ABSTRACT

Title of Document: SHORT-TERM EFFECTS OF AMBIENT OZONE ON STROKE RISK IN SOUTH CAROLINA

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Recent reports have suggested that exposure to ozone is associated with stroke events; however, findings have been inconsistent. Utilizing a case-crossover study design, we explored the association between acute ozone exposure (maximum 8-hour daily average) and risk of stroke hospitalization among South Carolina residents and effect modification by race and gender. For total stroke (ischemic and hemorrhagic combined), a 10 ppb increase in ozone exposure on the day of hospitalization was associated with an increased risk of stroke hospitalization (OR: 1.08; 95% CI, 1.06, 1.11). Effects were similar for other lag days; however, the association was strongest for lag days 0–6 (OR: 1.20; 95% CIs 1.16, 1.24). We observed subtle differences in total stroke risk by gender, with females having a slightly lower risk than males, although CIs overlapped considerably. For hemorrhagic stroke, there was evidence of effect modification by race for all time periods of ozone exposure considered.

SHORT-TERM EFFECTS OF AMBIENT OZONE ON STROKE RISK IN SOUTH CAROLINA

By

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Short-term ambient air pollution exposures may be associated with cerebrovascular diseases including stroke (Andersen et al. 2010) through potential effects on blood clotting mechanisms, alteration of heart rate, or other biological changes (Henrotin et al. 2007). There are several different types of stroke, but all stroke events occur when the flow of oxygenated blood to the brain is blocked or interrupted, potentially leading to permanent brain damage or death (NHLBI 2011). Stroke is an important public health issue in the U.S. as these events occur approximately once every 40 seconds (Roger et al. 2011), and costs associated with stroke and stroke-related disability are estimated to reach nearly $67 billion annually (Alkadry et al. 2011).

Previously conducted studies have reported associations between acute levels of ambient air pollutants and stroke risk or mortality (Andersen et al. 2010; Bedada et al. 2012; Wellenius et al. 2012), although existing research has largely focused on one specific air pollutant: particulate matter (PM). Only a limited number of studies have explored the association between acute ozone exposure and stroke risk, with some studies reporting inconclusive evidence or no association (Corea et al. 2012; Oudin et al. 2010) and others reporting a positive association (Henrotin et al. 2007; Lisabeth et al. 2008). Previous studies have largely been conducted outside of the U.S., and study populations have been limited in size and racial distribution.

Further research is warranted to explore the association between acute ozone exposure and risk of stroke, particularly in the U.S where stroke currently ranks third

among all causes of death (Roger et al. 2011). Though this need has been long recognized, limitations in the availability of appropriate health outcome data and limitations in exposure assessment have prevented widespread evaluation of these associations in the U.S. As the number of Americans who have a higher risk for stroke events (age 65 and over) continues to increase rapidly, information regarding potentially modifiable or preventable risk factors such as ozone exposure may become particularly important by contributing to the development of public policy guidelines which may help reduce the substantial health impacts and costs associated with stroke. Additional factors such as race/ethnicity or gender may modify the relationship between acute ozone exposure and risk of stroke, but while gender differences have been previously explored and reported (Oudin et al. 2012; Henrotin et al. 2007), there is a paucity of information regarding effect modification by race because existing research has largely utilized racially homogeneous populations (Corea et al. 2012; Oudin et al. 2012). South Carolina was selected as the study location for the present investigation due to the state's racially diverse population distribution (U.S. Census 2008), as well as its location in the buckle of the "Stroke Belt", a geographical region in the Southeastern U.S. where individuals suffer a disproportionately higher rate of stroke than the rest of the country (Ducey et al. 2012). In 2009, 3.1% of adults in South Carolina were affected by stroke, compared to 2.4% of adults nationwide (DHEC 2011). By utilizing stroke hospitalization data originating from South Carolina and modeled ozone exposure estimates, the following research questions will be addressed:

Research Question 1: Do individuals with acute exposure to higher levels of ozone have an increased risk of developing stroke?

Research Question 2: Does the association between acute ozone exposure and stroke status differ by race/ethnicity or gender?

Chapter 2: Background

Stroke

Stroke events occur when there is a lack of oxygenated blood flow to the brain, often presenting as an inability to move limbs on one side of the body or failure to understand and formulate speech, which may lead to permanent neurological damage or death (NHLBI 2011). There are two main types of stroke: ischemic and hemorrhagic. Ischemic stroke occurs when a blood vessel that supplies oxygen-rich blood to the brain becomes blocked, while hemorrhagic stroke occurs when an artery in the brain leaks or ruptures. Ischemic strokes are more common, accounting for 87% of all stroke cases (NHLBI 2011). In addition, transient ischemic attack (TIA) or "mini-stroke" occurs when blood flow to the brain is blocked for a short time. Each year, approximately 800,000 Americans experience a new or recurrent stroke (Roger et al. 2011).

Ozone

Ozone (O_3) is an odorless gas composed of three oxygen atoms. Stratospheric ozone forms high above the Earth's surface and creates a protective layer against ultraviolet radiation (DHEC 2012). In contrast, ground-level ozone is harmful to human health and the environment. Excess ozone is formed when chemical reactions occur between nitrogen oxides and volatile organic compounds in the presence of heat and sunlight, although it also has natural sources mainly related to lightning. Ozone is a designated Criteria Air Pollutant, and the EPA has set National Ambient Air Quality

Standards (NAAQS) under the Clean Air Act to protect public health and the environment (DHEC 2012). The current standard for ozone is 75 parts per billion (ppb) averaged over an 8-hour time period. Ozone concentrations that are equal to or even slightly below the standard level may cause adverse health effects, including airway irritation, coughing, wheezing, difficulty breathing, inflammation, and aggravation of asthma (Akinbami et al. 2010; Song, Tag, and Zhang 2011; Alexis et al 2010). Unlike some other criteria air pollutants, ozone levels across the U.S. have not decreased considerably over time (EPA 2010a).

Recent reports have suggested that exposure to ambient air pollutants, including ozone, is associated with stroke events as measured by emergency room or inpatient hospitalizations (Andersen et al. 2010; Wellenius et al. 2012). While the underlying biologic mechanism is not fully understood, several pathophysiological hypotheses have been suggested to explain the increased risk of stroke, including alteration of blood coagulation mechanisms, endothelial dysfunction, systemic inflammatory responses, oxidative stress, arterial vasoconstriction, or irregular heart rate (Henrotin et al 2007; Oudin et al. 2012). Consequences of these effects include atherosclerosis and thrombosis, both of which are risk factors for stroke (Henrotin et al 2007). However, the hypothesized biological mechanisms have been more conclusively linked with exposure to PM (Wang et al. 2013). Results from toxicological animal experiments are mixed regarding the mechanisms through which ozone may be associated with stroke (Kodavanti et al. 2011; Wang et al. 2013).

Chapter 3: Methods

Study Population

The study population consists of residents of the state of South Carolina. South Carolina covers approximately 30,000 mi^2 (U.S. Census 2012), and is located in the "Stroke Belt", a region in the southeastern part of the U.S. where stroke incidence is significantly higher than the rest of the country (DHEC 2011). Recent population estimates indicate that the total number of residents is approximately 4.6 million (U.S. Census 2012). Approximately 68.5% of South Carolina residents identify as Caucasian and 28.1% identify as African American (U.S. Census 2012). There are two regions in the state that are currently designated by EPA as non-attainment areas for ozone, meaning that ozone levels persistently exceed the NAAQS (EPA 2012).

Cases

The study sample (N=35,413) includes patients who were hospitalized for incident stroke classified as ICD-9 codes 430–438 (430 subarachnoid hemorrhage, 431 intra-cerebral hemorrhage, 432 other and unspecified intracranial hemorrhage, 433 occlusion and stenosis of pre-cerebral arteries, 434 occlusion of cerebral arteries, 435 transient cerebral ischemia, 436 acute but ill-defined cerebrovascular disease, 437 other and ill-defined cerebrovascular disease, 438 late effects of cerebrovascular disease) in South Carolina from 2002–2006. Data on stroke hospitalizations were obtained prior to this study by the South Carolina Office of Research and Statistics

(ORS) from South Carolina hospitals. Patients with prior strokes in the previous 24 months and individuals under 18 years of age were excluded. Additionally, patients residing outside of South Carolina were excluded. The dataset also included the date of the diagnosis, race, age, gender, zipcode, census tract and county of residence, and primary payer. Approval for the usage of this information was obtained by institutional review boards (IRB) at the University of Maryland and the University of South Carolina, as well as ORS.

Using published criteria (Kokotailo and Hill 2005), stroke types were assigned to patients based on ICD code classification. ICD codes 430 and 431 were designated as hemorrhagic stroke (N=3,207; 9.1%). ICD codes 433, 434, and 436 were designated as ischemic stroke (N=22,719; 64.2%). ICD codes 432, 435, 437, and 438 were designated as other stroke types (N=9,487; 26.8%); other strokes were excluded from the final analysis. There were 2,844 (8.0%) individuals missing ozone exposure estimates due to addresses that were unable to be geocoded at the street level, such as P.O. boxes, rural routes, or errors related to incomplete/missing address information. Compared to the final study population, this subset of individuals was slightly older and contained more females and African Americans; however, the percentage of stroke types was similar among the groups. In addition, 0.5% of participants were missing data on weather covariates (N=147), race (N=7), zipcode (N=6), and gender (N=2). Races and ethnicities other than African American and Caucasian (N=475; 1.3%) were excluded because low numbers limit the analyses by other designated groups. After excluding patients with missing data, the final study population included 23,360 individuals.

Exposure Assessment and Meteorological Parameters

Daily maxima of 8-hour mean ozone concentrations were predicted during the study period using previously generated output from the EPA's Hierarchical Bayesian Model (HBM) (EPA 2010b). This model allows spatially and temporally varying O_3 concentrations to be estimated across the U.S. at locations far from the physical location of air quality monitors on a 12-km x 12-km grid. The HBM estimates are generated by statistically combining measured air monitor ozone concentration values with predicted concentrations from EPA's Community Multiscale Air Quality (CMAQ) model (EPA 2010b). The CMAQ model also provides estimates of pollutant concentrations based on a 12-km x 12-km grid. The ozone dataset was spatially subsetted to include only those cells in South Carolina, North Carolina, and Georgia, and then sent to ORS. Using ArcGIS, ORS projected the data to create a surface and overlay residential locations (latitude and longitude) of the stroke hospitalization patients to assign HBM ozone values at the nearest 12-km grid cell daily from 15 days prior to admission through the day of admission. The correlation between ozone levels on different days throughout this time period will be reported. All exposure and covariate information was assigned to residential geocodes at the ORS offices.

Data on ambient air temperature (K) and relative humidity (%) for unique latitude and longitude locations corresponding to South Carolina zipcode centroids for 2002–2006 were obtained from the National Air and Space Administration's (NASA) Modeling and Assimilation Data and Information Services Center (MDISC) (Rienecker et al. 2011).

Validation of Exposure Estimates

In order to validate the HBM-generated exposure estimates, hourly ozone concentration values from national monitoring stations were downloaded from the Air Quality System (AQS), EPA's repository of national ambient air quality data, for years 2001–2006 (EPA 2013). Monitor data was reduced to include only South Carolina, North Carolina, and Georgia, and maximum daily 8-hour moving average ozone concentrations were calculated. Monitor derived averages were compared with HBM derived averages at the locations of ozone monitors in South Carolina during the study period using Pearson correlation analysis and linear regression.

Study Design and Statistical Analyses

A case-crossover design was used to examine the association between acute ozone exposure and risk of stroke hospitalization. Case crossover studies are efficient for evaluating associations between short-term exposures and the onset of acute events such as stroke (Wang et al. 2011). This type of design involves a comparison of each subject's exposure during a case period to his/her own exposure during a control period, which effectively controls for confounding associated with differences in measured or unmeasured stable characteristics that differ between subjects, such as age. In the present study, the case period of exposure was defined as selected days across lag day 0 (the day of hospitalization) through lag day 6 (6 days prior to the hospitalization). The control period of exposure was defined as selected days across lag days 7–13. Ozone exposure on lag days 0, 1, and 2 was compared to ozone exposure on corresponding days during the control period. Cumulative average lags were also examined for lag days 0–1, 0–2, and 0–6. Case and control periods were

matched by day(s) of the week to address differences in traffic volume and other potential trends. For example, ozone exposure on lag day 0 was compared with ozone exposure on lag day 7 and ozone exposure on lag days 0–1 was compared with ozone exposure on lag days 7–8.

Descriptive statistics for the study population were generated, which included the following measures: mean age, mean and median ozone concentrations during the study period, mean temperature and relative humidity during the study period, and stroke types by race and gender. Conditional logistic regression analysis was utilized to estimate the association between stroke hospitalization and acute ozone exposure (Wang et al. 2011); odds ratios and 95% confidence intervals were calculated. Regression models were adjusted for relative humidity and ambient temperature because variations in stroke incidence have been independently linked with both of these elements (Nascimento et al. 2012; Henrotin et al. 2007). Stratified analyses by subgroup were conducted to determine effect modification by race and gender as well as differences between stroke types. All statistical analyses were conducted using SAS 9.2 (Carey, NC).

Chapter 4: Results

Figure 1 displays the location of AQS ozone monitors throughout South Carolina and the variation in HBM predicted ozone concentrations on the 12-km x 12-km grid across the state from 2002–2006. There was a very strong correlation between daily maximum 8-hour average ozone concentrations from ozone monitors and HBM derived estimates during the study period (r=0.95). Linear regression analysis indicated a very strong agreement between monitor and HBM derived ozone concentrations (R^2=0.90) in South Carolina in this time period. However, the model also identified a 21% negative bias, indicating that HBM derived estimates were underestimated compared to monitor data.

Table 1 presents characteristics of the study population. In South Carolina from 2002 to 2006, there were 23,360 stroke hospitalizations with complete data; 52.7% of the study population was female, 69.9% was Caucasian, and 30.1% was African-American. Ischemic stroke accounted for 87.9% of total stroke hospitalizations, while hemorrhagic stroke accounted for 12.2%. Mean age at stroke hospitalization was 68.7 (SD: 13.8) years. Mean and median ozone concentrations for the average of lag days 0-13 were 45.8 (SD: 8.4) and 46.4 (IQR: 12.3) ppb, respectively. The correlation between ozone concentrations on any two days was never higher than 0.84, and in most cases, it was less than 0.5.

The associations between ozone exposure and risk of all stroke (ischemic and hemorrhagic stroke combined) hospitalization are presented in Table 2. Adjusting for

temperature and humidity, a 10 ppb increase in ozone exposure on lag day 0 and lag day 1 was significantly associated ($p<0.001$) with an increased risk of stroke hospitalization among residents of South Carolina between 2002–2006 [(OR: 1.08; 95% CIs: 1.06, 1.11) and (OR: 1.08; 95% CIs: 1.05, 1.10), respectively]. Effects were similar among other lag days; however, the relationship between ozone exposure and risk of stroke hospitalization was strongest for lag days 0–6 (OR: 1.20; 95% CIs 1.16, 1.24). Effects were also similar among females and males and Caucasians and African Americans.

Table 3 presents ORs and 95% CIs for the relationship between ischemic stroke hospitalization and ozone exposure. A 10 ppb increase in ozone exposure on lag day 0 and lag day 1 was significantly associated ($p<0.001$) with an increased risk of stroke hospitalization [(OR: 1.09; 95% CIs: 1.06, 1.11), (OR: 1.08; 95% CIs 1.05, 1.10), respectively]. Overall, ORs are similar to those presented in Table 2, which was expected given that ischemic strokes accounted for nearly 90% of all strokes in the study population. Adjusting for temperature and humidity, females had a slightly lower risk of stroke hospitalization than males and African Americans had a slightly lower risk than Caucasians, but with significant overlap between the CIs for each.

Table 4 presents ORs and 95% CIs for the relationship between hemorrhagic stroke hospitalization and ozone exposure. There is evidence of effect modification by race for all time periods of ozone exposure considered. For example, on lag day 0, the OR for Caucasians was 1.00 (95% CI: 0.91, 1.09) and for African Americans it was 1.22 (95% CI: 1.10, 1.34). Effects among Caucasians were not statistically significant in either crude or adjusted models. There is also a suggestion of effect modification by

gender. In adjusted models, effects among females were not statistically significant compared to statistically significant increases for males on lag days 1, 0–1, 0–2, and 0–6, although the confidence intervals for males and females overlap considerably.

Chapter 5: Discussion

The main finding from this study is evidence of a significant association between short-term ozone exposure and risk of hospitalization for stroke. For total strokes (ischemic and hemorrhagic combined), this result was observed at lag days 0, 1, 2, 0–1, 0–2 and 0–6 in both males and females as well as Caucasians and African Americans. Effects were strongest for cumulative exposure occurring on lag days 0–6. In addition, gender and racial differences were observed; generally, the association was weaker among females and differed by race based on stroke type, with a stronger association observed among African Americans hospitalized for hemorrhagic stroke.

The main finding is consistent with the results of other studies which have reported an association between ozone exposure and risk of ischemic stroke (Henrotin et al. 2007; Tsai et al. 2003; Lisabeth et al. 2008). Utilizing a case crossover design, Henrotin et al. (2007) observed a significant association between ischemic stroke occurrence (N=1,487) and ozone levels in France with a one-day lag (OR: 1.08, 95% CI 1.02, 1.13). Tsai et al. (2003) also reported a positive association between hospitalization for ischemic stroke (N=23,179) and ozone in Taiwan on warm days (OR: 1.15, 95% CI: 1.07, 1.23) using a case crossover approach. In addition, an ecologic study conducted in Texas (Lisabeth et al. 2008) reported borderline significant associations between risk of ischemic stroke (N=2,350) and TIA (N=1,158) and same day ozone concentrations (RR: 1.03, 95% CI 0.97, 1.08) as well as previous day ozone concentrations (RR: 1.04, 95% CI: 0.99, 1.09).

However, previous studies have not reported associations between hospitalization for hemorrhagic stroke and exposure to ozone (Henrotin et al. 2007; Oudin et al. 2010). The lack of association may be explained by several factors, including a lower level of ozone pollution in some study areas. For example, the median ozone level in Dijon, France (Henrotin et al. 2007) and Scania, Sweden (Oudin et al. 2010) at the time of study was 26.0 and 31.5 ppb, respectively, compared to 46.4 ppb in South Carolina. In addition, previous analyses have included relatively small numbers of hemorrhagic stroke cases, such as 220 (Henrotin et al. 2007) and 1,161 (Oudin et al. 2010) compared to 2,839 cases in the present study.

The finding of effect modification by gender is also consistent with previous investigations. Henrotin et al. (2007) reported gender differences in the association between ozone exposure and risk of stroke hospitalization, with a stronger association observed for men (OR: 1.13, 95% CI: 1.05, 1.22) compared to women (OR: 1.03, 95% CI: 0.96, 1.10). Although the exact reasons for the weaker association among women remain unclear, it has been reported that some of the underlying biological mechanisms associated with stroke differ among the sexes (Iemolo et al. 2003). For example, men are more prone to developing arterial plaque deposits while women are more prone to the development of stenotic lesions, and while both are related to the development of stroke, plaque areas are a stronger predictor of stroke outcome. Thus, the stronger association between ozone and stroke in men may suggest that arterial plaque is more sensitive to ozone pollution (Henrotin et al. 2007).

In the present study, a stronger association between ozone exposure and risk of hospitalization for hemorrhagic stroke was reported among African Americans for all

time periods of exposure considered. However, mean ozone exposure was similar among Caucasians and African Americans who were hospitalized for hemorrhagic stroke, at 45.6 ppb (SD: 8.4) for Caucasians and 44.6 (SD: 8.4) ppb for African Americans. Previous studies which investigated effect modification by race could not be identified, as existing research has largely been conducted using homogeneous populations (Henrotin et al. 2007; Oudin et al. 2010). Although higher rates of hemorrhagic stroke have been reported among African Americans (Alkadry et al 2011), reasons for this difference are unknown. The observed association may potentially be explained by differences in socioeconomic status (SES) or access to care, both of which have been highly correlated with race in previous studies (Howard et al. 2011; Pathak and Sloan 2009). Unfortunately, we were unable to assess effect modification by SES because the hospitalization data available for the present analysis did not include this information. Future research should explore effect modification of the association between stroke and ozone by race and whether there is also effect modification by SES, or related factors such as diet and access to care.

Strengths of the present study include the validated HBM ozone exposure estimates used in the analysis which incorporated data from multiple sources, including ozone monitors throughout the state of South Carolina and neighboring states, as well as a sophisticated computational prediction tool. Other studies generally relied on ozone concentration measurements from one or a few monitoring stations (Oudin et al. 2007; Henrotin et al. 2010). The exposure estimate validation exercise suggested that HBM derived ozone concentrations were underestimated compared to monitor data,

which may have led to an underestimation in the association between stroke and ozone exposure. However, additional information regarding the predictive accuracy of the HB model, which may be obtained through cross-validation or external validation measurements, would be useful and is needed to fully validate the model. We also addressed stroke and ozone in an area of the U.S. which is disproportionally affected by stroke (DHEC 2011), selecting a statewide population for analysis. Additionally, previous research has largely focused on urban populations (Tsai et al. 2003; Nascimento et al. 2012), whereas the present study included rural populations. In addition, the large sample size (N=23,360) provided greater statistical power to detect small associations.

Additional limitations of this study include possible exposure misclassification because the timing of stroke onset was unavailable. In some cases, stroke onset and stroke hospitalization may not have occurred on the same day; thus, the ozone exposure assigned for the day of the hospital admission would actually be the exposure measurement for the day prior to the stroke. Information regarding the timing of stroke symptoms is also considered to be particularly important for providing insight into the mechanisms by which exposures may trigger stroke onset (Wellenius et al. 2012). In addition, information regarding exposure to other ambient air pollutants, such as PM, which have been previously associated with an increased risk of stroke (Oudin et al. 2012; Wellenius et al. 2012) was not incorporated in the analysis. However, in another study, the association between stroke occurrence and ozone exposure remained significant after adjustment for PM, sulfur dioxide, nitrogen dioxide, and carbon monoxide (Henrotin et al. 2007).

In conclusion, the observational data presented in this analysis suggest an association between stroke hospitalization (all stroke, ischemic stroke, and hemorrhagic stroke) and ozone exposure. The underlying biological mechanisms remain unclear and need to be further explored. Mechanisms related to ozone induced oxidative stress have been linked with vascular impairments in animal experiments (Kodavanti et al. 2011) and may be of particular interest. Effect modification by race and slight differences in the strength of association by gender were observed and should be confirmed by future studies.

Appendix A: Figures and Tables

Figure 1. Hierarchical Bayesian Model Predicted Ozone Concentrations across South Carolina from 2002 to 2006

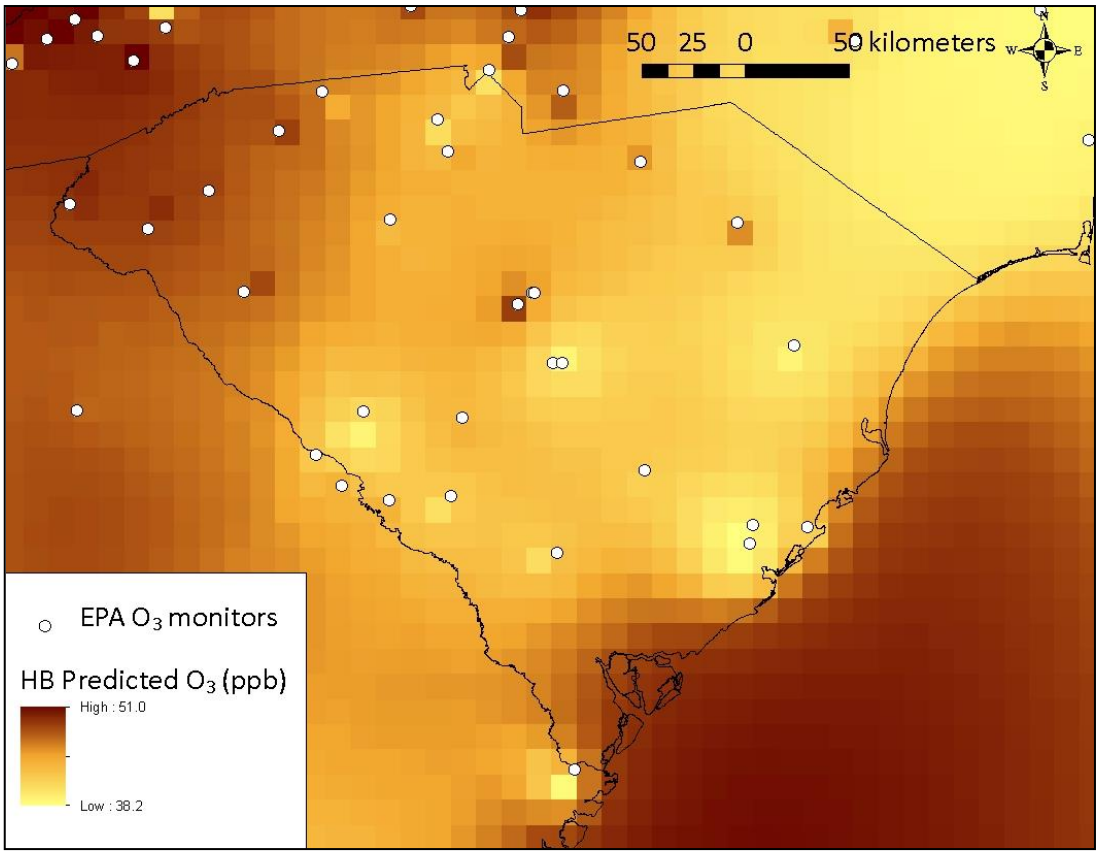

Table 1. Characteristics of the study population, South Carolina stroke hospitalizations from 2002 to 2006

Variable	Total Stroke	Ischemic Stroke	Hemorrhagic Stroke
Stroke Hospitalizations, n (%)	23360 (100.0)	20521 (87.9)	2839 (12.2)
By Gender			
Female	12315 (52.7)	10723 (52.3)	1592 (56.1)
Male	11045 (47.3)	9798 (47.8)	1247 (43.9)
By Race			
Caucasian	16325 (69.9)	14566 (71.0)	1759 (62.0)
African American	7035 (30.1)	5955 (29.0)	1080 (38.0)
Age (years), mean (SD)	68.7 (13.8)	69.3 (13.2)	63.8 (16.3)
Ozone (ppb)*			
Mean (SD)	45.8 (8.4)	45.8 (8.4)	45.2 (8.4)
Median (IQR)	46.4 (12.3)	46.4 (12.3)	45.7 (12.3)
Temperature (C), mean (SD)**	21.6 (4.7)	21.6 (4.7)	21.4 (4.8)
Humidity (%), mean (SD)**	63.3 (7.4)	63.2 (7.4)	63.6 (7.4)

*Average of daily 8-hr max. O_3 concentrations for lag days 0-13

**Average of daily means for lag days 0-13

Table 2. Odds ratios and 95% CIs for the relationship between stroke hospitalization and concentration of ozone in South Carolina from 2002 to 2006

		Stratified by Gender		Stratified by Race		Stratified by Stroke Type	
	All Stroke	Female	Male	Caucasian	African American	Ischemic	Hemorrhagic
	n=23360	n=12315	n=11045	n=16325	n=7035	n=20521	n=2839
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lag 0							
Crude	1.06 (1.04, 1.07)	1.06 (1.03, 1.08)	1.05 (1.03, 1.08)	1.06 (1.03, 1.08)	1.06 (1.02, 1.09)	1.05 (1.03, 1.07)	1.06 (1.01, 1.12)
Adjusted	1.08 (1.06, 1.11)	1.08 (1.05, 1.12)	1.09 (1.05, 1.12)	1.08 (1.06, 1.11)	1.09 (1.04, 1.13)	1.09 (1.06, 1.11)	1.07 (1.00, 1.14)*
Lag 1							
Crude	1.05 (1.03, 1.07)	1.05 (1.03, 1.08)	1.05 (1.02, 1.07)	1.05 (1.03, 1.07)	1.04 (1.01, 1.08)	1.05 (1.03, 1.07)	1.05 (1.00, 1.11)
Adjusted	1.08 (1.05, 1.10)	1.07 (1.04, 1.11)	1.08 (1.04, 1.11)	1.07 (1.04, 1.10)	1.09 (1.04, 1.13)	1.08 (1.05, 1.10)	1.08 (1.01, 1.15)
Lag 2							
Crude	1.06 (1.04, 1.08)	1.06 (1.04, 1.09)	1.06 (1.04, 1.09)	1.06 (1.04, 1.09)	1.06 (1.02, 1.09)	1.06 (1.04, 1.08)	1.10 (1.04, 1.15)
Adjusted	1.07 (1.05, 1.09)	1.06 (1.02, 1.09)	1.09 (1.05, 1.12)	1.07 (1.04, 1.10)	1.07 (1.03, 1.12)	1.07 (1.01, 1.10)	1.07 (1.00, 1.14)*
Lag 0-1							
Crude	1.06 (1.04, 1.08)	1.06 (1.04, 1.09)	1.06 (1.03, 1.09)	1.06 (1.04, 1.09)	1.06 (1.02, 1.09)	1.06 (1.04, 1.08)	1.07 (1.01, 1.13)
Adjusted	1.10 (1.07, 1.13)	1.10 (1.06, 1.14)	1.11 (1.07, 1.15)	1.10 (1.07, 1.13)	1.11 (1.06, 1.16)	1.10 (1.07, 1.13)	1.10 (1.02, 1.18)
Lag 0-2							
Crude	1.08 (1.05, 1.10)	1.08 (1.05, 1.11)	1.07 (1.04, 1.10)	1.08 (1.05, 1.10)	1.07 (1.03, 1.11)	1.07 (1.05, 1.10)	1.10 (1.03, 1.16)
Adjusted	1.12 (1.09, 1.15)	1.11 (1.07, 1.15)	1.13 (1.09, 1.18)	1.11 (1.08, 1.15)	1.13 (1.07, 1.19)	1.12 (1.09, 1.15)	1.11 (1.02, 1.20)
Lag 0-6							
Crude	1.14 (1.11, 1.17)	1.14 (1.10, 1.18)	1.14 (1.09, 1.18)	1.14 (1.10, 1.17)	1.14 (1.09, 1.20)	1.13 (1.10, 1.16)	1.22 (1.14, 1.31)
Adjusted	1.20 (1.16, 1.24)	1.17 (1.11, 1.23)	1.23 (1.17, 1.30)	1.21 (1.16, 1.26)	1.18 (1.10, 1.26)	1.20 (1.15, 1.24)	1.23 (1.10, 1.36)

Models are adjusted for temperature and relative humidity; *P value is non-significant

Table 3.Odds ratios and 95% CIs for the relationship between ischemic stroke hospitalizations and concentration of ozone in South Carolina from 2002 to 2006

	All Stroke n=23360 OR (95% CI)	Total Ischemic n=20521 OR (95% CI)	Female n=10723 OR (95% CI)	Male n=9798 OR (95% CI)	Caucasian n=14566 OR (95% CI)	African American n=5955 OR (95% CI)
Lag 0						
Crude	1.06 (1.04, 1.07)	1.05 (1.03, 1.07)	1.06 (1.03, 1.09)	1.05 (1.02, 1.08)	1.06 (1.03, 1.10)	1.04 (1.00, 1.08)
Adjusted	1.08 (1.06, 1.11)	1.09 (1.06, 1.11)	1.09 (1.05, 1.12)	1.09 (1.05, 1.12)	1.10 (1.06, 1.13)	1.06 (1.01, 1.11)
Lag 1						
Crude	1.05 (1.03, 1.07)	1.05 (1.03, 1.07)	1.05 (1.03, 1.08)	1.04 (1.02, 1.07)	1.06 (1.02, 1.09)	1.03 (1.00, 1.07)*
Adjusted	1.08 (1.05, 1.10)	1.08 (1.05, 1.10)	1.08 (1.04, 1.12)	1.07 (1.03, 1.11)	1.08 (1.05, 1.11)	1.07 (1.02, 1.12)
Lag 2						
Crude	1.06 (1.04, 1.08)	1.06 (1.04, 1.08)	1.06 (1.03, 1.08)	1.06 (1.03, 1.09)	1.07 (1.04, 1.09)	1.04 (1.00, 1.08)
Adjusted	1.07 (1.05, 1.09)	1.07 (1.01, 1.10)	1.06 (1.02, 1.10)	1.08 (1.04, 1.12)	1.07 (1.04, 1.11)	1.06 (1.01, 1.11)
Lag 0-1						
Crude	1.06 (1.04, 1.08)	1.06 (1.04, 1.08)	1.07 (1.04, 1.10)	1.05 (1.02, 1.08)	1.07 (1.04, 1.09)	1.04 (1.00, 1.08)
Adjusted	1.10 (1.07, 1.13)	1.10 (1.07, 1.13)	1.10 (1.06, 1.14)	1.10 (1.06, 1.14)	1.11 (1.07, 1.14)	1.09 (1.03, 1.14)
Lag 0-2						
Crude	1.08 (1.05, 1.10)	1.07 (1.05, 1.10)	1.08 (1.05, 1.11)	1.07 (1.03, 1.10)	1.08 (1.06, 1.11)	1.05 (1.01, 1.09)
Adjusted	1.12 (1.09, 1.15)	1.12 (1.09, 1.15)	1.11 (1.07, 1.16)	1.13 (1.08, 1.17)	1.13 (1.09, 1.16)	1.10 (1.04, 1.17)
Lag 0-6						
Crude	1.14 (1.11, 1.17)	1.13 (1.10, 1.16)	1.13 (1.09, 1.17)	1.13 (1.08, 1.17)	1.14 (1.10, 1.18)	1.09 (1.04, 1.15)
Adjusted	1.20 (1.16, 1.24)	1.20 (1.15, 1.24)	1.18 (1.11, 1.24)	1.22 (1.15, 1.29)	1.22 (1.17, 1.27)	1.14 (1.06, 1.23)

Models are adjusted for temperature and relative humidity; *P value is non-significant

Table 4.Odds ratios and 95% CIs for the relationship between hemorrhagic stroke hospitalizations and concentration of ozone in South Carolina from 2002 to 2006

	Total Hemorrhagic n=2839 OR (95% CI)	Female n=1592 OR (95% CI)	Male n=1247 OR (95% CI)	Caucasian n=1759 OR (95% CI)	African American n=1080 OR (95% CI)
Lag 0					
Crude	1.06 (1.01, 1.12)	1.04 (0.97, 1.11)*	1.09 (1.01, 1.18)	1.01 (0.95, 1.08)*	1.16 (1.07, 1.24)
Adjusted	1.07 (1.00, 1.14)*	1.06 (0.96, 1.15)*	1.09 (0.98, 1.20)*	1.00 (0.91, 1.09)*	1.22 (1.10, 1.34)
Lag 1					
Crude	1.05 (1.00, 1.11)	1.03 (0.96, 1.10)*	1.09 (1.00, 1.17)	1.01 (0.94, 1.08)*	1.13 (1.05, 1.22)
Adjusted	1.08 (1.01, 1.15)	1.04 (0.95, 1.14)*	1.12 (1.01, 1.23)	1.01 (0.92, 1.10)*	1.20 (1.08, 1.34)
Lag 2					
Crude	1.10 (1.04, 1.15)	1.08 (1.01, 1.16)	1.11 (1.03, 1.19)	1.05 (0.98, 1.12)*	1.17 (1.08, 1.25)
Adjusted	1.07 (1.00, 1.14)*	1.04 (0.94, 1.14)*	1.11 (1.00, 1.22)*	1.02 (0.93, 1.11)*	1.15 (1.03, 1.27)
Lag 0-1					
Crude	1.07 (1.01, 1.13)	1.04 (0.96, 1.12)*	1.11 (1.02, 1.19)	1.01 (0.94, 1.09)*	1.17 (1.07, 1.26)
Adjusted	1.10 (1.02, 1.18)	1.07 (0.96, 1.18)*	1.14 (1.01, 1.31)	1.01 (0.91, 1.11)*	1.27 (1.13, 1.40)
Lag 0-2					
Crude	1.10 (1.03, 1.16)	1.07 (0.99, 1.15)*	1.13 (1.04, 1.23)	1.03 (0.95, 1.11)*	1.21 (1.11, 1.31)
Adjusted	1.11 (1.02, 1.20)	1.07 (0.96, 1.19)*	1.17 (1.03, 1.31)	1.02 (0.90, 1.13)*	1.29 (1.14, 1.44)
Lag 0-6					
Crude	1.22 (1.14, 1.31)	1.22 (1.10, 1.34)	1.23 (1.10, 1.37)	1.08 (0.97, 1.20)*	1.48 (1.33, 1.62)
Adjusted	1.23 (1.10, 1.36)	1.13 (0.96, 1.30)*	1.37 (1.17, 1.56)	1.10 (0.93, 1.26)*	1.47 (1.25, 1.68)

Models are adjusted for temperature and relative humidity; *P value is non-significant

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