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SUPPORTING INFORMATION

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DOI: 10.1111/all.13932

Food impactions in Eosinophilic esophagitis and acute exposures to fine particulate pollution

To the Editor,

Eosinophilic esophagitis (EoE) is emerging as the most common cause of esophageal food impactions in emergency visits.¹ Seasonal aeroallergens (ie, pollen) have been postulated to influence the presentation of EoE.² Pollution influences expression of TSLP (thymic stromal lymphopoietin), a pivotal EoE-related cytokine.³ We hypothesized that airborne particulate matter may result in excitation of inflammation and, thus, increase the risk for esophageal dysfunction in EoE.

We conducted a case-crossover analysis of Emergency Department (ED) visits among EoE patients in Utah to test the hypothesis that exposure to particulate matter with aerodynamic diameter ≤ 2.5 microns ($PM_{2.5}$) associates with exacerbations of EoE.

Our study was conducted in Utah in which 79% of the residents live in counties prone to wintertime pollution episodes (without pollen influence).⁴ The population was all persons coded for EoE via International Classification of Disease, 9th revision (ICD-9) code 530.13 who could be followed from January 2000 to May 2014 (the time period with robust pollution data). Medical data were obtained from Intermountain Healthcare and University of Utah Health; accounting for approximately 85% of all medical encounters in Utah. Medical record data were linked to residential ZIP code over time using the Utah Population Database.⁵ The ICD-9 code for EoE had been shown to predict esophageal eosinophilia based on chart review of medical records from this database.⁶

Emergency Department visits were the endpoint studied for disease exacerbations because they are connected temporally to

complications of disease (ie, food impactions). We identified the subset of EoE patients with an ED visit with any of the following ICD9 diagnosis or CPT procedure codes: chest pain or heartburn (ICD-9 786.50, 786.59, 787.1), dysphagia (ICD-9 787.20, 787.29), impaction (935.1), and upper gastrointestinal endoscopy (CPT 43215, 43235, 43239, 43247) between January 2000 and May 2014. We defined two outcomes of interest: (a) any of the codes listed above and (b) impaction, see Table 1. Impactions are severe and distinctive to EoE.

Daily air quality data were downloaded from the US Environmental Protection Agency (EPA).⁷ We obtained all available data for $PM_{2.5}$ in Utah in the defined period.

We used household ZIP code as proxy for the location of each person. We estimated $PM_{2.5}$ exposure for each person using the spatial interpolation method, kriging, which calculates a weighted average of $PM_{2.5}$ obtained from air pollution monitors in a region and distance from the ZIP code, giving greater weight to closer monitors.⁸ The kriging method performed better than using the closest monitor (data not shown). We selected $35 \mu\text{g}/\text{m}^3$ as the cut point for defining extreme air pollution because this is the EPA's National Ambient Air Quality Standard (NAAQS) for daily concentrations.⁹

We used a case-crossover design, which is becoming a standard method for researching the health impacts of air pollution. Case-crossover analysis controls for confounding because each case serves as its own control. This controls for variables that do not typically vary within a subject over the course of several weeks such as smoking, disease severity, diet, medications, and endoscopic therapy. We examined $PM_{2.5}$ concentrations during the 1-week period leading up to and including the date of the EoE event (hazard period) compared with the $PM_{2.5}$ concentrations during 1-week periods preceding and following the hazard period (2 control periods per event). Figure S1. Control periods both before and after the hazard period are included to avoid bias that would otherwise be introduced from seasonal and long-term trends in air pollution concentrations.

TABLE 1 Emergency events identified from 242 EoE cases. ED is Emergency Department

Description	Any ED visit	Impaction
# ED visits	242	145
% male	64	70
Median age (IQR) years	38 (28–52)	38 (26–50)

Abbreviation: IQR, interquartile range.

TABLE 2 Association of Emergency Department (ED) visits and high vs low PM_{2.5}

Type of ED visit	Sample size ^a	Odds ratio	95% CI	P-value	Median (MAD) PM _{2.5} (µg/m ³) of Hazard periods	Median (MAD) PM _{2.5} (µg/m ³) of control periods
Any ED	181	2.85	1.07-7.58	0.04	12.6 (5.3)	11.3 (4.5)
Impaction	108	5.52	1.35-22.5	0.02	12.8 (5.2)	10.3 (3.9)

Abbreviations: CI, confidence interval; MAD, median absolute deviation.

^aSample size indicates how many ED visits could be assigned PM_{2.5} data.

During winter in Utah, PM_{2.5} concentrations gradually build up over the course of several days at a rate of about 10 µg/m³/day. We chose a 1-week hazard period to allow a few days for the PM_{2.5} concentrations to build up and a few days for delayed reactions. If any of the days during the week-long hazard/control periods were above 35 µg/m³, that period was classified as high concentration. All analyses were conducted using SAS (Release 9.4; SAS Institute). We used conditional logistic regression models adjusted for ozone, nitrogen dioxide, and temperature.

242/4381 patients with a diagnosis of EoE had an ED visit with at least one ICD-9/CPT codes for esophageal symptoms as stated above. Table 1 shows the number of events as well as the age distribution of the EoE cases. Table 2 shows the results of the case-cross-over analysis of PM_{2.5} exposure and ED visits. Exposure to PM_{2.5} increased the odds of food impactions in EoE patients. The odds ratios increased in size as the outcomes increased in EoE specificity (OR = 2.85 for any ED visit to OR = 5.52 for impaction), although not statistically different.

Although all emergency visits coded for heartburn, chest pain, and dysphagia were associated with recent exposures to poor air, the significance increased when esophageal food impactions were analyzed separately, strengthening the argument that esophageal symptoms worsen with exposures to poor air quality.

In summary, we found a significant association for ED visits for chest pain, dysphagia, and food impaction and exposure to PM_{2.5} concentrations exceeding the NAAQS standard. The findings of this study suggest that high levels of PM_{2.5} might trigger EoE exacerbations via effects on TH2-mediated responses. Thymic stromal lymphopoietin (TSLP) expression, a pivotal EoE-related cytokine linking innate and Th2 adaptive immune disorders, is affected by ambient particulate matter and diesel exhaust particles. Additionally, high levels of PM_{2.5} exacerbate Th2-mediated responses. Thus, exacerbations of EoE from exposures to ambient pollution are physiologically plausible.

The study design and analysis methods used for this study were selected a priori to control for possible confounding by medication, dilation, or change in diet that may occur after first impaction which can affect risk of subsequent impactions. We confirmed our findings by isolating our analysis to esophageal impactions with consistently significant results.

In conclusion, we found that PM_{2.5} exposures appear to influence esophageal dysfunction in EoE. Current patients with EoE should be aware of pollution warnings and use strategies to reduce exposure to high air pollution.

ACKNOWLEDGMENTS

We would like to acknowledge the Utah Population Database, Intermountain Healthcare, University of Utah Healthcare, Heidi Hanson, Yuan Wan, Micky Daurelle, Vikrant Deshmukh, Kent Korgenski, Jacob Wilkes, and Kerry Rowe for making this project possible. We appreciate comments from Colleen Reid. The support and resources from the Center for High Performance Computing at the University of Utah are gratefully acknowledged. We acknowledge funding through a University of Utah seed grant from the Vice President of Research; the sponsor had no involvement in the collection, analysis, and interpretation of data, writing of this report, nor the decision to submit the article for publication. All authors approved the final version of the article.

CONFLICTS OF INTEREST

We acknowledge funding through a University of Utah seed grant from the Vice President of Research; the sponsor had no involvement in the collection, analysis, and interpretation of data, writing of this report, nor the decision to submit the article for publication. No authors have conflicts of interest.

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SUPPORTING INFORMATION

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DOI: 10.1111/all.13933

Development and validation of an Allergen Challenge Theater for grass and ragweed

Allergen challenge facilities are useful to test new allergy medications because pollen levels can be controlled, studies can be conducted outside the natural pollen season, and statistical significance can be obtained with fewer subjects. Fundamentally, the facility must maintain consistent allergen concentrations within tests (exposures ≥ 3 hours) as well as between tests.¹

The Ottawa Allergen Challenge Theater (ACT) (Figure S1) consists of four quadrants of theater seating, each having a dedicated allergen supply. This allows flexibility to run quadrants independently or simultaneously. In the present configuration, quadrants are run independently using different allergens. The objective of this work was to perform independent validation studies for Timothy-grass (*Phleum pratense*) and ragweed (*Ambrosia artemisiifolia*) (Greer) in the largest quadrant having a 40-person capacity (8 seats across, 5 rows deep). Future validations will be necessary for operating other zones, other allergens, and for running multiple zones simultaneously.

Pollen concentrations were measured by laser particle counters (LPC) (Model R5102, Lighthouse Worldwide Solutions, Inc). The output from the driving LPC was fed back into a programmable logic controller which adjusted the amount of pollen injected into the airflow in order to maintain the selected level in the ACT. LPC provide rapid

assessments of particle counts but do not discriminate between dust and pollen. Therefore, pollen counts were verified using impact samplers (IS) (GRIPS-99M, Aerobiology Research Laboratories), which capture pollen on the surface of two rotating rods. The rods were stained, and the pollen identified and counted using light microscopy.

Technical validation studies evaluated (a) the relationship between LPC counts and IS pollen counts, (b) stability of pollen levels, and (c) variability of pollen counts in the seating area.

The LPC-IS relationship for both pollens was linear over a wide range of concentrations: grass r^2 : 0.85 ragweed r^2 : 0.93, (Figure S3). Ragweed and grass concentrations were found to be stable over several hours, responsive to changes in the pollen setpoint (Figure 1B), and sufficient to induce symptoms. Multiple IS or LPC were placed within the seating area and demonstrated acceptable uniformity of pollen exposure (See Appendix S1 for details). These studies demonstrated that the ACT is able to generate reproducible pollen concentrations comparable to those seen in other facilities²⁻⁴ which are associated with the ability to induce ocular and nasal symptoms of appropriate intensity.

Clinical validation studies were performed to test reproducibility of the allergic response to grass and ragweed in participants meeting

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Feb. 1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28 (1)
March 1	2	3	4	5	6	7 ** (event time)
8	9	10	11	12	13	14 (2)
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	April 1	1	2	3

Supplemental Figure. Time frames used in case-crossover analysis with an example event (i.e. food impaction) on March 7**. The control periods are shown in grey while the hazard periods are shown in black. The end of each control period is denoted by a number in parentheses for one week hazard and control periods.

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