Published in final edited form as:

Environ Pollut. 2017 May ; 224: 352–356. doi:10.1016/j.envpol.2017.02.014.

Association between chronic exposure to air pollution and mortality in the acute respiratory distress syndrome[☆]

Barret Rush^{a,b,c,*}, Robert C. McDermid^d, Leo Anthony Celi^e, Keith R. Walley^{a,c}, James A. Russell^{a,c}, and John H. Boyd^{a,c}

^aDivision of Critical Care Medicine, St. Paul's Hospital, University of British Columbia, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

^bHarvard T.H. Chan School of Public Health, Harvard University, 677 Huntington Ave, Boston, MA 02115, USA

^cCentre for Heart Lung Innovation (HLI), University of British Columbia, Vancouver, Canada

^dDepartment of Critical Care Medicine, Surrey Memorial Hospital, Surrey, BC, Canada

^eBeth Israel Deaconess Medical Center, Boston, MA, USA

Abstract

The impact of chronic exposure to air pollution and outcomes in the acute respiratory distress syndrome (ARDS) is unknown. The Nationwide Inpatient Sample (NIS) from 2011 was utilized for this analysis. The NIS is a national database that captures 20% of all US in-patient hospitalizations from 47 states. Patients with ARDS who underwent mechanical ventilation from the highest 15 ozone pollution cities were compared with the rest of the country. Secondary analyses assessed outcomes of ARDS patients for ozone pollution and particulate matter pollution on a continuous scale by county of residence. A total of 8,023,590 hospital admissions from the 2011 NIS sample were analyzed. There were 93,950 patients who underwent mechanical ventilation for ARDS included in the study. Patients treated in high ozone regions had significantly higher unadjusted hospital mortality (34.9% versus 30.8%, $p < 0.01$) than patients in cities with control levels of ozone. After controlling for all variables in the model, treatment in a hospital located in a high ozone pollution area was associated with an increased odds of in-hospital mortality (OR 1.11, 95% CI 1.08–1.15, $p < 0.01$). After adjustment for all variables in the model, for each increase in ozone exposure by 0.01 ppm the OR for death was 1.07 (95% CI 1.06–1.08, $p < 0.01$). Similarly, for each increase in particulate matter exposure by $10 \mu\text{g}/\text{m}^3$, the OR for death was 1.08 (95% CI 1.02–1.16, $p < 0.01$).

Chronic exposure to both ozone and particulate matter pollution is associated with higher rates of mortality in ARDS. These preliminary findings need to be confirmed by further detailed studies.

[☆]This paper has been recommended for acceptance by David Carpenter.

*Corresponding author. Division of Critical Care Medicine, Department of Medicine, St. Paul's Hospital, University of British Columbia, 1081 Burrard Street, V6Z 1Y6, Canada.

1. Introduction

The Acute Respiratory Distress Syndrome (ARDS) is a state of diffuse alveolar inflammatory damage characterized by acute-onset non-cardiogenic pulmonary edema and severe hypoxemia (Ferguson et al., 2012). Despite advances in mechanical ventilation techniques and overall critical care, the mortality rate from ARDS remains above 30% (Phua et al., 2009; Villar et al., 2011). Patients with underlying lung dysfunction, such as chronic cigarette smokers have increased incidence and worse outcomes in ARDS (Calfee et al., 2015; Iribarren et al., 2000).

High levels of air pollution, both particulate matter as well as ozone have been demonstrated to adversely affect overall health, especially pulmonary diseases (Guarnieri and Balmes, 2014; Jerrett et al., 2009; Kurt et al., 2016; To et al., 2016). The impact of air pollution on the incidence and outcomes in patients with ARDS is not well understood. One recent analysis found that living in an area with higher amounts of ozone pollution resulted in a higher risk of developing ARDS (Ware et al., 2016). No similar study has been performed on levels of particulate matter (PM) and the risk of developing ARDS. There has been no examination as to the outcomes of patients with chronic exposure to air pollution who develop ARDS.

In order to examine the association between high levels of air pollution and the outcome of patients with ARDS, we conducted a nationwide retrospective cohort analysis. Accordingly, our hypothesis was that increased levels of chronic ozone and particulate air pollution are associated with increased in-hospital mortality for patients with ARDS.

2. Methods

This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (Vandenbroucke et al., 2007). A waiver of consent for this study was granted by the Institutional Review Board of the University of British Columbia.

The Nationwide Inpatient Sample (NIS) for the 2011 sample year was utilized for this analysis. The NIS is a national database which captures approximately 20% of all in-patient hospital admissions from 47 contributor states. It is produced by the Agency for Health Care Research and Quality (AHRQ). The complex nature of the survey allows for estimation of 97% of all in-patient care delivered across the United States by utilizing a weighting scheme for national projections. (Introduction to the HCUP Nationwide Inpatient Sample, 2011).

2.1. Cohort selection

All patients 18 years of age who were admitted with a diagnosis of ARDS and received mechanical ventilation from the 2011 NIS Sample were included in the analysis. The definition for ARDS using administrative data we used has been widely utilized in many other studies (Reynolds et al., 1998; Rincon et al., 2014, 2012; Rush et al., 2016; Veeravagu et al., 2014). Our definition of ARDS was consistent with previous authors and included (1) International Classification of Diseases, Ninth Revision (ICD -9) codes for acute respiratory

failure following trauma and surgery (518.51); (2) other pulmonary insufficiency, not elsewhere classified, following trauma and surgery (518.52); (3) acute and chronic respiratory failure following trauma and surgery (518.53); (4) acute respiratory failure (518.81); (5) and other pulmonary insufficiency, not elsewhere classified (518.82)(Reynolds et al., 1998; Rincon et al., 2014; Veeravagu et al., 2014). Unfortunately, due to the lack of detailed granular variables in the NIS dataset we were unable to classify patients according to the Berlin definition of ARDS(Ferguson et al., 2012). Only patients who received mechanical ventilation were included in the cohort. Mechanical ventilation was defined as the presence of any ICD9 codes for invasive mechanical ventilation (96.70, 96.71, 96.72 and 96.04). A flow diagram for patient cohort selection is displayed in Fig. 1.

For each patient from the dataset we obtained: age, gender, length of stay, in-hospital mortality, race (White, Black, Hispanic, Asian, Other), health insurance coverage (yes vs no), zip-code median household income as well as the 29 Elixhauser co-morbidity indices (Elixhauser et al., 1998). The use of any form of hemodialysis for renal failure was also captured (39.95).

2.2. Air pollution exposure definition and measurement

Ideally, the exact location of a patient's residence would be used to categorize their chronic exposure to air pollution. Linking the geographic location of their home to known locations of air pollution monitoring stations could give detailed exposure information. Unfortunately, the NIS does not provide patients home address information in order to secure patient privacy by preventing patient identification. However, the county of the treatment hospital is provided by the NIS for the majority of states. For this analysis, we make the assumption that a large percentage of patients treated in a hospital reside in the general area and are exposed chronically to some mean level of air pollution. The levels of pollution for these counties is used by the Environmental Protection Agency (EPA) to create county level pollution maps.(Environmental Protection Agency, 2016) We excluded patients who were treated in states that refused to provide detailed hospital location information (data from 30 states was included in the final analysis).

To define residence in a high air pollution region, we used the top 15 cities with the highest levels of ozone pollution as described by the American Lung Association for 2011. (Association, 2016) The ozone concentrations are calculated based on the highest 8 h concentrations on a daily basis.(Environmental Protection Agency, 2016) From the Top 15 list there were three cities in states that did not provide detailed hospital location information (Dallas-Ft Worth, Houston, El Paso). The final 15 areas included in the high exposure group were: Los Angeles/Long Beach CA, Bakersfield CA, Visalia/Porterville/Hanford CA, Fresno/Madera CA, Phoenix/Mesa/Scottsdale AZ, Sacramento CA, Modesto/Merced CA, Denver/Aurora CO, Las Vegas NV, Fort Collins CO, El Centro CA, San Diego CA, New York/Newark Metropolitan Area, and San Jose/San Francisco CA.

In order to investigate the dose response effect of air pollution on mortality in ARDS we cross referenced the county level data on both 8 h ozone exposure and annual mean 2.5 μm particulate matter ($\text{P}_{2.5}$) pollution levels. For the county level analysis, we excluded counties

that contributed less than 25 cases of ARDS as well as counties that did not report detailed pollution data.

2.3. Statistical analysis

All data was analyzed in SAS v9.4 (SAS Institute, Cary NC) utilizing all appropriate procedures to preserve the complex survey nature of the NIS. All testing was done with a two sided alpha level of 0.05. Categorical variable analysis was preformed using a Chi-Squared analysis. Normally distributed continuous variables were analyzed with an independent *t*-test. In the case of non-normally distributed data, the Wilcoxon Rank Sum test was utilized.

A multivariate logistic regression model predicting the risk of in-hospital mortality was created. All variables in the model were selected *a priori* and included: pollution exposure, age, gender, renal failure requiring hemodialysis, and the 29 Elixhauser co-morbidity indices. Three models were created: one analyzing those residents in the Top 15 ozone pollution cities compared to the residents of all other areas, one model where ozone and particulate matter were treated as continuous variables.

3. Results

A total of 8,023,590 hospital admissions from the 2011 NIS sample were analyzed. There were 93,950 patients who underwent mechanical ventilation for ARDS included in the study. Of these, 27,761 (29.5%) were treated in a hospital located in a high ozone pollution area whereas 66,189 (70.5%) were not. The baseline characteristics and univariate analysis of the subgroups are displayed in Table 1. There were significant differences in several baseline characteristics between patients in high vs. low ozone pollution cities. Patients treated in high pollution areas were: older (64.2 years SD 17.6 vs 62.5 years SD 17.0, $p < 0.01$), more likely to have insurance coverage (92.3% vs 89.3%, $p < 0.01$), require hemodialysis (12.2% vs 9.9%, $p < 0.01$) and have longer lengths of hospital stays (9.1 days IQR 3.9–17.3 vs 8.4 days IQR 3.5–16.0, $p = 0.05$). The ethnic composition of the two cohorts also differed, with more minorities in the higher pollution cohort ($p < 0.01$). There was no difference in female gender between the two groups (46.1% vs 46.8%, $p = 0.17$). Patients treated in high ozone regions had significantly higher unadjusted hospital mortality (34.9% versus 30.8%, $p < 0.01$) than patients in cities with control levels of ozone.

It was important to do adjusted analyses especially because of the differences in prevalence of baseline characteristics, some of which are associated with the outcome of ARDS. The results of multivariate analysis modeling cities with high vs. control pollution for in-hospital mortality are displayed in Table 2. After controlling for all variables in the model, treatment in a hospital located in a high ozone pollution area was associated with an increased odds of in-hospital mortality (OR 1.11, 95% CI 1.08–1.15, $p < 0.01$). Other factors in the model associated with significantly higher rates of mortality included: age (per 5 year increase, OR 1.15, 95% CI 1.14–1.16, $p < 0.01$), Black race (compared to White, OR 1.08, 95% CI 1.04–1.11, $p < 0.01$) and need for hemodialysis (OR 1.43, 95% CI 1.37–1.49, $p < 0.01$). The presence of health insurance coverage was associated with a lower odds of mortality (OR 0.86, 95% CI 0.82–0.89, $p < 0.01$).

The results of the multivariate analysis treating ozone and particulate matter as a continuous variable are displayed in Tables 3 and 4 respectively. After adjustment for all variables in the model, for each increase in ozone exposure by 0.01 ppm the OR for death was 1.07 (95% CI 1.06–1.08, $p < 0.01$). Similarly, for each increase in particulate matter exposure by 10 $\mu\text{g}/\text{m}^3$, the OR for death was 1.08 (95% CI 1.01–1.16, $p < 0.01$). The results for both models stratified by states which contributed at least 500 cases is displayed in Table 5.

4. Discussion

In this national retrospective analysis, we found that being treated for ARDS in a hospital located in one of the top 15 highest cities in the USA for ozone pollution was associated with an increased risk of in-hospital mortality. This association was preserved after adjustment for demographic variables and co-morbidities. When treated as continuous exposure variables, both particulate matter and ozone exposure were also associated with increased odds of mortality in ARDS. These results are the first to examine the relationship between air pollution exposure and death in ARDS.

Exposure to ozone pollution has been shown in both animal and human studies to cause a variety of adverse molecular and physiologic effects including: free radical formation, lung inflammation, peroxidation of lipids, alteration of membrane permeability and loss of enzyme function (Mustafa, 1990). Exposure to ozone has been associated with acute and chronic lung inflammation as well as accentuated bronchial hyperreactivity in asthma and COPD (Koren et al., 1989; Mustafa, 1990). Bronchial reactivity and lung inflammation may make mechanical ventilation more difficult as well as contribute to the severity of acute lung injury (Pinheiro de Oliveira et al., 2010; Ranieri et al., 1999). All of these physiological factors may have contributed to the worse outcomes observed in patients treated in high ozone areas.

Particulate matter exposure has similarly been linked to a host of pro-inflammatory reactions as well as lung dysfunction in humans. For each 10 $\mu\text{g}/\text{m}^3$ increase in $\text{P}_{2.5}$ exposure per year, there is an additional attributable 10.5 mL decline in forced expiratory volume (FEV1) per year (Rice et al., 2015). Exposure to particulate matter has been associated with worse clinical as well as functional outcomes in adults with chronic respiratory diseases (Balmes et al., 2014; Kariisa et al., 2015; Park et al., 2005). The mechanism by which particulate matter exposure causes adverse health outcomes is not fully understood. Particulate matter has been demonstrated to: generate reactive oxygen species, activate cell signalling pathways as well as alter respiratory barrier functions (Hogervorst et al., 2006; Janssen et al., 2015). Additionally, PM exposure has been associated with a pro-inflammatory plasma profile, including elevated levels of monocytes and T lymphocytes, as well as increased endothelial cell apoptosis (Pope et al., 2016).

The results of the state stratified analysis in Table 5 warrant some discussion. Unfortunately, with the stratification by state, the absolute number of patients in each analysis decreased dramatically, with resulting increased confidence intervals. Nevertheless, the large variation in OR for both ozone and particulate matter demonstrate heterogeneity of our findings. Further research will be needed to explain these state-by state differences in effect size.

There are some limitations to our study. First, the clarity of definition of our exposure variable is less than ideal to investigate a potential causal relationship between air pollution exposure and increased mortality in ARDS, even in an association study. Second, there are potentially other confounders in the relationship between residence in one of the counties examined and survival in ARDS. Systematic differences in the health of patients residing in these cities may differ compared to other cities in the United States. Access to greenspaces, physical activity levels, occupational exposures as well as smoking status may contribute to risk of death from ARDS and were not controlled for in our analysis. Although smoking is potentially a strong confounder, we suggest that the influence of smoking on our results may be small because a large number of the ozone exposure patients resided in California which has one of the lowest smoking rates in the United States.(Center for Disease Control, 2016).

The results of this analysis must be interpreted in the context of key features of the study design. The use of administrative data contains the inherent possibility of coding errors and selection bias. It would have been more beneficial to have more detailed clinical information such as the degree of hypoxemia (P/F ratio) in order to more accurately control for severity of ARDS. As well, we were unable to use the current Berlin definition of ARDS in order to define inclusion in our cohort given the inherent lack of granular data available in the NIS(Ferguson et al., 2012). However, the definition for ARDS using administrative data we used has been widely utilized and validated in many other studies(Reynolds et al., 1998; Rincon et al., 2014, 2012; Rush et al., 2016; Veeravagu et al., 2014).

The main strength of our study is generalizability - the large sample size taken from across the entire United States. The ability to capture data from multiple states and different types of hospitals increases the generalizability of our findings. The examination of a nationwide cohort captures regional practice variation and patient characteristics. The use of the Elixhauser co-morbidity indices in our model allows for a robust adjustment for medical conditions which would influence mortality rates. Although it is unfortunate we were unable to have an ARDS specific severity of illness marker included in our modeling, the combination of the Elixhauser indices and the inclusion of only patients receiving mechanical ventilation is a reasonable approximation of severity between the two cohorts.

While these preliminary associations are interesting, further more detailed investigations incorporating more objective severity of illness markers for ARDS need to be undertaken. Additionally, more definitive ascertainment of actual patient exposure levels utilizing patient address information would add strength to this association. Nevertheless, with chronic air pollution exposure being already linked to a myriad of worse health outcomes, our findings only increase the urgency for regulations aimed at lowering ambient pollution levels.

5. Conclusion

In this preliminary analysis, treatment in hospitals located in areas with high levels of ozone air pollution was associated with increased rates of mortality for patients with ARDS. These findings are hypothesis generating and this association needs further more detailed investigations for confirmation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.envpol.2017.02.014>.

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Fig. 1.
Patient cohort selection flow diagram.

Table 1

Results of univariate analysis between patients treated in hospitals located in the top 15 high ozone regions vs those who were not.

	High Ozone Cohort n = 27,761	Control Cohort n = 66,189	p value
Age, mean (SD)	64.2 (16.5)	63.1 (16.1)	0.09
Length of stay, median (IQR)	9.1 (3.9–17.3)	8.5 (3.6–16.3)	0.11
In-hospital mortality, n (%)	9715 (34.9)	20,440 (30.8)	<0.01
Female gender, n (%)	12,811 (46.1)	30,854 (46.6)	0.42
Insurance coverage, n (%)	25,677 (92.2)	60,405 (91.3)	0.24
Race, n (%)			
White	15,621 (56.6)	44,432 (72.5)	
Black	3675 (13.9)	10,739 (17.4)	
Hispanic	5077 (18.4)	3485 (5.7)	
Other	3006 (10.9)	2700 (4.4)	<0.01
Hemodialysis use	3401 (12.2)	6135 (9.2)	<0.01

Table 2

Results of multivariate logistic regression analysis modeling in-hospital mortality for patients living in Top 15 highest ozone polluted cities. For Race, White serves as the reference category. The 29 Elixhauser co-morbidities included in the model can be found in Supplementary Table 1.

	Odds Ratio	95% CI	p value
Age, per 5 year increase	1.15	1.14–1.16	<0.01
Top 15 Ozone exposure	1.13	1.09–1.16	<0.01
Female Gender	0.99	0.96–1.02	0.43
Insurance coverage	0.84	0.80–0.90	<0.01
White Race	–	–	–
Black Race	1.08	1.03–1.12	<0.01
Hispanic Race	0.97	0.92–1.02	0.10
Other Race	1.05	0.98–1.11	0.25
Hemodialysis Requirement	1.40	1.33–1.47	<0.01

Table 3

Results of multivariate logistic regression analysis modeling in-hospital mortality for continuous exposure to ozone by county. For Race, White serves as the reference category. The 29 Elixhauser co-morbidities included in the model can be found in Supplementary Table 2.

	Odds Ratio	95% CI	p value
Age, per 5 year increase	1.15	1.14–1.16	<0.01
Ozone exposure, per 0.01 ppm increase	1.07	1.06–1.08	<0.01
Female Gender	1.00	0.97–1.03	0.99
Insurance coverage	0.81	0.76–0.86	<0.01
White Race	–	–	–
Black Race	1.01	0.97–1.06	0.59
Hispanic Race	0.97	0.92–1.02	0.24
Other Race	1.05	0.98–1.12	0.17
Hemodialysis Requirement	1.42	1.35–1.50	<0.01

Table 4

Results of multivariate logistic regression analysis modeling in-hospital mortality for continuous exposure to particulate matter by county. For Race, White serves as the reference category. The 29 Elixhauser co-morbidities included in the model can be found in Supplementary Table 3.

	Odds Ratio	95% CI	p value
Age, per 5 year increase	1.15	1.14–1.16	<0.01
Particulate exposure, per 5 $\mu\text{g}/\text{m}^3$ increase	1.04	1.01–1.08	<0.01
Female Gender	0.99	0.96–1.03	0.66
Insurance coverage	0.81	0.75–0.87	<0.01
White Race	–	–	–
Black Race	1.07	1.01–1.12	0.02
Hispanic Race	1.04	0.98–1.11	0.19
Other Race	1.05	0.97–1.12	0.20
Hemodialysis Requirement	1.40	1.32–1.48	<0.01

Results of multivariate logistic regression analysis modeling in-hospital mortality, stratified by states that contributed at least 500 cases. Where values are missing, detailed pollution data for that type was not produced by those states.

Table 5

	Ozone Pollution			Particulate Matter		
	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Arizona	1.74	1.11–2.72	<0.01	1.81	1.13–2.90	<0.01
California	1.05	1.03–1.08	<0.01	1.40	1.23–1.60	<0.01
Colorado	1.09	0.01–2.64	0.86	0.63	0.16–2.28	0.47
Connecticut	0.97	0.79–1.19	0.78	0.50	0.13–1.95	0.32
Florida	1.34	1.25–1.44	<0.01	–	–	–
Illinois	0.98	0.82–1.17	0.80	–	–	–
Kentucky	1.33	1.13–1.57	<0.01	4.81	1.29–17.9	<0.01
Massachusetts	1.85	1.25–2.74	<0.01	0.93	0.25–3.50	0.91
Maryland	0.78	0.54–1.13	0.19	0.49	0.09–2.79	0.42
North Carolina	0.93	0.86–1.02	0.10	0.38	0.17–0.87	0.02
New Jersey	0.85	0.65–1.10	0.21	1.01	0.33–3.08	0.99
New York	1.15	1.07–1.25	<0.01	0.82	0.55–1.22	0.32
Pennsylvania	1.12	1.03–1.22	<0.01	0.99	0.67–1.44	0.94
Virginia	1.53	1.05–2.25	0.02	–	–	–
Wisconsin	1.33	1.00–1.78	0.05	1.06	0.57–1.97	0.85
West Virginia	1.27	0.83–1.94	0.28	1.98	0.57–6.90	0.27