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ORIGINAL ARTICLE

Low to Moderate Air Pollutant Exposure and Acute Respiratory Distress Syndrome after Severe Trauma

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Abstract

Rationale: Exposure to air pollution has molecular and physiologic effects on the lung that may increase the risk of acute respiratory distress syndrome (ARDS) after injury.

Objectives: To determine the association of short- and long-term air pollutant exposures and ARDS risk after severe trauma.

Methods: We analyzed data from a prospective cohort of 996 critically ill patients presenting with acute trauma and an injury severity score greater than 15. Exposures to ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide, and particulate matter less than 2.5 μm were assessed by weighted averages of daily levels from all monitors within 50 km of the geocoded location of a patient's residence. Patients were followed for 6 days for the development of ARDS according to Berlin Criteria. The association between each exposure and ARDS was determined via multivariable logistic regression adjusting for potential confounders.

Measurements and Main Results: ARDS developed in 243 (24%) patients. None of the short-term exposures averaged over the 3 days before presentation was associated with ARDS, except sulfur dioxide, which demonstrated a nonlinear association. Nitrogen dioxide, sulfur dioxide, and particulate matter less than or equal to 2.5 μm in aerodynamic diameter exposure over the 6 weeks before presentation was significantly associated with ARDS ($P < 0.05$). All long-term exposures (3 yr) were associated with ARDS ($P < 0.01$) in adjusted models, despite exposure levels largely below U.S. and European Union air quality standards.

Conclusions: Long-term low- to moderate-level air pollutant exposure is associated with a greater risk of developing ARDS after severe trauma and represents a novel and potentially modifiable environmental risk factor for ARDS.

Keywords: air pollution; ARDS; acute lung injury; epidemiology; trauma

Similar to the compounds in cigarette smoke, the chemicals produced during the combustion of fossil fuels by motor vehicles and power plants are known to induce alveolar injury and vascular inflammation in animal and *in vitro* models (1, 2). Specifically, air pollutants induce oxidative stress, recruit inflammatory cells to the lung, and provoke release of cytokines, even at low to moderate levels, in rodent models. In humans, short- and long-term exposure to high levels of ambient air pollutants, including ozone and particulate matter, has been associated with decreased life expectancy and acute exacerbations of cardiovascular and pulmonary disease (3–8). However, whether exposure to low or moderate levels of ambient air pollutants increases the risk of specific acute respiratory diseases, such as the acute respiratory

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At a Glance Commentary

Scientific Knowledge on the Subject: Exposure to high levels of ambient air pollutants is associated with increased mortality and morbidity as well as with acute exacerbations of cardiovascular and pulmonary disease. A previous study identified an association between long-term elevated ozone exposure and an increased risk of acute respiratory distress syndrome (ARDS). In animal and cell models, there is substantial evidence that components of air pollution contribute to lung inflammation, oxidative stress, and injury.

What This Study Adds to the Field: We conducted an analysis of a large prospectively enrolled cohort of patients with severe trauma and identified associations between long-term exposure to elevated ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide, and particulate matter less than or equal to 2.5 μm in aerodynamic diameter and risk of ARDS. To our knowledge, this is the first study to report independent associations between exposures to nitrogen dioxide, sulfur dioxide, carbon monoxide, and particulate matter less than or equal to 2.5 μm in aerodynamic diameter and ARDS risk, and validates previous findings of an association between exposure to ozone and ARDS. The average exposures largely fell below current U.S. Environmental Protection Agency and European Union air quality standards. These findings have implications for ARDS prevention and public health air pollution standards.

distress syndrome (ARDS), has not been well studied.

ARDS is a syndrome of noncardiogenic pulmonary edema and acute respiratory failure that is characterized by inflammation and alveolar capillary barrier dysfunction (9). In a recent multinational observational study, ARDS occurred in 7% of ICU admissions (10). Mortality in ARDS is greater than 30% despite improvements in supportive care and ventilator management (11). This high incidence and substantial morbidity and mortality identify ARDS as a major global public health concern. Severe traumatic injuries are a common precipitating factor for ARDS, with ARDS developing in an estimated 10–30% of critically ill trauma patients (12, 13). Although potentially modifiable environmental exposures have been reported to alter ARDS risk in the setting of a precipitating factor, such as severe trauma, including cigarette smoke (14), and alcohol abuse (15), only one study has examined ambient air pollutant exposure as a possible modifier of ARDS risk (16). In that study of 1,558 critically ill patients within the Tennessee region presenting with a variety of precipitating factors for ARDS, there was an independent association between increasing long-term ozone exposure and ARDS risk (16). This association was strongest in the subgroup of patients with trauma as their risk factor for ARDS. In this cohort, other air pollutants were not independently associated with ARDS; however, the low density of air pollutant monitors in the region studied likely limited exposure estimates. Of note, median ozone exposures in that study were in the low to moderate range, well below current U.S. and European standards, suggesting that even low-level air pollutant exposures could influence the risk of ARDS.

In the current study, the primary objective was to test the association of both short- and long-term exposure to ambient air pollutants and the risk of developing ARDS in a large cohort of critically ill patients presenting after severe trauma in a region with a high density of air pollutant monitors and low to moderate levels of ambient air pollutants. We hypothesized that long-term, but not short-term, exposures to low to moderate levels of the air pollutants ozone, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and particulate matter less than or equal to 2.5 μm in aerodynamic diameter ($PM_{2.5}$) would be associated with the development of ARDS in the setting of acute traumatic injury.

Some of the results of this study have been previously reported in the form of an abstract (17).

Methods

Additional methods are provided in the online supplement.

Study Population

We prospectively enrolled patients who presented to the University of Pennsylvania with acute traumatic injury and were subsequently admitted to the ICU between 2005 and 2015 (18–21). Patients were included if they presented within 24 hours of injury, had an age greater than 13, and an injury severity score greater than 15 (22). Patients were excluded if they suffered isolated severe head injury or died or were discharged within 24 hours of presentation. The institutional review board of the University of Pennsylvania (Protocol #802428) approved the study with a waiver of informed consent.

Air Pollution Exposure

Short- and long-term air pollutant exposures were estimated using levels from the Environmental Protection Agency's Aerometric Information Retrieval System collected before the date of presentation from all monitors within 50 km of a geocoded location of residence for each participant. Daily measurements of NO_2, SO_2, CO, and $PM_{2.5}$ were obtained. Because ozone is typically monitored only during the day and in summer months, we restricted ozone data to the highest 8-hour average level to calculate daily exposure during available months.

We estimated patients' addresses using the centroid of a patient's zip + 4 postal code. Pollutant exposures were estimated by the inverse-distance–squared weighted average levels measured from all monitors within 50 km of the geocoded residence (5). Short-term exposures were estimated using average pollutant levels for the 3 days and 6 weeks before hospital admission. Long-term exposures were estimated as average pollutant levels for 3-year periods before admission. Additionally, in secondary analyses, we estimated average air pollutant exposure levels for 1- and 5-year periods.

ARDS Outcome

Patients enrolled in the Penn Trauma Cohort Study were followed for 6 days from presentation for the development of ARDS based on the Berlin Definition while intubated and mechanically ventilated (23). If an arterial blood gas was not available within 24 hours of a chest radiograph consistent with ARDS, the oxygen saturation as measured by pulse oximetry/$F_{I_{O_2}}$ ratio was used to determine if

Table 1. Patient Clinical Characteristics by ARDS Diagnosis

Patient Characteristic	No ARDS (*n* = 753)	ARDS (*n* = 243)	Total Population (*n* = 996)	*P* Value
Age	36 (24–56)	40 (25–53)	38 (24–56)	0.937
Male sex	550 (73)	192 (79)	742 (75)	0.063
White race	341 (47)	129 (55)	470 (49)	0.052
APACHE III	40 (29–57)	54 (39–73.7)	42.5 (31–61)	<0.001
ISS	22 (19–29)	26 (21–34)	24 (19–29)	<0.001
Current smoker	303 (42)	93 (41)	396 (42)	0.705
Alcohol use	115 (15)	39 (16)	154 (16)	0.745
Medicare/federal/private insurance (vs. Medicaid/uninsured)	362 (48)	106 (44)	468 (47)	0.268
Distance to Penn, km	8.2 (3.9–22.9)	11.0 (4.3–28.7)	8.6 (4.0–24.2)	0.018
Median household income, ×$1,000	44 (31–72)	47 (32–75)	44 (31–74)	0.119

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ISS = injury severity score.
Data are reported as median (interquartile range) or *n* (%). *P* values were obtained using the Wilcoxon rank sum test for continuous variables or the chi-square test for categorical variables. Race was missing in 40 subjects, smoking status in 46, alcohol use in 8, insurance status in 6, and household income in 3.

a patient met the hypoxemia criteria for ARDS (24).

Statistical Analysis

Characteristics of patients with and without ARDS were compared using Pearson chi-square or Wilcoxon rank sum tests, as appropriate. To evaluate associations between the pollutant level and risk of ARDS we analyzed short-term (3-d lag), mid-term (6-wk average), and long-term (3-yr averages) exposures of ozone, NO_2, SO_2, CO, and $PM_{2.5}$. Ozone and NO_2 were analyzed together in a multivariable logistic regression model because of the inversely correlated nature of the two air pollutants. Specifically, ozone interacts with NO released nearby air pollution sources to generate NO_2 and oxygen, resulting in the lowest levels of ozone in regions of high NO_2. All other air pollutants were analyzed in separate models. In all models, we adjusted for the following prespecified potential confounders: age, race, sex, month of enrollment, smoking history, alcohol use, type of trauma (blunt vs. penetrating), massive transfusion of greater than or equal to 10 red blood cell units, pulmonary contusion, insurance status, median household income, distance to the hospital, Acute Physiology and Chronic Health Evaluation-III score, and injury severity score.

Additionally, we conducted *a priori* defined sensitivity analyses excluding patients with chest radiographs equivocal for ARDS (25), and using a more restrictive definition of ARDS including only moderate and severe cases (23). These sensitivity analyses were conducted to assess the impact of potential outcome misclassification bias given the substantial challenge of phenotyping ARDS. We also conducted a sensitivity analysis limiting to monitors within 15 km of a patient's residence, and examined interactions between pollutant levels and smoking history, mechanism of injury, age, and race. Pollutant exposures were available in all included subjects; however, multiple imputation using chained equations was used in regression models to address missing confounder data

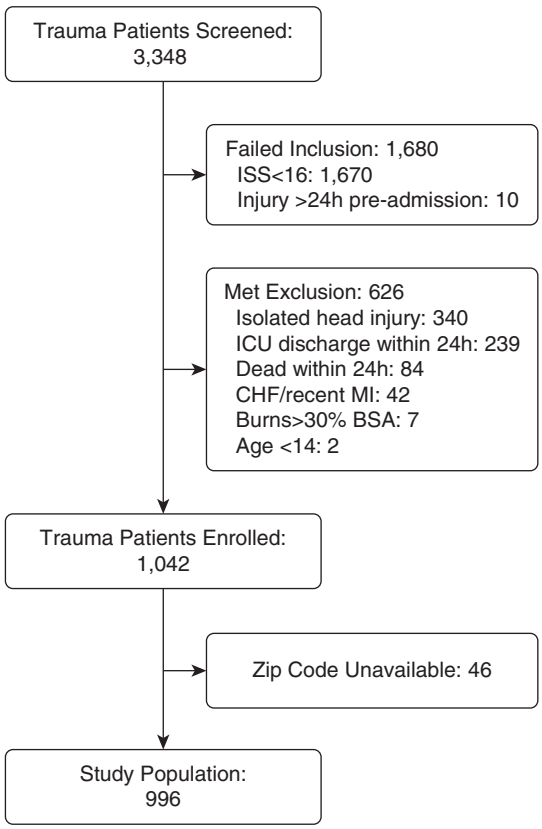

Figure 1. Enrollment flow diagram. Some subjects met more than one exclusion criteria. BSA = body surface area; CHF = congestive heart failure; ISS = injury severity score; MI = myocardial infarction.

(26, 27). The version implemented was the aregImpute function in *rms* R-package (28). Statistical significance was considered for two-sided *P* values less than 0.05. Data analyses were conducted using R version 3.3.

Results

Cohort Characteristics

The Penn Trauma Cohort enrolled 996 patients who met the inclusion and exclusion criteria for the current study, of whom 243 (24%) developed ARDS within 6 days of presentation (Figure 1). Patients that developed ARDS were more likely to be white, lived further from the hospital, and had higher injury severity and severity of illness scores then patients who did not develop ARDS (Table 1). The median number of air quality monitors within 50 km of a patient's residence ranged from 14 to 28 depending on the pollutant (*see* Table E1 in the online supplement), a substantially higher density of monitors compared with our previous study in the Tennessee region (16). All enrolled patients lived within 50 km of at least one air quality monitor. The distribution of patient addresses and monitor locations within the Philadelphia region are shown in Figure 2. Median levels of each air pollutant averaged over 3 years are provided in Table 2. Notably, ozone exposure levels were lower in the Penn Trauma Cohort than in our prior Tennessee region VALID (Validating Acute Lung Injury Biomarkers for Diagnosis) study (16), and NO_2 levels were higher. Correlations between individual patient's 3-year average pollutant exposures were moderately positive, with the exception of an inverse correlation between ozone and NO_2 (*see* Table E2). The distributions of ARDS cases, age, sex, race, injury severity score, distance to the hospital, and insurance status across quartiles of pollutant exposures were not uniform and are provided in Table 3. Subjects living closer to the hospital and nonwhite subjects had higher exposures to NO_2 and CO, and lower exposures to ozone.

Long-Term Pollutant Exposure

In the long-term air pollutant exposure models, increased 3-year exposure to ozone, SO_2, CO, and $PM_{2.5}$ was associated with increased risk of ARDS (Table 3). Specifically, unadjusted ARDS risk ranged from 25% to 29% in the lowest and highest quartiles of 3-year ozone exposure, 17–31% for SO_2 exposure, 20–29% for CO exposure, and 18–30% for $PM_{2.5}$ exposure. In multivariable logistic regression models that adjusted for potential confounders, 3-year exposure estimates for all five of the measured air pollutants were strongly and independently associated with risk of ARDS (Table 4, Figure 3; *see* Table E3). Findings for 1 year and 5 years of exposure were similar (*see* Table E4).

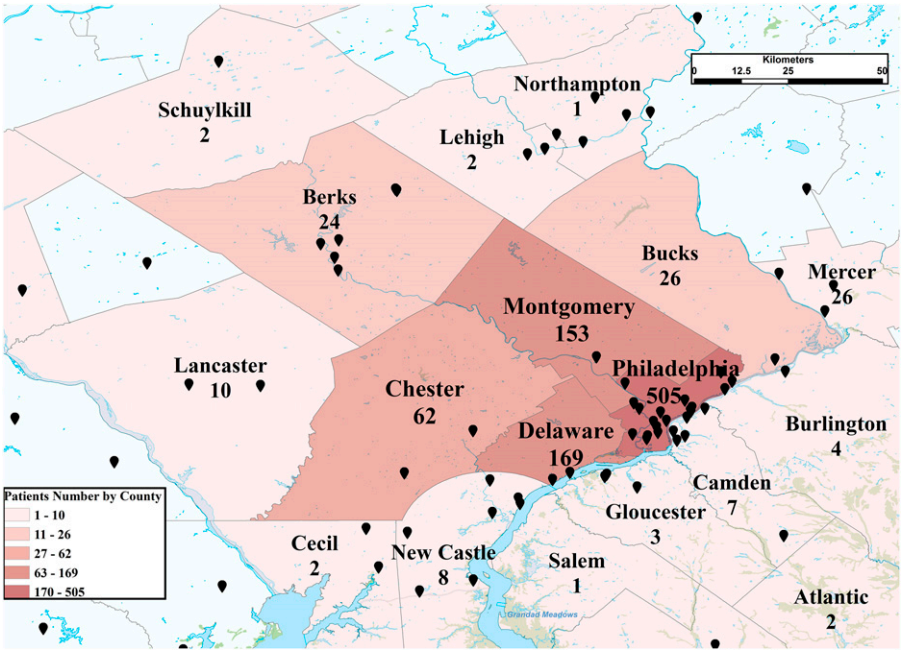

Figure 2. Geographic distribution of patient addresses included in the current study and distribution of Environmental Protection Agency–approved air quality monitors in the Philadelphia region (black symbols). Counties are shaded from light to dark red based on patient enrollment and the number of patients for each county is indicated by the black number at the center of each county.

Short-Term Pollutant Exposure

Three-day exposure estimates for ozone, NO_2, CO, and $PM_{2.5}$ were not associated with ARDS (Table 4). In multivariable models, increased 3-day exposure to SO_2 was associated with increased risk of ARDS; however, the relationship was nonlinear with the third exposure quartile having the highest ARDS risk (Table 4; *see* Figure E1). Exposure estimates for NO_2, SO_2, and $PM_{2.5}$ over the 6 weeks before presentation were associated with increased ARDS risk (Table 4). The estimated effect sizes (odds ratios) increased with longer durations of exposure in all of the pollutant exposures (Table 4). Pollutant exposure estimates at 6 weeks, 1 year, 3 years, and 5 years were

Table 2. Median Levels of 3-Year Air Pollutant Exposure in the Penn Trauma and the Previously Studied Tennessee Region VALID Cohort (8)

Pollutant	Penn Trauma (*n* = 996)	VALID (*n* = 1,558)	*P* Value
Ozone, ppb (summer only)	47.1 (45.5–48.2)	51.5 (49.0–53.5)	<0.001
NO_2, ppb	18.1 (15.9–19.9)	15.4 (8.3–16.8)	<0.001
SO_2, ppb	3.58 (2.12–4.65)	2.77 (2.37–3.07)	<0.001
CO, ppm	0.287 (0.258–0.405)	0.677 (0.594–0.742)	<0.001
$PM_{2.5}$, $\mu g/m^3$	12.2 (10.8–13.6)	13.2 (12.1–13.7)	<0.001

Definition of abbreviations: $PM_{2.5}$ = particulate matter less than or equal to 2.5 μm in aerodynamic diameter; VALID = Validating Acute Lung Injury Biomarkers for Diagnosis Study.
Data are reported as median (interquartile range). *P* values were obtained using the Wilcoxon rank sum test.

Table 3. Patient Characteristics by Quartiles of 3-Year Exposure Estimates for Each Air Pollutant

Pollutant	Quartiles	ARDS (*Case; %*)	Age (*yr*)	Sex (*Male; %*)	Race (*White; %*)	ISS	Distance (*km*)	Medicare, Federal, Private Insurance (%)
Ozone, ppb	Q1 (37.9–45.5)	25	32 (23–51)	81	24	24 (19–29)	5.2 (3.0–9.2)	42
	Q2 (45.6–47.1)	17	33 (24–54)	74	37	22 (19–29)	5.4 (3.5–10.0)	56
	Q3 (47.2–48.2)	27	40 (27–60)	73	56	24 (19–29)	9.4 (4.0–26.9)	48
	Q4 (48.3–52.8)	29	42 (25–58)	70	79	25 (20–30)	26.4 (18.8–39.7)	43
	P value	0.009	0.001	0.052	<0.001	0.008	<0.001	0.009
SO_2, ppb	Q1 (0.52–2.12)	17	44 (26–63)	72	50	24 (19–29)	9.8 (5.2–23.2)	76
	Q2 (2.13–3.58)	24	36 (24–53)	79	48	25 (20–29)	6.6 (3.7–22.5)	52
	Q3 (3.59–4.65)	26	36 (24–51)	76	40	22 (19–29)	5.7 (3.3–19.4)	33
	Q4 (4.66–7.35)	31	38 (24–52)	72	57	23 (19–29)	14.0 (4.7–32.0)	28
	P value	0.006	0.008	0.226	0.002	0.154	<0.001	<0.001
NO_2, ppb	Q1 (2.7–15.9)	25	44 (28–62)	69	81	25 (20–30)	31.3 (21.7–53.8)	60
	Q2 (16.0–18.1)	25	40 (24–60)	69	63	24 (19–29)	12.2 (5.7–23.4)	52
	Q3 (18.2–19.9)	20	33 (24–53)	77	31	22 (20–29)	5.3 (3.7–10.8)	47
	Q4 (20.0–24.6)	28	32 (23–47)	82	22	21 (19–27)	3.6 (2.5–5.8)	30
	P value	0.222	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CO, ppb	Q1 (0.043–0.258)	20	42 (26–61)	71	58	24 (19–29)	17.3 (4.9–34.9)	65
	Q2 (0.259–0.287)	21	42 (26–58)	75	49	25 (19–29)	7.7 (4.1–19.4)	59
	Q3 (0.288–0.405)	29	35 (23–52)	75	50	22 (19–29)	10.0 (4.1–27.3)	37
	Q4 (0.406–0.771)	29	33 (24–47)	76	40	22 (19–27)	6.0 (3.4–15.0)	27
	P value	0.017	<0.001	0.476	0.001	0.048	<0.001	<0.001
$PM_{2.5}$, $\mu g/m^3$	Q1 (7.9–10.8)	18	44 (26–61)	73	49	24 (19–29)	8.8 (4.5–22.4)	72
	Q2 (10.9–12.2)	25	38 (24–55)	76	54	24 (19–29)	9.6 (4.4–32.9)	55
	Q3 (12.3–13.6)	26	37 (24–54)	73	48	22 (19–29)	9.4 (4.0–22.6)	37
	Q4 (13.7–16.7)	30	36 (24–50)	76	46	22 (19–27)	6.4 (3.3–24.7)	25
	P value	0.016	0.022	0.720	0.315	0.102	0.015	<0.001

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ISS = injury severity score; $PM_{2.5}$ = particulate matter less than or equal to 2.5 μm in aerodynamic diameter.
Data are reported as median (interquartile range) or %. *P* values were obtained using the Pearson chi-square test for categorical variables and Wilcoxon rank sum test for the continuous variables. Race was missing in 40 subjects, and insurance status in six. The table demonstrates the nonuniform distribution of unadjusted ARDS risk and potential confounders across the quartiles of air pollution exposure.

all moderately correlated, with the long-term exposure more closely correlated than the 6-week exposure period (*see* Table E5).

Sensitivity Analyses

Restricting analyses to patients with definitive chest radiographs with or without ARDS (excluding equivocal patients) did not substantially change any reported results. Comparisons between moderate and severe ARDS with all other subjects also did not substantially change any reported results. Limiting exposure data to only air quality monitors within 15 km of a patient's geocoded address did not substantially change our results (*see* Table E6). We did not identify significant statistical interactions between air pollutant exposures and smoking status, age, race, or mechanism of traumatic injury (blunt vs. penetrating).

Discussion

Among a cohort of patients presenting to a major metropolitan level 1 trauma center after severe trauma, long-term exposures to NO_2, SO_2, CO, $PM_{2.5}$, and ozone were associated with the subsequent development of ARDS. These associations were independent of confounders including known ARDS risk factors, distance from the trauma center, and insurance status. Although a previous study reported an association between long-term ozone exposure with ARDS risk (16), and another between ozone and particulate matter exposure with ARDS mortality (29), to our knowledge, this represents the first study reporting associations between exposures to SO_2, CO, and $PM_{2.5}$ and ARDS risk. Additionally, this study has replicated the previously reported association between ozone exposure and ARDS risk after severe trauma and identified that higher exposure levels of a duration as short as 6 weeks are associated with ARDS risk for three pollutants, NO_2, SO_2, and $PM_{2.5}$. The unadjusted difference in ARDS risk between the lowest and highest quartiles of exposure was largest for SO_2 (14%) and $PM_{2.5}$ (12%). We did not identify an association between short-term air pollution exposure levels during the 3 days before trauma and risk of ARDS, supporting the conclusion that exposures of at least 6-weeks duration are required to prime the lung for injury following severe traumatic injuries.

Several individual air pollutants formed predominately from the combustion of fossil

Table 4. Logistic Regression Analysis for the Association of Exposure to Individual Air Pollutants and ARDS Risk

Pollutant	Three-Year Average Exposure		Six-Week Average Exposure		Three-Day Average Exposure	
	OR* (95% CI)	*P* Value	OR* (95% CI)	*P* Value	OR* (95% CI)	*P* Value
Ozone†	1.44 (1.12–1.86)	0.005	1.13 (0.88–1.46)	0.248	0.90 (0.64–1.26)	0.203
NO_2†	2.39 (1.72–3.33)	<0.001	1.77 (1.28–2.43)	0.002	1.42 (0.99–2.04)	0.111
SO_2	3.56 (2.40–5.28)	<0.001	2.31 (1.61–3.31)	<0.001	1.78 (1.26–2.50)	0.005
CO	1.92 (1.47–2.53)	<0.001	1.23 (0.97–1.56)	0.157	1.15 (0.90–1.48)	0.385
$PM_{2.5}$	3.58 (2.40–5.34)	<0.001	1.59 (1.21–2.11)	<0.001	1.05 (0.81–1.36)	0.715

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval; OR = odds ratio; $PM_{2.5}$ = particulate matter less than or equal to 2.5 μm in aerodynamic diameter.

*The ORs are for the comparison of the 75th to the 25th percentile for each air pollutant. All models controlled for age, race, sex, type of trauma (blunt vs. penetrating), massive transfusion of ⩾10 red blood cell units or more, pulmonary contusion, enrollment month, smoking, alcohol use, insurance status, median household income, distance to trauma center, Acute Physiology and Chronic Health Evaluation-III, and injury severity score. Full details of these models are provided in Table E2.

†The results for ozone and NO_2 were from the ozone-NO_2 bipollutant models.

fuels have well-established physiologic effects on the lung and have been associated with morbidity and mortality in humans. Particulate matter exposure has been linked to a decline in lung function (30, 31); exacerbations of chronic respiratory disease (6, 7); and the generation of reactive oxygen species, altered alveolar barrier functions, and recruitment of inflammatory cells (32, 33). Similarly, high-dose ozone exposure induces acute lung injury in animal models and causes airway inflammation in lower-dose controlled human exposures (34, 35). In large epidemiologic studies, ambient ozone has been associated with respiratory disease–related mortality and morbidity (4, 36). Although studied to a lesser degree, SO_2 and NO_2 have also been linked to increased airway hyperresponsiveness (37, 38), worsening lung function (39), and lung inflammation (40). Although CO poisoning has known detrimental effects on oxygen uptake and delivery, CO is unlike the other air pollutants in that it has antiinflammatory and antioxidant effects (41). In fact, low-dose CO is being evaluated as a potential therapy for ARDS (42). It is possible that the association observed in our study is a result of CO functioning as a marker of combustion-related air pollution mixtures, or alternatively that chronic low-dose CO exposure has distinct biologic effects relative to acute exposure. This wealth of previous evidence supports the biologic plausibility of our findings, although the specific mechanisms at play and the role of each air pollutant in ARDS alone or as a mixture remain unknown.

The average air pollution concentrations observed in our study were largely below the current European Union and U.S. air quality standards (43, 44). Despite low- to moderate-range exposures, we observed a significant increase in ARDS risk in a patient population that was mostly young, and largely healthy before acute traumatic injury. Our findings support the conclusion that air pollution impacts diverse individuals including those with no prior pulmonary or cardiac disease. Additionally, our findings raise concern that current efforts in the United States and other countries to relax air pollution standards may lead to an increased risk of ARDS after trauma, a complication of critical illness with high morbidity and mortality. The increased risk of ARDS among trauma patients also may indicate potential adverse pathologic effects of pollution on the lung with wider implications for health and disease.

In a previous study of 1,558 critically ill patients at risk for ARDS who presented to Vanderbilt University Medical Center, exposure to ozone but not to other pollutants, was associated with the development of ARDS (16). This risk was strongest in the subgroup of 552 patients with trauma as their ARDS risk factor and in patients who were current smokers. There are several reasons that our current study may have identified novel associations that were not identified in the prior study. First, the region of the country presenting to the University of Pennsylvania is geographically and demographically distinct from that of the previous study with different pollutant exposure levels. Second, exposure estimates in the current study were more precise because patients enrolled in the current study lived, on average, within 50 km of three to four times as many air quality monitors and had a distance to the closest monitor less than half that of the previous study. The higher density of air quality monitoring in the current study may have significantly reduced exposure misclassification, increasing the likelihood of identifying true associations. Lastly, although the current study is smaller, it included nearly twice as many trauma patients, the subgroup with the strongest association between ozone and ARDS risk in the prior study. We did not observe an interaction by smoking status in our current study; however, we acknowledge the high potential for misclassification of patient- or surrogate-assessed smoking status in an acute trauma population (14).

We observed a U-shaped association between ozone and ARDS. This finding is distinct from the previous study reporting a near linear association between ozone exposure and ARDS (16); however, the previous study was conducted in a significantly higher ozone exposure region of the United States. Almost no patients in the prior study had ozone exposure levels within the lowest quartile of ozone exposure observed in the Penn Trauma cohort. The likely reason for this U-shaped finding lies in the complex relationship of ozone with other air pollutants. Ozone is not directly emitted as a pollutant but rather is formed from the interaction of nitrogen oxides, volatile organic compounds, and sunlight (34). Increasing emissions of nitrogen oxides increase ozone production initially; however, in areas of the highest emissions (e.g., near roadways and industrial plants), nitrogen oxide reacts with ozone to generate NO_2 resulting in the

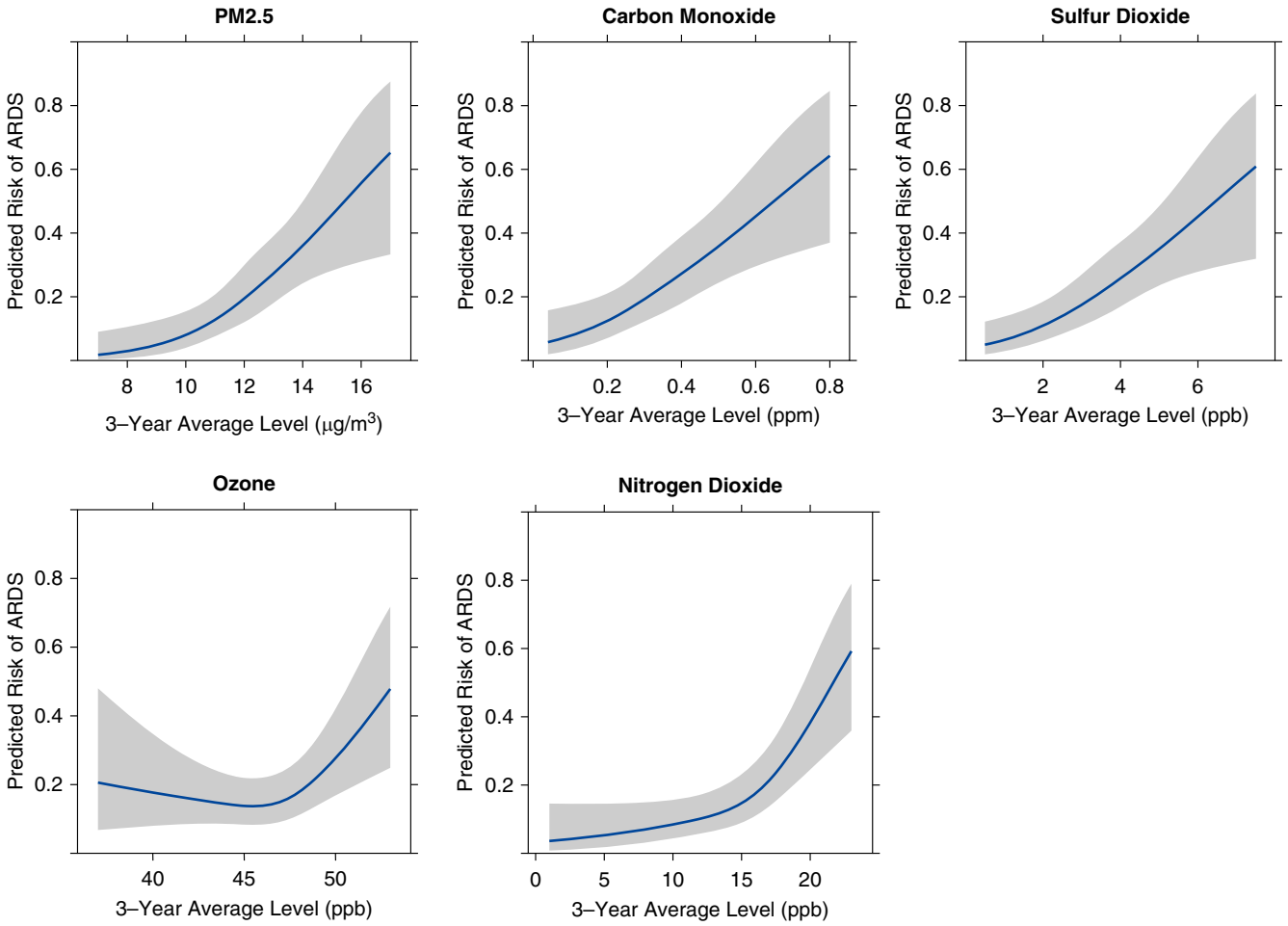

Figure 3. Relationship between 3-year average air pollutant exposure and predicted risk or probability of acute respiratory distress syndrome in a logistic regression model controlling for age, race, sex, enrollment month, smoking, alcohol use, insurance status, median household income, distance to trauma center, Acute Physiology and Chronic Health Evaluation-III, and injury severity score. The ozone model was also adjusted for 3-year nitrogen dioxide exposure. The nitrogen dioxide model was also adjusted for 3-year ozone exposure. Gray bars represent 95% confidence intervals around the predicted risks. ARDS = acute respiratory distress syndrome; $PM_{2.5}$ = particulate matter less than or equal to 2.5 μm in aerodynamic diameter.

local depletion of ozone (36). These areas have the lowest levels of ozone, but the highest levels of other pollutants that may be contributing to ARDS risk as evidenced. Our data demonstrating an inverse relationship between ozone and NO_2 exposure support the hypothesis that this interaction explains these results.

Our study has several strengths. First, we studied a large cohort of patients presenting with trauma from a racially, socioeconomically, and geographically diverse region of the United States with extensive Environmental Protection Agency monitoring of air pollutants. We limited the cohort to critically ill patients with an injury severity high enough to put them at risk for ARDS. Second, patients were prospectively enrolled and followed for the development of ARDS via extensive chest radiograph and chart review by two trained physician investigators. We included several sensitivity analyses varying the ARDS definition, none of which altered our results. Finally, we prospectively collected extensive potential confounders and performed multivariable regression to reduce the possibility of residual confounding.

Our study also has some limitations. First, we did not directly measure long-term exposure to air pollutants, but rather relied on estimates based on address of home residence provided at hospital admission. Information about patients' prior addresses, occupational exposures, or time spent indoors versus outdoors was unavailable, potentially introducing exposure misclassification bias. Additionally, our analysis assumes patients did not change residences during the study period. Second, patients presented predominately from one geographic region of the country. However, the referral region to the University of Pennsylvania is heterogeneous, with diverse air pollutant exposures. Third, as in any observational study, residual confounding continues to be possible despite adjustment for measured potential confounders. Given the improvements in air pollution over the decade of observation and improvements in trauma care over the same time period, it is possible that an unmeasured confounder that also improved over time explains our results. However, the lack of an association between 3-day

pollution exposures and ARDS argues against an unmeasured confounder, because all time periods of exposure would be similarly confounded.

Fourth, the collinearity of some air pollutants makes it difficult to determine the causal pollutants in our observational data and limits our ability to analyze multipollutant models. It is possible that one pollutant may be a marker of another rather than a causal mediator of increased ARDS risk. This collinearity might particularly be the case for CO, which could be serving as a marker of traffic-related air pollutant exposure rather than a mediator of lung injury in this study. Fifth, we did not replicate an interaction with tobacco seen in our prior study (16); however, we acknowledge the challenges in obtaining accurate smoking histories, particularly in trauma patients. Lastly, our data do not provide information regarding the potential mechanisms underlying the association between air pollution and ARDS.

In conclusion, we have identified an association between long-term exposure to multiple components of air pollution and the development of ARDS in a large cohort of critically ill trauma patients. Our study replicates the prior associations of exposure to ozone and ARDS risk in a geographically distinct cohort and extends them to include novel associations of particulate matter, SO_2, and CO with ARDS. In addition, the overall exposure estimates were in the low to moderate range and on average fell below current Environmental Protection Agency and European Union air quality standards, thus suggesting that even low to moderate exposure levels may have significant adverse health effects that can predispose an individual to ARDS after major trauma. Our findings suggest multiple components of air pollution are potential modifiable risk factors for ARDS with important implications for ARDS prevention and public health. ■

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