HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
Department of Environmental Health

Air pollution and risk of ARDS

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Outline

ARDS

Risk factors for ARDS

Scientific evidence of air pollution and ARDS

Summary of current evidence

Acute Respiratory Distress Syndrome (ARDS)

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Acute Respiratory Distress Syndrome The Berlin Definition, The ARDS Definition Task Force 2012

Acute Respiratory Distress Syndrome (ARDS)

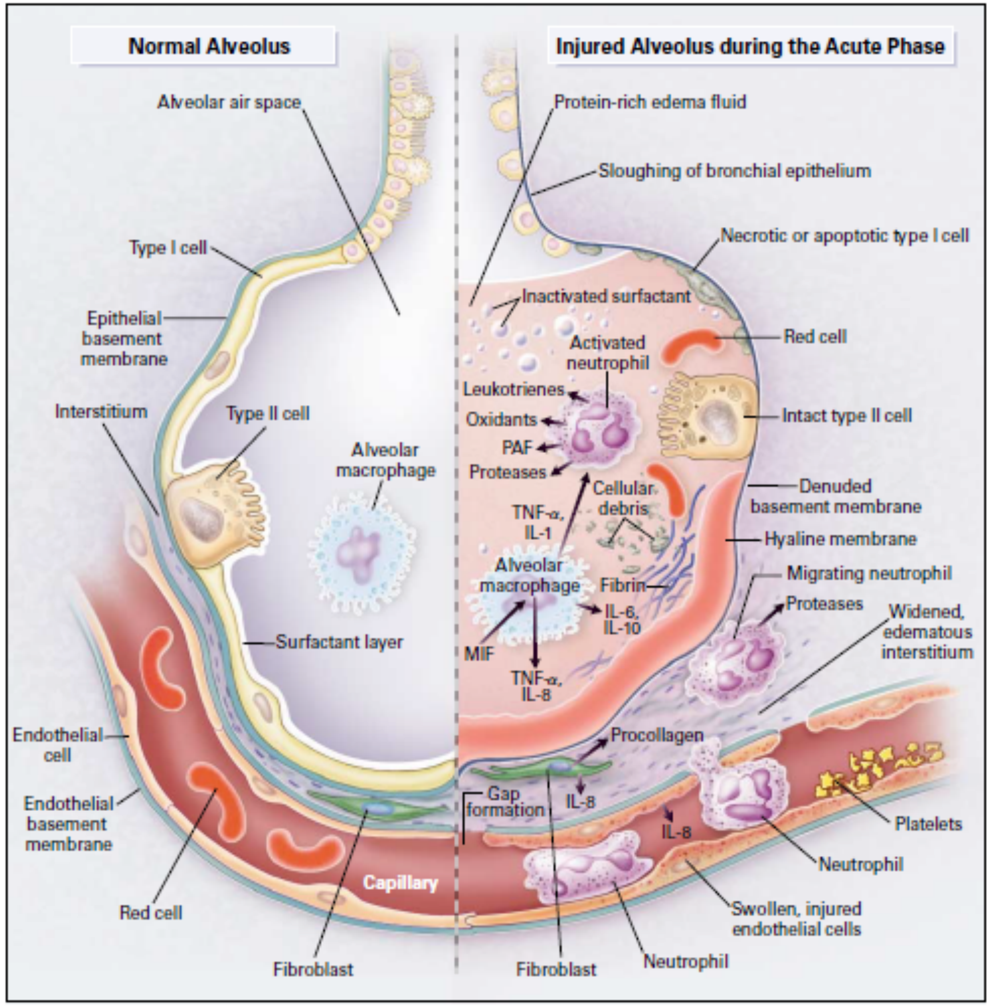

Figure 3. The Normal Alveolus (Left-Hand Side) and the Injured Alveolus in the Acute Phase of Acute Lung Injury and the Acute Respiratory Distress Syndrome (Right-Hand Side).

Ware et al. 2000 The Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (ARDS)

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Mild	200 mm Hg $< PaO_2/FIO_2 \leq$ 300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O[c]
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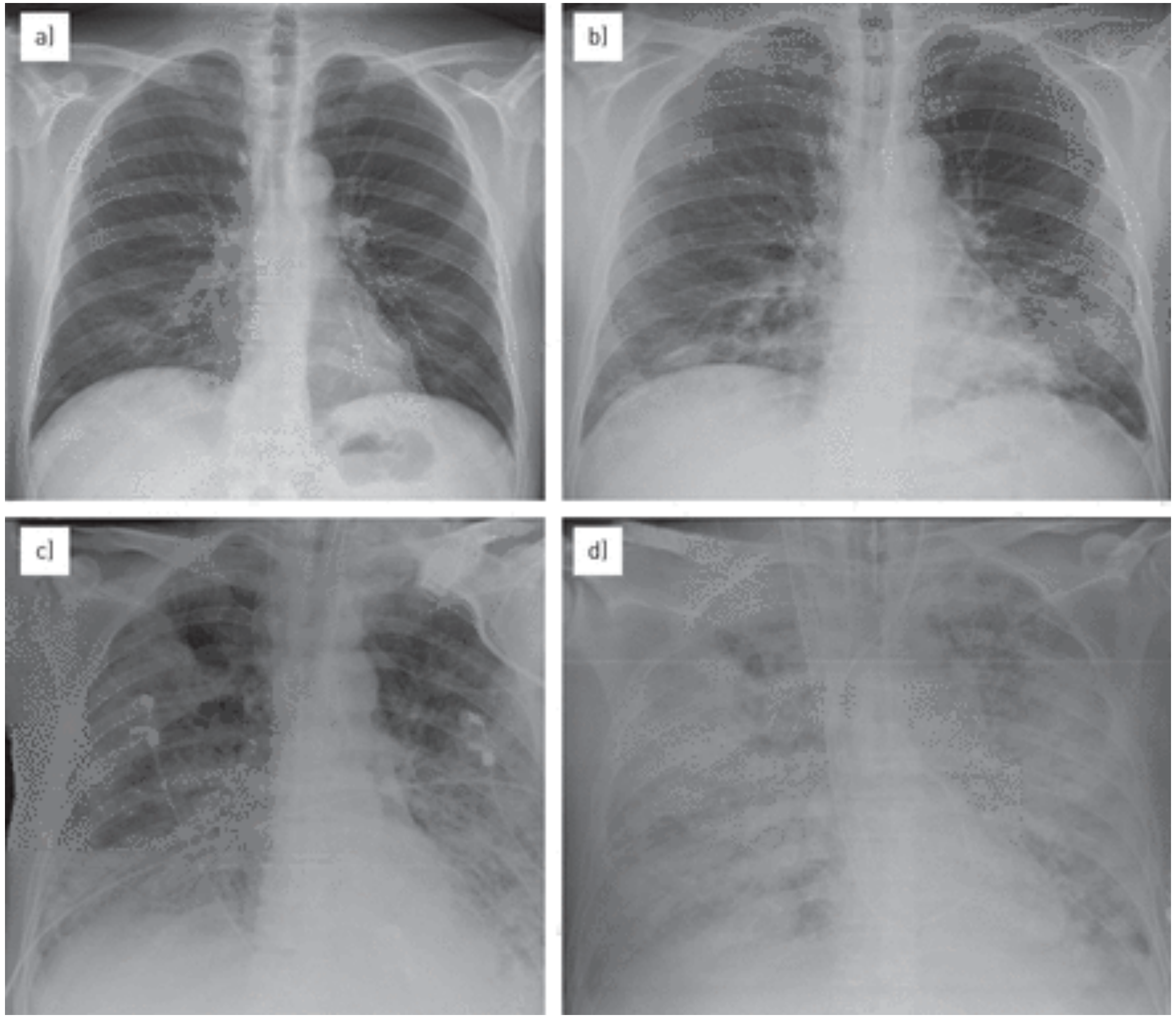
Acute Respiratory Distress Syndrome The Berlin Definition, The ARDS Definition Task Force 2012

Acute Respiratory Distress Syndrome (ARDS)

“White lung”



Zompatori et al 2014 Overview of current lung imaging in acute respiratory distress syndrome

Acute Respiratory Distress Syndrome (ARDS)

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Acute Respiratory Distress Syndrome (ARDS)

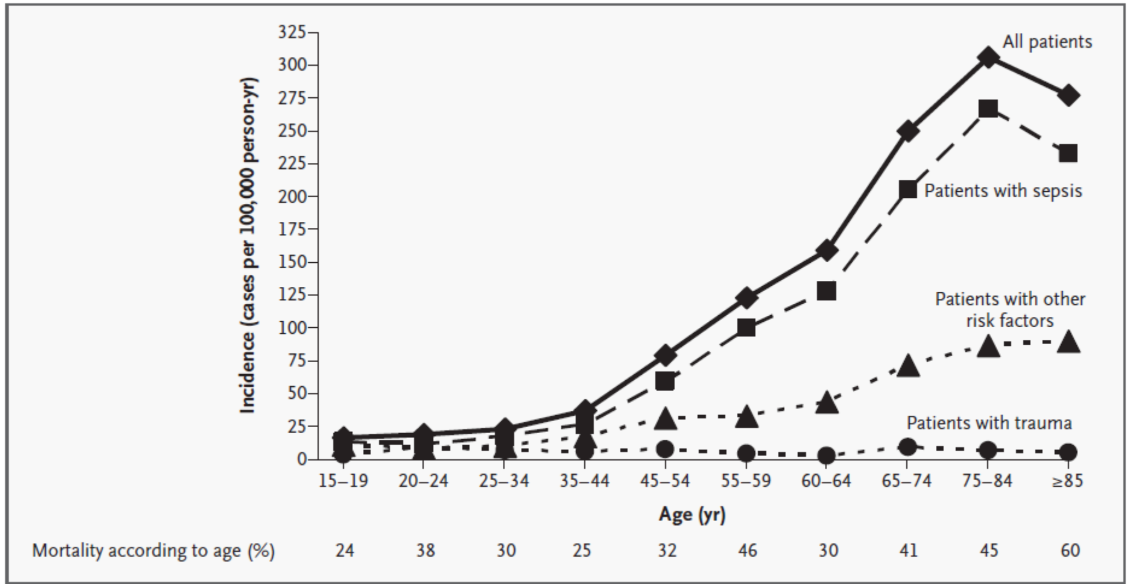


Figure 2. **Age- and Risk-Specific Incidence of and Age-Specific Mortality from Acute Lung Injury.**
Risk-factor categories are not mutually exclusive; P<0.001 for trend for the comparison of age-specific mortality rates.

Rubenfeld et al. 2005 Incidence and Outcomes of Acute Lung Injury

- The incidence of ARDS: 64.2 to 78.9 cases/ 100,000 population-year in U.S.
- Older adults are at high risk of developing ARDS (average 62 years)
- Mortality rate ranges from 40-60%

Clinical risk factors for ARDS

- Sepsis remains the most common cause of ARDS (46%)
- Clinical risk factors account for ~ 85% of ARDS cases
- **What are other risk factors associated with ARDS?**

TABLE 2. CLINICAL DISORDERS ASSOCIATED WITH THE DEVELOPMENT OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.

DIRECT LUNG INJURY	INDIRECT LUNG INJURY
Common causes	**Common causes**
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple transfusions
Less common causes	**Less common causes**
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

Ware et al. 2000 The Acute Respiratory Distress Syndrome

Environmental risk factors for ARDS

Studies evaluating the relationship between ARDS and alcohol use

Author	Year	Study Size	Odds Ratio (history of alcohol abuse vs no abuse)	P value
Moss et al[6]	1996	351	1.98*	< 0.001
Moss et al[8]	2003	220	3.70	< 0.001
Licker et al[9]	2003	879	1.87	0.012
Gajic et al[10]	2007	148	**	0.006
Gajic et al[12]	2011	5584	¶	0.028
Toy et al[11]	2012	253	5.90	0.028

Studies examining the relationship between smoking and ARDS

Author	Year	Study Size	Odds Ratio (active smokers vs nonsmokers)	P value
Christenson et al[56]	1996	3,848	2.01*	< 0.001
Iribarren et al[57]	2000	121,012	2.85 (< 1 pack/day)* 4.59 (≥ 1 pack/day)*	< 0.05 <0.05
Gajic et al[12]	2011	5,584	**	NS
Calfee et al[59]	2011	144	2.77	0.01
Toy et al[11]	2012	253	3.40	0.02
Diamond et al[60]	2013	1,255	1.80	0.002

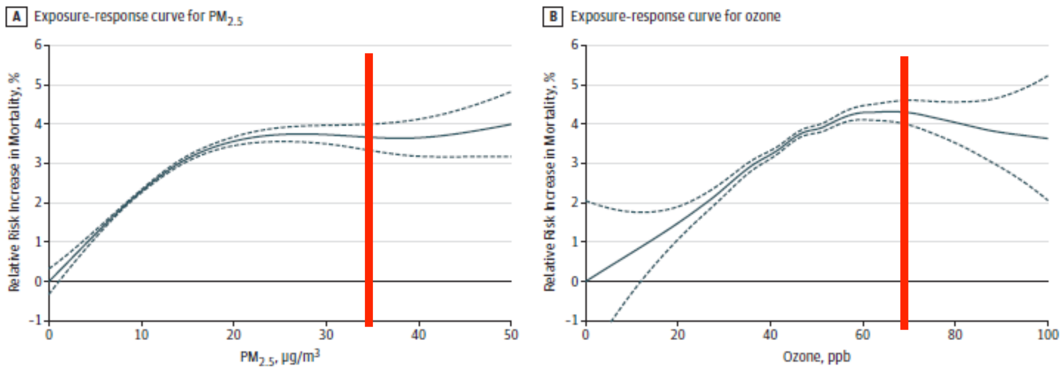
*Relative risk **No odds ratio or relative risk reported
Moazed 2014 Environmental Risk Factors for ARDS

Air pollution

- Fine particles ($PM_{2.5}$) and ozone are associated with morbidity and mortality due to respiratory disease
- **Short-term**: 24-hour National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$: 35 μg/m^3; 8-hour ozone: 70 ppb
- **Long-term**: annual NAAQS for $PM_{2.5}$: 12 μg/m^3; No annual standard for ozone
- Increased risk of all-cause mortality even below current standard (Di et al 2017 (1), Di et al 2017 (2))

Short-term

Figure 5. Estimated Exposure-Response Curves for Short-term Exposures to Fine Particulate Matter ($PM_{2.5}$) and Ozone



A 2-pollutant analysis with separate penalized splines on $PM_{2.5}$ (A) and ozone (B) was conducted to assess the percentage increase in daily mortality at various pollution levels. Dashed lines indicate 95% CIs. The mean of daily exposure on the same day of death and 1 day prior (lag 01-day) was used as metrics of exposure to $PM_{2.5}$ and ozone. Analysis for ozone was restricted to the warm season (April to September). Ppb indicates parts per billion.

Long-term

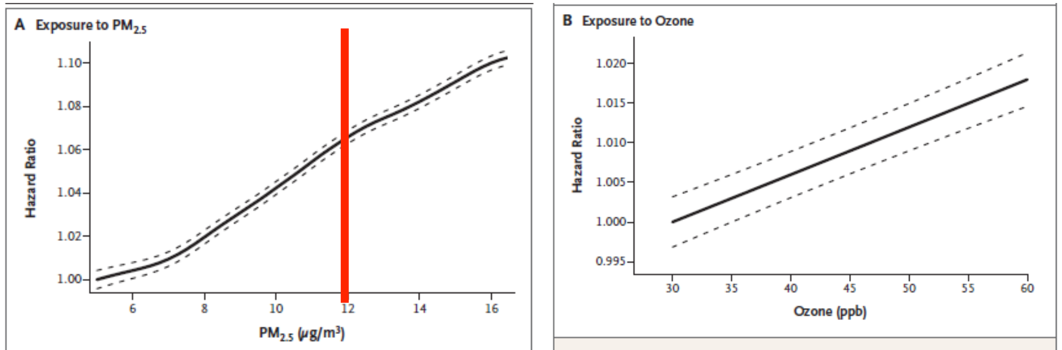


Figure 3. Concentration–Response Function of the Joint Effects of Exposure to $PM_{2.5}$ and Ozone on All-Cause Mortality.

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Scientific evidence on air pollution and ARDS

Short-term air pollution

Journal of Exposure Science & Environmental Epidemiology (2018) 28:392–399
https://doi.org/10.1038/s41370-018-0034-0

ARTICLE

Ambient particulate matter air pollution associated with acute respiratory distress syndrome in Guangzhou, China

Hualiang Lin[1] · Jun Tao[2] · Haidong Kan[3] · Zhengmin Qian[4] · Ailan Chen[5] · Yaodong Du[6] · Tao Liu[7] · Yonghui Zhang[8] · Yongqing Qi[9] · Jianjun Ye[9] · Shuangming Li[9] · Wanglin Li[10] · Jianpeng Xiao[7] · Weilin Zeng[7] · Xing Li[7] · Katherine A. Stamatakis[4] · Xinyu Chen[11] · Wenjun Ma[7]

Long-term air pollution

ORIGINAL ARTICLE

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

Lorraine B. Ware[1,2], Zhiguo Zhao[3], Tatsuki Koyama[3], Addison K. May[4], Michael A. Matthay[5,6], Fred W. Lurmann[7], John R. Balmes[5,8], and Carolyn S. Calfee[5,6]

ORIGINAL ARTICLE

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

John P. Reilly[1,2], Zhiguo Zhao[3], Michael G. S. Shashaty[1,2], Tatsuki Koyama[3], Jason D. Christie[1,2,4,5*], Paul N. Lanken[1], Chunxue Wang[6], John R. Balmes[5,7,8*], Michael A. Matthay[8,9], Carolyn S. Calfee[8,9], and Lorraine B. Ware[6,10]

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ELSEVIER

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], John H. Boyd[a,c]

[Original Research]

CHEST

Impact of Long-Term Exposures to Ambient $PM_{2.5}$ and Ozone on ARDS Risk for Older Adults in the United States

Jongeun Rhee, ScD; Francesca Dominici, PhD; Antonella Zanobetti, PhD; Joel Schwartz, PhD; Yun Wang, PhD; Qian Di, ScD; John Balmes, MD; and David C. Christiani, MD, MPH

ARTICLE

Check for updates

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Study description

- An ecological time-series analysis (2009-2011)
- Daily emergency visit for ARDS in Guangzhou, China (daily count)
- Daily concentrations for PM_{10} , $PM_{2.5}$, PM_1
- Same day air pollution, up to 5 days prior to emergency visit & moving average

Short-term air pollution

ARTICLE

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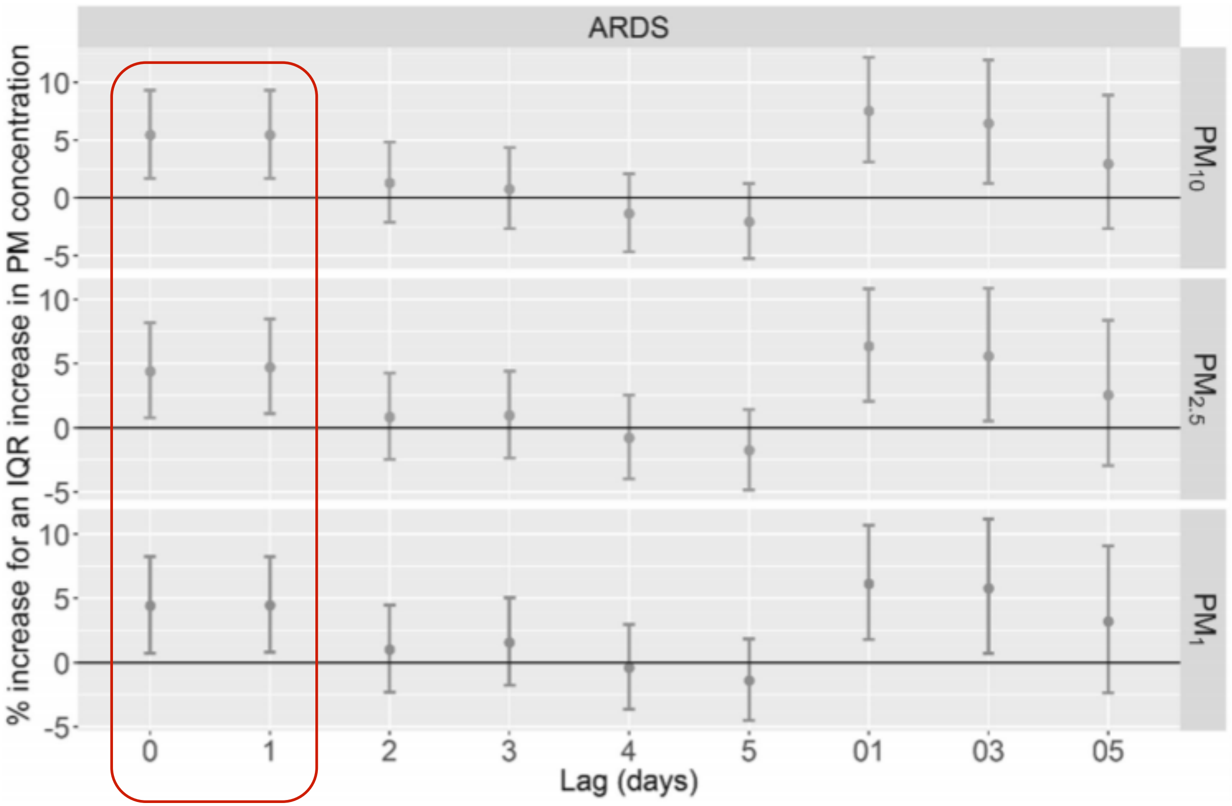

Fig. 1 Excess risk (ER with 95% CI) of EADs for ARDS in single-pollutant models for an interquartile range increase in particulate pollutants with different lag days (single lags for the current day (lag0) to 5 days before the current day (lag5) and multiday lags for the current day and prior 1 day before (lag01), 3 days (lag03), or 5 days (lag05))

Main results

- 17,002 emergency visit for ARDS
- A 5% increased risk of ARDS for an interquartile range (IQR) increase in 1-day lagged PM_{10} concentration, 5% for $PM_{2.5}$, and 4 % for PM_1.
- IQR for PM_{10} (45 μg/m^3) $PM_{2.5}$ (32 μg/m^3) PM_1 (29 μg/m^3)

Short-term air pollution

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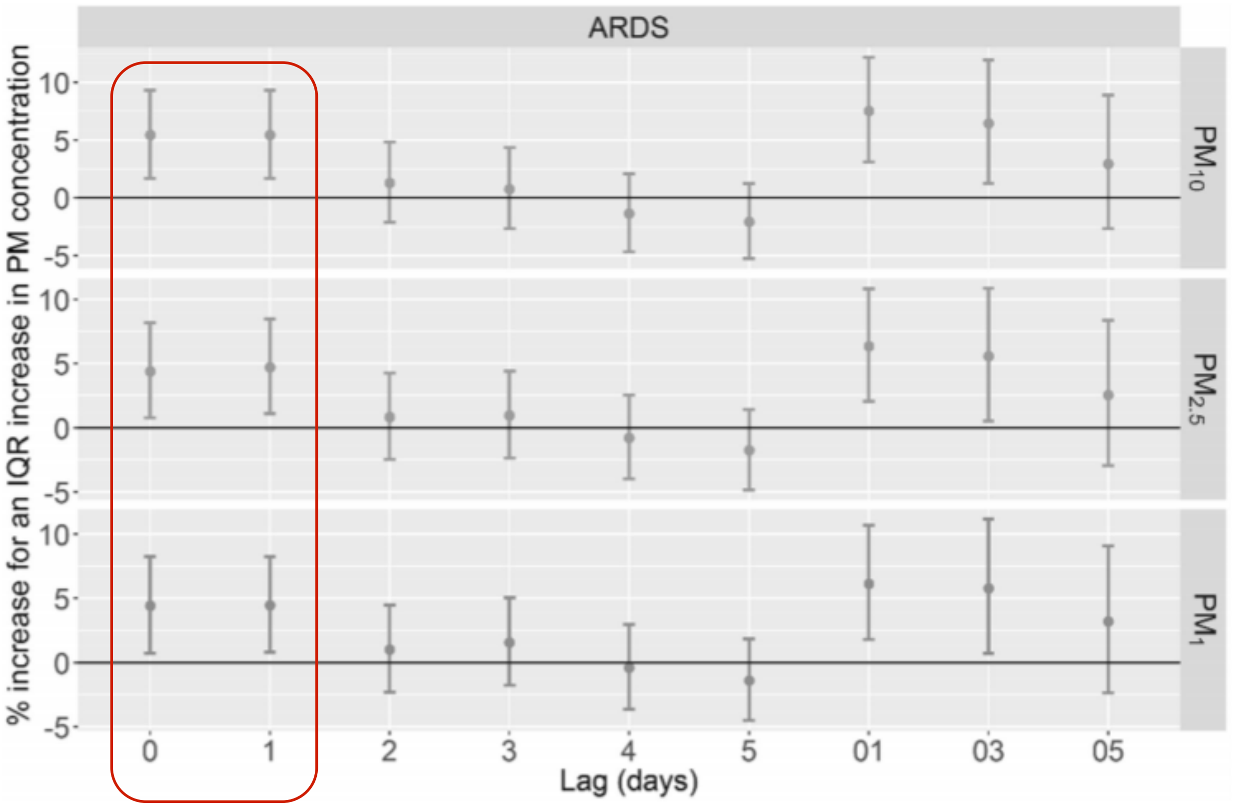

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Strengths

- First study in China

Limitations

- No adjustment for confounders (e.g. age, sex, smoking) other than weather effect & day of week

Long-term air pollution

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

Study description

- A cross-sectional analysis of air pollution and risk of in-hospital mortality among ARDS patients
- The 2011 Nationwide Inpatient Sample (NIS): 8,023,590 hospital admissions
- EPA county-level annual mean $PM_{2.5}$ and annual daily maximum 8-hour ozone (2011)
- Comparing risk of in-hospital mortality for patients with ARDS in highly ozone polluted cities (e.g. LA, NYC, Las Vegas etc) vs the rest

Long-term air pollution

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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

Main results

- 93,950 ARDS patients. 30% were treated in a hospital located in a high ozone pollution area
- A 13% increased odds of in-hospital mortality for patients with ARDS treated in a hospital located in the high ozone pollution area vs the control area
- A 7% increased odds for each increase in annual ozone exposure by 0.01 ppm
- An 8% increased odds for each increase in annual average $PM_{2.5}$ by 10 $\mu g/m^3$

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Hemodialysis Requirement	1.40	1.33–1.47	<0.01

Strengths

- Nation-wide data, large sample size

Limitations

- A cross-sectional analysis
- Crude exposure assessment

[Original Research]

CHEST

Impact of Long-Term Exposures to Ambient $PM_{2.5}$ and Ozone on ARDS Risk for Older Adults in the United States

Jongeun Rhee, ScD; Francesca Dominici, PhD; Antonella Zanobetti, PhD; Joel Schwartz, PhD; Yun Wang, PhD; Qian Di, ScD; John Balmes, MD; and David C. Christiani, MD, MPH

Study description

- Medicare inpatient data (aged ≥ 65 years) (~ 60 million, 2000-2012)
- ARDS defined as ICD-9-CM codes 518.51-3, 518.82 for either primary or secondary diagnosis (1.2 million ARDS hospital admissions)
- Annual counts of hospital admissions with ARDS per zip code (37,167 zip codes)

TABLE 1] Demographic Information for Patients With ARDS Hospital Admissions (1,164,784) in the Medicare Cohort (2000-2012)

Age	77.5 ± 7.9
Length of hospital stay, d	13.9 ± 14.1
Length of ICU stay, d	6.7 ± 10.5
Sex	
Male	558,373 (47.9%)
Female	606,411 (52.1%)
Race	
White	1,010,159 (86.7%)
Black	97,979 (8.4%)
Asian	14,981 (1.3%)
Hispanic	12,160 (1.0%)
Native American	21,273 (1.8%)
Other	8,232 (0.8%)

Data are presented as mean ± SD unless otherwise indicated.

Long-term air pollution

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[Original Research]

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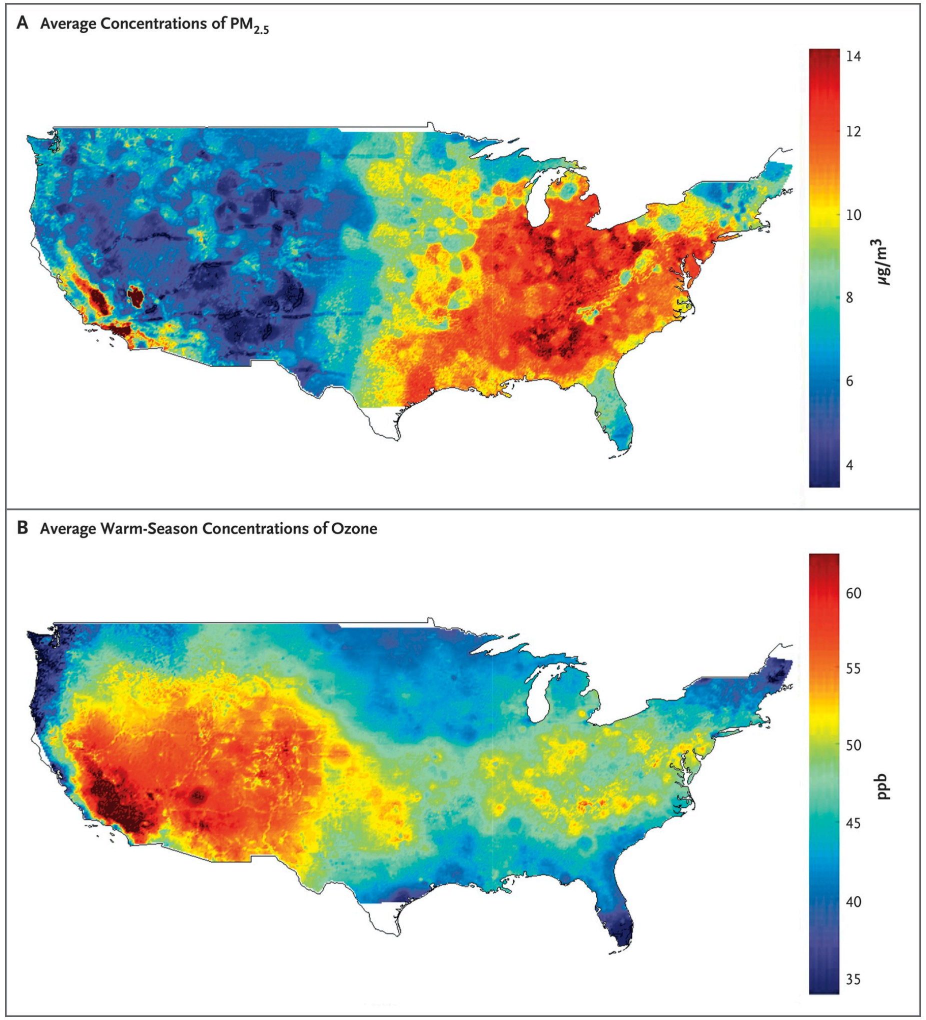
Air pollution data

- Estimated ambient levels of $PM_{2.5}$ and ozone using previously published prediction models
- Zip code level annual average concentrations for $PM_{2.5}$ and ozone during the warm season (Apr-Sep)



Di et al. 2017 A hybrid model for spatially and temporally resolved ozone exposures in the continental United States.
Di et al. 2016 Assessing PM2.5 exposures with high spatiotemporal resolution across the continental United States.

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Statistical analyses

- Two-pollutant generalized linear mixed model with a random intercept assuming a Poisson distribution
  - Adjusted for zip-code level covariates (age, sex, racial distribution, median household income, smoking, temperature, humidity) and year
- Restricted zip codes with low air pollution
  - $PM_{2.5}$ levels <12 $\mu g/m3$ or ozone levels <45 ppb

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Main results

TABLE 3] Percent Change in Hospital Admission Rates for ARDS According to 1 μg/m³ Increase in Annual Average $PM_{2.5}$ Concentrations or 1 ppb Increase in Annual Average Ozone Concentrations (95% CI)

Pollutant	ARDS	
	Two-Pollutant	Single-Pollutant
$PM_{2.5}$	0.72 (0.62 to 0.82)	0.76 (0.66 to 0.86)
Ozone	0.15 (0.08 to 0.22)	0.24 (0.18 to 0.31)

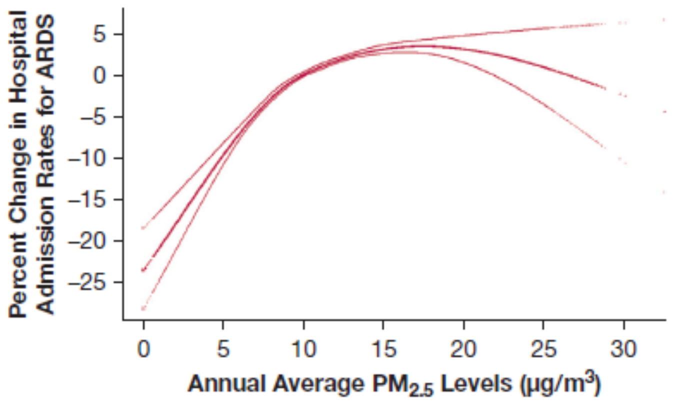

Figure 2 – Concentration-response function of the exposure to annual average $PM_{2.5}$ on percent change in hospital admission rates for ARDS. $PM_{2.5}$ = particulate matter with an aerodynamic diameter < 2.5 μm.

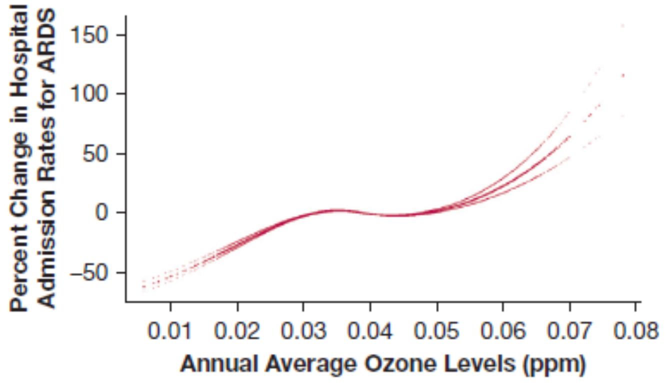

Figure 3 – Concentration-response function of the exposure to annual average ozone on percent change in hospital admission rates for ARDS. ppb = parts per billion.

- Long-term exposures to $PM_{2.5}$ and ozone were associated with increased hospital admission rates for acute respiratory distress syndrome (ARDS)

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Main results

TABLE 4] Percent Change in Hospital Admission Rates for ARDS According to 1 μg/m³ Increase in Annual Average $PM_{2.5}$ Concentrations or 1 ppb Increase in Annual Average Ozone Concentrations (95% CI) in Regions of Low Air Pollution

All Regions (N = 483,171)	Two-Pollutant Model
Low $PM_{2.5}$ regions (n = 310,590)	
$PM_{2.5}$	1.31 (1.11-1.51)
Ozone	0.30 (0.21-0.40)
Low ozone regions (n = 446,429)	
$PM_{2.5}$	0.78 (0.67-0.88)
Ozone	0.16 (0.08-0.23)
Low $PM_{2.5}$ and ozone regions (n = 283,237)	
$PM_{2.5}$	1.50 (1.27-1.72)
Ozone	0.27 (0.16-0.38)

Low $PM_{2.5}$ regions include ZIP codes with annual average $PM_{2.5}$ < 12 μg/m³; low ozone regions include ZIP codes with annual average ozone < 45 ppb. See Table 2 legend for expansion of abbreviations.

- In low air pollution regions, the same annual increases in $PM_{2.5}$ and ozone were associated with higher percent increases in hospital admission rates
- **Increased admission rates even below current national standard (NAAQS for $PM_{2.5}$: 12 μg/m³)**

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TABLE 4] Percent Change in Hospital Admission Rates for ARDS According to 1 μg/m^3 Increase in Annual Average $PM_{2.5}$ Concentrations or 1 ppb Increase in Annual Average Ozone Concentrations (95% CI) in Regions of Low Air Pollution

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Low $PM_{2.5}$ and ozone regions (n = 283,237)	
$PM_{2.5}$	1.50 (1.27-1.72)
Ozone	0.27 (0.16-0.38)

Low $PM_{2.5}$ regions include ZIP codes with annual average $PM_{2.5}$ < 12 μg/m^3; low ozone regions include ZIP codes with annual average ozone < 45 ppb. See Table 2 legend for expansion of abbreviations.

Strengths

- Largest study
- First study investigating the older adults
- Estimated air pollution data, investigating areas not monitored by the EPA

Limitations

- Unmeasured confounders
- Using ICD-9-CM codes to define ARDS

Summary of current evidence

- Long-term exposure to $PM_{2.5}$ and ozone are associated with increased risk of ARDS
- Increased admission rates for ARDS associated with long-term exposure to $PM_{2.5}$ were found even below current national standard

Next steps

- Individual-level analyses for both short-term and long-term exposure to air pollution associated with risk of ARDS and ARDS mortality
- Replicating studies in racially/ethnically diverse populations
- Mediation analyses (air pollution-comorbidities-ARDS)

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