Air Pollution and Asthma Outcomes: Using an asthma registry and electronic medical records to compose environmental health studies

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Asthma is a heterogeneous disease with variable severity and clinical presentation that may be exacerbated by environmental factors, such as air pollution.[1-5] Allegheny County PA estimated asthma rates are higher than the national average, with estimates for adults at 10%, [6] and children 11%.[7] We used a combination of electronic medical records (EMR) and data from an established asthma registry to study associations of asthma control and severity with air pollution.

The objective of these studies was to examine the associations between asthma severity and control of air pollution and socioeconomic factors. Our primary hypothesis states "Asthma control and severity will be worsened by exposure to air pollutants and factors associated with environmental justice areas." The aim of the current study was, therefore, (i) to establish the prevalence of asthma exacerbations concerning acute pollutant exposures within patients who reside in Allegheny County (ii) to determine whether specific socio-demographic variables and chronic air pollution events are associated with poor asthma control and severity within patients from an asthma research registry; and (iii) to examine the association of asthma and acute air pollution exposure after a factory fire that occurred near residential homes.

We devised epidemiological studies that used descriptive and inferential statistics comparing odds ratios and generalized linear regression models to examine the relationships between variables of interest in acute and chronic air pollution exposure and EJ factors.

Strengths of this research reveal: (i) an association between O_3 exposure in children and NO_2 and CO exposure in adults with asthma-related ED visits within the greater Pittsburgh area;

(ii) Severe asthma patients living in areas with the highest NO_2 exposure had increased odds of uncontrolled asthma (not observed in milder patients), and disease duration was associated with uncontrolled asthma for patients living in EJ areas; and (iii) a novel association between acute real-world exposures to increased SO_2 and worsened asthma control in a vulnerable population living close to the source of pollution.

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1.0 Introduction

1.1 Asthma Prevalence within the United States

Asthma is a complex disease with variable severity and clinical presentation, which may be exacerbated by environmental factors, such as air pollution. [1-4] In 2016-2018, approximately 8% of The U.S population reported a current diagnosis of asthma. The highest rates were found to be within the country's Northeast region. Within Pennsylvania (PA), larger metropolitan areas tend to have the highest rates of asthma when compared to rural areas.[5] Overall, Allegheny County, PA, estimated asthma rates are higher than the national average, with estimates for adults at 10%,[6] and children at 11%.[7] However, regions of Allegheny county, especially in schools, appear to have much higher rates[8]. The prevalence of asthma varies significantly by racial and ethnic minority groups, region, and socioeconomic status (SES).[9] The underlying contributors to such variation may be examined through a combination of factors such as biological, sociocultural, and the built environment.[10,11]

1.1.1 Severe and Uncontrolled Asthma

Within the U.S, roughly 5-10% of patients diagnosed with asthma are estimated to suffer from severe and uncontrolled asthma.[12-14] People with severe and/or uncontrolled asthma may experience poorer quality of life and face additional burdens in managing and treating their disease than their less severe and well-controlled counterparts. Asthma prevalence may readily be determined through local, state, and federal surveillance programs. However, establishing accurate

rates of severe asthma may be more challenging due to the heterogeneous nature of severe disease and the difficulty diagnosing severe asthma. Well-defined scientific studies are needed to determine the prevalence of different subtypes of severe asthma. Insightful data could come from implementing longitudinal survey methodologies using interactive asthma registries to capture cumulative impacts of environmental exposures alongside disease progression.

1.2 Challenges in the Treatment of Asthma

1.2.1 Substandard Provider Care

The initial diagnosis and even long-term treatment of asthma may often come from a primary care provider (PCP). Not everyone diagnosed with asthma is referred to or receives care from a specialist. The treatment course can be suboptimal, and even an accurate diagnosis can be in question. Difficult or poorly controlled asthma may arise from suboptimal treatment, adherence to treatment, or underlying biology, making the disease more refractory to standard therapy, which may contribute to increased health care utilization and overall costs. Exacerbation-prone asthma is not always related to severe asthma[15] Even patients with what was thought to be less severe asthma may face an increased risk of exacerbation or death. Thus, appropriate treatment regimens are imperative to improve the quality of life for asthma patients. However, determine which patients are undertreated vs. those who are well treated and yet remain poorly controlled.

Asthma morbidity and mortality have been associated with inappropriate prescribing of asthma treatments.[16] To improve these prescribing practices and outcomes, the U.S. National Asthma Education and Prevention Program (NAEPP) was developed.[17] Recommendations from

the NAEPP and similar entities such as The Global Initiative for Asthma (GINA)[18] periodically gather evidence from current studies and may update treatment recommendations accordingly. In 2020, the NAEPP and GINA released new guidance on treating mild asthma. Even those with mild persistent asthma still can be at risk for severe exacerbations, with most guidelines recommending treatment with low dose inhaled corticosteroid (ICS).[19] Furthermore, the development of targeted humanized monoclonal antibodies, typically to elements of Type-2 (IL-4, 5, and -13), has enabled precision medicine, which has revolutionized patient care, particularly for the most severe asthma, but at the cost of costly therapy. Implementation of practices promoted in guidelines is often less than adequate, leaving many patients still poorly treated for their asthma severity and control.[20] These guidelines should not be considered the standard of care for all patients and cannot be applied to all patients equivalently.[21] Rather, a multidimensional approach that provides an appropriate asthma diagnosis determines severity, optimizes treatment, and considers social and environmental factors unique to the patient is imperative.[22]

1.2.2 Social-Cultural Factors that may Influence Asthma Diagnosis and Treatment

Beyond the clinical arena, patients with asthma face many challenges controlling and treating their asthma. Sociocultural factors may present barriers amongst different populations with asthma.[23] In many underprivileged communities, people with asthma often utilize their local hospitals for emergency department (ED) care because they do not have the resources to seek treatment from a physician.[24] Patients who are socio-economically challenged may struggle to adhere to their treatment plan, mainly if the medication regimen is complex and very often expensive (Combination inhalers still commonly cost 50-300 dollars per inhaler). These challenges may occur due to barriers or individual factors, including lack of transportation or

childcare, limited health literacy, or personal health beliefs.[25-27] Inability to adhere for whatever reason may lead to significant health consequences, especially when available therapies could effectively treat their illness.[28]

1.2.3 Environmental Factors (allergens, viruses, and pollution)

In addition to physician awareness of socioeconomic barriers, the built environment in which asthma patients live may present additional challenges. Both patients and physicians need to consider environmental factors that may exacerbate asthma. Patients with asthma tend to be more sensitive to symptoms from poor air quality than healthy populations[1]. Understanding these factors is crucial in helping to devise a successful treatment regimen for patients.

Environmental factors that exacerbate asthma include allergens, respiratory viruses, and air pollution.[29-31] Both indoor and outdoor air pollution aggravate asthma. Particulate matter, like (PM) <2.5 $\mu g/m^3$ is inhaled through the air and may serve as a transport mechanism for a virus or allergen deep into the lower lung, thus augmenting asthma symptomology. Patient and clinician awareness of the triggers present in the patient's home and work environment can lead to better management of their disease and a better quality of life for asthma patients.

1.3 Air Pollution

According to the World Health Organization (WHO), air pollution is the leading cause of death globally. It is also "one of the greatest environmental risks to our health".[32,33] Air pollution is defined by abnormally high levels in composite mixtures of particulate matter of various sizes

and various gasses in the atmosphere produced by industrial, commercial, and individual activities.[34,35]

1.3.1 Types of Air Pollution

Primary pollutants such as nitrogen oxides (NOx), carbon monoxide (CO), Sulfur oxides (SOx), and particulate matter (PM) are those directly emitted into the atmosphere. They do not need to react biochemically with the atmosphere to form. Secondary pollutants such as ozone (O_3), nitrogen dioxide (NO_2), NOx, and PM must react with the atmosphere to form (note some pollutants may be "primary" and "secondary"). Lastly, gaseous chemical pollution such as benzene, hydrogen chloride, and dioxin pose risks to our health and may adversely affect lung health. These types of exposures have been associated with occupational asthma.[36] Air pollutants designated as both "primary" and "secondary" have been related to asthma-related environmental health studies. The enactment of the Clean Air Act of 1970 (1970 CA) led to the designation of "criteria air pollutants" (O_3, PM, CO, Lead, SO_2, and NO_2) to be regulated at the federal level by the Environmental Protection Agency (EPA). These pollutants vary regionally and hyper-locally. Allegheny County is an ideal location to study air pollution and health effects because areas within the county are routinely designated as "non-attainment" zones, meaning they exceeded the EPA thresholds determined to be "safe" for human populations. Since 2015, Allegheny County has been designated "non-attainment" for 8-hour O_3, SO_2, and $PM_{2.5}$.[37] The Monongahela Valley (Mon Valley), located in southern Allegheny County, experiences a disproportionate burden from $PM_{2.5}$ and SO_2 related to emissions from coke and steel industries in that region.

1.3.2 Exposure Data and Policy; Implications to Human Health

The WHO recently made a historic move by reducing the recommended exposure threshold of nitrogen dioxide (NO_2) to public health. This change was instituted based on the culmination of the most recent literature supporting adverse health outcomes involving air pollution. The hope is that countries worldwide follow suit and lower their thresholds acceptable for population levels. Some of the most informative literature involving public and environmental health have come from measuring responses in human health outcomes alongside extreme disruptions to ambient air quality. For example, the Landmark Utah study reported a decrease in respiratory events when a steel mill was temporarily shut down.

Conversely, an increase in adverse respiratory events when steel production resumed.[38] Another informative study was derived from the pollution mitigation efforts during the 2008 Olympics in Beijing, China. Researchers measured clinical and biological data in a small cohort of participants during the Olympics compared to before and after. They found biomarkers indicative of oxidative stress tracked with changing ambient air pollutants.[39] More recently, the shutdown events related to the current covid-19 pandemic have improved our knowledge by quantifying "pre" and "post" shutdown events that impacted air quality levels[40,41], and health outcomes[42]. Environmental impact data from the covid-19 pandemic reveal how important policymaking is to help protect human health.

1.4 Pathogenesis of Asthma and Air Pollution

The heterogeneous nature of asthma involves various inflammatory cell types, which may differ by subtype of asthma. Historically asthma was thought to present two core phenotypes, atopic and non-atopic. However, advancements in research have led to an increased understanding aided by identifying distinct asthma phenotypes.[43] Airway infiltration of white blood cells such as eosinophils or neutrophils induces a cascade of immunomodulatory cytokines derived from T helper cells such as interleukins (IL) -4, IL-5, and IL-13.[44] When the lungs are infiltrated by granulocytic cells, in particular eosinophils, their products cause the airways to constrict, due to contraction of the airway muscle. Mucus build-up further disrupts gas exchange within the lungs and leads to poor asthma symptomology.

1.4.1 Air Quality and Asthma

Most environmental pollution-related epidemiologic studies of asthma have focused on asthma control, often addressing the relationship of air quality to emergency department visits or hospitalizations. These studies often lack context, as these are population-based studies instead of individualized data. In these instances, little is understood regarding the individual factors that may modify a person's response to pollutants. The literature is limited on the relationship between asthma severity and acute and chronic air pollution effects in adults with asthma. The primary outcome is asthma control, often only measured by ED visits. Our attempt to study control and severity together is a strength of this dissertation work. Chronic and acute exposures have been associated with adverse lung function and poor asthma symptomology.[45-47] Many studies have reported more inferior lung function in children,[48-51] fewer exist for adults[52]. Furthermore, the

mechanisms involving air pollution-induced exacerbations remain poorly defined. Depending on the underlying cause, the pathologic mechanisms could vary significantly. Damage to the airway epithelium may induce oxidative stress and has been shown to worsen asthma during exacerbations potentially attributable to air pollution.[53]

Epigenetics allows us to map gene-environment interactions and paves the way for future studies to examine potential mechanistic pathways that air pollutants could activate. This methodology will enable us to link air pollutants to worsened asthma through alterations in DNA methylation, leading to increased production of pro-inflammatory cytokines within the airway.[46] Likewise, air pollution exposure has been associated with methylation of immunoregulatory genes and protein expression in associated immune cell types.[54] With the advancement in machine learning, which aids in "big data" analytics, newly defined and characterized asthma subtypes could emerge.[55]

1.5 Environmental Justice and Asthma

1.5.1 Environmental Justice

Environmental justice (EJ) is an ideology that began in the early 1980s in the US. EJ is the idea that all people in all communities (regardless of race and ethnicity) have a human right to live in a safe and healthy environment. An environment free from poor water and air quality and free of contamination from sanitation and industrial processes.[56] Furthermore, EJ embraces the idea that all communities should have equal environmental protection under U.S. law. Robert Bullard, known as the "father of environmental justice" for his efforts in the 1970s, first reported that the

burden of pollution disproportionately affects minority communities.[57] Both lower income and communities of color tend to be disproportionally impacted by environmental factors associated with adverse health outcomes.[10] While elements of race and environmentalism are indeed intertwined, environmental justice goes beyond just race.

Climate change is an example of an existential threat to humanity and, in my opinion, the most significant threat currently facing public health. Climate change does not consider socioeconomic differences between neighborhoods and regions; instead, extreme weather events linked to climate change are causing drought, extreme heatwaves, damaging habitats, and influencing human migration patterns.[58] The migration of people because of climate change will cause added pressure on resources in communities already managing limited resources. The earth's carrying capacity (resources available from the world to support living organisms) is reached earlier each year. This means many communities worldwide lack adequate food, water, and resources. Climate change disproportionately impacts communities, which is environmental injustice from a global perspective. According to the WHO, "Disparities in air pollution exposure are increasing worldwide, particularly as low- and middle-income countries are experiencing growing levels of air pollution because of large-scale urbanization and economic development that has largely relied on the burning of fossil fuels."[59]

1.5.2 Disproportionate Burden of Asthma and Environmental Justice Factors

Because EJ areas often include impoverished and minority populations, we should examine health outcomes from various perspectives. The multitude of confounding factors from neighborhood impacts on health extends beyond just environmental pollution. For example,

exposure to community violence and poor housing stock has been linked to increased use of rescue medications, activity limitation, and increased asthma-related ED visits.[23,60]

There are significant differences in asthma outcomes when comparing racial and ethnic groups. Interestingly, studies suggest Black asthmatic patients have increased eosinophilic related inflammation within the airway compared to white patients.[11] However, there were no data linking these patients to their environmental location. Through the lens of air pollution specifically, a 2014 study examined the inequality of ambient NO_2 air pollution exposure between White and Nonwhite communities throughout the U.S..[61] This study found Nonwhites are on average exposed to 38% more NO_2 than Whites. These studies suggest underlying mechanistic differences based on race may exist.

1.5.3 Geographical Designation of Environmental Justice Tract

States are broken down into counties, and counties can be reduced to census tracts. These may be reduced to block groups and blocks (the population decreases with each classification). A census tract has an average population size of 4,000 people per tract.[62] There is no universal definition for what variables should be considered to define an EJ tract. Factors included in the definition vary significantly across the US. The Pennsylvania Department of Environmental Protection (PADEP) defines an EJ census tract based on population data (> 20% poverty and/or > 30% non-white minority)[63]. Notably, a recent study reported impoverished and minorities are most populated in areas with the highest NO_2 and BC.[64] This is an unfortunate definition. As we learned above, other social determinants of health (SDOH) may need to be considered. Within Allegheny County, the geographic focus for this dissertation work, studies have found asthma outcomes in communities of color are worse overall than in the county. At least, we have a reason

for optimism, as asthma outcomes within communities of color have shown improvement over recent years.[65] Despite this improvement, researchers need to proactively engage research participants from diverse communities to help unravel why such disparities exist.

1.6 From Population to Patient-Related Data for use in Environmental Studies (EMR, Surveys, and Registries)

1.6.1 Electronic Medical Records (EMR)

EMRs have improved patient care overtime[66], streamlining information, making it readily available to clinicians, and allowing greater access to research. The availability of EMRs has changed how clinicians and researchers share and communicate patient outcomes. EMR records typically contain basic demographic information and "clinical only" data such as patient diagnosis, physician-ordered test results, and patient care plans. Furthermore, although population geocoding may be available, EMR data sources usually do not contain standardized environmental health-related data. Despite the electronic nature of EMR data, data often remain siloed, whether from other clinician offices, hospitals, or hospital systems. Depending on the type of information, barriers to obtaining EMR data for research purposes include the absence of informed consent from patients to share personally identifiable (granular) information. Data involving identifiable metrics, such as an address, for example, require the involvement of an Institutional review board (IRB).

EMR data may enable the identification of specific patients to generate survey information to identify associations between health outcomes and behaviors or patient perceptions associated

with their disease. This provides a closer look into the relationships of patient responses with their disease state. EMR and survey data linkage is an improved approach from traditional mail or electronic/phone survey data which is limited in the personal health information they can collect.

1.6.2 Phone Surveys

Health survey collection may utilize "available" phone/email directories and commercial lists to engage research participants. These phone lists may introduce bias and confounders depending on the research questions and the source of the directories or lists. Random digit dialing (RDD), though not without error, is commonly used in population health studies, though, not without error. Theoretically, this is a more randomized approach to telephone sampling because "all available" phone numbers can be obtained. Improvements in data transfer and storage capabilities have allowed for the growth of database technology that can provide more readily available and cost-effective study sampling compared to RDD and traditional survey collection stratgies.[67]

1.6.3 Health Registries

Health registries may vary from simple to complex. They may only serve as a data repository or contain interactive features such as annual participant engagement to keep the registry data current. They also make it possible to combine targeted clinical, physiologic, and biological information with extensive demographic information and environmental factors, including the ability to geocode participants by matching them to their residential address. This level of data access would require IRB approval and informed consent from patients. "Patient-

level data provide the opportunity to conduct complex multivariate analyses to understand potential relationships between multiple risk factors and outcomes. Additionally, it provides a level of risk to the patient rather than for a group (e.g., age group, country) to track patient progress longitudinally over time and analyze response to treatment and changes in medical management."[68]

The Asthma Environmental and Lung Health Institute (AELHI) registry (previously known as "The University of Pittsburgh Asthma Registry") at the University of Pittsburgh is a modern interactive registry and served as the primary data source for my dissertation work. A comprehensive, robust registry, such as that associated with the AELHI, can collect and analyze research obtained data such as physiologic (spirometry and exhaled nitric oxide (FeNO)) and survey questionnaire data in a targeted and standardized way. Standardization and scalability features of data collection and storage can improve the overall quality of the data used in research studies. The database's comprehensive nature allows the AELHI to track asthma symptomology, exacerbations, and disease progression. Additionally, patients may elect to provide a blood sample, which enhances our ability to advance epidemiological studies through access to bio-banked repositories. This offers new opportunities to examine novel genetic and epigenetic factors combined with geographical, clinical, and physiologic data.

The AELHI also serves as a research recruitment registry for clinical trials and environmental studies. The interactive nature of the registry ensures contact information and clinically relevant information such as medication lists remain updated. The registry is also advantageous to the participant, as they may opt into communication via social media and text messaging to receive alerts about community-level events that could influence the acute health of the asthma community. Lastly, the registry can put a voice behind the research. Therefore,

participants may consent to be contacted and could be interviewed about their research experience. We had a participant consent to an interview with a news reporter after our Clairton study. While the AELHI provides a "convenience sample," participation in the registry is optional and open to anyone who has asthma and wishes to participate. Engaging participants more often and in innovative ways to help make research less intimidating for potential participants and make it more inclusive.

1.7 Hypothesis and Scope of Dissertation

The overall hypothesis states, "Asthma control and severity will be worsened by exposure to air pollutants and factors and socioeconomic factors."

Data from each study comprised within this dissertation were obtained from residents who lived within Allegheny County, PA. The objective of these studies was to compare the relationship between asthma severity, control, and underlying treatment with inhaled corticosteroids (ICS) in environmental considerations.

The aims of the current study were, therefore, (i) to establish the prevalence of asthma exacerbations about acute pollutant exposures within patients who reside in Allegheny County, (ii) to determine whether specific socio-demographic variables and chronic air pollution events are associated with poor asthma control and severity within patients from an asthma research registry; and (iii) to examine the association of asthma and acute air pollution exposure after a factory fire that occurred in close near residential homes.

Strengths of this research reveal (i) a novel association between acute natural world exposures to increased SO_2 and worsened asthma control in a vulnerable population living close

to the source of pollution (ii) an association between O_3 exposure in children and NO_2 and CO exposure in adults and asthma-related ED visits within the greater Pittsburgh area, and (iii) Odds of severe asthma increased for patients diagnosed as an adult living in EJ tracts versus not in an EJ tract, and high exposure to NO_2 significantly increased the odds of uncontrolled asthma in severe asthma patients. This was not observed in milder patients.

2.0 Lagged Association of Ambient Outdoor Air Pollutants on Asthma Related Emergency Department Visits within the Pittsburgh Region

2.1 Introduction

Asthma is a common chronic lung disease with varying phenotypes, some of which may be worsened by environmental factors such as air pollution. Air pollution is a complex mixture of gases and particulate matter (PM) that varies in concentration across the United States. The variability in concentration and composition is due to different weather patterns and pollution sources.[69] Air pollution also varies from day to day and season to season.[67] Numerous studies have associated air pollutants with adverse health outcomes, such as asthma exacerbations.[73-77] Short-term exposure to $PM_{2.5}$ (PM smaller than 2.5μm in diameter), O_3, and other gaseous pollutants such as SO_2, NO_2, and CO (everyday products associated with the burning of fossil fuels and industrial emissions) have been shown to trigger asthma exacerbations and result in increased emergency department (ED) admissions in both children and adults.[78,79] O_3 is unique from the other pollutants since it is not a primary pollutant. Instead, it is a secondary pollutant formed by photochemical reactions between sunlight and pollutant precursors, such as volatile organic compounds and nitrogen oxides. In some instances, the literature on the health effects of air pollution is inconsistent and thus warrants further investigation.[80] The U.S. Environmental Protection Agency (EPA) sets the National Ambient Air Quality Standards for pollutants based partly on controlled human exposure studies assessing airway hyper-responsiveness(AHR).[81] These controlled exposure studies help understand how the lung responds to air pollutants. Pittsburgh, located in southwestern Pennsylvania, has a unique topography because its metropolis

is built within the hilly Appalachian Mountains.[82] According to the American Lung Association's 2020 annual air quality report, Pittsburgh ranks poorly for year-round particle pollution and O_3[83], thus making this region an excellent location to study pollution-related health effects. A previously published study in Pittsburgh examined the potential influence of gender and ethnicity on asthma-related ED visits between 2002 and 2005 and found O_3 and $PM_{2.5}$ to be significantly associated with an increased likelihood of ED visits for Black and White Americans.[82] This prior study used a two-pollutant model and did not assess differential effects based on age. Other studies have found similar associations between ED visits and O_3;[84-86] however, few of these studies included five pollutant models. The primary objective of this study was to examine the association between ambient air pollution and the risk of asthma-related ED visits in both children and adults using a five-pollutant model.

2.2 Materials and Methods

A time-stratified case-crossover study design with conditional logistic regression examined the short-term associations of fine particulate matter ($PM_{2.5}$) and gaseous pollutants with asthma ED visits. The case-crossover design is commonly chosen to investigate transient effects on the risk of acute health events.[87] Specifically, this method is frequently used in epidemiology studies to examine the short-term effects of air pollution on respiratory disease events.[88] This design uses defined cases only and compares an individual's exposure experience just before the event with exposure at other times (the referent periods). An advantage of the case-crossover design is that, since each case serves as its control, confounding invariant risk factors (such as age, sex, and race) or slowly changing (such as tobacco smoke exposure and socio-economic factors) are controlled

for by design. Data on ED visits from Allegheny Health Network (AHN), a six-hospital regional health system with a primary discharge diagnosis of asthma from 1 July 2008 to 30 June 2013, were included in our analysis. All have hospital-based emergency departments staffed by emergency physicians with up-to-date diagnostic and treatment capabilities. The visits to each of these EDs ranged from 25,000 to 55,000 per year. Data for each visit included: name of the hospital; pseudo-ID; dates of admission and discharge; primary discharge diagnosis and up to three secondary diagnoses; zip code of residence; age, gender, and race; and disposition from ED (whether an individual was subsequently admitted as an in-patient or discharged to home). Specifically included in these analyses were visits with a primary discharge diagnosis of asthma, defined as ICD-9 Codes 493.XX. Studies were limited to Allegheny County residents ages five years and older.

2.2.1 Environmental Exposure Measures

Ambient pollutant data were downloaded from the Environmental Protection Agency (EPA) website and included concentrations and air quality index (AQI) values for this study. A reference monitor in urban Pittsburgh (air quality system (AQS) ID: 420030038) measured $PM_{2.5}$, O_3, NO_2, and CO. SO_2 measurements were obtained from a separate reference monitor in Avalon, PA (AQS ID:420030002). This monitor was used as an indicator of regional SO_2air pollution since $SO_2$was not measured at the Pittsburgh location. These monitoring sites are part of the EPA AQS used to monitor compliance with the Clean Air Act. These reference monitors were selected because they measured the pollutants of interest, provided temporal data, and were centrally located between the six hospitals where asthma ED visit data were collected (Figure 1). To address missing values from the monitors due to technical errors in their functioning, we imputed missing values using

the mean of the nearest valid values (one before and one after) to fill gaps in the data. The validation of this imputation has been deemed an acceptable process and scrutinized in many studies.[83-92]

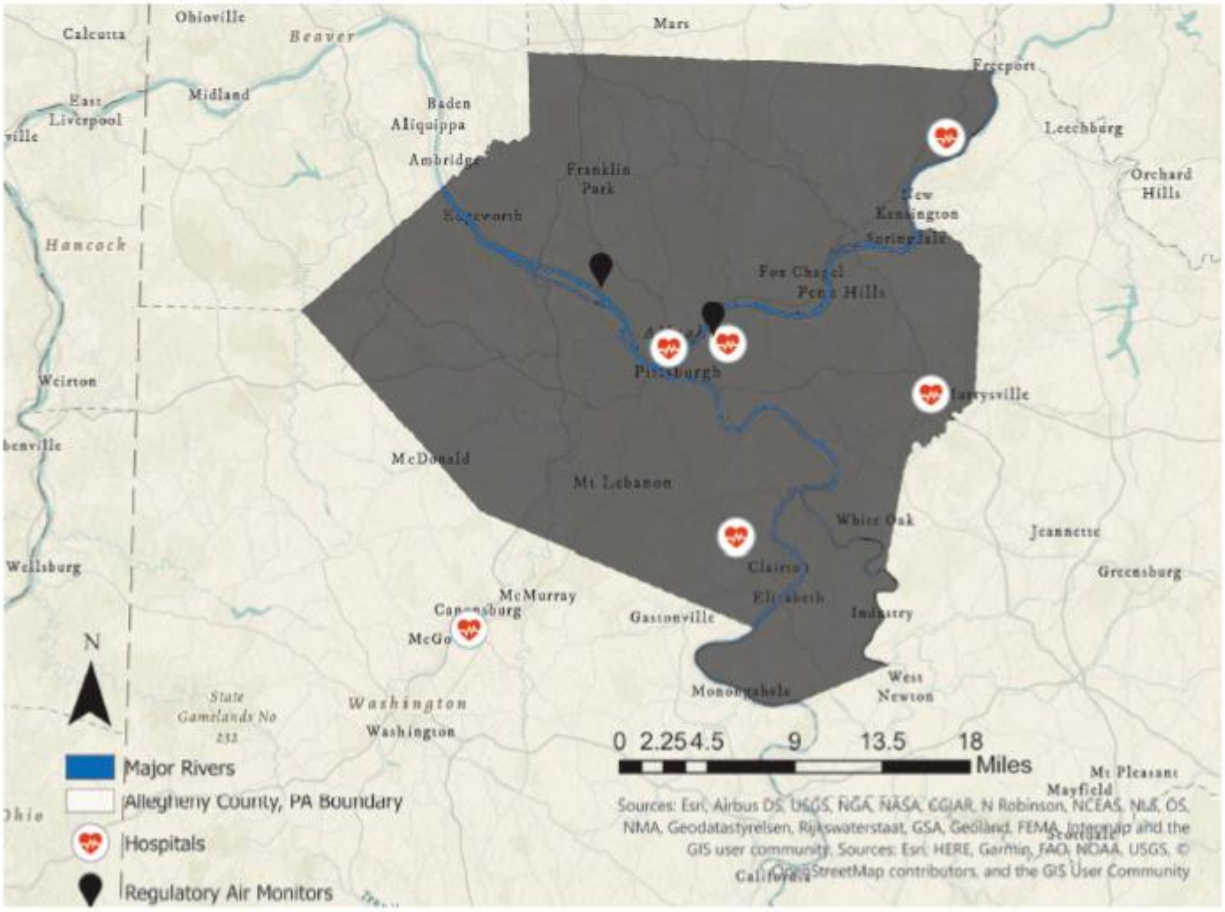


Figure 1. Map of Allegheny County, PA, depicting locations of regulatory air monitors and hospitals where asthma-related Emergency Department (ED) visits were recorded between 2008 and 2013.

Meteorological variables, including the daily minimum and maximum air temperatures, were obtained from the Pittsburgh International Airport for July 2008 to June 2013.These data were downloaded from the National Oceanic Atmospheric Association (NOAA) Climate Data online website. The average daily temperature was defined as the average of the

minimum and maximum air temperatures for that day. Like the pollutant monitoring, missing values were imputed from the nearest days' values.

2.2.2 Statistical Analysis

For our analyses, the level of ambient air pollution at the time of day zero (day of admission) and lagged days just before an individual visited the ED were compared with levels at referent times. This approach is commonly used to evaluate the acute effects of transient air pollution exposures by comparing outcome risks in the same individual. We used a time-stratified approach to select referent periods in 7-day intervals to minimize confounding factors such as the day of the week, which could be associated with adverse pollution events. With this approach, the overall period is divided into strata and exposure in the period before the event, and exposures in multiple reference periods are compared within that stratum of time. We used a 28-day strata and referent periods of 7, 14, and 21 days (either before or after the ED event) within each stratum. To assure the independence of events within strata, a washout period of 7 days was used to remove recurrent events (ED visits) for an individual to ensure the independence of events within the strata. We evaluated the effect of exposure to pollutants on the day of the ED visit and prior days; lag 0 represents exposure on the same day as the ED visit. We also examined the effects of cumulative days of exposure to calculate average exposures over several days. The average of lag days 0–5 was calculated as the mean of lag days 0, 1, 2, 3, 4, and 5, respectively. Pollutant effects were examined with models containing just one day or an average of lag days 0–5. We controlled for temperature effects in all models by including average temperature at the same lag(s) as the pollutant(s).

Because case-crossover is so tightly controlled by the referent definition of "within 28 days", cubic splines were not used. In addition to the single-pollutant models for $PM_{2.5}$, O_3, NO_2, SO_2, and CO, we ran two-pollutant models for $PM_{2.5}$and O_3 adjusted for temperature. Lastly, we conducted multi-pollutant models with all five pollutants. The results are presented as odds ratios (ORs) and the associated 95% confidence intervals for every 10μg/m3 increase in $PM_{2.5}$; 10 ppb for O_3, NO_2, and SO_2; and 1 ppm for CO. Only significant findings are included within the text; however, the complete data set may be found within Tables S1–S14. Data analyses were conducted using the case-crossover tool (C-CAT) developed by Apex Epidemiology Research in collaboration with the New York State Department of Health for use with SAS (Abraham JH and Bateson TF, 2016). C-CAT is public domain software that provides an easy-to-use interface for SAS code to implement the time-stratified case-crossover analysis. Separate analyses were conducted for children (ages 5–17 years) and for adults (ages 18 years and older).

2.3 Results

The study population distribution by age and sex is shown in Figure 2. Most ED cases within our sample population were adults (n=6682). Specifically, 87% were adults (n=5842) and 13%were children (n=840). Overall, there were higher rates of ED visits among women compared to men.

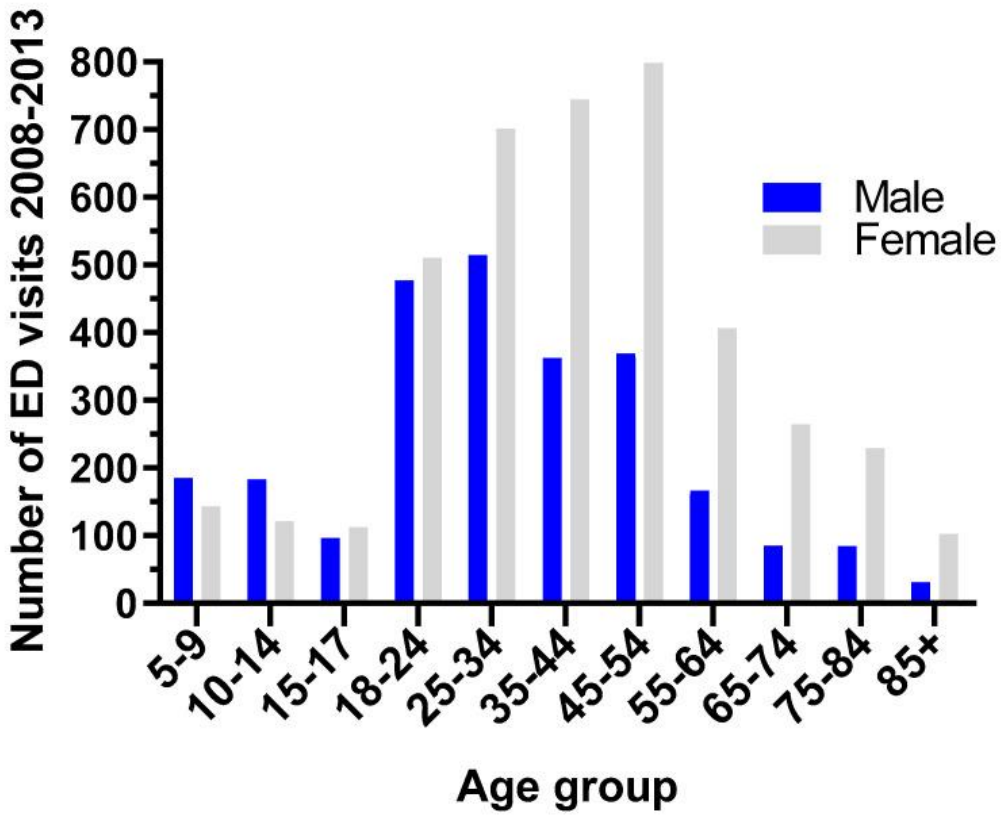


Figure 2. Cases of asthma-related ED visits between 2008 and 2013 separated by sex and age.

2.3.1 Air Pollution Data

The time scale for each pollutant recorded varies and is dependent upon EPA reporting requirements. The odds of an asthma ED visit related to an increase in exposure per increase of 10 (unit dependent on pollutant as referenced in the methods section) for a single day was significant at different lags for different pollutants. The strongest associations between pollutant levels and ED visits were observed for O_3within single-, double-, and five-pollutant models for children, in addition to NO_2 and CO within single-pollutant models for adults. Adjusted odds ratios for ED visits for asthma, according to ambient air pollution levels for each pollutant,

may be found in Tables S1–S14.The average levels for the five years were: $PM_{2.5}$: 11.41µg/m3, SD±5.95; O_3:38.5 ppb SD±15.9;SO_2: 9.25 ppb, SD±10.89; NO_2: 22.7 ppb, SD±9.4; and CO: 0.51 ppm, S.D.±0.27; and average temperature was 11.7 degrees Celsius SD±18.1.

2.3.2 Children Ages 5-17 Years

Statistically significant effects of O_3were noted for lag day 1 in the single- and two-pollutant models (OR: 1.12, 95% CI: 1.02–1.22,$p<0.01$) in the single pollutant model; and two-pollutant model (OR: 1.10, 95% CI: 1.01–1.20,$p<0.01$) (Figure 3). This same effect was evident in the multi-pollutant model adjusting for $PM_{2.5}$, temperature, and the other pollutants (Supplementary Section S1, Table S14). There were no significant positive associations between SO_2, NO_2, and CO and ED visits. See Supplementary Section S1, Table S4 for complete data. Of note, $PM_{2.5}$ in the two-pollutant model had a marginally significant protective effect, which requires further study.

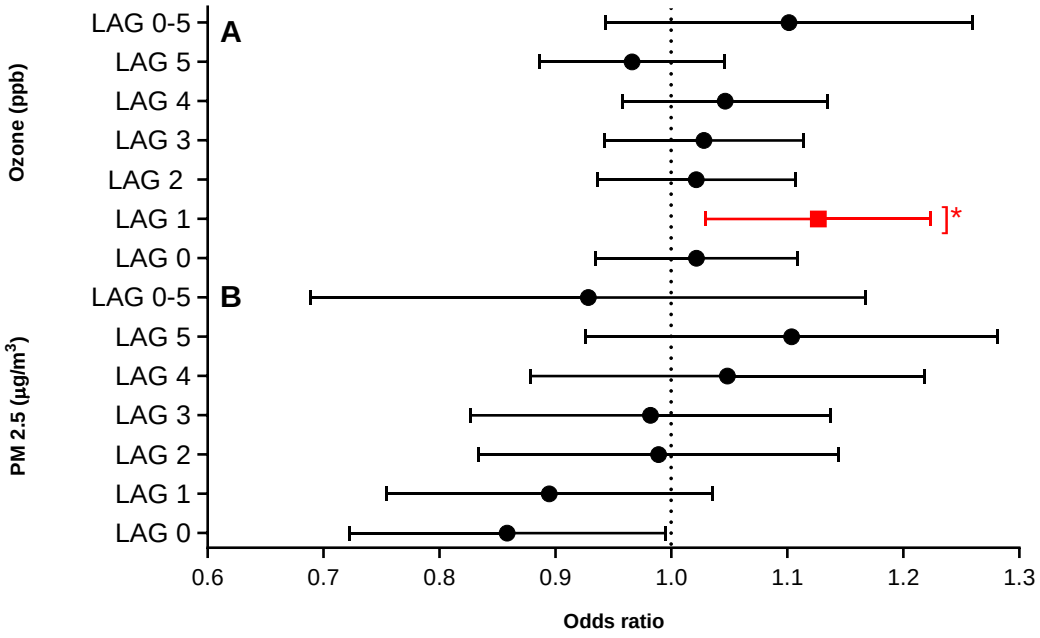


Figure 3. Figures 3A and 3B show odds ratios of an asthma-related ED visit and significant lag days for children ages 5-17 using a two-pollutant model, which includes $PM_{2.5}$ and O_3, adjusted for temperature.

Definition of abbreviations: * = P-value >0.05

2.3.3 Adults Aged 18 Years and Older

Statistically significant positive effects of CO were noted in adult ED visits for asthma on lag day5 (OR: 1.13, 95% CI: 1.00–1.28,p<0.01) and average lag days 0–5 (OR: 1.22, 95% CI: 1.00–1.49,p<0.01)in the single-pollutant model. Similarly, a statistically-significant positive effect of $NO_2$was seen in adult ED visits for asthma for lag day 5 (OR: 1.04, 95% CI: 1.00–1.07, p<0.01) in the single-pollutant model (Figure 4). No significant associations were observed for SO_2 and O_3. See Supplementary Section S1, Tables S12 and S13, for complete data on CO and NO_2, respectively. In the five-pollutant model, no statistically significant positive effects were seen for any of the pollutants at any of the lags examined (Supplementary Section S1, Table S14).

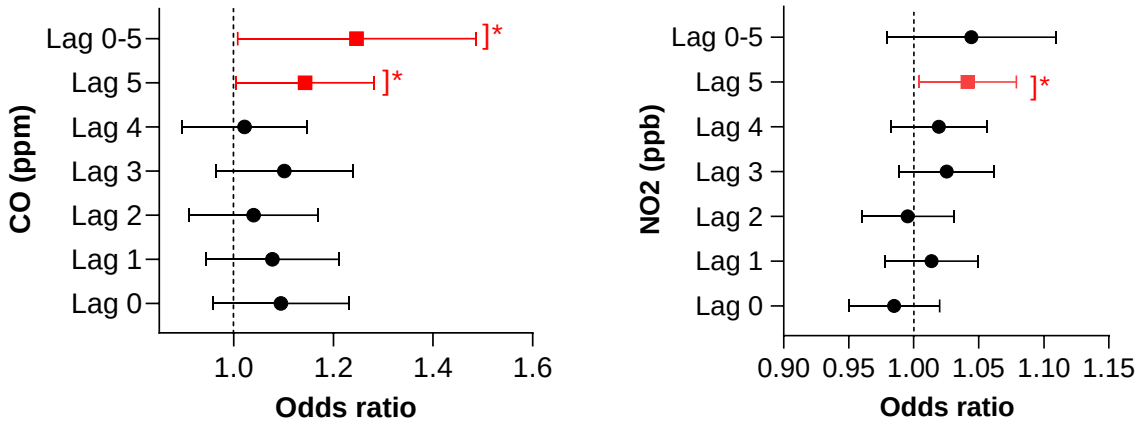


Figure 4. (A,B) Odds ratios of an asthma-related ED visit and significant lag days for adults aged 18 and older using a single-pollutant model for CO and NO_2, adjusted for temperature. The referent period is 28 days. * *p*-value < 0.05.

2.3.4 Summary of Results

In children aged 5–17 years, there were statistically significant increases in asthma-related ED visits for O_3 on lag day 1 (one day before the visit) in all models. Typically, this was found because of the delay in seeking care. In adults 18 years and older, there was no statistically significant effect of ozone on asthma-related ED visits in any of the models. Instead, we found statistically significant results of CO on lag day 5 and average lag days 0–5, and NO_2 on lag day 5 in the single-pollutant model only.

2.4 Discussion

Our analysis showed significant associations between daily pollution levels and asthma-related ED visits for children and adults during the five-year study period. Higher ambient levels of O_3 were associated with increased ED visits in children, though not in adults. Increased ambient levels of NO_2 and CO were associated with increased odds of an ED visit in adults. Additionally, our study demonstrates differences in asthma-related ED visits based upon sex. This finding is in line with a prior report that post-pubescent women have been shown to have poorer asthma outcomes compared to their male counterparts.[94] A strength of our study was the extended lagged analyses through day 5. Some previous studies examined lag days 1–3 and found no association between pollution levels and ED visits. Significant associations observed at extended lag periods in the current study (e.g., lag day 5) suggest the potential for underlying biological mechanisms as potential contributors to this delayed response. Another possibility is the possible delay in asthmatics seeking ED treatment. It was unexpected that our study did not show an association between $PM_{2.5}$ and ED visits in the single-pollutant model. The association of asthma exacerbations with elevations in short-term exposures to $PM_{2.5}$ are well established.[95-98] Studies suggest $PM_{2.5}$ may activate pathways associated with oxidative stress, increasing airway hyper-responsiveness.[98] An interesting feature of $PM_{2.5}$ is its ability to serve as a transport vessel for airborne gaseous particles to travel deep into the bronchial airway. Therefore, it is important to consider how $PM_{2.5}$ concentrations change when combined with gaseous pollutants, as we did in our analysis.

Although the sample size used for the analysis in children was smaller than for adults, there were statistically significant increases in asthma-related ED visits for O_3 noted on lag day 1 (one day before the visit). Typically, this lag occurs because of the delay in seeking care. This finding

was noted to overcome the collinearity among pollutants after adjustment for both temperature and $PM_{2.5}$. This finding is consistent with other studies showing an association between O_3 and asthma-related ED visits in children. Another study showed that after adjusting for seasonal variation, high levels of O_3 and SO_2 were associated with asthma exacerbations in children.[99] An additional study demonstrated a positive relationship between O_3 levels and asthma-related ED visits, with associations being the strongest during the warm season.[84,100,101] In contrast to our findings in children, we did not find a positive association between O_3 and asthma-related ED visits in adults. Consistent with our findings, an Australian study showed increased air pollution affected ED visits for children but not adults.[102] There are several explanations for these discrepant findings in children and adults. Toxicological studies have shown that children tend to breathe in more air through their mouths, as opposed to adults, who breathe primarily through their nasal passages, which help to filter the air before reaching the lungs.[103] A systematic review of 27 epidemiological studies concluded that contrary to adults, children might be at higher risk from O_3 because of their immature immune systems, increased durations of time spent outside, and increased air exchange relative to body mass. Therefore, higher exposure levels may be why we see effects from O_3 in children.[76] Lag day 5 was implicated in the adult analyses of NO_2 and CO. This lag may be related to the potential occupational exposures experienced by adults. Additional studies are needed better to understand the significance of this extended lag effect. Some studies suggest that delayed effects between various pollutants and asthma outcomes are related to delayed physiologic responses.[76] Our finding of an association between NO_2 exposure, a known marker of traffic-related pollution associated with lung inflammation, and asthma-related ED visits in adults is consistent with several previous studies. NO_2 was not linked to asthma-related ED visits in children in our study. Lastly, the direct effects of high outdoor CO exposures have been related to hypoxia, which results in

confusion, headache, and nausea.[104] CO might be a marker for other noxious combustion products, such as the burning of wood, coal, gas, and tobacco.[104] CO pollution has decreased lung function in adults with asthma.[105-108] CO was not linked with asthma ED visits in children within our study; however, a prior study reported increased odds of school-based health clinic visits related to high ambient levels of CO.[109]

2.5 Study Limitations

As with all epidemiological studies, limitations exist for this study. For example, environmental factors such as elevation could not be completely controlled for and may have influenced the results.O_3 tends to be increased at higher elevations.[110] Furthermore, we used two EPA-grade reference monitors from distinct locations within Allegheny County to perform the analyses. Because of this small air monitor network, we relied on regional pollution data rather than hyper-local conditions. Therefore, we could not capture local-scale spatial variations that may have occurred for various pollutants. In addition, the more distant monitor that provided SO_2 concentrations may not have been representative of the entire cohorts' ambient exposure since the participating hospitals were clustered near the Pittsburgh reference monitor.

Furthermore, due to the limited nature of our dataset, confounders such as socioeconomic status, type of health insurance, the severity of asthma, and use of controller therapy were not examined. Lastly, ED visits for asthma are only one piece of a larger picture that describes asthma burden. Future studies should consider multiple endpoints (i.e., ED visits, school-based clinic visits, and outpatient physician office visits) to obtain a more comprehensive picture of how air pollutants exacerbate asthma control.

2.6 Conclusion

There is an association between O_3 exposure in children and NO_2 and CO exposure in adults and asthma-related ED visits within the greater Pittsburgh area. Public health intervention(s) aimed at mitigating the effects of air pollutants targeted to the entire population may have significant benefits for children and adults with asthma and the public as a whole.

3.0 Use of an Asthma Registry to Examine the Association of Environmental Justice Factors and Traffic Pollutant Exposure on Asthma Control and Severity (publication in progress)

3.1 Chapter 3.0 Abstract

Background: The objective of this study is to examine the relationship between asthma severity and control in the context of environmental justice factors and traffic-related pollution (TRAP). The primary aim of this study is to determine whether residents living in designated environmental justice (EJ) areas have increased odds of severe and uncontrolled asthma outcomes and whether this relationship is modified by the effects of high TRAP, tobacco exposure, demographics, early age of onset (EOA) and disease duration.

Methods: This retrospective study of 1526 adult asthma patients living in Allegheny County, PA, enrolled in the University of Pittsburgh Asthma Institute Registry (AIR) from 2007 to 2021. Asthma severity and asthma control were assigned following ERS/ATS guidelines. Patients were geocoded by residential address and EJ tract classification assigned based on the population composed of $\geq$ 30% non-white and/or $\geq$ 20% impoverished individuals residing in that census tract. TRAP pollution was determined for each census tract and normalized into quartiles (Q1 lowest- Q4 highest) of pollution. Generalized Linear Model (GLM) analyses with a specification of binomial distribution determined the effect of EJ tract on asthma severity and control after adjustment for significant contributory, confounding, and modifying effects.

Results: The entire cohort deviated from the overall county population with more females (70% versus. 51.5%), minorities (32% versus. 18.8%), and higher education levels (48% versus. 39% with at least a college degree). Of the AIR Cohort, 47% lived within EJ tracts compared to only 28% of all county residents. The percentage of SA cases relative to non-severe appeared unchanged across BC exposure but increased with NO_2 exposure. Odds of severe asthma (SA) rose for patients diagnosed as an adult (≥12 years of age) for those living in EJ tracts versus those, not in an EJ tract (OR 1.45 (95% CI 1.00, 2.08), $p<0.05$). This effect of duration was not true for patients diagnosed as children. In those with non-severe disease, odds of uncontrolled asthma were similarly and significantly increased for those within versus not within an EJ tract. A similar trend with disease duration was observed in patients with SA but did not reach significance in the smaller subset of patients. Interestingly, high exposure to NO_2 (Q4 versus. Q3-Q1) significantly increased the odds of uncontrolled asthma in SA patients (OR 3.54 and OR 2.86, respectively, $p<.05$).

Conclusions: Patients living in an EJ tract diagnosed with asthma as an adult were more likely to meet the definition of SA, particularly with a longer duration of disease. In severe patients, living in areas with the highest NO_2 exposure significantly increased the odds of uncontrolled asthma. This was not observed in patients with less severe diseases. Lastly, in non-severe patients, the odds of uncontrolled conditions were significantly increased for patients living within an EJ tract. A similar trend was noted in the severe patients, though our analysis had limited power to generate a meaningful comparison.

3.2 Introduction

The external environment we live in may affect our health directly and indirectly. Factors that influence a person's lifespan include 1) where you live; 2) educational attainment; 3) financial status, and 4) race. [111-115] These factors intersect and become more complicated in diseases such as asthma. A growing body of research recognizes how the external environment (where and how people live) impacts people with asthma. [116,117]

In recent years, more attention has been paid to environmental justice (EJ), which may incorporate some of the known factors influencing the lifespan listed above. In its simplistic form, according to the EPA, EJ is the "fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income, with respect concerning, implementation, and enforcement of environmental laws, regulations, and policies."[118] The concept grew in significance when it became clear that communities of color and poverty frequently bore a disproportionate burden of exposure to environmental pollution compared to more affluent areas. Not surprisingly, this was accompanied by a more considerable burden of environmentally mediated disease in these areas. Therefore, policymakers have sought to identify those geographic areas most at risk for environmental injustice and earmarked EJ-sensitive areas simply based on racial composition and poverty.

While race and poverty were a good starting point to initially craft the definition of an EJ area, additional metrics have since been incorporated, and a universally accepted definition of an "EJ area" is still lacking. Race and poverty alone fail to capture environmental exposures and more refined socioeconomic indicators linked to the description of an EJ area in recent years. Because neighborhood-level impacts on health extend beyond just race and poverty, other factors such as environmental pollution are associated with these vulnerable EJ communities. Therefore, we

should examine health outcomes within EJ areas from various perspectives and work toward developing a universal definition of an EJ designation.

Census tracts (defined geographical units) state-wide were designated by the Pennsylvania Department of Environmental Quality (PA DEP) as environmental justice (EJ) tracts when the population is at least 30% non-white and/or 20% impoverished.[120] These tracts represent about one-quarter of all tracts in Allegheny County.[119] However, multiple confounding factors could influence asthma outcomes in PA DEP-defined EJ tracts beyond poverty and race. For instance, it is also likely that impoverished communities may reside in areas with the highest environmental pollution. Air pollutants such as nitrogen dioxide (NO_2) and black carbon (BC) have been described in the literature as "traffic-related pollutants" (TRAP). These pollutants are known oxidative insults and have adversely affected lung function.[121-124] However, some studies have demonstrated no effect of TRAP pollution on asthma.[125] Despite inconsistencies in the literature, TRAP pollutants have been shown to affect vulnerable communities unjustifiably and may contribute to increased asthma prevalence in these communities. A recent study reported that impoverished and minority communities (consistent with EJ tracts) were disproportionally represented in the areas with the highest exposure to NO_2 and BC.[119] Pittsburgh and Allegheny County, PA, have a history of heavy industrialization and air pollution challenges.[126,127] Our study is the first to model the interplay between socioeconomic factors, asthma severity, asthma control, environmental justice metrics, and TRAP pollution.

Often environmental health studies involve service utilization surrogates of asthma control, such as emergency department (ED) visits or pharmacy prescription refill history.[128–130] However, studies that use the type and number of prescription refills may be inadequate because of barriers patients may experience to obtaining their meds or medication adherence issues. A strength of our

study lies in using the robust Asthma Institute Registry (AIR) registry comprised of clinical, demographic, and physiologic data combined with refined exposure estimates at the census tract level to investigate multiple asthma outcomes. We were able to take a multifaceted approach to explore the complex relationship between "place" (an EJ tract), SES factors, and pollution in a group of asthma patients across a continuum of disease severity and control.

The primary aim of this study was to determine whether residents living in areas designated as "Environmental Justice" have increased odds of severe and uncontrolled asthma outcomes and whether environmental exposures modify those outcomes.

3.3 Methods

3.3.1 Recruitment and disease severity designation

This retrospective study of 1526 adult asthma patients in Allegheny County, PA, enrolled in Asthma Institute Registry (AIR) from 2007 to 2021. Patients were geocoded by residential address and mapped to determine residency within an EJ census tract or not. EJ tracts were defined by the criteria adopted by the PA DEP as a population of ≥ 30% non-white and/or ≥ 20% impoverished, determined from demographic data contained in the 2010 census and contemporaneous American Community Surveys as previously described.[119] Asthma severity scores were assigned following ERS/ATS guidelines, with SA defined by haled corticosteroids.[131] Medications prescribed to each AIR participant were designated as low or high doses as specified for individual formulations. Uncontrolled asthma was based on having one or more of the following indicators 1) Two or more steroid bursts or two or more ED visits in the past year; 2)

Asthma Control Questionnaire (ACQ) score at the time of enrollment ≥1.5; 3) One or more overnight hospitalization or Intensive care unit (ICU) stay; 4) Forced expiratory volume in 1 sec (FEV1) <80% predicted. Lastly, patients who self-reported having a current prescription for inhaled corticosteroid (ICS) were designated as "treated with ICS" compared with those who were not (Figure 1).

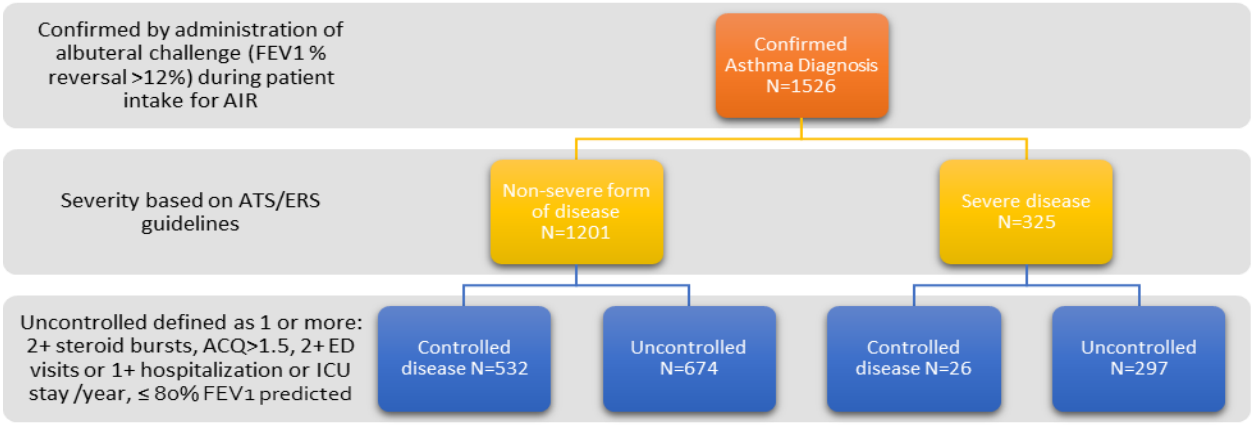


Figure 5. Stratification of study patients from the University of Pittsburgh Asthma Institute Registry (AIR).

3.3.2 Air pollution exposure estimates

Exposure estimates for black carbon (BC) and nitrogen dioxide (NO_2) census tracts were generated using a land-use regression model, and exposure estimates were ranked ordered into quartiles from low (Q1) to high (Q4) by pollutant concentration. Patients were assigned to a quartile based on their residential street address, Figure 2.

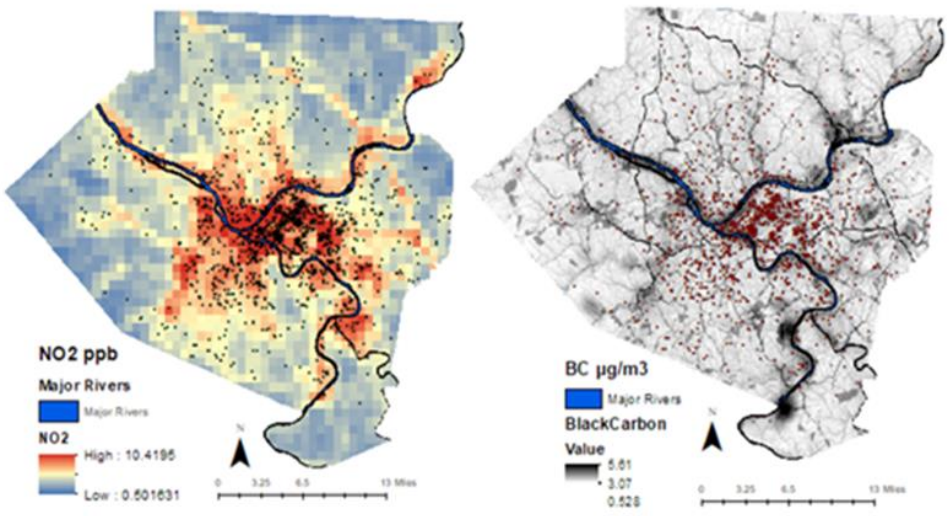


Figure 6. Distribution of AIR cases (indicated by black dots (NO_2 map) and red dots (BC map) within Allegany County, PA, overlaid on pollution maps for nitrogen dioxide (NO_2) and black carbon (BC).

3.3.3 Statistical Analyses

Characteristics of severe disease (Mild vs. Severe) and living in an EJ area were initially examined in bivariate analysis and tested for significance using Chi-square test statistic and independent t-test for categorical and continuous variables. Predictors of asthma control (uncontrolled vs. controlled) were determined through the initial stratum by disease severity (non-severe and severe patients) due to potential confounding of concurrent severity possibly relating to asthma control and living in an EJ tract area. Treatment differences associated with the level of control were evaluated as appropriate treatment should theoretically decrease symptoms and improve management.

Characteristics of study patients were described by percentage with a defining trait for categorical and mean (SD) or median [IQR] for continuous variables. A General Linear Model (GLM)analysis with a specification of binomial distribution determined the effects of

demographic, clinical history, and exposure variables in models that examined the relationship between EJ tract and asthma outcomes of severe disease and uncontrolled asthma. The composite of factors related to increased odds of SA was determined by stepping variables into the model in order of significance in bivariate analyses. The EJ tract was forced into the equation as the primary independent variable of interest. Effect modification between the EJ tract and each factor was evaluated for significance (two-way interaction effects).

The final multivariate model retained variables when the primary term itself or an interaction effect that included it was significant at the 0.05 level. Regardless of significance, factors that confound the relationships were retained if they produced a >10% change in EJ tract odds ratios of a SA diagnosis. A similar multivariate analysis was performed to examine the EJ tract involving increased odds of uncontrolled asthma after stratification by severity. Clinical reasoning sought to determine the significance of the 3-way interaction effect between EJ tract, age at diagnosis (early-onset or adult), and disease duration in each model. Analyses were adjusted for the potential clustering effect of year of enrollment with binary variables defined by contrast comparisons showed a difference in primary outcomes between the first five years of the registry (2007-2011) and (2012-2021). Analyses were conducted using SPSS for Windows V18.0.

3.4 Results

3.4.1 Characteristics of the study population about environmental exposures and residency in an Environmental Justice Tract

Adult asthma patients enrolled in AIR were predominately female (72.9%), employed (63.5%), college-educated (82.8%), and had been living with asthma for an average of 22.9 years (SD 13.9). Approximately 66.1% were White, 29.1% were Black, and 4.8% were from other racial groups. Forty-four percent were obese. Although personal smoking history was limited to 20 pack-years, 25% of the cohort had smoked in their lifetime, and 28% were exposed to SHS. A disproportionate percentage (39.2%) resided in areas in the highest quartile of NO_2 exposure, while the distribution of patients in each BC quartile ranged from 20.6% to 28.3% (Table 1). Contrary to the 27% of the Allegheny County population living in EJ tracts, 40.4% of AIR patients resided in a designated EJ tract area.

Table 1.Characteristics of study patients, (N=1526).

	Overall
Demographics:	
Age (years), mean (SD)	41.9 (16.2)
Female sex, %	72.9%
Race [a]:	
Black	29.1%
White	66.1%
Other	4.8%
BMI (kg/m^2), mean (SD)	30.5 (8.7)
Obese (BMI >=30 kg/m^2), %	44.4%
Public Health Insurance, %	29.2%
Employed, %	63.5%
Education, partial or completed college, %	82.8%
Married, %	26.1%
Environmental Justice (EJ) Census Tract, %	40.4%
Clinical History:	
Early onset (<12 years @ Dx), %	46.6%
Age at diagnoses (years), median [IQR]	13.0 [5.0, 29.0]
Duration of asthma, mean (SD)	22.9 (13.9)
FEV1% predicted, mean (SD)	85.3 (18.9)
Not on ICS therapy, %	58.3%
Severe asthma, %	21.5%
Uncontrolled asthma, %	64.9%
Exposure-related Variables:	
Smoke exposure (SHS or Ever smoked), %	44.1%
Secondhand Smoke Exposure (SHS), %	28.0%
Ever Smoked, %	25.2%
NO_2 quartile for residence:	
Quartile 1	15.4%
Quartile 2	20.2%
Quartile 3	25.2%
Quartile 4	39.2%
BC quartile for residence:	
Quartile 1	20.6%
Quartile 2	24.2%
Quartile 3	28.3%
Quartile 4	26.9%

3.4.2 Characteristics of registry patients by EJ tract versus non-EJ tract

As expected by the EJ tract definition, the population was 48.5% Black (versus 15.9% in non-EJ tracts), with 37.7% on Medicaid (versus 23.4% in non-EJ) and 45.3% unemployed outside the home (versus 30.4% in non-EJ) (Table 2). Asthma patients in EJ tracts were more obese,

more likely to be diagnosed with early onset asthma (EOA), and overall younger than those not living in an EJ tract. They were less likely to be married and there was a tendency to lower lung function.

Table 2. Demographic and Clinical Factors associated with primary independent variable of interest, EJ census tract, N=1526.

	EJ Census Tract		
	No	Yes	P-value [a]
Demographics:	N=910	N=616	
Age (years), mean (SD)	42.7 (16.6)	40.5 (15.4)	**.008**
Female sex, %	72.9%	73.1%	.933
Race [b]:			**<.001**
Black	15.9%	48.5%	
White	79.2%	46.8%	
Other	4.8%	4.7%	
BMI, mean (SD)			
Obese, %	42.2%	47.6%	.042
Medicaid, %	23.4%	37.7%	**<.001**
Unemployed, %	30.4%	45.3%	**<.001**
College, partial or complete, %	85.4%	79.1%	**.001**
Married, %	32.9%	16.1%	**<.001**
Clinical History:			
Early onset (<12 years @ Dx), %	43.8%	50.6%	**.009**
FEV1% predicted, mean (SD)	86.0 (18.5)	84.2 (19.5)	.068
Not on ICS therapy, %	57.8%	58.9%	.662

[a] P-value based on Chi-square test statistic for categorical factors with the significance of the difference in average age based on the independent t-test (equal variances not assumed due to relevance of Levene's test for equality of variance, p=.008).

[b] Minority representation within respective tract implicit to EJ Tract definition, although not exclusively as poverty composition is another metric considered in the definition.

3.4.3 EJ tracts are associated with worse TRAP pollution.

Exposure and pollution-related variables were strongly associated with living in an EJ tract. SHS and BC exposure were higher in EJ tract patients. Even more extreme was exposure to NO_2, with over three times the proportion of patients in EJ tracts being also exposed to the highest NO_2 quartile compared to those in non-EJ tract areas (Table 3).

Table 3. Exposure variables associated with primary independent variable of interest, EJ census tract, N=1526.

	EJ tract (No) N=910	EJ tract (Yes) N=616	P-value
Exposure-related Variables:			
SHS exposure, %	23.5%	34.5%	**<.001**
Ever Smoked, %	23.7%	27.4%	.108
NO_2 quartile for residence:			**<.001**
Quartile 1	24.4%	2.1%	
Quartile 2	24.3%	14.1%	
Quartile 3	30.5%	17.4%	
Quartile 4	20.8%	66.4%	
BC quartile for residence:			**<.001**
Quartile 1	25.6%	13.1%	
Quartile 2	26.0%	21.4%	
Quartile 3	31.3%	23.9%	
Quartile 4	17.0%	41.6%	

3.4.4 Demographic and environmental factors associated with a severe asthma diagnosis

Given the higher environmental exposures in EJ tract patients, we proceeded to examine the relationship of various demographic and environmental factors and a residency in an EJ tract to the definition of SA (or not) (Table 4). While there were differences in self-reported race, obesity, and indicators of socioeconomic status, there were no differences in EJ tract residency or

exposure to environmental pollutants between patients with SA and those with milder asthma. In the multivariate model of potential contributors to SA, increasing age and disease duration, obesity, and less than a college education were independently associated with SA (Table 5).

Table 4. Characteristics of study patients grouped by disease severity (N=1526)

	Patients without severe asthma N=1201	**Patients with severe asthma N=325**	**P-value**
Demographics:	**No. (%) or mean ± SD**	**No. (%) or mean ± SD**	
Female	877 (73)	89 (73)	0.88
Non-White	360 (30)	142 (56)	**<0.0001**
Age	40.4 ± 16.0	46.8 ± 15.8	**<0.0001**
Obese	474 (41)	167 (51)	**<0.0001**
Medicaid	324 (27)	121 (37)	**0.0003**
Unemployed	414 (35)	138 (42)	**0.02**
Completed College	653 (54)	154 (47)	**0.08**
Married	307 (26)	89 (27)	0.67
Lives in EJ Tract	475 (40)	141 (43)	0.21
Clinical History:			
Age at Diagnosis	18 ±16.2	21.5 ± 18.8	**0.001**
FEV1% Predicted	87.8 ± 17.2	75.9 ± 21.6	**<0.0001**
Not prescribed ICS	898 (75)	11 (3)	**<0.0001**
Uncontrolled	694 (58)	297 (91)	**<0.0001**
Exposure-related Variables:			
Ever Smoked	281 (23)	99 (30)	**0.04**
SHS exposure	328 (27)	96 (30)	0.56
NO_2 quartile for residence:			0.73
Quartile 1	182 (15)	53 (16)	
Quartile 2	237 (20)	71 (22)	
Quartile 3	308 (26)	77 (24)	
Quartile 4	474 (39)	124 (38)	
BC quartile for residence:			0.14
Quartile 1	238 (20)	76 (23)	
Quartile 2	282 (23)	87 (27)	
Quartile 3	345 (28)	87 (27)	
Quartile 4	336 (28)	75 (23)	

Table 5. Final multivariate model examining the relationship of EJ tract to severe asthma, after adjustment for contributory, confounding, and effect modification terms, (N=1526).

Terms in Model:	Severe Asthma OR (95% CI)	p-value
Age, per one year increase	1.02 (1.01, 1.04)	**.001**
Obese vs. non-obese	1.46 (1.10, 1.92)	**.008**
College, partial/comp. (Y vs. N)	0.61 (0.43, 0.85)	**.004**
The influence of EJ tract on increased odds of SA depends on the age of onset and duration of the disease:		
Onset age (adult vs. early onset)	0.78 (0.46, 1.33)	.362
Duration, per one-year increase	1.03 (1.01, 1.05)	**.009**
EJ Tract (Y vs. N)	1.11 (0.68, 1.81)	.686
*EJ Tract*Onset age*		*.270*
*EJ Tract*Duration*		*.113*
*Onset age*Duration*		***.002***
*EJ Tract*Onset age*Duration*		*.055*

GLM analyses determined OR (95% CI) and significance level with the binomial distribution.
They are adjusted for the clustering effect of enrollment year in the model with 2007-2011 vs. 2012-2021.

3.4.5 Demographic and environmental factors, including EJ tract and the presence of uncontrolled asthma, stratified by severity

In our study, severity was only defined based on current treatment with high dose inhaled corticosteroids. This definition does not consider the degree of control either with or without this therapy. However, given the range of background therapy (none to high dose inhaled corticosteroids to systemic corticosteroids), we evaluated the potential factors contributing to control by the background of severe asthma (or not). Interestingly, using our definition of controlled asthma (see methods), many SA patients were uncontrolled (91%), while (58%) were uncontrolled among non-severe asthma patients. Furthermore, in a bivariate analysis of control

(unlike asthma severity), residence in an EJ tract and living in the higher NO_2 exposure quartile were significantly associated with uncontrolled asthma (Table 6).

Table 6. Bivariate relationship between characteristics and uncontrolled asthma within each severity group.

	Non-severe Patients N=1201		**Severe Patients N=325**	
Outcome:	**Uncontrolled Asthma N=694**		**Uncontrolled Asthma N=297**	
	OR (95% CI)	**p-val**	**OR (95% CI)**	**p-val**
Demographics:				
Age, per one year increase	1.03 (1.02, 1.03)	**<.001**	1.02 (0.99, 1.05)	.127
Female vs. male	0.76 (0.58, 0.99)	**.038**	0.70 (0.28, 1.80)	.462
BMI per one unit increase	1.05 (1.03, 1.06)	**<.001**	1.05 (1.00, 1.10)	.060
Obese vs. non-obese	2.02 (1.58, 2.59)	**<.001**	1.98 (0.86, 4.56)	.109
Medicaid vs. other insurance	2.31 (1.75, 3.05)	**<.001**	2.95 (1.09, 7.97)	**.033**
Unemployed vs. employed	1.32 (1.03, 1.68)	**.026**	1.39 (0.62, 3.11)	.426
College, partial/comp. (Y vs. N)	0.57 (0.41, 0.80)	**.001**	1.32 (0.56, 3.14)	.525
Married vs. unmarried	0.81 (0.62, 1.05)	.110	0.78 (0.34, 1.80)	.563
EJ Census Tract (Y vs. N)	1.32 (1.05, 1.68)	**.020**	2.47 (1.02, 5.98)	**.046**
Clinical History:				
Age@Dx (>=12 vs. <12)	1.03 (0.82, 1.29)	.833	0.96 (0.44, 2.11)	.926
Exposure-related Variables:				
SHS exposure (Y vs. N)	1.91 (1.46, 2.50)	**<.001**	1.30 (0.53, 3.17)	.561
Ever Smoked (Y vs. N)	1.84 (1.39, 2.45)	**<.001**	2.16 (0.80, 5.86)	.130
NO_2 quartile for residence:		**.058~**		**.020**
Quartile 1	Reference		Reference	
Quartile 2	1.39 (0.94, 2.07)	.103	2.70 (0.85, 8.59)	**.093**
Quartile 3	1.04 (0.72, 11.51)	.833	1.37 (0.52, 3.64)	.527
Quartile 4	0.89 (0.63, 1.25)	.500	6.14 (1.80, 20.94)	**.004**
BC quartile for residence:		.628		**.066**
Quartile 1	Reference		Reference	
Quartile 2	1.11 (0.78, 1.58)	.556	1.85 (0.71, 4.80)	.205
Quartile 3	0.97 (0.70, 1.36)	.876	3.89 (1.20, 12.63)	**.024**
Quartile 4	1.17 (0.84, 1.64)	.361	3.33 (1.02, 10.84)	**.046**

GLM analyses determined OR (95% CI) and significance level with the binomial distribution.

A multivariate analysis was performed after severity stratification to determine the potentially most relevant and independent factors contributing to poor control. In non-severe

asthma, increasing age, male gender, obesity, being unmarried, and SHS exposure. Early age of onset and living in an EJ tract both tended to associate with uncontrolled disease (Table 7).

In contrast, in patients with severe asthma, using a similar approach, factors that increased the odds of uncontrolled asthma included being on Medicaid and living in areas with the highest NO_2 exposures. For example, in patients with SA, increased exposure to NO_2 (Q4 versus. Q3-Q1) and being on Medicaid insurance increased the odds of uncontrolled asthma (OR 3.54 and OR 2.86, respectively, p<.05) (Table 8).

Table 7. Final multivariate model examining the relationship of EJ tract to uncontrolled asthma in less severe patients after adjustment for contributory, confounding, and effect modification terms.

	In Non-severe Patients, N=1201	
	Uncontrolled Asthma N=694	
	OR (95% CI)	p-value
Terms in Model:		
Age	1.03 (1.02, 1.05)	**<.001**
Female vs. Male	0.69 (0.51, 0.92)	**.012**
Obese (Y vs. N)	1.64 (1.25, 2.16)	**<.001**
Married (Y vs. N)	0.58 (0.42, 0.80)	**.001**
SHS exposure (Y vs. N)	1.85 (1.37, 2.50)	**<.001**
Onset age (adult vs. early onset)	0.68 (0.46, 1.00)	.051
The influence of the EJ Tract on increased odds of uncontrolled asthma depends on the duration of the disease:		
EJ Tract (Y vs. N) [a]	1.28 (0.98, 1.68)	**.070**
Duration, per one-year increase [b]	1.00 (0.98, 1.01)	.683
EJ Tract*Duration:		***.024***

GLM analyses determined OR (95% CI) and significance level with the binomial distribution.
They are adjusted for the clustering effect of enrollment year in the full model with 2007-2011 vs. 2012-2020.
[an] Effect of EJ Tract (Y vs. N) was evaluated at 22.6 yrs.
[b] Effect of time per one year increase estimated at distribution for EJ Tract in the cohort

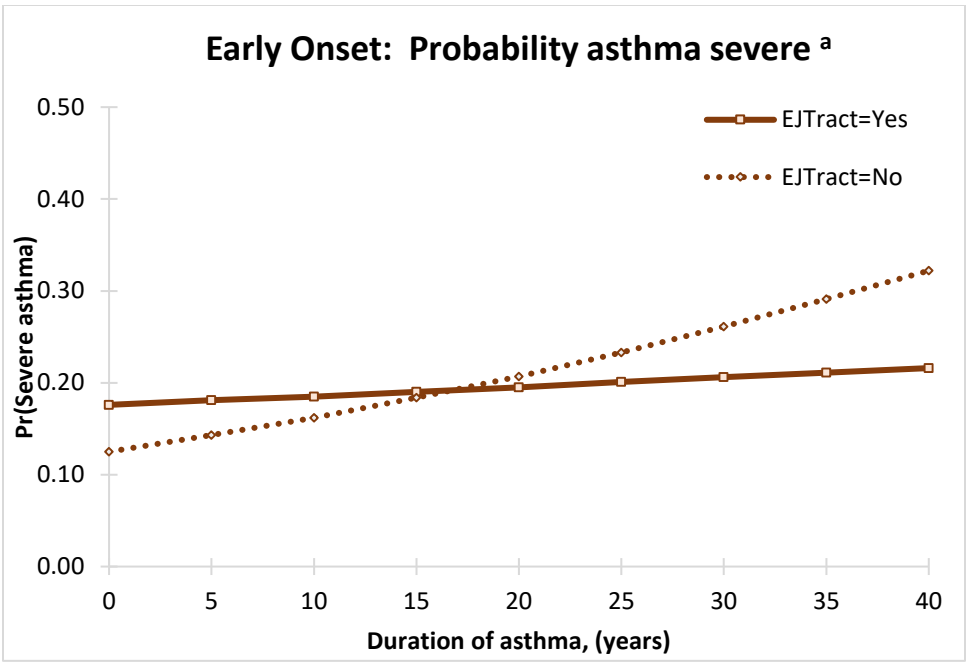
Table 8. Final multivariate model examining the relationship of EJ tract to uncontrolled asthma in severe patients after adjustment for contributory, confounding, and effect modification terms.

	In Severe Patients, N=325	
	Uncontrolled Asthma N=297	
	OR (95% CI)	p-value
Terms in Model:		
Medicaid (Y vs. N)	2.86 (1.01, 8.12)	**.049**
NO_2 (4^{th} quartile vs. lower quartiles 1-3)	3.54 (1.01,12.39)	**.048**
The influence of the EJ Tract on increased odds of uncontrolled asthma depends on the duration of the disease:		
EJ Tract (Y vs. N) [a]	2.21 (0.49, 9.84)	.300
Duration, per one-year increase [b]	1.01 (0.98, 1.04)	.417
*EJTract * Duration*		.063

GLM analyses determined OR (95% CI) and significance level with the binomial distribution.
They are adjusted for the clustering effect of enrollment year in the full model with 2007-2011 vs. 2012-2021.
[a] Effect of EJ Tract (Y vs. N) was evaluated at 25.5 yrs.
[b] Effect of duration per one year increase estimated at distribution for EJ tract in the cohort.

3.4.6 Duration of disease interacts with age at onset and EJ tract residency to associate with both asthma severity and control.

From Table 2, 50.6% of patients living within an EJ tract reported EOA compared to 43.8% not residing in an EJ tract. Additionally, increasing age and disease duration were associated with both severity and/or poor asthma control. To further investigate whether living in an EJ tract impacted both age at diagnosis and disease duration to contribute to asthma control or severity, we modeled two and three-way interaction effects combining EJ tract, age of asthma diagnosis, and disease duration. EJ tract residence alone did not associate with asthma severity and had only a borderline contribution to asthma control in non-severe asthma patients (Tables 5-7).



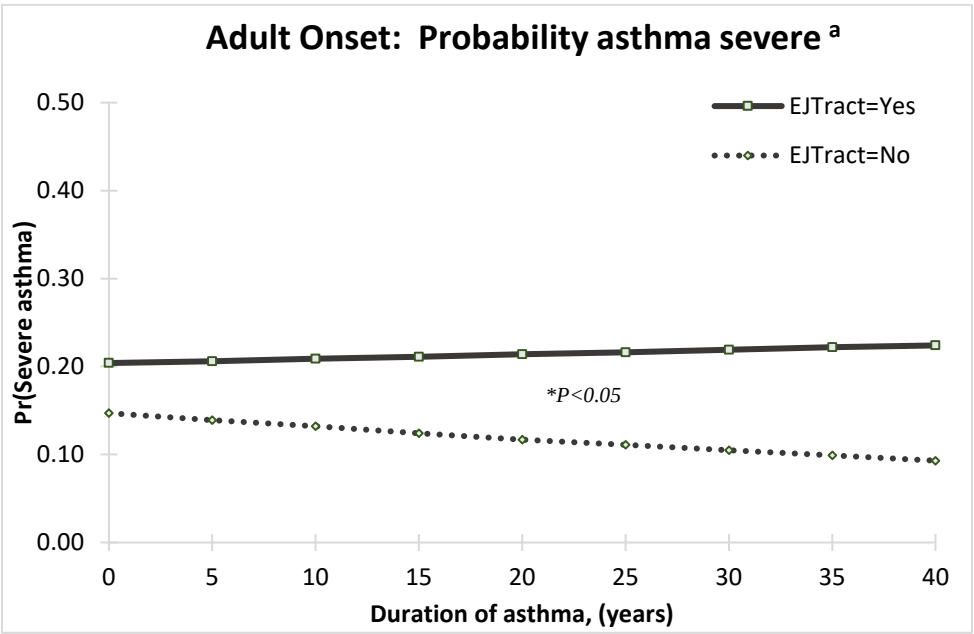


Figure 7. Influence of EJ tract on severe asthma depends on onset age (adulthood or early-onset) and disease duration. The probability of severe asthma is determined by the distribution of remaining factors in the final multivariate model (see Table 3) (mean age=41.7 years, 44.4% obese, 83.8% college P/C, 81.5% enrolled in the registry during years 2012-2021). ***A total number of patients with severe disease (EJtract-yes: early-onset (N=61), adult-onset (N=80); EJtract-no: early onset (N=81), adult onset (N=103). A total number of patients***

with less severe disease (EJtract-yes: early-onset (N=215), adult-onset (N=224); EJtract-no: early-onset (N=318), adult onset (N=408).

The odds for uncontrolled disease in patients with non-severe asthma increased for those within the EJ tract. They became significant when factoring in the longer duration of the disease, regardless of age at onset, Figure 4. Like non-severe asthma, residency in EJ tracts increased the odds of uncontrolled asthma as the disease duration increased in patients with SA. However, significance was not achieved, likely due to the small percentage of SA patients classified as controlled.

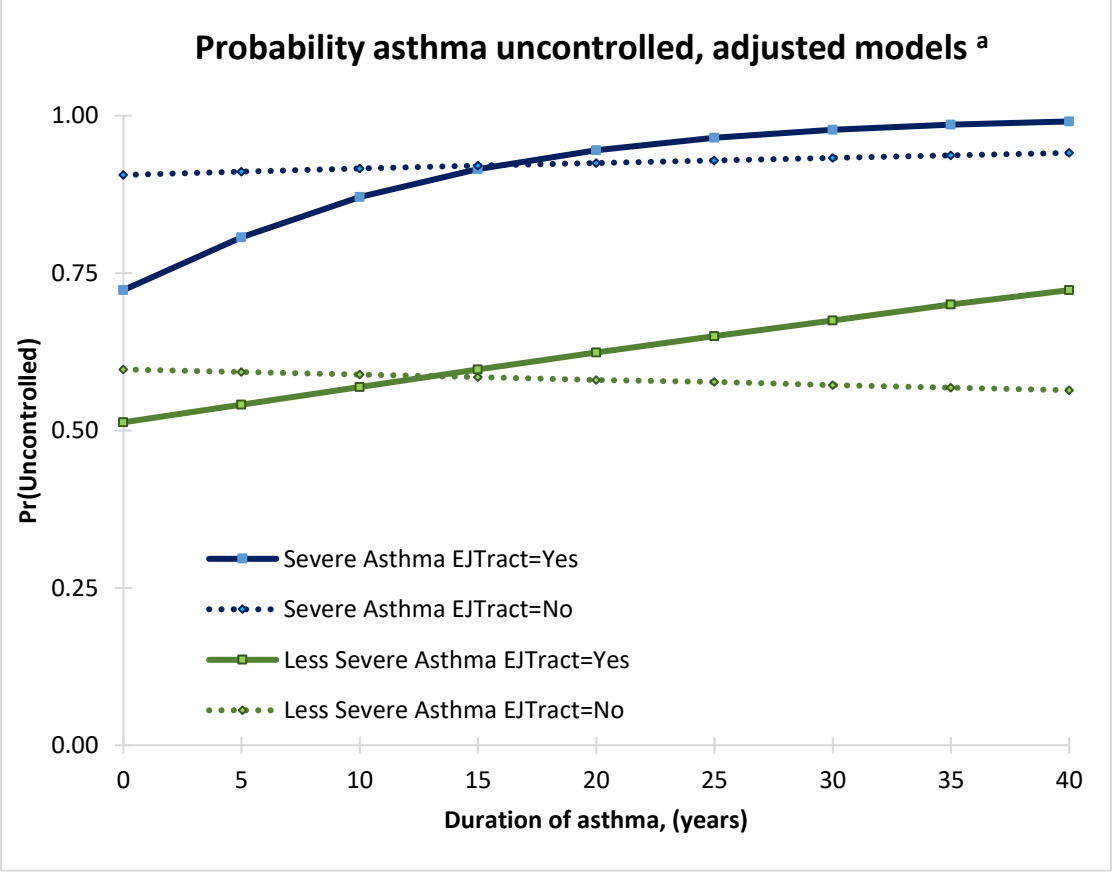


Figure 8. Displays influence of the EJ tract on uncontrolled asthma depends on the disease duration in non-severe patients, with a similar trend noted in severe patients. The probability of uncontrolled asthma is

determined by the distribution of remaining factors in respective final multivariate models. Severe (37.5% in NO_2 4th quartile, 38.1% Medicaid, 70.2% enrolled in registry during years 2012-2021); Less severe (mean age 40.3 years, 73.0% female, 41.2% obese, 25.1% married, 27.0% SHS exposure, 83.5% enrolled in registry during years 2012-2021).

3.5 Discussion

3.5.1 Major Findings

This study evaluated the relationship between residency in an EJ tract, defined by race and poverty, and was associated with exposure to worsening environmental pollution and worsened asthma severity or control. The results confirm a strong association between residency in EJ tracts and exposure to higher levels of TRAP, specifically higher exposure to both NO_2 and black carbon, as well as the higher levels of lower SES and higher percentages of Black residents, as expected given the definition of EJ tracts at the time of the study. Despite this increase in TRAP exposure, multivariate analysis of factors associated with severity did not identify either EJ tract residency or pollution associated with asthma severity as defined by treatment with high doses of inhaled corticosteroids. In contrast, when evaluating factors related to poor asthma control, in the presence of severe asthma, exposure to higher quartile of NO_2 levels and residency in EJ tracts was associated with poorly controlled asthma in both bivariate and multivariate analysis. When the EJ tract was added to the models, it failed to associate with asthma severity or control. However, a significant interaction was identified between asthma duration and EJ tract residency as related to poor asthma control in non-severe asthma, with similar tendencies in severe asthma, suggesting the environment may have a more significant influence over time. Throughout all the analyses,

indicators of lower SES, including use of Medicaid, marital status, education, and SHS exposure also associated with both more severe asthma and poorly controlled asthma. Thus, our findings suggest that indicators of worsening poverty, longer asthma duration, and environmental influences (both EJ tract and NO_2 exposure) in the registry population studied here may well contribute to more severe and poorly controlled asthma.

Notably, the asthma registry population studied here did not reflect the overall population of Allegheny County. Overall, asthma registry patients were more likely to live in EJ tracts and be exposed to higher levels of TRAP, particularly NO_2. They were more likely to be Black people, women, and more economically disadvantaged (yet better educated) than the population. This association between asthma and lower SES has long been recognized, yet the integration with environmental exposures is much less. Medicaid is an element of SES; though not explicitly included in our EJ case definition, other studies have shown a positive association between increased asthma rates and patients on Medicaid.[132] Our bivariate analysis also identified a history of smoking tobacco as significantly associated with SA. This is consistent with previous studies that associated tobacco smoking with SA.[133] However, SHS or tobacco history were not primary variables of interest for this study, and smoking history was limited to 20 pack-years or less.

An extensive body of literature on air pollution and asthma control has been reported in adults and children.[134-138] Yet, studies are inconsistent when reporting the effects of NO_2 on asthma.[139] This is likely due to the differences in study design and granularity of exposure data. Fewer studies have examined associations between air pollutants and SA in adults[141]. There is no published research to model the interplay between SES, pollution, and multiple asthma outcomes as we have done in this study. However, a 2020 study evaluated a similar combination of metrics (SES and air pollution ($PM_{2.5}$) concerning asthma prevalence).[142] Despite this gap, other studies

have examined TRAP pollutants and singular asthma outcomes such as early-onset asthma.[143] Our data showing an increase in EOA in residents of EJ tracts would be consistent with these findings. Moreover, a 2020 study revealed TRAP pollution disproportionately impacts vulnerable neighborhoods and may contribute to increased asthma rates. [144]

Interestingly, using treatment with high dose corticosteroids to define SA, we did not find that EJ tracts and TRAP directly influenced asthma severity. However, asthma severity is only a single element of the clinical presentation of asthma. All clinical guidelines further incorporate asthma control as defined by exacerbations, symptoms, and lung function. Our asthma registry is uniquely positioned to address the multiple factors which make up asthma control. Unfortunately, nearly two-thirds of our asthma registry participants did not meet the well-controlled asthma criteria. Both residencies in EJ tract and TRAP were associated with poor control, unlike asthma severity. Fascinatingly, disease duration interacted with these exposures, suggesting the longer the disease duration, the greater the environmental effect. Further studies are needed to directly link disease duration to long-term residency in poor environmental situations to confirm this effect. However, biologically, it would appear likely that the longer the exposure to ongoing oxidative threats could dramatically disrupt airway homeostasis.

3.5.2 Patients with a longer duration of disease were more likely to live in an EJ area

A novel finding was the differing effect of age of diagnosis on the presence of SA in patients living in EJ tracts. We categorized patients into two groups (adult or childhood-onset of disease) and whether they lived in an EJ tract. Patients with "adult-onset" asthma had a significantly higher probability of meeting the definition of *SA* when residing in an EJ area than those not living in an EJ area. Thus, ongoing EJ tract factors (poverty, high environmental

pollution, others) could lead to the *development* of asthma, and with longer duration of "exposure" to these EJ-tract factors contribute to the progression of SA later in life. Residency in an EJ tract did not appear to influence the presence of SA when asthma was diagnosed in childhood. This discrepancy might suggest that childhood-onset asthma (and then progression to SA) is more influenced by genetic/hereditary factors, with less environmental influence. Early-onset asthma is more strongly associated with heredity and with the 17q12-21 asthma susceptibility genetic locus than late-onset asthma, where genetics have appeared to be less clear.[146-149]

Looking at factors associated with poorly controlled SA is problematic, as most SA patients in our registry are uncontrolled. However, uncontrolled asthma can also be present in a patient who does not meet the treatment (high dose ICS) criteria for SA. In contrast to potential risk factors for SA, risks for *uncontrolled* asthma in patients not meeting the SA definition were more significant in patients with childhood-onset asthma, only if they lived in an EJ area, with a longer duration of the disease again changing the effect. The differences between SA versus poorly controlled asthma in patients not on adequate (high dose ICS) therapy remain unclear. However, the stronger association between poorly controlled (and undertreated) asthma in EJ tracts, which becomes significant with longer disease duration, may suggest ongoing issues with access to proper health care. Patients living in EJ areas may have more difficulty controlling their asthma because of gene-environment interactions associated with poorer SES factors and pollution, both associated with residing in EJ areas.

3.5.3 A standardized definition of an EJ area is needed

The definition of an EJ area is still inconsistently defined. Traditionally the criteria of race and income were used to find potentially at-risk areas, given the observations that such areas frequently encounter more considerable pollution burdens than whiter and more affluent neighborhoods. In recent years, federal definitions of EJ have expanded to include $PM_{2.5}$ and proximity to major roadways (a proxy of NO_2). Locally in the Pittsburgh region, the definition is still unchanged. NO_2 is a pollutant-related TRAP and was investigated in this study. NO_2 has not exclusively been added as an environmental indicator for EJ at the federal level. However, the EPA did add "traffic proximity and volume" as an environmental indicator to consider.[150] Newer methods involving geospatial analysis have helped provide a research repository to support expanding the EPA EJ definition to include pollution such as particulate matter ($PM_{2.5}$) and Ozone (O_3).[151-152] Data from this study and others support the further investigation to determine whether incorporating NO_2 levels into the EJ definition may help identify vulnerable areas or begin to identify areas with compounding adverse environmental effects.

3.6 Study Limitations

This cohort was generated using convenience sampling rather than random sampling. Since our study population was not evenly distributed throughout the county, our exposure estimates are lower than what our population was exposed to. However, we redevise quartiles based on our population distribution to calculate exposure estimates for NO_2 and BC for only the census tracts our population lived. Because the cohort is predominately found in the urban Pittsburgh area, we

lost a difference in mean NO_2 concentrations between quintiles, weakening hyperlocal variances. Thus, quartiles of exposure were ordered from low to high pollution concentrations.

Lastly, the population of patients with SA is two-fold higher (~20%) in our cohort compared to other studies (5-10%), and almost all these patients were poorly controlled. This could stand for bias since AIR targets people with more SA for research purposes. In recent years, the purpose of the registry has evolved not just to target severe patients but rather all asthma patients. Regardless, it is helpful to have such a significant representation of people with SA to aid our studies involving environmental influences on asthma. We may be able to capture the effects that other registries are having on non-severe patients.

3.7 Conclusion

Living in an EJ tract is highly associated with worsened TRAP exposure. Yet, EJ tract alone was not associated with severe disease. However, in SA patients, living in areas with the highest NO_2 exposure significantly increased the odds of uncontrolled asthma; this was not seen in patients with less severe disease. Furthermore, in both non-severe and SA patients, the odds of uncontrolled disease were significantly or marginally increased for patients living within an EJ tract when evaluating this association with disease duration. Thus, the impact of environmental justice factors on asthma control and disease severity is an area in need of more research.

4.0 Impact of a Pollution Control Breach at a Coke Oven Factory on Asthma Control in Nearby Vulnerable Adults

4.1 Introduction

Patients with asthma tend to be more sensitive to development of symptoms from poor air quality than healthy populations. Overwhelming evidence that particulate matter (at levels of 10 ppb and at levels of 2.5 ppb)[153,154] and gases such as nitrogen dioxide[155,156] and ozone[157,158] can worsen asthma control and lead to exacerbations has accumulated. Although the mechanisms remain inadequately defined, experimental exposure to various air pollutants increases oxidative stress, which can contribute to greater airway reactivity and bronchial inflammation.[159] Although much of the recent work has focused on traffic-related emissions common in urban settings,[160,161] major industrial point sources remain in this country, including coal-fired power plants and various manufacturing plants, as well as plants related to the steel industry.

Significant industrial point sources of emissions in Allegheny County, Pennsylvania (home to Pittsburgh), that are related to its legacy as a steel industry center continue to exist. Steel manufacturing requires the use of highly refined coal, or coke, as fuel for blast furnaces to produce steel. Coke is generated from extreme heating of coal under anaerobic conditions to volatilize and remove impurities, of which hydrogen sulfide (H_2S) and, to a lesser extent, sulfur dioxide (SO_2) are major components.[162,163] Although the primary form of sulfur is in reduced form as H_2S, fugitive emissions of H_2S can spontaneously oxidize to SO_2 in the air or following deliberate flaring of coke oven gas, thereby contributing to release of SO_2 into the atmosphere. Although pollution control equipment collects and eliminates most H_2S emissions, disruption of these controls, as was

seen following a catastrophic fire at the US Steel Clairton Coke Works plant (the largest in the United States) can (and did) render this equipment inoperable. Consequently, the coke works burned a large volume of coke oven gas to eliminate the noxious H_2S and released an unprecedented amount of SO_2 into the environment over the 102 days before repairs to the damaged pollution control equipment were completed.

SO_2 is a recognized air pollutant that is monitored and regulated by the US Environmental Protection Agency (EPA). SO_2 is biochemically transformed in the atmosphere, and on the airway mucosa, SO_2 can oxidize to sulfurous acid and sulfuric acid, which function as powerful lung irritants.[164,167.] Also formed are sulfites and bisulfites, which have been reported to increase mucus production in bronchial airways.[170] These known toxic effects led to studies that associated SO_2 with both asthma exacerbations and worsened lung function, including lower lung function in children.[171,172] However, other studies have failed to show such an effect.[173]

Based on this convergence of acute large-scale increases in a known toxicant in a defined locale, prior controversies regarding SO_2 and asthma, and our institute's ability to rapidly engage patients with asthma in the regions affected by the fire, we hypothesized that compared with individuals living further away from the coke works, patients living within close proximity to it would acutely demonstrate a measurably higher asthma symptomology. We correlated these results with local air quality (in particular, SO_2 levels) during and after the fire.

4.2 Materials and Methods

The participants (n = 83) were recruited from The University of Pittsburgh Asthma Institute registry (AIR). This registry was established in 2007 and contains approximately 2200 patients

with physician-diagnosed asthma. All registrants had asthma questionnaire data and agreed to be contacted in the future for additional studies, and most of them had baseline pulmonary function testing from time of enrollment. Immediately after the fire, a 13-question environmental health survey (EHS) (see Data File EI in this article's Online Repository at www.jacionline.org) was developed for distribution to existing patients in the AIR who had been recruited to the study. A Consolidated Standards of Reporting Trials diagram outlining recruitment is presented in Fig I , and a map of the study area and patient locations within that area is presented in Fig E 1 (available in this article's Online Repository at www.jacion line.org). The buffer was set to reflect the municipalities listed as "potentially affected" by the health department, in addition to the natural break in the distribution of patients in the AIR who resided around the Pitts burgh area. Recruitment began with the identification of all patients in the AIR who resided within a 10-mile radius of the coke works fire (CWF) (n = 177). Second, individuals included in the AIR (n = 1920) were identified as potential controls if they lived distal to the CWF (i.e., those residing > 10 miles from the plant). Participant s were ordered based on their most recent involvement with the asthma institute and then contacted. Because of the time-sensitive nature of the event, recruitment was stopped after slightly more than 200 people had been contacted, leading to more than 40 participants in both the proximal and distal groups from whom rapid consent was obtained by completed phone surveys. To obtain a snapshot of their health during the *immediate* aftermath of the CWF, the patients with asthma were asked to recall information specific to the 4 weeks immediately before the date of the CWF.

Following recruitment, baseline demographic, clinical, and physiologic data were pulled from the historical AIR. An asthma severity designation of mild or moderate-to-severe was assigned to each participant by using a combination of FEV_1 percent predicted, prescribed

inhaled dosage of corticosteroid s and/or oral steroids, and symptom type and frequency. The initial cohort recruitment and questionnaire administration occurred between February l and 20, 2019, which represented the period corresponding to the pollution control failure and high emissions.

After the pollution control equipment was operational (i.e., 2-month s later), participants were invited to return to the asthma institute in person to repeat the EHS; complete an updated asthma control questionnaire; and undergo additional pulmonary function testing and determination of exhaled nitric oxide value to assess asthma severity, control, and inflammation. The University of Pittsburgh's institutional review board approved all studies.

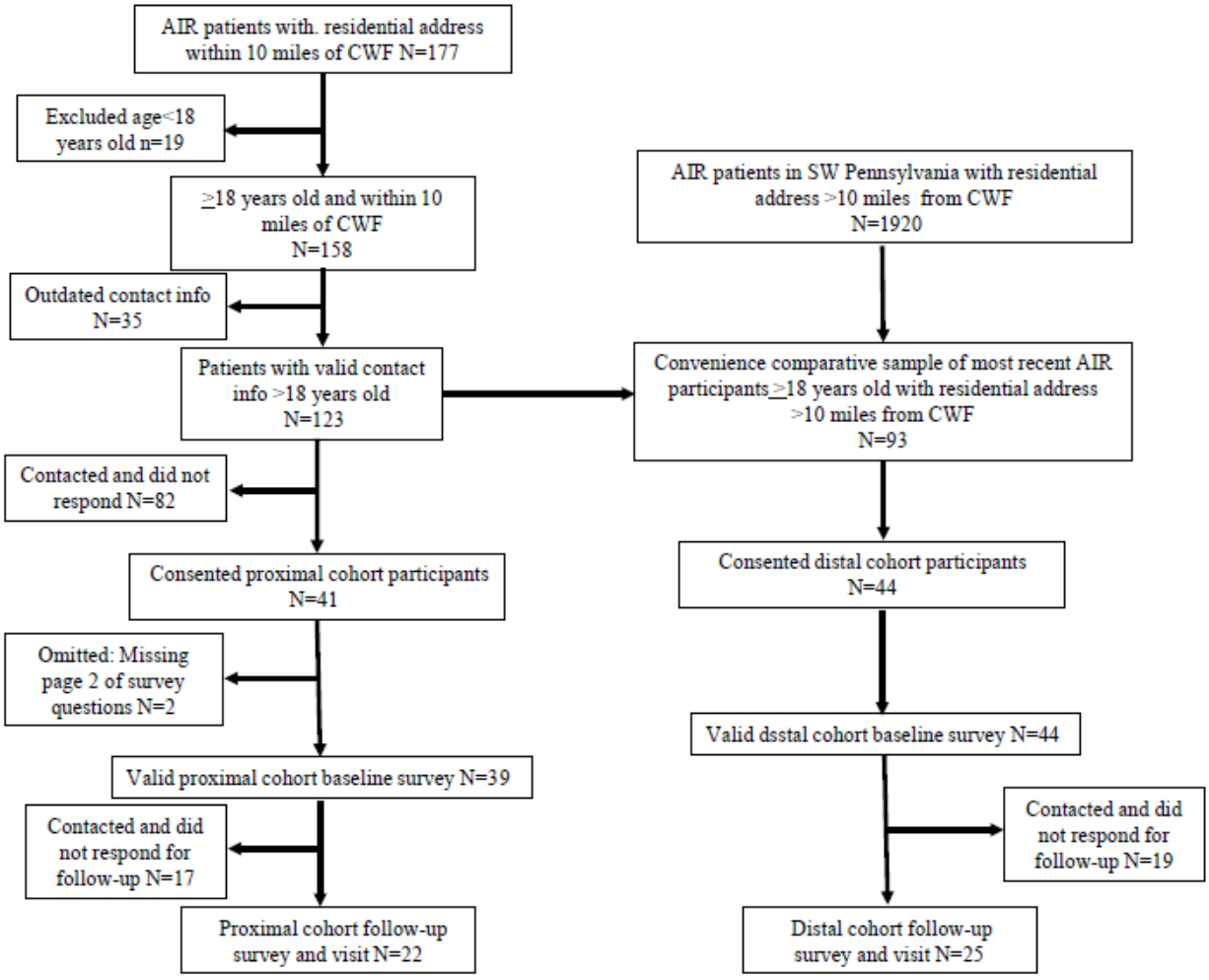


Figure 9. Consolidated Standards of Reporting Trials flow diagram outlining study recruitment, SW, Southwest.

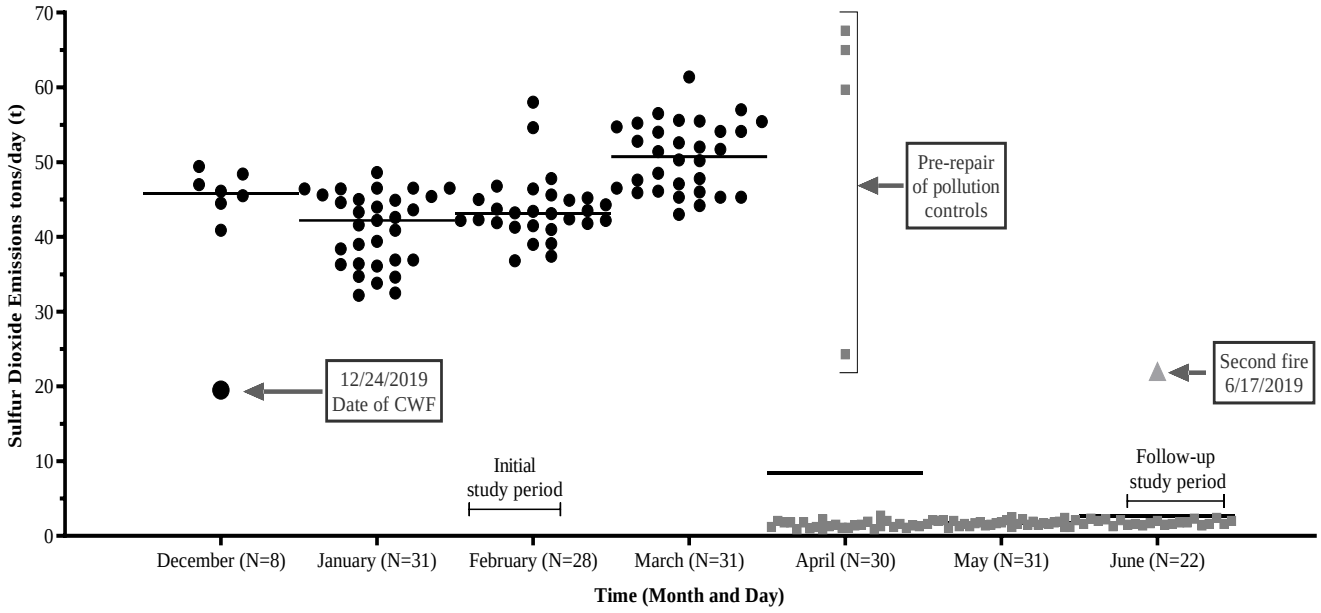


Figure 10. Each point represents a single day of Coke Works factory emissions. The larger black dot indicates the date pollution control equipment was damaged and inoperable. The grey triangle indicates a second fire that damaged pollution controls for a single day. The horizontal error bars indicate the initial baseline study and follow-up periods.

4.2.1 SO_2 Emission and Regulatory Air Monitor Data

Daily SO_2 emission estimates from the coke works corresponding to the first 6 months of 2019 were obtained from the Allegheny County Health Department. The emission data are reported as tons per day and include the amount of SO_2 released into the atmosphere directly through a variety of processes (e.g., fugitive, flaring of coke gas), as well as through secondary conversion from reduced H_2S. To determine whether elevated emissions during the time of the CWF translated into changes in ambient air quality, we compared readings at EPA regulatory air monitors proximal and distal to the CWF.

4.2.2 Statistical Analysis

Allegheny County Health Department air monitoring data were analyzed by using the nonparametric Kruskal-Wallis test followed by the Dunn multiple comparisons test. EHS responses were set up in contingency table s, and risk ratios (RRs) were calculated by using the following formula: RR = Rate[l]/Rate[2], where Rate is the proportion in the group with the condition present; is accompanied the ratios .Chi -square tests of association and the Fisher exact probability test were used in combination with the RR to determine statistical significance between group responses . Continuous data (emission, age, and lung function) are reported as means plus or minus SDs. Mann Whitney *U* tests were performed on continuous nonparametric data. The acute survey results (before the control room repair) were compared with the follow up responses (after the control room repair) by using paired *t* tests. *P* values le ss than .05 were considered significant. Data analysis and graphs were generated by using JMP Pro 14 software (SAS Inc, Cary, NC) and GraphPad Prism 8 (GraphPad Software, San Diego, California).

4.3 Results

In the immediate aftermath of the fire, SO_2 emissions from the coke works averaged between 40 and 50 tons per day. At times (especially in the months of March and April), daily emissions exceeded 50 tons per day (which was 25 times higher than the typical levels). Immediately following repair of the pollution control room, daily emissions of SO_2 declined dramatically to levels that were less than 5% of those reported during the breach (Fig 2).

In 2019 (coinciding with the large emissions of SO_2 from the coke works during the pollution control breach), daily maximal SO_2 readings and air quality index values were elevated at monitor 1 (the monitor closest to the coke works) as compared with in the previous 2 years (Fig 3). In contrast, time dependent changes in measurements of SO_2 in ambient air were not observed at either of the other 2 monitors (see Table EI in this article's Online Repository at www.jacionline.org). Thus, enhanced emission(s) of SO_2 during the pollution control breach were associated with measurable changes of SO_2 content in ambient air near the coke works.

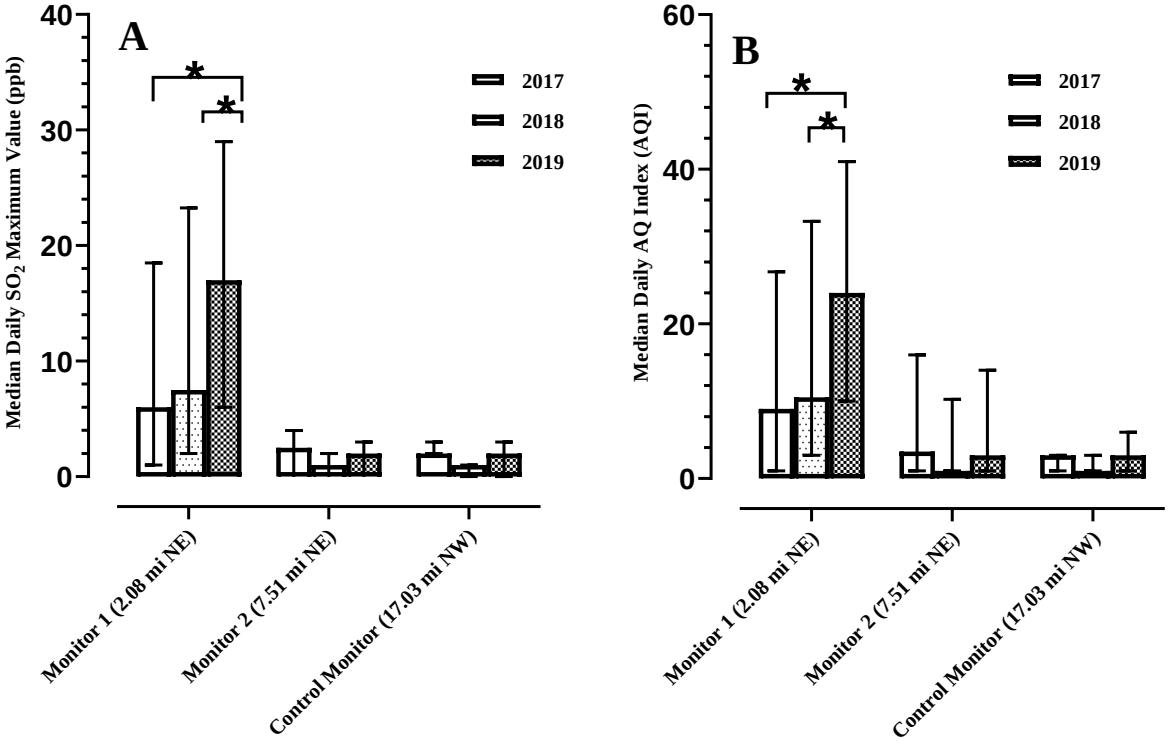


Figure 11. Figures A and B depict two proximal regulatory air monitors located within 10 miles of the CWF and one distal control monitor beyond the 10-mile range and their relative location from the Clairton Coke Works. Figures compare daily ambient SO_2 expressed as median maximum and AQI values for 2019, and after the CWF compared with historical data in 2017 and 2018 for reference.

4.3.1 Impact during the acute exposure (during loss of pollution control system)

To determine the impact of these increased emissions on asthma control, we recruited and surveyed proximal and distal (control) cohorts of patients with asthma both before and after thepollution controls had been repaired. Historical registry data (collected 1-8 years before the fire) indicated that both the proximal and distal groups were well matched regarding a variety of demographic factors, including age, race, sex, and type of health insurance (Table I). Both educational attainment and marital status tended toward being or were statistically different across the groups (*P* = .07 for education and *P* =.04 for marital status), supporting the idea of higher socioeconomic status (SES) in the distal/control group. Despite this, the groups were well matched from the standpoint of known confounders of asthma such as exposure to or history of smoking and body mass index. Notably, there was a significant difference m historical FEV1 percent predicted, and asthma-related emergency department visits compared with the values for the control group (Table I).

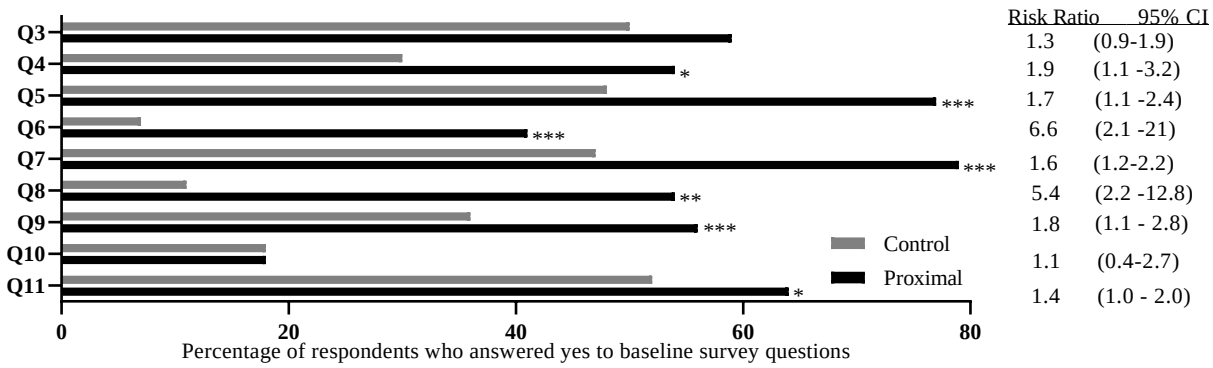
Table 9. Baseline comparison of the control and proximal cohorts using Asthma Institute Registry data. Data represents registry metrics at time of enrollment into AIR (N=83).

Characteristics	**Distal Control N=44** n (%) or Mean ± SD	**Proximal Group N=39** n (%) or Mean ± SD	*P-Value*
Age	45.1 ± 14.6	45.6 ± 14.6	0.41
Female	39 (84.0)	32 (86.0)	0.76
Non-White	16 (36)	16 (41)	0.82
Body Mass Index (BMI)	31.9 ± 11	33.1 ± 10.5	0.41
Asthma Indicators			
Mean Fev_1% predicted (SEM)	84.8 (7.1)	77.2 (12.1)	0.04*
Moderate-Severe Asthma	18 (41)	19 (49)	0.51
Health Insurance			
Medicaid	12 (27)	14 (36)	0.47
Other	32 (72)	25 (64)	
Employment Status			
Outside of Home	31 (70)	24 (62)	0.36
Education			
High School Graduate or I	4 (9)	10 (26)	0.04
Partial or College Graduat	40 (90)	29 (74)	
Marital Status			
Single or Other	22 (50)	27 (69)	0.07
Married	22 (50)	11 (28)	
Smoking Status			
History of Smoking	13 (29)	9 (23)	0.62
Secondhand Smoke	8 (18)	11 (28)	0.31

*Definition of abbreviations: * = P-value <0.05*

Given the need for rapid assessment of a potentially "at-risk" population, the first patient questionnaires given to these 2 cohorts were administered by telephone. Not surprisingly (and consistent with the SO_2 data), more patients in the proximal group than in the distal/control group reported the presence of rotten egg smells near their home and more were aware of the CWF event (Fig 4). During the period corresponding to the pollution control breach, more individuals in the proximal group than in the distal control group also self-reported an increase in asthma exacerbations (question 5) (RR = 1.7; 95% CI = 1.1-2.8; $P < .01$), as well as

increased medication use (RR= 1.4; 95% CI 1.0-2.0; *P* <.05) (Fig 4). Nearly all the patients in the proximal group (77%), as opposed to 48% of the distal controls, reported that their asthma had worsened and attributed the worsening to air pollution.



ID Questions
Q3 Over the past 30 days: Have your asthma symptoms worsened WHILE OUTDOORS
Q4 Over the past 30 days: Have your asthma symptoms worsened WHILE INDOORS
Q5 Over the past 30 days: Have you noticed a 'rotten egg' smell in the outside air near your home
Q6 Over the past 30 days: Have you noticed any other smell in the outside air near your home
Q7 Do you think air pollution in your area sometimes worsens your asthma symptoms
Q8 Are you aware of any recent events (within the last 30-60 days) that may have affected the outside air near your home (events like gas explosion, factory accidents, or fires)
Q9 Over the past 30 days: Did you have an asthma attack (coughing, wheezing, trouble breathing) that required you to take more asthma medicines than usual for you
Q10 Over the last 30 days: Did you seek medical attention (clinic visit, ER, or ambulance) for your asthma
Q11 Over the last 30 days: Have you needed to use more of your asthma medications

Figure 12. Graph depicts difference by percentage of respondents (N=83) who answered "yes" between both control and proximal groups. *Definition of abbreviations.* * = P-value < 0.05, ** = P-value < 0.005, *** = P-value < 0.0005; Rate= proportion in-group with response "yes" to "no", Risk Ratio= Rate [1]/Rate [2]; Cl= Confidence Interval. Survey questions (ID) are listed above and correspond with the question number on the y-axis.

To account for boundary effects of potential "edge bias" [133] to our 10-mile buffer zone that defined the proximal group, we examined whether there were differences in those residing less than 5 miles (n=13 [33%]) from the CWF and those residing 5 to 10 miles away (n=26 [67%]), As expected, those living closer to the factory (<5 miles away) were more likely to notice industry

smells (question 5, *P* =.01; question 6, *P* =.009) and were more aware of the CWF (question 8, *P*=.0002) than were those in the 5- to 10-mile group (see Table E2 in this article's Online Repository at www.jacionline.org). However, there were no differences in asthma control between the near and far proximal groups in the aftermath of the fire.

Lastly, because general news coverage of the CWF may have selectively influenced survey responses, we compared responses within the proximal group that was based on their expressed knowledge of the CWF (54% aware vs 46% unaware), No differences in survey responses regarding medication and/or asthma-related exacerbations based on stated awareness were observed. Of note, those reporting less awareness of the CWF tended to be more likely to report having Medicaid (53% *[P* =.16]) as their primary insurance, and they were less likely to have a college degree (71% *[P* = .07]) than those who were aware of the CWF, suggesting lower SES.

4.3.2 Follow-up (after repair)

To assess the potential impact of changing exposure to SO_2 more directly on measures of asthma control and to determine the relationship of location to current pulmonary function and airway inflammation, 2 months after repair of the pollution control room we recontacted those patients who had completed the initial survey to arrange an in-person visit Of the original cohort, 57% (22 from the proximal group and 25 from the distal control group) returned to the asthma institute after resolution of the breach for an in-person evaluation. There were baseline differences between those who completed only the phone survey and those who completed both the phone and in-person surveys, particularly within the proximal cohort (see Table E3 in this article's Online Repository at www.jacionline.org).Those in the proximal group who agreed to the follow-up visit tended to report better asthma control at the time of the phone survey than did those who answered

only the initial phone survey (see Table E3). Although there were no differences in asthma severity or FEV_1 value, those who returned reported a higher percentage of employment outside the home and a lower percentage of having Medicaid insurance than did those who did not return for the in-person survey, which is consistent with potential differences in SES. In contrast, within the distal/control group, the initial contact-only and follow-up subgroups differed solely in terms of secondhand smoke exposure (see Table E2).

Paired testing of those who completed both the phone and in person questionnaires was used for initial and follow-up comparisons of the questionnaire responses. Our analysis of the proximal group indicated persistent industry smells (question 6) and improved asthma control (questions 9 and 11) (Fig 5, *A),* which coincided with the improved factory emissions. There were no longitudinal changes in responses to the asthma control questions in the distal/control group. However, a heightened perception that adverse air quality may sometimes affect their asthma control was observed in the members of the distal/control group (question 7), on account of the repeat nature of the survey (Fig 5, *B).* Lastly, all participants who came to the asthma institute were evaluated by determination of fraction of exhaled nitric oxide, FEV_1, and asthma control questionnaire results. Overall, the proximal group had worse asthma control and more inflammation than the distal controls did, although the small sample size limited significance (Table II). A paired analysis of historical and follow-up mean FEV_1% predicted value over a 2.5-year period revealed no change in the control group *(P* = .7) but values of 73.7 versus 76.1 *(P* = .2) within the proximal group.

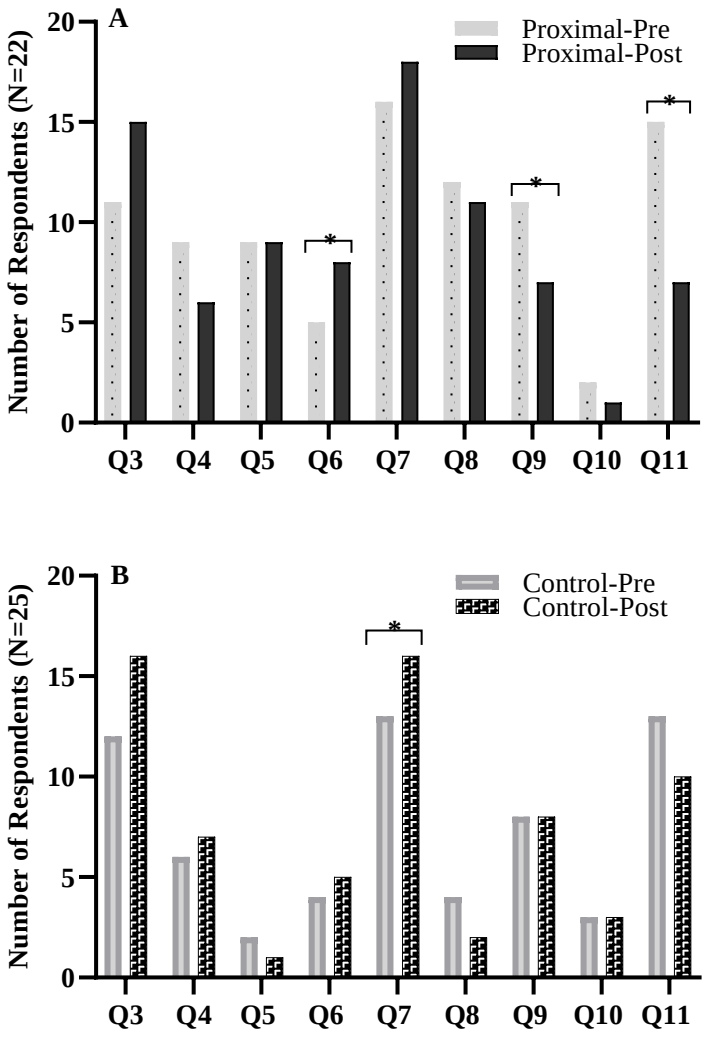


Figure 13. Figure A and B compare responses of "yes" to our survey at baseline following the CWF relative to their follow-up responses post factory repair. Reference Figure 4 for survey questions. Definition of abbreviations * = P-value <0.05.

Table 10. Baseline comparison of the control and proximal cohorts using Asthma Institute Registry data.

Data represents registry metrics at time of enrollment into AIR (N=83).

Patient Characteristics	Distal Control n (%) or Mean ± SD	Proximal Group n (%) or Mean ± SD	P-Value
Post Factory Repair			
Exhaled Nitric Oxide (FeNO)	20.3± 12.6	27.1±19	0.2
Asthma Control (ACQ)	1.32±.95	1.61±1.2	0.3
Mean Fev_1% predicted (SEM)	82.4 (16.7)	76.1 (19.6)	0.3

Definition of abbreviations: * = P-value < 0.05; Rate = proportion in groups with response "yes" to "no", Risk Ratio = Rate [1]/Rate [2], CI = Confidence Interval.

4.4 Discussion

This study provided the opportunity to examine short-term asthma outcomes relative to an individual's proximity to a major industrial event that resulted in emission of 20 times more SO_2 than is typically discharged per day over a period of several months. Key findings include measurable differences detected in self-reported asthma control between those living proximal to and distal from the CWF that corresponded to substantial changes in factory emissions and air quality. Despite the persistently poor air quality in this region, historical air monitoring data sup port our assertion that air quality during our study period was exceptionally poor and contributed to acute negative effects on asthma outcomes in our small cohort of individuals with asthma. To our knowledge, this study is the first of its kind to describe the short-term impact of real-world factory emissions from a coke works plant on well-characterized patients with asthma and to identify decrements in air quality-related health outcomes within a population of adults with asthma.

Short-term controlled (chamber) exposures to SO_2 have been shown to augment bronchoconstriction in patients with asthma.[176] Although the mechanisms of its effects are unclear, SO_2 can function as both an oxidizing agent and a reducing agent, depending on its environment.

Exposure to SO_2 has been reported to increase mucus production and lead to bronchoconstriction through un clear molecular pathways.[177] Exposure has also been linked to ex acerbations and reductions in pulmonary function (in particular, FEV_1 value).[178,179] In adults, higher SO_2 exposure during the winter months was associated with lower lung function in individuals with poorly controlled asthma.[180] Similarly, SO_2 levels were high in the winter months of our study and may have affected lung function. Other studies, however, failed to demonstrate consistent associations.[181] This may be attributable to the spectrum of study designs in the literature, combined with different outcomes. Furthermore, some individuals with asthma may respond to SO_2, whereas others may not.[182] This suggests a rationale for deeper phenotyping of these patient s to identify potential SO_2 hyper-reactive patients with asthma. Lastly, a recent study has implicated ambient SO_2 exposure to increased emergency department visits over extended lag periods.[183] These studies suggest that a multifaceted approach is needed to create a holistic picture of the impact that SO_2 has on adults with asthma.

Although a direct measure of SO_2 was not obtained at the homes of the participants, data from regulatory-grade air monitors near the plant at which the CWF occurred were publicly available. Despite persistently prominent levels of factory SO_2 emissions (over 102 days), the most proximal monitor indicated that the EPA threshold (75 ppb) was exceeded on only 9 days. This is due to a combination of meteorologic and topographic factors that in addition to emissions, influence ground-level SO_2 concentrations. The highest SO_2 concentrations occur during meteorologic inversions, which are periods when vertical mixing in the atmosphere is limited, and emissions are concentrated near the Earth's surface. The net result is that the actual ground-level SO_2 concentrations are a complex function of multiple factors influenced by both emissions and meteorology that may not be reflected in monitor measurements. Five of the days on which

the thresholds were exceeded occurred during the period of the acute survey following the CWF (i.e., from January **1** through February 20, 2019 [the baseline survey period]) (see Fig E2 in this article's Online Repository at www.jacionline.org). Importantly, these instances of the threshold being exceeded were reported only at the most proximal monitor, suggesting that the location of monitoring equipment is especially important. Communities that rely on a few citywide air monitors are unable to model a population's true exposure. This is especially true in communities with varying topography and/or with major point sources that can have disproportionate impacts on areas immediately downwind. In-home monitoring may be needed to better reflect the more localized impact of point source pollution.

The acute health effects measured throughout this study trended with air quality and emission changes. First, those living close to the CWF reported worse outcomes than did those who lived further away during the same period, corresponding to elevated emissions. This minimizes the chance that weather, or prevalence of seasonal respiratory infections contributed the differences. Supporting this, longitudinal data on those patients who completed both phases of the study indicated that asthma control improved from the immediate post-fire period in the proximal group, when pollution controls were operational and air quality improved.

To control for information bias, we examined whether participants who knew about the CWF answered their questions differently from participants who did not know about it. Responses did not differ between those with and those without knowledge of the fire. However, those who were less likely to be aware (nearly 50% of the proximal group) of the CWF also reported a lower SES.

This study demonstrates the benefits of having a preexisting interactive asthma registry of well-characterized patient s with asthma. Participant consent gave us the ability to quickly gain access to patients following an environmental disaster. This study also revealed some potential

reasons why some patients may be more likely to follow up or participate in environmental health research than others. Patients with poorer SES indicators and less education may have transportation issues or work in occupations with limited paid time off, and therefore, such patients are less likely to visit the asthma institute. Because participant dropout is an unfortunate reality of research studies, our aim was to better understand the population that did not complete our study. The asthma registry data allowed us to compare various SESs and other metrics between groups. Participants who did not return to the asthma institute for the follow-up visit tended to have poorer asthma control, and according to the baseline survey, these participants were more likely to report a clinic, emergency department, or ambulance visit because of their asthma. Additionally, this subgroup tended to have poorer SES indicators. These factors may have influenced communication and transportation efforts within this subgroup. Unfortunately, because this subgroup did not complete the follow-up questionnaire, we were unable to discern how their asthma control may have changed with improved air quality.

Some incidental findings of our study alluded to the potential for more chronic asthma-related issues within this cohort based on their residential proximity to the coke works. When considering the historical registry data, we identified significant baseline differences in mean lung function between those proximal to the coke works and those distal from it. Although multiple factors could have contributed to these differences, the 2 groups were well matched for baseline demographics, as well as for smoking status and SES. This suggests that chronic exposures may adversely affect lung health, and it warrants further study in larger patient surveys.

This study focused specifically on emissions associated with an operational failure at a single point source near Pittsburgh. Excess emissions after the CWF, modified by meteorology and topography, affected ground-level air pollution as well as the resultant exposure and health impacts

cataloged here. Exposure assessment was limited because the sparse network of air pollutant monitors did not enable neighborhood-level air quality assessment. Com munities in other cities are also affected by nearby point sources, and exposure estimates in those locations may be similarly affected by a lack of nearby monitors.

4.5 Study Limitations

As with all human and environmental studies, the potential for confounders exists. The largest concern is the small cohort, in which confounders may have influenced the observed differences. Overall, however, the 2 groups were well matched, and in the proximal group, differences improved in concert with improved air quality when other factors were constant. Our study population was not a random population; rather, it was derived from an existing asthma registry. However, given the historical information on these patients, including the results of standard lung function testing, it is very likely that these patients did indeed have asthma, as compared with individuals contacted through use of random dialing approaches.[183] Importantly, only 50 % of patients returned to the asthma institute for full evaluation after the repairs had been completed, and consequently, they returned in a different season (winter vs spring). There were substantial differences between those who returned and those who did not, which may explain the resolution of all clinical differences between the 2 groups at the later follow-up.

4.6 Conclusion

Data from this study reveal an association between acute exposures to increased ambient levels of SO_2 and worsened asthma control in a potentially vulnerable population living close to the source of the pollution. However, it also supports the loss of acute effects when EPA-established air quality levels are reestablished. Although our data additionally suggest that chronic long-term exposure may negatively influence lung function, further study is needed.

5.0 Summary and Health Significance

5.1 Overview

The primary objective of these studies was to examine outdoor air pollution in combination with sociodemographic factors as predictors of asthma severity and control. We selected study designs based on the nature of our hypothesis, such that adequate power would be obtained to address each aim effectively. Below, I present the specific aims and discuss the main findings reported in previous chapters. I then explain how each aim contributed to the cumulative impact of these studies and describe what our results infer about asthma. For a more comprehensive discussion of these results, please refer to the "discussion" section within the respective chapter for each study.

Strengths of this research reveal: (i) an association between O_3 exposure in children and NO_2 and CO exposure in adults with asthma-related ED visits within the greater Pittsburgh area; (ii) Severe asthma patients living in areas with the highest NO_2 exposure had increased odds of uncontrolled asthma (not observed in milder patients), and disease duration was associated with uncontrolled asthma for patients living in EJ areas; and (iii) a novel association between acute real-world exposures to increased SO_2 and worsened asthma control in a vulnerable population living close to the source of pollution.

5.2 Summary of Research Progression

5.2.1 Time Stratified Case- Crossover Study: Study 1

Initially, we wanted to identify the prevalence of asthma exacerbations within the general county population. We included both children and adults in this study. Utilizing EMR patient records, we used asthma-related ED visits as a surrogate to identify patients with asthma. We then characterized the timing of the ED visit relative to local ambient air pollution from two centrally located county air monitors. To study this, we devised a time-stratified case-crossover study (study 1); case-crossover is a method widely used in environmental epidemiology. We first used single pollutant models for $PM_{2.5}$, O_3, NO_2, SO_2, and CO. We gradually increased the model complexity to investigate whether the odds of an ED visit observed in a single pollutant model persisted in the presence of PM or other gaseous pollutants. Key findings from this study include 1) a positive association between O_3 exposure and ED visits in children at lag day one that persisted in the multipollutant model and 2) NO_2 and CO exposure in adults and ED visits at lag day 5 see only in the respective single pollutant models.

We reported increased odds of asthma-related ED visits corresponding to specific air pollutants in children compared with adults. Many studies focus solely on adult or child populations and do not typically combine both groups in a single study. A strength of our research was in our extended lag day analysis (through day 5) and our statistical approach using single, double, and multi-pollutant models. Often studies rely on single models or examine lag days 1-3, which may potentially impact their findings.

Ambient O_3 was associated with increased odds of asthma-related ED visits in children, though not adults. This association persisted in the single, double, and multi-pollutant models at

similar odds ratios suggesting a strong independent effect of O_3 on ED visits. In adults, increases in NO_2 and CO were associated with increased odds of an ED visit at lag day 5, though only in single pollutant models. While both pollutants demonstrated a positive association between exposure and disease control, we cannot infer the additive or antagonist cumulative effect these pollutants may have because their significance was lost in the multi-pollutant models. This raises the potential to overestimate the health effect of these pollutants. Extended lags (lag 5) have been linked to occupational exposures associated with combustible engines such as petroleum refineries, warehouses, or working around traffic. Additional studies are needed better to understand the significance of this extended lag effect. This is a limitation to our interpretation, as other pollutants may also compound the health effect. Some studies suggest delayed effects might exist between various pollutants and asthma outcomes related to delayed biologic and physiologic responses[76]. Our findings suggest NO_2, and CO exposure (known markers of traffic-related pollution) may contribute to asthma exacerbations and urgent ED visits in adults.

Significant associations observed at extended lag periods in the current study (e.g., lag day 5) suggest the potential for underlying biological mechanisms as potential contributors to this delayed response. Another possibility is the possible delay in asthmatics seeking ED treatment. Such a delay may be different for adults than for children. This study observed increased odds of ED visits that tracked increased pollution within the general county population. Furthermore, our approach in combining both children and adults allowed us to observe the striking differences in ED visits by age and sex.

5.2.2 Retrospective Study: Study 2

Next, we wanted to focus on a defined asthma population. Thus, we utilized an established asthma research registry. We applied a retrospective study methodology and built a statistical model to interpret the registry data and spatially improve air pollution data. This approach allowed us to investigate geographic and demographic factors as predictors of asthma severity and control.

Using an asthma registry, we evaluated whether the relationship between residency in an EJ tract, defined by race and poverty, was associated with exposure to worsening environmental pollution and worsened asthma severity or control. Our decision to incorporate disease severity (and control) was based on clinical reasoning obtained from the literature, which describes a significant overlap between indicators of control and severity. We hypothesized that asthma severity and control would be worsened by living within a *designated EJ census tract*. Additionally, we used *neighborhood-level* pollution concentrations (generated in collaboration with Carnegie Mellon University), as opposed to *county-level* estimates (previously used in study 1), to calculate exposure estimates for these smaller geographical units (census tracts). Key findings from this study include 1) Severe asthma patients living in areas with the highest NO_2 exposure had increased odds of uncontrolled asthma (not seen in milder patients), and 2) Disease duration was associated with uncontrolled asthma for patients living in EJ areas.

A novel finding was the differing effect of age of diagnosis on the presence of severe asthma in patients living in EJ tracts. We categorized patients into two groups (adult or childhood-onset of disease) and whether they lived in an EJ tract. Patients with "adult-onset" asthma had a significantly higher probability of meeting the definition of *severe* asthma when living in an EJ area than those not living in an EJ area. Thus, ongoing EJ tract factors (poverty, high environmental pollution, others) could lead to the *development* of asthma, and with longer duration of "exposure"

to these EJ-tract factors contribute to progression of severe asthma later in life. Residency in an EJ tract did not appear to influence the presence of severe asthma when asthma was diagnosed in childhood. This discrepancy might suggest that childhood onset asthma (and then progression to severe asthma) is more influenced by genetic/hereditary factors, with less environmental influence. In fact, early-onset asthma is more strongly associated with heredity and with the 17q12-21 asthma susceptibility genetic locus than late-onset asthma, where genetics may be less influential.[146-149]

Interestingly, previous studies suggest minorities have a disproportionate risk of developing severe and uncontrolled asthma. Within the asthma registry, minorities were represented in higher proportions than the county. Our initial paper (study 1) did not include race or poverty metrics. Looking at factors associated with poorly controlled severe asthma is problematic, as most severe asthma participants in our registry are uncontrolled. However, uncontrolled asthma can also be present in patients who do not meet the treatment (high dose ICS) criteria for severe asthma.

In contrast to potential risk factors for severe asthma, risks for *uncontrolled* asthma in patients not meeting the severe asthma definition were more significant in patients with childhood-onset asthma, only if they lived in an EJ area, with a longer disease duration again changing the effect. The reasons for these differences between severe asthma versus poorly controlled asthma in participants not on adequate (high dose ICS) therapy remain unclear. However, the stronger association between poorly controlled (not on ICS) asthma in EJ tracts, which becomes significant with longer disease duration, may suggest ongoing issues with access to proper health care. Patients living in EJ areas may have more difficulty controlling their asthma because of gene-environment interactions associated with poorer SES factors and pollution, both associated with residing in EJ areas.

The definition of an EJ area is still inconsistently defined. Traditionally the criteria of race and income were used to find potentially at-risk areas, given the observations that such areas frequently encounter more considerable pollution burdens than whiter and more affluent neighborhoods. In recent years, federal definitions of EJ have expanded to include $PM_{2.5}$ and proximity to major roadways (a proxy of NO_2). Locally in the Pittsburgh region, the definition is still unchanged. NO_2 is a pollutant-related TRAP and was investigated in this study. NO_2 has not exclusively been added as an environmental indicator for EJ at the federal level. However, the EPA did add "traffic proximity and volume" as an environmental indicator to consider.[150] Newer methods involving geospatial analysis have helped provide a research repository to support expanding the EPA EJ definition to include pollution such as particulate matter ($PM_{2.5}$) and Ozone (O_3).[139-140] Data from this study and others support further investigating whether incorporating NO_2 levels into the EJ definition may help identify additional vulnerable areas. Lastly, this study demonstrates the importance and complexity of considering many clinical and demographic factors with environmental pollution. Further studies are needed to understand better some of the interactions we reported.

Cohort Study: Study 3

While working on this dissertation project, the Clairton Coke Works factory fire happened. Since we were well-positioned to engage participants quickly, we utilized the asthma registry again to devise a rapid-response cohort study to research the potential health impacts of prolonged factory emissions on people with asthma.

This study is the first to describe the short-term impact of real-world factory emissions from a coke works plant on well-characterized patients with asthma and identify decrements in air quality-related health outcomes within a population of adults with asthma. Key findings include

measurable differences in self-reported asthma control between those living proximal to and distal from the CWF, corresponding to substantial changes in factory emissions and air quality.

Despite the persistently poor air quality in this region, air monitoring data support our assertion that air quality after the acute event was exceptionally poor and was likely to contribute to the loss of asthma control observed in our small proximally located cohort of individuals with asthma. Exposure to SO_2 has been reported to increase mucus production and lead to bronchoconstriction through unclear molecular pathways.[155] Exposure has also been linked to exacerbations and reductions in pulmonary function (in particular, FEV1 value).[156-157] In adults, higher SO_2 exposure during the winter months was associated with lower lung function in individuals with poorly controlled asthma. Similarly, SO_2 levels were increased in the winter months of our study and may have affected lung function. Other studies, however, failed to demonstrate consistent associations.[138] This may be attributable to the spectrum of study designs in the literature, combined with different outcomes.

Furthermore, some individuals with asthma may respond to SO_2, whereas others may not. This suggests a rationale for deeper phenotyping of these patients to identify potential SO_2-hyperreactive patients with asthma. Lastly, a recent study has implicated ambient SO_2 exposure to increased emergency department visits over extended lag periods.[140] These studies suggest that a multifaceted approach is needed to create a holistic picture of the impact that SO_2 has on adults with asthma. Although a direct measure of SO_2 was not obtained at the participants' homes, data from regulatory-grade air monitors near the plant where the CWF occurred were publicly available.

Data from this study reveal an association between acute exposures to increased ambient levels of SO_2 and worsened asthma control in a nearby susceptible population living close to the

source of the pollution. However, it also supports the loss of acute effects when EPA-established air quality levels are reestablished. Although our data suggest that chronic long-term exposure may negatively influence lung function, further study is needed.

Public Health Significance and Air Quality Standards

Our studies report asthma-related health effects at levels below the current EPA standards. Our initial paper demonstrated a 10 µg/m3 rise in atmospheric ozone concentrations, regardless of ambient levels, increased the odds of an asthma-related ED visit in children. Additionally, our data suggest an extended lag effect for NO_2 and CO (ppm) and ED visits in adults. The second study we performed reported associations between the highest quartile of NO_2 (mean 10.4 ppb) with a 3-fold increase in predicting severe uncontrolled asthma even when accounting for differences in SES and race. Lastly, while we did not directly measure personal exposures to SO_2, we demonstrated the association between worsened asthma control and increases in ambient SO_2 that tracked with increased factory emissions and the loss of acute health effects when factory emissions declined. We were surprised to find that while EPA regulatory air monitor (hourly) exceedances of SO_2 did occur, they did not persist despite factory emission concentrations remaining consistent for approximately three months to repair the factory's pollution controls. This inconsistency suggests stationary EPA regional monitors may not provide adequate spatial-temporal variances of air pollution. This may be from contributions including but not limited to meteorological variables such as wind direction and temperature inversions.

Similar to previously published studies, our research report health effects at levels below the EPA standard. Collectively, the literature suggests health impacts occur from both acute and chronic exposures to low levels of air pollution. A recent 2021 study provided evidence of causal

factors between air pollution and mortality. They estimated 69,385 preventable "early" deaths could be spared annually if we lowered the air quality standard for each air pollutant.[77].

Health outcomes from prior European cohorts have recently been remodeled using new exposure models with an increased spatial resolution of 100 m x 100 m. Their analyses provide objective evidence of health effects at low levels of exposure.[78] Studies consistently reveal cardiovascular and respiratory health effects below the national (U.S.) and global (WHO) air pollution standards.[78],[79] Newer models using enhanced spatial resolution have been developed.[79]. These and similar data could be informative in re-assessing the appropriateness of the current air quality standards and may justify new thresholds. Modeling approaches used by the EPA to estimate health effects were initially set using single pollutant models. For instance, does it make sense to average the pollutant concentrations nationally? Perhaps not.

The impact of pollution on asthma exacerbations is an area in need of more research.[142] Managing indoor and outdoor air pollution has been linked to reductions in asthma symptomology. Reducing air pollution is key to improving the quality of life for people living with this disease. Thus, studies like ours investigating external environmental influences on asthma control and disease progression are critical since asthma symptoms are often triggered by inhaled substances and particles that irritate the airways.[143]

5.3 Study Limitations

As with all epidemiological studies, limitations exist. Each of the three studies used a different surrogate for air pollution exposure estimates. While many studies have been published using similar exposure assessment methods, the chosen method for a particular analysis may

influence the results, leading to possible under (or over) estimations of exposure. Except for paper 2, where land-use regression data was used to determine exposure estimates, relying on a small air monitor network for pollution data rather than hyper-local conditions may impact the analysis. Furthermore, results can vary with each study depending on the case definition and quality of exposure data.

Study size is another limitation. While a more extensive study size is desirable to achieve ample power, we had a small cohort of children for our first study and a small cohort of adults in our 3rd study. This leaves to question whether the reported effects would be observed in a larger study population. See each below for specific limitations associated with each study design.

5.3.1 Small Air Monitor Network

Study 1) Environmental factors such as elevation could not be controlled entirely and could have influenced the results. O_3 tends to be increased at higher elevations.[46] Furthermore, we utilized two EPA grade reference monitors from distinct locations within Allegheny County to perform the analyses. Because of this small air monitor network, we relied on regional pollution data rather than hyper-local conditions. Therefore, we could not capture local-scale spatial variations that may have occurred for various pollutants. This is one plausible reason that the effects of ozone, considered a regional pollutant with less spatial variability, was more consistent across multi-pollutant models, then other pollutants which could have much more spatial variability. The more distant monitor that provided SO_2 concentrations may not have been representative of the entire cohorts' ambient exposure since the participating hospitals were clustered near the Pittsburgh reference monitor.

Furthermore, due to the limited nature of our dataset, confounders such as socioeconomic status, type of health insurance, the severity of asthma, and use of controller therapy were not examined. Lastly, ED visits for asthma are only one piece of a larger picture that describes the asthma burden. Future studies should consider multiple endpoints (i.e., ED visits, school-based clinic visits, and outpatient physician office visits) to understand better how air pollutants exacerbate asthma control.

5.3.2 Pollutant Modeling

In our published study, we did not elaborate on the implications of model selection. Depending on the strength of the correlations between pollutants (which may change with the seasons), it is possible to under-or- overestimate adverse health effects from short-term exposures (Parajuli et al., 2021). Additionally, since NO_2 and CO were significantly associated in the single pollutant models but lost significance in the multipollutant model, this raises concerns about the potential overestimation of their health effects.

5.3.3 Convenience Sampling

Study 2) The study cohort was generated using convenience sampling rather than randomization. Because the distribution of the registry population was clustered in the Pittsburgh area, our approach reduced the ability to assign exposure estimates at the census tract level. We reassigned quartiles based on population distribution, not actual pollution concentrations, to determine the most appropriate method to estimate exposure. This led to a difference in mean

NO_2 concentrations between quartiles, weakening hyperlocal variances. Quartiles of exposure were instead ranked by pollutant concentration (designated as low to high) Q1-Q4.

Using the existing asthma registry was a convenience sample rather than randomly sampling the county population. Our study population is unevenly distributed throughout the county within the registry. Additionally, registry participants were enrolled over ten years rather than within a single year for this study. We adjusted for the enrollment period (by year) to account for clustering effects by year within our models.

Lastly, the population of patients with severe asthma is two-fold higher (~20%) in our cohort compared to other studies (5-10%). This could stand for bias since AIR targets people with more severe asthma for research purposes. In recent years, the purpose of the registry has evolved not just to target severe patients but rather all asthma patients. Regardless, it is helpful to have such a significant representation of people with severe asthma to aid our studies involving environmental influences on asthma. We may be able to capture the effects that other registries having less severe patients would not capture.

5.3.4 Small Cohort Size

Study 3) The most considerable concern is the small cohort, in which confounders may have influenced the observed differences. Overall, however, the two groups were well matched, and in the proximal group, differences improved in concert with improved air quality when other factors were constant. Our study population was not random; instead, it was derived from an existing asthma registry. However, given the historical information on these patients, including % reversal data from an albuterol challenge, we ensured patients we recruited had physician-

diagnosed asthma rather than relying on a self-reported asthma diagnosis if contacted individuals through a random dialing approach.

Notably, only 50% of patients returned to the asthma institute for full evaluation after completing the repairs. Consequently, they returned in a different season than when they were initially surveyed. There were substantial differences between those who returned and those who did not, which may explain the resolution of all clinical differences between the two groups at the last follow-up.

For exposure estimates, we analyzed factory emission data alongside local EPA grade reference monitors to assess air quality in our study and then compared it with prior years for reference. Without obtaining hyperlocal measurements, we could not precisely determine differences in exposure within our group proximal to the event.

5.3.5 Limitations of Convenience Sampling from an Asthma Registry

While there are numerous advantages to using an asthma registry, a form of convenience sampling, obvious limitations must be considered when interpreting the data. Several factors influence the decision of prospective participants to join a registry with the potential to bias outcomes, including the perceived benefit of participation, availability of time, perceived relevance of the research to oneself, the credibility of the registry, and incentives for participation. Incentivizing participation has been reported to increase survey response rates. The AELHI compensates participants for their travel and time and provides an ongoing benefit to the enrollee through information sharing and social media updates.

5.3.6 Misclassification Bias

Misclassification bias occurs when inaccurate information is reported by or about the participant. For example, assigning a study participant as exposed or unexposed is critical to the outcome studied in exposure studies. An instance where this type of bias might occur may be from the participant's outdated or incorrect address. This is an example of “differential misclassification.”

5.3.7 Recall Bias

Studies have shown that a participant’s ability to recall events beyond 30 days diminishes accurately. This is especially true when requesting detailed information about their health status or circumstance. Additionally, their current health status can alter their perception of their past health status.

5.3.8 Self-Report Bias

Surveys are standard approaches for gathering data within a registry. Self-report bias may occur when participants are asked to assess their health or type/level of exposure. Recall bias is intertwined with self-reporting errors and may synergistically influence how participants respond. We can minimize these effects by comparing self-reported health/exposure information to objective data such as EMR or pollution measurements.

5.4 Public Health Significance

Our data report adverse health effects below actionable limits set by the EPA. Reductions in air quality and reassessment of old methods used to quantify air pollution for setting thresholds should be reconsidered. The current EPA thresholds were developed based on single pollutant models. These data are especially advantageous to Allegheny County and help local citizens, and lawmakers understand the impacts of air pollution and asthma locally.

Moreover, despite the best efforts from public health officials to spread information via (television and social media) that could help communities make informed decisions related to their health, not everyone will receive that information, especially those in vulnerable communities. More work needs to be done to engage county residents and improve communication efforts regarding environmental impacts on local health.

Furthermore, publishing our data in a journal that health care providers worldwide can access helps spread awareness amongst clinicians about the role changes in air pollution can have on people with asthma. These data highlight the importance of considering environmental triggers patients may experience, and conscience efforts should be made to reduce them.

Lastly, having a registry like the AELHI has numerous advantages for research and surveillance, intervention efforts, and two-way communication. Allegheny County is unique because the local health department is the guardian of public health and regulatory/enforcement entity for industry activities. They are the protectors of public health and have the exclusive ability to craft public health policies that match their regulatory efforts. In 2018, ACHD launched the "Asthma Task Force," which helped pave the way for collaboration with the University of Pittsburgh. These efforts led to the enhancement and expansion of the AELHI registry to harmonize community and clinical efforts, establish 2-way communication with participants, and

advance research that could positively influence the lives of people with asthma. Because different communities experience different environmental challenges, I would encourage this type of registry in other communities to improve the knowledge related to environmental impacts on those with a pre-existing condition, like asthma.

5.5 Concluding Interpretations from these Studies

Cumulatively, these data support our assertion that chronic exposure to poor air quality, particularly exposure to ambient increases in criteria pollutants, can worsen asthma control and may influence the severity of the disease. While demographic and SES can influence asthma outcomes, how these factors work in synergy with air pollution remains unclear. Future studies with a similar focus would benefit from harmonizing methods for collecting health outcomes and air pollution data to obtain high-quality data and strengthen findings.

6.0 Next Steps and Future Directions

6.1 Unexpected Findings

6.1.1 Study 1: Lagged Association of Ambient Outdoor Air Pollutants on Asthma Related Emergency Department Visits within the Pittsburgh Region

Interestingly, our model found no association between lagged ED visits and $PM_{2.5}$. Many studies have found significant associations between increased ED visits and $PM_{2.5}$ exposure. A potential factor influencing our findings may be using a centralized stationary air monitor. Particulate matter may vary significantly depending on the proximity of sources that produce such air pollution. Therefore, the exposure estimates used in our model may not sufficiently represent the actual exposures to which our study population was exposed.

6.1.2 Study 2: Use of an Asthma Registry to Examine the Association of Environmental Justice Factors and Traffic Pollutant Exposure on Severe Asthma and Control (publication in progress)

Overall, my hypotheses were not supported. My initial hypothesis "SA and poor control will be increased in areas of highest pollution (both NO_2 and BC) and EJ tracts" was partially supported in that "control status" was influenced by pollution and EJ factors independent of clinical and demographic characteristics, but not severity alone. However, when exposure variables were incorporated into a fully adjusted model, the statistical significance went away

despite the positive association remaining. Lastly, it was unexpected that residing in the State of Pennsylvania Department of Environmental Protection (PADEP) defined EJ tracts alone was not a predictor of severe asthma. Although our model did indicate elements of EJ such as race and poorer SES indicators were associated with an increased likelihood of a severe asthma diagnosis.

6.1.3 Study 3: Impact of a pollution breach at a coke oven factory on asthma control in nearby vulnerable adults

Overall, my hypothesis was supported. We captured both the dramatic increase in sustained ambient sulfur dioxide (SO_2) emissions resulting from a real-world environmental disaster and the impact on asthma control. A registry in place allowed us to recruit previously consented patients for this study quickly. I was impressed to learn how well-positioned we were to engage swiftly and recruit asthma registry patients for this cohort study!

6.2 Lessons Learned

I had the fortunate opportunity and resources to devise studies that utilized both EMR (paper 1) and robust registry data (papers 2 and 3). I found myself left with many unanswered questions due to the limited nature of the EMR data. I learned many advantages of having in-depth data when addressing my research questions. Air pollution and asthma studies can yield discrepant results. More concordant results could be possible if data collection were standardized, and consistent measures of air pollutants were used to evaluate the impact of the environment on asthma outcomes.

I regret not including follow-up participants in our Clairton study that were unable to come into the Asthma Institute; they still may have been able to complete a survey by phone. In addition to the impact of the pollution breach, we learned that in-person follow-up might be more difficult for some individuals than others. Yet, their data are no less important. This study showed that it might be even more critical to obtain, as these participants had worse asthma and lower social and economic advantages. It would have been advantageous to have more participants included in the survey responses, which could have quickly been completed by phone. Instead, our focus was on those committed to coming into the Asthma Institute to receive pulmonary function testing, capture their current asthma control status, and complete the initial baseline questionnaire. We were well-positioned to move quickly to devise and conduct this study. The timing for the eventual resolution of the elevated emissions and closing of the exposure window was uncertain. Unfortunately, we had to tolerate certain shortcomings to gather the data quickly because we were time constrained. However, we will devise studies that recognize that participants may not have equal opportunities to participate in in-person research in the future.

6.3 Future Directions and Next Steps

Our data revealed interesting associations between asthma and the proximity to point pollution sources. My dissertation work's focus has been on the impact of outdoor ambient air pollution and SES factors on asthma. We have established a measurable health effect based on proximity to high ambient outdoor emissions and asthma control. Additionally, anecdotal evidence from our registry suggests lung function may worsen with increasing proximity to a point pollution source. Furthermore, those who lived east of the point source had poorer lung function than that

west of the point source, suggesting that living downwind of the pollution source may affect lung function instead of living upwind. This needs to be investigated further, and I propose a method to accomplish this below.

Because outdoor air pollution is not the only air we breathe, future studies should consider indoor and outdoor air quality measurements. While I did not explicitly look at asthma outcomes and indoor air pollution, devising a subsequent study to evaluate indoor and outdoor pollution would provide a more holistic view of the exposure-effect relationship among asthma patients.

Since my work was in Southwestern PA, and this location is ideal for studying asthma and air pollution, I would propose a pilot study located in the Mon Valley of Allegheny County to answer the following hypothesis.

"Adults with asthma living within 3 miles, and downwind from a point pollution source will have higher indoor/outdoor air pollution and poorer lung function than their upwind counterparts."

I propose a cross-sectional study to capture lung function and air pollution exposure simultaneously. Specific aims would include

I. Establish whether asthma patients within 3 miles and downwind from point pollution sources have higher outdoor/indoor air pollution than those living upwind

II. Model the exposure-response relationship between indoor air pollution concentration and lung function to determine whether residing downwind from a point source modifies this relationship in healthy and asthmatic patients.

Lastly, as a separate and more cost-effective option, I would propose evaluating the bio-banked blood samples from the patients in the Coke Works cohort to examine global methylation patterns to determine whether methylation increases with increasing proximity to the pollution

source. Furthermore, genes associated explicitly with asthma control could be targeted for epigenetic analysis.

Appendix A (Supplementary Tables S1-S14) Odds Ratios for ED visits using Single and Multi-Pollutant Models

Supplementary Table 1. Children/Teens Age 5–17: Asthma ED Visits, for $PM_{2.5}$ (per 10 µg/m^3). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
$PM_{2.5}$_10µg	−0.15351	0.07907	3.7692	0.0522	0.858	0.735	1.001
AvgTemp	0.00632	0.00486	1.6929	0.1932	1.006	0.997	1.016
Lag 1							
$PM_{2.5}$_10µg	−0.06593	0.07801	0.7143	0.3980	0.936	0.803	1.091
AvgTemp	0.00939	0.00482	3.7993	0.0513	1.009	1.000	1.019
Lag 2							
$PM_{2.5}$_10µg	−0.01152	0.07831	0.0216	0.8831	0.989	0.848	1.153
AvgTemp	0.00297	0.00486	0.3741	0.5408	1.003	0.993	1.013
Lag 3							
$PM_{2.5}$_10µg	−0.01554	0.07864	0.0390	0.8434	0.985	0.844	1.149
AvgTemp	0.00442	0.00486	0.8289	0.3626	1.004	0.995	1.014
Lag 4							
$PM_{2.5}$_10µg	**0.05658**	0.08091	0.4891	0.4843	1.058	0.903	1.240
AvgTemp	0.00249	0.00499	0.2484	0.6182	1.002	0.993	1.012
Lag 5							
$PM_{2.5}$_10µg	0.07370	0.08001	0.8484	0.3570	1.076	0.920	1.259
AvgTemp	−0.00064	0.00505	0.0165	0.8977	0.999	0.990	1.009
Lag 0–5							
$PM_{2.5}$_10µg	−0.04453	0.12565	0.1256	0.7230	0.956	0.748	1.224
AvgTemp	0.00850	0.00686	1.5345	0.2154	1.009	0.995	1.022

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 2. Children/Teens Age 5-17: Asthma ED Visits for Ozone (per 10 ppb). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
O_3_10ppb	-0.00022	0.04200	0.0000	0.9958	1.000	0.921	1.086
AvgTemp	0.00389	0.00496	0.6167	0.4323	1.004	0.994	1.014
Lag 1							
O_3_10ppb	0.09963	0.04240	5.5230	0.0188	1.105	1.017	1.200
AvgTemp	0.00455	0.00493	0.8507	0.3564	1.005	0.995	1.014
Lag 2							
O_3_10ppb	0.01652	0.04155	0.1581	0.6909	1.017	0.937	1.103
AvgTemp	0.00211	0.00493	0.1830	0.6688	1.002	0.992	1.012
Lag 3							
O_3_10ppb	0.02213	0.04150	0.2843	0.5939	1.022	0.943	1.109
AvgTemp	0.00331	0.00491	0.4528	0.5010	1.003	0.994	1.013
Lag 4							
O_3_10ppb	0.04718	0.04227	1.2459	0.2643	1.048	0.965	1.139
AvgTemp	0.00182	0.00499	0.1336	0.7147	1.002	0.992	1.012
Lag 5							
O_3_10ppb	-0.02610	0.04141	0.3973	0.5285	0.974	0.898	1.057
AvgTemp	0.00179	0.00507	0.1249	0.7237	1.002	0.992	1.012
Lag 0-5							
O_3_10ppb	0.07201	0.06932	1.0789	0.2989	1.075	0.938	1.231
AvgTemp	0.00517	0.00711	0.5295	0.4668	1.005	0.991	1.019

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 3. Children/Teens Age 5-17: Asthma ED Visits for $PM_{2.5}$ (per 10 µg/m^3) and Ozone (per 10 ppb). Two Pollutants, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
PM 2.5_10µg	-0.16130	0.08112	3.9540	0.0468	0.851	0.726	0.998
O_3_10ppb	0.01891	0.04337	0.1901	0.6628	1.019	0.936	1.110
AvgTemp	0.00575	0.00503	1.3045	0.2534	1.006	0.996	1.016
Lag 1							
PM 2.5_10µg	-0.11943	0.08064	2.1937	0.1386	0.887	0.758	1.039
O_3_10ppb	0.11657	0.04410	6.9866	0.0082	1.124	1.031	1.225
AvgTemp	0.00585	0.00500	1.3700	0.2418	1.006	0.996	1.016
Lag 2							
PM 2.5_10µg	-0.01931	0.08038	0.0577	0.8101	0.981	0.838	1.148
O_3_10ppb	0.01879	0.04269	0.1937	0.6599	1.019	0.937	1.108
AvgTemp	0.00237	0.00505	0.2207	0.6385	1.002	0.993	1.012
Lag 3							
PM 2.5_10µg	-0.02641	0.08076	0.1070	0.7436	0.974	0.831	1.141
O_3_10ppb	0.02534	0.04271	0.3520	0.5530	1.026	0.943	1.115
AvgTemp	0.00366	0.00503	0.5297	0.4667	1.004	0.994	1.014
Lag 4							
PM 2.5_10µg	0.03845	0.08296	0.2148	0.6431	1.039	0.883	1.223
O_3_10ppb	0.04266	0.04331	0.9703	0.3246	1.044	0.959	1.136
AvgTemp	0.00122	0.00516	0.0556	0.8136	1.001	0.991	1.011
Lag 5							
PM 2.5_10µg	0.09023	0.08232	1.2013	0.2731	1.094	0.931	1.286
O_3_10ppb	-0.03665	0.04233	0.7496	0.3866	0.964	0.887	1.047
AvgTemp	0.00047	0.00521	0.0084	0.9269	1.000	0.990	1.011
Lag 0-5							
PM 2.5_10µg	-0.09659	0.13249	0.5316	0.4659	0.908	0.700	1.177
O_3_10ppb	0.08952	0.07351	1.4830	0.2233	1.094	0.947	1.263
AvgTemp	0.00592	0.00718	0.6788	0.4100	1.006	0.992	1.020

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 4. Children/Teens Age 5-17: Asthma ED Visits for Carbon Monoxide (CO) (per 10 ppm).Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
CO_ppm	-0.15182	0.17157	0.783	0.3762	0.859	0.614	1.203
AvgTemp	0.00496	0.00485	1.0453	0.3066	1.005	0.995	1.015
Lag 1							
CO_ppm	-0.21203	0.1649	1.6533	0.1985	0.809	0.586	1.118
AvgTemp	0.00988	0.00481	4.2115	0.0401	1.01	1	1.02
Lag 2							
CO_ppm	-0.29423	0.17175	2.9349	0.0867	0.745	0.532	1.043
AvgTemp	0.00486	0.00481	1.0221	0.312	1.005	0.995	1.014
Lag 3							
CO_ppm	-0.19924	0.16565	1.4467	0.2291	0.819	0.592	1.134
AvgTemp	0.00554	0.00479	1.3345	0.248	1.006	0.996	1.015
Lag 4							
CO_ppm	-0.07304	0.16261	0.2017	0.6533	0.93	0.676	1.278
AvgTemp	0.00419	0.00487	0.7414	0.3892	1.004	0.995	1.014
Lag 5							
CO_ppm	-0.12825	0.1598	0.6441	0.4222	0.88	0.643	1.203
AvgTemp	0.00152	0.00489	0.0967	0.7558	1.002	0.992	1.011
Lag 0-5							
CO_ppm	-0.4145	0.26956	2.3644	0.1241	0.661	0.39	1.121
AvgTemp	0.00941	0.00671	1.9697	0.1605	1.009	0.996	1.023

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 5. Children/Teens Age 5-17: Asthma ED Visits for NO_2 (per 10 ppb). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
NO_2_10ppb	-0.05374	0.04799	1.2542	0.2628	0.948	0.863	1.041
AvgTemp	0.00501	0.00481	1.0863	0.2973	1.005	0.996	1.015
Lag 1							
NO_2_10ppb	-0.02798	0.0483	0.3356	0.5624	0.972	0.885	1.069
AvgTemp	0.00887	0.00475	3.4873	0.0618	1.009	1	1.018
Lag 2							
NO_2_10ppb	-0.00601	0.04736	0.0161	0.8991	0.994	0.906	1.091
AvgTemp	0.00288	0.00474	0.3692	0.5435	1.003	0.994	1.012
Lag 3							
NO_2_10ppb	-0.02201	0.04755	0.2141	0.6435	0.978	0.891	1.074
AvgTemp	0.00456	0.00474	0.9264	0.3358	1.005	0.995	1.014
Lag 4							
NO_2_10ppb	0.03801	0.04836	0.6178	0.4319	1.039	0.945	1.142
AvgTemp	0.00281	0.00483	0.339	0.5604	1.003	0.993	1.012
Lag 5							
NO_2_10ppb	0.01623	0.04838	0.1126	0.7372	1.016	0.924	1.117
AvgTemp	0.00044	0.0049	0.0081	0.9284	1	0.991	1.01
Lag 0-5							
NO_2_10ppb	-0.01663	0.08187	0.0412	0.8391	0.984	0.838	1.155
AvgTemp	0.00804	0.00668	1.4485	0.2288	1.008	0.995	1.021

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 6. Children/Teens Age 5-17: Asthma ED Visits for SO_2 (per 10 ppb). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
SO_2_10ppb	-0.02384	0.04292	0.3085	0.5786	0.976	0.898	1.062
AvgTemp	0.00399	0.0047	0.7183	0.3967	1.004	0.995	1.013
Lag 1							
SO_2_10ppb	-0.02135	0.04121	0.2685	0.6044	0.979	0.903	1.061
AvgTemp	0.00845	0.00466	3.2845	0.0699	1.008	0.999	1.018
Lag 2							
SO_2_10ppb	0.03405	0.03945	0.7449	0.3881	1.035	0.958	1.118
AvgTemp	0.00264	0.00465	0.3222	0.5703	1.003	0.994	1.012
Lag 3							
SO_2_10ppb	0.03605	0.04052	0.7913	0.3737	1.037	0.958	1.122
AvgTemp	0.00399	0.00466	0.7334	0.3918	1.004	0.995	1.013
Lag 4							
SO_2_10ppb	-0.03651	0.04481	0.6638	0.4152	0.964	0.883	1.053
AvgTemp	0.00391	0.00473	0.6831	0.4085	1.004	0.995	1.013
Lag 5							
SO_2_10ppb	0.00796	0.04304	0.0342	0.8533	1.008	0.926	1.097
AvgTemp	0.0007	0.00482	0.0212	0.8844	1.001	0.991	1.01
Lag 6							
SO_2_10ppb	0.00564	0.08212	0.0047	0.9452	1.006	0.856	1.181
AvgTemp	0.00785	0.00662	1.4034	0.2362	1.008	0.995	1.021

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 7. Children/Teens Age 5-17: Asthma ED Visits for $PM_{2.5}$ (per 10 µg/m^3), Ozone (per 10 ppb), CO (ppm), NO_2 (per 10 ppb), SO_2 (per 10 ppb). Multiple Pollutant models, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
PM 2.5_10µg	-0.15374	0.09685	2.5198	0.1124	0.857	0.709	1.037
O_3_10ppb	0.02007	0.04376	0.2103	0.6465	1.02	0.936	1.112
NO_2_10ppb	-0.00874	0.06113	0.0205	0.8863	0.991	0.879	1.117
SO_2_10ppb	-0.00984	0.04365	0.0508	0.8217	0.99	0.909	1.079
CO_ppm	0.01393	0.2072	0.0045	0.9464	1.014	0.676	1.522
AvgTemp	0.00571	0.00511	1.2504	0.2635	1.006	0.996	1.016
Lag 1							
PM 2.5_10µg	-0.09026	0.09486	0.9054	0.3413	0.914	0.759	1.1
O_3_10ppb	0.11326	0.04447	6.4854	0.0109	1.12	1.026	1.222
NO_2_10ppb	0.00478	0.06123	0.0061	0.9377	1.005	0.891	1.133
SO_2_10ppb	-0.01675	0.04192	0.1597	0.6894	0.983	0.906	1.068
CO_ppm	-0.14172	0.19506	0.5279	0.4675	0.868	0.592	1.272
AvgTemp	0.00653	0.00508	1.6524	0.1986	1.007	0.997	1.017
Lag 2							
PM 2.5_10µg	0.02553	0.09711	0.0691	0.7926	1.026	0.848	1.241
O_3_10ppb	0.00819	0.0432	0.0359	0.8496	1.008	0.926	1.097
NO_2_10ppb	0.03892	0.06044	0.4148	0.5196	1.04	0.924	1.17
SO_2_10ppb	0.03843	0.04007	0.9199	0.3375	1.039	0.961	1.124
CO_ppm	-0.41287	0.21113	3.8242	0.0505	0.662	0.438	1.001
AvgTemp	0.00404	0.00513	0.6199	0.4311	1.004	0.994	1.014
Lag 3							
PM 2.5_10µg	0.01468	0.09777	0.0225	0.8807	1.015	0.838	1.229
O_3_10ppb	0.01931	0.04314	0.2005	0.6544	1.02	0.937	1.109
NO_2_10ppb	-0.00249	0.05998	0.0017	0.9669	0.998	0.887	1.122
SO_2_10ppb	0.04162	0.04119	1.0208	0.3123	1.042	0.962	1.13
CO_ppm	-0.23171	0.20048	1.3358	0.2478	0.793	0.535	1.175
AvgTemp	0.00464	0.00509	0.8303	0.3622	1.005	0.995	1.015
Lag 4							
PM 2.5_10µg	0.0473	0.09885	0.229	0.6323	1.048	0.864	1.273
O_3_10ppb	0.03848	0.04364	0.7774	0.3779	1.039	0.954	1.132
NO_2_10ppb	0.0542	0.06079	0.7948	0.3727	1.056	0.937	1.189
SO_2_10ppb	-0.04513	0.04617	0.9556	0.3283	0.956	0.873	1.046
CO_ppm	-0.18486	0.1969	0.8814	0.3478	0.831	0.565	1.223

AvgTemp	0.00176	0.0052	0.1143	0.7353	1.002	0.992	1.012
Lag 5							
PM 2.5_10µg	0.1359	0.09834	1.9098	0.167	1.146	0.945	1.389
O_3_10ppb	-0.04685	0.04295	1.1898	0.2754	0.954	0.877	1.038
NO_2_10ppb	0.02737	0.06059	0.204	0.6515	1.028	0.913	1.157
SO_2_10ppb	0.00456	0.04382	0.0108	0.9171	1.005	0.922	1.095
CO_ppm	-0.29678	0.19516	2.3125	0.1283	0.743	0.507	1.09
AvgTemp	0.00117	0.00524	0.0497	0.8236	1.001	0.991	1.011
Lag 0-5							
PM 2.5_10µg	-0.05342	0.16391	0.1062	0.7445	0.948	0.688	1.307
O_3_10ppb	0.07167	0.07456	0.9239	0.3364	1.074	0.928	1.243
NO_2_10ppb	0.08093	0.11367	0.5069	0.4765	1.084	0.868	1.355
SO_2_10ppb	0.02648	0.08488	0.0973	0.755	1.027	0.869	1.213
CO_ppm	-0.54617	0.34314	2.5334	0.1115	0.579	0.296	1.135
AvgTemp	0.00709	0.00724	0.9596	0.3273	1.007	0.993	1.022

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 8. Adults 18+: Asthma ED Visits for $PM_{2.5}$ (per 10 µg/m^3). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
$PM_{2.5}$_10µg	0.00225	0.02926	0.0059	0.9387	1.002	0.946	1.061
AvgTemp	0.0025	0.00184	1.8602	0.1726	1.003	0.999	1.006
Lag 1							
$PM_{2.5}$_10µg	-0.00056	0.02919	0.0004	0.9846	0.999	0.944	1.058
AvgTemp	0.00246	0.00185	1.7602	0.1846	1.002	0.999	1.006
Lag 2							
$PM_{2.5}$_10µg	-0.01998	0.02949	0.4591	0.4981	0.98	0.925	1.039
AvgTemp	0.0024	0.00185	1.6773	0.1953	1.002	0.999	1.006
Lag 3							
PM 2.5_10µg	-0.00769	0.02956	0.0677	0.7948	0.992	0.936	1.052
AvgTemp	0.00353	0.00185	3.6423	0.0563	1.004	1	1.007
Lag 4							
$PM_{2.5}$_10µg	0.00947	0.03002	0.0995	0.7524	1.01	0.952	1.071
AvgTemp	0.00076	0.00188	0.1672	0.6826	1.001	0.997	1.004
Lag 5							
$PM_{2.5}$_10µg	0.03075	0.03016	1.0393	0.308	1.031	0.972	1.094
AvgTemp_	-0.00148	0.00191	0.601	0.4382	0.999	0.995	1.002
Lag 0-5							
$PM_{2.5}$_10µg	0.0094	0.0481	0.0382	0.8451	1.009	0.919	1.109
AvgTemp	0.00335	0.0026	1.6641	0.1971	1.003	0.998	1.008

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 9. Adults 18+: Asthma ED Visits for Ozone (per 10 ppb). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
O_3_10ppb	-0.03208	0.01624	3.9023	0.0482	0.968	0.938	1
AvgTemp	0.0037	0.00187	3.9303	0.0474	1.004	1	1.007
Lag 1							
O_3_10ppb	-0.03221	0.01623	3.9384	0.0472	0.968	0.938	1
AvgTemp	0.00359	0.00188	3.6649	0.0556	1.004	1	1.007
Lag 2							
O_3_10ppb	-0.04174	0.0162	6.6368	0.01	0.959	0.929	0.99
AvgTemp	0.00359	0.00188	3.6439	0.0563	1.004	1	1.007
Lag 3							
O_3_10ppb	-0.03376	0.01613	4.3812	0.0363	0.967	0.937	0.998
AvgTemp	0.00464	0.00188	6.1001	0.0135	1.005	1.001	1.008
Lag 4							
O_3_10ppb	-0.03166	0.01602	3.9072	0.0481	0.969	0.939	1
AvgTemp	0.00209	0.00189	1.2239	0.2686	1.002	0.998	1.006
Lag							
O_3_10ppb	-0.0188	0.01601	1.3791	0.2403	0.981	0.951	1.013
AvgTemp	-0.00019	0.00193	0.0103	0.919	1	0.996	1.004
Lag 5							
O_3_10ppb	-0.08902	0.0272	10.7116	0.0011	0.915	0.867	0.965
AvgTemp	0.00653	0.00268	5.9361	0.0148	1.007	1.001	1.012

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 10. Adults 18+: Asthma ED Visits for $PM_{2.5}$ (per 10 µg/m^3) and Ozone (per 10 ppb).

Two Pollutants, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
$PM_{2.5}$_10µg	0.01687	0.0301	0.3143	0.5751	1.017	0.959	1.079
O_3_10ppb	-0.03427	0.01668	4.2232	0.0399	0.966	0.935	0.998
AvgTemp	0.0035	0.0019	3.3991	0.0652	1.004	1	1.007
Lag 1							
$PM_{2.5}$_10µg	0.014	0.03003	0.2172	0.6412	1.014	0.956	1.076
O_3_10ppb	-0.03404	0.01668	4.1667	0.0412	0.967	0.935	0.999
AvgTemp	0.00342	0.00191	3.2013	0.0736	1.003	1	1.007
Lag 2							
$PM_{2.5}$_10µg	-0.00141	0.03041	0.0022	0.963	0.999	0.941	1.06
O_3_10ppb	-0.04155	0.01669	6.1959	0.0128	0.959	0.928	0.991
AvgTemp	0.00361	0.00192	3.5457	0.0597	1.004	1	1.007
Lag 3							
$PM_{2.5}$_10µg	0.00681	0.03034	0.0503	0.8225	1.007	0.949	1.069
O_3_10ppb	-0.03459	0.01655	4.3715	0.0365	0.966	0.935	0.998
AvgTemp	0.00456	0.00191	5.6744	0.0172	1.005	1.001	1.008
Lag 4							
$PM_{2.5}$_10µg	0.02347	0.03075	0.583	0.4451	1.024	0.964	1.087
O_3_10ppb	-0.03436	0.01637	4.4072	0.0358	0.966	0.936	0.998
AvgTemp	0.00176	0.00194	0.8284	0.3627	1.002	0.998	1.006
Lag 5							
$PM_{2.5}$_10µg	0.04042	0.03092	1.7093	0.1911	1.041	0.98	1.106
O_3_10ppb	-0.02345	0.01636	2.0555	0.1517	0.977	0.946	1.009
AvgTemp	-0.00075	0.00197	0.1463	0.7021	0.999	0.995	1.003
Lag 0-5							
$PM_{2.5}$_10µg	0.06431	0.05075	1.606	0.2051	1.066	0.965	1.178
O_3_10ppb	-0.1	0.02851	12.3004	0.0005	0.905	0.856	0.957
AvgTemp	0.00603	0.00271	4.9599	0.0259	1.006	1.001	1.011

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 11. Adults 18+: Asthma ED Visits for Carbon Monoxide (per 10 ppm). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0-5							
CO_ppm	0.08524	0.0638	1.7849	0.1816	1.089	0.961	1.234
AvgTemp	0.0019	0.00184	1.0715	0.3006	1.002	0.998	1.006
Lag 1							
CO_ppm	0.06997	0.06324	1.2241	0.2686	1.072	0.947	1.214
AvgTemp	0.00195	0.00184	1.1213	0.2896	1.002	0.998	1.006
Lag 2							
CO_ppm	0.03378	0.06376	0.2806	0.5963	1.034	0.913	1.172
AvgTemp	0.00182	0.00184	0.9807	0.322	1.002	0.998	1.005
Lag 3							
CO_ppm	0.09172	0.06325	2.103	0.147	1.096	0.968	1.241
AvgTemp	0.00279	0.00183	2.326	0.1272	1.003	0.999	1.006
Lag 4							
CO_ppm	0.0162	0.06277	0.0666	0.7963	1.016	0.899	1.149
AvgTemp	0.000833	0.00185	0.2032	0.6522	1.001	0.997	1.004
Lag 5							
CO_ppm	0.12878	0.06224	4.2815	0.0385	1.137	1.007	1.285
AvgTemp_	-0.00173	0.00187	0.8604	0.3536	0.998	0.995	1.002
Lag 0-5							
CO_ppm	0.20214	0.10229	3.905	0.0481	1.224	1.002	1.496
AvgTemp_	0.00261	0.00255	1.0472	0.3062	1.003	0.998	1.008

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 12. Adults 18+: Asthma ED Visits for NO_2 (per 10 ppb). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
NO_2_10ppb	-0.01558	0.01826	0.7282	0.3935	0.985	0.95	1.02
AvgTemp	0.00286	0.00181	2.4996	0.1139	1.003	0.999	1.006
Lag 1							
NO_2_10ppb	0.01325	0.01826	0.5271	0.4678	1.013	0.978	1.05
AvgTemp	0.00219	0.00182	1.445	0.2293	1.002	0.999	1.006
Lag 2							
NO_2_10ppb	-0.00483	0.01826	0.0701	0.7912	0.995	0.96	1.031
AvgTemp	0.00215	0.00182	1.3991	0.2369	1.002	0.999	1.006
Lag 3							
NO_2_10ppb	0.02436	0.01822	1.7864	0.1814	1.025	0.989	1.062
AvgTemp	0.00296	0.00181	2.6654	0.1026	1.003	0.999	1.007
Lag 4							
NO_2_10ppb	0.01858	0.01825	1.0362	0.3087	1.019	0.983	1.056
AvgTemp	0.00057	0.00184	0.0967	0.7559	1.001	0.997	1.004
Lag 5							
NO_2_10ppb	0.03992	0.01839	4.7107	0.03	1.041	1.004	1.079
AvgTemp	-0.00171	0.00186	0.8465	0.3576	0.998	0.995	1.002
Lag 0-5							
NO_2_10ppb	0.04196	0.03162	1.761	0.1845	1.043	0.98	1.11
AvgTemp	0.003	0.00254	1.3916	0.2381	1.003	0.998	1.008

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 13. Adults 18+: Asthma ED Visits for SO_2 (per 10 ppb). Single Pollutant, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
SO_2_10ppb	-0.00923	0.01553	0.3533	0.5522	0.991	0.961	1.021
AvgTemp	0.0026	0.00177	2.1423	0.1433	1.003	0.999	1.006
Lag 1							
SO_2_10ppb	-0.00954	0.01559	0.3746	0.5405	0.991	0.961	1.021
AvgTemp	0.00249	0.00179	1.9471	0.1629	1.002	0.999	1.006
Lag 2							
SO_2_10ppb	-0.0386	0.01606	5.7775	0.0162	0.962	0.932	0.993
AvgTemp	0.00223	0.00178	1.5629	0.2112	1.002	0.999	1.006
Lag 3							
SO_2_10ppb	0.01014	0.01557	0.4236	0.5151	1.01	0.98	1.042
AvgTemp	0.00335	0.00178	3.5164	0.0608	1.003	1	1.007
Lag 4							
SO_2_10ppb	-0.00623	0.01529	0.166	0.6837	0.994	0.964	1.024
AvgTemp	0.00096	0.0018	0.2896	0.5905	1.001	0.997	1.005
Lag 5							
SO_2_10ppb	0.00287	0.01542	0.0348	0.8521	1.003	0.973	1.034
AvgTemp	-0.00093	0.00183	0.2593	0.6106	0.999	0.995	1.003
Lag 0-5							
SO_2_10ppb	-0.03014	0.03035	0.9862	0.3207	0.97	0.914	1.03
AvgTemp	0.00356	0.00251	2.0007	0.1572	1.004	0.999	1.009

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Supplementary Table 14. Adults 18+: Asthma ED Visits for $PM_{2.5}$ (per 10 µg/m^3), Ozone (per 10 ppb), CO (ppm), NO_2 (per 10 ppb), SO_2 (per 10 ppb). Multiple Pollutant models, Single day lags and average lag.

Parameter	Estimate	Std Error	Chi-Square	P-value	Chi-Square Ratio	95-Confidence Intervals	
Lag 0							
$PM_{2.5}$_10µg	0.02193	0.0359	0.3732	0.5412	1.022	0.953	1.097
O_3_10ppb	-0.03005	0.0168	3.1968	0.0738	0.97	0.939	1.003
NO_2_10ppb	-0.03612	0.02325	2.4141	0.1202	0.965	0.922	1.009
SO_2_10ppb	-0.00864	0.01581	0.2991	0.5844	0.991	0.961	1.023
CO_ppm	0.13596	0.07659	3.1513	0.0759	1.146	0.986	1.331
AvgTemp	0.00305	0.00193	2.498	0.114	1.003	0.999	1.007
Lag 1							
$PM_{2.5}$_10µg	-0.00576	0.03564	0.0261	0.8715	0.994	0.927	1.066
O_3_10ppb	-0.03319	0.01682	3.8911	0.0485	0.967	0.936	1
NO_2_10ppb	0.01498	0.02312	0.4194	0.5172	1.015	0.97	1.062
SO_2_10ppb	-0.0108	0.01586	0.4636	0.4959	0.989	0.959	1.02
CO_ppm	0.05448	0.07603	0.5134	0.4737	1.056	0.91	1.226
AvgTemp	0.00309	0.00194	2.5427	0.1108	1.003	0.999	1.007
Lag 2							
$PM_{2.5}$_10µg	-0.00281	0.03612	0.006	0.938	0.997	0.929	1.07
O_3_10ppb	-0.04036	0.01681	5.7604	0.0164	0.96	0.929	0.993
NO_2_10ppb	0.00157	0.02297	0.0047	0.9455	1.002	0.957	1.048
SO_2_10ppb	-0.03851	0.01629	5.5865	0.0181	0.962	0.932	0.993
CO_ppm	0.05366	0.07731	0.4817	0.4877	1.055	0.907	1.228
AvgTemp	0.00336	0.00194	2.9991	0.0833	1.003	1	1.007
Lag 3							
$PM_{2.5}$_10µg	-0.03443	0.0364	0.8946	0.3442	0.966	0.9	1.038
O_3_10ppb	-0.03373	0.01669	4.0833	0.0433	0.967	0.936	0.999
NO_2_10ppb	0.02868	0.02308	1.5442	0.214	1.029	0.984	1.077
SO_2_10ppb	0.00924	0.01585	0.3399	0.5599	1.009	0.978	1.041
CO_ppm	0.06849	0.07721	0.7869	0.375	1.071	0.921	1.246
AvgTemp	0.0042	0.00193	4.7154	0.0299	1.004	1	1.008
Lag 4							
$PM_{2.5}$_10µg	0.0117	0.03693	0.1003	0.7515	1.012	0.941	1.088
O_3_10ppb	-0.03637	0.01655	4.8275	0.028	0.964	0.934	0.996
NO_2_10ppb	0.02858	0.02297	1.5483	0.2134	1.029	0.984	1.076
SO_2_10ppb	-0.00775	0.01554	0.2486	0.6181	0.992	0.963	1.023
CO_ppm	-0.04151	-0.04151	0.0761	0.2976	0.5854	0.959	0.826
AvgTemp	0.00179	0.00196	0.8412	0.359	1.002	0.998	1.006
Lag 5							
$PM_{2.5}$_10µg	-0.00387	0.03728	0.0108	0.9173	0.996	0.926	1.072

O_3_10ppb	-0.02249	0.01654	1.8495	0.1738	0.978	0.947	1.01
NO_2_10ppb	0.03416	0.02321	2.1676	0.1409	1.035	0.989	1.083
SO_2_10ppb	-0.00142	0.01575	0.0082	0.928	0.999	0.968	1.03
CO_ppm	0.07339	0.07517	0.9533	0.3289	1.076	0.929	1.247
AvgTemp	-0.00113	0.00199	0.323	0.5698	0.999	0.995	1.003
Lag 0-5							
$PM_{2.5}$_10µg	0.00246	0.06333	0.0015	0.969	1.002	0.885	1.135
O_3_10ppb	-0.0968	0.02892	11.2029	0.0008	0.908	0.858	0.961
NO_2_10ppb	0.04295	0.04435	0.9381	0.3328	1.044	0.957	1.139
SO_2_10ppb	-0.03956	0.03091	1.6375	0.2007	0.961	0.905	1.021
CO_ppm	0.14951	0.13189	1.285	0.257	1.161	0.897	1.504
AvgTemp	0.00572	0.00273	4.4001	0.0359	1.006	1	1.011

Data were adjusted for apparent temperature (at same lag) analyses with a 7-day washout and 28-day referent periods.
Abbreviation Definitions: AvgTemp = Average temperature; Std Error=Standard Error

Appendix B Chapter 4 Supplementary Tables

Table E 1. Summarizes participant responses of "yes" to survey questions compared by proximity to the factory. Proximal group < 10 miles and Control group > 10 miles from CWF.

	Distal Control N=44		Proximal Group N=39							
Survey Questions	n (% Pre)	P-value	n (% Pre)	n (% Post)	P-value	n (% Pre)	P-value	n (% Pre)	n (% Post)	P-value
Q3. Past 30 days asthma worse outdoors	10(55)	0.48	12(48)	16(64)	0.16	11(68)	0.39	11(50)	15(68)	0.18
Q4. Past 30 days asthma worse indoors	7(35)	0.35	6(24)	7(28)	0.71	12(70)	*0.06*	9(40)	6(27)	0.32
Q5. Past 30 days notice rotten egg smell	1(5)	0.71	2(8)	1(4)	0.57	7(41)	0.98	9(40)	9(40)	1
Q6. Past 30 days notice any bad smells	3(15)	0.95	4(16)	5(20)	0.66	6(22)	0.26	5(22)	8(36)	0.08
Q7. Feels air pollution near home sometimes worsens asthma symptoms	9(47)	0.35	13(52)	16(64)	**0.04***	15(93)	0.21	16(72)	18(81)	0.57
Q8. Aware of any events affected outside air near your home	1(5)	0.24	4(16)	2(8)	0.32	8(47)	0.64	12(54)	11(50)	1
Q9. Past 30 days asthma attack required more asthma meds than usual	8(42)	0.4	8(32)	8(32)	1	10(66)	0.31	11(50)	7(31)	**0.04***
Q10. Past 30 days sought medical attention for asthma	5(25)	0.22	3(12)	3(12)	0.57	5(31)	*0.08*	2(9)	1(4)	1
Q11. Past 30 days needed to use more asthma medications	10(50)	0.96	13(52)	10(40)	0.32	12(75)	0.64	15(68)	7(31)	**0.02***

Table E 2. Baseline characteristics of the proximal and control groups separated by those who completed the survey compared with those who completed the entire study.

	n (%)	n (%)	P-value	n (%)	n (%)	P-value
Female	18 (95)	18 (72)	0.5	14 (82)	19 (86)	0.7
White	14 (74)	14 (56)	0.4	8 (47)	15 (68)	0.1
Married	11 (58)	11 (44)	0.5	6 (35)	5 (23)	0.3
Employed outside home	14 (74)	16 (64)	0.8	7 (41)	17(77)	0.02*
Medicaid	7 (37)	5 (20)	0.2	9 (53)	5 (23)	0.05
College Graduate	14 (74)	13 (52)	0.2	9 (53)	9 (41)	0.4
Exposure to 2nd hand smoke	6 (32)	1 (4)	0.01*	7 (41)	6 (27)	0.2
Ever smoke	8 (40)	5 (22)	0.2	5 (29)	4 (18)	0.4
Fev1 % predicted	83.5	82.4	0.7	81.6	76.1	0.2
Asthma severity (Mod-Severe)	8 (42)	10 (40)	0.9	8 (47)	12(55)	0.6

*Definition of abbreviations: *= P-Value <0.05*

Table E 3ummarizes participant responses of "yes" to survey questions. Table is divided into two main groups (Proximal and Control). Within each group are subgroup comparisons of those who only completed the survey, with those who completed both the baseline survey and the follow-up visit.

	Pre n (%)	**Survey + Visit n (%)**	**P value**	**Survey n (%)**	**Survey + Visit n (%)**	**P value**
Q3. Past 30 days asthma worse outdoors	10 (53)	12 (63)	0.48	11 (65)	11 (65)	0.39
Q4. Past 30 days asthma worse indoors	7 (37)	6 (32)	0.35	12 (71)	9 (53)	0.06
Q5. Past 30 days notice rotten egg smell	1 (5)	2 (11)	0.71	7 (41)	9 (53)	0.98
Q6. Past 30 days notice any bad smells	3 (16)	4 (21)	0.95	6 (35)	5 (29)	0.26
Q7. Feels air pollution near home sometimes worsens asthma symptoms	9 (47)	13 (68)	0.35	15 (88)	16 (94)	0.21
Q8. Aware of any events affected outside air near your home	1 (5)	4 (21)	0.24	8 (47)	12 (71)	0.64
Q9. Past 30 days asthma attack required more asthma meds than usual	8 (42)	8 (42)	0.4	10 (59)	11 (65)	0.31
Q10. Past 30 days sought medical attention for asthma	5 (26)	3 (16)	0.22	5 (29)	2 (12)	0.08
Q11. Past 30 days needed to use more asthma medications	10 (53)	13 (68)	0.96	12 (71)	15 (88)	0.64

Appendix B.1 Data file E1. Asthma Institute Registry Environmental Health Assessment Questionnaire

Asthma Institute Registry Environmental Health Assessment Questionnaire

AR__ __ __ __ __ __ __ Was verbal consent via phone script obtained to complete this form? □ Yes

Date: _____

Current Address: □ Same address

□ New address _____

1. In general, during the winter months, do your asthma symptoms usually….

□ Get worse

□ Get better

□ No change

□ Don't Know

2. In general, during the summer months, do your asthma symptoms usually….

□ Get worse

□ Get better

□ No change

□ Don't Know

3. Over the past 30 days: Have your asthma symptoms worsened WHILE OUTDOORS?

□ Yes

□ No

□ Don't Know

4. Over the past 30 days: Have your asthma symptoms worsened WHILE INDOORS?

□ Yes

□ No

□ Don't Know

5. Over the past 30 days: Have you noticed a 'rotten egg' smell in the outside air near your home?

□ Yes

□ No

□ Don't Know 6. Over the past 30 days: Have you noticed any other smell in the outside air near your home? □ Yes, please describe smell_____

□ No

□ Don't know

7. Do you think air pollution in your area sometimes worsens your asthma symptoms?

□ Yes

□ No

□ Don't Know

8. Are you aware of any recent events (within the last 30-60 days) that may have affected the outside air near your home (events like gas explosion, factory accidents, or fires)?

□ Yes

o Please describe event_____

o Do you think that event made your asthma symptoms worse?

□ Yes

□ No
□ Don’t Know
□ No
□ Don’t Know
9. Over the past 30 days: Did you have an asthma attack (coughing, wheezing, trouble breathing) that required you to take more asthma medicines than usual for you?
□ Yes
□ No
□ Don’t Know
10. Over the last 30 days: Did you seek medical attention (clinic visit, ER, or ambulance) for your asthma?
□ Yes
□ No
□ Don’t Know
11. Over the last 30 days: Have you needed to use more of your asthma medications?
□ Yes
□ No
□ Don’t Know
12. In an event that caused a change in the outside air near your home that could worsen your asthma, would you like to be notified?
□ Yes
o How would you like to be notified?
□ Cell phone app
□ Text message
□ Email
□ Phone call
□ News/TV
□ Other: _____
o How soon would you like to be notified?
□ Immediately
□ Within 3 days
□ Within a week
□ Within a month
□ No
13. If you are warned about harmful air pollution near your home, would you shorten your time spent OUTDOORS?
□ Yes
□ No
□ Don’t Know

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