HHS Public Access

Author manuscript

Sci Total Environ. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Sci Total Environ. 2019 December 01; 694: 133744. doi:10.1016/j.scitotenv.2019.133744.

A case-crossover analysis of the relationship of air pollution with out-of-hospital sudden unexpected death in Wake County, North Carolina (2013–2015)

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Abstract

Out-of-hospital sudden unexpected deaths are non-accidental deaths that occur without obvious underlying causes and may account for 10% of natural deaths before age 65. Short-term exposure to ambient air pollution is associated with all-cause (non-accidental) and cause-specific (e.g., cardiovascular) mortality, and with immediate exposures often yielding the highest magnitude risk estimates. Few studies have focused on short-term exposure to air pollution and sudden unexpected deaths. Using the University of North Carolina Sudden Unexpected Death in North

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Declarations of interest: none

The Wake County EMS Data System supports, maintains, and monitors EMS service delivery, patient care, and disaster preparedness for the Wake County, NC community at large. This manuscript has been reviewed by Wake County EMS Data System investigators for scientific content and consistency of data interpretation with previous Wake County EMS Data System publications

The research described in this article has been reviewed by the National Health and Environmental Effects Research Laboratory, US EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency, nor does the mention of trade names of commercial products constitute endorsement or recommendation for use.

Computational code may be requested by emailing the corresponding author at rappazzo.kristen@epa.gov. Subject data may be requested through the UNC SUDDEN project page at https://www.med.unc.edu/medicine/cardiology/sudden/contact-us/data-requests. Air pollutant concentrations are available through the AQS Datamart at https://aqs.epa.gov/api.

Carolina population, we examine associations between short-term criteria air pollutant exposures with sudden unexpected deaths using a time-stratified case-crossover design, with data on criteria air pollutants from the Environmental Protection Agency's Air Quality System. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression with air pollutant exposures scaled to roughly inter-quartile ranges; models were adjusted for average temperature and relative humidity on event day and preceding 3 days. Potential for confounding by co-pollutants were examined in two pollutant models. ORs for $PM_{2.5}$ at lag day 1 were elevated (adjusted OR for 5 μg/m^3 increase: 1.17 (0.98, 1.40)), and were robust to co-pollutant adjustment. Elevated odds were observed for SO_2 at lag day 0, and reduced odds for O_3 at lag day 0; however, these associations were somewhat attenuated towards the null (SO_2) or were not robust (O_3) to co-pollutant adjustment. This analysis in a racially and socioeconomically diverse cohort, with a more inclusive definition of sudden unexpected death than is typically employed offers evidence that $PM_{2.5}$ may be a clinically relevant trigger of sudden unexpected deaths in susceptible individuals.

Keywords

sudden unexpected death; air pollution; particulate matter; environmental epidemiology

1. Introduction

The adverse health effects of air pollution are notable for cardiovascular and respiratory morbidity and mortality[1,2]. Specifically, an extensive body of evidence exists showing that exposure to ambient particulate matter (PM) causes mortality, and this evidence remains robust when studies are conducted in different countries, over the range of PM concentrations evaluated, and for various statistical and analytic methods used to evaluate this relationship[2–12]. Other criteria pollutants (ozone, nitrogen dioxide (NO2), sulfur dioxide (SO2), carbon monoxide (CO)) also exhibit positive associations with mortality across a variety of conditions[8,13–18]. While the associations reported across this large body of evidence are well established and considered causal[6,14,17], cause-specific subtypes of deaths may have different etiologies and relationships with ambient air pollution[19,20].

Out-of-hospital sudden unexpected deaths (SUD) are non-accidental deaths that occur without obvious underlying causes, and may account for 10% of natural deaths under age 65[21]. Definitions of SUD vary across studies, countries, and usage[22] leading to uncertainty in estimates of SUD incidence. Many definitions, including the World Health Organization's, restrict identification of events based on timing of death (e.g., within 1 hour of witnessed or 24 hours of unwitnessed events) or cardiac causes[23–25]. While it is believed that sudden cardiac deaths make up the majority of SUD[26,27], this may be due, in part, to the definitional restrictions which often exclude unwitnessed deaths or specifically focus on sudden cardiac deaths. However, a broader definition of SUD without timing restriction, may capture more deaths/events which share similar risk factors and be more appropriate to assess population based risk.

The definitional requirements of timing and witnessing of death may lead to under-reporting of SUD in economic and racially diverse populations[21]. Because of this and the fact that

previous studies have largely been conducted among affluent or middle-class white populations[26–28], generalizability from these studies may be limited. The University of North Carolina at Chapel Hill's Sudden Unexpected Death in North Carolina (SUDDEN) project[29] was designed to address these concerns by collecting data on SUD occurring in a racially and socioeconomically diverse population, with a broader definition of SUD than previously employed.

Short-term (i.e., from hours up to 4 weeks) exposure to ambient air pollution is associated with all-cause (non-accidental) and cause-specific (e.g., cardiovascular) mortality, and with immediate exposures often yielding the highest magnitude risk estimates[8,30–33]. Fewer studies have focused on short-term exposure to air pollution and SUD as opposed to specifically sudden cardiac arrest. Additionally, methods to identify sudden cardiac death are more likely to exclude low income and minority populations. Using the UNC SUDDEN pilot population, and therefore a more inclusive definition of SUD than has been previously employed, we examine associations between short-term "criteria pollutant" concentrations with SUD using a time-stratified case-crossover design.

2. Methods

In order to better understand the causes and contributors to SUD, UNC at Chapel Hill researchers developed a project to collect detailed information on SUD cases occurring in Wake County, North Carolina (Figure 1). For this case registry, deaths could be either witnessed or unwitnessed with no time constraint, and SUD is defined as sudden pulseless condition in the absence of terminal disease or overdose at the time of death. All emergency management systems (EMS) attended out-of-hospital deaths from March 1, 2013 to February 28, 2015 (n = 1,592) were reported to the study coordinator, using an electronic query of the Emergency Medical Services (EMS) patient care reporting software (ESO Solutions V 4.8, Austin, Texas). Two research assistants then used EMS scene, medical examiner, toxicology, and autopsy reports when available to sequentially restrict the population to adults aged 18 to 64 (n = 757), "community dwelling" NC residents (i.e., not in institutions such as hospice, prison, etc.) (n = 704), and non-violent deaths (n = 639). Medical records within the last 5 years were systematically obtained for all cases, and cases were then adjudicated to ascertain sudden unexpected deaths using all available information by a majority decision of 3 independent cardiologists using medical and post-mortem records (also used for individual characteristics), leaving a final analytic population of n = 399. The population and selection procedures are described in further detail in Nanavati, et al.[28], Mirzaei, et al.[34], Patel, et al.[35].

To study the temporal effects of air pollution on SUD, we employed a case-crossover design using a time-stratified referent selection approach. In this design, individuals serve as their own controls and time-invariant variables are controlled for by design[36–39]. Time-stratified referent selection is done so that long (e.g., yearly and seasonal) and short-term (e.g., day of week) trends are accounted for[37]. In this analysis, referent days were selected within the same month and calendar year of the SUD event, and on all the same days of week. For example, if an individual experienced SUD on March 14, 2014 (event day), a Friday, then all other Fridays within March 2014 (7th, 21st, and 28th) become referent days. Single day lags

of 0 to 3 days, and the average of lag 0–1 day, before event and referent periods were chosen as exposure windows. The lag days selected for inclusion are based off the extensive epidemiologic literature reporting evidence of immediate effects of air pollution on mortality (i.e., within the first few days after exposure, 0 to 3 days)[6,14,17].

We acquired hourly measurements of $PM_{2.5}$, temperature, and relative humidity for 2013 – 2015 from the Wake County central site monitor though the EPA's Air Quality System (AQS) data mart[40]; and daily 8-hr maximums for ozone (O_3) and carbon monoxide (CO), and daily 1-hr maximums for nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) were obtained from the EPA's Air Data site[41]. For $PM_{2.5}$, temperature, and relative humidity, we calculated daily values by averaging over 24-hour periods (midnight to midnight). Pollutant and weather data were then linked to health data via date. Note that NO_2 data were only available from 2014 onward, therefore analyses including NO_2 will be restricted to those dates.

Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression, conditioning on participant ID[42–44]. All exposures were examined as continuous variables, with a roughly IQR across lag days increase for air pollutants used as exposure contrast: single day lags $PM_{2.5}$ = 5 μg/m^3, CO = 0.02 ppm, NO_2 = 15 ppb, SO_2 = 1 ppb, O_3 = 0.016 ppm (i.e., 16 ppb); for lag 0–1: $PM_{2.5}$ = 4 μg/m^3, CO = 0.15 ppm, NO_2 = 12 ppb, SO_2 = 1 ppb, O_3 = 0.016 ppm. Models were performed individually for exposure to air pollutant assigned to the day of the SUD event, as well as the first, second, or third day before the event (lag days 1, 2, 3), and the combined 0–1 day lag. When examining air pollutant concentrations as the main exposures, we adjusted for average temperature and average relative humidity for day of death/referent day (lag 0) and preceding lag days (lags 1 to 3) (natural cubic splines), this model was selected a priori based on previous work[45]. We also estimated effects using co-pollutant models that included two criteria air pollutants, to examine robustness of single-pollutant ORs.

Sensitivity analyses were conducted using an unconstrained distributed lag model, all lags entered into the model simultaneously, to examine the cumulative versus single lag effects. In addition, we also stratified deaths by flu season (October to May) and non-flu season (June to September) to examine the potential influence of seasonal variation.

This research was approved by the University of North Carolina at Chapel Hill's Office of Human Research Ethics as exempt from review. The EPA's Human Subjects Research Officer similarly reviewed this work and declared it non-human subjects research as all individuals were deceased at time of data collection.

3. Results

3.1 Variable distribution and descriptive statistics

Daily ambient air pollutant concentrations were generally low for gaseous pollutants over the two-year study period compared to average US levels[46], while $PM_{2.5}$ levels were more typical of nation-wide average concentrations (Table 1). Daily co-pollutant correlations were generally low to moderate, with 8 hour maximum CO and 1 hour maximum NO_2 being the

highest (Pearson correlation coefficient: 0.66) (Table 2). Partial correlations for air pollutants, adjusted for weather variables, were similar to unadjusted correlations (Supplemental Table S.1); with the exception of SO_2 which had substantially reduced correlations with both CO and NO_2. For assigned exposure concentrations, adjacent lag days had moderate correlations, which were attenuated with increasing time for $PM_{2.5}$, NO_2, SO_2, CO, O_3, and relative humidity, while adjacent days for temperature were highly correlated.

The study population is approximately two-thirds male, and two-thirds white, with the majority of the deaths occurring after age 45 years (>80%) and a mean age of 54 years (Table 3). The study population has a higher proportion of black individuals compared to Wake County in general (35.1% in study population v. 20.7% Wake County[47]). Hypertension, hypercholesterolemia, diabetes, coronary artery disease, and pulmonary disease were all highly prevalent in the study population[35].

3.2 Results for single air pollutant models

In unadjusted analyses ORs were elevated from the null for ambient 24-hour average $PM_{2.5}$ at lag days 1 and 2 (OR for 5 $\mu g/m^3$ increase: 1.12 (0.97, 1.30) and 1.11 (0.96, 1.28) respectively), and null for lag days 0 and 3 and lag 0–1 (Table 4). In models adjusted for temperature and relative humidity ORs for $PM_{2.5}$ at lag day 1 remained elevated (OR for 5 $\mu g/m^3$ increase: 1.17 (0.98, 1.40)) (Table 4, Figure 2). In both unadjusted and adjusted models, effect estimates for SO_2 exposure were elevated at lag day 0 (adjusted OR for 1 ppb increase: 1.09 (0.97, 1.22)) and negative at lag day 1 (adjusted OR for 1 ppb increase: 0.90 (0.79, 1.03)) (Table 4, Figure 3). ORs for CO and NO_2 were generally null in both unadjusted and adjusted models (Table 4, Figures 4 and 5 respectively). For O_3, effect estimates from unadjusted models were null, however in adjusted models the lag day 0 effect estimate moved away from the null in an negative direction (OR for 0.016 ppm increase: 0.90 (0.74, 1.09)) (Table 4, Figure 6).

3.3 Results for co-pollutant models

In co-pollutant models, also adjusting for temperature and relative humidity, the effect estimate for exposure to $PM_{2.5}$ at lag day 1 was robust to inclusion of any of the other air pollutants (Table 5, Figure 7). Interestingly, the OR for lag day 2 does move away from the null with co-pollutant adjustment (Table 5, Figure 7). The effect estimate for SO_2 lag day 0 was somewhat attenuated towards the null with adjustment for same-day NO_2 and CO (Table 5, Supplemental Figure S.1). The effect estimate for O_3 at lag day 0 was highly unstable with co-pollutant adjustment, moving substantially toward the null with $PM_{2.5}$ and CO adjustment, no movement with SO_2 adjustment, and crossing the null and becoming elevated with NO_2 adjustment (Table 5, Supplemental Figure S.2). Associations between NO_2 and CO, and SUD remained null (Supplemental Figure S.3 and S.4, respectively).

3.4 Results for sensitivity analyses

Unconstrained distributed lag models show similar effect estimates to single day lag models, with a cumulative OR of 1.09 (0.84, 1.42) for $PM_{2.5}$ (Supplemental Table S.2). In analyses stratified by flu (267 deaths) and non-flu (132 deaths) season, there is some suggestion of separation (suggestive of modification) or potential shifting (suggestive of confounding) of

effects (Supplemental Table S.2). However, the stratified odds ratios are fairly unstable due to smaller sample size and should be examined with caution. Odds ratios for $PM_{2.5}$ lag 1 remain robust to different analyses.

4. Discussion

In this study, we examined associations between the U.S. Clean Air Act's "criteria pollutants" and SUD, using a more inclusive definition of SUD than has been previously employed. We observed increased odds of SUD with increased daily average ambient $PM_{2.5}$ exposures 1 day before recorded death, and with daily 1-hour maximum SO_2 on day of recorded death, and a negative association with daily 8-hour maximum O_3 on day of recorded death. The increased odds of death with increased $PM_{2.5}$ exposures were robust to adjustment by co-pollutants, while ORs for SO_2 exposure were slightly attenuated toward the null and were unstable for O_3 exposure. Instability of the estimate for O_3 exposure may reflect sensitivities to how temperature is treated[48], while SO_2 concentrations at lag day 0 may actually reflect $PM_{2.5}$ concentrations at lag day 1[49,50]. It is also possible that exposures occurring on the recorded event day (lag 0) may occur after death, as exact timing of actual death is uncertain in this study population. Concentrations for gaseous pollutants in Wake County, NC were generally low for the period under study; it is possible that these lower concentrations are more likely to be related to either subclinical health effects or potentially be more relevant for long-term exposures.

Previous studies have not examined SUD with the exact definition used here, however, many studies have established associations with mortality in general, especially in older populations[3,5,6,9–11,14,17], and several have examined sudden or out-of-hospital cardiac death (SCD/OHCD) or arrest (SCA/OHCA). There are also a few studies that examine out-of-hospital mortality or mortality in populations restricted to ages less than 65 years. While not all studies reported positive associations, in a meta-analysis of 15 studies of short-term air pollution exposure and OHCA, Zhao, et al.[18] found positive pooled associations with increased PM_{10}, $PM_{2.5}$, and ozone, while findings for SO_2 and NO_2 were inconsistent. Heterogeneity was large for all exposures and there was evidence of publication bias in studies of ozone, adjustment of which attenuated the pooled effect estimated but did not nullify it. For $PM_{2.5}$, pooled effect estimates were strongest with cumulative exposure on lag days 0 and 1[18]. The studies included in this analysis (and that were earlier reviewed by Teng, et al.[51]), included individuals over 65, and typically had mean ages in the 60s[18]. In a time-series study of OHCD in Shanghai from 2006–2011, Dai, et al.[4] observed positive associations with same day PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO and temperature changes above or below thresholds, but no association between NO_2 or ozone levels; no associations were observed with in-hospital cardiac death. Pollutant levels in this area were high, and all the pollutants were highly correlated with one another except for ozone[4]. In an Italian study of over 5,000 cases of OHCD, Forastiere, et al.[7] observed associations with particle number (a proxy of ultrafine PM) at lag days 0, 1, 2, and 0–1 with a lessening of effect estimate magnitude at the lags further from event day. They also observed associations with PM_{10} exposure on lag days 0 and 1, though PM_{10} levels were relatively high (mean 52.1 $\mu g/m^3$) in the study area.

For out-of-hospital mortality, a study of those over 65 in 8 Italian cities reported a 1.80% (95% CI: 0.83, 2.77) change in mortality per 10 μg/m^3 increase in $PM_{2.5}$[52]. However, an earlier study found no evidence of association between PM_{10} increases and OHCD in those aged 35–64 in the same cities[12]. In two US based studies, Schwartz et al. examined out of hospital deaths with: total suspended particles in Philadelphia, PA finding increased risk of death in those with the 35–64 year age categories[10]; and PM_{10} in 11 US cities finding a percent change in mortality of 0.89 (0.67, 1.10) per 10 μg/m^3 increase[11].

Outcomes, population ages, area, air pollutants examined, and timing vary across these studies. Outcomes reported are typically categorized within a more restricted period (within 24 hours unwitnessed or 1 hour witnessed) than used for SUD, so we might expect differences in timing between our study and previous work. However, despite these differences, our observed effect estimates are generally congruent with those reported for $PM_{2.5}$ in previous studies.

The main mechanisms by which short-term air pollutant exposure may lead to mortality in general, and PM in particular, are through perturbations of the cardiovascular and respiratory systems and mainly rely on oxidative stress or inflammatory response[6,53–55]. Inflammatory responses and oxidative stress can cause local damage in the respiratory system and become systemic, potentially leading to vascular dysfunction or alterations in lung function and response to allergens[6,56,57]. Local inflammatory response in the lung can alter the balance between pro- and anti-coagulants, which increases potential for thrombosis[55]. Soluble PM components can also be translocated across the lung membrane to act more directly on other organ systems[53]. There are also pathways that may lead to activation of the autonomic nervous system, potentially leading to vascular dysfunction and plaque rupture[6,53,58]. The people experiencing SUD in this population are generally a vulnerable population in terms of health conditions; there is a high prevalence of: diabetes, hypertension, dyslipidemia, and coronary artery disease. These underlying conditions are likely to lead to increased susceptibility to the effects of air pollutant exposure[53].

In terms of exposure assessment and the potential for spatial and temporal variability in air pollutant concentrations to lead to exposure measurement error, $PM_{2.5}$ is relatively stable both spatially and temporally, lending itself to this type of analysis/exposure ascertainment. Conversely, gaseous pollutants like SO_2 tend to be more spatially and temporally heterogeneous; SO_2 in the environment travels in plumes and concentrations peak over very short time periods. For SO_2 those peak concentrations may be a more relevant exposure metric for a health effect, as opposed to the general low background levels captured though the single county monitor. NO_2 is highly source dependent, which in this case is traffic, and the single monitor will only capture general background levels. Related to NO_2 exposure, in a spatial analysis of the effects on greenspace, major road density was not observed to have an association within this population[59], which suggests that NO_2 may not be associated with SUD for long-term exposures in this population. There may be some aspect of exposure misclassification both spatial and temporal, acting in the observed associations with SO_2 and NO_2. One way to address this would be to examine other metrics and indicators of air pollution exposure, such as using a more spatially refined model to estimate exposure concentrations for individuals rather than a single monitor for the study area. However, this

may also introduce the possibility of spatially-related confounding. High correlations between temperature lags may affect adjusted results, but air pollution effect estimates adjusted for temperature were similar to the unadjusted ORs.

The UNC SUDDEN study definition of SUD is broader than previously used sudden cardiac death and WHO-defined SUD, which lends itself to both strengths and limitations. A major strength of this pilot study is that the population is racially and economically diverse, much more so than previous cohorts in which the use of time and witnessing restrictions are likely to systematically exclude many individuals[21,28,60]. Other strengths of the study include: the case-crossover design employed, such that confounding by time-invariant and long-term trending factors are controlled for by the design and residual or unmeasured confounding is unlikely; and the case ascertainment, which given its thoroughness leaves less opportunity for selection bias to occur.

A corresponding limitation to the broader definition of SUD is that the exact timing of death may be unknown due to the inclusion of unwitnessed deaths, and time of death may be estimated to the time an individual was found. As this analysis is of a temporally based exposure, this likely adds an element of exposure misclassification which may attenuate effect estimates toward the null. While the county used in this study is racially and socioeconomically diverse, it is still only a single county with a moderate population for the US. As such, case numbers of SUD are limited, which may affect our ability to observe effects, particularly with environmental exposures where effect estimates may be expected to be small. In addition, in Wake County, NC, air pollution levels are generally low (with the exception of $PM_{2.5}$ which is around the national average), leaving the possibility of stronger associations between air pollutants and SUD at higher concentrations.

Another potential limitation is that there may be different underlying etiologies of SUD across age groupings. The cause of a sudden death at age 25 is likely to differ from a cause at age 45. These differences could potentially be explored through cluster analysis, or through stratified or interaction analysis with a population of sufficient size. Relatedly, effects of air pollution exposure may be greater in those aged over 65[6,61] and observed effect estimates for an adult population below this threshold may be reduced compared to what would be observed in older adults. However, the CDC and CMS have identified the sub-population of adults aged 34–64 years as a high priority group because of increasing mortality, and this study may offer new insight.

The goal of the University of North Carolina at Chapel Hill's SUDDEN project is to better define the clinical, social, economic, and environmental determinants of SUD so that more effective SUD prevention strategies can be developed. The present study provides further evidence that environmental conditions can modify the risk for SUD. In the present study SUD is associated with short-term exposure to ambient $PM_{2.5}$ suggesting that exposure to particle pollution can serve as a clinically relevant trigger of SUD in susceptible individuals. In an independent analysis of the same SUD registry, we previously showed that both greenway density and the percentage of forest in Wake County, NC were inversely associated with SUD[59]. Taken together these findings suggest that modification of

environmental conditions might offer a way to decrease the overall risk of SUD in a population.

Several approaches to decrease an individual's risk for sudden death can be envisioned that include specific guidance on avoidance of exposure to air particle pollution and these are championed by the Center for Medicare and Medicaid Services (CMS) and Centers for Disease Control and Prevention (CDC) joint initiative, *Million Hearts*® (URL: millionhearts.hhs.gov)[62]. First, individuals at risk for SUD should optimize healthy behaviors and clinical management of health conditions giving rise to increased susceptibility to air pollution. Individuals can reduce air pollutant exposures by adjusting outdoor activities, or taking more specific actions like using in-home HEPA filtration and wearing an N-95 respirator outdoors when air particle pollution is high. At the population level, efforts should be made to bring airsheds into attainment with the U.S. Environmental Protection Agency's National Ambient Air Quality Standards. Increasing awareness of the association between air pollution and adverse health outcomes among the general population, and the utility of the Air Quality Index to guide responses to graded levels of air pollution for healthy and at-risk people is anticipated to improve health and decrease adverse clinical events. Approaches for this endeavor would be to connect health care professionals with information about air quality, and consider strategies to better inform the public about risks of air pollution, particularly if they are individuals who have clinical conditions or at risk for cardiopulmonary conditions, e.g., older adults, that may make them particularly vulnerable to the adverse effects of air pollution. Further studies of SUD in economically and socially diverse populations could offer more information about relevant exposure timing, examine potential modifying factors such as underlying disease, and potentially further specify components of air pollution and particulate matter of particular concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The SUDDEN project is funded by private donations, The Heart and Vascular Division of the University of North Carolina at Chapel Hill, and the McAllister Heart Institute, Chapel Hill, North Carolina. The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Award Number 1UL1TR001111.

We would like to thank Jason Sacks and Thomas Luben for their insight and comments.

Abbreviations:

SUD	Out-of-hospital sudden unexpected deaths

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Highlights

- Environmental causes of out-of-hospital sudden unexpected death are largely unknown
- Paper presents a case-crossover study of air pollution and sudden unexpected death
- Increased odds of death seen with day before death fine particulate matter exposure
- Association with air pollution in young, racially, and economically diverse population
- Particulate matter may be a clinically relevant trigger of sudden unexpected death

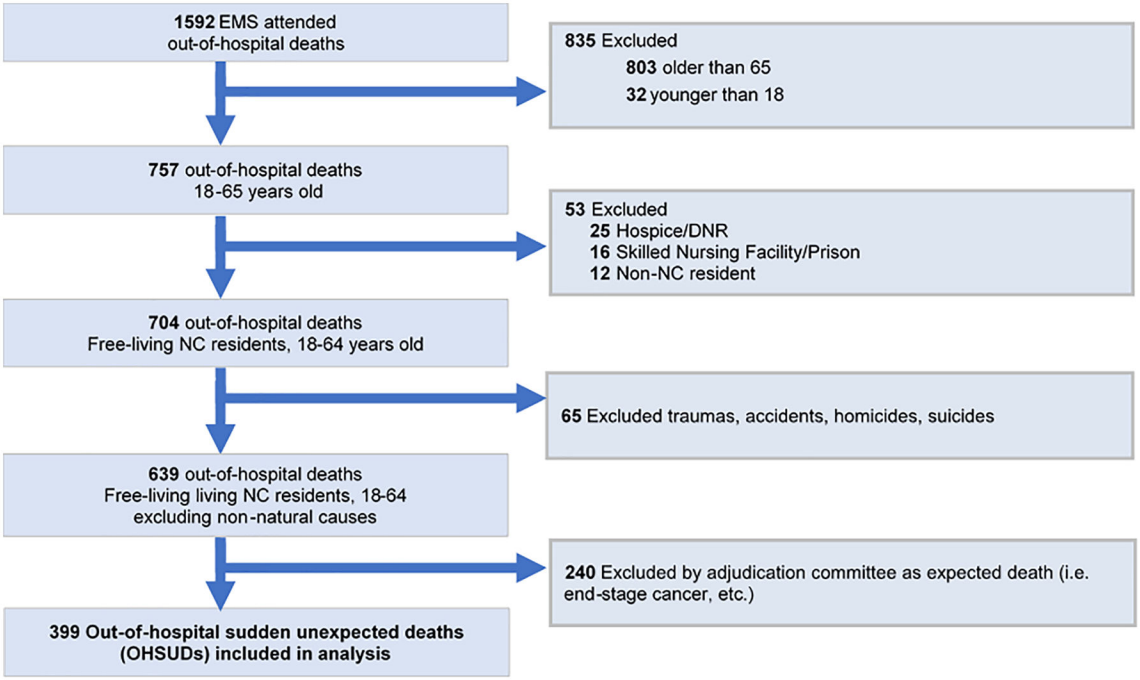

Figure 1:
Flow chart of SUDDEN project participant inclusion

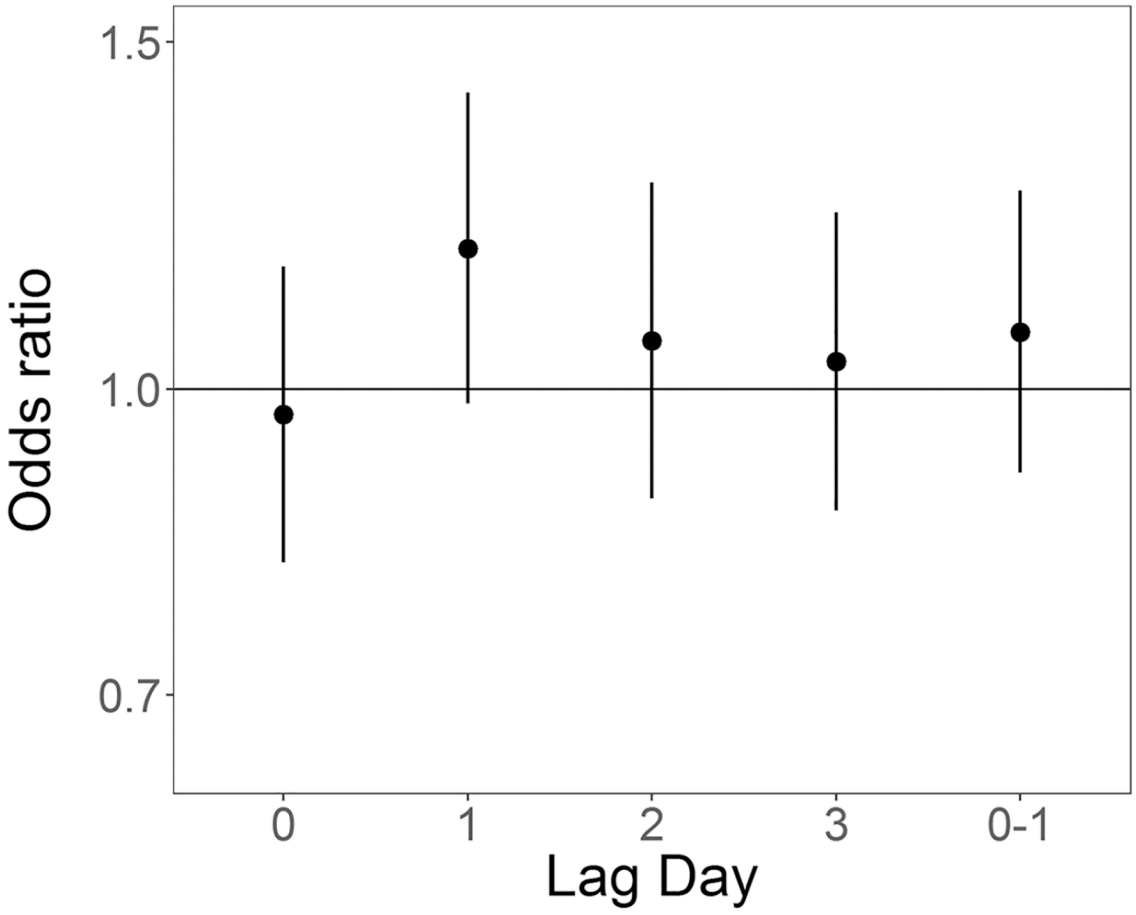

Figure 2:
Odds ratios and 95% confidence intervals for 5 μg/m^3 (4 μg/m^3 for lag 0–1) increase in daily average $PM_{2.5}$ and out-of-hospital sudden unexpected death in Wake County North Carolina March 1, 2013 to February 28, 2015, adjusted for average temperature and relative humidity, across single day lags from 0 to 3 days and multiday lag of 0 to 1 days.

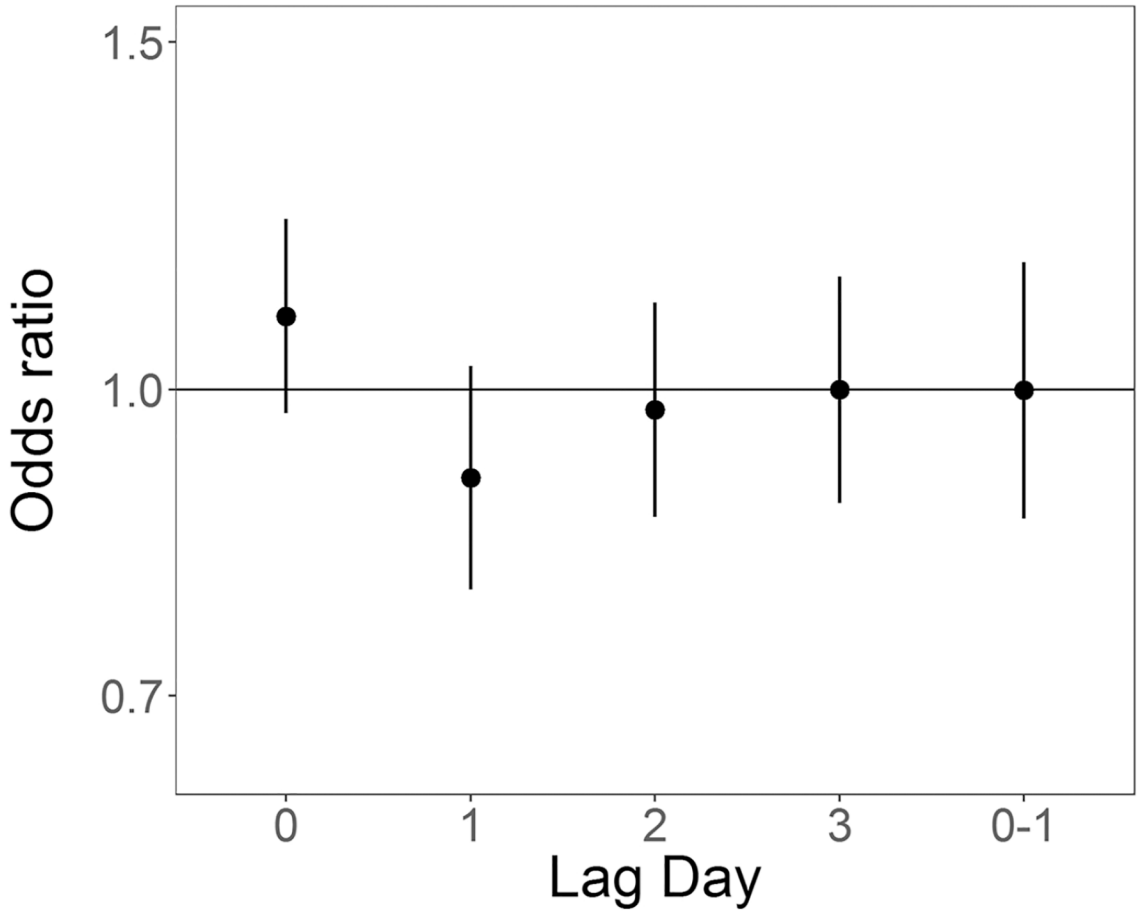

Figure 3:
Odds ratios and 95% confidence intervals for 16 ppb increase in 8-hr maximum ozone and out-of-hospital sudden unexpected death in Wake County North Carolina March 1, 2013 to February 28, 2015, adjusted for average temperature and relative humidity, across single day lags from 0 to 3 days and multiday lag of 0 to 1 days.

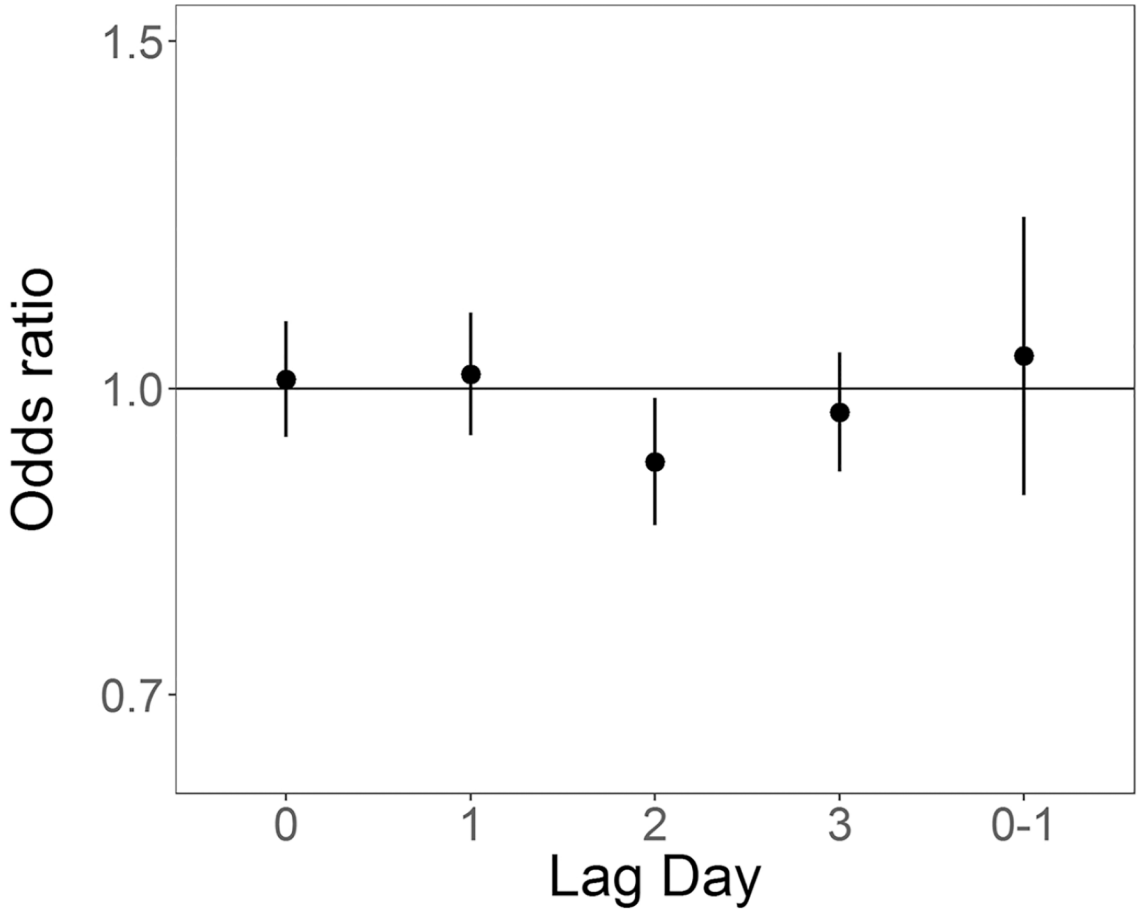

Figure 4:
Odds ratios and 95% confidence intervals for 0.2 ppm (0.15 ppm for lag 0–1) increase in 8-hr maximum CO and out-of-hospital sudden unexpected death in Wake County North Carolina March 1, 2013 to February 28, 2015, adjusted for average temperature and relative humidity, across single day lags from 0 to 3 days and multiday lag of 0 to 1 days.

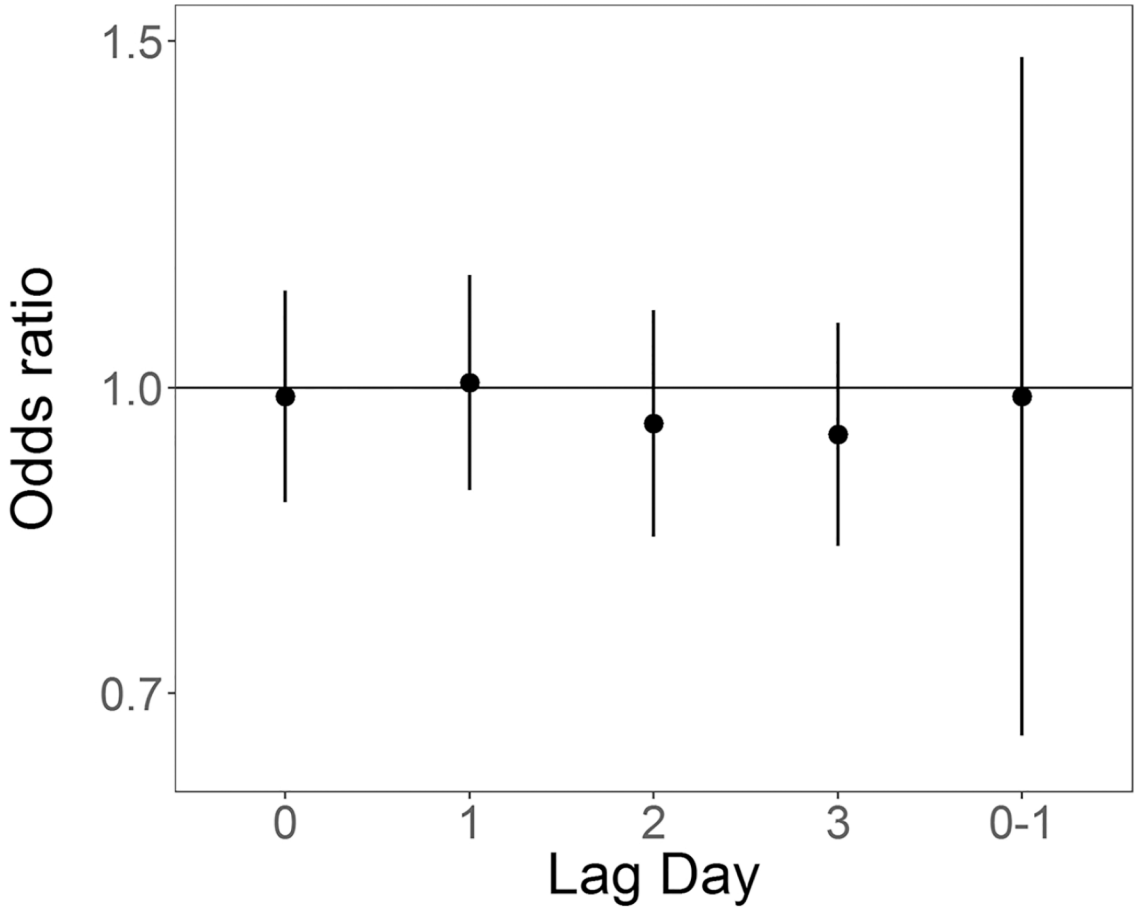

Figure 5:
Odds ratios and 95% confidence intervals for 1 ppm increase in 1-hr maximum SO_2 and out-of-hospital sudden unexpected death in Wake County North Carolina March 1, 2013 to February 28, 2015, adjusted for average temperature and relative humidity, across single day lags from 0 to 3 days and multiday lag of 0 to 1 days.

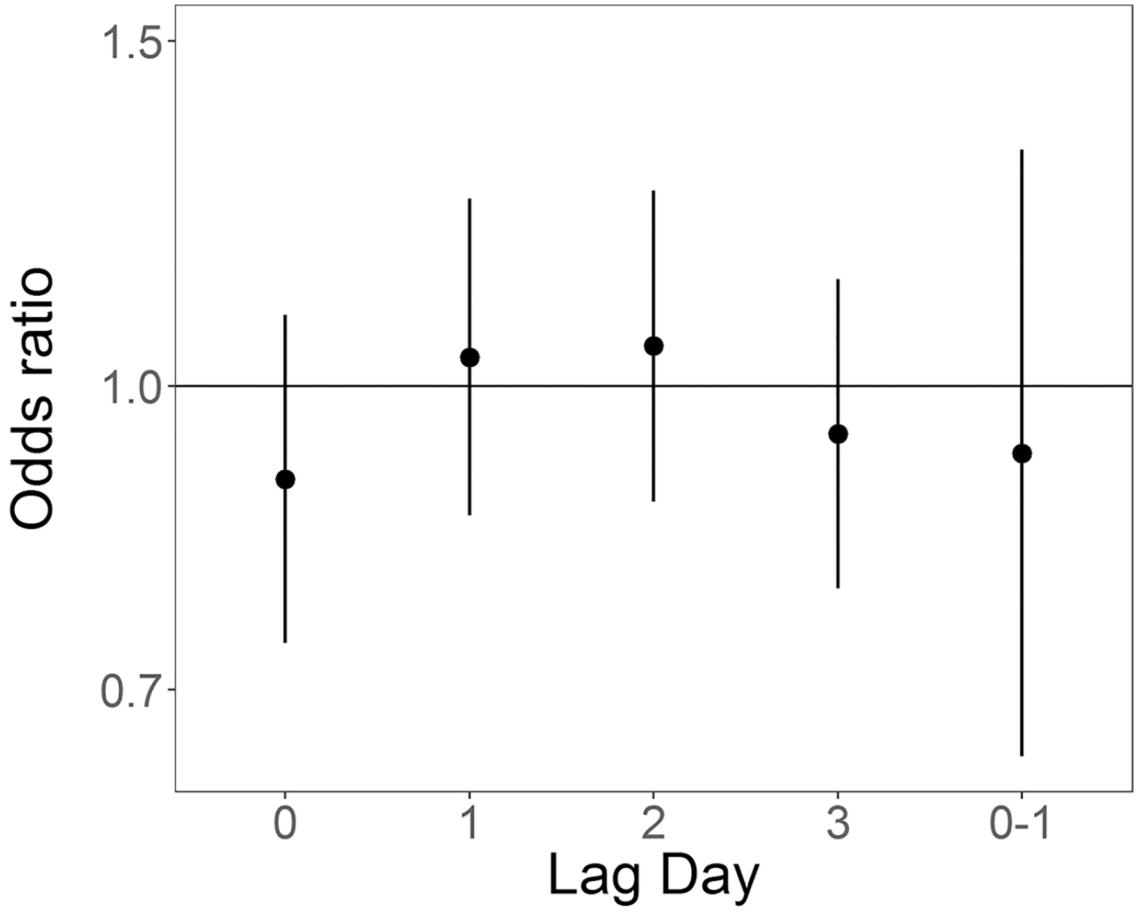

Figure 6:
Odds ratios and 95% confidence intervals for 15 ppm (12 ppm for lag 0–1) increase in 1-hr maximum NO_2 and out-of-hospital sudden unexpected death in Wake County North Carolina March 1, 2013 to February 28, 2015, adjusted for average temperature and relative humidity, across single day lags from 0 to 3 days and multiday lag of 0 to 1 days.

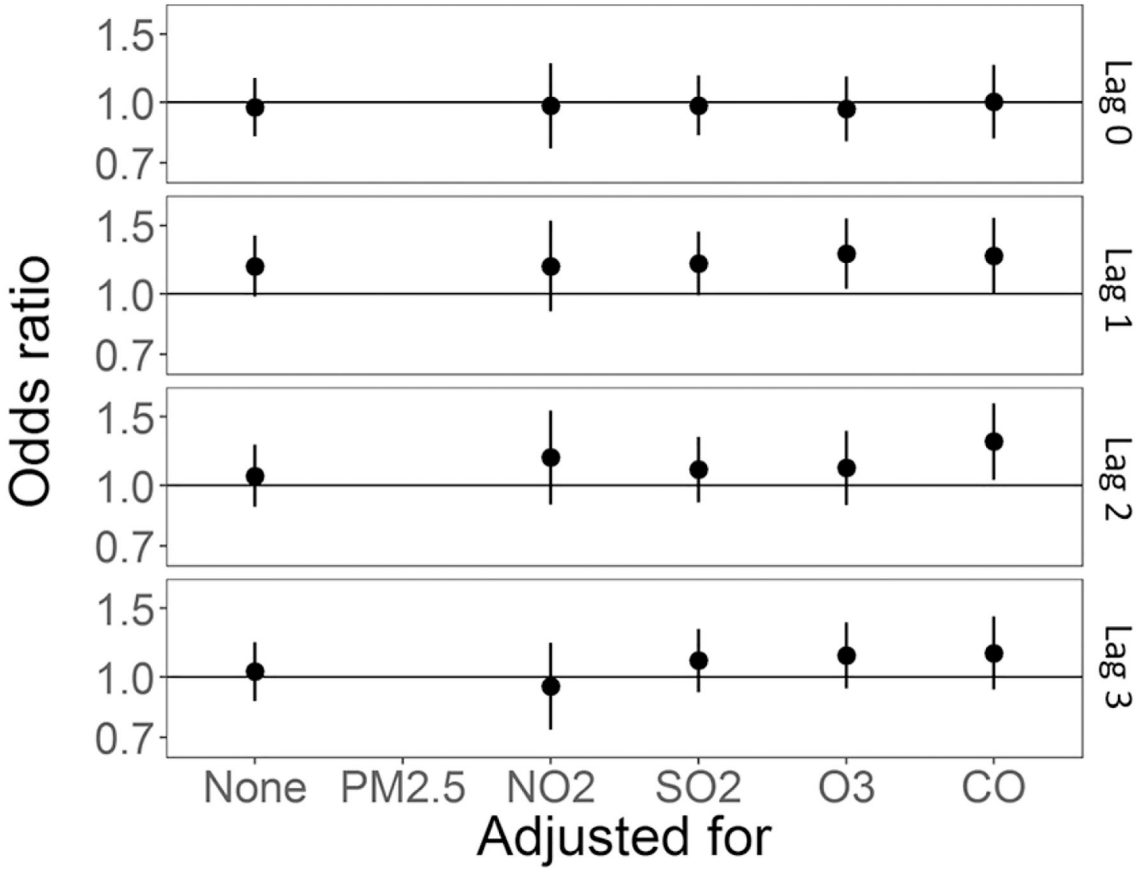

Figure 7:

Co-pollutant adjusted odds ratios and 95% confidence intervals for 5 μg/m^3 (4 μg/m^3 for lag 0–1) increase in daily average $PM_{2.5}$ and out-of-hospital sudden unexpected death in Wake County North Carolina March 1, 2013 to February 28, 2015, also adjusted for average temperature and relative humidity. Each panel is for a single day lag: 0, 1, 2, and 3 from top to bottom, odds ratio unadjusted for other co-pollutants is furthest to the left, followed by odds ratio adjusted for NO_2, SO_2, O_3, and CO.

Table 1:

Descriptive statistics for daily air pollutant concentrations and weather variables for Wake County NC from March 1 2013 to February 28 2015

Exposure	Time averaging	Mean	STD	Min	25th	Median	75th	Max	IQR
$PM_{2.5}$ (ug/m^3)	Daily average	10.93	4.33	1.82	8.03	10.25	13.22	31.14	5.20
CO (ppm)	8 hr maximum	0.36	0.18	0.20	0.20	0.30	0.40	1.30	0.20
NO_2 (ppb)	1 hr maximum	15.80	9.74	1.10	7.90	13.70	23.30	42.60	15.40
SO_2 (ppb)	1 hr maximum	1.08	1.30	−0.10	0.20	0.65	1.40	9.50	1.20
O_3 (ppb)	8 hr maximum	37.51	11.94	0	29	37	46	71	17
Temperature (°F)	Daily average	59.38	16.53	14.54	44.92	62.33	74.29	85.67	29.38
Relative humidity (%)	Daily average	65.56	15.57	3.08	55.46	66.96	77.04	96.00	21.58

CO: carbon monoxide

IQR: inter-quartile range

NO_2: nitrogen dioxide

O_3: ozone

$PM_{2.5}$: particulate matter under 2 $\mu g/m^3$ in aerodynamic diameter

SO_2: sulfur dioxide

STD: standard deviation

Table 2:

Correlations between daily air pollutant and weather variables for Wake County NC from March 1 2013 to February 28 2015

	CO	NO_2	O_3	PM_{25}	SO_2	Temperature	Relative humidity
CO	1	0.66	−0.10	0.45	0.40	−0.33	−0.10
NO_2	0.66	1	−0.00	0.36	0.40	−0.44	−0.40
O_3	−0.10	−0.00	1	0.22	−0.06	0.37	−0.42
PM_{25}	0.44	0.36	0.22	1	0.18	−0.11	−0.11
SO_2	0.40	0.40	−0.06	0.18	1	−0.53	−0.37
Temperature	−0.33	−0.44	0.37	−0.11	−0.53	1	0.27
Relative humidity	−0.10	−0.40	−0.42	−0.11	−0.37	0.27	1

CO: carbon monoxide

NO_2: nitrogen dioxide

O_3: ozone

$PM_{2.5}$: particulate matter under 2 $\mu g/m^3$ in aerodynamic diameter

SO_2: sulfur dioxide

Table 3:

Demographic characteristics of the SUDDEN project population

Characteristic	N	%
Total	399	100
Sex		
Female	126	31.58
Male	273	68.42
Race		
White	249	62.41
Black	140	35.09
Asian or other	10	2.51
Age group	5	1.25
<30	12	3.01
30 – 39	31	7.77
40 – 49	69	17.29
50 – 59	181	45.36
60 – 64	101	25.31
Coronary artery disease		
Yes	94	23.56
No	277	69.42
Missing	28	7.02
History of hypertension		
Yes	224	56.14
No	147	36.84
Missing	28	7.02
Diabetes mellitus		
Yes	109	27.32
No	262	65.66
Missing	28	7.02
Dyslipidemia		
Yes	146	36.59
No	225	56.39
Missing	28	7.02
Heart Failure		
Yes	51	12.78
No	320	80.2
Missing	28	7.02
Smoker		

Characteristic	N	%
Yes	173	43.36
No	114	28.57
Missing or unknown	112	28.07
History of stroke		
Yes	26	6.52
No	345	86.47
Missing	28	7.02
Chronic kidney disease		
Yes	44	11.03
No	327	81.95
Missing	28	7.02
Chronic respiratory disorder		
Yes	123	30.83
No	248	62.16
Missing	28	7.02

Table 4:

Odds ratios and 95% confidence intervals for air pollutant and out of hospital sudden unexpected death, unadjusted and adjusted for temperature and relative humidity

Exposure	Lag Day	Unadjusted	Adjusted for temperature and relative humidity
Temperature	0	1.00 (0.98 ,1.01)	
Temperature	1	0.99 (0.98 ,1.01)	
Temperature	2	1.00 (0.99 ,1.02)	
Temperature	3	1.00 (0.99 ,1.02)	
$PM_{2.5}$	0	0.97 (0.84 ,1.12)	0.97 (0.82 ,1.15)
$PM_{2.5}$	1	1.12 (0.97 ,1.30)	1.18 (0.98 ,1.41)
$PM_{2.5}$	2	1.11 (0.96 ,1.28)	1.06 (0.88 ,1.27)
$PM_{2.5}$	3	1.05 (0.91 ,1.20)	1.03 (0.87 ,1.23)
$PM_{2.5}$	0–1	1.05 (0.92 ,1.19)	1.07 (0.91 ,1.26)
NO_2	0	0.99 (0.90 ,1.08)	0.99 (0.88 ,1.12)
NO_2	1	0.98 (0.89 ,1.08)	1.01 (0.89 ,1.14)
NO_2	2	0.93 (0.84 ,1.03)	0.96 (0.84 ,1.10)
NO_2	3	0.91 (0.82 ,1.01)	0.95 (0.83 ,1.08)
NO_2	0–1	0.94 (0.71 ,1.25)	0.99 (0.67 ,1.47)
SO_2	0	1.09 (0.99 ,1.20)	1.09 (0.97 ,1.22)
SO_2	1	0.92 (0.82 ,1.02)	0.90 (0.79 ,1.03)
SO_2	2	0.96 (0.87 ,1.07)	0.98 (0.86 ,1.11)
SO_2	3	0.97 (0.86 ,1.08)	1.00 (0.88 ,1.14)
SO_2	0–1	1.01 (0.89 ,1.14)	1.00 (0.86 ,1.16)
O_3	0	0.97 (0.85 ,1.11)	0.90 (0.74 ,1.09)
O_3	1	1.01 (0.88 ,1.15)	1.03 (0.86 ,1.25)
O_3	2	1.06 (0.93 ,1.20)	1.05 (0.87 ,1.26)
O_3	3	1.00 (0.87 ,1.14)	0.95 (0.79 ,1.13)
O_3	0–1	0.98 (0.77 ,1.25)	0.92 (0.65 ,1.32)
CO	0	0.97 (0.85 ,1.11)	0.90 (0.74 ,1.09)
CO	1	1.01 (0.88 ,1.15)	1.03 (0.86 ,1.25)
CO	2	1.06 (0.93 ,1.20)	1.05 (0.87 ,1.26)
CO	3	1.00 (0.87 ,1.14)	0.95 (0.79 ,1.13)
CO	0–1	0.98 (0.77 ,1.25)	0.92 (0.65 ,1.32)

CO: carbon monoxide

NO_2: nitrogen dioxide

O_3: ozone

$PM_{2.5}$: particulate matter under 2 $\mu g/m^3$ in aerodynamic diameter

SO_2: sulfur dioxide

Table 5:

Odds ratios and 95% confidence intervals for air pollutant and out of hospital sudden unexpected death, co-pollutant adjusted models

Lag Day	Adjusted* for	$PM_{2.5}$	NO_2	SO_2	O_3	CO
0	None	0.97 (0.82 ,1.15)	0.99 (0.88 ,1.12)	1.09 (0.97 ,1.22)	0.90 (0.74 ,1.09)	1.01 (0.95 ,1.08)
	$PM_{2.5}$		0.98 (0.86 ,1.13)	1.08 (0.97 ,1.21)	0.97 (0.79 ,1.21)	1.01 (0.94 ,1.09)
	NO_2	0.98 (0.76 ,1.26)		1.04 (0.89 ,1.21)	1.21 (0.85 ,1.72)	1.06 (0.94 ,1.20)
	SO_2	0.98 (0.82 ,1.17)	0.98 (0.87 ,1.12)		0.91 (0.74 ,1.11)	1.01 (0.94 ,1.08)
	O_3	0.96 (0.80 ,1.17)	0.97 (0.84 ,1.11)	1.08 (0.96 ,1.21)		1.00 (0.93 ,1.07)
	CO	1.00 (0.81 ,1.25)	0.95 (0.79 ,1.13)	1.06 (0.91 ,1.24)	0.97 (0.77 ,1.22)	
1	None	1.18 (0.98 ,1.41)	1.01 (0.89 ,1.14)	0.90 (0.79 ,1.03)	1.03 (0.86 ,1.25)	1.02 (0.95 ,1.09)
	$PM_{2.5}$		0.99 (0.87 ,1.13)	0.89 (0.78 ,1.02)	0.97 (0.79 ,1.19)	0.99 (0.91 ,1.07)
	NO_2	1.18 (0.90 ,1.54)		0.92 (0.78 ,1.10)	1.12 (0.81 ,1.56)	1.02 (0.90 ,1.16)
	SO_2	1.20 (0.99 ,1.45)	0.99 (0.87 ,1.13)		1.04 (0.86 ,1.27)	1.05 (0.97 ,1.13)
	O_3	1.27 (1.03 ,1.56)	0.97 (0.83 ,1.12)	0.91 (0.80 ,1.04)		1.00 (0.92 ,1.08)
	CO	1.25 (1.00 ,1.57)	1.01 (0.85 ,1.21)	0.87 (0.71 ,1.06)	1.16 (0.92 ,1.47)	
2	None	1.06 (0.88 ,1.27)	0.96 (0.84 ,1.10)	0.98 (0.86 ,1.11)	1.05 (0.87 ,1.26)	0.92 (0.85 ,0.99)
	$PM_{2.5}$		0.93 (0.80 ,1.08)	0.96 (0.83 ,1.10)	1.03 (0.84 ,1.27)	0.89 (0.81 ,0.96)
	NO_2	1.18 (0.89 ,1.56)		1.08 (0.91 ,1.29)	0.98 (0.73 ,1.32)	0.96 (0.84 ,1.10)
	SO_2	1.10 (0.90 ,1.33)	0.94 (0.82 ,1.09)		1.09 (0.89 ,1.32)	0.91 (0.84 ,0.99)
	O_3	1.11 (0.89 ,1.38)	0.97 (0.83 ,1.12)	0.97 (0.85 ,1.11)		0.91 (0.84 ,0.98)
	CO	1.30 (1.04 ,1.63)	1.01 (0.84 ,1.23)	1.02 (0.85 ,1.22)	1.07 (0.85 ,1.34)	
3	None	1.03 (0.87 ,1.23)	0.95 (0.83 ,1.08)	1.00 (0.88 ,1.14)	0.95 (0.79 ,1.13)	0.97 (0.91 ,1.04)
	$PM_{2.5}$		0.97 (0.83 ,1.12)	1.02 (0.88 ,1.17)	0.92 (0.76 ,1.13)	0.95 (0.88 ,1.03)
	NO_2	0.95 (0.73 ,1.22)		1.00 (0.85 ,1.19)	1.08 (0.79 ,1.47)	1.03 (0.92 ,1.16)
	SO_2	1.10 (0.91 ,1.33)	0.97 (0.85 ,1.11)		0.98 (0.81 ,1.19)	0.96 (0.89 ,1.04)
	O_3	1.14 (0.93 ,1.38)	1.00 (0.86 ,1.16)	1.01 (0.88 ,1.16)		0.97 (0.90 ,1.04)
	CO	1.15 (0.93 ,1.43)	0.91 (0.76 ,1.09)	1.06 (0.88 ,1.28)	0.98 (0.78 ,1.23)	

*all models are adjusted for temperature and relative humidity

CO: carbon monoxide

NO_2: nitrogen dioxide

O_3: ozone

$PM_{2.5}$: particulate matter under 2 μg/m3 in aerodynamic diameter

SO_2: sulfur dioxide