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Amelia H. Blumberg Date

Impact of ambient air pollution on sickle cell

disease exacerbations in Atlanta, GA

By

Amelia H. Blumberg

Master of Science in Public Health

Environmental Health – Epidemiology

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By

Amelia H. Blumberg

Bachelor of Arts (BA)

Washington University in St. Louis

2015

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Abstract

Impact of ambient air pollution on sickle cell disease exacerbations in Atlanta, Georgia

By Amelia H. Blumberg

Background

Approximately 100,000 Americans are affected by sickle cell disease (SCD) with varying symptoms and several risk factors. The cause of such symptom variability is not known, although the environment may play a considerable role. The recurrent vaso-occlusive painful crises that people with SCD experience are the main reason they go to the emergency department (ED). Research on the role of environmental factors, such as air pollution, in sickle cell disease is limited however.

Objective

Given the limited prior research, we sought to assess if daily ambient air pollution concentrations are associated with acute sickle cell disease exacerbations in Atlanta, Georgia, using ED visit data for SCD exacerbations over a 15-year (1998-2013) period. Furthermore, we assessed potential heterogeneity of associations by age and sex.

Methods

ED visit data were from 41 of 42 hospitals in the 20-county Atlanta, GA area. Air pollution data were from the Jefferson Street monitoring site, which provided daily information for 12 air pollutants of interest: carbon monoxide (CO), nitrogen dioxide (NO_2), nitrogen oxides (NOx), ozone (O_3), sulfur dioxide (SO_2), particulate matter less than 10 μm and less than 2.5 μm in aerodynamic diameter (PM_{10} and $PM_{2.5}$, respectively), sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), elemental carbon (EC), and organic carbon (OC). Associations of daily air pollution levels and counts of sickle cell disease related ED visits were estimated using Poisson models.

Results

For 1998-2013, associations of air pollutants and sickle cell ED visits were generally consistent with the null. For the later period (2005-2013), however, we observed statistically significant positive associations between traffic pollutants (CO, NOx, EC) and SCD ED visits [e.g., rate ratio of 1.022 (95% CI: 1.002, 1.043) per interquartile range increase in CO]. In the later period, analyses stratified by age groups indicated stronger associations with these traffic pollutants among children (0-18 years) than older age groups.

Conclusion

This work highlights that traffic pollutants in particular may affect the number of ED visits for sickle cell disease exacerbations for children (ages 0-18 years) in Atlanta, GA.

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Introduction

Sickle cell disease is a serious illness with the potential to reduce median life expectancy, in diagnosed individuals, by more than 30 years (O. S. Platt et al., 1994). Sickle cell disease is an inherited disease that results from inheriting the sickle hemoglobin gene. This is a recessive inherited mutation in a nucleotide. In sickle cell disease patients, the sickle hemogloblin polymerizes and the typically round red blood cell becomes a crescent (sickle) shape. The sickle shape causes vaso-occlusive events to occur (Lal, 2011). There are different genotypes of sickle cell disease that exist. The most common type is Hemoglobin SS disease, which is also referred to as sickle cell anemia (HbS or HBSS). Other types exist as well such as different compound heterozygous states of HbS paired with various hemoglobins (C, D, or E). Additionally, other combinations of the gene can occur in conjunction with thalassemia, such as hemoglobin S-Thalasemmia syndrome (Beutler, 2006; Lal, 2011).

The sickle cell trait and disease is commonly found in places where malaria transmission occurs. A majority of people with sickle cell disease live in developing countries, with a large portion in sub-Saharan Africa (McGann, 2014). However, migration of peoples from where malaria is endemic, has led to increased cases of sickle cell disease in other, non-malarial locations globally (Piel et al., 2010). Of the people around the world with sickle cell disease, people of Black African and Afro-Caribbean descent are especially affected with sickle cell disease genotype. Additionally, people from the Mediterranean, Middle East, and parts of India have been shown to have a disproportionate rate of the disease (Dick, 2007).

While some patients do not experience symptoms as a normal part of their disease phenotype, others with the disease express very severe, debilitating symptoms. Sickle cell symptoms typically begin around 5-6 months of age. The number and severity of symptoms may change for a person throughout their lifetime (NIH, 2016). It is estimated that 30-40% of sickle cell disease patients have no painful crises in a given year while 1% has more than 6 crises in a given year (O.S. Platt et al., 1991). Some more common symptoms include jaundice (yellowing of the skin), fatigue, and dactylitis (hands and feet painfully swelling). More serious symptoms include acute pain, or the vaso-occlusive crises, which often requires immediate treatment, frequently in an emergency department (ED) setting. In a vaso-occlusive crisis, oxygen is decreased in the body due to the sickle shaped cells blocking blood flow. In contrast, healthy disc shaped cells do not block blood flow typically. The pain from a crisis can be in one or multiple areas of the body and typically feels like an intense stabbing and throbbing pain. Additionally, some people may suffer from chronic pain, severe anemia, and various infections. Another symptom, acute chest syndrome (ACS) can be due to sickle cell disease with hemoglobin S, C, D, or E. With ACS, it is common for there to be a pulmonary infiltrate as the blood vessels in the lung prevent oxygen to the lungs (NIH, 2016).

It is not completely understood what causes the vaso-occlusive crisis, but triggers include illness, temperature change, stress, dehydration, and high altitude (NIH, 2016). In developed countries, those with sickle cell disease usually live in urban areas where air pollution tends to be worse, and therefore likely can cause exacerbated sickle cell disease symptoms (Tewari et al., 2015). There is minimal research explaining why the spectrum of severity of symptoms exists, but environmental factors, such as air pollution, have been

hypothesized to contribute to the difference in people with sickle cell disease (Barbosa et al., 2015). Previous work has suggested that wind and low humidity are associated with increased hospital admissions for sickle cell disease (Jones et al., 2005).

Many epidemiologic studies have evaluated the association between ambient air pollution and various health effects on humans including increased mortality and illness (Kampa et al., 2008). In particular, studies have focused on ubiquitous ambient air pollutants, such as those regulated via National Ambient Air Quality Standards in the United States [carbon monoxide (CO), nitrogen oxides (NOx), sulfur dioxide (SO_2), ozone (O_3), and particulate matter less than 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$)] (Bascom et al., 1996; Brunekreef et al., 2002; Chen et al., 2015; Tolbert et al., 2000). To characterize the health impacts of emissions source-based mixtures, studies have also examined air pollutants associated with specific sources, such as traffic pollutants (e.g., CO NOx, $PM_{2.5}$) (Gauderman et al., 2005; Jerrett et al., 2008; McConnell et al., 2002; Sarnat et al., 2008).

ED visits for sickle cell disease may be a sensitive indicator of population-based sickle cell disease exacerbations for application in environmental health studies as the recurrent vaso-occlusive painful crises that people with sickle cell experience are the main reason they go to the ED (Kato et al., 2009). However, only limited research has been conducted on ambient air pollution and ED visits for sickle cell disease, with mixed results. A study in Brazil (Barbosa et al., 2015), a study in France (Mekontso Dessap et al., 2014), and a study in Britain (Yallop et al., 2007) were conducted to assess air pollution and either ED visits or hospital admissions due to sickle cell disease exacerbations. The three studies observed various associations. Barbosa et al. studied various lags of CO, PM_{10}, NO_2, SO_2, and O_3 concentrations and suggested that air pollution variations may trigger vaso-occlusive

events in sickle cell disease children in Brazil, with O_3 having a more delayed effect (Barbosa et al., 2015). Mekontso Dessap et al. found higher emergency hospital admissions in France for sickle cell disease patients with higher levels of nitrogen dioxide (NO_2) $PM_{2.5}$, PM_{10}, and daily mean wind speed, but with lower daily levels of CO, O_3, SO_2, daily temperature, daily sunshine, and occurrence of storms (Mekontso Dessap et al., 2014). Yallop et al. observed higher hospital admissions in Britain with low levels of nitric oxide, low levels of CO, and high levels of O_3, with the CO and O_3 findings being statistically significant (Yallop et al., 2007). Thus, both Mekontso Dessap et al. and Yallop et al. observed more hospital admissions with lower levels of CO, but observed differing results for O_3.

Tewari et al. evaluated environmental determinants of sickle cell disease exacerbation severity since not much is known about why severity of exacerbations varies within and between sickle cell disease patients through a review of published articles surrounding environmental factors and sickle cell disease (Tewari et al., 2015). They concluded cold and windy weather was associated with more hospital attendance for sickle cell disease. Tewari et al. concluded that the specific link between environmental factors and pathophysiological events is confusing and not clear. Additionally, they explained how some studies have had conflicting findings for specific air pollutants.

While there is limited research on the association between environmental triggers of air pollution and sickle cell disease, more is known regarding children being especially susceptible to sickle cell disease symptoms and, independently to the effects of air pollution in children at large. For example, children are a more susceptible population to sickle cell disease symptoms than older populations since their physiology is still developing. For

example, the risk of septicemia (bacterial infection when bacteria enters the bloodstream) due to sickle cell disease primarily affects young children (Overturf, 2003). Children who have sickle cell disease are at an increased risk of osteomyelitis (bone infection). In addition, children with osteomyelitis and sickle cell disease have bone that is vulnerable to vaso-occlusive episodes (Atkins et al., 1997). Children, generally, without SCD are also thought to be more susceptible to air pollution as their immune systems are not as developed as adults, they have higher minute ventilation (Dixon, 2002; Gilliland et al., 1999), and they typically spend more time outside than adults (Trasande L, 2005). Of the previous studies, Barbosa et al. focused on children and concluded that air pollution was associated with sickle cell disease vaso-occlusive events in children, assessed using ED visit data (Barbosa et al., 2015).

Given the limited prior research, and to our knowledge no prior US-based studies, here we sought to assess if daily ambient air pollution concentrations are associated with acute sickle cell disease exacerbations in Atlanta, Georgia, using data on ED visits for sickle cell disease, thalassemia, and subsets of visits with sickle cell (vaso-occlusive) crises over a 15-year (1998-2013) period. Moreover, given potential susceptibility among children and other demographic factors, we assessed potential heterogeneity of associations by age and sex.

Methods

The source of the air pollution data used in the current analysis is from the Jefferson Street monitoring site located 4 kilometers northwest of downtown Atlanta. This site is part of The Southeastern Aerosol Research and Characterization Network (SEARCH), which is a complete set of data with levels of various pollutants for every day. This study focused on 12 air pollutants: daily 1-hr maximum CO, NO_2, NOx, SO_2, daily 8-hr maximum O_3, 24-hr average PM_{10}, $PM_{2.5}$, and major $PM_{2.5}$ components sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), elemental carbon (EC), and organic carbon (OC). This study analyzed air pollution data for the period June 1, 1998 to December 31, 2013.

The ED visit data was collected from individual hospitals (for the period 1998-2004) and from the Georgia Hospital Association (for the period 2005-2013). The data collected for this study spans the period June 1, 1998 through December 31, 2013. These data were collected previously for the Studies of Particles and Health in Atlanta (SOPHIA), and included data from 41 of 42 hospitals in the 20 county-Atlanta area. Specific data elements included admission date, hospital, and primary and secondary International Classification of Diseases 9th Revision (ICD-9) diagnosis codes, as well as age, sex, and race of the patient. The Emory University Institutional Review Board approved this study.

Sickle cell disease case groups within the ED data were defined using primary and secondary International Classification Diseases 9th Revision (ICD-9) codes. The outcomes included overall primary visits by sickle cell patients for thalassemia and sickle cell disease, primary visits for sickle-cell with vaso-occlusive pain or crisis, and primary visits for sick-cell with vaso-occlusive pain with underlying acute chest syndrome. Specifically, the outcomes and their ICD-9 codes include thalassemia (THAL, 282.4), sickle cell disease – all

(SCD, 282.6), sickle cell thalassemia with crisis (SCTH, 282.42), sickle cell disease HbS/HbS with crisis (HBSS, 282.62), sickle cell disease HbS/HbC with crisis (HBSC, 282.64), sickle cell disease HbS/HbD (HbE) with crisis (HBSD, 282.69), and sickle cell with vaso-occlusive pair or crisis with underlying ACS in a secondary ICD-9 code (SCCR_ACS, 517.3). SCTH is a subset of THAL, and HBSS, HBSC, and HBSD are each a subset of SCD. The ED visits for each outcome were aggregated by day.

Poisson generalized linear models were used to estimate associations of daily ambient air pollution levels and daily counts of sickle cell related ED visits. Modeling was conducted in SAS v9.2 statistical software with the GENMOD procedure. Models were similar to previous air pollution ED visit studies in Atlanta, GA (Krall et al., 2017; Winquist et al., 2014; Ye et al., 2017). Single-pollutant models were run with each sickle cell outcome of interest, using 3-day moving average (of lag days 0, 1, and 2) air pollution levels. Models included the following covariate control for temporal trends and meteorology: time splines with monthly knots, cubic terms of same-day maximum temperature, cubic terms of lag 1-2-day moving average minimum temperature, cubic terms of lag 0-2-day mean dew point temperature, day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods to control for differential participation by hospitals over time.

The estimated associations were reported as rate ratios (RRs) per interquartile range (IQR; 75^{th} -25^{th} percentile) increase in pollutant concentrations, to represent a meaningful change in exposure when expressing rate ratios. For example, the IQR for the entire time period for carbon monoxide (CO) was 0.73 since the 75^{th} percentile was 1.18 and the 25^{th} percentile was 0.45.

Analyses for each outcome were first run for the whole time period. Given concerns over specific aspects of the data quality for the earlier time period (1998-2004), including hospital ED completeness and reporting quality for SCD outcomes, we also stratified analyses by time period (1998-2004 and 2005-2013). These analyses focused on two outcomes with highest daily counts: all sickle cell disease (SCD), and sickle cell disease HbS/HbS with crisis (HBSS). The same model structure with the same control variables were used when running models by time period. Additional analyses were stratified by demographic factors in the later period, specifically by age (0-18, 19-39, 40+ years) and by sex (female/male). All main models were single-pollutant models. To assess potential confounding by co-pollutants, sensitivity analyses included selected two-pollutant models in order to assess the relationship between SCD and the main air pollutant of interest while controlling for a second air pollutant.

Additionally, sensitivity analyses were conducted to examine the influence of various covariate changes on the estimated rate ratios. The sensitivity analyses focused on the CO-SCD association in the later time period. The various sensitivity analyses included use of year, month, and a year and month interaction term in place of time splines, omitting minimum temperature control variables, omitting season and any season interaction terms, and replacing the same-day maximum temperature and 1-2 day minimum temperature control with a 3-day moving average maximum or mean temperature cubic terms.

Results

Descriptive statistics of all seven of the outcomes for the entire time period June 1, 1998 through December 31, 2013 as well as stratified by time period (June 1, 1998-December 31, 2004 and January 1, 2005 – December 31, 2013) are presented in Table 1. The daily ED counts were extremely low for most outcomes, which in turn limited power and reduced model stability and were thus excluded from the epidemiologic analyses. Four outcomes were chosen for analysis of the full time period: SCD, HBSS, HBSC, and SCCR_ACS. The main outcome of interest in our study, SCD had the most ED visits in the full time period (95,779, daily mean of 16.9) with a majority of the ED visits being HBSS (77,093, daily mean 13.6), our second main outcome of interest. The counts were much higher in the later time period as expected with more hospitals reporting. In the earlier time period, our database included 18,469 visits for SCD, while it had 77,310 visits for SCD in the later time period. Figure 1 shows the number of daily ED visits plotted for the outcome SCD for the entire time period. The figure shows a large increase in the number of ED visits at the beginning of 2005, which we attribute to more complete data capture.

Descriptive statistics for the two main outcomes, SCD and HBSS stratified by time period and also stratified by age, sex, and race categories are shown in Table 2. In this analysis, age groups included ages 0-18 years, 19-39 years, and 40 years and older based on their integer age at ED visit. Sex was stratified by male and female, while the race data was stratified by Black, White, Hispanic, and Other. For SCD and HBSS, the ED visit counts were highest for the 19-39 age group and next highest for ages 0-18 in both time periods. When looking at the outcomes SCD and HBSS by sex, the number of ED visits was slightly higher for females in both the earlier and later time periods. For the race stratification, a

large majority (over 95%) of the ED visits for the each time period and for both SCD and HBSS were Black patients. In the later time period, the mean ED visit for SCD for Black patients was 21.1 visits. 1,112 days of race information were missing due to race information not being available from 2007 to 2009 and for the last 16 days of 2013.

Descriptive statistics for the twelve air pollutants of interest for the entire time period June 1, 1998 through December 31, 2013, and the mean and standard deviation for the two time periods is shown in Table 3. The concentrations of all pollutants decreased from the first time period to the later time period. Table 4 presents Pearson correlations for each pairwise combination of pollutants. Of the 78 pairwise comparisons, 11 of them were "strong" with a Pearson correlation coefficient greater than 0.7, 15 of them where moderate with a Pearson correlation coefficient between 0.5 and 0.7, and the other 52 had Pearson correlation coefficients of less than 0.5. The strongest coefficient was 0.96 between NH_4 and SO_4 with a p-value of <0.0001. The 52 coefficients below 0.5 ranged in value from -0.43 to 0.40.

The rate ratio estimates for the entire study period along with 95% confidence intervals and p-values for the four outcomes are shown in Table 5. For SCD, HBSS, and HBSC, all of associations were consistent with the null. For SCCR_ACS, however, there was a positive association for NO_2 (p-value = 0.002) and NOx (p-value = 0.030), as well as a negative associative for NO_3 (p-value = 0.020).

Table 6 presents the estimated rate ratios for the two main outcomes of interest, SCD and HBSS, stratified by time period. The rate ratios were standardized by the IQR of the air pollutant for the entire time period. For the earlier time period, all associations were consistent with the null expect for a negative association between O_3 and SCD [RR of 0.943

(95% CI: 0.900, 0.999) per IQR]. For the later time period 2005-2013, the associations between the traffic-related pollutants CO, NOx, and EC and SCD ED visits were statistically significant and positively associated.

Table 7 shows estimated rate ratios for the main outcome of interest, SCD for each air pollutant for the later time period stratified by age groups (0-18, 19-39, and ≥40 years) and also by sex. When examining the stratification by age, all associations observed were consistent with the null for ages 19-39 and ages greater than or equal to 40. In the age group 0-18 years, however, four of the air pollutants had positive associations with significant p-values (<0.05), with RRs per IQR of 1.072 (95% CI: 1.026, 1.121, p-value: 0.0022) for CO, 1.055 (95% CI: 1.017, 1.095, p-value: 0.0046) for NO_2, 1.049 (95% CI 1.020, 1.080, p-value: 0.0009) for NOx, and 1.049 (95% CI 1.012, 1.087, p-value: 0.0092) for EC (Figure 2). For the stratification by sex, all associations observed for females were consistent with the null, while there were three positive significant associations observed for males with RRs of 1.04 (95% CI 1.01,1.07, p-value: 0.0199) for CO, 1.02 (95% CI: 1.00, 1.04, p-value: 0.0229) for SO_2 and 1.03 (95% CI: 1.01, 1.05, p-value: 0.0104) for EC.

Selected two air pollutant models for the later time period for the main outcome SCD are shown in Table 8. This table shows each of the main pollutants (all traffic pollutants) in the table CO, NOx, and EC, with the addition of O_3, SO_2, $PM_{2.5}$, SO_4, and OC. Each of these three air pollutants for the later time period had positive associations in the original single-pollutant models. For CO, the addition of O_3, SO_2, and SO_4 each individually gave similar confidence intervals for the positive association, but a null association was observed with the addition of $PM_{2.5}$ and OC individually. NOx and EC followed the same pattern as CO with the addition of O_3, SO_2, and SO_4 producing positive associations, but null associations when

$PM_{2.5}$ or OC was added as the second air pollutant in the model. The two-pollutant models all had p-values that were less than 0.10 for the main air pollutant. The traffic pollutants also tended to be correlated with $PM_{2.5}$ or OC. These results show the robustness of traffic pollutant results as the point estimates barely changed with the addition of a second pollutant.

Sensitivity analysis was performed as part of this project for the later time period for the air pollutant CO and the main outcome of interest, SCD. All of the other models compared to the original mode, had rate ratio estimates that were slightly lower than the rate ratio estimate of the original model, but were less than 1% different from the original. The sensitivity analysis shows that the model was robust to minor changes to the model.

Discussion

Using 15 and a half year time series of ED visits in the 20 county Atlanta, GA area, this study evaluated associations of ambient air pollution and sickle cell disease ED visits, and furthermore explored stratifying by age and sex. This work expanded upon the Barbosa et al. study in Brazil, Mekontso Dessap et al. study in France, and Yallop et al. study in Britain by being the first analysis done in the U.S. to our knowledge. The present findings provide indication that variability in ambient air pollution, especially those related to traffic emissions, are associated with sickle cell disease exacerbations for the outcome SCD. These results were driven by strong estimated associations with traffic-related pollutants in children and in males in the later time period (January 1, 2005 – December 31, 2013).

Collectively, the current findings provide evidence of susceptibility to air pollution exposures in individuals with sickle cell disease and contribute to the small number of previous investigations on this topic. Barbosa et al., for example, assessed air pollution and ED visits for sickle cell disease among children in Brazil in a time-series ecological study (Barbosa et al., 2015). The ED visits in their study were primarily pain manifestation, and their study suggested that air pollution variations may trigger vaso-occlussive events in sickle cell disease patients. Another study in France studied the effect of various single day lag environmental influences on daily emergency hospital admissions (EHA) for sickle cell disease patients over 8 years (Mekontso Dessap et al., 2014). EHAs in the study included visits for vaso-occlusive crisis or chest disease ("any new onset lower acute respiratory tract disease that was compatible with ACS") in SCD patients. The study in their univariate analysis found that the risk of an EHA for a sickle cell disease patient was higher when there were higher levels of NO_2, higher levels of $PM_{2.5}$, higher levels of PM_{10}, and higher daily

mean wind speed. Another time series study of environmental determinants of sickle cell disease conducted in Britain (Yallop et al.) evaluated air pollution and severity of exacerbations for sickle cell disease by hospital admission (Yallop et al., 2007). Their observations suggest increased hospital admissions with high levels of O_3. Yallop's study concluded that air pollution does have an association with hospital admissions for sickle cell disease patients.

Previous studies, such as Barbosa et al. analyzed the relationship between sickle cell disease and air pollution in only children ages 0-18 (Barbosa et al., 2015), while Mekonsto Dessap et al. analyzed all patients ages 2 to 70 years old (Mekontso Dessap et al., 2014). Yallop et al. included all hospital admissions for sickle cell diagnoses at their hospital of focus (Yallop et al., 2007). No studies, to our knowledge, have analyzed the association between air pollution and sickle cell disease exacerbation ED visits stratified by age. Barbosa et al. restricted their study to children, however, and found that air pollution variations may trigger vaso-occlusive events in sickle cell disease patients, as well as noting that O_3 compared to the other pollutants may have more of a delayed effect.

We observed significant positive associations for traffic pollutants (CO, NO_2, NOx, and EC) for the children age group (ages 0 – 18 years), but not for the other two age groups when analyzing the outcome SCD in the later time period. These findings are of particular interest since the counts of ED visits for SCD by age group were not highest in the children population. The counts were 6,394 for ages 0-18 (children), 8,782 for ages 19-39 years, and 3,238 for ages >40 years, so it was not just the number of counts (and thus power) driving the differential results by age group. This is significant as these are the first findings to our knowledge that children with sickle cell disease are especially susceptible to traffic air

pollutants. Future studies that further characterize air pollutants and sickle cell disease ED visits by age are needed to fully investigate the reason, and especially biologically, that associations were only seen in the children population in this study.

While we believe the CO findings in children most likely reflect air pollution from traffic pollutants, it is of interest to compare these findings with those from a tobacco smoking study. Sadreameli et al. enrolled children and young adults (IQR: 5 to 15) who had sickle cell disease into a cohort study in order to study the association between tobacco secondhand smoke exposure and sickle cell disease hospital admissions and ED visits (Sadreameli et al., 2016). Salivary cotinine was measured in the participants in order to assess secondhand smoke exposure while hospitalizations were divided into pain related ones and ACS. The smoke from cigarettes, however, is primarily nitrogen, oxygen, CO, and carbon dioxide (Guerin, 1980). Thus, it is interesting that Sadreameli et al. found for second hand smoke and SCD ED visits for a child and young adult population, the incidence rate ratio was 5.7 (95% CI: 2.2 – 15), while it was 4.3 (95% CI: 1.8 – 10) for all hospitalization since CO is a component of secondhand smoke, and we found an association with CO. Their study is different, however, in that secondhand smoke is a modifiable risk factor while in our study it is difficult to avoid outdoor ambient air pollution.

The Barbosa et al. study focused only on children, but also found associations with traffic pollutants, NO_2 and CO (Barbosa et al., 2015). The biological explanations are limited in the current literature, but there is some explanation that can be provided. Studies have shown that moderate exercise in children with sickle cell disease can deprive children of oxygen (Halphen et al., 2014) as well as increase oxidative stress (Faes et al., 2014). Oxidative stress is essentially an imbalance between reactive oxygen species and the ability

of the body to detoxify anything potentially harmful. Furthermore, a characteristic of sickle cell disease is a continuous oxidative stress process (Nur et al., 2011). There are some air pollutants which promote oxidative stress such as $PM_{2.5}$ (Kelly, 2003; Lodovici et al., 2011). Especially for children since moderate exercise can increase oxidative stress, it is concerning that air pollutants can increase it as well. This is concerning as Atlanta is similar to other urban areas with a large pediatric population and traffic pollution, and the findings suggest that this may be a significant health burden on children.

The research on biology involved between sickle cell disease and air pollutants is still evolving rapidly. Yallop et al. actually found less hospital admissions for sickle cell disease acute pain with high levels of CO for people aged 2-70 (Yallop et al., 2007). Yallop et al. in their discussion suggested that CO could be protective against sickle cell disease. They explained it by saying "high levels of atmospheric CO form increased amounts of sickle carboxyhaemoglobin which does not polymerise. The rate of haemoglobin S (HbS) polymerization is known to be critically dependent on the concentration of deoxyHbS. The increase in carboxyhaemoglobin associated with higher atmospheric levels of CO might dilute the deoxyHbS sufficiently to be of clinical benefit." Mekontso Dessap et al. also found increased admission risk with lower levels of CO (Mekontso Dessap et al., 2014). One explanation that they provided was that CO inhibits vasoconstriction (Belcher et al., 2006). Their findings and discussion section suggested that CO may be beneficial to patients with sickle cell disease. Other studies as well suggest that the half-life of red blood cells is extended with the presence of CO (Beutler, 1975). Due to the conflicting findings, additional research would be beneficial as our study found increased ED visits for increased CO in children.

The previous three studies (Yallop et al., Mekontso Dessap et al., and Barbosa et al.) on sickle cell disease and air pollutants did not discuss stratification by sex in the analysis. The findings in our study found no significant associations for female, but three significant associations for males (CO, SO_2, and EC). It is possible that different physiological processes between males and females may play a role. Another speculation is that males may have higher exposure to air pollutants than females based on their occupational choice or recreational activities. Clougherty et al. performed a qualitative review of differences between gender and sex in their response to air pollution on respiratory health (Clougherty, 2011). They said the source of effect modification by sex and gender is still not clear, but suggest there are sex differences, such as dermal thickness and permeability. A limitation in our study is that we do not know how much each individual was exposed to air pollutants outdoors as some may be exposed more based on their occupation or lifestyle. The difference in findings by sex presents an opportunity for further analysis to understand why there were associations observed for males, but not for females.

We did not conduct analyses stratified by race, but descriptive statistics were included in Table 2. Over 95% of the ED visits for both SCD and HBSS in the earlier and later time period were Black patients. This is expected because people of Black African descent are especially affected by sickle cell disease (Dick, 2007) since the sickle trait is commonly found in places where malaria occurs as a preventive measure to malaria. A limitation of the analysis by race is that the race coding was missing for two years of the study. While this is a limitation, there is no reason to believe that the racial distribution of ED visits would be greatly different for the two years missing compared to the other years. Another limitation is

that race was self-reported and confined to the categories of White, Black, Hispanic, and Other.

We observed results that were robust to change in both the two-pollutant models and in the sensitivity analysis, and suggest that the significant findings observed in the analysis cannot simply be explained by model specification.

Conclusion

In evaluating associations between air pollutants and various sickle cell disease exacerbation ED visits in Atlanta, GA, this time series had a special focus on the visits with ICD-9 codes relating to SCD and HBSS. In particular we explored the association in the later time period (January 1, 1998 – December 31, 2013) during which the ED visit data were more complete. Additionally, we explored these associations for heterogeneity by age, sex, and race for the outcomes SCD and HBSS.

We found that in the full time period (June 1, 1998 – December 31, 2004), that ED visits decreased with higher levels of O_3 for outcome SCD, and that ED visits decreased for SCCR_ACS for higher levels of NO_3. When stratifying the time periods, we found decreased ED visits for SCD for higher levels or O_3 in the earlier time period (June 1, 1998 – December 31, 2004). In the later time period (January 1, 2005 – December 31, 2013), we found increased ED visits for SCD for higher levels of CO, NOx, and EC. A special focus was placed on the later time period in which associations were stratified by age and sex. For the age group 0-18 years, ED visits for SCD were higher with higher levels of CO, NO_2, NOx, $PM_{2.5}$, and EC, while there were no such associations in the other age groups. By sex, there were more SCD ED visits for males with higher levels of CO, SO_2, and EC. The two

air pollutant models and sensitivity analysis showed the robustness of the model. The work highlights the importance of traffic pollutants, and especially with the more susceptible children population.

While the current results are intriguing, there are limitations that warrant further investigation. One limitation is that the air pollution data were taken from a single monitoring site in downtown Atlanta while the ED visits were from 41 hospitals in the 20 county area. For further research, data from additional monitoring sites could be used, if available, that are closer to the hospitals and where the patients live in order to assign air pollutant levels that are more representative of patients' actual exposures. In this population-based study, however, it is not possible to obtain information on all patient's time-activity location patterns that would ideally be used to estimate exposures. More analysis could be done to further investigate the interesting association between traffic pollutants and sickle cell disease as the biological components are still not very well understood, and no other air pollutant and sickle cell disease studies exist to our knowledge in the U.S. Collectively, the current findings provide support for public policy that helps to reduce air pollutant concentrations in order to reduce the health burden of traffic pollutants. This is especially true for those individuals thought to be susceptible, which likely include children with sickle cell disease based on our findings and epidemiologic evidence from other investigations.

Tables and Figures

Table 1. Descriptive Statistics of ED Visits Overall and by Time Period

	All Visits (June 1, 1998 - Dec 31, 2013)*			Earlier Visits (June 1, 1998 - Dec 31, 2004)			Later Visits (Jan 1, 2005 - Dec 31, 2013)[1]		
Outcome Acronym	Count	Daily Mean	SD	Count	Daily Mean	SD	Count	Daily Mean	SD
THAL	2,514	0.4	0.8	203	0.1	0.3	2,311	0.7	0.9
SCD	95,779	16.9	9.1	18,469	7.7	3.2	77,310	23.6	5.4
SCTH	2,052	0.4	0.7	85	0.0	0.2	1,967	0.6	0.9
HBSS	77,093	13.6	7.8	14,168	5.9	2.7	62,925	19.2	5.0
HBSC	4,682	0.8	1.4	117	0.0	0.3	4,565	1.4	1.6
HBSD	1,494	0.3	0.6	141	0.1	0.3	1,353	0.4	0.7
SCCR_ACS	2,569	0.5	0.8	133	0.1	0.3	2,436	0.7	0.9

[1]ED data for the last sixteen days of 2013 is missing

Table 2. Descriptive Statistics of ED Visits by Time Period Stratified by Age, Sex, and Race

Age, Sex, and Race	Earlier Visits (June 1, 1998 - Dec 31, 2004)						Later ED Visits (Jan 1, 2005 - Dec 31, 2013)[1]					
	SCD			HBSS			SCD			HBSS		
Stratification	Count	Mean	SD	Count	Mean	SD	Count	Mean	SD	Count	Mean	SD
Age												
0-18	6,394	2.7	1.9	4,678	1.9	1.5	17,262	5.3	2.8	10,226	3.1	2.0
19-39	8,782	3.7	2.0	6,839	2.8	1.8	46,237	14.1	3.9	41,115	12.6	3.8
>40	3,238	1.3	1.1	2,603	1.1	1.1	13,811	4.2	2.1	11,584	3.5	2.0
Sex												
Female	9,111	3.8	2.1	6,954	2.9	1.8	40,804	12.5	3.8	33,131	10.1	3.5
Male	8,739	3.6	2.1	6,736	2.8	1.7	36,503	11.2	3.5	29,791	9.1	3.2
Race												
Black	9,944	4.1	2.1	7,583	3.2	1.8	45,816	21.1	5.2	37,323	17.2	5.0
White	77	0.0	0.2	33	0.0	0.1	121	0.1	0.2	96	0.0	0.2
Hispanic	36	0.0	0.1	21	0.0	0.1	454	0.2	0.5	327	0.2	0.4
Other	383	0.2	0.4	336	0.1	0.4	678	0.3	0.6	481	0.2	0.5

[1]ED data for the last sixteen days of 2013 is missing

Table 3. Descriptive Statistics of Three Day Moving Average of Ambient Air Pollution Data: June 1, 1998 - December 31, 2013

	Entire Time Period									Stratified Time Period	
	June 1, 1998 - Dec 31, 2013									June 1, 1998 - Dec 31, 2004	Jan 1, 2005 - Dec 31, 2013
Pollutant (units)	**N[1]**	**Mean**	**SD**	**Minimum**	**25th Pctl**	**50th Pctl**	**75th Pctl**	**Maximum**	**IQR[2]**	**Mean ± SD**	**Mean ± SD**
1-hr max CO (ppm)	5684	0.91	0.65	0.16	0.45	0.73	1.18	5.13	0.73	1.32 ± 0.72	0.62 ± 0.38
1-hr max NO2 (ppb)	5689	37.72	12.84	6.76	28.63	36.33	45.33	106.00	16.71	42.33 ± 13.63	34.36 ± 11.08
1-hr max NOx (ppb)	5689	102.81	78.78	9.67	49.00	79.00	130.33	589.67	81.33	127.04 ± 92.71	85.11 ± 60.99
8-hr max O3 (ppb)	5689	42.68	18.36	3.63	28.35	40.61	54.49	122.67	26.14	43.71 ± 21.43	41.93 ± 15.69
1-hr max SO2 (ppb)	5690	12.25	9.85	1.00	4.58	9.79	17.33	86.00	12.75	14.05 ± 9.79	10.94 ± 9.69
24-hr avg PM10 (ug/m3)	5195	22.61	9.38	4.56	15.81	20.99	27.43	86.88	11.62	25.39 ± 10.25	20.24 ± 7.82
24-hr avg PM2.5 (ug/m3)	5693	14.53	6.63	2.83	9.67	13.10	17.80	53.83	8.13	17.23 ± 6.98	12.54 ± 5.58
24-hr avg SO4 (ug/m3)	5640	3.90	2.67	0.52	2.05	3.07	4.91	20.07	2.87	4.91 ± 2.98	3.18 ± 2.16
24-hr avg NO3 (ug/m3)	5635	0.81	0.65	0.01	0.35	0.60	1.09	4.92	0.74	1.00 ± 0.68	0.68 ± 0.59
24-hr avg NH4 (ug/m3)	5617	1.40	0.90	0.14	0.78	1.15	1.71	8.04	0.93	1.74 ± 1.03	1.14 ± 0.69
24-hr avg EC (ug/m3)	5451	1.25	0.79	0.17	0.72	1.06	1.55	8.87	0.83	1.62 ± 0.91	1.00 ± 0.57
24-hr avg OC (ug/m3)	5519	3.67	1.66	0.88	2.54	3.34	4.38	17.93	1.84	4.36 ± 1.85	3.18 ± 1.30

[1]N is number of days in study

[2]IQR is 75th percentile minus 25th percentile

Table 4. Pearson Correlations Between Three Day Moving Average Ambient Air Pollution Concentrations, June 1, 1998 – December 31, 2013

Pollutant (units)	Abbreviation	CO	NO2	NOx	O3	SO2	PM10	PM2.5	SO4	NO3	NH4	EC	OC
1-hr max CO (ppm)	CO	1.00											
1-hr max NO2 (ppb)	NO2	0.68*	1.00										
1-hr max NOx (ppb)	NOx	0.80*	0.75*	1.00									
8-hr max O3 (ppb)	O3	0.00	0.27*	-0.11*	1.00								
1-hr max SO2 (ppb)	SO2	0.33*	0.39*	0.34*	-0.01	1.00							
24-hr avg PM10 (ug/m3)	PM10	0.46*	0.57*	0.39*	0.57*	0.21*	1.00						
24-hr avg PM2.5 (ug/m3)	PM2.5	0.52*	0.57*	0.40*	0.51*	0.28*	0.89*	1.00					
24-hr avg SO4 (ug/m3)	SO4	0.21*	0.29*	0.03*	0.62*	0.18*	0.76*	0.83*	1.00				
24-hr avg NO3 (ug/m3)	NO3	0.34*	0.26*	0.37*	-0.43*	0.26*	0.00	0.18*	-0.06*	1.00			
24-hr avg NH4 (ug/m3)	NH4	0.25*	0.32*	0.07*	0.56*	0.17*	0.75*	0.84*	0.96*	0.11*	1.00		
24-hr avg EC (ug/m3)	EC	0.79*	0.69*	0.74*	0.15*	0.36*	0.65*	0.70*	0.39*	0.28*	0.42*	1.00	
24-hr avg OC (ug/m3)	OC	0.69*	0.68*	0.68*	0.25*	0.26*	0.68*	0.74*	0.38*	0.26*	0.40*	0.80*	1.00

*=$p<0.05$

Table 5. Estimated Rate Ratios for Four SCD Related ED Visit Outcomes per IQR Increase in Pollutant Concentrations for June 1, 1998 - December 31, 2013[1]

Pollutant (units)	IQR[2]	SCD RR (95% CI)	P-Value	HBSS RR (95% CI)	P-value	HBSC RR (95% CI)	P-value	SCCR_ACS RR (95% CI)	P-value
1-hr max CO (ppm)	0.73	1.007 (0.992, 1.021)	0.374	1.005 (0.988, 1.021)	0.580	1.003 (0.927, 1.085)	0.946	1.052 (0.967, 1.145)	0.240
1-hr max NO2 (ppb)	16.71	1.002 (0.988, 1.017)	0.779	0.993 (0.977, 1.010)	0.411	1.039 (0.977, 1.104)	0.222	1.132 (1.046, 1.222)	0.002
1-hr max NOx (ppb)	81.33	1.000 (0.992, 1.016)	0.533	1.000 (0.984, 1.008)	0.759	1.033 (0.984, 1.085)	0.144	1.067 (1.008, 1.121)	0.030
8-hr max O3 (ppb)	26.14	0.972 (0.949, 0.997)	0.031	0.974 (0.947, 1.003)	0.076	0.947 (0.855, 1.048)	0.291	1.045 (0.908, 1.204)	0.537
1-hr max SO2 (ppb)	12.75	1.006 (0.995, 1.018)	0.314	1.004 (0.991, 1.017)	0.542	0.999 (0.941, 1.059)	0.952	1.022 (0.958, 1.091)	0.508
24-hr avg PM10 (ug/m3)	11.62	1.002 (0.987, 1.019)	0.724	1.001 (0.984, 1.019)	0.919	0.983 (0.908, 1.064)	0.672	0.983 (0.898, 1.076)	0.708
24-hr avg PM2.5 (ug/m3)	8.13	1.005 (0.992, 1.019)	0.460	1.002 (0.988, 1.018)	0.724	0.998 (0.935, 1.000)	0.952	0.984 (0.910, 1.064)	0.679
24-hr avg SO4 (ug/m3)	2.87	1.001 (0.987, 1.015)	0.906	1.003 (0.988, 1.018)	0.706	0.978 (0.907, 1.055)	0.565	0.935 (0.854, 1.025)	0.152
24-hr avg NO3 (ug/m3)	0.74	1.001 (0.987, 1.015)	0.892	0.996 (0.981, 1.012)	0.631	1.041 (0.977, 1.108)	0.213	0.917 (0.852, 0.987)	0.020
24-hr avg NH4 (ug/m3)	0.93	1.000 (0.988, 1.013)	0.961	1.002 (0.988, 1.016)	0.806	0.985 (0.919, 1.055)	0.662	0.940 (0.867, 1.020)	0.141
24-hr avg EC (ug/m3)	0.83	1.005 (0.993, 1.018)	0.410	1.002 (0.988, 1.016)	0.812	1.002 (0.938, 1.071)	0.945	1.065 (0.991, 1.146)	0.945
24-hr avg OC (ug/m3)	1.84	1.001 (0.990, 1.013)	0.794	1.000 (0.987, 1.013)	0.987	1.010 (0.954, 1.068)	0.739	1.011 (0.950, 1.077)	0.726

[1]ED data for the last sixteen days of 2013 is missing

[2]IQR is 75th percentile minus 25th percentile

Table 6. Estimated Rate Ratios for SCD and HBSS ED Visits per IQR Increase in Pollutant Concentrations, Stratified by Time Period

		June 1, 1998 - December 31, 2004				January 1, 2005 - December 31, 2013[1]			
Pollutant (units)	**IQR[2]**	**SCD RR (95% CI)**	**P-Value**	**HBSS RR (95% CI)**	**P-Value**	**SCD RR (95% CI)**	**P-Value**	**HBSS RR (95% CI)**	**P-Value**
1-hr max CO (ppm)	0.73	0.994 (0.972, 1.017)	0.604	1.003 (0.978, 1.029)	0.823	1.022 (1.002, 1.043)	0.032	1.010 (0.988, 1.033)	0.370
1-hr max NO2 (ppb)	16.71	0.977 (0.951, 1.004)	0.093	0.972 (0.943, 1.002)	0.070	1.015 (0.997, 1.032)	0.102	1.004 (0.985, 1.024)	0.683
1-hr max NOx (ppb)	81.33	0.987 (0.968, 1.005)	0.154	0.992 (0.970, 1.013)	0.440	1.015 (1.002, 1.029)	0.029	1.005 (0.989, 1.020)	0.560
8-hr max O3 (ppb)	26.14	0.943 (0.900, 0.999)	0.015	0.950 (0.900, 1.003)	0.063	0.986 (0.956, 1.016)	0.357	0.985 (0.953, 1.019)	0.394
1-hr max SO2 (ppb)	12.75	1.012 (0.988,1.037)	0.319	1.005 (0.978, 1.033)	0.732	1.004 (0.990, 1.017)	0.598	1.003 (0.988, 1.018)	0.708
24-hr avg PM10 (ug/m3)	11.62	0.987 (0.961, 1.013)	0.314	0.989 (0.960, 1.020)	0.478	1.017 (0.997, 1.037)	0.101	1.011 (0.990, 1.033)	0.309
24-hr avg PM2.5 (ug/m3)	8.13	0.996 (0.973, 1.020)	0.758	1.003 (0.976, 1.031)	0.829	1.012 (0.995, 1.029)	0.164	1.005 (0.987, 1.024)	0.599
24-hr avg SO4 (ug/m3)	2.87	0.996 (0.973, 1.020)	0.749	0.999 (0.973, 1.026)	0.950	1.005 (0.987, 1.023)	0.589	1.005 (0.986, 1.024)	0.602
24-hr avg NO3 (ug/m3)	0.74	1.001 (0.976, 1.028)	0.928	0.995 (0.966, 1.026)	0.759	1.005 (0.988, 1.022)	0.585	0.999 (0.980, 1.018)	0.920
24-hr avg NH4 (ug/m3)	0.93	0.995 (0.973, 1.016)	0.616	0.997 (0.973, 1.022)	0.835	1.005 (0.989, 1.021)	0.578	1.004 (0.986, 1.021)	0.680
24-hr avg EC (ug/m3)	0.83	0.993 (0.973, 1.014)	0.515	1.001 (0.977, 1.024)	0.959	1.019 (1.003, 1.036)	0.022	1.008 (0.991, 1.026)	0.371
24-hr avg OC (ug/m3)	1.84	0.991 (0.972, 1.011)	0.387	1.000 (0.977,1.023)	0.972	1.010 (0.995, 1.025)	0.188	1.003 (0.987, 1.019)	0.750

[1]ED data for the last sixteen days of 2013 is missing

[2]IQR is 75th percentile minus 25th percentile

Table 7. Estimated Rate Ratios for SCD ED Visits per IQR Increase in Pollutant Concentrations, Stratified by Age and Sex for January 1, 2005 - December 31, 2013[1]

		Age Stratification			Sex Stratification	
		Ages 0 - 18 years	Ages 19 - 39 years	Ages >40 years	Female	Male
Pollutant (units)	IQR[2]	SCD RR (95% CI)	SCD RR (95% CI)	SCD RR (95% CI)	SCD RR (95% CI)	SCD RR (95% CI)
1-hr max CO (ppm)	0.73	1.072 (1.026, 1.121)*	1.012 (0.987, 1.038)	1.005 (0.960, 1.052)	1.011 (0.983, 1.040)	1.035 (1.005, 1.065)*
1-hr max NO2 (ppb)	16.71	1.055 (1.017, 1.095)*	1.005 (0.984, 1.027)	1.000 (0.961, 1.040)	1.019 (0.995, 1.044)	1.010 (0.985, 1.035)
1-hr max NOx (ppb)	81.33	1.049 (1.020, 1.080)*	1.009 (0.991, 1.026)	0.996 (0.965, 1.028)	1.012 (0.993, 1.031)	1.019 (0.999, 1.039)**
8-hr max O3 (ppb)	26.14	0.988 (0.924, 1.056)	0.982 (0.945, 1.020)	0.997 (0.930, 1.069)	1.000 (0.959, 1.042)	0.970 (0.929, 1.014)
1-hr max SO2 (ppb)	12.75	1.018 (0.988, 1.050)	0.998 (0.982, 1.015)	1.007 (0.977, 1.038)	0.987 (0.969, 1.005)	1.023 (1.003, 1.042)*
24-hr avg PM10 (ug/m3)	11.62	1.036 (0.991, 1.083)	1.013 (0.988, 1.038)	1.009 (0.965, 1.055)	1.011 (0.984, 1.039)	1.023 (0.994, 1.052)
24-hr avg PM2.5 (ug/m3)	8.13	1.038 (1.000, 1.077)**	1.008 (0.987, 1.029)	1.000 (0.963, 1.038)	1.009 (0.986, 1.033)	1.015 (0.991, 1.040)
24-hr avg SO4 (ug/m3)	2.87	1.028 (0.987, 1.070)	1.002 (0.980, 1.024)	0.995 (0.958, 1.033)	1.003 (0.979, 1.027)	1.007 (0.982, 1.032)
24-hr avg NO3 (ug/m3)	0.74	1.026 (0.990, 1.063)	1.003 (0.981, 1.025)	0.985 (0.947, 1.024)	1.009 (0.986, 1.033)	1.001 (0.976, 1.025)
24-hr avg NH4 (ug/m3)	0.93	1.024 (0.987, 1.063)	1.002 (0.982, 1.022)	0.997 (0.962, 1.032)	1.007 (0.985, 1.030)	1.001 (0.979, 1.025)
24-hr avg EC (ug/m3)	0.83	1.049 (1.012, 1.087)*	1.012 (0.992, 1.033)	1.011 (0.975, 1.048)	1.008 (0.986, 1.031)	1.030 (1.007, 1.054)**
24-hr avg OC (ug/m3)	1.84	1.023 (0.991, 1.057)	1.007 (0.988, 1.025)	1.005 (0.973, 1.039)	1.007 (0.987, 1.028)	1.013 (0.992, 1.035)

[1]ED data for the last sixteen days of 2013 is missing

[2]IQR is 75th percentile minus 25th percentile

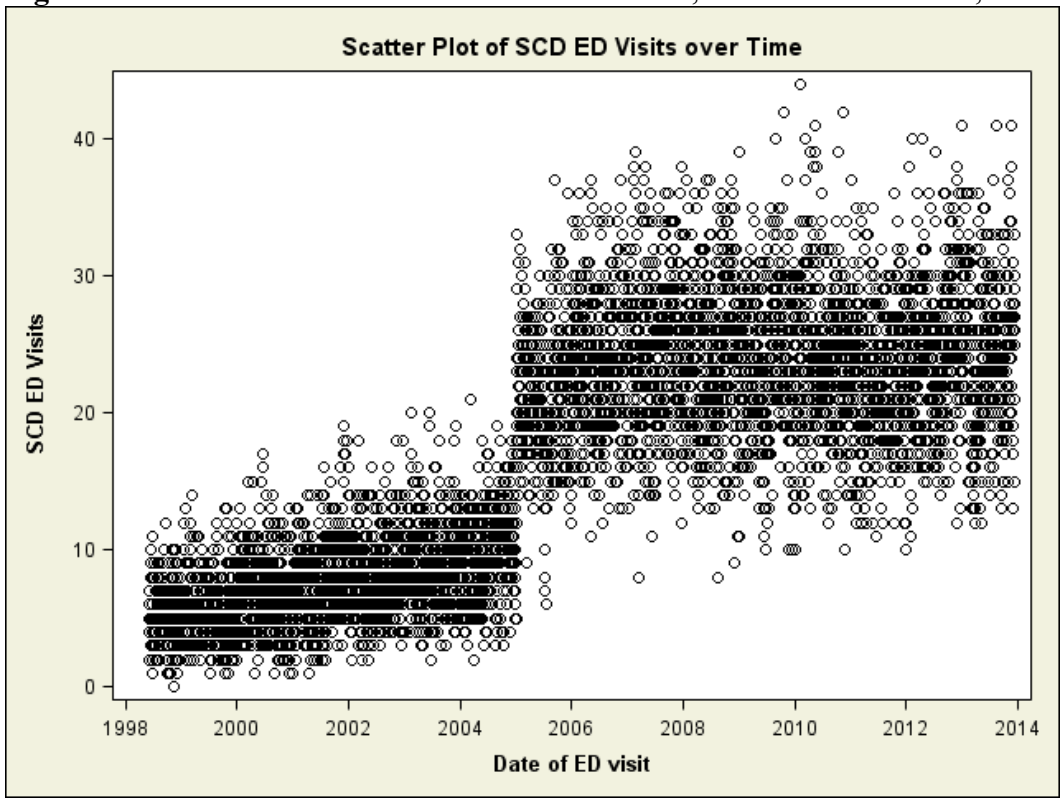
*** = P-value <0.05; ** = P-Value <0.10**

Table 8. Estimated Rate Rations from Selected Two-Pollutant Models for SCD ED Visits per IQR Increase in Pollutant Concentrations for January 1, 2005 - Dec 31, 2013[1]

Main Pollutant (units)	IQR[2]	Second Pollutant (units)	SCD RR (95% CI)	Main Pollutant P-Value	Second Pollutant P-Value
1-hr max CO (ppm)	0.73		1.022 (1.002, 1.043)	0.032	
		8-hr max O3 (ppb)	1.025 (1.004, 1.046)	0.020	0.201
		1-hr max SO2 (ppb)	1.022 (1.001, 1.043)	0.037	0.872
		24-hr avg PM2.5 (ug/m3)	1.020 (0.997, 1.044)	0.093	0.698
		24-hr avg SO4 (ug/m3)	1.022 (1.001, 1.043)	0.037	0.824
		24-hr avg OC (ug/m3)	1.023 (0.998, 1.050)	0.075	0.999
1-hr max NOx (ppb)	81.33		1.015 (1.002, 1.029)	0.029	
		8-hr max O3 (ppb)	1.016 (1.002, 1.031)	0.021	0.233
		1-hr max SO2 (ppb)	1.015 (1.001, 1.029)	0.034	0.856
		24-hr avg PM2.5 (ug/m3)	1.014 (0.998, 1.029)	0.082	0.639
		24-hr avg SO4 (ug/m3)	1.015 (1.001, 1.029)	0.032	0.791
		24-hr avg OC (ug/m3)	1.015 (0.998, 1.032)	0.084	0.874
24-hr avg EC (ug/m3)	0.83		1.019 (1.003, 1.036)	0.022	
		8-hr max O3 (ppb)	1.022 (1.005, 1.039)	0.010	0.120
		1-hr max SO2 (ppb)	1.019 (1.002, 1.036)	0.025	0.989
		24-hr avg PM2.5 (ug/m3)	1.020 (0.998, 1.043)	0.071	0.854
		24-hr avg SO4 (ug/m3)	1.020 (1.003, 1.038)	0.022	0.721
		24-hr avg OC (ug/m3)	1.025 (1.000, 1.050)	0.054	0.679

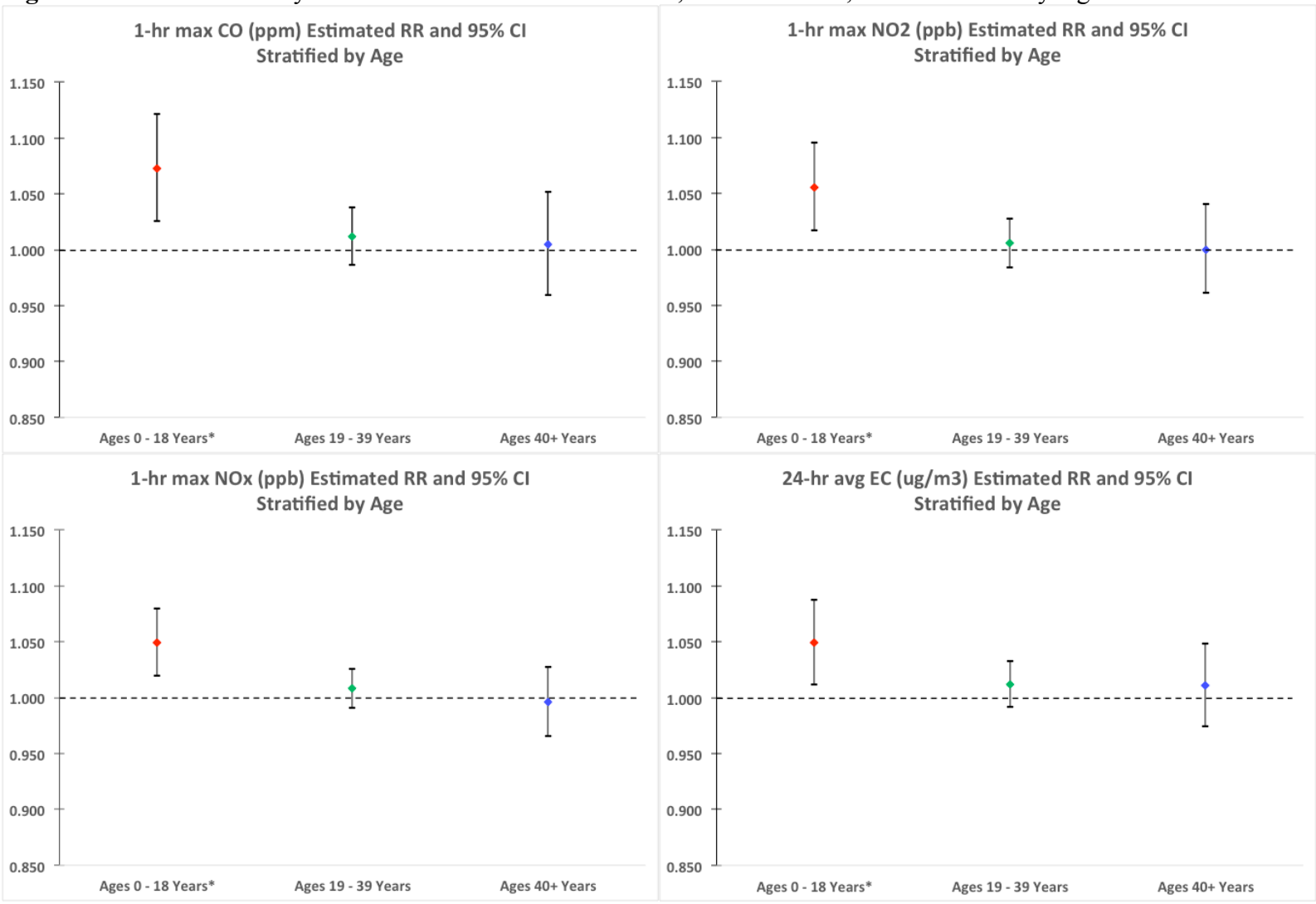
[1]ED data for the last sixteen days of 2013 is missing
[2]IQR is 75th percentile minus 25th percentile

Figure 1. Scatter Plot of SCD ED Visits from June 1, 1998 – December 31, 2013*



*ED data for the last sixteen days of 2013 is missing

Figure 2. Time-series Analysis of Selected Air Pollutants Jan 1, 2005 – Dec 31, 2013 Stratified by Age



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