ASSOCIATION OF OUT-OF-HOSPITAL CARDIAC ARREST WITH EXPOSURE TO FINE PARTICULATE AND OZONE AMBIENT AIR POLLUTION FROM CASE-CROSSOVER ANALYSIS RESULTS: ARE THE STANDARDS PROTECTIVE?

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Abstract

About 300,000 cardiac arrests occur outside of hospitals in the United States each year; most are fatal. Studies have found that a small but significant percentage of the cardiac arrests appear to be triggered by exposure to increased levels one of two air pollutants: fine particulate matter and ozone.

We analyzed seven key studies to determine if Environmental Protection Agency (EPA) standards protect the public from out-of-hospital cardiac arrests (OHCA) triggered by exposure to fine particulate matter and ozone. Using Houston, Texas, data, we found evidence of an increased risk of cardiac arrest on the order of 2% to 9% due to an increase of fine particulate levels (a daily average increase of 10 $\mu g/m^3$) on the day of, or day before, the heart attack. The EPA fine particulate standard of 35 $\mu g/m^3$ (35 micrograms per cubic meter of air) therefore does not effectively protect the public from OHCA triggered by exposure to fine particulates. However, the EPA's ozone standard does appear to adequately protect public health from OHCA triggered by exposure to ozone.

Introduction

The first decisive regulatory move toward protecting public health from impacts of air pollution occurred in 1971 through passage of the Clean Air Act (CAA). Section 109 directs the Environmental Protection Agency (EPA 1971) to promulgate standards for certain pollutants found in ambient air. These pollutants—ozone, carbon monoxide, nitrogen dioxide, sulfur dioxide, particulate matter and lead—were believed to represent a present or future threat to public health.

The CAA further requires that the standards be set at a level sufficient to protect health with an adequate margin of safety. The phrase "adequate margin of safety" has been defined to be the maximum permissible ambient air level that will protect the health of any sensitive group, while accounting for uncertainties with risk assessment and toxicology studies and still protecting against hazards not yet identified.

While the congressional action was decisive 40 years ago, even today it is unclear whether the public health has been adequately protected with regard to at least two of the criteria pollutants: fine particulate matter and ozone. Fine particulate matter (PM2.5) is made up of particles 2.5 microns in size or smaller (EPA 2005). Ozone, on the tropospheric level, is a photochemical oxidant formed when volatile organic compounds and nitrogen oxides combine under certain atmospheric conditions (EPA 2006). The standards for these two pollutants have existed in a state of flux, changing as the health effects, magnitude of association, and latency of effect are better understood with emerging evidence.

Out-of-hospital cardiac arrest (OHCA) is an important new example of a health effect with an association with short-term exposure to air pollutants. Defined as a condition characterized by an unexpected cardiovascular collapse due to an underlying cardiac cause occurring out of the hospital, approximately 300,000 persons in the United States experience an OHCA each year; more than 90% of those persons who experience an OHCA die (McNally et al. 2011).

It appears that one trigger for OHCA is exposure to PM2.5 air pollution (Ensor et al. 2012; Dennekamp et al. 2010; Silverman et al. 2010); recently researchers have found that another trigger of OHCA may be ozone (Ensor et al. 2012). This epidemiological evidence is supported by pathophysiologic arguments that link PM2.5 and ozone air pollutants to cardiac endpoints (see Dockery et al. 2005; Gold et al. 2000; Peters et al. 1997; Peters et al. 2000; Riediker et al. 2004; Srebot et al. 2009).

Given these recent findings, we ask, "Are the current air pollution standards for PM2.5 and ozone protective of health in terms of OHCA for the public and sensitive subpopulations?"

We seek to answer the question by first, presenting the case-crossover analysis studies that have examined the risk of OHCA from exposure to PM2.5 and ozone, and then assessing the findings in relationship to existing PM2.5 and ozone standards.

Overview of Case-Crossover Method

The method increasingly used to study the association between air pollution and OHCA is a case-crossover design analyzed with conditional logistic regression. In addition to OHCA, this methodology has been used to assess asthma attacks (Lin 2002), congestive heart failure (Kwon et al. 2001), strokes (Tsai et al. 2003; Wellenius et al. 2012), and other episodic health events that have followed short-term exposure to air pollution.

Case-crossover design was first introduced 20 years ago (Maclure 1991). In the case-crossover design, each individual experiencing a health event serves as his or her own reference; in other words, individuals serve as their own control. Ambient air pollution is used as a proxy for personal exposure. The ambient air pollution concentrations at times when the study individual is not experiencing the OHCA health event are the reference concentrations. The reference concentrations are statistically compared with the concentrations during or around the time the study individual experienced the OHCA health event. Conditional logistic regression is applied to estimate the association of pollution and increased relative risk of the health event while controlling for confounding factors.

The number of events used in case-crossover analysis for OHCA ranges from a little more than 350 (Levy et al. 2001) to more than 11,000 (Ensor et al. 2012). More cases are needed when the exposure concentration range is narrower (i.e., smaller interquartile range). The number of cases included in these studies has been increasing over time, resulting in stronger statistical power of the analysis.

The reference concentration periods are chosen to minimize multiple competing biases present from the absence of stationarity in air pollution time series. Researchers have found that reference periods are best taken the same day of the week, hour of the day, and month as the event (Bateson and Schwartz 1999; Greenland 1996; Lumley and Levy 2000; Levy et al. 2001; Navidi 1998).

Temperature is included in the case-crossover analysis to control for effects of heat or cold on OHCA. Apparent temperature—the body's perceived temperature—is calculated from temperature and dew point (Steadman 1979) and is often used over temperature alone. The effect of temperature or apparent temperature on OHCA may be nonlinear depending upon the temperature range in the study area (Baus and Samet 2002; Braga et al. 2001; Curriero et al. 2002; Stafoggia et al. 2006). In a case-crossover analysis of air pollution and OHCA in New York City (Silverman et al. 2010), immediate and delayed nonlinear temperature effects were found and adjusted using natural cubic splines of the same-day and the average of the past three days' apparent temperature. Alternatively, in a similar study conducted in Melbourne (Dennekamp et al. 2010), temperature effects were found to be linear.

Conditional logistic regression is used and a linear exposure-effect model is assumed. The relative risk and 95% confidence intervals from lags of daily or hourly concentrations are estimated usually for a concentration change equivalent to the interquartile range where lag 0 day refers to the day of the event, while a lag 1 day is the day before the event, etc. To check the validity of the linear exposure-effect assumption, lag estimates of effect are found by quartile of pollution for a given lag and by using regression spline smoothers of one and three knots (Levy et al. 2001). If the effect is linear it should be constant across quartiles.

Cardiac hospital admissions and daily mortality statistics are often used in these case-crossover studies. These health statistics are available as daily counts. The weakness of daily counts is that more transient effects (hours to minutes) cannot be assessed. In addition, there is unknown error in results for lag 0, defined as the day of the event, because the researcher cannot rule out that the time of the cardiac arrest may have preceded most of the exposure (Levy et al. 2001). Some studies use emergency medical service (EMS) health data. The EMS data, in which the 911 call time acts as the time of the OHCA, provides the ability for a more refined analysis on the hourly, as opposed to daily, scale. The hourly scale of both the health event and the pollution concentration enable an analysis of ambient concentration standards of less than a day. However, since both cardiac arrest and pollutant data may have diurnal patterns, temporal confounding must be considered (Silverman et al. 2010).

Some researchers extend their full analysis into a subset by season: warm or cold. This is conducted to better understand if effects are more extreme in a given season as a consequence of changes in the pollution profile by season. For example, ozone is higher in the warmer months, and PM2.5 concentrations and chemical composition may vary by season. In addition, exposure patterns (e.g., time spent outdoors) could vary by season. Researchers also generally explore the pollution and OHCA association by gender and age, and some have examined presenting heart rhythm or pre-existing co-morbidities.

Pollution data are obtained from ambient air monitors used to measure hourly concentrations. The most accurate measurements will be those analyzed using an EPA analytical reference method. If multiple monitors are available, the majority of researchers average the concentrations across the monitors to obtain one pollution level (Ensor et al. 2012; Levy et al. 2001; Silverman et al. 2010). Because there can be spatial variability in both PM2.5 and ozone concentrations, the average concentration is more representative of the general pollution in the area than data from a single monitor.

Case-Crossover Method vs. the Alternative

The case-crossover method is an alternative to Poisson or Extended Cox traditional time-series regression models used to assess the short-term effects of air pollution. The methods have produced almost identical results (Tsai et al. 2003; Peters et al. 2006). For example, in a reanalysis that compared the two methods, Neas et al. (1999) confirmed the association between total suspended particulate pollution and daily mortality in Philadelphia, Pennsylvania, using a Poisson regression analysis with case-crossover analysis.

The weaknesses of the regression analyses are that they are more sophisticated and require more investigator decisions than the case-crossover approach. For example, the regression requires the adequate controlling for confounding from trends of pollution by time and season. Typically, non-parametric smoothing functions of time are used to model and control seasonality. The smoothing functions, used to fit each model term, are sensitive to the degrees of freedom determined by the investigator. Generally Poisson regression requires knowledge of the size of

the population at risk. This parameter enters the regression analysis through the offset term. The assumption of a constant, and thereby unnecessary, offset is reasonable if the population at risk is very large relative to the daily number of events and the size and makeup of the population at risk does not vary with the exposure of interest. If, for example, the susceptible portion of the total population at risk increases over time from multiple exposures or decreases over time from harvesting, the assumption that the risk does not vary with the exposure would not be met (Neas et al. 1999). In addition, the researcher must be aware of and incorporate in the model, or remove from consideration, periods of anomalous events (e.g., sickness, natural disaster, power outage). For studies with a large number of cases, anomalous events should have little to no impact on the results, but the potential impact of the outliers should be considered.

The strength of the case-crossover method is that, in contrast with traditional time series models, confounding is controlled by design rather than by modeling, thereby obviating the need for sophisticated modeling. Time-invariant and subject-specific variables are not confounders. Because the subjects serve as their own control, the size of the population at risk is not an issue. The pollution reference periods are chosen so that times of day, day of week, seasonality, or longer term pollution trends are not possible confounding factors.

One weakness of the case-crossover design compared to Poisson regression is that the case-crossover has lower statistical power (Neas et al. 1999). In a comparison of methods conducted by Neas et al. (1999), larger standard errors were found using case-crossover compared with Poisson regression. In their application in New York City, Silverman et al. (2010) explain that the risk estimates from case-crossover were less significant than those found from time series analysis because the case-crossover method effectively used 12 degrees of freedom/year while the times series used 7 degrees of freedom/year. Another weakness of the case-crossover method compared to the Poisson regression model is that times series accounts for over dispersion of the Poisson variance while the case-crossover analyses typically do not (Lu and Zeger 2007). Finally, Peters et al. (2006) feels that the Poisson regression may be preferred simply because it is less time consuming.

Researchers have moved from viewing time series and case-crossover models as competing methods to application of the models in tandem to verify and validate findings. Many researchers avoid discussion of weakness in their results from using one model over another by applying both (e.g., Dennenkamp et al. 2010; Silverman et al. 2010).

Key Components of Qualifying Studies

For use in the present work, the strongest evidence would come from studies that incorporate key components of the state-of-the-science in the design and analysis. The key components drawn from the literature described above are summarized into eight items in Table 1.

Table 1. Key Components of Qualifying Studies

1. Number of cases	Studies contain a large number of cases to increase the statistical power of the analysis.
2. Referent selection	Referents are selected on same day of the week (and hour of the day, if appropriate) and month as the event to minimize bias.
3. Temperature control	Temperature is controlled and the temperature effect relationship investigated to allow nonlinear modeling, if appropriate.
4. Health data	The health endpoint is out-of-hospital-cardiac arrest.
5. Pollution data analysis	The analytical method to determine the pollution concentration for PM2.5 and ozone is an EPA federal reference method to ensure high-quality analytical results.
6. Pollution data spatial coverage	Pollution data is available on an hourly scale from multiple monitors to ensure the ambient exposure concentration is representative of the area.
7. Validation of results	The case-crossover result is verified using time series modeling.
8. Study populations	The study population is representative of the population of individuals that have experienced an OHCA in that area.

Studies that Examine the Link

Case-crossover studies that looked specifically at the association between PM2.5 and ozone and OHCA were found by searching PubMed and Google Scholar for the following key words in the title and/or abstract: (1) ozone, O3, air pollution, fine particulate, or PM2.5, (2) case cross over, case cross-over, case-crossover (3) out-of-hospital cardiac arrest. While there are numerous studies that use a different statistical analysis method or examine PM2.5 and/or ozone

association with hospital admissions, overall mortality, or cardiac mortality (Bell et al. 2004; Guo et al. 2010; Ito et al. 2005; Ji et al. 2011; Lee et al. 1999; Moore et al. 2010; Neas et al. 1999; Xu et al. 2008), we focused only on those that best fit the criteria identified for this study and were conducted in the last 15 years. This search resulted in seven studies that were most applicable according to the key components listed in Table 1. These studies and their qualifying components are listed in Table 2. There are two case-crossover studies, Peter et al. (2001) and Stafoggia et al. (2010), that while not explicitly included in Table 2, provide valuable supporting information and warrant mention in the discussion.

Table 2. Qualifying Case-Crossover Studies and Key Components

Study Title, Author, Location, Pollutant	Presence of Key Components								
	1	2	3	4	5	6	7	8	Total
A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Levy, D., L. Sheppard, et al.; Seattle and King County, WA (**PM2.5**)		√		√		√			3
Exposure to ambient fine particulate matter and primary cardiac arrest among persons with and without clinically recognized heart disease. Sullivan, J., N. Ishikawa, et al.; Seattle, WA (**PM2.5**)	√	√	√	√		√			5
A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. Forastiere, F., M. Stafoggia, S. Picciotto, et al. (**ozone**)	√	√		√				√	4
Out-of-hospital cardiac arrest and airborne fine particulate matter: a case-crossover analysis of emergency medical services data in Indianapolis, IN. Rosenthal, F.S., J.P. Carney, M.L. Olinger (**PM2.5**)	√	√	√	√	√			√	6
Association of ambient fine particles with out-of-hospital cardiac arrests in New York City. Silverman, R.A., Ito, K., Freese, J., et al. (**PM2.5 and ozone**)	√	√	√	√	√	√	√	√	8
Outdoor air pollution as a trigger for out-of-hospital cardiac arrests. Dennekamp, M., Akram, M., Abramson, M.J., et al.; Melbourne, Australia (**PM2.5 and ozone**)	√	√	√	√	√*		√	√	7
A case-crossover analysis of out-of-hospital arrest and air pollution in Ensor, K., Raun, L., Persse, D.; Houston, TX (**PM2.5 and ozone**)	√	√	√	√	√	√	√	√	8

*refers to PM2.5 method

Study Descriptions

Table 3 lists a summary of the study details. The <u>number of cases</u> of OHCA examined in the studies ranges from 362 to 11,677. Overall, there has been an increasing trend in the number of cases included in studies over time.

All studies included the preferred <u>referent selection</u>. In addition, all studies controlled for ambient <u>temperature</u> or apparent temperature and all studies except, possibly, Levy et al. (2001) and Forastiere et al. (2005) allowed for nonlinear modeling of temperature, if appropriate. The methods used to incorporate temperature in the model in the Levy et al. (2001) and Forastiere et al. (2005) studies are unknown.

The <u>health endpoint</u> of interest for this analysis, OHCA, is the endpoint identified by Rosenthal et al. (2008), Silverman et al. (2010), Dennekamp et al. (2010), and Ensor et al. (2012). Levy et al. (2001), and Sullivan et al. (2003) report an endpoint of primary cardiac arrest, which is interpreted here as OHCA. The word "primary" is usually used to indicate there is no other suspected cause (e.g., trauma, drugs, or environmental factors). Finally, Forastiere et al. (2005) reports an endpoint of out-of-hospital cardiac death. While this endpoint does not completely encompass all OHCA events, it can be argued that it is likely representative because the majority of those experiencing an OHCA do not survive.

Studies will be most comparable if the PM2.5 and ozone <u>pollution samples</u> are analyzed using an EPA federal reference method or equivalent. An EPA federal reference method is a method explicitly specified using a combination of design-and performance-based criteria. Approval as an equivalent method is based on the degree of similarity to the reference method and reference method specification. All studies that analyzed PM2.5 except two, Levy et al. (2001) and Sullivan et al. (2003), used an EPA reference method. These two studies used a different method, nephelometry, to estimate the PM2.5 fraction. The quality of the measurements obtained from nephelometry as a proxy for estimation of PM2.5 does not meet the standards of measurement set by EPA reference method. Of the studies that analyzed ozone, the methods used in the study

by Forastiere et al. (2005) and Dennekamp et al. (2010) are not reported; the other studies used EPA reference methods.

The number of monitor locations used in the studies ranges from one to 33 for PM2.5 and one to 47 for ozone. The larger the study location or the more variable the concentration in the area, the more monitors are needed; however, most studies that used only one location consider the small number a possible limitation of their research regardless of spatial coverage needs or variability (e.g., Dennekamp et al. 2010). Rosenthal et al. (2008), Forastiere et al. (2005), and Dennekamp et al. (2010) relied on one location. Rosenthal et al. (2008) reported that the surrounding monitors were correlated to the extent that one monitor was representative. Levy et al. (2001) and Sullivan et al. (2003) relied on three locations. Silverman et al. (2010) relied on 33 ozone and 16 PM2.5 monitors while Ensor et al. (2012) relied on 47 ozone and 12 PM2.5 monitors.

The validation of case-crossover results with the Poisson time series method was reported by Silverman et al. (2010), Dennekamp et al. (2010), and Ensor et al. (2012).

The study population of interest for the purposes of the present analysis is the general population that experiences an OHCA that is not trauma related. The study population for Levy et al. (2001) is more limited and possibly not as representative of the overall population, which would include sensitive subgroups, because it excludes those with a life threatening co-morbidities or clinically recognized heart disease. Those who belonged to a health maintenance organization made up the study population for Sullivan et al. (2003). Because this choice limited the population to those who were insured, this population may not have been representative of the overall population. Rosenthal et al. (2008), Silverman et al. (2010), and Ensor et al. (2012) used Emergency Medical Service 911 call databases, and therefore the population was limited to the portion of cases that used this service. The other studies relied on medical records.

All studies stratified by some age grouping and all but Levy et al. (2001) stratified by gender. The next most common stratification parameters include pre-existing condition (Levy et al. 2001; Sullivan et al. 2003; and Forastiere et al. 2005) and race (Levy et al. 2001; Sullivan et al. 2003; and Ensor et al. 2012), followed by warm versus cold season (Silverman et al. 2010 and

Ensor et al. 2012). In order to conduct an analysis on an association with pollution on the hourly level, Rosenthal et al. (2008) subset the OHCA event dataset into only those events that were witnessed.

Table 3. Study Descriptions

	Seattle & King County, WA	Seattle & King County, WA	Rome, Italy	Indianapolis, IN	New York, NY	Melbourne, AUS	Houston, TX
Time Frame	Oct. 1988 to July 1994	1985 to 1994	1998 to 2000	July 2002 to July 2006	2002-2006	2003 to 2006	2004 to 2011
Authors	Levy et al.	Sullivan et al.	Forastiere et al.	Rosenthal et al.	Silverman et al.	Dennekamp et al.	Ensor et al.
No. of Cases	362	1,206	5,144	1,374	8,216	8,434	11,677
Referent Selection	All studies used preferred referent selection same day of week (and or hour) within a month of the event						
Method to Control for Temperature	Ambient temp.; unknown	Ambient temp.; linear and quadratic	Apparent temp. of day of event and day 1-3 before; unknown	Ambient temp.; two-segment linear model	Apparent temp.; natural cubic	Ambient temp; linear functional form (GAM)	Apparent temp.; natural cubic
Endpoint	Primary Cardiac Arrest	Primary Cardiac Arrest	OHCA Death	OHCA	OHCA	OHCA	OHCA
Monitors	3	3	1	1	33 PM2.5, 16 Ozone	1	12 PM2.5, 47 ozone
Study Population	No pre-existing cardiac condition or life threatening disease	HMO members	No pre-existing cardiac condition, age 35 and older	911 EMS data	Assumed primary cardiac arrest, 911 EMS data	Age 35 and older	Age 18 and older, 911 EMS data
Stratification	Age; season; pre-existing condition; smoking; physical activity; alcohol; aspirin use; time of day	Gender; race; pre-existing condition; smoking	Age; gender; pre-existing condition	Age; gender; race; heart rhythm; witnessed	Age; gender; season	Age; gender	Age; gender; race; season

Study Findings and Comments

The seven studies either implemented single lag models or, in a few cases, a constrained distributed lag model consisting of an average over two days. The single lag models provide an estimate of a relative risk for increase in pollution levels equivalent to the interquartile range (IQR) of the pollutant during the stated lag period. The constrained distributed lag models provide an estimate of the cumulative effect over more than one lag. Table 4 and 5 list the increase in risk from the main result for each study from single and/or constrained distributed lags by IQR of concentration used in the study location for PM2.5 and ozone, respectively. Because different locations used different IQRs, the odds ratios in the table are not directly comparable.

Levy et al. (2000) conducted a case-crossover analysis of particulate matter and OHCA and found a null result (e.g., no effect). However, there were several aspects to the study that do not meet the criteria of strong evidence for use in the present analysis. The study by Levy et al. (2001), used nephelometry to measure fine particulate; nephelometry is not an EPA reference method for measuring fine particulates. In addition, it was unclear how temperature was included in the logistic regression and there was not an alternative statistical validation. Finally, the small number of cases (n=362) may have resulted in low statistical power. Ozone was not investigated.

Following Levy et al. (2000), the next case-crossover analysis investigating the OHCA and particulate association was conducted by Sullivan et al. (2002). This investigation also found null results, except for a subgroup of smokers with preexisting heart disease. While this study had more cases (n=1206) than the previous study and controlled for temperature with accommodation for nonlinearity, it also did not use an EPA reference method (nephelometry) to measure PM2.5 or include an alternative statistical validation. In addition, the study subjects consisted of members of a health maintenance organization (HMO) and may not be generalizable to the population at risk for OHCA. Known risk factors for heart disease are low income, low education populations and African American ethnicity (Roger et al. 2011). Only 6% of the cases were of African American ethnicity and low income groups may not have insurance and may not be represented in an HMO. Again, ozone was not investigated.

In 2005, Forastiere et al. (2005) published a case-crossover analysis (n=5144) showing a statistically significant association between OHCA and ultrafine and coarse particulate air pollution in Italy. This study did not assess fine particulate pollution. However, the results provide evidence of the likelihood there is an effect at the PM2.5 range since a significant effect was found at the lower and higher range than PM2.5. This study did investigate ozone but only during the warm season; they did not find a significant association.

Rosenthal et al. (2008) conducted a case-crossover analysis to explore the association between OHCA and fine particulate matter and if risk was dependent on subject characteristics or pre-existing heart rhythm. This study, based on EMS data (n=1374), was the first to look at hourly association of pollution and OHCA. The study found a null result overall, except for a subgroup of OHCA witnessed by bystanders (n=511). For this witness group, OHCA risk significantly increased with a 10 μg/m^3 increase in PM2.5 exposure during the hour of the event.

As summarized in Table 2, the three most recent studies, Silverman et al. (2010), Dennekamp et al. (2010), and Ensor et al. (2012), had the strongest evidence because they incorporate the most key components of the state-of-the-science in the design and analysis.

Silverman et al. (2010) conducted a case-crossover analysis of air pollution and OHCA (n=8216) and found an increase of 10.0 μg/m^3 in PM2.5 over two days (average of lag 0 and 1) was associated with an increase in OHCA risk of 4% (95% CI -1 to 8). During the warm season, the case-crossover analysis yielded a result of stronger effect; an increase of 10.0 μg/m^3 in PM2.5 over two days (average of lag 0 and 1) in the warm season was associated with an increase in OHCA risk of 8% (95% CI 2 to 15). They did not find a difference in risk between men and women and between age groups. Ozone was not found to be significant using case-crossover analysis and was not explicitly reported in the paper; however, an estimate of the Poisson time-series design results indicates that there was an increase in OHCA risk of 5% (95% CI -1 to 11) per 22 ppb ozone using the eight-hour average daily maximum for the average of 0-1 day lagged.

Dennekamp et al. (2010) conducted a case-crossover analysis of air pollution and OHCA (n=8434) and found an increase of 4.26 μg/m^3 in PM2.5 over two days (average of lag 0 and 1)

was associated with an increase of OHCA risk of 3.6% (95% CI 1.3 to 6.0). While the two-day distributed lag model was the strongest effect, significant effects were also found at the single lag models: day of the event (2.44%, 95% CI 0.54 to 4.37) and previous day (2.46%, 95% CI 0.33 to 4.65). The study did not find an effect for longer lags of PM2.5 or for any lag of ozone. Men were found to be more susceptible than women, and the largest effect was seen in age group 65-74.

Ensor et al. (2012) conducted a case-crossover analysis of air pollution and OHCA (n=11,677) and found an increase of 6 μg/m^3 in PM2.5 over two days (average of lag 1 and 2) was associated with an increase of OHCA risk of 4.6% (95% CI 1.2 to 8.2). While the two day average lag was the strongest effect, significant effects were also found for the previous day 3.5% (95% CI 0.5 to 6.6) and two days prior 3.7% (95% CI 0.7 to 6.8). The study did not find an effect on OHCA rates for PM2.5 levels more than two days out. The study also found an increase of 20 ppb ozone for the eight-hour average daily maximum was associated with an increased risk of OHCA on the day of the event, and the 20 ppb ozone increase was associated with an increase of OHCA on the previous one, two, and three hours before the event: day of event 3.8% (95% CI 0.4 to 7.2); one hour prior 4.2% (95% CI 0.4 to 8.2); two hours before 4.6% (95% CI 0.8 to 8.7); three hours before 4.0% (95% CI 0.2 to 8.0). This was the first study to find a significant effect with respect to ozone. The study acknowledges the potential confounding from OHCA time of day with ozone time of day since OHCAs are known to have an hourly pattern (e.g., peaking in the morning). However, the significance seen on the day of the event (lag 0) is indicative that the hour result is not simply picking up on the OHCA hourly pattern.

Table 4. PM2.5 Study Findings

	Seattle and King County, WA	Seattle and King County, WA	Indianapolis, IN	New York, NY	Melbourne, AUS	Houston, TX
Time Frame	October 1988 to July 1994	1985 to 1994	July 2002 to July 2006	2002 to 2006	2003 to 2006	2004 to 2011
Authors	Levy et al.	Sullivan et al.	Rosenthal et al.	Silverman et al.	Dennekamp et al.	Ensor et al.
No. of Cases	362	1,206	1,374	8,216	8,434	11,677
$PM_{2.5}$ % Change (95% CI) ($\mu g/m^3$)	-10.7 (-22.1 to 2.4)	-6 (-12 to 2)	2 (-6 to 11)	4 (-1 to 8)	3.61 (1.29 to 5.99)	3.5 (.5 to 6.6)
			12 (1 to 25)		2.44 (.54 to 4.37)	
$PM_{2.5}$ Metric	Daily average (24-hr avg.)	Daily average (24-hr avg.)	Daily average	Daily average	Daily average	Daily average
			Hour			
IQR at Location	Nephelometry (.51 X 10^{-1} $km^{-1}b_{sp}$)	13.8 $\mu g/m^3$ based on Nephelometry (.54 X 10^{-1} $km^{-1}b_{sp}$)	10 $\mu g/m^3$	10 $\mu g/m^3$	4.26 $\mu g/m^3$	6 $\mu g/m^3$
Lag	1 (day)	1 (day)	0 (day)	0 to 1 (day)	0 to 1 (day) / 0 (day)	1 (day)

Table 5. Ozone Study Findings

	Rome, Italy	New York, NY	Melbourne, AUS	Houston, TX
Time Frame	1998 to 2000	2002 to 2006	2003 to 2006	2004 to 2011
Authors	Forastiere et al.	Silverman et al.	Dennekamp et al.	Ensor et al.
No. of Cases	5,144	8,216	8,434	11,677
O_3 % Change (95% CI) (ppb)	-1 (-12.5 to 12)	5 (-1 to 11) (estimated from time-series design) not statistically significant	2.94 (-2.42 to 8.59)	3.8 (.4 to 7.2)
			3.78 (-1.32 to 9.14)	4.6 (.8 to 8.7)
Ozone Metric	Daily average (Apr-Sep)	Daily average	Daily average	8 hour daily max
				Hour
IQR at Location	71.4 $\mu g/m^3$ (Apr-Sep) 35.7 ppb	22 ppb	8.02 ppb	20 ppb
Lag	0 (day)	0 to 1	0 to 1 (day) / 0 (day)	0 (day) / 2 (hr)

The Link is Established

The odds ratio of increased risk of OHCA associated with an increase of 10 $\mu g/m^3$ daily average PM2.5 on the day, day before, or the average of the day of OHCA onset and the day before onset are presented in Figure 1 for four of the six studies examining the relationship. The results shown in the figure have been scaled from the IQR of the pollution in the study location to an equivalent

IQR, 10 μg/m³ of PM2.5, for comparison between studies. The IQR of the PM2.5 in the study location is noted in the figure.

The two studies not included in the plot, Levy et al. (2001) and Sullivan et al. (2003), are different from the other four because they did not use an EPA reference method to measure PM2.5 and are therefore not directly comparable. These two studies both found a null result (i.e., no association). The authors speculate that low statistical power may be an issue given that the number of cases was small (n= 362 and 1206). Equally important, the null results these studies found may be due to the composition of the particulate in the study area, both in Seattle. Seattle particulate is relatively sparse in transition metals and sulfites and is dominated by wood smoke. There is growing evidence that the composition of particulates is an important consideration when studying the health impact (Franklin et al. 2008; De Hartog et al. 2009).

As depicted in Figure 1, statistically significant effects are found with an increasing number of cases. While the study of the association in New York City (Silverman et al. 2010) is not quite significant at an increased risk of 4.5% (95% CI -.9 to 10) for a daily average increase of 10 μg/m³, the point estimate is in line with those in Melbourne (Dennekmap et al. 2010) and Houston (Ensor et al. 2012).

Taken as a whole, results from studies that had more than 8,000 cases support the likelihood that there is an increased risk of OHCA of perhaps 2% to 9% associated with 10 μg/m³ daily average increase of PM2.5 on the day before, the day of, or the average of the day before and the day of the OHCA onset.

The study of Indianapolis (Rosenthal et al. 2008) also found an association of OHCA and hourly PM2.5 for OHCA that were witnessed of 12% (CI 1 to 25). This is shown as the last study on Figure 1. While this is the first case-crossover study on OHCA to find an association on the hourly scale, the results are supported by a case-crossover on a different cardiac endpoint. Peters et al. (2001) examined the association of increased particulate air pollution and the triggering of myocardial infarction. This study with a rather small number of cases (n=772) by Peters et al. (2001) found a significant increase in relative risk with an increase in PM2.5 concentration and

found no effect for ozone. The unique finding of the study by Peters et al. (2001) was that the association with PM2.5 was found at both the 24-hour average lag exposure time scale and the hourly exposure time scale (two hours). The vast majority of cardiac and PM2.5 association research has been focused on the daily scale only. The Peters et al. (2001) study, while not a perfect match with respect to health endpoint, is similar enough to be considered as supporting evidence of possibly more transient (hourly) time scale effects of PM2.5 air pollution on OHCA as seen by Rosenthal et al. (2008).

Figure 1. Forest plot of city-specific odds ratios of OHCA associated with a 10 μg/m^3 daily average increase in PM2.5
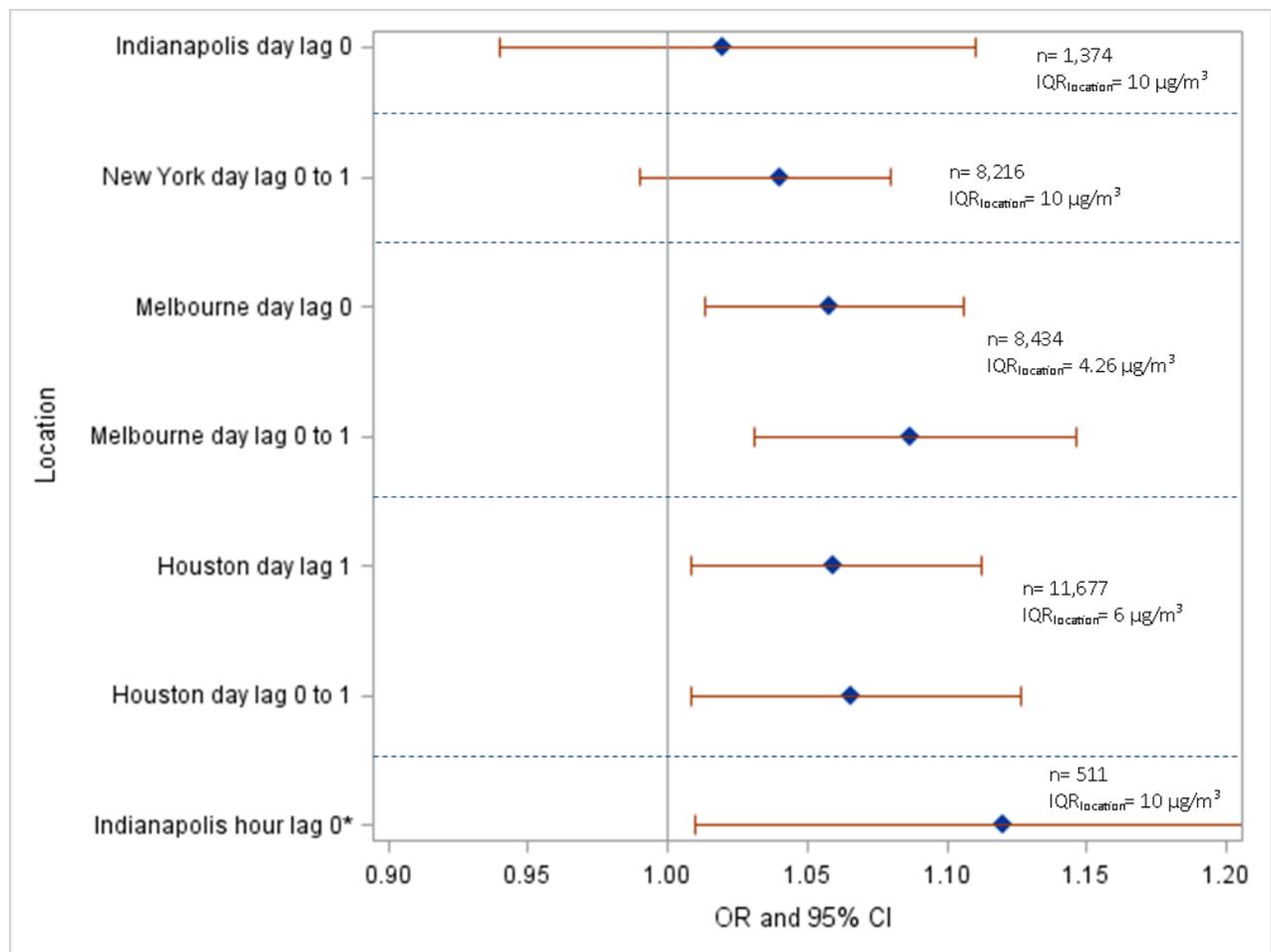
*hourly scale, witnessed OHCA

Figure 2 presents the odds ratio of four studies examining the increased risk of OHCA associated with an increase of 20 ppb in the daily average of ozone for various day lags (single lags 0,1,2

and/or average of 0-1 lag) and hour lags (0,1,2). Similar to the scaling of PM2.5 results, the results shown in Figure 2 have been scaled from the IQR of the study location to an equivalent IQR, 20 ppb of ozone, for comparison across studies. As before, the IQR of the ozone in the study location is noted in the figure.

While the evidence in the figure regarding the association between ozone air pollution and OHCA events is inconsistent, a closer examination of the comparability of the studies is warranted.

The first study shown in Figure 2 of Rome (Forastiere et al. 2005) indicates a null result, or no association between OHCA and ozone. This study may not be as representative as some of the other studies for several reasons. First, the event size is smaller than the other studies; the study of Rome was based on 5144 events, while there were 8216, 8434, and 11677 events used in the studies in New York, Melbourne, and Houston, respectively. In addition, the ozone exposure concentration in the Rome study was based on one monitor and the analytical method used to quantify the ozone concentration was not reported (i.e., EPA reference method); the studies in New York and Houston were based on data analyzed using an EPA reference method and the exposure concentration metric represented data from a network of monitors—16 and 47 respectively—instead of a single location. Finally, the health endpoint is not specifically OHCA but out-of-hospital coronary death.

The Melbourne study focused on OHCA as an endpoint and also was based on a large number of cases. However, as in the Rome study, the Melbourne study used only one monitor location and no ozone analytical method was reported. The potential for a larger uncertainty with the exposure concentration defined by one location, coupled with the fact that the ozone pollution in Melbourne is both the lowest in magnitude and variation (has the smallest IQR), also renders the study of Melbourne less directly comparable to the study of New York City and Houston. Box plots of ozone concentrations, reconstructed or estimated from the publications, and monthly average temperature of the study location are shown in Figure 3.

Overall, the studies of New York City and Houston are most comparable. They both have a large number of cases extracted from an EMS 911 database, limited exposure concentration uncertainty, and similar ozone IQR. The only obvious difference, besides the larger number of cases in the study of Houston, is the difference in climate. Except that the results of New York City are not significant at the 95% confidence level—4.5 (-0.9 to 10) for a daily average increase of 20 ppb—the point estimate of the association between OHCA and ozone in New York is approximately the same as that found to be statistically significant in Houston (Ensor et al. 2012): as much as a 4% increased risk of OHCA with a daily or eight-hour running maximum average daily increase of 20 ppb ozone on the day or average of day and day before the onset of the OHCA.

The results found in New York City and Houston are consistent with findings from an important case-crossover study with a more encompassing health endpoint. Stafoggia et al. (2010) examined susceptibility factors to ozone mortality. Of interest to our objective is their examination of ozone-related mortality in those with preexisting cardiovascular conditions. The researchers estimated a 5.1% (95% CI 0.65 to 19.45) increase in mortality for a 20 ppb increase in the daily eight-hour ozone running maximum average.

Given the comparability between the studies of Houston and New York City and the corroborating study by Stagoggia et al. (2010), current results of the comparable studies support the likelihood that there is an increased risk of OHCA of a range of 1% to 8% associated with a daily eight-hour maximum increase of 20 ppb on the day, or the average of the day of OHCA onset and the day before onset.

As noted previously, the study of Houston (Ensor et al. 2012) also found an hourly association of OHCA and ozone (e.g., 4.6% increase, 95% CI 0.8 to 8.7) at hour lag two. This is the first case-crossover study of OHCA to find an association with ozone on the hourly scale.
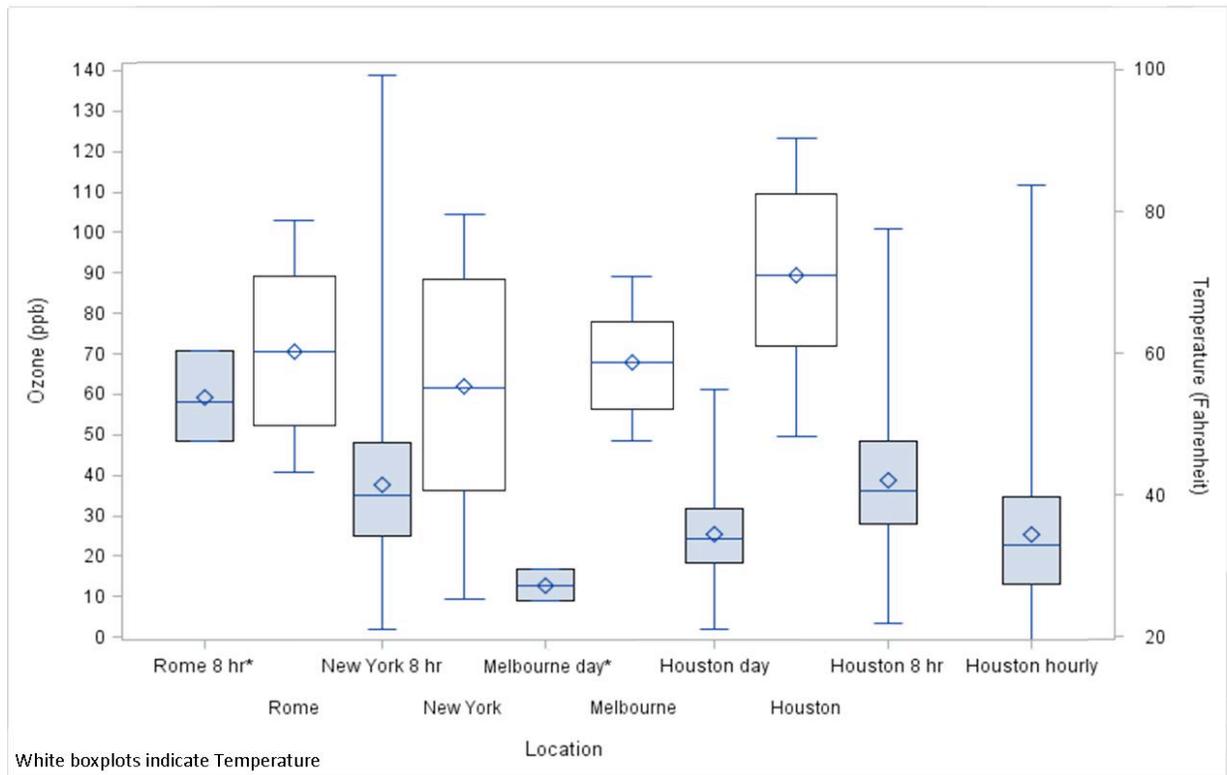
Figure 2. Forest plot of city-specific odds ratios of OHCA associated with a 20 ppb daily average increase in ozone
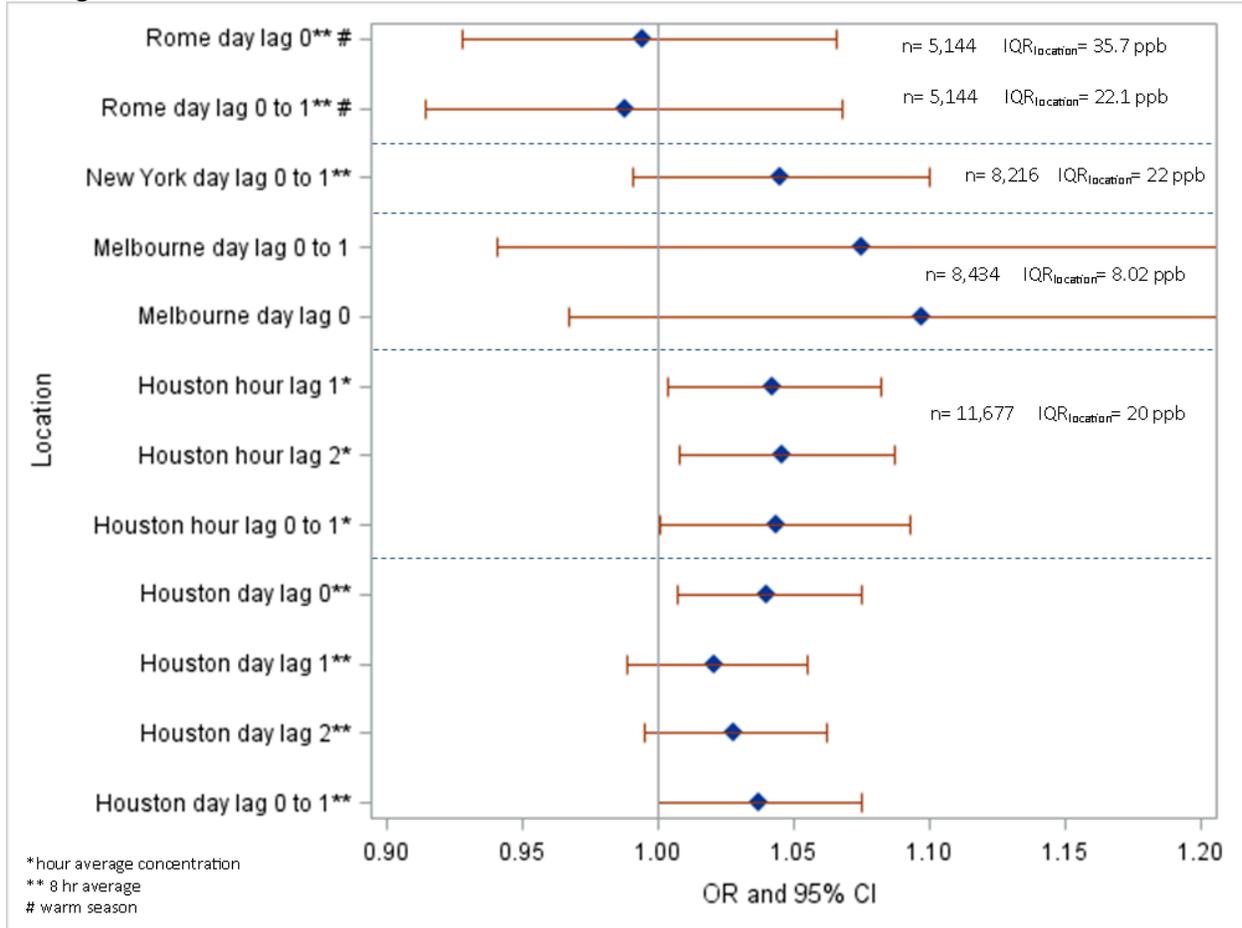
Figure 3. Box plots of city-specific ozone concentrations and monthly average temperature

*The analytical method used to measure ozone concentrations in Rome and Melbourne was not reported. Note: Concentrations are reconstructed or estimated from those reported in the publications.

Are the Standards Protective?

The case-crossover analysis research discussed above indicates that there is evidence of an increased risk of OHCA of approximately

- 2% to 9% associated with a 10 μg/m^3 increase of the daily average PM2.5 on the day before, the day of, or the average of the day before and day of the OHCA onset as well as some evidence of risk on an hourly scale; and
- 1% to 8% associated with a daily or daily eight-hour running average maximum increase of 20 ppb ozone on the day, or average of day and day before the onset of the OHCA, and also some evidence of risk on an hourly scale.

While there are many possible methods to evaluate if the EPA standards of these pollutants are protective (i.e., dose or concentration response curves), a logical way to evaluate the standards in this study is to use the same data and approach that initially identified the risk.

Using the Houston study data, we conduct a case-crossover analysis identical to the initial research examining the association of OHCA and exposure to PM2.5 and exposure to ozone; however, we remove the OHCA events from the analysis where the concentration on the day of the event was above the respective standards. Then we compare the increased risk from the initial research and the risk from the analysis where days above the standard are eliminated and see if the risk changes and by how much. If the hypothetical dataset where only concentrations below the standard occur results in no increased risk, we deem the standard protective for OHCA.

The current (as of June 2012) National Ambient Air Quality Standard (NAAQS) for PM2.5 is two-pronged; to protect against short-term effects, the 24-hour average must not exceed 35 $\mu g/m^3$ and to protect against long-term effects, the annual average must be less than 15 $\mu g/m^3$.

The current (as of June 2012) NAAQS for ozone is an eight-hour maximum of 75 ppb of the 24 possible running eight-hour average concentrations for each day.

The focus of this research is on short-term health effects; therefore, only the PM2.5 24-hour average standard of 35 $\mu g/m^3$ and the ozone daily eight-hour average maximum of 75 ppb are of interest. After removing all events (and referents) from the data set where the PM2.5 concentration was 35 $\mu g/m^3$ or above, the increased risk associated with OHCA and PM2.5 remained 3.4% (95 CI 0.4 to 6.5) (see Figure 4). In fact, there were only two events that were eliminated from the original dataset because they exceeded the standard. Based on this analysis, the 35 $\mu g/m^3$ standard is not effective at protecting the public with respect to OHCA triggered from exposure to PM2.5. The increased risk of OHCA from exposure to PM2.5 is occurring at levels lower than the standard.

On the other hand, after removing all events (and referents) from the data set where the ozone concentrations were above the daily eight-hour maximum of 75 ppb, the results drastically changed, and there was no statistically significant risk of OHCA associated with ozone at any short-term metric: daily eight-hour maximum running average and one- or two-hour average (Figure 4). In this case, there were 139 events that were eliminated from the original dataset because they exceeded the standard. This fraction of events eliminated would not substantially reduce the statistical power of the analysis. The ozone standard appears to be effective at protecting the public with respect to OHCA triggered from exposure to ozone.

Figure 4. Forest plot of increased risk of OHCA associated concentrations of PM2.5 and ozone comparing cases of those observed in Houston from 2004 to 2011, and a hypothetical database of those during this time frame with only events where the concentration was below the standard.
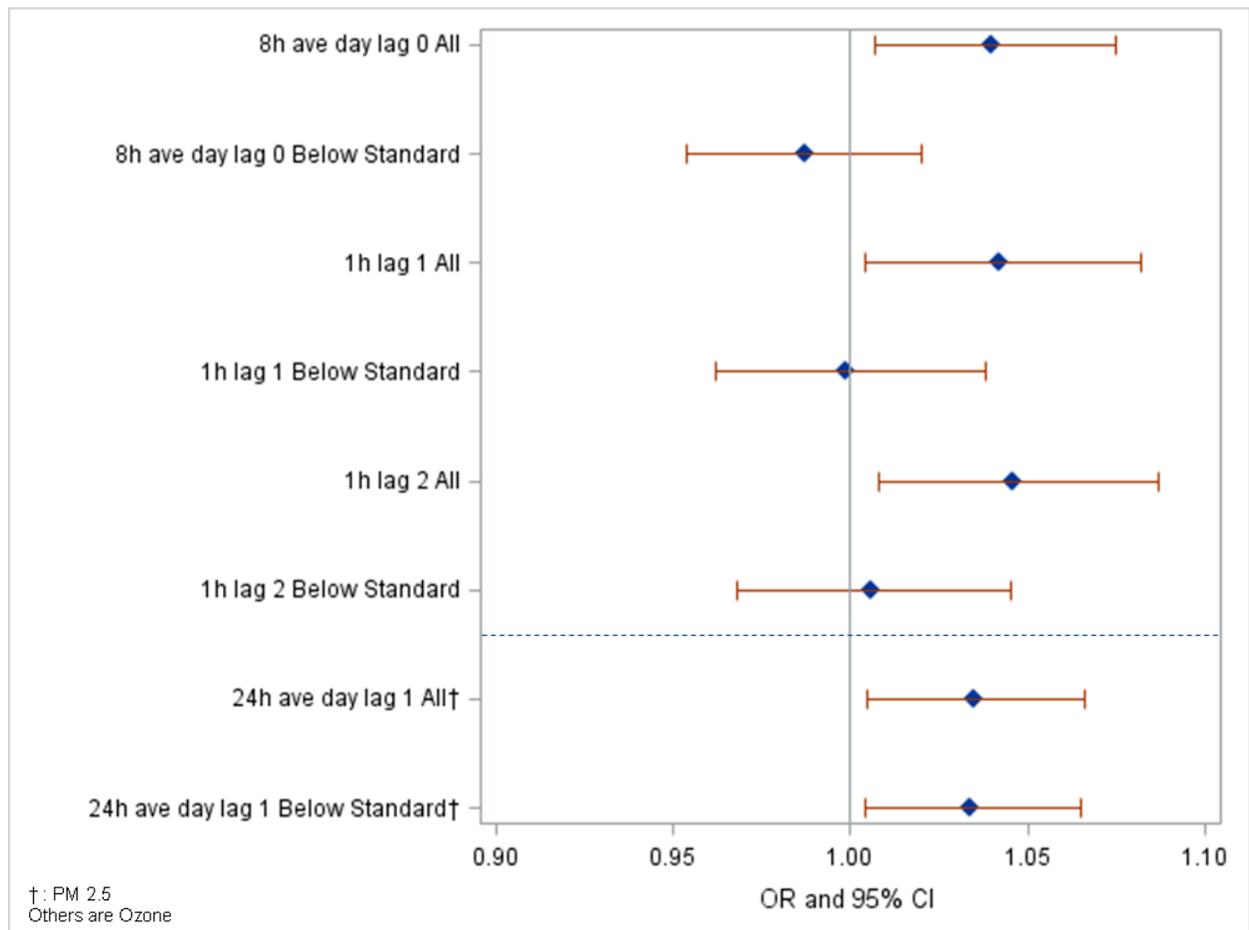
Conclusion

The seven studies identified for review occurred within the last 15 years, addressed out-of-hospital cardiac arrest as the health endpoint, and considered the ambient pollutants of PM2.5 and ozone. Further, the chosen method of analysis discussed was the case-crossover design coupled with a conditional logistic regression of the resulting case-control events. The case-crossover design allows subjects to serve as their own control and thereby mitigates the impact of confounding subject factors. Several of the seven studies also performed a comparative and/or confirmatory analysis using Poisson time series regression.

The studies vary in the number of cases considered as well as the quality and certainty of the measure of pollution. These factors are discussed extensively in the paper. One of the most critical issues to consider is the quality of the pollution measurements. Another issue with PM2.5 is the composition of the particulate matter limits our comparability, as differential composition has shown differential impact on health outcomes. Studies such as those in New York City and Houston, which rely on a large number of monitors throughout the study region, provide a better representation of the pollution for the region over studies that rely on a single monitor.

In general, there is evidence of a 2% to 9% range of increased risk of OHCA due to increases of 10 μg/m³ daily average PM2.5 levels on a given day, as well as the day before. Further, there is nascent evidence that the impact may be more local in time, namely within an hour of the OHCA. When examining the ozone, we observe an approximate 1% to 10% range of increased risk of OHCA when the maximum daily eight-hour average levels increase 20 ppb ozone on the day and day before the onset of the OHCA. Again, there is evidence of increased risk due to ozone changes at an hour time scale.

A further examination of the data from Houston demonstrates the effectiveness of the ozone standard in protecting the population from an OHCA event triggered from exposure to ozone but a failure of the standard in achieving this goal for PM2.5.

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