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Adam Babcock-Fitch Benson Date

Acute Effects of Ambient SO_2 Exposure on Pediatric Asthma Emergency Department Visits in Atlanta, GA

By

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Master of Science in Public Health

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An abstract of
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Abstract

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By Adam Benson

Purpose: Previous epidemiological and limited clinical and mechanistic evidence supports an association between sulfur dioxide (SO_2) and asthma exacerbation events in children. However, further investigations at a monitors-specific scale are needed to better understand this relationship due to insufficient monitor networks and the large spatial heterogeneity of SO_2. Furthermore, little is known whether exposure to traffic-related pollutants modifies the association between SO_2 and asthma exacerbation events.

Methods: A case-crossover study was conducted using emergency department visits from 2002 - 2013 for asthma or wheeze among children aged 1 to 17 within a 5 (n = 15,610), 4 (n = 8,522), and 3 (n = 6,742) kilometer radius of four ambient SO_2 monitoring stations in the Metropolitan Atlanta Area. Concentrations of traffic-related near-surface particulate matter ($PM_{2.5}$) were estimated using an R-LINE model to examine effect modification by traffic-related pollution. Odds ratios were calculated using conditional logistic regression for multiple-day moving averages of 1-hour maximum SO_2 concentrations.

Results: There were trends of positive associations between SO_2 and asthma-related emergency department visits overall (OR: 1.044, 95% CI: 1.006 – 1.084 at 4 Km, Lag 0), and in both warm and cold season analyses. Strongest associations were observed in the cold season using a 3-day moving average of SO_2, and tended to increase as distance to monitor decreased (OR: 1.105, 95% CI: 1.013 – 1.204 at 4 Km, Lag 0 – 3, in the cold season). Odds ratios between cases exposed to high versus low concentrations of traffic-related pollution tended to be positive overall, and in season-specific analyses. Strongest associations were observed using 3-day moving averages of SO_2 and during the warm season (OR: 1.031, 95% CI: 0.957 – 1.110 at 4 Km, Lag 0 – 3, for a 1 ppm increase in SO_2 in the warm season).

Conclusions: These findings provide additional evidence supporting previously documented associations between $SO_2$and asthma exacerbation events despite concerns due to large spatial heterogeneity of SO_2 and a limited quantity of monitors. Furthermore, the association between SO_2 and asthma exacerbation may be susceptible to modification by traffic-related pollutants, particularly during the warm season.

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TABLE OF CONTENTS

CHAPER I: LITERATURE REVIEW

I. Introduction

Asthma is a chronic disease characterized by episodes of reversible airflow obstruction, affecting approximately 8.4% of the U.S. population, or more than 16.5 million adults and 7.0 million children nationwide (Guarnieri & Balmes, 2014; Moorman et al., 2012). In Georgia, 13.5% of adults and 16% of children aged 0-17 have asthma. Children are a sub-group of concern as a susceptible population, particularly in Georgia with asthma prevalence among children higher than the U.S. average (Annor et al., 2014; Atkinson et al., 2014; Peden, 2005).

Important precipitators include exercise, airway infections, airborne allergens, occupational exposure, and environmental airborne irritants (Annor et al., 2014; Guarnieri & Balmes, 2014). Although SO_2 is a pollutant of concern, there are limited studies examining the relationship between SO_2 exposure and pediatric asthma ED visits, and the role of SO_2 in asthma etiology remains unclear (Lai et al., 2013; Penard-Morand et al., 2010). Several studies have included SO_2 as an exposure of interest in models of ambient air pollution and ED visits, and have reported small independent associations of SO_2 and pediatric ED visits. (Strickland et al., 2010; Restrepo et al., 2012; Winquist et al., 2014). An important challenge is the large spatial heterogeneity in SO_2, which Strickland et al. (2013) reports is the largest among any commonly found primary or secondary pollutants. This is of particular concern for SO_2 given the generally small quantity of monitors, and that a primary source of SO_2 is coal power plant plumes, which may produce variable regional concentrations (Guarmieri & Balmes, 2014; Smith et al., 1978).

The examination of asthma events by resident locations near SO_2 monitors may help elucidate the association between SO_2 exposure and acute asthma events.

II. Mechanisms

General Mechanisms of Air Pollutants:

Air pollutants are thought to contribute to harmful health effects, including the development and exacerbation of asthma, through four primary mechanisms: oxidative stress and damage, airway remodeling, inflammatory pathways and immunological responses, and sensitization of respiratory system to inhaled allergen (Brunekreef & Holgate, 2002; Guarnieri & Balmes, 2014; Trasande & Thurston, 2005). Additionally, there is evidence of interaction between these mechanisms, particularly through the indirect effects of oxidants. Many pollutants act as oxidants not only through direct effects on lipids and proteins, but also through indirect activation of oxidant pathways. Indirect oxidant pathways can result in remodeling, inflammation, and sensitization as well (Brunekreef & Holgate, 2002; Guarnieri & Balmes, 2014; Johns & Linn, 2011).

Plausible indirect mechanisms include depletion of intracellular glutathione, initiation of cytokines, chemokines, cellular adhesion expression, and synthesis of allergic antibody IgE in animals and humans. Additional evidence for these mechanisms included the observation of increased white blood cell counts, and increased levels of C-reactive protein, a biomarker of inflammation (Brunekreef & Holgate, 2002; Trasande & Thurston, 2005).

A greater number of studies exist examining mechanisms of ozone, though NO_2, PM, and SO_2 are thought to act via direct oxidative damage or indirect oxidation pathways; however, potentially to a lesser degree than ozone (Brunekreef & Holgate, 2002; COMEAP, 2011). Indirect oxidative pathways appear to overlap, though pollutant specific responses have been seen, such as the ability of NO_2 to impair alveolar macrophages and epithelial cells (Brunekreef & Holgate, 2002).

There is also evidence of a strong genetic role in differing individual responses to exposure. Several candidate genes for ozone exposure responses include TNFα, manganese superoxide dismutase, glutathione peroxidase, NAD(P) quinone oxidoreductase, and glutathione S transferases. These genetic factors may be important in other air pollutant responses as well (Brunekreef & Holgate, 2002; COMEAP, 2011; Peden, 2005). The individual variability in response to environmental exposures, combined with growing evidence of genetic variability, indicates that dietary and genetic factors affecting local antioxidant availability may be important in varying individual inflammatory responses (Peden, 2005).

Despite extensive research on the association between air pollutants and respiratory health, specific mechanisms for individual air pollutants remains poorly understood, particularly for long-term exposures, and in understanding the interaction of pollutants in mixtures.

SO_2 Specific Mechanisms:

In comparison to ozone and PM, even more limited research exists on specific mechanisms of action for SO_2. Though SO_2 can act as a reductant under certain conditions, it is believed to act by direct and indirect oxidative mechanisms in similar manners as other common air pollutants. It has been also documented to lead to increased bronchoconstriction and enhanced responses to inhaled allergens (Johns & Linn, 2011). Liu et al. (2009) have also documented decreases in forced expiratory flow (-3.0%; 95% CI, -5.8 to -0.3) and increases in TBARS (an oxidative stress marker) (36.2%; 95% CI, 15.7 to 57.2) (Liu et al., 2009).

Similar results have been reported in controlled exposure studies among animals. Mice models have provided additional evidence for oxidative stress, particularly to the cardiovascular system over a variety of acute exposure scenarios (Meng et al., 2003). Acute exposures in rats have identified altered genetic expression important in allergenic response, in addition to DNA

damage to cells in the lung, and lipid peroxidation in brain and livers (COMEAP, 2011; Meng et al., 2005). A long-term study in rats by Wagner et al., also identified concentrations of 20 ppm to be associated with airway remodeling and mucus hypersecretion (COMEAP, 2011.).

Among those with asthma, in addition to increased bronchoconstriction and enhanced responses to allergens, there is limited evidence to suggest that a parasympathetic nervous response and inflammatory pathways are elevated through sensory receptors or mast cells in the trancheobroncial airways. This response can be substantially exacerbated when breathing patterns are switched from nasal to oral or oronasal breathing due to the dominant absorption of SO_2 in the nasal passage (Johns & Linn, 2011).

While, acute and chronic toxicity has been identified in both animal and human subjects, additional research is necessary to understand the specific mechanisms of action for SO_2, particularly among susceptible populations, and in the context of multi-pollutant mixtures.

Unique Susceptibility of Children:

Biological: Children are thought to be identified as particularly susceptible to air pollution exposure due to a combination of biological and behavioral differences, compared to adults at similar ambient air pollution concentrations. One biological susceptibility includes the ongoing organogenesis of the lung in children; extensive alveoli growth occurs in the first four years and continues through adolescence. Additionally, air pollution has the potential to alter normal processes of lung development that may result in permanent damage or susceptibility to future insults (Trasande & Thurston, 2005). Regarding SO_2, it is unclear if altered lung development is due to oxidative mechanisms or a by other casual mechanisms. A meta-analysis by Lai et al. (2013) indicated no observable patterns in SO_2 relative risk among current literature,

providing no evidence to point towards whether altered lung development is associated with SO_2 or pollutants such as PM_{10}, NO_2, or ozone (Lai et al., 2013).

A second biological susceptibility is due to an incomplete development of the epithelium in children. This results in greater permeability of the epithelial layer, allowing for greater potential damage to lung tissue for a given exposure compared to adults or adolescents (Trasande & Thurston, 2005). Additionally, the immune systems of young children are still developing, suggesting increased susceptibility to insults and the potential for inappropriate immune system responses (Holt, 1998; Trasande & Thurston, 2005). Though few studies have been conducted, there is some evidence to suggest environmental exposures influence the development of T_H2 instead of T_H1 immunological phenotypes. Development and dominance of T_H2 cells induce cytokine secretion and are associated with allergic reactions compared to a protective allergen reducing T_H1 pattern of cytokine secretion (Holt, 1998). Additionally, children also have differing abilities to biologically process environmental exposures, including variable metabolic, detoxifying, and excretion abilities associated with incomplete development of organ and immune systems (Trasande & Thurston, 2005).

Behavioral: On average, children also have higher respiration rates and greater levels of physical activity than adults, resulting in increased exposures to air pollutants compared to adults at the same ambient concentrations. A study of California children estimated that on average, children spend 124 minutes a day in outdoor recreation, which is five times more than adults spend outdoors (Trasande & Thurston, 2005). Additionally, a study in The Netherlands estimated personal exposures for PM_{10} in adults were only two-thirds that of children at similar outdoor concentrations (Janssen et al., 1998; Janssen et al., 1997). Finally, increased activity among children can be potentially more harmful as children are less likely to stop physical

activity when they do experience harmful respiratory or asthma symptoms (Trasande & Thurston, 2005).

The unique biological and behavioral vulnerabilities are well documented and have resulted in a focus on pediatric health outcomes due to air pollution exposure, including pediatric asthma. There is a limited understanding of the specific biological mechanisms of action, and dose-response information among humans is limited. Further mechanistic and epidemiological investigations are necessary to better understand the association of SO_2 and asthma, particularly as additional controlled exposure studies are unlikely due to ethical and safety considerations among the most susceptible populations, such as severely asthmatic children; nor would such studies address the limited information on long-term SO_2 exposure.

III. Methods: Time-Series and Case-Crossover Design

Both time-series analysis and case-crossover design have been used to examine the association of short-term pollutant variation with acute outcomes, such as asthma ED visits (Atkinson et al., 2014; Fung et al., 2003; Jalaludin et al., 2008; Strickland et al., 2010).

Time-series:

Time-series analysis is a common technique, particularly in combination with Poisson regression to attempt to better control for time trends such as seasonality (Jaakkola, 2003). One challenge is choosing appropriate time span when using methods to control for confounding. The development of local smoothing methods (LOESS) using Generalized Additive Models (GAM) has improved the ability to control for confounding; however, issues of concurvity, indicating a high degree of multicollinearity, can remain. This can lead to the understatement of variance and unstable estimates. The use of parametric natural cubic splines in a generalized linear model (GLM) has been proposed as an alternative to the LOESS method (Fung et al., 2003).

Case-crossover:

Case-Crossover design has been proposed as an alternative for short-term environmental exposures, in which cases serve simultaneously as their own controls at different points in time (Fung et al., 2003; Jalaludin et al., 2008; Levy et al., 2001; Strickland et al., 2010). One advantage of a case-crossover study is that potential confounders due to individual traits can be controlled for by design, as the case serves as their own control. Additionally, using a bi-directional design that samples control dates both pre and post-event is able to control for time trends in both exposures and outcomes, such as important seasonal trends in air pollutants and asthma exacerbations (Fung et al., 2003).

However, the case-crossover design does have some disadvantages. Though, individual traits can be controlled for by design, it may not control for characteristics that change over time. In case-control studies the referent-spacing time, or the time between a case and control selection must be chosen for a duration that will not biased due to autocorrelation of the data (Fung et al., 2003); however, shorter referent-spacing time may help reduce selection bias, and bias due to confounding (Bateson & Schwartz, 2001).

In a simulation analysis by Fung et al. (2003), hospital admission data was generated and used to compare mean results across 500 iterations in various parameters with time-series and case-crossover designs. The authors concluded that both time-series and case-crossover design provided reasonable estimates of risk of adverse health outcomes due to short-term air pollution exposure; however, time-series analyses with a short admission span provided more precise estimates than the bi-directional case-crossover method using an exact calculation method for ties, which resulted in larger 95% confidence intervals. This imprecision is reflected in larger standard errors for parameter estimates, and lower power in the case-crossover methods (Fung et al., 2003), which is generally consistent with the reported 50% lower power of

case-crossover analysis compared to time-series analysis (Bateson & Schwartz, 1999; Jaakkola, 2003).

While concerns still remain about case-crossover design, further exploration of these methods by Lu & Zeger (2007) have indicated that when there is a common exposure, case-crossover methods using conditional logistic regression are actually a special case of time-series analysis. Additionally, time-series methods account for over-dispersion of the Poisson variance, while case-crossover analyses typically do not (Lu & Zeger, 2007). These findings are particularly applicable for many air pollution studies, where many people can be assumed to have the same ambient exposures, such as when there is regional homogeneity in ambient ozone concentrations.

The implications of Lu & Zeger's work suggest that the issues identified by Fung et al. (2003) are not a concern in certain implementations of case-crossover design. However, in a monitor-specific study of SO_2 and examination of effect modification by traffic-related pollution, there may still be advantages to using a time-series analysis. Monitor specific SO_2 concentrations will mean there are no longer shared exposures between subjects in each time interval, unless analyses are stratified by monitor. Traffic-related population will also differ by location and exposure to high traffic-flow roads. While case-crossover design allows for computational convenience, a comparison of results using time-series methods would allow for identification of potential bias due to the absence of shared exposures.

IV. Sulfur Dioxide (SO_2)

Sources of SO_2:

SO_2 is primarily formed during the extraction of metal from ore, the refinement of petroleum products, or when raw materials and fuel containing sulfur are burned, such as coal and oil. Mobile sources do contribute due to burning high sulfur fuels in locomotives, large

diesel ship engines, and non-road equipment (U.S. EPA, 2015). On a global scale, natural SO_2 emissions, particularly from volcanoes, are important, but do not contribute significantly to ambient concentrations in an urban setting (Lowe, 2007; Jacobson, 2002).

According to the 2011 U.S. National Emissions Inventory, 94% of emissions are due to point sources, 3% are due to area sources, and 2.4% are due to mobile sources. Additionally, 83% of SO_2 total emissions are due to fuel combustion, and 73% of total emissions are due specifically due to fossil fuel power plants (U.S. EPA, 2011). SO_2 emissions in Georgia related to fossil fuel electricity production are even higher than national levels, with an estimated 88% contribution to statewide SO_2 emissions in 2002 (U.S. EPA, 2015).

There are five major point sources for SO_2 in the Metropolitan Atlanta Area: Plant Bowen, Plant McDonough, Plant Wansley, Plant Yates, and Lafarge Building Materials. Though neither are the largest contributors of SO_2, Plant McDonough and Lafarge Building Materials the two closest to the metro area (Lowe, 2007). Additionally, in 2005, Lafarge Building Materials closed their last coal-fired kiln for cement production, and in 2012 Plant McDonough converted to natural-gas turbines for electricity production. Though these changes resulted in essentially the elimination of SO_2 emissions, both of these sources do make important emission contributions throughout 2002 – 2013 (Lowe, 2007).

Analysis of SO_2 monitor data at Georgia Tech and Jefferson Street, wind speed and direction, and point-source emission plumes identified highest ambient SO_2 concentrations blowing from the northwest (Lowe, 2007; Wade, 2005). This indicates that Plant McDonough and Plant Bowen are likely the two greatest contributors to metro Atlanta ambient SO_2 levels. Plant Bowen is likely to contribute lower concentrations, but more often and less dependent on wind direction as plumes consistently touchdown in the Atlanta area. Alternatively, plumes from

Plant McDonough are likely responsible for peak concentration levels, though are more dependent on wind direction (Lowe, 2007).

However, an important consideration is that SO_2 emissions increase as power output increased, indicating that growing electricity demand in the Atlanta area will be a factor in SO_2 emissions even with control methods and changes in technology (Lowe, 2007). Other potential sources in the Atlanta area include industrial facilities for chemical manufacturing, pulp and paper processing, and metal processing. Potential mobile sources are railroad equipment and diesel vehicles; however, limited data is available on emissions or their contribution to the Atlanta area (Lowe, 2007; Wade, 2005).

Spatial Heterogeneity and Measurement Error:

Though several studies have incorporated SO_2 into their analyses of air pollution and asthma emergency department visits, including using data from Atlanta, multiple studies have identified spatial heterogeneity and measurement errors as important sources of bias in air pollution time-series analyses (Goldman et al., 2010; Sarnat et al., 2010; Strickland et al., 2013; Wade et al., 2006). Biased estimates are particularly concerning for SO_2 due to the large reported spatial heterogeneity, combined with the generally small quantity of monitors, and that a primary source of SO_2 is coal fired power plants, which may produce variable regional concentrations (Lowe, 2007; Smith et al., 1978; Wade et al., 2006)

Personal Exposure Error: Individual exposures may differ from central monitor locations due to differences between indoor and outdoor concentrations, microclimates such as car environments, and behavioral differences due to travel for work, education, or recreation (Zeger et al., 2000). These unique individual exposure profiles may result in two types of this error: the difference between individual exposure and average personal exposures, as well as between

average personal exposures and ambient monitor-based levels (Goldman et al., 2010; Zeger et al., 2000).

One challenge is the absence of studies examining adult or child behavior data in the U.S. or Atlanta that may assist in characterizing geographic patterns of travel or quantity of time spent at residence location. Determining how often children and adolescents are at home, the distance between schools and extra-curricular activities and residence location could help estimate if residence location is sufficient to characterize exposure by monitor location.

While behavior data is lacking, several quantitative assessments of exposure error between personal exposure and ambient concentrations exist, though the studies primarily focus on PM components, NO_2, and ozone. There was considerable variation between personal PM exposure data and ambient concentrations based on central monitors (Janssen et al., 1998, 1997; Wallace, 1996, 2000). However, there were differences in whether outdoor concentrations overestimated or underestimated personal exposures by pollutant and by study.

A review conducted by Wallace (1996) found relatively poor correlation between the data for PM_{10} and $PM_{2.5}$, though these correlations improve when studies repeated measurements seven or more times, and as particle size became finer (Wallace, 1996). Additionally, when controlling for environmental tobacco smoke, correlations improve, though outdoor ambient concentrations underestimated personal exposures (Janssen et al., 1998). Several of these studies did report data on sulfate components of $PM_{2.5}$ or elemental sulfur (Monn, 2001; Oglesby et al., 2000; Wallace & Williams, 2005). While Wallace & Williams (2005) did report low differences in outdoor and indoor concentrations due to few indoor sulfate sources, there was still low-to-moderate correlations between personal exposures and ambient concentrations.

Among studies that did explicitly examine SO_2, most are written about the Six Cities Study series conducted in the 1970's and reported large variability in correlations (Dockery et al., 1993). However, as this series of studies were conducted in the 1970's they may not accurately reflect important changes in the built environment or behavioral patterns of children, such as outdoor exposure time, or distance to school facilities.

Though there is limited evidence to assist in quantifying the potential individual and average personal exposure misclassification for SO_2, misclassification is likely greater than what is suggested by the data available for PM_{10} and $PM_{2.5}$ due to greater spatial variability in SO_2.

Evidence of Heterogeneity and Variability: In addition difficulties of assessing individual exposures, evidence of strong spatial heterogeneity comes partly from the study of plume behavior in coal power plants and other large point source emitter (Smith et al., 1978). Furthermore, an examination of SO_2 monitors in the metropolitan Atlanta area identified detectable annual, monthly, weekly, and diurnal trends in SO_2 concentrations. Dirurnal trends in particular varied by monitor location, and though all monitors examined recorded mid-day peaks, the profile of peaks varied in duration, and rate of SO_2 concentration change. Furthermore, two year diurnal 1-hr maximum averages though similar, did vary by monitor location (Lowe, 2007). Day-to-day variation of ambient SO_2 is likely due to point sources that either do not emit every day, or are not reaching the limited number of monitors in Atlanta. Meteorological influence on plume properties and transit are likely a primary reason for day-to-day variations (Johns & Linn, 2011; Lowe, 2007; Wade et al., 2006).

The conclusions about SO_2 variation at various monitor sites is supported with an analysis by Wade et al. (2006) using wind rose plots for monitors within the Metro Atlanta area. Results showed a large degree of variability in concentration of SO_2 at each monitor that could largely be attributed to regional point source emissions, such as Plant Bowen, McDonough,

Wansley, Yates, and coal fired cement production facilities. Most importantly, there was significant variability between monitor locations in the metropolitan areas (Wade et al., 2006).

Classical and Berkson Measurement Error: One framework presented by Goldman et al. (2010) separates error types of concern into classical error, and Berkson error. Classical error occurs when ambient pollutant measurements vary about the true concentrations (Goldman et al., 2010). Classical error is typically associated with instrument imprecision, and generally results in a bias towards the null; however, in simulations using air pollution data from Atlanta and emergency department visits, error due to instrument imprecision was estimated to be a small contribution (Goldman et al., 2010; Strickland et al., 2013).

Alternatively, Berkson error occurs when true ambient concentrations vary about the measurement. Goldman et al. (2010) conclude that due to the dominant error associated with spatial heterogeneity between monitors, rather than instrument imprecision, measurement error is dominated by Berkson error. The author's estimate that primary pollutants (SO_2, NO_2, CO, and EC) had between a 19% and 31% bias away from the null in RR parameter estimates (Goldman et al., 2010).

Spatial Heterogeneity and Spatial Variability Measurement Error: Expanding on the classical and Berkson error framework, Strickland et al. (2013) identified measurement error into four main components: spatial heterogeneity, spatial variability, instrument imprecision, and monitor metric selection. Air pollution data and population level health data was generated for the purpose of determining true associations between air pollution and ED visits, and subsequent measurement error (Strickland et al., 2013).

Spatial heterogeneity is defined as when the average concentration of a pollutant is not uniformly distributed across space, and is considered to be modeled as Berkson error. Strickland et al. (2013) report median bias in estimates for SO_2 to be 23.91% (82% CI: 18.29%, 29.99%)

away from the null. Spatial variability is defined as when the day-to-day changes in concentration are not uniform across space, and generally results in a bias toward the null. As identified in Goldman et al. (2010), instrument imprecision can be modeled as classical error and likely contributes only a small portion to overall error.

For the purpose of time-series studies, pollutant data can be averaged in different ways, which may result in different biases. Strickland et al. (2013) tested an unweighted metric form, a population-weighted metric form, and a central monitor weight metric form. All three methods resulted in biases towards the null; however, the central monitor metric generated substantially larger biases than either other form. The population-weighted metric form generally produced the lowest biases; however, differences between the unweighted and population-weight forms were reduced when associations were measured in per IQR increase in concentration, as opposed to per unit increase in concentration. Though reduced bias for unweighted and centric forms when results are scaled to an IQR, the authors concluded a population-weighted metric form will generally produce lower biases (Strickland et al., 2013).

Despite bias away from the null due to spatial heterogeneity, net bias tended to be towards the null due to bias due to spatial variability, instrument imprecision, and metric selection. The lowest net bias scenario for SO_2 still resulted in a 22.6% (82% CI: -26.9%, -17.9%) bias towards the null (Strickland et al., 2013). A relevant limitation of the study is the lack of incorporation of meteorological variables as potential confounders. This could be problematic, particularly for SO_2, as weather patterns can drive spatial heterogeneity and spatial variability (Lowe, 2007; Wade et al., 2006).

Though there are limitations both in using observed data, or performing a simulation based analysis, the results from Goldman et al. (2010) and Strickland et al. (2013) both indicate that measurement error, largely due to spatial heterogeneity and variability, can introduce bias

into measures of association, typically a net bias towards the null. Furthermore, SO_2 has the largest reported bias for any commonly measured primary or secondary pollutant, indicating that existing measures of association for health effects and ambient SO_2 are potentially underestimating the strength of association.

V. Epidemiology of SO_2 and Asthma

Introduction and Cross-Sectional Studies:

Numerous studies have examined single-pollutant and multi-pollutant relationships between air pollution and asthma exacerbation and prevalence. Only one study was found that focused solely on SO_2 and asthma ED visits; however, many studies included SO_2 in their analysis. While there is strong epidemiologic evidence supporting an association of asthma with air pollution, results varied across studies on the association between not only SO_2 and asthma prevalence, but also SO_2 and asthma-related ED visits.

A cross-sectional study based on the U.S. National Health Interview Survey from 2001 – 2004 found no association between SO_2 and childhood asthma prevalence using annual SO_2 concentration averages (Akinbami et al., 2010).

Alternatively, a cross-sectional study by Penard-Morand et al. (2010) investigated long-term exposures using a validated dispersion model for school children from 108 schools in France. The OR for SO_2 were estimated based on outcomes of exercise-induced asthma (1.27, 95% CI: 1.11 – 1.53), asthma symptoms within the last year (1.29, 95% CI: 1.03 – 1.71), lifetime asthma (1.26, 95% CI: 1.11 – 1.42), and sensitization to pollens (1.02, 95% CI: 0.83 – 1.31). The OR for lifetime asthma was also stratified by duration of residence at address recorded in the survey. As residence time increased, the OR increased from 1.26 to 1.38; however, the OR was not statistically significantly different. Furthermore, among residents who lived at the same address for at least eight years, or since birth, associations were either borderline statistically

significant, or not statistically significant (Pénard-Morand et al., 2010). Though this study has statistically significant ORs for asthma related outcomes, the study is limited by cross-sectional survey design.

Lastly, a meta-analysis of cross-sectional studies conducted by Anderson et al. (2011) found the association between asthma prevalence and SO_2 ranged from ORs of 0.94 to 1.51, with variable statistical significance for a 10 $\mu g/m^3$ increase in SO_2 concentration, indicating a lack of consistent results in the cross-sectional literature (Anderson et al., 2011).

SO_2 and Emergency Department Visits:

Many studies have examined associations between air pollution and asthma using time-series analysis. Five recent studies have been reviewed for their inclusion of single pollutant and mutli-pollutant results of SO_2 and asthma ED visit associations. Out of the five, only one study focused exclusively on the association SO_2 and asthma exacerbation.

A study by Sunyer et al. (2003) conducted a time-series analysis of daily counts of ED admissions using data from the European APHEA 2 study. For an increase of 10 $\mu g/m^3$ of ambient SO_2, daily asthma ED admissions among 0-14 year olds increased 1.3% (95% CI: 0.4%, 2.2%). The authors also identified issues of strong correlations between SO_2 and other confounding air pollutants, such as CO and PM_{10} (Sunyer et al., 2003).

Restrepo et al. (2013) used negative binomial regression, which is similar to time-series methods using Poisson regression, to model the association of SO_2 and asthma exacerbation using air pollution and hospital admission data from 1996 – 2000 in New York City counties. The authors stratified by age, between children (0-17) and adults (18+).

The relative risk for the IQR of same day 24-hour average SO_2 concentrations was 1.023 (95% CI: 1.004, 1.042). When 1, 3, 5, and 7-day lag periods were applied in the model, RRs

increased with each additional lag period time; however, only the 7-day lag period was statistically significantly larger than same day, or 1-day lag periods. Analysis by individual county revealed differing RR trends by lag period differentiation; however, no results were statistically significantly different by county. Though seasonal analysis and comparison of daily averages to daily 1-hour maximums for concentrations measurements was performed for $PM_{2.5}$, these analyses were not carried out for SO_2; however, results from $PM_{2.5}$ highlight the importance of accounting for time trends such as seasonality, along with the use of 1-hour maximums if data is available (Restrepo et al., 2013). An additional limitation was the inclusion of children from 0 – 5 years old; as their inclusion can be problematic due to the difficulty in diagnosing asthma (Annor et al., 2014; Strickland et al., 2010).

A study by Strickland et al. (2010) examined daily counts of ED visits for asthma or wheeze among children aged 5 – 17 from Atlanta hospitals during 1993-2004. The authors' report a warm season rate ratio (RR) of 1.030 (95% CI: 1.002-1.058) from a Poisson generalized linear model for SO_2 IQR range increases, using a three-day moving average. Overall, cold season RRs were not statistically significant. Similar results were produced when examining the association by quintile, with small, but statistically significant RRs only found for warm season 3rd and 4th quintiles of SO_2 concentrations (7 to < 13ppb, 13 to < 24.2ppb). In a cubic polynomial distributed lag model, using IQR concentration increases, SO_2 RRs remained consistent across a choice of 0 – 7 lag day periods. These results differ from analyses performed by Restrepo et al. (2013), who observed increasing relative risks as lag period increased; however, the analyses in Restrepo et al. (2013) did not account for seasonal trends, and other confounders to the same extent as Strickland et al. (2010).

Strickland et al. (2010) also performed a sensitivity analysis, utilizing alternative model specifications including case-crossover study design. Though cold season results consistently

indicate no statistically significant associations, model results differ for the warm season, with smaller associations that are not statistically significant.

In a follow-up study to Strickland et al. (2010) and using similar data, Winquist et al. (2014) examined the joint-effects of air pollutants on pediatric asthma ED visits in Atlanta from 1998-2004. Single pollutant model results are similar to results reported in Strickland et al. (2010) for warm and cold season models. Joint effects models based on a combination of SO_2 and SO_4^{-2}, representing a typical power plant combination, resulted in statistically significant associations with asthma ED visits in warm season models incorporating linear, quadratic, and cubic interaction terms for each pollutant (1.0634, 95% CI: 1.0060, 1.1240). However, a joint effect model with no interaction terms, but controlling for ozone, CO, NO_2, and elemental carbon did not result in statistically significant positive associations with asthma ED visits (Strickland et al., 2010; Winquist et al., 2014).

Conclusions:

The literature presents inconsistent conclusions regarding the association of SO_2 and asthma exacerbations, identifying that many challenges remain in obtaining more accurate estimates. Variable methodologies and geographic locations in the reviewed studies make it difficult to always directly compare results. Sensitivity analysis presented by Strickland et al. (2010) identified that there can be sufficient variation in modeling results using different methodologies to alter statistical significance, even using the same data. Furthermore, additional challenges have been identified in controlling for measurement error and spatial heterogeneity. The ability to control for confounding due to other pollutants and to estimate the joint effects of pollutants remains a challenge as well, though Winquist et al. (2014) offers important insight in estimating joint effects using multi-pollutant models.

Also as Strickland et al. (2010) notes, there are advantages to using single-city area data sources. The focus on a specific geographic area allows for detailed consideration of local idiosyncrasies and potentially more accurate modeling, even though the study may not be statistically as robust. Strickland et al. (2010) also noted their skepticism of warm season associations of SO_2 and asthma exacerbations due to concerns of low monitor density, and the spatial heterogeneity of SO_2 concentrations that is likely due to variable SO_2 plume touch-down. Furthermore, they note that there is inconsistent evidence of an association between SO_2 and harmful pediatric respiratory health effects. These discrepancies are further present in results for warm season RRs following sensitivity analysis.

Uncertainty clearly remains in understanding the association between SO_2 and asthma exacerbation indicating the continued need for robust methods of analysis that are able to account for complex joint effects.

VI. Effect Modification of Traffic on SO_2 and Asthma Association

The association between traffic pollutants and asthma is well established (Brugge et al., 2007; Brunekreef & Holgate, 2002; COMEAP, 2011; Guarnieri & Balmes, 2014; McConnell et al., 2006; McCreanor et al., 2007; Winquist et al., 2014). Furthermore, at least two studies have specifically examined the relationship between traffic flow and pediatric asthma ED visits (English et al., 1999; Hwang et al., 2005); however, little is known if traffic flow intensity modifies the association between SO_2 exposure and asthma ED visits. To my knowledge, no studies exist examining effect modification of traffic on the association between SO_2 and asthma.

VII. Contribution of Proposed Study

This study intends to examine the association of asthma events by residence location within 5 kilometers of SO_2 monitors within the Metropolitan Atlanta Area. As identified in this literature review, a critical challenge remains in characterizing the association of SO_2 and asthma exacerbation. Measurement error due to spatial heterogeneity and spatial variability may produce biased estimates of association and are difficult to control for given the limited SO_2 monitoring network. In examining asthma ED cases from 2002 – 2013 within a small radius of monitoring locations, it may be possible to obtain a less biased measurement of SO_2 exposure compared to existing studies that use various weighting methods to estimate regional SO_2 concentrations.

Additionally, it is unclear if traffic flow intensity modifies the association between SO_2 exposure and asthma emergency room visits. This study will help improve the understanding if there is any modification of the association between SO_2 and asthma exacerbation due to traffic flow density. An improved understanding of these associations may help identify the most vulnerable populations and provide recommendations to reduce frequent asthma ER visits and exacerbations.

CHAPTER II: MANUSCRIPT

Introduction

In the U.S. and in the state of Georgia, asthma, a chronic disease characterized by episodes of reversible airflow obstruction, affects more than 16.5 million adults and 7.0 million children nationwide (Guarnieri & Balmes, 2014; Moorman et al., 2012). In Georgia 13.5% of adults and 16% of children aged 0 – 17 years have asthma. Children are a sub-group of concern as a susceptible population, particularly in Georgia with asthma prevalence among children higher than the U.S. average (Annor et al., 2014; Atkinson et al., 2014; Peden, 2005). Important precipitators include exercise, airway infections, airborne allergens, occupational exposure, and environmental airborne irritants (Annor et al., 2014; Atkinson et al., 2014; Peden, 2005).

There is strong clinical, mechanistic, and epidemiologic evidence supporting an association of asthma with air pollution (Guarnieri & Balmes, 2014; Peden, 2005; Trasande & Thurston, 2005). Examination of emergency department (ED) visits with the primary cause of asthma have been previously identified, and used throughout the literature to investigate an association of air pollution with asthma exacerbation among both adults and children (Atkinson et al., 2014; Jaakkola, 2003; Tolbert et al., 2000). A case-crossover design has been used to examine the association of short-term pollutant variation with acute outcomes, such as asthma ED visits (Jalaludin et al., 2008; Strickland et al., 2010).

Although SO_2 is a pollutant of concern, there are limited studies examining the relationship between SO_2 exposure and pediatric asthma ED visits, and the role of SO_2 in asthma etiology remains unclear (Lai et al., 2013; Pénard-Morand et al., 2010). Several studies have included SO_2 as an exposure of interest in models of ambient air pollution and ED visits, and have reported small independent associations of SO_2 and pediatric ED visits (Restrepo et al., 2013; Strickland et al., 2010; Winquist et al., 2014). An important challenge is the large spatial

heterogeneity in SO_2, which Strickland et al. (2013) reports is the largest among any commonly found primary or secondary pollutants. This is of particular concern for SO_2 given the generally small quantity of monitors, and that a primary source of SO_2 is coal power plant plumes, which may produce variable regional concentrations (Guarnieri & Balmes, 2014; Lowe, 2007; Smith et al., 1978). The examination of asthma events by resident locations near SO_2 monitors may help elucidate the association between SO_2 exposure and acute asthma events.

Additionally, the association between traffic pollutants and asthma is well established (Brunekreef & Holgate, 2002; Guarnieri & Balmes, 2014; McConnell et al., 2006; James McCreanor et al., 2007). Furthermore, at least two studies have specifically examined the relationship between traffic flow and pediatric asthma ED visits (English et al., 1999; Hwang et al., 2005); however, little is known if traffic flow intensity modifies the association between SO_2 exposure and asthma ED visits.

In this study, we assessed the association of SO_2 and asthma ED visits using a case-crossover design with data from non-federal acute care hospitals in Atlanta, and data from four monitoring locations throughout metropolitan Atlanta. Asthma cases within 5, 4, and 3 kilometers of monitoring sites were analyzed using conditional logistic regression, controlling for meteorological variables, seasonal trends, and school holidays. Furthermore, we investigated effect modification by dichotomized traffic flow due to an interest in seeing if the association between SO_2 and pediatric asthma ED visits is modified given the known role of traffic emissions and asthma exacerbation.

Methods

Study Design:

This study used a symmetric bi-directional case-crossover design and conditional logistic regression to estimate associations between daily ambient SO_2 concentrations and pediatric

asthma emergency department (ED) visits. The case-crossover design is a variation of the case-control study, utilizing cases as their own controls at variable points in time. This study design is useful for studying intermittent and variable exposures associated with rare outcomes. This design has previously been used in the literature to examine acute effects of ambient air pollution (Jaakkola, 2003; Lumley & Levy, 2000) in addition to asthma ED visits related to air pollution (Jalaludin et al., 2008; Strickland et al., 2010). Estimates from symmetric bi-directional case-crossover design have been shown to be equivalent to time-series analysis (Darrow, 2010; Fung et al., 2003; Jaakkola, 2003).

This study was approved by the Institutional Review Board of the Georgia Department of Public Health, and of Emory University.

Environmental Data:

Daily ambient one-hour maximum SO_2 concentrations were obtained from four Atlanta Metropolitan Area monitor sites. Three sites were from the U.S. Environmental Protection Agency's Air Quality System (EPA AQS) (AQS Site IDs: 13-089-0002, 13-121-0048, & 13-121-0055) with data obtained from the EPA AirData AQS Data Mart, in addition to one monitoring site from the Southeastern Aerosol Research and Characterization Network (SEARCH, ID: JST).

Hourly temperature and relative humidity data were obtained for the SEARCH JST monitor, and daily maximum temperature, daily minimum temperature and daily mean relative humidity were calculated. SEARCH JST meteorological data was considered representative for the Atlanta Metropolitan Area.

Traffic flow exposure was defined as exposure to ambient surface level $PM_{2.5}$ concentrations related to traffic exhaust and was estimated by locally generated model data from the Research – LINE source dispersion model for near-surface releases (R-LINE) developed

by EPA's Office of Research and Development and applied to Atlanta Regional Commission 2011 road network and traffic data. R-LINE estimates for each ED case were selected by the nearest R-LINE model 250 meter grid cell using ED case residence locations.

Study Population:

We obtained ED visit data from the Georgia Department of Public Health for all non-federal hospitals in the state of Georgia from 2002 – 2013. We defined ED visits for pediatric asthmas as all visits with the International Classification of Diseases, 9th Revision, code for asthma (493.xx) or wheeze (786.07) among children age 1 – 17 years who did not have a code for external injury or poisoning (E800 – E999), or for acute respiratory infections (460.0 – 466.0). Children under 12 months of age were excluded due to the inability to accurately diagnose asthma (Annor et al., 2014; Strickland et al., 2010; Wardlaw, 1993).

ArcMap 10.2.2 and ArcCatalog 10.2.2 (ESRI; Redlands, CA, 2014) were used to identify asthma and wheeze ED cases within 5, 4, and 3 kilometer radii of each SO_2 monitor base on residence location. ED case data were merged with environmental data, and control days were generated using a symmetric bi-directional design, with controls using available environmental data at 7 and 14 days before and after the event. When all requisite environmental data were not available, controls were excluded to allow for case-control strata with 4, 3, 2, or 1 controls days. To avoid overlap bias due to repeat cases by the same individuals, we removed all repeat cases within 7 days in either direction of the event and selected the earliest case for analysis. Final case sample size for each radius were 5 Km (n = 15,610), 4 Km (n = 8,522), and 3 Km (n = 6,742).

Statistical Analyses:

SO2 and ED Data Only:

Odds ratios for associations between SO_2 and pediatric asthma-related ED visits were estimated using conditional logistic regression. The dependent variable was the radii specific count of pediatric asthma visits. Independent variables were monitor specific 1-hour maximum SO_2 concentrations for each case-control strata, daily maximum temperature, daily minimum temperature, and daily mean relative humidity. Statistically significant meteorological interaction terms were identified using likelihood ratio tests, resulting in a final model containing independent variables, and interaction terms between maximum and minimum temperature, and each temperature variable and relative humidity, respectively.

Analyses were run using day-of SO_2 (Lag 0) concentrations and meteorological terms, and were repeated using 1-day, 3-day, 5-day, and 7-day moving averages (Lag 0 – 1, Lag 0 – 3, Lag 0 – 5, & Lag 0 – 7, respectively). Analyses were conducted by repeating all analyses with case populations within 5 Km, 4 Km, and 3 Km of monitors, and by warm season (May – October) and cold season (November – April) stratifications.

Traffic Data:

Traffic-related $PM_{2.5}$ data were categorized into higher and lower exposures by three different methods: dichotomization around the median (4.86 $\mu g/m^3$), dichotomization at 10 $\mu g/m^3$ (91^{st} percentile), and categorization by quintiles of $PM_{2.5}$ concentration. Use of the median and quintiles was selected due to lack of normality in the data, and dichotomization at 10 $\mu g/m^3$ was performed as an exploratory analysis given previously reported increased rate-ratios between $PM_{2.5}$ and asthma-related ED events above 10 $\mu g/m^3$. Data were also included as a continuous variable.

Four new models were created by adding a variable for categorization of traffic-related $PM_{2.5}$ and an interaction term between traffic-related $PM_{2.5}$ and SO_2 exposure to the original model. Likelihood ratio tests were performed on each model iteration to determine which categorization of traffic-related $PM_{2.5}$ had significant interaction terms.

Odds ratios for associations between SO_2 and pediatric asthma-related ED visits were run for high versus low traffic-related $PM_{2.5}$. Analyses were repeated at day-of (Lag 0) and 3-day moving averages (Lag 0 – 3) of SO_2 concentrations for overall data, and during cold and warm seasons. Day-of (Lag 0) and 3-day moving averages (Lag 0 – 3) were selected based on results of primary analyses for associations between SO_2 and asthma-related ED visits showing the strongest association at these lag periods.

All analyses were performed in SAS 9.3 (Gary, NC, 2014).

Results

Descriptive Statistics

Monitor locations and selection of pediatric asthma emergency department cases by resident location are shown in Figure 1. The closest distance between monitors was 1.9 Km apart and the furthest 15.3 Km.

Selected characteristics of ED cases are summarized by search radius in Table 1 and by individual monitor in Table 2. Proportionally, a higher number of cases were boys (60.6%), had family insurance coverage (86.2%), aged 1- 4 years old (41.5%), and were black (90.5%). The number of cases decreased by age category, with 8.5% of cases being between ages 15 and 17. These demographic trends were consistent across all examined search radii. Demographic trends were also consistent across individual monitors. Sample size differed by monitor, with monitor #3 having the largest total case count and monitor #4 the smallest (8,514 vs. 1,421 at 5 Km, respectively). Though the proportion of cases who were black was consistent by radius and

monitor, it was substantially higher than the proportion of black residents by census tract, with the exception of monitor #4 (Table 3).

Descriptive characteristics for ambient SO_2 concentrations are shown in Table 4. Monitor #3 had approximately half the median SO_2 value compared to monitor #1, and #2; however, all three monitors had a similar range of concentrations. Monitor #4 differed from other monitors, with a median SO_2 concentration of 1.0 ppb, and an IQR of 2.1 ppb. When monitor #4 was excluded from the aggregate, the data remained similar. Due to limited sample size, all monitor data in aggregate were selected for inclusion in models. There were substantial seasonal differences across monitors, particularly for monitor #1. Despite differences in SO_2 concentrations by monitor, Spearman correlation coefficients showed moderate-to-strong positive correlations between monitors (Table 5). There were no differences in correlations by season.

Analysis of Ambient SO_2Exposure:

Results from primary analysis for associations between ambient SO_2 concentrations and pediatric asthma or wheeze emergency department visits based on all monitor data by radii and multi-day moving averages are shown in Table 6. Associations were not statistically significant, with the exception of day-of SO_2 (Lag 0) exposure for cases within a 4 Km radius (OR: 1.044, 95% CI 1.006 – 1.084). Associations between ambient SO_2 exposure and asthma-related ED visits generally became larger as moving average increased from day-of (Lag 0) to 3-day moving averages models, with declining strength of association during 5-day and 7-day moving averages. Odds ratios also increased as search radius decreased, with 3-day moving average for cases within a 3 Km radius resulting in the largest odds ratio; however, confidence intervals were wider.

Results from exploratory cold and warm season analyses by radius and lag period are shown in Table 7. We observed one statistically significant association of ambient SO_2 exposure and asthma-related ED visits during the cold season using day-of SO_2 (Lag 0) exposure. Though not statistically significant, cold season models using 1-day and 3-day SO_2 moving averages exhibited stronger associations than 5-day and 7-day moving averages. Additionally, the strength of positive associations increased as search radius decreased, similar to overall results. There were no statistically significant associations during the warm season for cases within a 5 Km radius; however, sample sizes for both cold and warm seasons were small. Trends were similar at smaller radii, though, models during the warm season at 3 Km radius showed an increasing association as moving average lag period increased.

Due to lack of normality in SO_2 data we conducted further exploratory analysis assessing SO_2 exposure by quintile of SO_2 concentration. Results are presented for overall and season specific analysis in Table 8. Analyses focused on day-of (Lag 0) exposure and 3-day moving averages due to evidence of stronger associations in this range in primary analyses. Positive associations were generally strongest for quintiles 2 and 5 using 3-day SO_2 moving averages. Associations were slightly stronger during cold season. Day-of (Lag 0) exposure was inversely associated in overall and warm season analyses. Results were consistent by search radius; however, no associations were statistically significant.

Analysis of Effect Modification by Traffic-related $PM_{2.5}$:

Descriptive characteristics of traffic-related $PM_{2.5}$ estimated by R-LINE modeling are presented in Table 9. We categorized traffic-related $PM_{2.5}$ in higher and lower exposures using four methods: Dichotomized exposure around the median (4.86 $\mu g/m^3$), dichotomized around the 91st percentile (10 $\mu g/m^3$), by quintile of $PM_{2.5}$ exposure, and as a continuous variable.

Interaction terms between categorized traffic-related $PM_{2.5}$ and ambient SO_2 exposure were statistically significant when $PM_{2.5}$ was modeled as a continuous variable and as quintiles (Table 10).

Odds ratios between high and low traffic-related $PM_{2.5}$ for the association between ambient SO_2 exposure and asthma ED visits are shown in Table 11. Generally, traffic-related $PM_{2.5}$ assessed as a continuous variable showed weak positive associations for a 1 $\mu g/m^3$ increase in $PM_{2.5}$. When dichotomized at 10 $\mu g/m^3$ we observed positive associations for high traffic exposure at all lag periods across season and overall analysis; however, no associations were statistically significant. For cases within a 4 Km radius, positive associations for continuous and dichotomization at 10 $\mu g/m^3$ were stronger and statistically significant in overall analysis and by season, except for day-of SO_2 (Lag – 0) exposure during the cold season. For cases within a 3 Km radius results were not consistent. We observed inverse associations across all categorization schemes except during the warm season.

Odds ratios of traffic-related $PM_{2.5}$ by quintile for the association between ambient SO_2 exposure and asthma ED visits are shown in Table 12. Confidence intervals for associations were generally much wider than in other categorization schemes. For cases within a 5 Km radius associations were generally positive and the strength of association increased as quintile of $PM_{2.5}$ exposure increased. Strongest associations were present during the warm season for quintile 5 of $PM_{2.5}$ exposure. Results were not consistent by radius, with inverse associations for all quintiles for cases within a 4 Km and 3 Km radius, with the exception of day-of SO_2 exposure during the warm season at 4 Km and for day-of SO_2 exposure during both warm season and overall analyses at 3 Km.

Discussion

We used a case-crossover design to examine the association between ambient SO_2 concentrations and over 15,000 pediatric asthma and wheeze emergency department visits within a 5 kilometer radius of SO_2 monitors in the Atlanta Metropolitan Area. By restricting analyses of ED cases to those that are in close geographic proximity of monitor sites, we have attempted to reduce exposure misclassification of SO_2 concentrations. Additionally, we examined whether higher exposures to traffic-related $PM_{2.5}$ modified associations between ambient SO_2 and emergency department visits.

We found positive trends between day-of (Lag 0) and 3-day moving averages of SO_2 exposure and asthma-related emergency department visits, as well as that associations increased as proximity to monitor location increased. However, most associations were not statistically significant. Positive associations were also observed in separate analyses of warm and cold seasons. The strongest associations, including statistically significant associations, were observed with 3-day moving average SO_2 concentrations during the cold season.

Association between Ambient SO_2 and Emergency Department Visits:

These results are generally consistent with several studies using case-crossover and time series methods that have observed small, but statistically significant associations between ambient SO_2 concentrations and asthma-related ED visits (Jalaludin et al., 2008; Peel et al., 2005; Strickland et al., 2010; Winquist et al., 2014). However, previous epidemiologic and experimental studies have not consistently associated ambient SO_2 concentrations with pediatric asthma-related ED visits, or other events of asthma exacerbation (Reiss et al., 2008; Schlesinger, 2008; Trasande & Thurston, 2005).

Strickland et al. (2010) in particular mentions concerns over the validity of reported associations due to local spatial heterogeneity of SO_2. Previous large sample epidemiologic studies often use regional estimates of SO_2 based on a limited number of monitors, which may not fully reflect local variability in plume touchdown and exposure concentrations (Strickland et al., 2010). In our study, observed variability in SO_2 concentration magnitude and range by monitor is consistent with reported local spatial heterogeneity (Strickland et al., 2013) .Though few of our reported associations were statistically significant, the trend of positive associations lends evidence to the validity of previous studies reporting associations between asthma-related emergency department visits and ambient SO_2.

One notable difference in our results were stronger associations during the cold season, compared to previous studies reporting stronger associations during the warm season (Barnett et al., 2005; Jalaludin et al., 2008; Peel et al., 2005; Strickland et al., 2010). These findings may be due to seasonal differences in SO_2 concentrations. Cold season median concentration and IQR (Median: 6 ppm, IQR: 13 ppm) were both larger than during the warm season (Median: 4 ppm, IQR: 10 ppm). This was particularly noticeable for monitor #1, whose median was almost double that of the warm season.

Another potential explanation is that rates of emergency department visits are more common during the cold season, with 55% of cases occurring from November to April and ED cases in June and July see a two to three fold reduction. Higher cases rates are thought to be attributable to exacerbations triggered by higher prevalence of viral infections (Annor et al., 2014; Strickland et al., 2010). However, both the phenomenon of higher SO_2 concentrations and greater ED rates during the cold season have been previously identified in the literature that also reported stronger warm season associations (Delfino et al., 2014; Jalaludin et al., 2008; Peel et al., 2005; Strickland et al., 2010).

It is possible our results differ from previous studies partly due to insufficient sample sizes in seasonal dichotomization; however, trends were consistent across study populations selected by variable distance from monitors (3 – 5 Km). Alternatively, though we controlled for interaction between meteorological variables, we did not control for interaction between SO_2 and meteorology. It is possible there is unaccounted synergism between SO_2 exposure and temperature; however, this seems unlikely to be a driving factor in our observations given the large differences in seasonal SO_2 and ED cases.

Effect Modification:

Additionally, we observed trends of larger associations between SO_2 and asthma-related ED visits among those with higher traffic-related $PM_{2.5}$ exposures in three of our four different modeling approaches to traffic-related $PM_{2.5}$. This effect modification was present at all distances, including statistically significant results in overall, warm, and cold season analyses at a 4 Km distance, with strongest associations occurring during warm season at the 3-day moving average of SO_2 exposure.

To the best of our knowledge, no other studies have examined effect modification of traffic-related $PM_{2.5}$ exposures on the association between ambient SO_2 and asthma emergency department visits. However, a recent study by Delfino et al. (2014) did examine effect modification of traffic-related air pollution using $PM_{2.5}$, NO_x, and particle number estimates from a similar near-surface dispersion model (CALINE4) as the R-LINE data in our study. The authors found associations between ambient CO, NO_x, NO_2, and $PM_{2.5}$ were stronger for those with greater than median dispersion-modeled $PM_{2.5}$, NO_x, and particle number for both cold and warm seasons, with strongest effect modification during the cold season. However, these results

differed by pollutant, for example, effect modification of traffic-related exposures on primary $PM_{2.5}$ was stronger during the warm season.

Given differential seasonal patterns by specific pollutant, it is difficult to interpret the results of Delfino et al. (2014) in the context of our study on SO_2; however, our results are generally consistent in observing statistically significant effect modification in both cold and warms seasons. A potential explanation for seasonal differences between Delfino et al. and our study's strongest observed effect modification may be due to our R-LINE's data being limited to traffic-related $PM_{2.5}$ and not accounting for NO_x and particle number. This may lead to effect modification being dominated by traffic-related $PM_{2.5}$, which saw stronger effect modification during the warm season in both our study and Delfino et al. (2014).

Alternatively, study geography may be important. Delfino et al. (2014) expected higher traffic-related exposures during the cool season due to lower mixing heights and air stagnation; however, this may be partially related to meteorological and topographical differences between Southern California and the Atlanta area. Furthermore, behavior patterns in car usage may differ between warmer year-round weather in Southern California and the Atlanta area. Previous studies have reported higher ambient concentrations of traffic-related pollutants in warmer months in Atlanta (Darrow et al., 2009; Li et al., 2009; Strickland et al., 2010). This was consistent with our observed data, which showed slightly higher median $PM_{2.5}$ concentrations, and a greater number of cases in quintiles 3 and 4 during the warm season.

Additionally, individual behavior differences, such as greater time spent outdoors and increased physical activity during the summer, may drive greater traffic-related exposures independently of higher ambient concentrations. Though, as hypothesized by Delfino et al. (2014), it is possible that effect modification among those with higher traffic exposure is due to greater levels of chronic airway inflammation. This chronic exposure could result in greater

susceptibility to short-term ambient exposures, particularly if there were cumulative effects over multi-day averages. Though our study did not extend effect modification analysis to 5-day and 7-day averages, we did observe strongest associations at 3-day average periods, potentially supporting the results found by Delfino et al. (2014). We did not examine 5-day and 7-day averages in effect modification models due to a lack of strong positive trends in our study at 5-day and 7-day averages in models without traffic-related $PM_{2.5}$. Given the absence of strong associations at 5-day and 7-day averages it is plausible that the relationship between SO_2 and asthma behaves differently than the pollutants studied by Delfino et al. (2014).

Finally, due to lower ED visit rates in the warm months, it may be that there are fewer competing causes of asthma exacerbations, and thus the influence of traffic-related pollutants will be more readily noticeable than in the cold season, rather than a physiochemical, biologically, or behaviorally driven differential effect (Strickland et al., 2010).

Limitations and Challenges:

There were also several limitations to our study. Principally, our study had relatively small sample sizes compared to previous studies of ambient air pollution and asthma-related ED visits in the Atlanta area, which likely contributes to the lack of observed statistically significant associations and wide confidence intervals of the estimates (Strickland et al., 2010; Tolbert et al., 2000; Tolbert et al., 2007; Winquist et al., 2014).

We also relied on administrative database records coded with principal diagnosis of asthma or wheeze from hospitals to identify ED visits for pediatric asthma. The inclusion of wheeze account for 15% of ED visits; however, analyses run without wheeze data yielded similar trends in results, but with wider confidence intervals. The difficultly of diagnosing children under age 5 with asthma, particularly in an ED setting, reduces our confidence that we are truly

observing asthma cases. This age group was included to maintain a larger sample size because over 40% of our cases were under age 5. There was also limited ability to address co-morbidities of ED visits primarily due to lack of data available in hospital records. Though we excluded cases with secondary codes for upper respiratory tract infections, we were unable to address chronic conditions that are associated with increased asthma exacerbation events (Annor et al., 2014; Neuzil et al., 2000).

Our study population also had unique demographic characteristics as over 90% of ED cases were black. While racial and ethnic differences in asthma prevalence and ED case rates have been reported in the literature, a previous study reported 57% of ED cases were black for the Atlanta Metropolitan Area (Strickland et al., 2014). Due to these demographic differences, our study population is not necessarily representative of ED cases for the entire Atlanta region. Though our results are not appropriate to support effect modification by race, the demographic differences in our study population may assist in explaining some of the observed differences in our results compared to previous studies.

Although we believe our restriction of cases to residential locations adjacent to SO_2 monitors more accurately characterizes case SO_2 exposure, there still remain challenges with exposure assessment. While monitor SO_2 data were generally positively correlated, we did observe large inter-monitor variability in concentration magnitude and range, even between monitors 1.2 Km apart. This suggests that a 5 Km radius around monitors for selecting ED cases may remain too large to properly assess SO_2 exposure; however, analyses at smaller radii from monitors resulted in similar general odds ratios, though were subject to wider confidence intervals due to decreased sample sizes. Additionally, monitor data was not available for all study years; additional sub-analyses for 2002 – 2009 may be beneficial despite loss in sample size.

The lack of control of secondary sulfur-related pollutants and additional primary pollutants in our model is another challenge. Our observed differences in seasonal associations compared to previous studies may be a result of our single pollutant modeling approach as previous studies have indicated the importance of controlling for confounding and interaction between other pollutants when examining associations with asthma-related ED visits (Strickland et al., 2010; Tolbert et al., 2007; Winquist et al., 2014). Strickland et al. (2010) observed attenuated single-pollutant associations when controlling for ozone, particularly among cold season analyses. This indicates inclusion of ozone is particularly important, though due to our limited sample size we would expect increased confidence intervals.

As indicated by Winquist et al. (2014), in addition to controlling for other pollutants, it may be more meaningful from an epidemiological and regulatory perspective to examine pollutant combination profiles rather than associations by individual pollutants; however, it is difficult to build multi-pollutant complex interaction models at a monitor specific scale due to necessary input from regional air pollutant models.

CHAPTER III: CONCLUSIONS AND IMPLICATIONS

In summary, our study of asthma-related ED cases with residence locations near SO_2 monitoring stations in Atlanta may provide evidence that despite concerns over modeling spatial heterogeneity in SO_2, associations reported in previous large city-wide, and multi-city studies are valid. Additionally, we observed some evidence of stronger associations between SO_2 and asthma-related ED visits among those with higher traffic-related pollution exposure, particularly in the warm seasons.

These data reinforce the importance of regional and national efforts to adequately control ambient air pollution. Though one of the largest sources of SO_2 emissions in the Atlanta Metropolitan Area, the John J. McDonough coal power plant, was converted to a natural gas facility in 2012, other industrial sources of SO_2 may still contribute to elevated ambient SO_2 concentrations in the region. When sufficient data are available, a comparison of asthma-related ED cases before and after the conversion of the McDonough plant may help establish the efficacy of such conversions for other regions with elevated ambient SO_2, such as communities near Plant Scherer in central Georgia.

A further beneficial step to improve this research is the use of a multi-pollutant model to control for primary and secondary pollutants and their interaction terms. Inclusion of ozone is particularly important due to observed attenuation of single-pollutant associations when controlling for ozone (Strickland et al., 2010). Improved modeling and subsequent understanding of the relationship between SO_2 and other pollutants will help inform which real-world exposures scenarios represent the greatest risk. Furthermore, with additional years of ED data added to analyses, it may be possible to better elucidate how the relationship between ED cases visits and distance from SO_2 monitors. This information will be useful in identifying how

heterogeneity of SO_2 has affected results of previous research on ambient air pollution and asthma-related ED visits.

Finally, though the emphasis of our study is not on demographic trends in asthma prevalence or asthma-exacerbation events, we would like to use these results to continue to call attention to the substantial racial and ethnic disparities in asthma-related ED cases observed not only in our study population, but that have been documented in the literature and statewide epidemiologic reports (Annor et al., 2014; Delfino et al., 2014; Guarnieri & Balmes, 2014)**.** Despite established knowledge regarding disparities in asthma prevalence, management, and ED visits, this study further highlights the need not only for programmatic interventions to improve long-term control of asthma symptoms, but the public health benefits of robust control of anthropogenic environmental exposures such as SO_2, particularly when complementary public health infrastructure is limitedly available to a population.

CHAPTER IV: REFERENCES

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Figure 1: Asthma Emergency Department Cases within a 5 Km Radius of SO_2 Monitor Locations in Atlanta Metropolitan Area

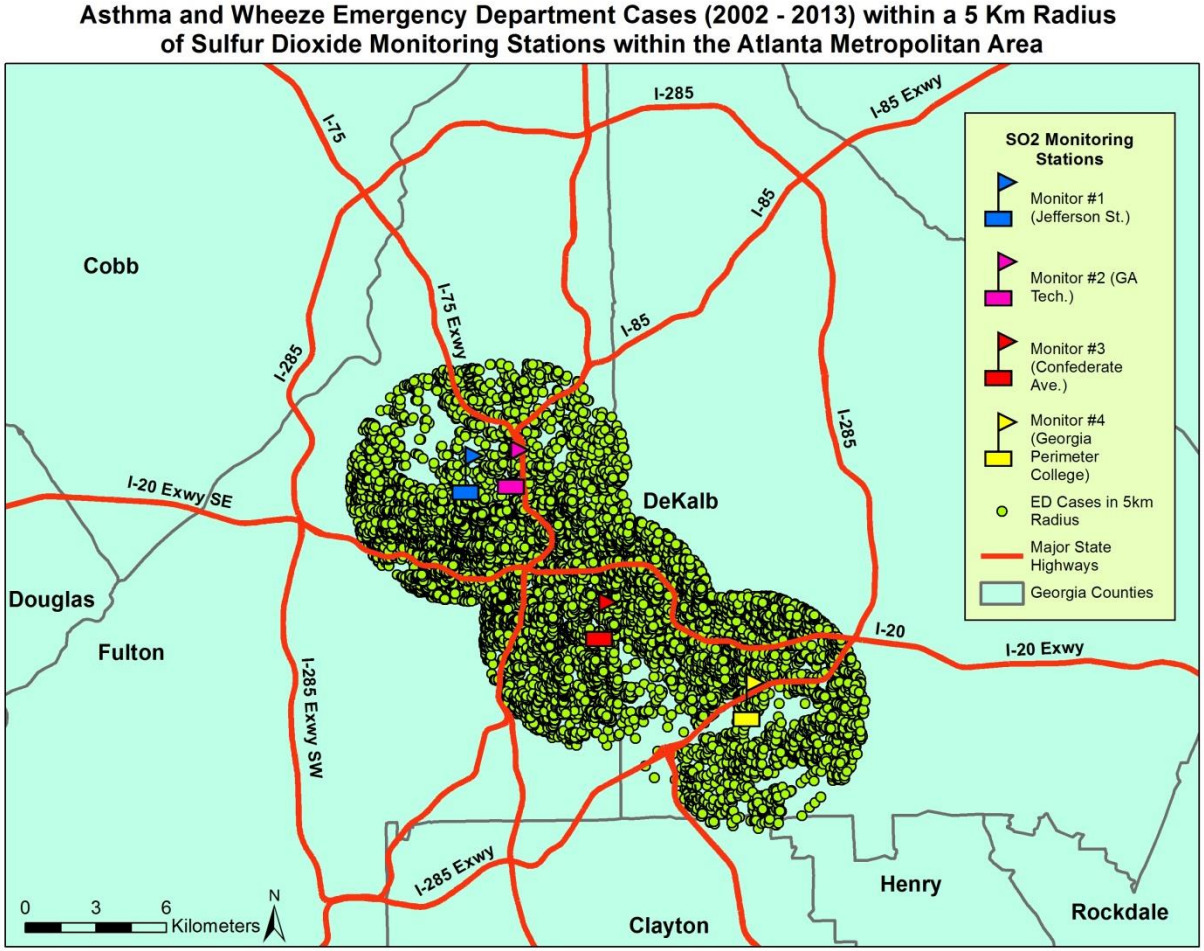

Table 1: Descriptive Characteristics of Asthma Emergency Department Cases for All SO_2 Monitors Combined

Descriptive Characteristics of Asthma and Wheeze Emergency Department Cases by Radius: All Monitors, Using Lag Period of 0 Days								
	Radius* Around Monitors							
Characteristics	**5 Km**		**4 Km**		**3 Km**		**2 Km**	
	N (15,610)	%	N (11,488)	%	N (6,953)	%	N (3,097)	%
Age (Years)								
1 - 4	6,475	41.5	4,803	41.8	2,874	41.3	1,357	43.8
5 - 9	5,066	32.5	3,674	32.0	2,380	34.2	992	32.0
10 - 14	2,741	17.6	1,981	17.2	1,146	16.5	495	16.0
15 - 17	1,328	8.5	1,030	9.0	553	8.0	253	8.2
Race/Ethnicity								
White	635	4.1	538	4.7	369	5.3	154	5.0
Black	14,121	90.5	10,303	89.7	6,208	89.3	2,749	88.8
Hispanic	331	2.1	281	2.5	158	2.3	92	3.0
Other	523	3.4	366	3.2	218	3.1	102	3.3
Sex								
Male	9,462	60.6	6,946	60.5	4,207	60.5	1,859	60.0
Female	6,148	39.4	4,542	39.5	2,746	39.5	1,238	40.0
Insurance Status								
No Insurance	2,148	13.8	1,596	13.9	929	13.3	403	13.0
Insurance	13,462	86.2	9,892	86.1	6,030	86.7	2,694	87.0

* Search radius around each monitor used to select case population

Table 2: Descriptive Characteristics of Asthma Emergency Department Cases by Individual SO_2 Monitor

Descriptive Characteristics of Asthma and Wheeze Emergency Department Cases by Monitor: Using 5 Km Radius and a Lag Period of 0 Days								
	Monitor Location							
Characteristics	**# 1 (Jefferson St.)**		**# 2 (GA Tech.)**		**# 3 (Confed. Ave.)**		**# 4 (Perimeter College)**	
	N (4,110)	%	N (1,565)	%	N (8,514)	%	N (1,421)	%
Age (Years)								
1 - 4	1,695	41.2	656	41.9	3,540	41.6	584	41.1
5 - 9	1,350	32.9	500	32.0	2,727	32.0	489	34.4
10 - 14	692	16.8	267	17.1	1,510	17.7	272	19.1
15 - 17	373	9.1	142	9.1	737	8.7	76	5.4
Race/Ethnicity								
White	147	3.6	56	3.6	361	4.2	71	5.0
Black	3,741	91.0	1,442	92.1	7,694	90.4	1,244	87.5
Hispanic	94	2.3	25	1.6	180	2.1	32	2.3
Other	128	3.1	42	2.7	279	3.3	74	5.2
Sex								
Male	2,459	59.8	948	60.6	5,187	60.9	868	61.1
Female	1,651	40.2	617	39.4	3,327	39.1	553	38.9
Insurance Status								
No Insurance	622	15.1	252	16.1	1,113	13.1	161	11.3
Insurance	3,488	84.9	1,313	83.9	7,401	86.9	1,260	88.7

Table 3: Race and Ethnicity of Census Tracts Containing Individual SO_2 Monitors

Distribution of Population by Race and Ethnicity in Census Tracts Containing Monitors

Characteristics	Monitor Location			
	# 1 (Jefferson St.)	# 2 (GA Tech.)	# 3 (Confed. Ave.)	# 4 (Perimeter College)
	% of Population			
Study Population				
White	3.6	3.6	4.2	5.0
Black	91.0	92.1	90.4	87.5
Hispanic	2.3	1.6	2.1	2.3
Other	3.1	2.7	3.3	5.2
2010 Census Data				
White	25.4	64.4	38.4	5.8
Black	70.5	9.2	45.3	92.0
Hispanic	3.4	4.7	18.7	1.1
Other	1.2	1.2	12.0	0.6
2000 Census Data				
White	14.9	N/A	28.2	7.9
Black	83.3	N/A	57.2	90.2
Hispanic	2.0	N/A	20.4	0.9
Other	1.1	N/A	14.1	1.9

Table 4: Descriptive Characteristics of Environmental Data by SO_2 Monitors

Descriptive Characteristics of Environmental Data by Monitor: Using 5 Km Radius and a Lag Period of 0 Days					
Monitor #	**Characteristics**				
	N*	Mean (SD)	Median	Range	IQR
All Monitors					
SO_2 (ppb)	77,382	9.8 (12.5)	5.0	129.5	11.4
Max. Temp. (^{0}C)	76,537	21.9 (8.0)	22.7	46.1	12.2
Min. Temp. (^{0}C)	75,847	11.0 (8.2)	11.2	41.7	13.7
Relative Humidity (%)	76,368	68.1 (15.2)	68.1	93.0	21.9
Monitors #1, 2, 3					
SO_2 (ppb)	70,350	10.6 (12.9)	5.7	129.5	12.6
Max. Temp. (^{0}C)	69,634	21.9 (8.1)	22.8	46.1	12.3
Min. Temp. (^{0}C)	68,886	11.0 (8.2)	11.3	41.7	13.8
Relative Humidity (%)	69,414	67.9 (15.3)	68.1	93.0	22.0
# 1 (Jefferson St.)†					
SO_2 (ppb)	20,142	14.1 (14.8)	8.8	129.3	15.8
Max. Temp. (^{0}C)	19,959	21.8 (8.2)	22.8	46.0	12.5
Min. Temp. (^{0}C)	19,777	10.8 (8.3)	11.0	41.5	14.0
Relative Humidity (%)	19,953	67.7 (15.1)	67.8	92.7	21.6
# 2 (GA Tech.)‡					
SO_2 (ppb)	8,081	13.1 (15.3)	7.0	124.0	17.0
Max. Temp. (^{0}C)	8,036	21.7 (8.1)	22.2	45.3	12.3
Min. Temp. (^{0}C)	7,870	10.7 (8.2)	10.6	41.0	14.1
Relative Humidity (%)	7,958	67.4 (15.9)	67.4	92.5	23.4
# 3 (Confederate Ave.)††					
SO_2 (ppb)	42,127	8.4 (10.8)	4.0	116.0	10.0
Max. Temp. (^{0}C)	41,639	21.9 (8.0)	22.8	46.1	12.2
Min. Temp. (^{0}C)	41,239	11.2 (8.1)	11.5	38.9	13.6
Relative Humidity (%)	41,503	68.2 (15.2)	68.3	91.7	21.8
# 4 (Perimeter College)‡‡					
SO_2 (ppb)	7,032	2.2 (2.9)	1.0	24.5	2.1
Max. Temp. (^{0}C)	6,903	21.2 (7.5)	21.8	43.9	11.7
Min. Temp. (^{0}C)	6,961	11.1 (7.5)	11.1	37.0	12.0
Relative Humidity (%)	6,954	69.4 (14.9)	68.7	75.2	22.1

* Sample size includes total number of observations of environmental parameters included in regression. This is based on the number of cases and controls. For number of ER cases, see descriptive characteristics of ER Cases.

† Measurements available January, 2002 through December, 2010

‡ Measurements available January, 2002 through April, 2009

†† Measurements available January, 2002 through December, 2013

‡‡ Measurements available October, 2010 through December, 2013

Table 5: Correlation Coefficients between Individual SO_2 Monitors

Spearman and Pearson Correlations between Monitor 1-hour Maximum SO_2 Concentrations (ppb)

	Monitor Location			
	# 1 (Jefferson St.)	**# 2 (GA Tech.)**	**# 3 (Confed. Ave.)**	**# 4 (Perimeter College)**
# 1 (Jefferson St.)				
Correlation Coefficient		0.75	0.76	0.77
P-Value		<0.0001	<0.0001	<0.0001
N		2543	3117	87
# 2 (GA Tech.)				
Correlation Coefficient	0.83		0.69	
P-Value	<0.0001		<0.0001	N/A
N	2543		2583	
# 3 (Confed. Ave.)				
Correlation Coefficient	0.82	0.77		0.79
P-Value	<0.0001	<0.0001		<0.0001
N	3117	2583		1159
# 4 (Perimeter College)				
Correlation Coefficient	0.78		0.84	
P-Value	<0.0001	N/A	<0.0001	
N	87		1159	

Pearson

Spearman

Table 6: Odds Ratios of Ambient SO_2 Exposure on Asthma Emergency Department Visits by Radius, and Lag Period

Odds Ratios and 95% Confidence Intervals of Ambient SO_2* Exposure on Asthma and Wheeze ED Visits By Radius and Lag Period

	Lag Period for SO_2				
	Lag 0	**Lag 0 - 1**	**Lag 0 - 3**	**Lag 0 - 5**	**Lag 0 - 7**
Radius†					
5 Km	1.029 (0.997 - 1.063)	1.023 (0.979 - 1.069)	1.021 (0.968 - 1.076)	0.999 (0.942 - 1.061)	1.002 (0.929 - 1.081)
4 Km	1.044 (1.006 - 1.084)	1.044 (0.992 - 1.099)	1.047 (0.984 - 1.113)	1.026 (0.958 - 1.100)	1.017 (0.933 - 1.110)
3 Km	1.043 (0.995 - 1.093)	1.060 (0.993 - 1.131)	1.080 (0.989 - 1.156)	1.066 (0.976 - 1.164)	1.041 (0.931 - 1.164)

* SO_2 Modeled as continuous variable

† Search radius around each monitor used to select case population

Model adjusted for maximum daily temperature, minimum daily temperature, and mean daily relative humidity, and meteorological interaction terms.

Table 7: Cold and Warm Season Odds Ratios of Ambient SO_2 Exposure on Asthma Emergency Department Visits

Cold and Warm Season Odds Ratios and 95% Confidence Intervals of Ambient SO_2* Exposure on Asthma and Wheeze ED Visits By Radius** and Lag Period					
	Lag Period for SO_2				
	Lag 0	**Lag 0 - 1**	**Lag 0 - 3**	**Lag 0 - 5**	**Lag 0 - 7**
Cold Season†					
5 Km	1.054 (1.010 - 1.101)	1.042 (0.981 - 1.108)	1.069 (0.992 - 1.153)	1.007 (0.926 - 1.095)	1.008 (0.905 - 1.122)
4 Km	1.063 (1.012 - 1.117)	1.072 (1.000 - 1.150)	1.105 (1.013 - 1.204)	1.053 (0.956 - 1.160)	1.013 (0.895 - 1.146)
3 Km	1.069 (1.003 - 1.139)	1.087 (0.992 - 1.190)	1.119 (1.000 - 1.251)	1.073 (0.946 - 1.218)	1.011 (0.861 - 1.118)
Warm Season†					
5 Km	1.000 (0.950 - 1.052)	1.001 (0.936 - 1.070)	0.980 (0.906 - 1.060)	0.980 (0.896 - 1.072)	0.973 (0.869 - 1.088)
4 Km	1.017 (0.959 - 1.079)	1.010 (0.934 - 1.092)	0.998 (0.911 - 1.094)	0.997 (0.898 - 1.107)	1.006 (0.883 - 1.147)
3 Km	1.012 (0.939 - 1.091)	1.037 (0.940 - 1.145)	1.032 (0.920 - 1.158)	1.054 (0.923 - 1.202)	1.053 (0.893 - 1.241)

*SO_2 Modeled as continuous variable scaled to 20 parts per billion (ppb)

** Search radius around each monitor used to select case population

†Cold Season defined as November to April; Warm Season defined as May to October

Model adjusted for maximum daily temperature, minimum daily temperature, and mean daily relative humidity, and meteorological interaction terms.

Table 8: Odds Ratios and 95% Confidence Intervals of Ambient SO_2 by Quintile by Radius, Lag Period, and Season

Quintiles of SO_2: Odds Ratios and 95% Confidence Intervals of Ambient SO_2 Exposure on Asthma ER Visits By Radius**, Lag Period, and Season						
Radius & Quintiles SO_2 (ppb)	**Overall ORs (95% CI) (n=15,610 at 5 Km)**		**Cold Season ORs (95% CI) (n=8,352 at 5 Km)**		**Warm Season ORs (95% CI) (n=6,742 at 5 Km)**	
	Lag 0	**Lag 0 - 3**	**Lag 0**	**Lag 0 - 3**	**Lag 0**	**Lag 0 - 3**
5 Km						
Q2 (1.0 to < 3.0)	0.988 (0.932 - 1.048)	1.007 (0.944 - 1.074)	1.031 (0.946 - 1.124)	1.000 (0.904 - 1.106)	0.943 (0.866 - 1.027)	0.995 (0.912 - 1.086)
Q3 (3.0 to < 7.0)	0.957 (0.899 - 1.018)	0.954 (0.877 - 1.024)	0.999 (0.911 - 1.096)	0.959 (0.855 - 1.076)	0.911 (0.833 - 0.966)	0.930 (0.844 - 1.026)
Q4 (7.0 to < 16.1)	0.938 (0.878 - 1.002)	0.991 (0.920 - 1.068)	0.981 (0.891 - 1.080)	1.036 (0.918 - 1.168)	0.911 (0.827 - 1.004)	0.924 (0.833 - 1.025)
Q5 (> 16.1)	0.998 (0.932 -1.069)	1.020 (0.942 - 1.104)	1.071 (0.967 - 1.185)	1.077 (0.948 - 1.222)	0.925 (0.838 - 1.023)	0.971 (0.870 - 1.083)
4 Km						
Q2 (1.0 to < 3.0)	0.988 (0.922 - 1.059)	1.024 (0.949 - 1.104)	1.058 (0.956 - 1.171)	0.942 (0.836 - 1.062)	0.925 (0.837 - 1.023)	1.054 (0.952 - 1.167)
Q3 (3.0 to < 7.0)	0.981 (0.913 - 1.055)	0.988 (0.909 - 1.074)	1.006 (0.903 - 1.121)	0.937 (0.820 - 1.071)	0.959 (0.864 - 1.065)	1.010 (0.901 - 1.133)
Q4 (7.0 to < 16.1)	0.931 (0.863 - 1.005)	1.007 (0.923 - 1.099)	0.980 (0.877 - 1.095)	0.985 (0.856 - 1.133)	0.906 (0.809 - 1.014)	0.993 (0.881 - 1.120)
Q5 (> 16.1)	1.031 (0.952 - 1.117)	1.081 (0.985 - 1.185)	1.096 (0.975 - 1.233)	1.098 (0.947 - 1.272)	0.966 (0.860 - 1.085)	1.030 (0.907 - 1.169)
3 Km						
Q2 (1.0 to < 3.0)	0.956 (0.874 - 1.047)	1.020 (0.925 - 1.125)	0.983 (0.861 - 1.123)	0.951 (0.812 - 1.113)	0.929 (0.815 - 1.058)	1.036 (0.909 - 1.181)
Q3 (3.0 to < 7.0)	0.996 (0.905 - 1.095)	0.950 (0.852 - 1.060)	0.984 (0.853 - 1.135)	0.898 (0.754 - 1.070)	1.014 (0.885 - 1.163)	0.969 (0.834 - 1.126)
Q4 (7.0 to < 16.1)	0.948 (0.858 - 1.047)	0.987 (0.882 - 1.104)	0.998 (0.864 - 1.154)	0.925 (0.771 - 1.110)	0.912 (0.786 - 1.057)	1.005 (0.862 - 1.172)
Q5 (> 16.1)	1.017 (0.916 - 1.130)	1.055 (0.935 - 1.189)	1.055 (0.904 - 1.232)	1.031 (0.850 - 1.250)	0.991 (0.850 - 1.156)	1.037 (0.879 - 1.224)

*SO_2 Modeled as categorical variable by quintile. Scaled to 20 parts per billion (ppb)

** Search radius around each monitor used to select case population

Model adjusted for maximum daily temperature, minimum daily temperature, and mean daily relative humidity, and meteorological interaction terms.

Table 9: Descriptive Characteristics of R-LINE Data by Categorization Type

Descriptive Characteristics of R-LINE Data by Categorization Type				
	Characteristics			
Categorization	**Mean (SD)**	**Median**	**Range**	**IQR**
Continuous	5.9 (3.6)	4.9	37.8	2.7
Dichotomized at 10 µg/m³	**N**	**%**		
Below	20,211	92.3		
Above	1,934	8.7		

Table 10: Statistical Significant of R-LINE Interaction Terms by Categorization Type

Likelihood Ratio Test for Significance of Interaction Term in Model: Using 5 Km and Lag 0	
Categorization	**Chi-Square P-Value**
Dichotomized at Median*	0.077
Dichotomized at 10 µg/m³	0.362
Continuous	0.020
Quintiles	0.009

***Median = 4.86 µg/m³**

Table 11: Effect Modification of Traffic Flow on Association of SO_2 and Asthma ED Visits

Effect Modification of Traffic-related $PM_{2.5}$: Odds Ratios and 95% Confidence Intervals of Ambient SO_2† Exposure on Asthma and Wheeze Emergency Department Visits By Radius††, Lag Period, and Season						
Radius & Categorization of Traffic-related $PM_{2.5}$	**Overall ORs (95% CI) (n = 15,610 at 5 Km)**		**Cold Season ORs (n=8,352 at 5 Km)**		**Warm Season ORs (95% CI) (n=6,742 at 5 Km)**	
	Lag 0	**Lag 0 – 3**	**Lag 0**	**Lag 0 – 3**	**Lag 0**	**Lag 0 - 3**
5 Km						
Median*	0.986 (0.942 - 1.031)	0.998 (0.955 – 1.042)	0.980 (0.919 - 1.045)	0.994 (0.934 – 1.057)	0.991 (0.927 - 1.059)	0.992 (0.931 – 1.058)
10 $\mu g/m^3$**	1.045 (0.977 - 1.118)	1.053 (0.984 – 1.128)	1.050 (0.954 - 1.156)	1.075 (0.975 – 1.185)	1.058 (0.959 - 1.167)	1.035 (0.937 – 1.144)
Continuous	1.001 (0.996 - 1.006)	1.003 (0.998 – 1.008)	1.000 (0.993 - 1.008)	1.003 (0.996 – 1.010)	1.003 (0.996 - 1.011)	1.004 (0.997 – 1.010)
4 Km						
Median	1.011 (0.959 - 1.067)	1.017 (0.966 - 1.069)	0.980 (0.910 - 1.057)	1.005 (0.935 - 1.081)	1.047 (0.969 - 1.132)	1.031 (0.957 - 1.110)
10 $\mu g/m^3$	1.098 (1.019 - 1.184)	1.123 (1.047 - 1.218)	1.076 (0.969 - 1.194)	1.141 (1.025 - 1.267)	1.147 (1.026 - 1.282)	1.121 (1.002 - 1.254)
Continuous	1.006 (1.000 - 1.012)	1.008 (1.002 - 1.013)	1.004 (0.995 - 1.012)	1.007 (1.000 - 1.015)	1.010 (1.001 - 1.018)	1.009 (1.001 - 1.017)
3 Km						
Median	0.966 (0.901 - 1.035)	0.970 (0.907 - 1.037)	0.894 (0.811 - 0.986)	0.915 (0.832 -1.007)	1.035 (0.935 - 1.146)	1.024 (0.929 - 1.130)
10 $\mu g/m^3$	0.966 (0.859 - 1.087)	0.973 (0.862 - 1.097)	0.941 (0.797 - 1.111)	0.961 (0.810 - 1.139)	1.034 (0.868 - 1.230)	1.034 (0.865 - 1.233)
Continuous	0.995 (0.985 - 1.005)	0.996 (0.987 - 1.005)	0.990 (0.976 - 1.004)	0.992 (0.979 - 1.005)	1.000 (0.986 - 1.016)	1.002 (0.989 - 1.016)

† SO_2 Modeled as continuous variable scaled to 20 parts per billion (ppb)

†† Search radius around each monitor used to select case population

* Median = 4.86 $\mu g/m^3$. Traffic-related $PM_{2.5}$ dichotomized at the median

** 91st percentile of R-LINE estimated $PM_{2.5}$ by 250 meter grid cell. Traffic-related $PM_{2.5}$ dichotomized at 10 $\mu g/m^3$

Separate models were run for each categorization of traffic-related $PM_{2.5}$. All models were adjusted for maximum daily temperature, minimum daily temperature, and mean daily relative humidity, and meteorological interaction terms.

Table 12: Effect Modification by Quintile of Traffic Flow and Association of SO_2

Effect Modification by Quintile of Traffic-related $PM_{2.5}$: Odds Ratios and 95% Confidence Intervals of Ambient SO_2† Exposure on Asthma and Wheeze Emergency Department Visits By Radius††, Lag Period, and Season						
Radius & Quintiles of Traffic-related $PM_{2.5}$ ($\mu g/m^3$)	**Overall ORs (95% CI) (n=15,610 at 5 Km)**		**Cold Season ORs (95% CI) (n=8,352 at 5 Km)**		**Warm Season ORs (95% CI) (n=6,742 at 5 Km)**	
	Lag 0	**Lag 0 - 3**	**Lag 0**	**Lag 0 - 3**	**Lag 0**	**Lag 0 - 3**
5 Km						
Q2 (3.8 to < 4.5)	1.017 (0.947 – 1.092)	1.033 (0.965 – 1.107)	0.982 (0.889 – 1.085)	1.022 (0.928 – 1.125)	1.038 (0.934 – 1.155)	1.039 (0.938 – 1.152)
Q3 (4.5 to < 5.6)	1.033 (0.896 – 1.912)	1.068 (0.930 – 1.226)	0.965 (0.791 – 1.177)	1.044 (0.862 – 1.266)	1.078 (0.871 – 1.334)	1.081 (0.880 – 1.327)
Q4 (5.6 to < 7.2)	1.054 (0.848 – 1.301)	1.103 (0.897 – 1.357)	0.948 (0.704 – 1.276)	1.067 (0.799 – 1.424)	1.120 (0.813 – 1.541)	1.124 (0.826 – 1.529)
Q5 (> 7.2)	1.068 (0.803 – 1.420)	1.140 (0.866 – 1.502)	0.931 (0.626 – 1.384)	1.095 (0.742 – 1.602)	1.163 (0.759 – 1.781)	1.168 (0.775 – 1.761)
4 Km						
Q2 (3.8 to < 4.5)	0.985 (0.903 – 1.074)	0.987 (0.907 – 1.074)	0.933 (0.826 – 1.054)	0.979 (0.869 – 1.101)	1.010 (0.885 – 1.152)	0.982 (0.865 – 1.115)
Q3 (4.5 to < 5.6)	0.970 (0.814 – 1.154)	0.974 (0.923 – 1.154)	0.871 (0.683 – 1.111)	0.958 (0.767 – 1.212)	1.019 (0.784 – 1.327)	0.965 (0.747 – 1.242)
Q4 (5.6 to < 7.2)	0.955 (0.735 – 1.240)	0.962 (0.746 – 1.239)	0.813 (0.565 – 1.171)	0.937 (0.757 – 1.212)	1.030 (0.694 – 1.528)	0.947 (0.646 – 1.388)
Q5 (> 7.2)	0.940 (0.663 – 1.333)	0.949 (0.677 – 1.332)	0.759 (0.465 – 1.234)	0.917 (0.573 – 1.468)	1.039 (0.614 – 1.760)	0.947 (0.647 – 1.389)
3 Km						
Q2 (3.8 to < 4.5)	1.045 (0.934 – 1.164)	0.969 (0.852 – 1.103)	0.971 (0.837 – 1.126)	0.951 (0.797 – 1.135)	1.099 (0.931 – 1.230)	0.957 (0.787 – 1.164)
Q3 (4.5 to < 5.6)	1.092 (0.879 – 1.346)	0.940 (0.727 – 1.217)	0.942 (0.700 – 1.268)	0.904 (0.635 – 1.288)	1.208 (0.867 – 1.683)	0.916 (0.619 – 1.355)
Q4 (5.6 to < 7.2)	1.141 (0.825 – 1.577)	0.912 (0.619 – 1.342)	0.915 (0.586 – 1.438)	0.859 (0.506 – 1.462)	1.328 (0.808 – 2.184)	0.877 (0.487 – 1.567)
Q5 (> 7.2)	1.192 (0.774 – 1.835)	0.884 (0.528 – 1.481)	0.888 (0.490 – 1.608)	0.818 (0.403 – 1.659)	1.460 (0.752 – 2.834)	0.839 (0.383 – 1.836)

† SO_2 Modeled as continuous variable scaled to 20 parts per billion (ppb)

†† Search radius around each monitor used to select case population

Model adjusted for maximum daily temperature, minimum daily temperature, and mean daily relative humidity, and meteorological interaction terms.