TITLE: A SYSTEMATIC REVIEW OF AIR POLLUTION AND INCIDENCE OF OUT-OF-HOSPITAL CARDIAC ARREST

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Abstract

Introduction: Studies have linked air pollution with the incidence of acute coronary artery events and cardiovascular mortality but the association with out of hospital cardiac arrest (OHCA) is less clear.

Aim: To examine association of air pollution with the occurrence of OHCA.

Methods: Electronic bibliographic databases (until February 2013) were searched. Search terms included common air pollutants and OHCA. Studies of patients with implantable cardioverter defibrillators and OHCA not attended by paramedics were excluded. Two independent reviewers (THT and TW) identified potential studies. Methodological quality was assessed by the Newcastle-Ottawa Scale.

Results: Of 849 studies, eight met the selection criteria. Significant associations between particulate matter (PM) exposure (especially $PM_{2.5}$) and OHCA were found in five studies. An increase of OHCA risk ranged from 2.4% to 7.0% per interquartile increase in average PM exposure on the same day and up to 4 days prior to the event. A large study found ozone increased the risk of OHCA within 3 hours prior to the event. The strongest risk (odds ratio) of 3.8% to 4.6% per 20 parts per billion ozone increase of the average level was within 2 hours prior to event. Similarly, another study found an increased risk of 18% within 2 days prior to the event.

Conclusion: Larger studies have suggested an increased risk of OHCA with air pollution exposure from $PM_{2.5}$ and ozone.

Key words: particulate matter; ozone; out-of-hospital cardiac arrest.

Background

Out-of-hospital cardiac arrest (OHCA) is a significant public health issue affecting an estimated 310,000 Americans per year.[1] Whilst OHCA incidence and outcome vary around the globe,[2] case fatality is consistently high, with overall survival to hospital discharge usually less than 10%.[2] Thus, there is an imperative to better understand factors that "trigger" the onset of cardiac arrest.

There is increasing evidence to support the association of ambient air pollution with overall cardiovascular mortality and morbidity.[3-5] Exposure to higher than usual levels of air-borne air pollutants over a few hours to several days has been reported to increase the risk of myocardial infarction,[4] arrhythmia,[6-8] stroke[9-12] and heart failure,[13-16] particularly in susceptible patients.[12-18] Inconsistent results have been found in the relationship between OHCA and air pollution.[3] There has not, however, been a systematic review of these studies and the aim of our paper is to identify, evaluate and summarise the studies of air pollution and OHCA to examine the hypothesis that air pollution is associated with the incidence of OHCA.

Methods

Search strategy

A literature search was performed to identify studies that had analysed the association between OHCA attended by emergency medical services (EMS) and exposure to any air pollutant of interest (see section on Exposure) in any lag period. The following bibliographic databases were searched (by authors THT and TW): MEDLINE (1946-February 2013); Embase (1980–February 2013), CINAHL (1982–February 2013), AUSTHealth (1997–February 2013), and the Cochrane Library (2004–February 2013). Scopus and Biosis Previews were searched for additional environmental science literature. Regional electronic bibliographic databases: Chinese Biomedical Literature Database (CBM), China Knowledge Resource Integrated Database (Cnki), CiNii (Japan), KoreaMed (Korea), IndMED (India), and LILACS (for Latin America and the Carribean) were also examined. Reference lists of relevant review articles and journals were hand-searched, and "Google" and "Google Scholar" search engines were used to search the internet.

Terms were mapped to the appropriate MeSH/EMTREE subject headings and "exploded": ["cardiac arrest" OR "heart arrest" OR "sudden cardiac death"] AND ["air pollution" OR "air

pollutants" OR "particulate matter" OR "airborne particles" OR "fine particles" OR environmental exposure" OR "soot" OR "elemental carbon" OR " carbon monoxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "ozone" OR "sulfur dioxide" OR " sulphur dioxide"] (Appendix 1).

Study selection

Inclusion criteria were comparative studies and articles published in any language in peer-reviewed journals that examined the relationship between air pollution and OHCA in adults and children, including neonates. Exposures from ambient airborne pollutant levels: particulate matter (PM) <2.5μm in aerodynamic diameter ($PM_{2.5}$), PM_{10}, ultrafine particles (UFP), nitrogen oxides (NO_x), ozone, sulphur dioxide (SO_2), and carbon monoxide (CO) were included.

Animal studies, toxicological studies, summaries, commentaries, reviews, case reports, editorials, duplicates and articles only published in abstract form were excluded. Studies of patients with implantable cardioverter defibrillators and OHCA not attended by EMS personnel were also excluded. No time limit on journal publication date was set. Where there were multiple reports related to the same study, the most comprehensive publication was selected for inclusion.

All abstracts and titles were screened by two independent reviewers (THT and TW). Full text articles of studies that met selection criteria were reviewed for eligibility for inclusion in the systematic review. If there was disagreement, arbitration was sought from a third reviewer (JF).

Data extraction

A standardised checklist was used to extract data from studies that met the inclusion criteria. Data collected were: study design, study setting, study population, demographic and baseline characteristics (including age, sex, aetiology, presenting cardiac rhythm if available, and comorbidities), sample sizes, EMS, methodology, exposure (pollutants), exposure levels, number of monitoring sites, effect measurement, control conditions and outcome measurement. Where necessary, further information was sought from the lead authors of the studies by personal communication. The data extraction and risk of bias assessment were done independently by authors, THT and TW.

Risk of bias assessment

The Newcastle-Ottawa Scale[19] was used to assess risk of bias in individual studies. Using the 'star system', each study was evaluated on three broad perspectives: i) selection of the study groups; ii) comparability of the groups; and iii) ascertainment of the exposure or outcome of interest. Study quality was graded as poor (1-3 stars), intermediate (4-6 stars), or high (7-9 stars). Emphasis was placed on the following components: ascertainment of OHCA occurrence (as a measure of outcome measurement); air-quality measurement (as a measure of exposure measurement noting potential exposure misclassification); representativeness of the study sample; and the extent of adjustment for confounders and sensitivity analysis undertaken.

Strategy for data synthesis

Narrative and tabular summaries of study characteristics were presented as guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] The occurrence of OHCA attended by EMS personnel was the primary outcome. Summaries of exposure effects were reported using risk ratio as a measure of effect size. Statistical significance was defined as $p<0.05$. A protocol was prospectively registered online with PROSPERO – an International prospective register of systematic reviews.[21]

Results

Of the 849 studies identified by the systematic search, the following were excluded: 118 (duplicates); 335 (no relevance to the research question); 161 (examined air pollution and all-cause mortality, other cause-specific mortality or hospitalizations or were editorials or case studies); 16 (were related to infant mortality, sudden infant death syndrome, children's and foetal health and not specific to OHCA). Twenty-one citations were considered potentially eligible and full text reports were retrieved. Of these, nine studies that examined the association of ambient air pollution and ventricular arrhythmias detected by implantable cardioverter defibrillators, one study with abstract only, and another study which examined out-of-hospital coronary deaths (ICD 9 codes 410-414)[22] were excluded. Three papers[23-25] described different aspects of the same study, so were considered as one study. Finally eight studies were included in the review (Supplementary Table 1).

Study characteristics

Eight studies examined the association of specific air pollutants with OHCA,[23, 26-32] with a total of 38,060 OHCA cases (range 362[23]-11,677[29]). All were case-crossover studies.[23, 26-32] (Supplementary Table 1). Five studies were conducted in the United States,[23, 26-29] two in Europe (Denmark,[32] Finland[31]) and one in Australia.[30] There were no studies reported from the developing countries. Exposure levels and measurement techniques, study characteristics, EMS systems, sample size and reporting methods varied widely.

Studies examined multiple pollutants, (including UFP,[31, 32] $PM_{2.5,}$[23, 26-29, 31, 32] $PM_{10,}$ [23, 28, 30-32] $PM_{2.5-10,}$[28, 30, 31] CO,[23, 26, 29-32] $N0_x$,[26, 30, 31] $S0_2$[23, 26, 28, 30, 31] and ozone[23, 26, 29-32]), with the exception of Rosenthal (2008)[27] that only examined ambient $PM_{2.5}$ (Table 2).

Four studies[23, 28-30] restricted their study to adults, while four had no age restriction (Appendix 2). Of the OHCA cases, mean age was 65 years, 64.5% were men and none were trauma-related. However the study populations were heterogeneous and ranged from OHCA cases of presumed cardiac aetiology where resuscitation was attempted by paramedics,[26, 29] non-dead on arrival (DOA) cases,[27, 29] and OHCA cases identified from EMS data irrespective of aetiologies,[27, 32] to a selective subpopulation of married residents whose spouses participated in a personal interview.[23] More recent studies [26, 29-32] had larger sample sizes than earlier studies.

Study quality

Six studies[26, 27, 29-32] were graded high quality and two[23, 28] were graded intermediate quality (Appendix 3).

Outcome data

Outcome data were derived mainly from the EMS records of the respective regions studied. OHCA cases were ascertained by reviewing medical records or death certificates,[23, 28, 31] by study physicians[23, 26, 31, 32] or both,[31] or restricted to non-DOA by EMS personnel.[27, 29]

Exposure data

For each study, air pollution from ambient air monitoring sites was used as a proxy for individual exposure. Various methods were used for exposure ascertainment. Three different

methods of particle mass measurement were used in the studies reviewed: nephelometry,[23, 28] beta-attenuation instrument[26, 29, 32] and tapered element oscillating microbalance (TEOM).[27, 30-32] Two studies,[23, 28] used the nephelometry method for estimation of the $PM_{2.5}$ fraction. Wichmann[32] used both TEOM and beta-attenuation instrument to measure exposure levels for $PM_{2.5}$ and $PM_{10,}$ as well as a Differential Mobility Particle Sizer to measure particle number concentration as a proxy for UFP. In two studies[26, 29] that examined ozone, exposure levels were the 8-hour daily maximum, while the 24-hour daily average level was used by other investigators.[30-32]

The number of air monitors used ranged from 1[27, 30] to 33[26] (for $PM_{2.5}$); 1[30] to 3[28] for PM_{10} ; 1[30] to 22 for NO_2[29]; up to 14 for SO_2[26], up to 19[26] for CO and up to 47[29] for ozone. Silverman[26] and Ensor[29] used the most extensive air-monitoring networks (Table 1) to capture the exposure data of the pollutants of interest.

Exposure metrics for the pollutants were measured as average hourly or 24-hourly exposure for all pollutants (including $PM_{2.5}$, PM_{10}, UFP, NO_x, SO_2 and CO), with the exception of ozone. Ozone level was measured using an 8-hour mean of daily maximum exposure metric[26, 29] or 24-hourly mean exposure.[30-32]

Mean exposure levels for $PM_{2.5}$ ranged from 6.35[30]–18.4[23] $\mu g/m^3$ and from 10.31[32]-31.9[23] $\mu g/m^3$ for PM_{10}. For ozone, it ranged from 13.34[30]–25.94[32] ppb. Mean ozone level in Helsinki[31] was reported as 46.8 $\mu g/m^3$ (equivalent to 23.87 ppb).

Lag periods varied from 0 to 6 days. Lag 0 hour (or day) was the same hour (or same day) exposure as the day of OHCA event. Lag 6 days was exposure 6 days prior to event.

Wichmann[32] validated the results of the association of OHCA with PM using data from two detection systems for $PM_{2.5}$ and $PM_{10.}$ Validation of the case-crossover results obtained using Poisson time series methodology was reported by three other studies.[26, 29, 30]

Although most studies used multivariable regression analyses, Checkoway[23] did not adjust for temperature and relative humidity. Rosenthal[27] did not adjust for effects of co-pollutants.

Overall results

Particulate matter

Five studies[26, 29-32] found significant positive associations between PM exposure (especially $PM_{2.5}$) and OHCA, with increased OHCA risk ranging from 2.4% to 7.0% per interquartile increase in average PM exposure on the same day up to 4 days prior to the event. However, three studies[23, 27, 28] did not (Figures 1 and 2).

Ozone

Five studies[26, 29-32] measured ozone, with positive associations observed in two.[29, 31] In a study with 11,677 OHCA cases using 47 monitors, Ensor[29] found increased odds of OHCA even with short-term exposure (within 3 hours prior to event), with the highest increases of 3.8%-4.6% per 20ppb ozone increase from the average level in lags of 0-2 hours. Rosenthal (2013)[31] found the odds of OHCA increased by 18% (3.0%-35%) in lag 2 days (two days prior to the event) (Figure 3). Earlier studies[26, 30] did not find any association of ozone with OHCA. Wichmann[32] only used ozone levels for statistical adjustment in the analysis of the association between OHCA and PM and found adjustment for ozone did not affect the relationship between OHCA and PM.

Other pollutants

Pollutants other than PM and ozone were measured in seven studies but only Wichmann[32] found positive associations between NOx and CO in lag 3 days with OHCA. Other studies did not find any association in any lag period for any gaseous pollutant.

Five studies[26, 27, 29, 30, 32] examined the effect of air pollutants (specifically on $PM_{2.5}$) for different age groups. Results were inconclusive, with conflicting results reported for the age groups examined. Two studies[29, 31] reported increased OHCA risk of 4.9%-6.0% (95% CI 0.0%-11.0%) in the age group 65-74 years for interquartile range increase of $PM_{2.5}$. Rosenthal[27] found a marked increase in OHCA risk [25% (95% CI 5.0%-49.0%)] with $PM_{2.5}$ for patients aged 60-75 years. By contrast Wichmann[32] and Silverman[26] found no age effect.

Reports of effect sizes were also heterogeneous; they included odds ratios, hazard ratios, and relative risks based on interquartile increases in the 24-hourly mean pollutant level or increases of 10$\mu g/m^3$ in the mean pollutant level. Therefore neither quantitative assessment of heterogeneity nor meta-analysis could be undertaken.

DISCUSSION

Our systematic review evaluated evidence of the effect of ambient air pollution on the occurrence of OHCA attended by EMS personnel. We found an increased risk of OHCA with ambient PM in the majority of the studies,[26, 29-32] consistent with results of cardiorespiratory, cardiovascular and all-cause mortality from other studies over the past 20 years.[3, 4, 33-35] Ozone was associated with OHCA in two of the five studies it was measured, while for other pollutants there were very few positive associations.

All of the studies were conducted in developed countries and measured pollution levels were often within the existing air quality standards for those countries. Despite air pollution being a major policy issue in many parts of Asia, and concentrations regularly exceeding those in developed countries, our literature search did not find any studies that examined the association of air pollution with the occurrence of OHCA from the developing countries: in the year 2000 two–thirds of 800,000 deaths and 4.6 million lost years of healthy life were attributed to air pollution.[36]

In a review of PM and CVD, the American Heart Association concluded there was sufficient evidence of a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality.[3] Of the three[23, 27, 28] studies that found no association of $PM_{2.5}$ with OHCA, two[23, 28] used nephelometry to estimate the $PM_{2.5}$ fraction. This method was not endorsed by the Environment Protection Agency,[37] as the data do not consistently reflect true PM levels and cannot be used to determine compliance to National Ambient Air Quality Standards. Furthermore, these studies[23, 27, 28] had smaller sample sizes, lower concentrations of $PM_{2.5}$ and/or different $PM_{2.5}$ composition compared to later studies.

Particulate matter concentrations in Melbourne[30], Copenhagen[32] and Helsinki[31] were similar. Not surprisingly, the effect estimates of $PM_{2.5}$ and PM_{10} with OHCA conducted in these cities were also similar. Although ozone was recognized to be an air pollutant that could increase the risk of mortality, until recently there was no reported association with OHCA.[38] A positive association between ozone and OHCA was reported in two studies.[29, 31] Notably, Ensor[29] collected the most comprehensive data to date on ozone in terms of study duration, number of pollution monitors and number of OHCA cases. The study results by Ensor[29] and Rosenthal[31] could possibly be attributed to a higher exposure concentration (mean: 23.87-25.52 ppb) compared to Dennekamp[30] (mean: 13.34 ppb). Heterogeneity in the studies and interactions between air pollutants could account for the lack of association in Silverman[26](mean not reported)..

Only one positive association of NO_x or CO with OHCA was found in our review.[32] Pollutants NO_x, CO and SO_2 have been reported to have moderately high collinearity.[32, 39] One large 17-city study, the China Air Pollution and Health Effects study[40], reported 10 $\mu g/m^3$ increase in two-day moving average of NOx was associated with increase in cardiovascular and respiratory mortality, but did not specifically address the association of NOx with OHCA.

Exposure assessment for air pollution studies is challenging. Potential exposure misclassification or error can arise when ambient air pollution is used as a surrogate for individual exposure. Ambient pollution levels at a given location may not reflect an individual's true exposure. The cross-sectional relationship between personal exposure and fixed monitoring sites concentrations varies from poor[41] to reasonably good,[42] although correlations improve when assessed on a longitudinal basis.[43] Furthermore, exposures to air pollutants take place over time and at multiple locations over subjects' daily activities. It is thus not feasible to have accurate exposure estimates for individual subjects. Zeger[44] highlighted the difference between population-average exposure and air concentration as an important potential source of bias that would influence the magnitude of the observed effect.

The number of monitoring sites varied considerably between the studies and most used five or less. Increased aggregation of monitoring station data has been reported to improve the representativeness of the exposure estimates by decreasing exposure misclassification, which is more profound when using individual stations versus regional averages.[45] Consequently, studies that utilised single sites for air pollution data assessment[27, 30, 32] are more likely than those with multiple sites to suffer from potential exposure misclassification.

Ascertainment of particle mass measurement with three different methods: nephelometry,[23, 28] beta-attenuation instrument[26, 29, 32] and tapered element oscillating microbalance;[27, 30-32] and the imprecision of exposure estimates also account for the degree of heterogeneity between studies. Regardless, Ensor[29] and Silverman[26] utilised the most extensive networks for air pollution data and their large studies demonstrated positive associations between air pollutants and OHCA.

In all the case-crossover studies, the time-stratified referent selection method was used to select control days, with day of OHCA event as case day and the same day of the week in the same month and year as control days. This method minimizes bias due to non-stationarity of

air pollution time series data,[23] and controls for confounding of exposure due to seasonal patterns.

The main reasons for down-grading of study quality were due to sample populations and exposure assessments. Two of these studies[23, 28] used nephelometric measures as a surrogate for $PM_{2.5}$, and had limited generalizability. Checkoway[23] was limited to 362 patients, a subset (but not a random sample) of all paramedic–attended OHCA at the study location. Sullivan[28] comprised subjects who belonged to the health maintenance organization and were insured.

Our systematic review has several limitations. The high degree of heterogeneity between studies and reporting methods meant that a meta-analysis could not be undertaken. Eligible studies reviewed were few and all were observational with inherent bias of observational studies. Potential confounders, such as diurnal patterns,[46-48] imprecision of exposure estimates and economic deprivation that increases the rates of morbidity and mortality attributed to air pollution[49] were not considered.

The strength of our study lies in its comprehensive search of multiple databases, including regional bibliographic databases and its inclusion of multiple air pollutants. Our review identified a gap in the literature from developing countries. Future studies should be directed to understanding the relationship in high exposure areas where mean PM levels are ten times higher[36] than those reported in this review.

Conclusion

The associations between OHCA occurrence and short-term exposure of ambient PM and ozone are inconsistent, but more recent studies have found positive associations. Large studies using similar sampling techniques are needed. Research is also needed to identify patients who are most at risk and to quantify personal exposure and risk.

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Competing Interest: None to declare.

Figure Legends

Legend for Supplementary Table 1: Summary of studies.

Legend for Table 2: Air pollutants, lags and effect measurement.

Legend for Appendix 1: Search strategy using EMBASE.

Legend for Appendix 2: Demographics of study population

Legend for Appendix 3: Newcastle-Ottawa Scale rating for study quality.

Legend for Figure 1: Association of PM2.5 and OHCA.
* Hazard ratio; ** Relative risk

Legend for Figure2: Association of PM_{10} with OHCA.

Legend for Figure 3: Association of ozone with OHCA.
** Relative risk

Summary box

What is already known on this subject?
There has been increasing evidence to support the association of ambient air pollution with overall cardiovascular mortality and morbidity. However, inconsistent results have been found in the relationship between out-of-hospital cardiac arrest (OHCA) and air pollution.
What this study adds?
More recent big studies have found positive associations of ambient particulate matter and ozone with OHCA. Large studies using similar sampling techniques are needed. Research is also needed to identify patients who are most at risk and to quantify personal exposure and risk.

Licence for Publication

Contributorship Statement

All authors made substantial contribution with the revisions to the manuscript to improve the intellectual content and gave the final approval of the revised manuscript. More clearly defined roles are as follows: authors THT, TW and JF contributed to the conception, design, data extraction and reviews, analysis and interpretation of the data. JF and IJ and AT provided the clinical expertise. PF provided the air pollution expertise. AB assisted with the the statistical advice and graphs. HT assisted with graphs and tables.

Supplementary Table 1

Authors (year)	Location	Period	Study design	No. of cases	Methodology	Study population	Analysis
Checkoway (2000)[23] Levy 2001[24]	Seattle, King County, Washington, US	Oct 1988-June 1994	Case-crossover	362	• Exposure data from 3 sites • Exposure levels with lags of 0-5 days • OHCA cases from EMS data • EMS reports and death certificates used to confirm absence of non-cardiac aetiology	• Subset of index OHCA EMS -attended cases • Included: age 25-75 years; sudden pulseless condition in absence of non-cardiac condition; married King County residents whose spouses participated in an interview • Excluded: those with cardiac and life-threatening comorbidities.	• Conditional logistic regression models. • Referent exposures selected by time stratified referent selection scheme. • Effect modification examined for selected variables (age, smoking exposure, alcohol consumption, physical activity, medications, period)
Dennekamp (2010)[30]	Melbourne, Australia	2003-2006	Case-crossover	8,434	• Exposure data from 1 monitoring station •Exposure window: 0-3 days lag • OHCA cases identified from Victorian Cardiac Arrest Registry	• OHCA cases within metropolitan Melbourne • Included: age ≥ 35 years with cardiac aetiology • Excluded: non-cardiac cases due to trauma and other causes	• Conditional logistic regression models • Poisson regression • Time-stratified referent period to select control days associated with each index case • Sensitivity analysis
Ensor (2013)[29]	Houston, US	2004-2011	Case-crossover	11,677	• Exposure data from 12 monitors for $PM_{2.5}$ and 47 monitors for ozone • Exposure levels with lags of 0 -3 hour for ozone and 0-5 days for $PM_{2.5}$ • OHCA cases from EMS data	• OHCA cases aged ≥ 18 years • Included: Non-DOA where chest compressions performed	• Conditional logistic regression• Referent exposures selected by time stratified referent selection scheme • Sensitivity analyses

Authors (year)	Location	Period	Study design	No. of cases	Methodology	Study population	Analysis
Rosenthal (2008)[27]	Indianapolis, US	2002-2006	Case-crossover	1,374	• Exposure data from 1 site in 2002 and another site in 2003-2006 • Exposure window of 0-3 days lag • OHCA data from EMS data	• OHCA cases (non- DOA) transported by ambulance within Indianapolis • Included: Non-DOA (1,374) or non-DOA incidents witnessed by bystanders (n=511)	• Conditional logistic regression models. • Referent exposures selected by referent time-stratified sampling. • Hazard ratios for an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ • Stratified analysis for age, sex, race and presenting rhythm
Rosenthal (2013)[31]	Helsinki, Finland	1998-2006	Case-crossover	2,134	• Exposure data from 4 sites in central Helsinki. • Lag periods of hourly exposures (0-3) and daily exposures (0-3) • OHCA cases from EMS data • OHCA and cause of death reviewed by physicians based on autopsy reports and hospital records	• All OHCA cases identified from the EMS data between 1998 and 2006 in study location • Included: OHCA cases with cardiac aetiology	• Conditional logistic regression. • Referent exposures selected by time stratified sampling. • Sub-analysis for acute myocardial infarction vs. those of other causes • Other stratified analyses were run by sex, season (cold-warm), survival to hospital admission
Silverman (2010)[26]	New York, US	2002-2006	Time series and case-crossover	8,216	• Data from 14-33 monitors within 32 km radius of New York • Exposure window of 0-1 day lag and 0-3 days as sensitivity analysis • OHCA data from EMS & Fire Department. • Cardiac aetiology ascertained by physicians.	• OHCA cases of presumed primary cardiac aetiology where resuscitation attempted by paramedics in the prehospital setting	• Poisson generalized linear model for time series analysis • Conditional logistic regression models for case-crossover analysis with time-stratified referent sampling • Estimated risk reported as relative risk

Authors (year)	Location	Period	Study design	No. of cases	Methodology	Study population	Analysis
Sullivan (2003)[28]	Western Washington State, US	1985-1994	Case-crossover	1,542	• Exposure data from 3 sites (nephelometry). • Exposure window of 0-2 days lag • OHCA data from EMS data. • Group Health Corporative HMO (for death record) • Clinical characteristics and medical history from medical record review	• Primary cardiac arrest cases with cardiac aetiology. • Included: age 19-79 years. • Excluded: non-cardiac OHCA; residents outside of study location.	• Conditional logistic regression analysis. • Incident primary cardiac arrest as primary outcome. • The primary exposure defined as the interquartile increase in 24-hr average light scattering • Referent exposures selected by time stratified referent selection scheme • Stratified analyses undertaken (with and without clinically recognized heart disease)
Wichmann (2013)[32]	Copenhagen, Denmark	2000-2010	Case-crossover	4,657	• Exposure data from 1 site. • Exposure window of hourly lag (0-7) and daily lag (0-5 days) • OHCA data from physician-staff MECU in study location	• OHCA cases identified from MECU between 2000-2010 within urban Copenhagen.	• Conditional logistic regression models • Referent exposures selected by time-stratified approach • Sensitivity analysis

OHCA, out-of-hospital cardiac arrest; EMS, emergency medical system; DOA, dead on arrival; MECU, Mobile Emergency Care Unit

Table 2

Author (year)	UFP	$PM_{2.5}$	PM_{10}	$PM_{2.5-10}$	CO	NO_2	SO_2	Ozone	Lag	Effect measurement
Checkoway (2000)[23]; Levy[24]		√	√		√		√	√	0-5 days	Relative risk associated with interquartile range exposures from nephelometry & PM_{10}, for lags 0-5 days.
Dennekamp (2010)[30]		√	√	√	√	√	√	√	0-3 days, 0-6 days for cold days	Percent change in risk of OHCA for an interquartile increase in air pollution
Ensor (2013)[29]		√			√	√	√	√	0-8 hours, 1-5 days	Odds ratio associated with an interquartile increase in pollutant level
Rosenthal (2008)[27]		√							0-7 hours, 0-1 day	Hazard ratio - increased risk for increase of $10\mu g/m^3$ in $PM_{2.5}$ exposure
Rosenthal (2013)[31]	√	√	√	√	√	√	√	√	0-8 hours, 0-3 days	Odds ratio for OHCA associated with an interquartile increase in pollutant level
Silverman (2010)[26]		√			√	√	√	√	0-3 days	Relative risk
Sullivan (2003)[28]		√	√	√			√		0-2 days	Odds ratio for incident cardiac arrest related to a 13.8 $\mu g/m^3$ increase in $PM_{2.5}$
Wichmann (2013)[32]	√	√	√	√	√	√		√	Hourly, 0-4 days	Odds ratio for OHCA associated with an interquartile increase in pollutant level.

UFP, ultrafine particle; OHCA, out-of-hospital cardiac arrest

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