Understanding the association between ozone pollution, asthma hospitalizations, and IgE biomarker levels for adolescents in Los Angeles, CA

EH 530
Dr. Ebelt, Dr. Shi
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Group 2: Haoran (Raymond) Cheng, Thao Lam, Xiajie Lyu, Marisa Wong, and Lifan Yang

Group Member	Contribution
Haoran Cheng	Analytic Approach, Study Design
Thao Lam	Background and Motivation
Xiajie Lyu	Data Sources and Key Variables, Background
Marisa Wong	Abstract, Sources of Error and Other Challenges, Final Review
Lifan Yang	Study Design

Table of Contents

Abstract

The concern over air pollution continues to rise along with the onset of global climate change. One of the major sources of air pollution is ozone in the troposphere. Ozone does not naturally occur at the ground level, but it is the result of other gaseous mixtures in our atmosphere. The primary sources of ozone emissions include cars and industrial manufacturers. The presence of high ozone concentrations accompanies the hazards of extreme heat; thus, it is common to have dangerous levels of ozone on warm sunny days (Environmental Protection Agency, 2021). Los Angeles, California is known for its dense urban population and extreme weather (including drought, heat, and wildfires); as a result, Los Angeles, CA will serve as the location of interest where the source population will be selected.

Areas with increased air pollution have higher likelihoods of respiratory disease prevalence. One of the most commonly studied respiratory illnesses related to ozone exposure is childhood asthma. Children are a specific target for asthma due to their developing lungs that are vulnerable to damage at a young age. While this relationship is often investigated, it ignores the adolescent age group and their risk of the body's respiratory response to hazardous levels of ozone. The need for research on adolescents is crucial for further understanding how their lungs develop and how asthma symptoms affect their growth, education, and social interactions.

Our research team is interested in studying the association between ground-level ozone exposure and the immunoglobulin E (IgE) biomarker's response to this exposure through asthma related-hospitalizations in adolescents aged thirteen to eighteen years old residing in Los Angeles, CA. We will derive the cases in our sample population from Los Angeles based hospitals and analyze the corresponding emissions reported by the South Coast Air Quality Management District (SCAQMD). These cases will undergo a blood draw to assess their IgE

biomarker responses and compare their responses with randomly selected controls from the source population. Analytical regressions will be used to model the meaningful covariates in the relationship to estimate the true association between adolescent exposure to ozone and their IgE inflammatory response.

Background and Motivation

Asthma is a condition that affects the lungs in which breathing airways are inflamed, narrow, and swollen. This often leads to symptoms such as wheezing and coughing, leading to difficulty in breathing. While chronic in adults, asthma is very often found in children, whose lung developments can lead to heightened susceptibility to asthma symptoms. Effects of asthma in children include missed school days, emergency department visits, and even hospitalizations (Mayo Clinic, 2021). While children's hospitalizations due to asthma have declined within the past two decades, about 6 million children ages 0-17 years have asthma in the United States, with more than half of asthmatic children having had 1 or more asthma attacks (Centers for Disease Control and Prevention, 2018). These asthma attacks can become severe (occurring as often as every year) where 1 in 20 asthmatic children are hospitalized (CDC, 2018). While asthma's exact causes are unknown, children are at risk for asthma, especially those aged 5-17 years old, those exposed to tobacco, and those subject to air pollution (Johns Hopkins Medicine, n.d., a).

Age has been shown to be a chronic effect modifier for asthma-related hospitalizations. A study published in the Journal of Allergy and Clinical Immunology found that children aged 6-18 years consistently had the highest risk, with a 20% increased hospitalization rate for increased ozone levels (Silverman and Ito, 2010). Studies on asthma-related visits to the emergency department found that across age groups, school-age children specifically aged 5-18 years old show the strongest association to air pollutants (Alhanti et al., 2015). During our literature

search, we came across many studies focused on children from 0-18 years old, especially younger children; however, we found a lack of studies concerning the adolescent age group, ages 13-18 years (Johns Hopkins Medicine, n.d., b). The adolescent body is still developing, usually past the age of 18, thus the effect on their respiratory system and time spent in hospitals could detrimentally impact their physical, mental, and emotional growth. With the understudied nature and underdevelopment of adolescents, there is urgency to study the adolescent ozone exposure and their body's response.

Air pollution has been found to be a significant factor contributing to children's asthmatic symptoms, even in regions with higher quality healthcare. Air pollution substances of interest include fine particulate matter ($PM_{2.5}$), carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone. While ozone found in higher atmospheres shields people from the UV rays, ground-level ozone where respiratory exposure occurs can become quite harmful, especially for children. Not only can ozone increase airway response to inhaled allergens, it can also increase airway hyper-responsiveness. On days of higher ozone levels in particular, asthmatic people tend to experience symptoms such as worsened airway inflammation, increased respiratory symptoms, increased medication usage, and hospitalizations in children (EPA, n.d., Mortimer et al., 2002). In a study focused on astmatic children in inner cities, high ozone exposures were associated with lower expiratory flow rate on mornings for days after (Mortimer et al., 2002). These reductions in morning respiratory functions and heightened symptoms are also symptoms of worsening asthma conditions.

Our literature review showed a large quantity of results on children's asthma-linked hospitalizations specifically located in New York and New York City, an area with high population density and vehicle emissions (Lin et al., 2008). Southern California shares such

similar anthropogenic air pollution factors with an included air pollution effect of extreme heat, and studies conducted in Southern California have shown ozone levels are particularly pertinent on increasing risks of hospitalizations in asthmatic children (Moore et al., 2008, Schwarz et al., 2021). Los Angeles, the most densely populated city in Southern California, was chosen as our study's U.S. city of interest. We also hope to understand more about ozone exposure specifically in Los Angeles, as studies completed in the city have cited mixed rates in asthma-linked hospitalization associated with ozone exposures (Delamater et al., 2012). Hence, we hope to shed more light on the biomarkers of ozone exposure and asthma-linked hospitalizations in adolescents specifically in Los Angeles.

Immunoglobulin E (IgE), which is an antibody produced by the immune system, will serve as our study's biomarker for analysis. IgE mediates Type 1 hypersensitivity reactions and plays a key role in the pathogenesis of allergic asthma (Wu & Zarrin, 2014). These antibodies travel to cells that release chemicals and cytokines that cause allergic reactions. It increases allergen sensitivity, and the released cytokines cause thickening of the bronchial walls, exacerbating symptoms of asthma. High serum IgE is observed in almost all patients with asthma. Serum levels of IgE rise rapidly after the onset of asthma and have a half-life of only 2-3 days in the blood. IgE has unique properties in that it both induces extremely rapid pathological responses and acts as a highly sensitive immunological amplifier. These unparalleled properties of IgE make this biomarker pertinent to our study.

Study Design

Our research is targeting adolescents aged 13 to 18 in Los Angeles, U.S., for a 10-year period from 2022 to 2032. We will mainly collaborate with the hospital system in Los Angeles to recruit asthma patients by accessing electronic health records for our matched case control study.

Patients admitted to the hospital due to an acute asthma attack will be invited to participate in our study, where their blood samples will be drawn to assess the IgE as biomarker to understand adolescent ozone exposure. A matched control participant residing in Los Angeles, CA will be selected and matched to a case based on a shared residential zip code. All blood drawn from cases and controls will then be sent to an approved laboratory that will analyze the IgE serum levels and provide the data back to our research team. We aim to recruit 500 participants in each asthmatic status group (controls being healthy non-asthmatic and cases being asthmatics with a hospital-admitted attack) for a total of 1000 participants.

For our exposure of interest, we will collect daily local ozone concentration and as well as whether a PSI (pollutant standard index) warning is issued provided by the local air quality agency. Daily meteorological conditions will also be collected from a national institution's public records, including temperature, relative humidity, and wind speed.

Personal demographic information (age, residential area, parent education, parent income) and medical history (related to respiratory diseases or any underlying medical conditions) will be collected from all study participants at the time of entry into the study. This will provide our research group the opportunity to determine if these factors act as confounders or effect measure modifiers on the relationship between adolescent exposure to ozone and their IgE biomarker response. We will request that all participants also complete an annual questionnaire concerning their outdoor activity and the amount of time they spent outdoors each day for the last year to improve our understanding of the participant's outdoor ozone exposure.

Lastly, to estimate the true relationship between adolescent ozone exposure and IgE biomarker response, we will analyze the covariates of interest by utilizing different regression techniques based on the characteristic of our outcome of interest. These models will include

covariates that create a meaningful difference on the exposure to outcome relationship, controlled confounders, and interaction terms of interest. Figure 1 depicts the intended flow of our study with data collection points and the ultimate analysis of our data.

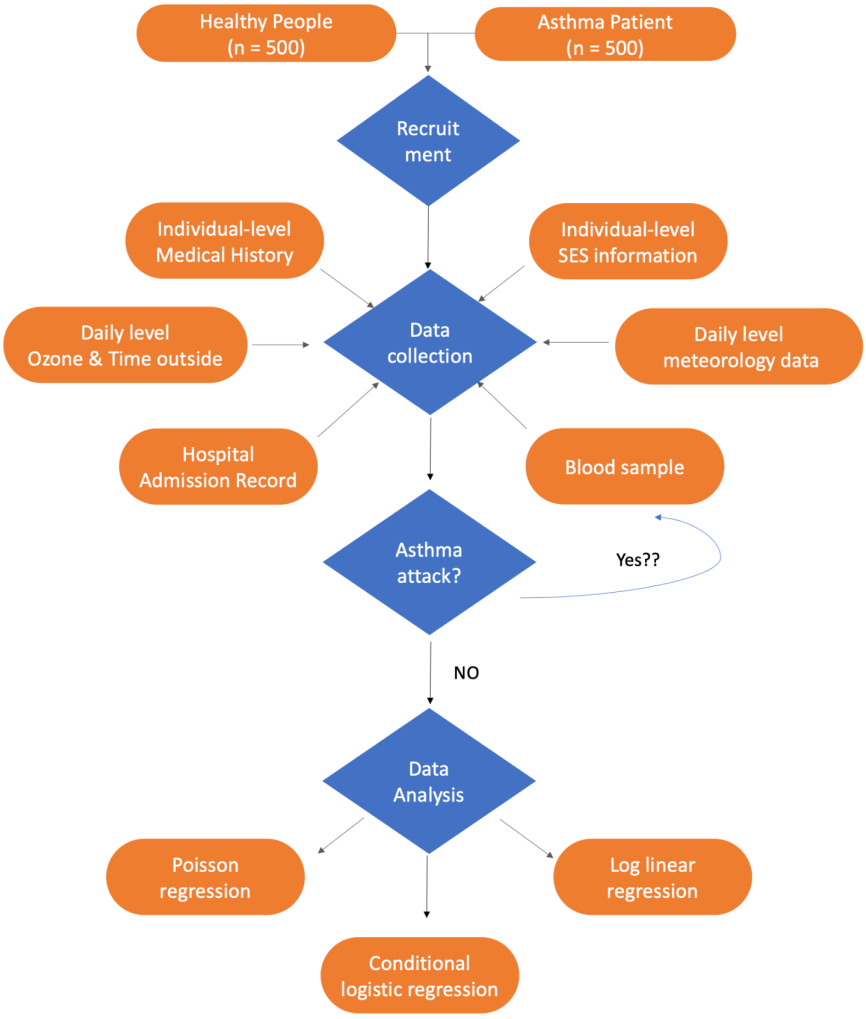

Figure 1. Flowchart analyzing the association between Adolescent Ozone Exposure and IgE Biomarker Response.

Data Sources and Key Variables

The data collected from the participants of our study for covariate information and health outcome data include general demographic information from an enrollment questionnaire,

medical history, blood samples and the corresponding IgE serum levels, and questionnaire information on time spent outdoors. Health outcomes will be based on the latest revision of the International Classification of Diseases (ICD-10) clinical diagnosis codes to identify patients admitted to the hospital for asthma. Other data on exposure levels and environmental factors are sourced from organizations and agencies outside of our research team's design. From our foundational literature review and our research team's underlying assumptions, two directed acyclic graphs (DAGs) were created to ensure information on all possible covariates were collected and assessed in our study (Figures 2 and 3).

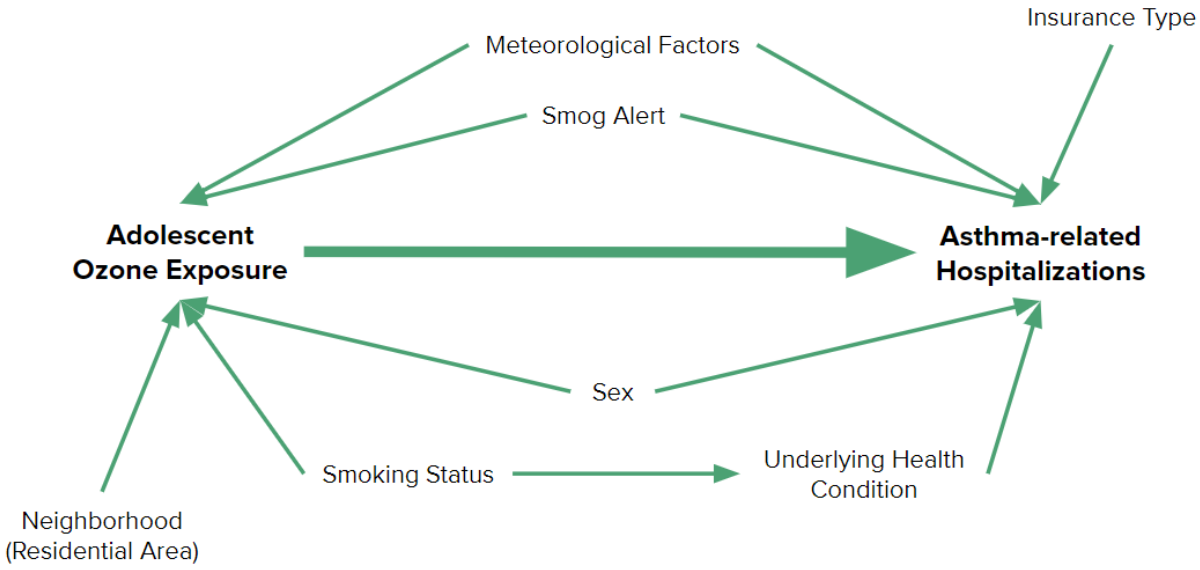

Figure 2. DAG of the covariates' relationships on Adolescent Ozone Exposure and Asthma-Related Hospitalizations.

The regional agency that provides air quality forecasts and issues smog alerts for Southern California is the South Coast Air Quality Management District (SCAQMD). The SCAQMD includes all of Orange County and the most populated portions of Los Angeles, Riverside, and San Bernardino counties. We will utilize source receptor areas (SRAs) within the Los Angeles city limits to provide daily maximum 8-hour average ozone concentration data.

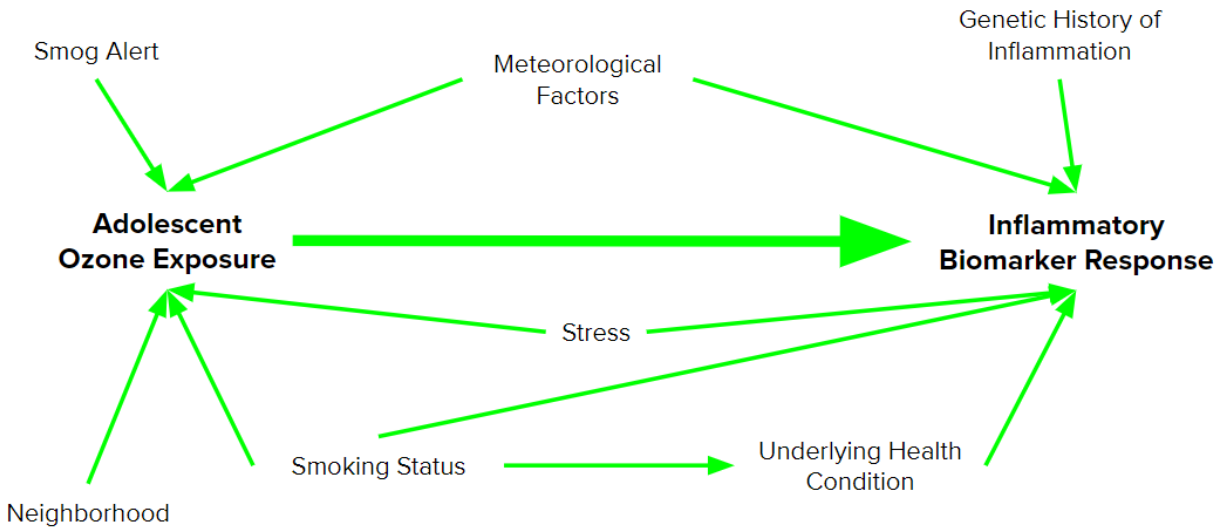

Figure 3. DAG of the covariates' relationships on Adolescent Ozone Exposure and Inflammatory Biomarker Response.

Recent evidence suggests that attendance at several outdoor facilities in Southern California decreases when smog alerts are issued (Neidell, 2009). Since ozone can degrade swiftly and allows for rapid clearance of the pollutant, health related notifications were established to warn the public about potential harms (Chang et al., 2000). Due to the rapid onset of symptoms associated with ozone exposure, the Pollutant Standards Index (PSI) was created to notify the public about projected air quality conditions and smog alerts, with the intention of minimizing outdoor ozone for the most vulnerable populations. To increase public awareness, a Stage 1 alert is activated when the PSI exceeds 200. At this point, sensitive populations such as the elderly, children, and people with respiratory illnesses are advised to stay indoors and reduce physical activity. Data on PSI alerts will be documented along with the date of release.

Due to the fact that weather is related to ozone levels and can have a direct impact on both exposure and health outcomes, we accounted for a variety of meteorological factors acquired from weather data including daily maximum and minimum temperature, precipitation, maximum relative humidity, sun cover, resultant wind speed, CO, and NO_2 can be obtained from National Center For Environmental Information (NCEI).

Analytic Approach

Various regression techniques will be utilized based on our different health endpoints and outcomes. All analysis will be conducted in R-Studio Cloud dplyr, tidyverse, and janitor packages for data cleaning, base R package for generalized linear model (glm) function of poisson regression and logistic regression, and MASS package for log linear regression (Batra et al., 2021).

A developed Poisson Regression will model the number of all hospital visits due to acute asthma attacks in the Los Angeles area, adjusting for ozone concentration, PSI, and meteorological conditions. The specific model is shown as follows:

$$Y_i = e^{(\beta_0+\beta_1*Ozone+\beta_2*PSI+\beta_3*Met)}$$

Y_i represents the number of daily asthma-related hospital admission in the Los Angeles city limits, Ozone represents the daily ozone concentration, PSI is represented as a binary variable on whether a PSI was issued or not, and Met refers to the group of associated meteorological covariates. We used an a priori method based on existing literature and our underlying assumptions to choose the most relevant covariates for this model.

A conditional logistic regression will model whether a confirmed case participant will develop an acute asthma attack on certain days with ozone concentration acting as the exposure, controlling for meteorological factors and issuance of PSI. The conditional logistic model is as follows:

$$\log\left(\frac{Y=1}{Y=0}\right) = \beta_0 + \beta_1 * Ozone + \beta_2 * PSI + \beta_3 * Met$$

The left hand-side of the equation is whether a confirmed asthma patient has a hospital admitted attack on a given day, ozone represents the daily ozone concentration, PSI is a binary variable indicating whether a PSI was issued, and Met represents associated meteorological covariates.

It is known that there is a lag effect between ozone exposure and asthma-related hospital admissions. Therefore, for our sensitivity analysis, we included different lag days (1, 2, 3, and 7 days post exposure) to see how this would affect the association between exposure and outcome. In addition, given the large number of covariates in our model, we are interested in using k-means clustering and principal component analysis to perform dimension reduction and reduce the number of covariates to deal with potential multicollinearity issues.

We use a log linear model to see the association between IgE biomarker levels between exposure ozone and other covariates. The log linear model is as follows:

$$\log(I_{IgE}) = \beta_0 + \beta_1 * Group + \beta_2 * Ozone + \beta_3 * Outdoor + \beta_4 * Ozone * Outdoor + \beta_5 * PSI + \beta_6 * Met + \beta_7 * SES + \beta_8 * MH$$

The left hand side of the equation is the log-transformed IgE concentration, group represents a categorical variable denoting whether a participant is a case or control, ozone is daily ozone concentration, outdoors is the continuous variable of time spent outdoors, PSI represents the issuance of PSI, SES are the grouped covariates representing socioeconomic status, Met represents the meteorological covariates, and MH includes covariates pertaining to medical history. Since we believe that time spent outdoors will have a statistically significant effect on ozone exposure, we included an interaction term between these two variables following β_4.

For sensitivity analysis, we are interested in flipping the position of log transformed IgE intensity and participant group and conducting a logistic regression to see if IgE intensity, ozone exposure, and other covariates can be an accurate predictor of health status of healthy controls or asthma admitted cases.

Sources of Error and Other Challenges

With the nature of this study's design, the study relies heavily on data acquired by sources outside of the principal investigator's control. A majority of the data collection that will

be used for analysis is provided by data from other agencies or organizations. A major source of information bias is plausible with the data provided from the SCAQMD through their air pollution monitors, from the NECI Sources, from the contracted laboratory returning the biomarker analysis, and from the hospital admission histories. Without complete control of data collection, our research team must entrust the accuracy of these measurements (through proper calibration of their respective machines) and information (through collection of accurate information of study participants' hospital admission) to the organizations who collect them.

Although our research group tried to identify all of the possible covariates that could affect the relationship between the adolescent ozone exposure and the asthma hospitalizations in a DAG, there is a possibility some variables were not considered in our assessment. Our primary literature search identified five broader covariate groups, in which factors that appear to be confounders were identified and the other factors seem to be only influencing either the exposure or the outcome. With the limited time and resources used to delve into scientific literature pertaining to potential covariates, there are bound to be other variables that were excluded due to a lack of a meaningful difference on the association and the limitations of our research group's capacity to conduct a vast literature review.

With the prospective 10 year study, we expect our participants to fall to selection bias primarily in loss to follow-up. Ten years during your adolescents is extremely impactful, and many things in our participants' lives can change during that time. Decisions to move out of Los Angeles, health conditions may miraculously improve, and the overall time, burden, and invasiveness of this study may no longer be attractive to our study participants. These factors will contribute to the selection bias of our study, even with control through the intended right-sided censoring of the cases that never experience the outcome of interest. To further adjust

for this bias, our team will research selection probabilities of both cases and controls and apply these probabilities to our analysis.

The last bias that our study might generate is recall bias. With the inclusion of a survey questionnaire documenting how much time is spent outside, many individuals may be unable to provide an accurate account of their average daily time outside more than one month ago. Recall bias is introduced when someone who is diagnosed with asthma has an improved recall of their time outside versus someone who is not as affected by ozone exposure.

In contrast to systematic error, we foresee external validity of our study to be a major challenge in applying our findings to other locations of interest. With our study heavily focusing on Los Angeles, CA, and the use of the SCAQMD's data, our study's results will not be applicable to other areas within the United States or internationally. The generalizability of this study is limited by the distinct source population and location. Los Angeles has a unique climate compared to the rest of the United States, and with the effects of climate change, the concentration of air pollutants in Los Angeles continues to rise. Los Angeles also houses some of the highest concentrations of residents within its city limits compared to other, more rural US locations. These unique factors of Los Angeles, its environment, and the health of those living in this state provide extreme differentiation from the experience of any other state or country's environment.

Our last possible challenge involves the collaboration with the SCAQMD and associated Los Angeles hospitals. Although it is unlikely that any issues arise with our collaboration with SCAQMD with the publicly available data, we see potential obstacles with delayed or non-responses form the agency regarding questions we might ask regarding data quality or missing data. The delay in retrieving answers from the local government has the ability to stall

our study from completion or serve as a largely unanswered or unexplained detail. On the other hand, we expect more challenges when working with the hospital administration on patient admission history. In California, many of the hospital and healthcare systems only allow the patient, patient representative, healthcare provider seeking records for patient treatment purposes, or a patient's attorney to access these records (Medical Board of California, 2022). Given that this is private information, we would need to work with the Emory Institutional Review Board (IRB) to gain approval for this study. Even with IRB approval, we could potentially run into further issues with confidentiality due to the stringent laws of patient protection. Ultimately, without the cooperation of the IRB and participating hospitals, this section of our study would be impossible.

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