Analysis of out-of-hospital cardiac arrest and ozone pollution: A qualitative study

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Abstract

Background: Air pollution is increasingly associated with cardiovascular events. As for ozone (O3) pollution, results are inconsistent though O3 levels are associated with hospital admissions, global mortality, and respiratory, and cardiovascular mortality.

Methods: In this time-stratified case-crossover study, the associations between short-term exposure to O3 (on an hourly and daily scale) and out-of-hospital cardiac arrests (OHCA) were investigated. Specific subgroups were explored by sex, age, diabetes status, for OHCA during non-holiday periods. Data were collected in the Nord-Pas-de-Calais region, France, in 2015. Data were statistically analyzed using conditional logistic regression (CLR).

Results: The study included 1039 cases of OHCA. Significant negative associations were found between OHCA and O3 levels measured in 3 or 4 days before the arrest for all the people, and 1, 2 or 3 days before the arrest for men. As for OHCA during non-holiday periods, there was no significant negative associations but a positive association was revealed for women between OHCA and O3 levels measured in 5 days before the arrest (OR=1.53, P= 0.008).

Conclusion: According to the results, OHCA should be investigated during non-holiday periods to control potential confounders that would lead to negative associations. Women might be a susceptible subgroup to O3 pollution.

Keywords: Heart arrest, Ozone, Air pollution, Epidemiology, Environmental health

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Introduction

Cardiac arrest refers to the abrupt loss of heart function and is an important public issue. The global incidence of sudden cardiac death (SCD) rates from 50 to 100 per 100 000 in the general population, is between 180 000 and 450 000 cases annually in the United States (1). Most cardiac arrests (85%) are out-of-hospital cardiac arrests (OHCA) (2), and the global incidence of OHCA is approximately 46 000 cases per year in France. Cardiac arrests survival rates remain low: 4.9% of OHCA patients survive for at least 30 days or to hospital discharge (3). Although the risk of SCD increases with age, OHCA is a socio-economic issue because the proportion of sudden deaths is larger among young people (4). According to the World Health Organization (WHO), outdoor air pollution is a major environmental health problem and it was estimated to cause 4.2 million premature deaths worldwide in 2016. In the literature, short-term
exposure to air pollution is being increasingly associated with cardiovascular morbidity and mortality (5-9). In particular, positive associations were revealed between OHCA and fine particulate matter with an aerodynamic diameter under 2.5 μm (PM2.5) in some studies (10-13). Results for ozone (O₃), PM smaller than 10 microns (PM10), carbon monoxide (CO), sulfur dioxide (SO₂), and nitrogen dioxide (NO₂), were inconsistent (12-17). More specifically, O₃ levels had a positive relationship with heart failure (18), hospital admissions, global mortality (19), and respiratory and cardiovascular mortality (19,20). Eight studies investigated the association between OHCA and short-term exposure to O₃ levels (10-12,15,21-24). Three studies found positive associations between O₃ exposure and OHCA (15,21,24).

The aims of this study were to evaluate the effects of short-term exposure to O₃ (on a daily and hourly scale) on the occurrence of OHCA in Nord-Pas-de-Calais (NPdC), France. The ratio of OHCA was investigated during non-holiday periods and for susceptible subgroups (by sex, age, diabetes status) so as to arouse political commitment on air pollution control strategies for vulnerable populations. Subgroup analyses could be a good alternative to overcome the problem of the small population-wide relative risks usually observed and to control confounding effects of holidays.

Materials and Methods
Out-of-hospital cardiac arrest data
Data on OHCA were collected from the French Cardiac Arrest Registry ‘Registre électronique des Arrêts Cardiaques’ (RéAC). RéAC is an electronic, web-based data management system that includes patients with OHCA when a mobile medical team (MMT) is involved (25). According to the recommended guidelines for uniform reporting of data of OHCA (26), the RéAC form follows the Utstein universal style. Thus, this registry provides patients data, such as gender, age, location of the arrest, place of residence, and cardiac arrest history. The participants participated in the study voluntarily. The registry was approved as a medical assessment registry without a requirement for patient consent by the French Advisory Committee on Information Processing in Health Research (CCTIRS) and the French National Data Protection Commission (CNIL, authorization number 910946). Ten mobile emergency and resuscitation services are involved in NPdC for a population representing 71.45% of the 4.2 million inhabitants. In this study, data were collected from January 1 to December 31, 2015, in NPdC. Of 1408 cases obtained, 235 cases of the arrest that were collected from January 1 to December 31. OHCA events occurring during non-holiday periods were excluded whenever less than two values were available for the reference exposures or if the value for the risk exposure was missed.

Study design
To control temporal trends of air pollution levels and OHCA incidence, this time-stratified case-crossover study was conducted. This design applies in the cases of brief exposures, transient changes in risk, and rare acute-onset diseases (27). It consists in confronting the exposure of the patients during a risk period to that during a reference period. The latter has to be chosen according to a number of constraints to control biases that could be resulted from long-term time trends, seasonal patterns, day-of-the-week effects, and autocorrelation of exposures. Thus, measures have to be assessed on the same day-of-the-week in the same month of the same year of the arrest (17,28-30). As an illustration, if the OHCA occurs on Saturday in March, the risk exposure will be measured on that day and will be compared to the reference exposures measured on all other Saturdays in March. As a result, stable personality traits are controlled over time. If a value was missing either for the risk exposure or for its reference exposures, therefore, the case was excluded.

Subgroups
Subgroup analyses were also conducted. In this study, it was focused on the occurrence of OHCA during non-holiday periods at different levels of pollutants (31). Then, subgroups of sex, age (50 to 75 years old versus over 75 years old), following recommendations made in June 2010 by the French Center for Strategic Analysis, Centre D’Analyse Stratégique), and diabetes status were investigated. In 2015, there were six holiday periods: from January 1 to 4, from February 21 to March 8, from April 25 to May 10, from July 4 to August 30, from October 17 to November 1, and from December 19 to 31. OHCA events occurring during non-holiday periods were excluded whenever less than two values were available for the reference exposures or if the value for the risk exposure was missed.
Lag times
In the present study, short-time effects of pollutants on the occurrence of OHCA were evaluated. Therefore, risk exposures were measured at different lag times close to the time of the OHCA: lag0h (for the hour of the OHCA), CA4h (from lag0h to lag3h, for the mean of the hour of the arrest and the three hours before the arrest), CAH12 (mean from lag0h to lag11h), lag0d (for the day of the OHCA) to lag5d (five days before the OHCA). If more than 25% of the values needed to compute the exposure for CA4h or CA12h were missing, the exposure was considered as missing.

Statistical analyses
To estimate odds ratios (OR) with 95% confidence intervals (CI) per interquartile range (IQR) increase, conditional logistic regression was used. First, a single-pollutant model with O\textsubscript{3} which was adjusted on temperature using a nonparametric smoothing spline of degree 3 with 4 knots optimally chosen, was built (32-36). If the evaluated lag time was statistically significant at \( P = 0.01 \), which provides very strong evidence (37) because of the multiple statistical tests, a multi-pollutant model was used. This multi-pollutant model was built by adding pollutants with concentrations moderately correlated with \( O_3 \) concentrations (absolute value of Spearman correlations, \( r = 0.40 - 0.60 \)) as a bias-variance trade-off. Thus, multi-pollutant models included \( O_3 \), PM2.5, NO\textsubscript{2}, and temperature. The same lag times were used for all concentrations within a model except for the hourly scale, in which the daily level was used for the temperature level. Data were statistically analyzed using the R statistical software (R Core Team, 2015).

Results
This study included 1039 cases of OHCA, 60.1% of which were men (n = 624), 46.4% aged 50 to 75 years (n = 482), 40.7% aged over 75 years (n = 423), and 16.4% were diabetic patients (n = 170). Air pollution and temperature data for OHCA in 2015 and during non-holiday periods are summarized in Table 1. On the day of the OHCA incidence, \( O_3 \) levels were moderately correlated with PM2.5 levels (\( r = -0.44 \)) and NO\textsubscript{2} levels (\( r = -0.59 \)); multi-pollutant models were then obtained by adding PM2.5 and NO\textsubscript{2}.

Table 2 shows the values for significant results at the 1% level of significance for single-pollutant models and then for multi-pollutant models. Figures 1 to 4 describe OR and 95% CI of single-pollutant models for the OHCA all year long (Figures 1 and 3) or for non-holiday OHCA (Figures 2 and 4) and for lag0h to lag0d (Figures 1 and 2) or for lag1d to lag5d (Figures 3 and 4).

While exploring the shortest lag times (on the day of the OHCA: lag0h, CA4h, CA12h, and lag0d), no significant association neither with OHCA all year long nor with non-holiday OHCA was found. While exploring longer lag times (from lag1d to lag5d), mainly negative associations were found with OHCA all year long (significant at lag3d and lag4d) and in men (significant at both lag1d and lag2d in multi-pollutant models, and at lag3d). The most significant associations were found in men at lag1d and lag2d (OR = 0.74, \( P = 0.004 \)). The only positive association was found with non-holiday OHCA at the longest lag time (lag5d) in women (OR = 1.53, \( P = 0.008 \)).

Discussion
In the literature, three studies found positive associations with lag times taking into account the exposure the day of the OHCA (CA2h, CA24h, and CA72h or mean of lag2h, lag3h, and lag0d) (15,21,24). In the present study, no significant association at those short lag times was found. Moreover, the significant associations were mainly negative,

Table 1. Description of data (µg/m\textsuperscript{3} for pollutants, °C for temperature)

| Hour of the OHCA | Mean (SD\textsuperscript{a}) | Median | IQR\textsuperscript{b} | Number of OHCA (%) | Number of Non-holiday OHCA (%)\textsuperscript{c} |
|------------------|-----------------------------|--------|------------------------|--------------------|-----------------------------------------------|
| PM2.5            | 15.03 (13.57)               | 11.10  | 12.00                  | 560 (54%)          | 377 (36%)                                      |
| PM10             | 22.24 (15.41)               | 18.60  | 15.50                  | 580 (56%)          | 388 (37%)                                      |
| NO\textsubscript{2} | 21.95 (16.12)              | 18.10  | 20.82                  | 614 (59%)          | 413 (40%)                                      |
| O\textsubscript{3} | 46.65 (25.19)               | 47.10  | 37.65                  | 616 (59%)          | 401 (39%)                                      |
| SO\textsubscript{2} | 2.59 (6.85)                | 1.50   | 2.00                   | 326 (31%)          | 307 (30%)                                      |
| CO               | 0.24 (0.26)                 | 0.20   | 0.17                   | 425 (41%)          | 329 (32%)                                      |

| Day of the OHCA  | Mean (SD\textsuperscript{a}) | Median | IQR\textsuperscript{b} | Number of OHCA (%) | Number of Non-holiday OHCA (%)\textsuperscript{c} |
|------------------|-----------------------------|--------|------------------------|--------------------|-----------------------------------------------|
| PM2.5            | 14.70 (10.52)               | 11.50  | 10.00                  | 814 (78%)          | 529 (51%)                                      |
| PM10             | 21.84 (11.96)               | 18.80  | 12.42                  | 848 (82%)          | 555 (53%)                                      |
| NO\textsubscript{2} | 20.98 (11.80)              | 19.40  | 16.80                  | 912 (88%)          | 584 (56%)                                      |
| O\textsubscript{3} | 64.51 (23.21)              | 64.85  | 27.94                  | 850 (82%)          | 538 (52%)                                      |
| SO\textsubscript{2} | 2.15 (3.12)                | 1.50   | 1.80                   | 610 (59%)          | 485 (47%)                                      |
| CO               | 0.23 (0.16)                 | 0.21   | 0.15                   | 707 (68%)          | 516 (50%)                                      |
| Temperature      | 11.08 (5.39)               | 11.30  | 7.50                   | 1026 (99%)         | 609 (99%)                                      |

\textsuperscript{a}Standard deviation; \textsuperscript{b}Interquartile range; \textsuperscript{c}Without missing values for the pollutant.
which can be explained by confounding factors, such as PM2.5 levels and holiday periods. Indeed, PM2.5 and O3 levels are negatively correlated ($r = -0.44$). Moreover, O3 is a secondary pollutant formed through a photochemical reaction requiring sunlight, and O3 local concentrations are reduced in the vicinity of heavy vehicular traffic due to scavenging by NO and volatile organic compounds (38), which could contribute to higher O3 levels during summer holidays. Thus, in this study, no negative association was found using multi-pollutant models or focusing on non-holiday OHCA. Furthermore, in the literature, from lag0h to lag5d, studies on O3 positive associations showed no association between PM2.5 and OHCA (15,21), also studies on PM2.5 positive associations, showed no association between O3 and OHCA (10,12,22,23). Negative associations could also be due to a reduction in the number of people at risk, as O3 levels may increase respiratory mortality (19,20). Although confounding factors can account for the negative associations, some studies reported the association between heart protective

### Table 2. Significant associations ($P < 0.01$) between O3 levels and OHCA incidence

| Lag     | Subgroup | O3 - Single-pollutant Model | O3 - Multi-pollutant Model |
|---------|----------|-----------------------------|---------------------------|
|         |          | OR per IQR (95% IC) | $P$ value | OR per IQR (95% IC) | $P$ value |
| OHCA all year long |          |                          |                        |                          |                        |
| Lag1d   | Male     | 0.74 (0.60-0.91) | 0.004  | 0.71 (0.55-0.91) | 0.008  |
| Lag2d   | Male     | 0.74 (0.61-0.91) | 0.004  | 0.67 (0.52-0.87) | 0.002  |
| Lag3d   | All      | 0.81 (0.69-0.94) | 0.006  | -                | -                |
|         | Male     | 0.75 (0.61-0.92) | 0.005  | -                | -                |
| Lag4d   | All      | 0.81 (0.69-0.95) | 0.008  | -                | -                |
| Non-holiday OHCA |          |                          |                        |                          |                        |
| Lag5d   | Female   | 1.53 (1.12-2.11) | 0.008  | -                | -                |

![Figure 1](image1.png) ![Figure 3](image3.png)

**Figure 1.** OR and 95% CI for OHCA versus O3 levels for lag0h to lag0d.

**Figure 3.** OR and 95% CI for OHCA versus O3 levels for lag1d to lag5d.

![Figure 2](image2.png) ![Figure 4](image4.png)

**Figure 2.** OR and 95% CI for non-holiday OHCA versus O3 levels for lag0h to lag0d.

**Figure 4.** OR and 95% CI for non-holiday OHCA versus O3 levels for lag1d to lag5d.
effects of $O_3$ with an increase in vasodilation (39), and an infarct size reduction (40). In the present study, a positive association was found when considering non-holiday OHCA in women. No significant associations were found among men, the 50-75 year old age group, and patients with diabetes. Indeed, we have previously shown positive associations between PM2.5 and OHCA among men, the 50-75 year old age group, and patients with diabetes whereas there were no associations between PM2.5 and OHCA among women (41). Two studies have found positive associations between $O_3$ and OHCA among women, suggesting hormonal cause (42,43). It is worth mentioning that there are various mechanisms of $O_3$ toxicity. An increased airway permeability reported by the measure of the pulmonary clearance of radioisotopelabeled organic molecule, ($^{99m}$TC-DTPA), could increase the uptake of other toxins or the release of inflammatory cells (44,45). Some studies have shown inflammatory processes with changes in cyclooxygenase metabolites of arachidonic acid (46), and with neutrophil influx into the airways (46-48). A stimulation of fibrinogenic processes was reported with higher levels of fibronectin, factor VII, and urokinase plasminogen activator (47). In a study, ultrafine carbon particles increased sympathetic nervous system activity and more so with added $O_3$ (48). $O_3$ may also lead to an increase in myocardial work and impairment of pulmonary gas exchange (49). In the study of $O_3$ effects, special consideration should be given to healthy people who exercise regularly outdoors, because of higher $O_3$ exposure, and those with asthma, because of increased symptomatic responses (19,50).

Most of the significant associations were found with OHCA occurring all year long. The significance of those associations may be due to temporal trends of $O_3$ pollution with different levels during holidays. However, by considering non-holiday OHCA, the periods in which $O_3$ pollution may impact health differently, were excluded. In addition, we have to be cautious when drawing conclusions with single-pollutant models because a pollutant level serves as a surrogate term for a complex mixture of pollutants, and ozone pollution may better reflect particulate matter personal exposure than exposure to $O_3$ itself (51). However, results from multi-pollutant models are also limited by overfitting (of correlated pollutant levels) or interactions (synergistic effects of $O_3$ and particulate matter) (52). Wherever the OHCA occurs (indoor, outdoor), the individual pollution exposure is given by measures of ATMO Hauts-de-France monitors which could result in imprecise results. Interpretation of the results of this study compared to the results of other studies is limited. The precision of the results depends on the number of monitors available, the number of cases included, and criteria used to define a case and pollution levels. Variability in pollution levels and composition makes it difficult to compare results obtained from different study periods and regions.

**Conclusion**

The investigation of the relationship between $O_3$ levels and the occurrence of OHCA showed mainly negative associations on the daily scale. There were no negative associations between $O_3$ levels and the occurrence of OHCA during non-holiday periods, but a positive association was reported between the occurrence of OHCA during non-holiday periods and $O_3$ levels five days before the OHCA, among women. Therefore, it would be interesting to analyze non-holiday OHCA to estimate health impact of exposure to ozone, in order to control for confounders, such as temporal trends and PM2.5 levels. The negative associations could also be due to the heart protective effect of $O_3$ and further investigation is necessary. Moreover, a special attention should be paid to the subgroup of women, for which the only positive association was found. Analyses of susceptible subgroups might show associations that do not usually appear because of the small population-wide relative risks and could lead to revised recommendations for the subgroups. Further studies under similar conditions are needed to assess the significance of the results of the present study. As a final point, models taking into account confounders should be further developed so as to evaluate the impact of $O_3$ itself.

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**Ethical issues**

The approval of the Ethics Committee was not necessary, because explorations were based on anonymized patient data.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

All authors were equally involved in the conception and design, analysis and interpretation of data, drafting of the article or revising it critically for important intellectual content, and manuscript approval.

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