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Review

The impact of short-term exposure to air pollutants on the onset of out-of-hospital cardiac arrest: A systematic review and meta-analysis

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ABSTRACT

Background: Acute exposure to outdoor air pollution was considered to be associated with the incidence of out-of-hospital cardiac arrest (OHCA). But the relation between specific air pollutants and OHCA remains controversial. We conducted a systematic review and meta-analysis to quantitatively assess the acute effects of air pollutants, including particulate matter (PM_{10} and $PM_{2.5}$), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3) on OHCA onset.

Methods: Six databases were searched to identify studies analyzing the association between OHCA and the main air pollutants. We summarized the pooled estimates using random-effect models. Heterogeneity within studies was assessed using Cochran's Q and I^2 statistics. Funnel plots, Egger's regression test and Begg's rank correlation method were constructed to evaluate publication bias. Subgroup analyses and sensitivity analyses were also conducted to evaluate the potential sources of heterogeneity.

Results: A total of 15 studies met the inclusion criteria. PM_{10}, $PM_{2.5}$, NO_2 and O_3 were found to be significantly associated with increase in OHCA risk (PM_{10} 1.021, 95%CI: 1.006–1.037; $PM_{2.5}$ 1.041, 95%CI: 1.012–1.071; NO_2 1.015, 95%CI: 1.001–1.030 and O_3 1.016, 95%CI: 1.008–1.024). The acute exposure to SO_2 and CO was not associated with the incidence of OHCA. Additional analyses verified the findings in the overall analyses except SO_2 and NO_2. Population attributable fractions for PM_{10}, $PM_{2.5}$, and O_3 were 2.1%, 3.9% and 1.6%, respectively.

Conclusion: The current evidence confirmed the associations between short-term exposure to $PM_{2.5}$, PM_{10} and O_3 and a high risk of OHCA, with the strongest association being observed for $PM_{2.5}$.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is defined as the cessation of cardiac mechanical activity occurring outside of the hospital setting and is a serious disease with a low survival rate [1–3]. In the United States, there were approximately 300,000 OHCA patients each year with a survival of less than 10% [4]. However, Survival can be as high as 70% if treatment is initiated within the first minutes after sudden cardiac arrest [5]. Therefore, prevention of OHCA could reduce burden for both individuals and society. With growing concerns, environmental factors were regarded as an important role for OHCA onset and the relationship between acute air pollutant exposure and OHCA has become a recent concern [6,7].

Although current epidemiological evidence supports the hypothesis that acute exposure to air pollution is associated with the incidence of OHCA, the effect of specific air pollutants, and of the size of the particles is uncertain. For fine particulate matter ($PM_{2.5}$), Checkoway et al. at first studied the association between exposure to $PM_{2.5}$ and the risk of OHCA and found there was no significant relationship between them [8]. But several years later, Rosenthal et al. found the acute exposure to $PM_{2.5}$ significantly increased the incidence of OHCA in Indianapolis, Indiana [9]. Subsequent studies have also confirmed this finding and found that the acute exposure to inhalable particles (PM_{10}), carbon monoxide (CO) and ozone (O_3) was also associated with OHCA risk [10–13]. However, some conflicting studies failed to discover the similar association between the acute exposure to $PM_{2.5}$ and OHCA onset and reported that the acute exposure to sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) was responsible for the high OHCA risk [7,14–16]. Although effect estimates from these studies are not large, the whole population is continuously exposed to air pollutants, combined with OHCA is a serious disease, so the cumulative effects of air pollutants on the OHCA could not be ignored. Considering the different sources of air

Abbreviations: CI, confidence interval; CO, carbon monoxide; EMS, emergency medical service; NO_2, nitrogen dioxide; O_3, ozone; OHCA, out-of-hospital cardiac arrest; PAF, population-attributable fraction; PM_{10}, inhalable particles; $PM_{2.5}$, fine particulate matter; RR, relative risk; SO_2, sulfur dioxide.

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pollutants, we need better estimates of the effect of acute exposure to air pollutants on OHCA onset to give a specific suggestion to policy makers.

Although Teng et al. reviewed studies for the short-term exposure to the primary air pollutants on the risk of OHCA in 2014, they have not estimated the pooled effects for limited studies [17]. Considering there is some recent evidence for this issue, we conducted a comprehensive meta-analysis to quantitatively assess the acute effects of air pollutants including particulate ($PM_{10}$and $PM_{2.5}$) and gaseous (SO_2, NO_2, CO, and O_3) air pollutants on OHCA risk.

2. Methods

2.1. Data sources and search strategy

Studies that had analyzed the association between OHCA and the main air pollutants were identified through a literature search of the following databases, PubMed, Embase, Cochrane Library, Web of Science, Cumulative Index to Nursing and Allied Health Literature(CINAHL) and the China National Knowledge Infrastructure, using the keywords: ("air pollutants" OR "air pollution" OR "environmental exposure" OR "particulate matter" OR "particles" OR "particle" OR "soot" OR "PM_{10}" OR "PM(10)" OR "$PM_{2.5}$" OR "PM(2.5)" OR "sulfur dioxide" OR "sulphur dioxide" OR "SO_2" OR "SO(2)" OR "nitrogen dioxide" OR "nitrogen oxides" OR "NO_2" OR "NO(2)" OR "carbon monoxide" OR "elemental carbon" OR "CO" OR "ozone" OR "O_3" OR "O(3)") AND ("heart arrest" OR "cardiac arrest" OR "sudden cardiac death"). The reference lists of the identified studies that had been selected for inclusion in our meta-analysis as well as relevant review articles were also searched in order to identify additional relevant studies. Articles published up to July 1st, 2016 were included in the study.

2.2. Study selection

All titles and abstracts were independently reviewed by two reviewers (RXZ and SC) in order to identify potentially eligible studies. The full-texts of potential articles were then reviewed to determine the eligibility for inclusion in the meta-analysis. Any disagreements between the two reviewers regarding eligibility were resolved by a third reviewer (SW).

Any study was included if it had reported an association between OHCA risk and short-term exposure to air pollutants. Reviews, meta-analyses, summaries, comments, editorials, case-reports, case series, animal studies, studies regarding mechanisms, duplicates, non-health studies and studies that reported other associations were excluded. If multiple articles utilized the same population, only the most comprehensive publication was selected for inclusion.

2.3. Data extraction

The data were extracted independently by two investigators (RXZ and SC) from studies that met the inclusion criteria using a unified data form. Conflicts were resolved by consensus or through the use of a third investigator (SW). The details extracted from each study include: title, author, journal, date of publication, study location, study periods, study design, study population, number of cases, pollutants studied and their concentrations, outcome source, effect measurement, method of control selected, statistical model and adjustments performed (long-term trend, seasonality, temperature, humidity, day of the week, and holidays). If any of the above-mentioned data were not available in the articles, or there was any uncertainty regarding the data, the additional data were requested through email by contacting the first or corresponding author of the study.

2.4. Study quality assessment

Since there are no validated tools to evaluate study quality for time-series studies or case-crossover studies, the Newcastle-Ottawa Scale was adapted to evaluate the methodological quality of included studies [17]. The Newcastle-Ottawa Scale evaluated each study using the 'star system' through three broad perspectives of eight items [18]. The three broad perspectives include: the selection of the study population, the comparability between groups and the assessment of the exposure or outcome. The quality of each study in our analysis was evaluated primarily on the following aspects: 1) how representative the study population was; 2) the assessment of the air pollutants; 3) the validation of OHCA occurrence and 4) the adjustment for confounders and the sensitivity analyses undertaken. Studies receiving 7–9 stars were determined to be of good quality, those receiving 1–3 stars were determined to be of low quality, and all other studies were determined to be of intermediate quality.

2.5. Data synthesis

Relative risk (RR) was used to measure the effect size. The concentration of CO was converted to mg/m^3 and other pollutant concentrations were converted to μg/m^3 when necessary. The standardized RR and 95% confidence interval (CI) were calculated for each 10 μg/m^3 increase in pollutants (PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3) and each 1 mg/m^3 increase in CO. A linear relation between air pollution and an outcome was assumed, and the standardized risk estimates were then calculated for each study using the following formula [19]:

$$RR_{standardized} = e^{\left(\frac{Ln\left(RR_{origin}\right)}{Increment_{origin}} \times Increment_{standardized}\right)}$$

The association between the short-term exposure to ambient air pollutants and an OHCA onset can be estimated by the time-series studies and the case-crossover studies. When both the time-series and the case-crossover were used to estimate the effect in an article, estimates from the time-series analyses were used to conduct the overall analyses because risk estimates obtained using the time series approach are more precise than those determined using a case-crossover design [20].

Different lag patterns were used in most of the included studies in order to evaluate immediate and delayed associations between pollutant exposure and OHCA risk. A few studies provided multiple estimates for single-day lags from lag0 (current day concentration) to lag6 (6 days prior to the event day) while other studies provided cumulative lags, such as lag 01 (being the mean concentration between the current day and the previous day). Thus, if several lag estimates were reported in the same article, the lags selected for the overall analyses were selected by following the protocol proposed by Shang: 1) the lag that the author emphasized or stated as a priori; 2) the lag with the most statistical significance; 3) the lag with the largest effect estimate [21].

When results were available from both the single-pollutant and multi-pollutant models, only the single-pollutant model results were included. The pooled estimates were then summarized using random-effect models.

The population-attributable fractions (PAFs) were also estimated for the main air pollutants in the overall analyses. The PAF was calculated using the following equation : $PAF = 100 \times k\,(RR - 1) / (k\,[RR - 1] + 1)$, for which k indicates the exposure prevalence in the population. There were three assumptions underlying the prevalence of air pollution exposure: 1) in urban areas of low and middle income countries it was assumed to be 100%; 2) in low and middle income countries, taken as a whole, including urban and rural areas, it was estimated as 80%; 3) in high income countries with low air pollution levels it was assumed to be 20% [22,23] .

Heterogeneity within studies was assessed using Cochran's Q and I^2 statistics. If the P value for heterogeneity was determined to be less than 0.05 or the I^2 value exceeded 50%, the presence of heterogeneity was taken into consideration. Publication bias was evaluated through the construction of funnel plots, and considering the limitations of this method, an Egger's regression test and Begg's rank correlation method were also performed [24]. If publication bias was found to be statistically significant, the trim and fill procedure was used to impute the number of potentially missing studies and then the adjusted overall effect size was recomputed [25].

2.6. Additional analyses

Subgroup analyses were performed using the different lags (lag0, lag1, lag2, lag3, and lag0–1), study designs (case-crossover vs. time-series), seasons (warm vs. cold), sex (male vs. female), age groups (<65 years, 65–74 years and ≥75 years), ethnicity (white vs. black), study locations (North America, Europe, Asian and Oceania) and pollutant concentrations. The groups of pollutant levels were based on the World Health Organization air quality guidelines and the distribution of pollutant concentrations in the included studies [26]. The pooled estimates were only conducted for subgroups with three or more studies. Considering the different age groups used in each study, a 5-year range was allowed for age subgroup analysis. Sensitivity analyses were also conducted in order to evaluate the potential sources of heterogeneity for pollutants with statistically significant heterogeneity.

Statistical significance was determined to be anything with a $P < 0.05$ and all tests were two-sided. All data analyses were performed using the STATA, version 10.0 (College Station, TX, USA).

This systematic review was performed according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27].

3. Results

3.1. Selection of study and characteristics of studies

A total of 7679 publications were identified in our initial literature search. After a screen of the titles and abstracts and eliminating redundant publications, only 20 publications were considered potentially eligible for our meta-analysis. Of these, three publications used data from the same population and three publications focused on coronary heart disease. Thus, only 15 studies met the inclusion criteria [6–16,28–31]. The meta-analysis was done utilizing 9 studies focusing on PM_{10}, 12 focusing on $PM_{2.5}$, 11 focusing on SO_2, 11 focusing on NO_2, 11 focusing CO, and 11 focusing on O_3 (Fig. A.1).

Detailed information from the 15 publications included in our meta-analysis is shown in Table 1. With the exception of two studies, which used both case-crossover and times-series designs, the other studies