

**Acute Exacerbation of Idiopathic Pulmonary Fibrosis Associated with Air Pollution
Exposure**

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Take-home message: Acute exacerbation of idiopathic pulmonary fibrosis is associated with increased ozone and nitrogen dioxide exposure.

Abstract

Question: Acute exacerbations of idiopathic pulmonary fibrosis are associated with high mortality and are of unknown cause. The effect of air pollution on exacerbations of interstitial lung disease is unknown. This study aims to define the association of air pollution exposure with acute exacerbation of idiopathic pulmonary fibrosis.

Materials and Methods: Patients with idiopathic pulmonary fibrosis and corresponding air pollution data were identified from a longitudinal cohort. Air pollution exposures were assigned to each patient for ozone, nitrogen dioxide, particulate matter, sulfur dioxide and carbon monoxide based on geo-coded residential addresses. Cox proportional hazards models were used to estimate the association of air pollution exposures and acute exacerbations.

Results: Acute exacerbation was significantly associated with antecedent 6 week increases in mean level, maximum level, and number of exceedances above accepted standards of ozone (Hazard Ratio=1.57, 95% CI=1.09-2.24; 1.42, 95% CI=1.11-1.82; and 1.51, 95% CI=1.17-1.94, respectively) and nitrogen dioxide (Hazard Ratio=1.41, 95% CI=1.04-1.91; 1.27, 95% CI=1.01-1.59; and 1.20, 95% CI=1.10-1.31, respectively).

Answer: Increased ozone and nitrogen dioxide exposure over the preceding 6 weeks was associated with an increased risk of acute exacerbation of idiopathic pulmonary fibrosis, suggesting that air pollution may contribute to the development of this clinically meaningful event.

Abstract Word Count: 199

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive parenchymal lung disease of unknown cause with an estimated median survival of 2-3 years from the time of diagnosis.(1) It is the most common of the idiopathic interstitial pneumonias and increases in prevalence substantially with age.(2) Many patients with IPF experience sudden step-wise acute respiratory worsenings, which are associated with high mortality.(3) In about half of cases, a cause for the acute worsening (e.g. infection, pulmonary embolism or congestive heart failure) cannot be diagnosed. These idiopathic acute respiratory worsenings are termed acute exacerbations of IPF.(4)

Preliminary evidence suggests that some cases of acute exacerbation of IPF may be triggered by occult viral infection(5), microaspiration(6) and procedures such as surgical lung biopsy.(7) However, in the majority of cases a trigger cannot be found. Exposure to environmental triggers, such as ambient air pollution, could be responsible for some of these cases.

The relationship between ambient air pollution and exacerbation of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) is well established.(8-11) Few studies have investigated the effects of ambient air pollution on interstitial lung diseases (ILD) despite epidemiological data linking exposure to inhaled agents such as cigarette smoke, organic antigens and metal and wood dusts to these conditions. In addition, translational data support a mechanistic relationship between air pollution exposure and the development of pulmonary fibrosis.(12-14) We hypothesized that the risk of acute exacerbations in patients with IPF would be higher following periods of increased air pollution exposure.

This study investigates the relationship between ambient air pollution exposure [ozone (O₃), nitrogen dioxide (NO₂), particulate matter less than 10 microns in aerodynamic diameter (PM₁₀), sulfur dioxide (SO₂) and carbon monoxide (CO)] and acute exacerbations of IPF in a large, well-characterized cohort with contemporaneous clinical and ambient air pollution data.

Materials and Methods

Study Cohort

Patients with IPF were identified from an ongoing IRB-approved longitudinal cohort developed at Asan Medical Center in Seoul, South Korea. Informed consent was waived as this was a retrospective observational study of existing data. The local institutional review board approved the study. The diagnosis of all enrolled patients was reconfirmed as IPF according to ATS/ERS/JTS/LATS consensus criteria.(1) Patients were excluded if the baseline forced vital capacity (FVC), smoking status, residential home address or corresponding air pollution exposure data were unavailable. A subgroup of patients identified for this study has been previously reported.(3)

Case definition

Patients experiencing acute exacerbation during the follow up period from Jan 1, 2001 to Dec 31, 2010 were considered cases. Acute exacerbations were defined by convention as a worsening of dyspnea within 30 days of presentation, the presence of new pulmonary opacities on high-resolution computed tomography of the lung, and the exclusion of known causes for respiratory worsening such as infection, pulmonary embolism or congestive heart failure.(4) All patients underwent evaluation for respiratory infection with 69% having invasive sampling procedures.

Due to potential effect modification between past and future exacerbations, patients experiencing more than one exacerbation only had their first event included as a case in the primary analysis. For each case, a pooled control population was constructed using all remaining patients in the cohort at the date of the case event, provided they had not yet experienced an acute exacerbation and did not develop one within 6 weeks following the date of the case event.

Measurements

Baseline clinical parameters were collected prospectively as part of the parent cohort and included patient demographics, smoking status (never, former or current), FVC percent predicted, and diffusion capacity for carbon monoxide (DLCO) percent predicted. A current smoker was defined as a patient who was actively smoking at the time of enrolment into the study cohort. The date and clinical features of all acute exacerbations were recorded. Air pollution data for each of the five pollutants (O₃, NO₂, PM₁₀, SO₂, CO,) were measured prospectively at Tele-Monitoring-Systems (TMS) situated throughout Korea (data purchased from AirKorea). Each TMS recorded hourly measurements of each pollutant during the study period. Ozone measurements were taken from the warmer months (April-September) and during an 8-hour period of daylight (1000h-1800h). Temperature and humidity values were obtained similarly at each TMS in a subgroup of patients where available. Hourly temperature and humidity measurements were averaged over the exposure period for each event. Each patient was geocoded to the nearest available TMS using his/her residential address. Data from the nearest TMS provided each patient's exposure during the study period.

Analysis

Mean and maximum exposures were defined as the average or highest of all 1-hour (NO₂, SO₂), 8-hour (O₃) or 24-hour (PM₁₀, CO) levels over the 42-day (6 week) period prior to acute exacerbation date (hereafter referred to as the “exposure period”), respectively. The number of exceedances above accepted standards was also determined for each pollutant over the exposure period according to published and well-documented regulatory standards (<http://www.epa.gov/air/criteria.html>) .(15, 16) The 42-day exposure period was chosen *a priori* to account for a potential lag time between exposure and the development of symptoms, and to allow for symptom onset (and therefore likely exacerbation onset) dating to 30 days before presentation, as per definition of acute exacerbation.(4)

Cox proportional hazards models were used to estimate the effect of air pollution exposure on incidence of acute exacerbation. Follow-up for each patient began at the date of IPF diagnosis, and ended at the earlier of lung transplantation, death, or Dec 31, 2010. Analyses were adjusted for smoking status and FVC, factors known a priori to be associated with risk of acute exacerbation in the parent cohort. As per the standard Cox model, controls for each event included all patients still at risk on the date of the event; thus patients could serve as controls for exacerbations of other patients between the date of IPF diagnosis and 42 days before their own first event, or censoring. For example, if a patient was diagnosed with IPF on January 22, 2002 and experienced an AE on August 6, 2008, she would serve as a control for any AE occurring between her date of diagnosis and June 25, 2008. To ensure adequate exposure measurement, all cases and controls were required to have pollution data for at least 21 days of the 42-day exposure period before the event.

Pre-defined secondary analyses included using different inclusion criteria for cases (patients whose home address was within 15 kilometers of the monitoring site; patients with exposure data that could be adjusted for average temperature and humidity), other cumulative exposure periods (1 to 8 weeks); different outcome definitions [all (first plus subsequent) acute exacerbations] and alternative published standards or guidelines for exceedance levels

(<http://www.airkorea.or.kr/airkorea/eng/information/main.jsp?action=standard>,

http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/index.html). (16, 17) Two-pollutant models were run to assess the independent effects of exposure variables that were statistically significant in single-pollutant models. Secondary analyses used the same analytic approach as the primary analysis.

Identical methodology was used to assess the association of cumulative air pollution exposure with mortality, and to examine potential increases in acute exacerbation and mortality risk among patients with a history of earlier acute exacerbation, in all cases controlling for age, gender, and FVC which are known predictors of mortality. For these analyses, cumulative exposures were calculated over the entire period from IPF diagnosis to date of censoring. All data analysis was performed using STATA v. 12.1 (College Station, TX), and statistical significance was defined as a p value < 0.05.

Results

Patient Population

Five hundred and five patients with IPF were identified from the longitudinal cohort; 69 were excluded for missing baseline data (n=22) or lack of air pollution exposure data (n=47). Four hundred and-thirty six patients were included in the final analysis, of which 75 experienced at least one acute exacerbation. A subset of patients (n=13) experienced more than one exacerbation. Baseline clinical characteristics of patients who experienced acute exacerbation of IPF and those who did not are presented in **Table 1**. Patients with acute exacerbation had lower baseline FVC and were more likely to have a history of prednisone use and/or been on therapy for gastro-esophageal reflux disease (GERD) at baseline assessment. There was no difference in the proportion of current, ex- or never smokers in the exacerbating versus non-exacerbating patients. Two patients without exacerbation underwent lung transplantation. The average distance from the patient's residence to the geocode-assigned TMS was 7.2 kilometers (**Supplementary Figure 1**).

Acute Exacerbation Incidence and Outcomes

There were 89 acute exacerbation events occurring over 1699 patient years, for an incidence rate of 5.2 exacerbations per 100 patient-years. Acute exacerbation events were characterized by fever (53%) and cough (37%) and had an average duration of symptoms prior to diagnosis of 10.7 days. Forty nine percent of patients were admitted to the intensive care unit, 8% required non-invasive positive pressure ventilation, and 45% required mechanical ventilation. Acute exacerbation was associated with high risk of subsequent acute exacerbation (HR 4.32, (95% CI=2.33-7.98)) and substantially decreased survival time (HR 6.14 (95% CI=4.03-9.34)). Short-term mortality was 37% at 1 month and 67% at 6 months.

Association of Air Pollution Exposure with Acute Exacerbation Risk

Acute exacerbation of IPF was significantly associated with increased mean levels, maximum levels, and number of exceedances of O₃ and NO₂ during the exposure period (**Figure 1**). There were no consistent relationships between PM₁₀, SO₂ or CO and acute exacerbation of IPF. Mean O₃ and NO₂ were weakly correlated and both were statistically significant independent predictors of acute exacerbation in a two-pollutant model. Hazard ratios for all five exposures remained consistent when cases were limited to only those occurring within 15 km of a monitoring station, those able to be corrected for temperature and humidity, or when all acute exacerbations (including those occurring in patients who had previously experienced an acute exacerbation) were included (**Table 2**). Ozone and NO₂ exposures remained generally associated with acute exacerbation when varying the exposure period from 1 to 8 weeks prior to acute exacerbation diagnosis (**Figure 2 and Supplementary Table 1**). The associations with O₃ and NO₂ were also consistent when exceedance analyses were performed according to alternative published reference standards or guidelines (**Supplementary Table 2**). Finally, these associations remained consistent when adjusted for history of prednisone and/or GERD therapy use (data not shown).

Association of Cumulative Air Pollution Exposure and Mortality

There were no statistically significant relationships between air pollution exposure and mortality. Hazard ratios for mean O₃ and NO₂ exposure were 1.03 (95% CI=0.90-1.17) and 0.97 (95% CI=0.86-1.10) respectively while those for maximum O₃ and NO₂ exposures were 1.02 (95% CI=0.90-1.16) and 1.06 (95% CI=0.93-1.20).

Discussion

Our study demonstrates a significant relationship between ambient O₃ and NO₂ levels and acute exacerbation of IPF, suggesting that increased exposure to these pollutants contributes to the development of acute exacerbation in some patients. The magnitude of the associated risk is comparable to what has been reported for exacerbation of other chronic lung diseases.(10, 18, 19) To our knowledge this is the first report describing this association in IPF. Air pollution is a potentially modifiable risk factor either via behavioural adaptation of the patient (i.e. exposure avoidance) or community-level reductions in exposure through environmental policy. Our findings suggest that reductions in ambient air pollution exposure may decrease the risk of acute exacerbation and improve the morbidity associated with IPF.

Based on the clinical presentations of patients with acute exacerbations of IPF, we hypothesized that ambient air pollution-associated events, unlike acute exacerbation of asthma or acute myocardial infarction, would have a delayed clinical presentation. The 6-week exposure period was defined *a priori* based on the assumption that an interval of up to 30 days might occur between symptom onset (and therefore likely exposure risk) and time of diagnosis, and to allow for a potential lag-time from pollutant exposure to symptom development. Sensitivity analyses varying the exposure period from 1 to 8 weeks prior to acute exacerbation demonstrated a consistent association, strengthening the results, and suggesting that the exposure period of highest risk lies between 2 and 8 weeks before diagnosis. Because O₃ levels are known to be lower during the winter and at night, outcomes were analyzed in relation to peak O₃ concentration using 8-hour mid-day levels during the warmer months only, an approach commonly used in epidemiologic studies of O₃(20, 21). For the exceedance analyses, the United

States Environmental Protection Agency National Ambient Air Quality Standards were chosen *a priori* because they are regulatory standards and not merely guidelines.

Ozone and NO₂ are known risk factors for poor outcomes and exacerbations in chronic lung diseases. (22-25) A long-term population analysis found a relative risk of respiratory-related death of 1.04 for every 10 parts per billion increase in O₃. (20) Ozone has been associated with increasing risk for the development of airways diseases like asthma and with increased exacerbation risk in asthma and cystic fibrosis. (18, 23, 26) NO₂ exposure has been associated with increased risk of respiratory hospitalization in COPD and asthma, and traffic-related air pollution exposure increases the risk of post lung transplant bronchiolitis obliterans syndrome. (8-10, 19) It is not entirely surprising, therefore, that exposure to O₃ and NO₂ appear to contribute to worsening of IPF.

Air pollution exposure may trigger acute exacerbation of IPF via the production of excess reactive oxygen species (ROS) such as hydroxide radical and superoxide anion. (27) Intrinsic anti-oxidants, such as glutathione, are generally capable of counter-balancing the effects of ROS, but when the production of ROS exceeds the lung's ability to remove them, cellular damage ensues. Patients with IPF have evidence of reduced anti-oxidant capacity, suggesting they may have increased vulnerability to excess ROS caused by exposure to air pollution. (28)

The greatest modifiable source of O₃ and NO₂ in the industrialized world is from motor vehicle emissions. While our results do not inform strategies for exposure reduction, they do suggest that patients with IPF might benefit from avoiding excess pollutant exposure perhaps through

reduced physical exertion or staying indoors on days with high air pollution levels. In addition, IPF patients might benefit from relocating to environments with lower emissions and better air quality. At a policy level, adherence to and enforcement of air quality standards may reduce the incidence of acute exacerbation of IPF overall. Understanding more fully the implications of these findings will require the continued integration of the fields of clinical research, environmental health and public policy.

The IPF cohort used for this study is well-characterized and likely represents the largest such cohort available for this type of analysis, but the sample size is still relatively small for air pollution studies. This makes the consistent relationship between O₃ and NO₂ exposure and acute exacerbation all the more striking. The consistency of hazard ratios across sensitivity analyses further strengthens the reliability of the results. It is possible that significant associations with fine or ultrafine particulate matter were missed, as the only particulate matter metric available for this analysis was PM₁₀. There is the potential for exposure misclassification given that exposure estimates were based on regional air quality monitoring data and therefore could not account adequately for individual-level exposure differences such as time spent indoors and in traffic or sub-regional geographic variation. Reported residential addresses were confirmed before geocoding but some patients may have moved or spent significant amounts of time in other locations. Due to the retrospective nature of this study, other potential sources of pollutant exposures (e.g. cook-stoves, biofuels) could not be assessed. It also was not possible to adjust for temperature and relative humidity for the whole cohort, but a sensitivity analysis in the subgroup with available temperature and humidity data showed a consistent relationship between air pollution and acute exacerbation.

We did not find any relationship between cigarette smoking, the use of immunosuppressive medications, or the use of anti-acid therapies and the risk of acute exacerbation. However, this study's small numbers and lack of detailed data regarding cigarette smoking and immunosuppressive use at the time of exacerbation limit any conclusions regarding these relationships. These questions can best be addressed in large prospective trials.

In summary, these data suggest that exposure to O₃ and NO₂ contributes to the risk of acute exacerbation of IPF, and we speculate that air pollution represents one of a series of factors (e.g. viral infection, microaspiration) that serve as triggers for these clinically important events. It is possible that variations in ambient pollutant exposure contribute to differences in rates of acute exacerbation by geographic region, but further study is required to evaluate this relationship. Ozone and NO₂ have the potential for mitigation through behavioral and environmental policy changes, which could reduce the risk to these susceptible patients. Further research is needed to validate these findings and to better delineate the pathobiological role of air pollution in IPF.

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Table 1: Baseline Patient Characteristics

Characteristic	Acute Exacerbation n=75	No Acute Exacerbation n=361	<i>P</i> -value ^a
Age, years (SD)	63.7 (8.4)	62.8 (7.9)	0.29
Female gender, n (%)	17 (23)	74 (20)	0.67
Smoking status, n (%)			
Never	26 (35)	89 (25)	
Former	32 (43)	177 (49)	0.20
Current	17 (22)	95 (26)	
Forced vital capacity, % predicted	69.3 (17.7)	78.1 (17.6)	<.001
Diffusion capacity for carbon monoxide, % predicted (subset)	62.5 (19.3) (n=58)	67.1 (19.2) (n=338)	0.11
Prednisone, n (%)	56 (74.7)	202 (56.0)	0.003
GERD treatment (Proton pump inhibitor or H ₂ - antagonist), n (%)	57 (76.0) ^b	192 (53.2)	<.001

Abbreviations: SD = standard deviation, GERD = gastro-esophageal reflux disease, H₂ = histamine 2 receptor. ^a*P*-value = Overall tests of heterogeneity. ^b11/57 on proton pump inhibitor, 46/57 on H₂-antagonist.

Table 2: Secondary Analyses for Air Pollution Exposure and Risk of Acute Exacerbation

Secondary Analysis		O ₃	NO ₂	PM ₁₀	CO	SO ₂
Within 15 Kilometers of TMS	HR (95% CI)	1.67 (1.08-2.57) ^a	1.47 (1.06-2.05)	0.97 (0.67-1.40)	1.29 (1.00-1.67)	0.97 (0.65-1.45)
	Mean (n=66)					
	HR (95% CI)	1.57 (1.14-2.16) ^a	1.24 (0.96-1.59)	1.03 (0.67-1.57)	1.09 (0.76-1.56)	0.97 (0.72-1.31)
	Maximum (n=66)					
Adjusted for Temperature and Relative Humidity	HR (95% CI)	1.43 (0.93-2.21) ^b	1.43 (1.00-2.06)	0.91 (0.60-1.37)	1.24 (0.83-1.83)	0.96 (0.65-1.41)
	Mean (n=51)					
	HR (95% CI)	1.60 (1.21-2.12) ^b	1.22 (0.91-1.63)	0.70 (0.36-1.35)	1.03 (0.65-1.65)	1.01 (0.73-1.39)
	Maximum (n=51)					
All Acute Exacerbations	HR (95% CI)	1.51 (1.06-2.15) ^c	1.40 (1.06-1.86)	1.17 (0.84-1.63)	1.29 (1.03-1.60)	1.09 (0.80-1.49)
	Mean (n=89)					
	HR (95% CI)	1.43 (1.15-1.78) ^c	1.27 (1.01-1.60)	1.22 (0.87-1.70)	1.18 (0.93-1.51)	1.08 (0.85-1.37)
	Maximum (n=89)					

Abbreviations: HR=hazard ratio, O₃=ozone, NO₂=nitrogen dioxide, PM₁₀=particulate matter 10 microns or less in aerodynamic diameter, CO=carbon monoxide, SO₂=sulphur dioxide, TMS=Tele-Monitoring System. HR expressed per standard deviation increase in measured exposure. ^a n=42, ^b n=33, ^c n=55.

Figure Legends

Figure 1: Ozone and Nitrogen Dioxide Exposure and Risk of Acute Exacerbation. Mean levels, maximum levels and number of exceedances above standards for O₃ and NO₂ exposure over a 6 week period were associated with significantly increased risk for acute exacerbation of IPF. There was no association of PM₁₀, CO or SO₂ exposure with acute exacerbation risk. There were no exceedances above CO or SO₂ standards.

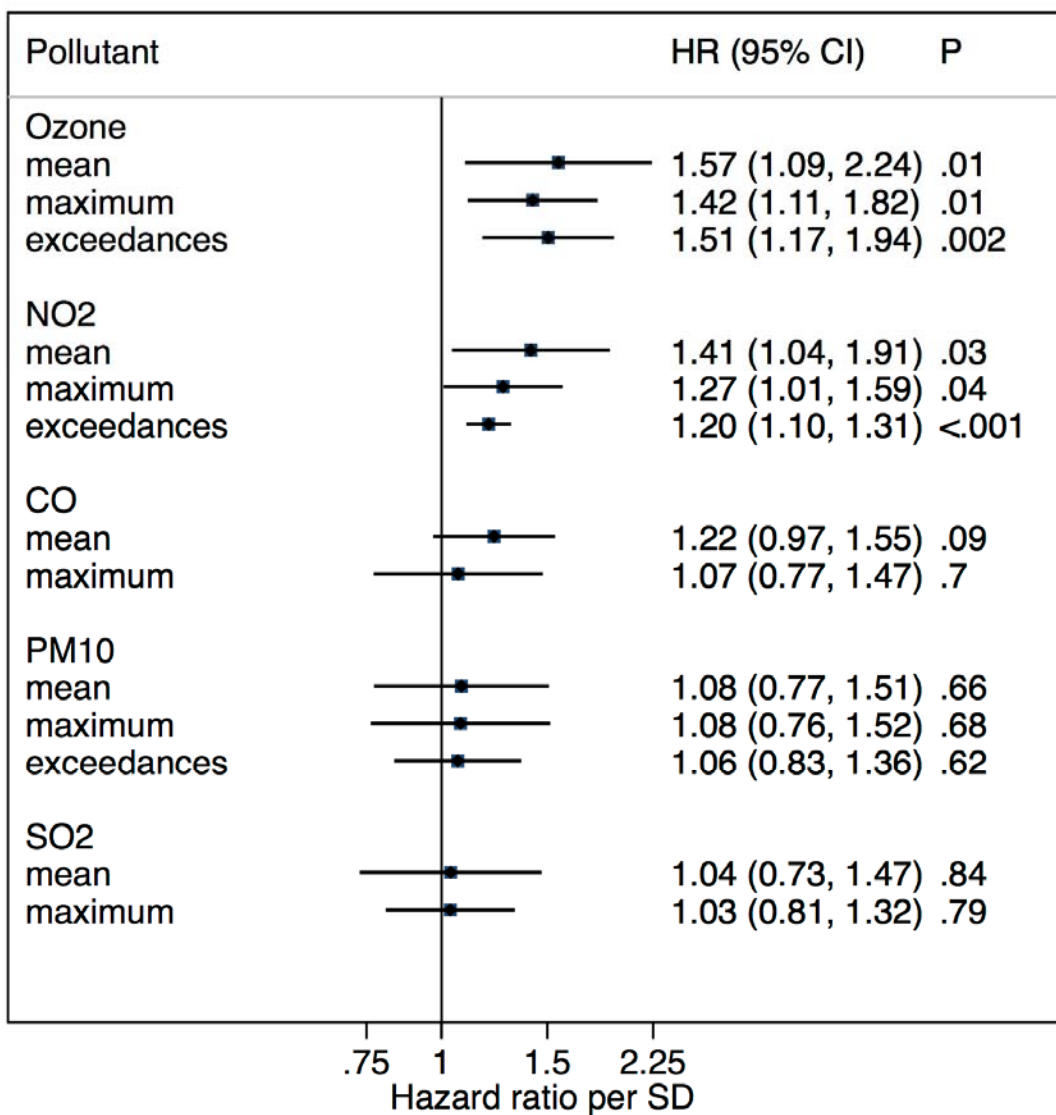
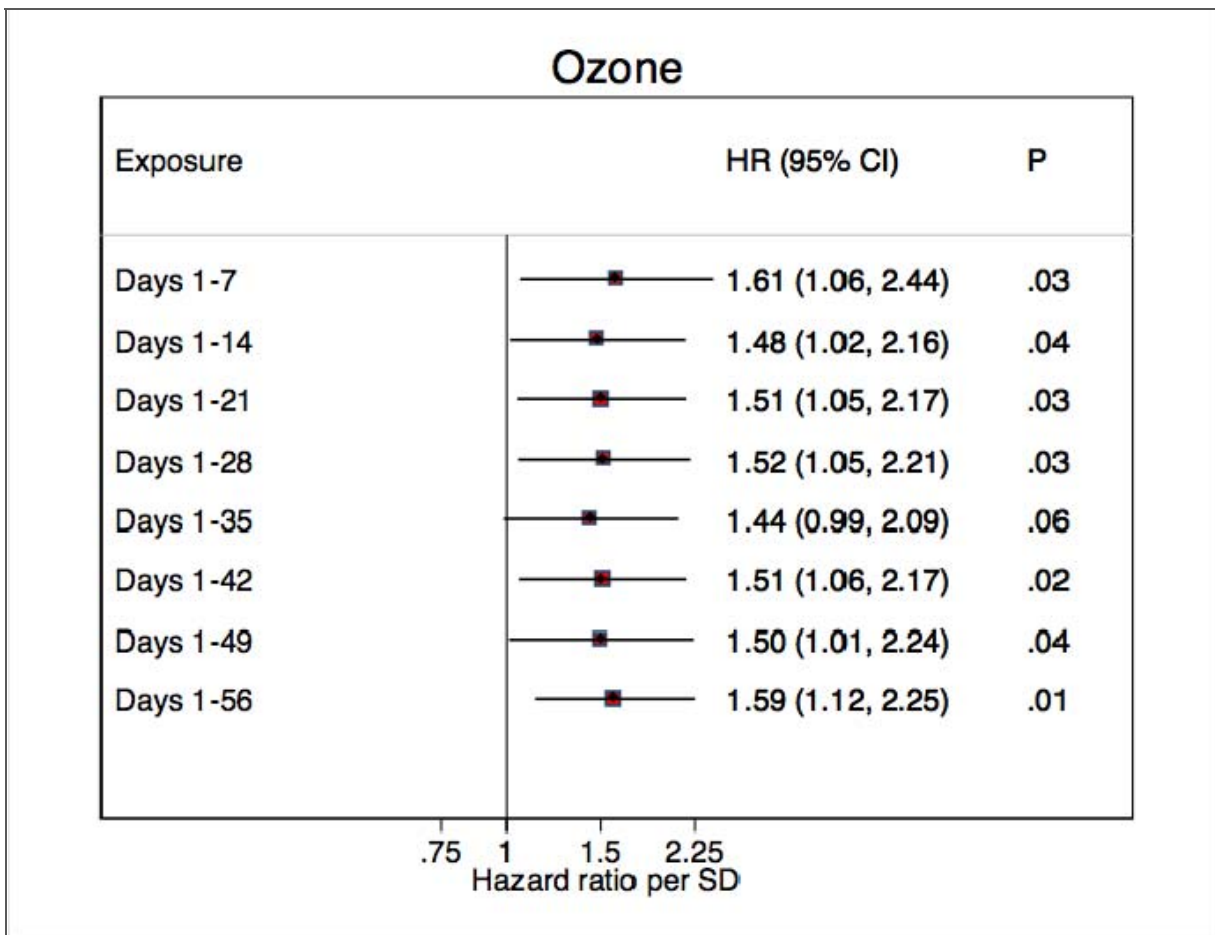


Figure 2: Secondary Analyses for Ozone and Nitrogen Dioxide Exposures and Risk of Acute

Exacerbation: (A) Sensitivity analyses of mean O₃ levels and (B) mean NO₂ levels show a consistent relationships with acute exacerbation across multiple cumulative exposure periods.

A)



B)

