20, and upper quartile is 31; ⁴ Lower quartile is 19.4, and upper quartile is 109; ⁵ Lower quartile is 35.8k, and upper quartile is 51.5k; ⁶ Lower quartile is 20, and upper quartile is 36.

Table E7. Clinical characteristics of patients included in the NO₂ analysis

	N	Included in NO ₂ Analysis (n = 1257)	ARDS (N = 449)	No ARDS (N = 808)	P Value*
Age (y, median, IQR)	1257	53 (38, 64)	54 (39,65)	52 (38, 64)	0.10
Male (n, %)	1257	752 (60%)	264 (59%)	488 (60%)	0.58
Caucasian (n, %)	1257	1015 (81%)	378 (84%)	637 (79%)	0.021
Current smoker (n, %)	1155	455 (39%)	156 (37%)	299 (41%)	0.18
Alcohol abuse (n, %)	1257	219 (17%)	71 (16%)	148 (18%)	0.26
Insurance Status (Group 1**) (n, %)	1240	839 (68%)	310 (70%)	529 (66%)	0.14
APACHE II (median, IQR)	1257	26 (20, 31)	28 (22, 32)	24 (19, 30)	< 0.001
Distance to VUMC (km, median, IQR)	1257	49 (16, 101)	50 (18, 101)	47 (14, 100)	0.20
Metro (vs Non-Metro) (n, %)	1257	954 (76%)	336 (75%)	618 (77%)	0.51
ARDS Risk Factor (n, %)	1257				< 0.001
Trauma		444 (35%)	133 (30%)	311 (39%)	
Sepsis		687 (55%)	291 (65%)	396 (49%)	
Other		126 (10%)	25 (5%)	101 (13%)	
Zip code-based median household income (\$1000)	1240	43.9 (36.6, 56.0)	44.8 (36.9, 56.9)	43.1 (36.4, 53.3)	0.11
NO ₂ (ppb, 3-year average)	994	15.4 (8.3, 16.8)	15.8 (8.2, 16.9)	15.3 (8.4, 16.8)	0.066

N is patients with non-missing data; * comparison between ARDS and no ARDS groups, ** Private, Medicare and Federal insurance

Table E8. Patient characteristics by quartile of estimated NO₂ exposure

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
NO₂ (ppb-3 yr avg)	1.7 - 8.4	8.4 - 15.4	15.4 - 16.8	16.8 - 17.7	
Age (y, median, IQR)	52 (37 – 63)	53 (35 – 64)	52 (41 – 63)	51 (38 – 62)	0.903
Male (n, %)	147 (59%)	147 (59%)	150 (60%)	140 (56%)	0.831
Caucasian (n, %)	215 (86%)	212 (85%)	177 (71%)	168 (68%)	<0.001
Current smoker (n, %)	93 (40%)	87 (39%)	81 (35%)	114 (50%)	0.013
Alcohol abuse (n, %)	40 (16%)	43 (17%)	42 (17%)	58 (23%)	0.132
Insurance (Group 1*)	184 (75%)	162 (66%)	155 (62%)	140 (58%)	<0.001
APACHE II (median, IQR)	26 (20 – 32)	25 (20 – 29)	25 (20 – 30)	26 (20 – 32)	0.056
Distance to VUMC (km, median, IQR)	91 (71 – 117)	41 (16 – 174)	16 (7 – 27)	14 (6 – 26)	< 0.001
Metro (vs Non-Metro) (n, %)	142 (57%)	199 (80%)	248 (100%)	248 (100%)	< 0.001
ARDS Risk Factor (n, %)	96 (38%)	97 (39%)	78 (31%)	83 (33%)	0.08
Trauma	126 (50%)	134 (54%)	150 (60%)	133 (54%)	
Sepsis	28 (11%)	17 (7%)	20 (8%)	32 (13%)	
Other					
Median Household Income	40.7 (37.1, 47.1)	45.3 (37.7, 57.3)	50.0 (39.2, 61.7)	47.9 (37.0, 57.0)	< 0.001
Percent with ARDS	88 (35%)	72 (29%)	86 (35%)	96 (39%)	0.152

*Private, Medicare, and Federal insurance

Table E9. Logistic regression analysis for ARDS in the NO₂ cohort

Variable	Comparator	Odds Ratio	95% Confidence Interval
NO₂	5 ppb increment (8.3 to 13.3)	1.29	1.02 – 1.62
Age	Q3 : Q1 ¹	0.98	0.80 – 1.20
Gender	Female : Male	1.01	0.79 – 1.30
Race	Non-Caucasian : Caucasian	0.75	0.52 – 1.07
Current smoker	Smoker : Non-smoker	0.88	0.67 – 1.17
Alcohol abuse	Yes : No	0.91	0.65 – 1.17
Insurance Status	Group 2 : Group 1 ²	1.00	0.74 – 1.35
APACHE II	Q3 : Q1 ³	1.82	1.51 – 2.19
Distance to VUMC	Q3 : Q1 ⁴	2.04	1.12 – 3.71
Residence County	Non-Metro : Metro	0.99	0.67 – 1.45
Enrollment month	September : March	0.94	0.75 – 1.18
Median Household Income	Q3 : Q1 ⁵	1.06	0.83 – 1.34

¹ Lower quartile is 38, and upper quartile is 64.

² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

³ Lower quartile is 20, and upper quartile is 31.

⁴ Lower quartile is 15.5, and upper quartile is 100.7.

⁵ Lower quartile is 36.5k, and upper quartile is 56.0k.

Table E10. Logistic regression model for ARDS including both ozone and NO₂ exposure estimates

Variable	Comparator	Odds Ratio	95% Confidence Interval
Ozone	5 ppb increment (49 to 54)	1.48	1.10 – 1.97
NO₂	5 ppb increment (8.3 to 13.3)	1.12	0.90 – 1.40
Age	Q3 : Q1 ¹	0.97	0.79 – 1.19
Gender	Female : Male	1.02	0.79 – 1.30
Race	Non-Caucasian : Caucasian	0.76	0.53 – 1.09
Current smoker	Smoker : Non-smoker	0.90	0.68 – 1.19
Alcohol abuse	Yes : No	0.89	0.63 – 1.25
Insurance	Group 2 : Group 1 ²	1.00	0.74 – 1.35
APACHE II	Q3 : Q1 ³	1.83	1.52 – 2.20
Distance to VUMC	Q3 : Q1 ⁴	1.07	0.53 – 2.16
Residence County	Non-Metro : Metro	1.10	0.74 – 1.63
Enrollment month	September : March	0.93	0.74 – 1.17
Median Household Income	Q3 : Q1 ⁵	0.97	0.75 – 1.25

¹ Lower quartile is 38, and upper quartile is 64.² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.³ Lower quartile is 20, and upper quartile is 31.⁴ Lower quartile is 15.5, and upper quartile is 100.7.⁵ Lower quartile is 36.5k, and upper quartile is 56.0k.

Table E11. Patient characteristics by quartile of estimated SO₂ exposure

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
SO₂ (ppb-3 yr avg)	1.12 – 2.37	2.37 – 2.77	2.77 – 3.07	3.07 – 9.48	
Age (y, median, IQR)	53 (37 – 66)	52 (41 – 64)	51 (38 – 61)	53 (37 – 62)	0.737
Male (n, %)	176 (60%)	172 (58%)	178 (60%)	181 (61%)	0.879
Caucasian (n, %)	271 (92%)	226 (76%)	200 (66%)	253 (86%)	<0.001
Current smoker (n, %)	107 (40%)	112 (40%)	123 (47%)	98 (36%)	0.067
Alcohol abuse (n, %)	50 (17%)	46 (16%)	62 (21%)	51 (17%)	0.353
Insurance (Group 1*, n, %)	191 (66%)	198 (68%)	167 (58%)	218 (74%)	<0.001
APACHE II (median, IQR)	26 (20 – 31)	25 (20 – 30)	26 (20 – 31)	27 (19 – 34)	0.852
Distance to VUMC (km, median, IQR)	83 (61 – 123)	23 (12 – 44)	13 (6 – 24)	82 (58 – 129)	0.296
Metro (vs Non-Metro) (n, %)	150 (51%)	270 (91%)	287 (97%)	247 (84%)	< 0.001
ARDS Risk Factor (n, %)					0.301
Trauma	123 (41%)	101 (34%)	105 (35%)	110 (37%)	
Sepsis	141 (48%)	172 (58%)	156 (53%)	156 (53%)	
Other	32 (11%)	23 (8%)	35 (12%)	29 (10%)	
Zip code-based median household income (\$1000)	40.2 (35.4, 46.4)	50.5 (39.2, 61.5)	44.8 (37.0, 58.8)	44.5 (38.1, 48.4)	<0.001
Percent with ARDS	110 (37%)	113 (38%)	101 (34%)	99 (34%)	0.578

*Private, Medicare, and Federal insurance

Table E12. Logistic regression model for ARDS in the SO₂ cohort

Variable	Comparator	Odds Ratio	95% Confidence Interval
SO₂	1 ppb increment (2.4 to 3.4)	1.00	0.84 - 1.19
Age	Q3 : Q1 ¹	0.95	0.78 - 1.16
Gender	Female : Male	1.05	0.83 - 1.33
Race	Non-Caucasian : Caucasian	0.73	0.51 - 1.04
Current smoker	Smoker : Non-smoker	0.89	0.67 - 1.18
Alcohol abuse	Yes : No	0.93	0.67 - 1.29
Insurance Status	Group 2 : Group 1 ²	0.95	0.71 - 1.27
APACHE II	Q3 : Q1 ³	1.85	1.54 - 2.21
Distance to VUMC	Q3 : Q1 ⁴	1.43	0.98 - 2.08
Residence County	Non-metro : Metro	0.84	0.57 - 1.23
Enrollment month	September : March	0.95	0.76 - 1.18
Zip code-based median household income	Q3 : Q1 ⁵	1.04	0.84 - 1.29

¹ Lower quartile is 38, and upper quartile is 64.

² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

³ Lower quartile is 20, and upper quartile is 31.

⁴ Lower quartile is 16.7, and upper quartile is 101.6.

⁵ Lower quartile is 36.4k, and upper quartile is 53.2k.

Table E13. Patient characteristics by quartile of estimated PM_{2.5} exposure

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
PM_{2.5} (µg/m³-3 yr avg)	8.7 – 12.1	12.1 – 13.2	13.2 – 13.7	13.7 – 19.4	
Age (y, median, IQR)	55 (40 – 65)	52 (39 – 64)	52 (38 – 62)	50 (34 – 62)	0.011
Male (n, %)	193 (57%)	198 (59%)	200 (59%)	207 (61%)	0.717
Caucasian (n, %)	287 (85%)	271 (80%)	279 (83%)	257 (76%)	0.03
Current smoker (n, %)	109 (35%)	114 (37%)	133 (44%)	138 (45%)	0.015
Alcohol abuse (n, %)	47 (14%)	50 (15%)	61 (18%)	78 (23%)	0.007
Insurance (Group 1*, n, %)	226 (67%)	237 (70%)	226 (68%)	194 (58%)	0.007
APACHE II (median, IQR)	26 (21 – 31)	25 (20 – 31)	26 (20 – 31)	25 (20 – 30)	0.128
Distance to VUMC (km, median, IQR)	54 (19 – 109)	62 (18 – 102)	48 (17 – 98)	47 (11 – 99)	0.073
Metro (vs Non-Metro) (n, %)	223 (66%)	230 (68%)	257 (76%)	297 (88%)	< 0.001
ARDS Risk Factor (n, %)					0.094
Trauma	128 (41%)	139 (41%)	124 (37%)	120 (36%)	
Sepsis	168 (50%)	171 (51%)	168 (50%)	184 (55%)	
Other	32 (10%)	28 (8%)	46 (14%)	33 (10%)	
Zip code-based Median Household Income (\$1000)	43.4 (36.0, 56.0)	44.1 (37.1, 52.2)	44.9 (37.7, 56.7)	43.3 (35.7, 52.8)	0.21
Percent with ARDS	116 (34%)	141 (42%)	102 (30%)	122 (36%)	0.017

*Private, Medicare, and Federal insurance

Table E14. Logistic regression model for ARDS in the PM_{2.5} cohort

Variable	Comparator	Odds Ratio	95% Confidence Interval
PM_{2.5}	1.0 µg/m ³ increment (12.1 to 13.1)	1.05	0.95 - 1.16
Age	Q3 : Q1 ¹	0.93	0.77 - 1.13
Gender	Female : Male	1.07	0.85 - 1.36
Race	Non-Caucasian : Caucasian	0.70	0.49 - 0.98
Current smoker	Smoker : Non-smoker	1.04	0.79 - 1.35
Alcohol abuse	Yes : No	0.97	0.70 - 1.35
Insurance Status	Group 2 : Group 1 ²	0.91	0.69 - 1.21
APACHE II	Q3 : Q1 ³	1.93	1.61 - 2.31
Distance to VUMC	Q3 : Q1 ⁴	1.36	0.97 - 1.90
Residence County	Non-metro: Metro	0.80	0.57 - 1.14
Enrollment month	September : March	0.90	0.72 - 1.11
Median Household Income	Q3 : Q1 ⁵	1.03	0.84 - 1.26

¹ Lower quartile is 38, and upper quartile is 63.

² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

³ Lower quartile is 20, and upper quartile is 31.

⁴ Lower quartile is 16.8, and upper quartile is 101.6.

⁵ Lower quartile is 37.0k, and upper quartile is 54.5k.

Table E15. Patient characteristics by quartile of estimated PM₁₀ exposure

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Value
PM₁₀ (µg/m³-3 yr avg)	13.4 – 20.3	20.3 – 22.3	22.3 – 24.3	24.3 – 40.9	
Age (y, median, IQR)	54 (37 – 65)	52 (36 – 62)	53 (38 – 64)	52 (39 – 61)	0.337
Male (n, %)	169 (64%)	158 (59%)	147 (56%)	162 (61%)	0.286
Caucasian (n, %)	230 (87%)	208 (78%)	191 (72%)	202 (76%)	<0.001
Current smoker (n, %)	89 (37%)	79 (32%)	110 (44%)	105 (43%)	0.026
Alcohol abuse (n, %)	33 (12%)	34 (13%)	57 (22%)	59 (22%)	0.001
Insurance (Group 1*, n, %)	196 (75%)	190 (71%)	164 (63%)	157 (60%)	<0.001
APACHE II (median, IQR)	25 (20 – 31)	25 (21 – 30)	26 (19 – 31)	26 (20 – 31)	0.967
Distance to VUMC (km, median, IQR)	96 (50 – 152)	47 (17 – 87)	18 (8 – 42)	19 (8 – 43)	< 0.001
Metro (vs Non-Metro) (n, %)	180 (68%)	228 (85%)	255 (96%)	253 (95%)	< 0.001
ARDS Risk Factor (n, %)					0.042
Trauma	114 (43%)	105 (39%)	85 (32%)	85 (32%)	
Sepsis	126 (47%)	147 (55%)	150 (57%)	152 (57%)	
Other	26 (10%)	15 (6%)	30 (11%)	29 (11%)	
Zip code-based Median Household Income (\$1000)	42.7 (36.3, 51.5)	46.5 (38.9, 56.4)	45.3 (37.0, 56.5)	48.8 (39.2, 63.6)	< 0.001
Percent with ARDS	92 (35%)	99 (37%)	93 (35%)	90 (34%)	0.879

*Private, Medicare, and Federal insurance

Table E16. Logistic regression model for ARDS in the PM₁₀ cohort

Variable	Comparator	Odds Ratio	95% Confidence Interval
PM₁₀	4.0 µg/m ³ increment (20.3 to 24.3)	0.92	0.73 - 1.15
Age	Q3 : Q1 ¹	0.90	0.73 - 1.11
Gender	Female : Male	1.00	0.77 - 1.30
Race	Non-Caucasian : Caucasian	0.71	0.49 - 1.03
Current smoker	Smoker : Non-smoker	0.91	0.67 - 1.23
Alcohol abuse	Yes : No	1.03	0.72 - 1.47
Insurance Status	Group 2 : Group 1 ²	0.98	0.72 - 1.35
APACHE II	Q3 : Q1 ³	1.92	1.58 - 2.35
Distance to VUMC	Q3 : Q1 ⁴	1.31	0.88 - 1.96
Residence County	Non-metro : Metro	0.80	0.52 - 1.24
Enrollment month	September : March	0.90	0.71 - 1.14
Median Household Income	Q3 : Q1 ⁵	1.06	0.85 - 1.31

¹ Lower quartile is 38, and upper quartile is 63.

² Group 1 = Private, Medicare, Federal; Group 2 = TennCare, Medicaid, None.

³ Lower quartile is 20, and upper quartile is 31.

⁴ Lower quartile is 13.9, and upper quartile is 98.0.

⁵ Lower quartile is 37.9k, and upper quartile is 56.5k.

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