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### Authors

Reilly, John

Zhao, Zhiguo

Shashaty, Michael

et al.

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## Exposure to Ambient Air Pollutants and Acute Respiratory Distress Syndrome Risk in Sepsis

John P. Reilly, MD, MSCE<sup>1,2</sup>, Zhiguo Zhao, MS<sup>4</sup>, Michael G. S. Shashaty, MD, MSCE<sup>1,2</sup>, Tatsuki Koyama, PhD<sup>4</sup>, Tiffanie K. Jones, MD, MSCE<sup>1,2,3</sup>, Brian J. Anderson, MD, MSCE<sup>1,2</sup>, Caroline A. Ittner, PhD<sup>1,2</sup>, Thomas Dunn<sup>1,2</sup>, Todd A. Miano, PharmD, PhD<sup>3</sup>, Oluwatosin Oniyide<sup>1,2</sup>, John R. Balmes, MD<sup>7,8</sup>, Michael A. Matthay, MD<sup>8,9</sup>, Carolyn S. Calfee, MD, MAS<sup>8,9</sup>, Jason D. Christie, MD, MSCE<sup>1,2,3</sup>, Nuala J. Meyer, MD, MS<sup>1,2</sup>, Lorraine B. Ware, MD<sup>5,6</sup>

<sup>1</sup>Division of Pulmonary, Allergy, and Critical Care, University of Pennsylvania, Perelman School of Medicine

<sup>2</sup>Center for Translational Lung Biology, University of Pennsylvania, Perelman School of Medicine

<sup>3</sup>Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Perelman School of Medicine

<sup>4</sup>Department of Biostatistics, Vanderbilt University School of Medicine

<sup>5</sup>Department of Medicine, Vanderbilt University School of Medicine

<sup>6</sup>Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine

<sup>7</sup>Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley

<sup>8</sup>Department of Medicine, University of California, San Francisco

<sup>9</sup>Department of Anesthesia and Cardiovascular Research Institute, University of California, San Francisco

### Abstract

**Correspondence to:** John P. Reilly MD, MSCE, Division of Pulmonary, Allergy, and Critical Care, University of Pennsylvania, Perelman School of Medicine, 5005 Gibson Building, 3400 Spruce Street, Philadelphia, PA 19104, John.Reilly@penmedicine.edu, 215-662-2824.

**Authors' Contributions:** JPR, ZZ, and LBW designed the study, acquired data, analyzed data, and wrote the manuscript. MGSS, TKJ, BJA, CAI, TD, TAM, OO, JDC, and NJM designed the study, acquired data, and revised the manuscript. TK analyzed data and revised the manuscript. JRB, MAM, CSC designed the study and revised the manuscript. JPR, NJM, CSC, and LBW obtained funds for the study. All authors approved the final version of the manuscript and are accountable for the work.

**Conflicts of Interest:** Dr. Ware reports consulting fees from Akebia, Santhera, Global Blood Therapeutics, and Boehringer Ingelheim and research contract support (paid to institution) from Genentech, Boehringer Ingelheim, and CSL Behring all unrelated to the topic of this article. Dr. Meyer reports consulting fees from Endpoint Health, Inc and research contract support to her institution from Quantum Leap Healthcare Collaborative and Biomarck, Inc. Dr. Calfee reports consulting fees from Vasomune, Gen1e Life Sciences, Cellenkos, NGMBio, and Janssen, and research support to her institution from Roche-Genentech and Quantum Leap Healthcare Collaborative, all unrelated to this article. Dr. Matthay reports research grant funding from Roche-Genentech and Quatum Therapeutics, and consultation for Novartis, Citius Pharmaceuticals, Johnson and Johnson, Gilead Pharmaceuticals, and ElifeScience.

**Purpose:** Exposures to ambient air pollutants may prime the lung enhancing risk of acute respiratory distress syndrome (ARDS) in sepsis. Our objective was to determine the association of short-, medium-, and long-term pollutant exposures and ARDS risk in critically ill sepsis patients.

**Methods:** We analyzed a prospective cohort of 1,858 critically ill patients with sepsis, and estimated short- (3-day), medium- (6-weeks), and long- (5-years) term exposures to ozone, nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), carbon monoxide (CO), particulate matter <2.5 μm (PM<sub>2.5</sub>), and PM<10 μm (PM<sub>10</sub>) using weighted averages of daily levels from monitors within 50 km of subjects' residences. Subjects were followed for 6 days for ARDS by the Berlin Criteria. The association between each pollutant and ARDS was determined using multivariable logistic regression adjusting for preselected confounders. In 764 subjects, we measured plasma concentrations of inflammatory proteins at presentation and tested for an association between pollutant exposure and protein concentration via linear regression.

**Results:** ARDS developed in 754 (41%) subjects. Short- and long-term exposures to SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub> were associated with ARDS risk (SO<sub>2</sub>: OR for the comparison of the 75<sup>th</sup> to 25<sup>th</sup> long term exposure percentile 1.43(95% CI 1.16, 1.77);p<0.01; NO<sub>2</sub>: 1.36(1.06, 1.74);p=0.04, PM<sub>2.5</sub>: 1.21(1.04, 1.41);p=0.03). Long-term exposures to these three pollutants were also associated with plasma interleukin-1 receptor antagonist and soluble tumor necrosis factor receptor-1 concentrations.

**Conclusion:** Short and long-term exposures to ambient SO<sub>2</sub>, PM<sub>2.5</sub>, and NO<sub>2</sub> are associated with increased ARDS risk in sepsis, representing potentially modifiable environmental risk factors for sepsis-associated ARDS.

#### TWEET:

Short and long-term exposures to the ambient air pollutants SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub> are associated with increased risk of ARDS in sepsis.

#### Keywords

Acute Respiratory Distress Syndrome; Acute Lung Injury; Sepsis; Air Pollution

## INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a common cause of respiratory failure characterized by the acute onset of diffuse bilateral non-cardiogenic pulmonary edema and severe hypoxemia occurring in the setting of a significant precipitating insult.(1, 2) Unfortunately, the syndrome carries a mortality greater than 30% and lacks pharmacologic therapies that target underlying biologic mechanisms.(3, 4) The most common precipitating insult for ARDS is sepsis, the dysregulated host response to infection.(5) Sepsis can result in ARDS either from a pulmonary or non-pulmonary source of infection,(6) is the sixth leading cause of hospitalization in the United States (US), and is the leading cause of death among the critically ill.(7) Environmental factors that alter ARDS risk in sepsis are incompletely understood;(8-11) however, there is an urgent need to identify modifiable ARDS risk factors and their underlying mechanisms in order to develop strategies to reduce sepsis-associated ARDS risk and mortality.

Components of ambient air pollution, including particulate matter (PM), ozone (O<sub>3</sub>), nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), and carbon monoxide (CO), have been linked to the development of lung disease, exacerbations of lung disease, and respiratory mortality. (12-19) The Industrial Revolution led to dramatic spikes in ambient air pollution that were linked to increases in acute respiratory hospitalizations and mortality, eventually spurring the development of air quality standards in the US and elsewhere. (20, 21) Concordant with these reports, healthy rodents exposed to high levels of O<sub>3</sub> and certain types of PM develop acute lung injury by the induction of oxidative stress, increased alveolar capillary barrier permeability, and recruitment of inflammatory cells to the lung. (22) In healthy humans, even low to moderate exposure to air pollutants results in a transient decline in lung function and recruitment of inflammatory cells. (23, 24) Additionally, exposure to ambient air pollution is not uniform across regions of the US, with individuals of lower socioeconomic status and racial minorities burdened by higher exposure, potentially contributing to health outcome disparities. (25, 26)

We previously reported associations between exposure to components of ambient air pollution and risk of ARDS in two geographically diverse cohorts. (10, 11) In our first study of 1,558 critically ill patients at risk for ARDS presenting to Vanderbilt University Medical Center, we identified an independent association between long-term O<sub>3</sub> exposure and risk of ARDS. (11) This association was strongest among the subgroup of patients whose ARDS risk factor was traumatic injury; however, the sepsis subgroup may have been underpowered to identify independent associations. In our second study, we identified associations between O<sub>3</sub>, fine PM < 2.5 μm in diameter (PM<sub>2.5</sub>), NO<sub>2</sub>, SO<sub>2</sub>, and CO with risk of ARDS in a prospective cohort of 996 critically ill patients presenting to the Penn Medicine Trauma Center after traumatic injury. (10)

The primary objective of the current study was to determine if our previous findings in trauma patients are also evident in the largest group of patients at risk for ARDS, those with sepsis. We aimed to determine the independent association of short-, medium-, and long-term exposure to the ambient air pollutants O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO, PM<sub>2.5</sub> and PM<sub>10</sub> with the risk of developing ARDS in a large well-phenotyped prospective cohort study of sepsis. Additionally, we aimed to determine the association of short-, medium-, and long-term exposure to ambient air pollutants and biomarkers of inflammation measured early after presentation with sepsis. Globally, we hypothesized that short-, medium-, and long-term exposure to elevated ambient air pollutants would prime the lung for injury, resulting in an increased risk of sepsis-associated ARDS. Some of the results of this study have been previously reported in the form of an abstract. (27)

## METHODS

Additional methods are provided in the online data supplement.

### Study Population

We included patients enrolled in the Molecular Epidemiology of SepSis in the Intensive care unit (MESSI) prospective cohort study between 2008 and 2018. MESSI enrollment criteria have been previously described. (28-31) Briefly, all patients admitted to a single-center

medical intensive care unit (ICU) are screened for sepsis according to the sepsis-2 criteria for severe sepsis or septic shock and enrolled if they had a primary indication for ICU admission of sepsis. MESSI exclusion criteria included admission from a long-term acute care facility and an active do-not-intubate order at the time of enrollment. For the current study, we excluded patients without an available residential address and those who did not live within 50 km of an EPA air quality monitor. The cohort protocol is approved by the Institutional Review Board of the University of Pennsylvania (Protocol #808542) with a waiver of timely informed consent with consent obtained at the earliest feasible timepoint.

### **Air Pollution Exposure**

Exposures to Environmental Protection Agency (EPA) criteria pollutants, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>, CO, PM<sub>2.5</sub>, and PM<sub>10</sub>, were estimated using the EPA's publicly available Aerometric Information Retrieval System. An individual patient's average exposure was assessed using the inverse-distance squared weighted average of daily levels from all EPA air quality monitors within 50 km of the geocoded location of the patient's residential address.(10, 11) Ozone levels were only measured in summer months. We defined short, medium, and long-term exposure based on prior literature as the average exposure over the 3 days, 6 weeks, and 5 years prior to presentation with sepsis, respectively.

### **ARDS Outcome**

Enrolled patients were followed for 6 days from presentation for the development of ARDS based on the Berlin definition, with the added requirement for intubation and invasive mechanical ventilation.(2, 32) We follow patients for 6 days for ARDS to identify ARDS directly related to sepsis. Prior studies demonstrate that nearly 100% of ARDS that occurs directly related to a precipitating factor develops within 5 days.(33, 34) All chest radiographs ordered for clinical purposes were reviewed by trained physician investigators for ARDS with consensus review for any discordant radiographs.

### **Plasma Biomarker Measurements**

Residual plasma initially drawn for clinical testing at emergency department, or, for transfers from the hospital ward, ICU presentation, was obtained by research personnel for biomarker testing. This approach allows us to obtain plasma drawn as close to admission as possible. Plasma concentrations of inflammatory proteins Interleukin (IL)-8, IL-6, IL-1 receptor antagonist (IL-1RA), and soluble tumor necrosis factor receptor-1 (sTNFR1) were measured in duplicate in a subset of 764 subjects enrolled in the larger cohort selected based on availability of plasma and cost using commercially available Meso Scale Discovery assays optimized for human plasma.

### **Statistical Analysis**

Our primary objective was to determine the association between long-term air pollutant exposure and ARDS risk, and our secondary objectives were to determine the association of short- and medium-term air pollutant exposure and ARDS risk. Patient characteristics were compared across quartiles of air pollutant exposure using the Pearson Chi-square test or Kruskal-Wallis test, as appropriate. We then estimated the association of short, medium,

and long-term exposure and risk of ARDS via multivariable logistic regression models adjusting for prespecified confounders chosen based on a directed acyclic graph including covariates hypothesized to confound the relationship between air pollutant exposure and ARDS.<sup>(35)</sup> Specifically, we adjusted for age, sex, self or surrogate reported race, smoking history, alcohol use, severity of illness based on the Acute Physiology and Chronic Health Evaluation (APACHE) III score, distance to the hospital, month of admission, and median household income of the patients' home addresses' 5-digit zip code. We *a priori* elected not to adjust for source of sepsis or initial management decisions as we hypothesized that these variables may be in the causal pathway linking air pollution to ARDS risk. Additionally, we conducted an *a priori* defined sensitivity analysis in which we limited derivation of the exposure estimates to EPA monitors within 15 km of patients' residences to reduce exposure misclassification. We also examined for interactions between pollutant levels and smoking history, age, and race using the likelihood ratio test. Statistical significance was considered for two-sided p-values less than 0.05.

The correlation between short-, medium-, and long-term exposure to air pollutants and plasma biomarker concentrations was first estimated and tested using Spearman's rho. We then fit multivariable linear regression models for each biomarker as the outcome adjusting for the pre-specified confounders. We did not adjust for sepsis severity or occurrence of ARDS in these models as we hypothesized these variables also exist in the causal pathway. Plasma biomarker concentrations were log transformed to improve model fit. Logistic regression was then used to determine the association of the biomarkers with ARDS risk.

## RESULTS

### Cohort Characteristics

We enrolled 1,858 septic patients with available residential addresses, 754 (41%) of whom developed ARDS within 6 days of presentation (Supplemental Figure E1). The source of sepsis was pulmonary in 34% of subjects, 58% of subjects were male, the median age was 61 years (interquartile range (IQR) 51 - 69), and the racial distribution was similar to the population of the Philadelphia Metropolitan Area that presents to the Hospital of the University of Pennsylvania (Table 1). All enrolled patients lived within 50 km of at least one air quality monitor, with the majority living within 50 km of multiple air quality monitors. The median number of air quality monitors within 50 kms ranged from 12 to 25 depending on the pollutant (Supplemental Table E1). Median (IQR) short-, medium-, and long-term concentrations of each air pollutant were largely lower than US air quality standards and are provided in Supplemental Table E2. Long-term concentrations of SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub> were moderately correlated with one another. Ozone demonstrated a negative correlation with NO<sub>2</sub> and PM<sub>10</sub>, and a weak correlation with CO (Supplemental Table E3). Short-, medium-, and long-term concentrations of each individual pollutant were moderately to highly correlated (Supplemental Table E4). Supplemental Table E5 provides patient characteristics and ARDS cases by quartiles of long-term 5-year average air pollutant concentrations. Notably, patients of non-white race and lower socioeconomic status were more likely to have a higher exposure to NO<sub>2</sub>, SO<sub>2</sub>, CO, PM<sub>2.5</sub>, and PM<sub>10</sub>. Additionally,

pulmonary source of sepsis was more common in the higher exposure quartiles for all air pollutants except PM<sub>10</sub>.

### **Pollutant Exposure and ARDS**

We identified several statistically significant associations between short-, medium-, and long-term air pollutant exposures and ARDS risk in sepsis (Table 2). Exposure to elevated SO<sub>2</sub> demonstrated the strongest association with ARDS risk at each time window of exposure (Figure 1a). Short- and long-term exposures to NO<sub>2</sub> were also associated with ARDS risk (Figure 1b). Results for medium-term exposure to NO<sub>2</sub> and ARDS risk were not statistically significant. Exposure to PM<sub>2.5</sub> demonstrated an association with ARDS risk with each time window of exposure (Figure 1c). Exposure to O<sub>3</sub> was significantly associated with ARDS risk only for medium-term exposure estimates; however, the relationship was non-linear (Figures 1d, Figure 2). We did not identify linear associations between increased exposure to CO or PM<sub>10</sub> and ARDS risk (Figure 1e-f).

### **Pollutant Exposure and Plasma Biomarkers**

Short-, medium-, and long-term exposure to the three air pollutants associated with ARDS, SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub>, were not positively correlated with any biomarker of inflammation (Supplemental Table E6) in unadjusted analyses. However, after adjustment for sex, race, and APACHE III score, increasing exposure to SO<sub>2</sub> was strongly associated with higher plasma concentrations of IL-1RA and sTNFR1 for short-, medium-, and long-term exposure windows (Table 3, Supplemental Table E6). In multivariable linear regression models, long-term exposures to PM<sub>2.5</sub> and NO<sub>2</sub> were also associated with plasma concentrations of IL-1RA and sTNFR1 (Table 3). Short- and medium-term exposures to PM<sub>2.5</sub> and NO<sub>2</sub> were not positively associated with any biomarker level (Supplemental Table E6). Plasma concentrations of IL1RA and sTNFR1 were strongly associated with ARDS (IL1RA: Odds Ratio (OR) per log increase 1.13 (95% CI 1.07, 1.18); p<0.001, sTNFR1: OR per log increase 1.36 (95% CI 1.16, 1.60); p<0.001).

### **Sensitivity Analysis**

Limiting exposure data to only air quality monitors within 15 km of a patient's geocoded address did not substantially change our results (Supplemental Table E7). We did not identify significant statistical interaction between air pollutant exposures and smoking status, age, or race.

## **DISCUSSION**

We identified strong and independent associations between short- and long- term exposure to SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub> with risk of ARDS in a large cohort of patients admitted to the ICU with sepsis. These findings are consonant with those of our previous study in trauma patients, and expand the link between ambient air pollution and ARDS to the largest at-risk population, those with sepsis.(10) Notably, as subjects who traveled further to the hospital had a higher severity of illness and lower air pollution exposure, adjustment for severity of illness and distance to the hospital revealed associations between air pollution and ARDS risk that might not have been seen without robust confounder ascertainment.



These associations represented an approximately 15 to 20% increases in adjusted ARDS risk between subject in the highest and lowest quartile of exposure and appeared linear for NO<sub>2</sub> and PM<sub>2.5</sub>. We did not identify associations between PM<sub>10</sub> or CO exposure and ARDS. The lack of an association between PM<sub>10</sub> may not be surprising as larger particulate matter cannot deposit in the most distal airways and alveoli where the alveolar-capillary barrier dysfunction of ARDS occurs. Additionally, CO is unlike the other air pollutants as it has anti-inflammatory and antioxidant effects and is being investigated as a potential therapy for ARDS.(36, 37)

Similar to our previous study in trauma patients, O<sub>3</sub> exposure had a non-linear, U-shaped associated with ARDS risk, and was significant at the 6-week exposure window.(10) It is possible that this relationship results from the complex interaction of O<sub>3</sub> with other pollutants on determining ARDS risk. Ozone is formed from the interaction of sunlight with volatile organic compounds and nitrogen oxides rather than being directly emitted as a pollutant. This reaction can also be reversed, whereby O<sub>3</sub> reacts with nitrogen oxide (NO) to generate NO<sub>2</sub> resulting in a local depletion of O<sub>3</sub>. This reverse reaction occurs in areas of the highest NO emissions such as near roadways and industrial plants. Therefore, areas with the highest pollution from these sources often have the lowest O<sub>3</sub> as demonstrated by the inverse relationship between NO<sub>2</sub> and O<sub>3</sub> exposure seen in our data.

There is now a growing body of literature linking acute and chronic exposure to air pollutants with ARDS, since the first published association of chronic O<sub>3</sub> exposure and ARDS risk in the Nashville region.(11) Lin and colleagues identified an association between exposure to PM and emergency ambulance dispatches for ARDS in Guangzhou, China,(38) and Rhee and colleagues identified an association between PM<sub>2.5</sub> and O<sub>3</sub> and hospitalization for ARDS among individuals >65 years old in a Medicare administrative database.(39) Our study adds to these findings by including a prospective cohort rather than an administrative dataset, with robust ARDS phenotyping that did not rely on comparatively insensitive classification based on clinician recognition and documentation.(3, 40) We additionally include robust collection of potential confounders and limit our study population to those at risk for ARDS from sepsis. Further supporting a potential link between air pollution and ARDS, Rush and colleagues identified an association between O<sub>3</sub> exposure and ARDS mortality,(41) and DeWeerd and colleagues identified associations between exposures to multiple air pollutants and duration of mechanical ventilation in a mixed population of acute respiratory failure.(42) Chronic exposure to air pollution has also been associated with sepsis mortality, but it is unknown if increased ARDS risk mediates this increased mortality.(43) Additionally, in COVID-19, severe air pollution exposure has been associated with cumulative SARS-CoV-2 cases and higher mortality.(44, 45)

A major finding in our study and others is that the burden of elevated air pollutant exposure is higher among racial minorities and individuals living in areas with a lower median household income.(25) Recent large epidemiologic studies have demonstrated marked improvement in air quality over the last several decades; however, there has not been an equivalent reduction in disparities of exposure between communities.(25) Lower income communities and communities of color, particularly Black communities, continue to experience disproportionately higher levels of air pollution.(46, 47) Elevated air pollution



exposure has also been linked to the development of severe COVID-19, a form of sepsis-associated ARDS, and has been hypothesized to explain some of the racial and economic disparities observed in COVID-19 outcomes.(48) While our study was conducted prior to the COVID-19 pandemic, our findings suggest that structural racial and economic inequalities impact ARDS risk in the larger sepsis population.(49, 50) It is likely that targeted interventions to reduce air pollution in these communities may have the greatest potential to reduce risk of ARDS in individuals who develop sepsis.

Ambient air pollutants have long been linked to respiratory and cardiovascular disease, such as ARDS; however, the exact pathologic mechanism underlying this link in each individual disease is incompletely understood. Exposure to elevated PM<sub>2.5</sub>, O<sub>3</sub>, SO<sub>2</sub>, and NO<sub>2</sub> has been linked to chronic lung inflammation, generation of reactive oxygen species, and alveolar capillary barrier leakiness in healthy humans and murine models.(51, 52) In a mouse model of nebulized lipopolysaccharide (LPS) induced acute lung injury, additional exposure to PM<sub>2.5</sub> was associated with increased broncho-alveolar lavage fluid leukocytes, increased cytokines, and impaired tissue remodeling compared to LPS exposure alone.(51) Our findings suggest that similar mechanisms may be relevant in human sepsis. Specifically, we identified associations between chronic air pollutant exposure and levels of IL1RA and sTNFR1, both markers of inflammation. It is possible that exposure to air pollutants primes the lung for injury in the setting of an exacerbating factor such as sepsis. Future research aimed at understanding the mechanisms of this lung priming could potentially lead to therapeutics to prevent or treat ARDS in those with high air pollution exposure.

Our study has several strengths. First, we studied sepsis-associated ARDS in a large cohort of patients with significant racial, socioeconomic, comorbidity, and geographical diversity in a large metropolitan area with extensive EPA monitoring of air pollutants. Second, all admissions to the medical ICU of the Hospital of the University of Pennsylvania were screened for sepsis and if enrolled, were followed for ARDS via individual chest radiograph and chart review by trained physician investigators. Third, we prospectively collected extensive confounders, including measures of severity of illness, and constructed adjusted regression models to reduce the effects of confounding. Finally, we conducted sensitivity analyses and examined for associations between air pollutant exposure and biomarkers of inflammation measured early after presentation with sepsis.

Our study has several limitations. Exposure misclassification is possible as we relied on estimates of air pollutant exposure based on subjects' zip code from their most recent address. Occupational exposures, time spent indoors versus outdoors, apartment floor, and time spent driving on highways were unavailable. Our study is single-centered and conducted prior to the COVID-19 pandemic which limits generalizability; however, it was conducted over 10 years at a large referral center with a population that is diverse in exposures, demographics, and comorbidities. Unmeasured confounding is possible; however, the prospective nature of our cohort allows us to measure potential confounders that would be unavailable in administrative datasets. Given the number of related analyses performed, there is risk for type 1 error; however, I findings are consistent with previous literature. Additionally, our biomarker analyses are exploratory, were measured in a random subset of subjects, and utilized residual blood initially drawn for clinical purposes. Lastly,

collinearity of some air pollutants as well as interaction between air pollutants makes it difficult to determine if one specific pollutant or multiple pollutants impact ARDS risk.

In conclusion, we have identified associations between short- and long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub> and ARDS development in the largest at-risk population, patients critically ill with sepsis. Additionally, we have identified a non-linear association between medium-term O<sub>3</sub> exposure and ARDS risk in sepsis. Importantly, the overall exposure estimates for all the pollutants are largely lower than current EPA air quality standards, suggesting that even low to moderate exposure levels may have impact on the risk of ARDS in sepsis. Elevated exposure to air pollution represents a potentially modifiable risk factor for ARDS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**TAKE HOME MESSAGE**

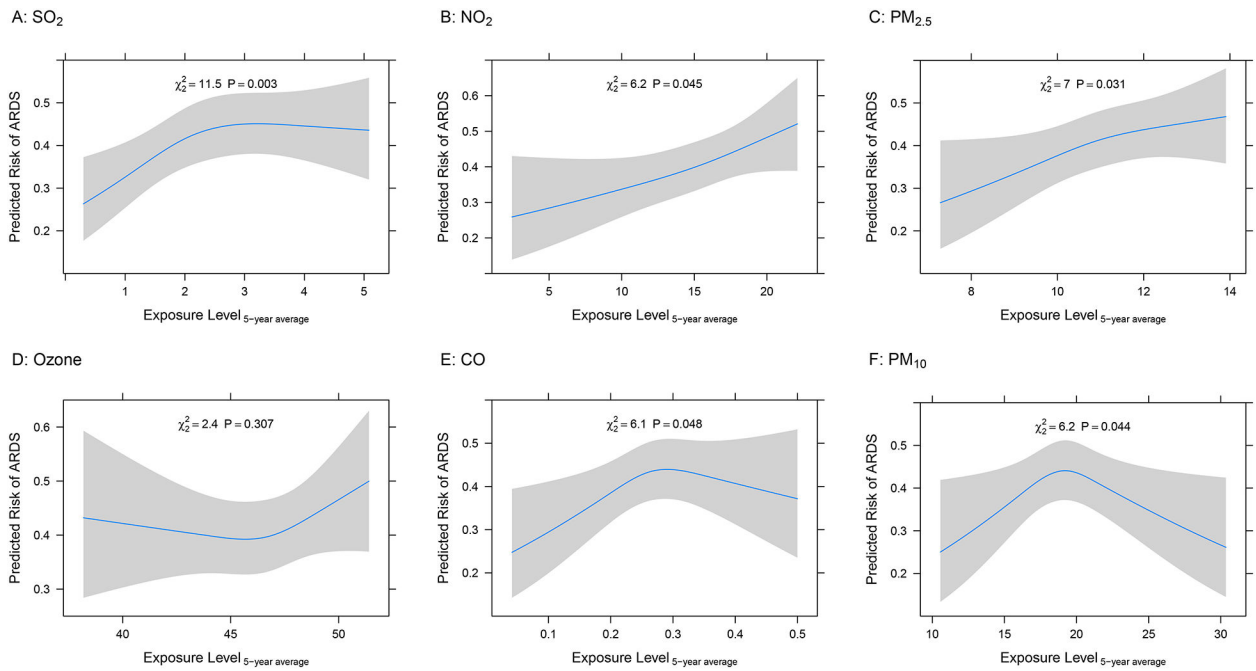
Air pollution exposure has long been linked to acute and chronic respiratory disease, but its role in sepsis-related ARDS risk is largely unknown. We identified associations between short- and long- term exposure to sulfur dioxide, nitrogen dioxide, and PM<sub>2.5</sub> with ARDS risk in sepsis, suggesting that short- and long- term exposures to ambient air pollutants are potentially modifiable environmental risk factors with implication for public health and environmental justice.

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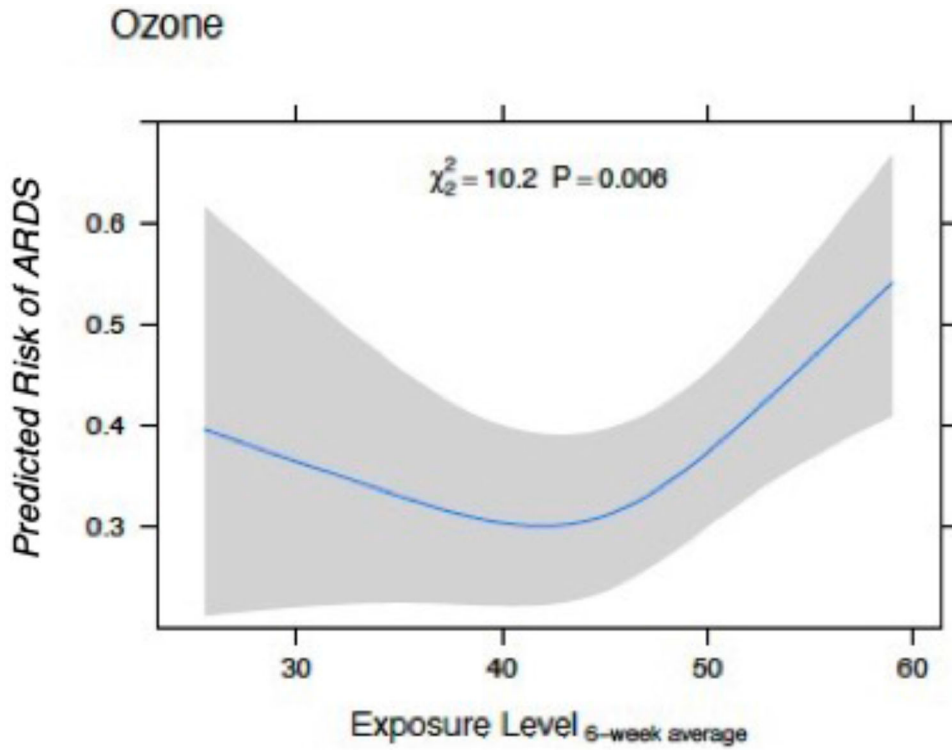
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**Figure 1.**

Standardized Risk Curves for the association of Long-Term Air Pollution Exposure (5-years) and Acute Respiratory Distress Syndrome (ARDS) Risk. The predicted risk of ARDS was estimated across air pollution exposures using logistic regression models adjusting for age, sex, race, smoking history, alcohol use, APACHE III score, distance to the hospital, month of admission, and median household income of the patients' home addresses' 5-digit zip code. Restricted cubic splines with three knots were used for each individual air pollutant to evaluate for non-linear associations with ARDS. A. SO<sub>2</sub> parts per billion (ppb), B. NO<sub>2</sub> ppb, C. PM<sub>2.5</sub> ug/m<sup>3</sup> D. Ozone ppb, E. CO parts per million (ppm), F. PM<sub>10</sub> ug/m<sup>3</sup>. Gray bars represent 95% confidence intervals around the predicted risks.





**Figure 2.** Standardized Risk Curves for Ozone Medium-Term Exposure (6-weeks) and Acute Respiratory Distress Syndrome (ARDS) Risk. The predicted risk of ARDS was estimated across parts per billion ozone exposures using a logistic regression model adjusting for age, sex, race, smoking history, alcohol use, APACHE III score, distance to the hospital, month of admission, and median household income of the patients’ home addresses’ 5-digit zip code. Restricted cubic splines with three knots were used for each individual air pollutant to evaluate for non-linear associations with ARDS. Gray bars represent 95% confidence intervals around the predicted risks.

**Table 1.**

## Patient Characteristics

Patient Characteristic	Sepsis Population (n=1858)
Age	61 (51, 69)
Male Sex	1078 (58%)
Race	
White	1119 (60%)
Black	586 (32%)
Asian	66 (4%)
Multiple/Unknown	87 (5%)
APACHE III	90 (66, 120)
Pulmonary Source of Sepsis	552 (34%)
Current smoker	203 (12%)
Alcohol Use	192 (11%)
Distance to Penn (km)	19.8 (4.7, 45.5)
Median household income (x 1000)	55 (35, 77)
Admission SOFA Score	10 (7, 13)
Administered Corticosteroids	628 (34%)
Intravenous Fluids in first 24 hours (L)	3.5 (1.9, 6.0)
ARDS	754 (41%)
Mild ARDS	76 (4%)
Moderate ARDS	204 (11%)
Severe ARDS	474 (26%)
Hypertension	951 (51%)
Diabetes Mellitus	544 (29%)
Chronic Renal Disease	288 (16%)
Cirrhosis	193 (10%)
Active Malignancy	741 (40%)

Data are reported as median (IQR) or n (%).

APACHE = acute physiology and chronic health evaluation.

**Table 2.**

Logistic regression analysis for the association of exposure to individual air pollutants and ARDS risk

Pollutant	Three-day Average Exposure		Six-week Average Exposure		Five-Year Average Exposure	
	OR* (95% CI)	P	OR* (95% CI)	P	OR* (95% CI)	P
Ozone	1.22 (0.98, 1.52)	0.12	1.24 (1.00, 1.54)	0.01	1.09 (0.96, 1.24)	0.31
NO <sub>2</sub>	1.37 (1.10, 1.71)	<0.01	1.18 (0.93, 1.51)	0.08	1.36 (1.06, 1.74)	0.04
SO <sub>2</sub>	1.31 (1.06, 1.63)	0.04	1.45 (1.19, 1.77)	<0.01	1.43 (1.16, 1.77)	<0.01
CO	0.99 (0.88, 1.12)	0.29	0.94 (0.81, 1.09)	0.71	1.25 (1.03, 1.52)	0.05
PM <sub>2.5</sub>	1.07 (0.90, 1.28)	0.03	1.17 (1.00, 1.39)	0.01	1.21 (1.04, 1.41)	0.03
PM <sub>10</sub>	0.99 (0.85, 1.17)	0.12	0.95 (0.81, 1.13)	0.72	1.04 (0.94, 1.14)	0.04

\*. The ORs are for the comparison of the 75<sup>th</sup> to the 25<sup>th</sup> percentile of exposure for each air pollutant adjusted for pre-specified confounders in multivariable logistic regression. The single air pollutant models included restricted cubic splines including 3 knots to assess for non-linear associations. Some 95% confidence intervals cross 1.0 despite a p-value <0.05 due to non-linear associations.

**Table 3.**

Association of Long-Term Exposure to SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub> with plasma biomarkers of inflammation adjusting for sex, race, and APACHE III score

Pollutant	IL1RA		sTNFR1		IL-8		IL-6	
	Beta* (95% CI)	P	Beta* (95% CI)	P	Beta#* (95% CI)	P	Beta* (95% CI)	P
SO <sub>2</sub> (ppb)	0.35 (0.18, 0.52)	<0.01	0.09 (0.03, 0.16)	<0.01	0.07 (-0.05, 0.18)	0.08	0.10 (-0.02, 0.22)	0.11
NO <sub>2</sub> (ppb)	0.07 (0.01, 0.13)	0.03	0.03 (0.01, 0.05)	0.01	0.03 (-0.01, 0.07)	0.21	0.03 (-0.01, 0.08)	0.11
PM <sub>2.5</sub> (ug/m <sup>3</sup> )	0.19 (0.04, 0.34)	0.01	0.06 (0.01, 0.11)	0.04	0.02 (-0.09, 0.12)	0.74	0.05 (-0.05, 0.17)	0.30

\* Multivariable linear regression models adjusting for sex, race, and APACHE III score. The natural log for the biomarkers was used as the outcome to approximate normality. The beta represents the increase in natural log of the biomarker per increase in ppb or ug/m<sup>3</sup> of the air pollutant.