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Out-of-hospital cardiac arrests in a large metropolitan area: synergistic effect of exposure to air particulates and high temperature

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Abstract

Aims: Air pollution and climate change are intrinsically linked to emerging hazards for global health. High air particulate matter (PM) levels may trigger out-of-hospital cardiac arrest (OHCA). High temperature could act synergistically with PM in determining OHCA. The aim of the present study was to investigate the effect of PM exposure alone, and in combination with temperature, on the risk of OHCA, in a large European metropolitan area with population >4 million.

Methods: We evaluated the association between short-term PM exposure, temperature, and the risk of OHCA over a two-year study period, allowing us to investigate 5761 events using a time-stratified case-crossover design combined with a distributed lag non-linear model.

Results: Higher risk of OHCA was associated with short-term exposure to PM_{10}. The strongest association was experienced three days before the cardiac event where the estimated change in risk was 1.70% (0.48–2.93%) per 10 $\mu g/m^3$ of PM. The cumulative exposure risk over the lags 0–6 was 8.5% (0.0–17.9%). We observed a joint effect of PM and temperature in triggering cardiac arrests, with a maximum effect of 14.9% (10.0–20.0%) increase, for high levels of PM before the cardiac event, in the presence of high temperature.

Conclusion: The present study helps to clarify the controversial role of PM as OHCA determinant. It also highlights the role of increased temperature as a key factor in triggering cardiac events. This evidence suggests that tackling both air pollution and climate change might have a relevant impact in terms of public health.

Keywords

Out-of-hospital cardiac arrests, air pollution, particulate matter, temperature, climate change, public health

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Introduction

Air pollution and climate change are intrinsically linked emerging hazards for global health.[1–3] High air particulate matter (PM) levels have repeatedly been linked to the occurrence of fatal and non-fatal acute cardiovascular events.[4–6]

Approximately one-half of cardiovascular deaths are due to out-of-hospital cardiac arrests (OHCAs), which are defined as the cessation of cardiac mechanical activity occurring outside the hospital. OHCA is characterized by a poor prognosis and very high mortality. Thus, a lot of effort has been made in clinical practice in order to identify the main modifiable factors that could

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trigger OHCA, in order to screen high-risk subjects and adopt ad hoc countermeasures. Some studies have shown that PM may be a trigger of OHCA.[7–10] High temperature and high humidity, which have increased in prevalence because of global warming, could create extremely stressful conditions for the cardiovascular system and may act with PM in a synergistic way to induce OHCA. A very recent paper showed some evidence of interactive effects between high temperature and ozone and PM_{10} levels on total mortality (non-accidental, cardiovascular and respiratory deaths), but this interaction was not observed during the cold season.[11] To date, no data are available on the potential synergistic effect of PM and temperature on OHCA.

Thus, the aim of the present study was to investigate the effect of PM exposure alone, and in combination with temperature, on the risk of OHCA, in a large European metropolitan area with population >4 million.

Methods

Study area and out-of-hospital records

The study population included all OHCA cases that occurred during a period of two years in the Large Metropolitan Milan Area, which is a highly populated urban area in Po Valley. This area has the highest PM levels in Western Europe. OHCA cases were recorded in the centralized registry of ambulance call-outs covering the entire area (AREU Lombardy Region) between January 2015 and December 2016.

OHCA was defined as the sudden cessation of cardiac mechanical activity, in the absence of any traumatic cause of cardiac arrest. OHCA diagnosis was made in the call to the dispatch centre and confirmed by the ambulance crew on the basis of clinical assessment. The cases of OHCA included are the first events only per individual to prevent potential overlap in control periods.

Air pollution and weather data

Under the hypothesis that short-term effects of air pollution may trigger cardiovascular events, we chose to investigate a one-week lag exposure time window prior to the day of the intervention. We collected daily measurements of PM_{10} and $PM_{2.5}$ concentration for the entire catchment area, throughout the study period (24 months). PM estimates were derived from the Flexible Air quality Regional Model (FARM), a three-dimensional Eulerian chemical transport grid model for dispersion, transformation and deposition of particulates, capable of simulating PM_{10} concentration at municipality resolution and were available as daily means at the level of the municipality, as reported in the ARPA Lombardia (Regional Agency for Environmental Protection) website (https://goo.gl/SbhMTb).[12]

Using ArcGIS® software by Esri, we assigned to each subject the daily PM concentration of the municipality, where the geographic coordinate of the ambulance call-out falls, the day of intervention and back to six days (i.e. from day –1 to day –6). The daily mean temperature was assigned to each subject at the geographic coordinate of the municipality where the ambulance call-out falls, on the day of the intervention. Information on meteorological variables, for example, temperature (T) and humidity (H), were obtained from ARPA monitoring stations spread throughout the regional territory (https://www.arpalombardia.it/Pages/ARPA_Home_Page.aspx). We linked to each subject the meteorological variables recorded from the nearest monitor to the place of intervention.

Statistical analysis

The analysis of the relationship between changes in the levels of PM_{10} and short-term variation in hospital call-out was carried out by applying a distributed lag non-linear model to a case-crossover design. We performed a bidirectional case-crossover analysis using a time-stratified design, considering each subject separately. Thus, for each case (call-out for OHCA) we compared each subject's exposure in a time period just before a case event (hazard period) with that subject's exposure at other times (control periods). The use of control periods after the event is allowed because the exposures cannot be influenced by the event.[13] Control days were taken respectively one, two, three and four weeks before and after the case and were additionally matched by day of the week to control for any weekly patterns in PM_{10} exposure. We assigned time-varying exposure to cases and control using the daily mean concentration of PM_{10}. Each subject serves as its own control so that known and unknown time-invariant confounders are inherently adjusted for by study design. Conditional logistic regression analysis was fitted to the data to calculate odds ratios (ORs) and standard deviations for an increase in $10\,\mu g/m^3$ in PM_{10} and we report results as the mean percentage change, computed as: $[\exp(\ln(OR)) \times 10)\ -1] \times 100]$. PM exposures on the day of the OHCA event (lag 0), as well as exposures from one to six days previous to the OHCA event (lag 1 to lag 6) in a distributed lag model framework. Time-independent factors (e.g. age, gender) and temporal trends are accounted for by design, by matching on person and time-window. To adjust for the potential confounding effect of influenza episodes, we obtained data on weekly consultation rates for influenza-like illnesses in the Lombardy region (https://old.

iss.it/site/RMI/influnet/pagine/stagioni.aspx) and we used that variable in the model. We conducted an exploratory analysis with single lag models fitting each lag term of PM_{10} exposure one at a time to examine the association of PM_{10} with OHCA. The temperature was included in the model as averages of the temperature on the same day and the previous three days (lag 0–3). We evaluated linearity and potential non-linearity in the response function for PM temperature (average lag 0–3), fitting univariate models using linear functions, polynomials and natural cubic splines, using a different degree of freedom (df), with knots placed at equally spaced percentiles of the distribution. A cubic function for temperature and a natural cubic spline for PM produce the best model fitting. We applied lag distributed non-linear models to account for the delayed effect of PM on daily OHCA adding a natural cubic spline with 3 df at equally spaced quantiles for the PM at lag 0–6. The choices of the knots, which define the degrees of freedom, were based on modified Akaike information criteria. We examined the potential interaction effect of temperature to assess whether the effect of PM_{10} exposure on OHCA differs, depending on the temperature levels. We investigated effect modification of temperature using an interaction term between the moving average of temperature lag 0–3 and the function of the lagged exposures. Log-likelihood ratio tests comparing models, with or without the interaction term, were used to assess effect modification between PM_{10} exposure (zero to six-day lags) and temperature in relation to risk of OHCA. We adjusted our model for temperature (moving average of lag 0–3), dew-point temperature, the interaction between PM, as a function of lag times from zero to six lags, and temperature, influenza-like illness. Lag-specific percentage change in risk of OHCA showing the effect of a specific temperature and lag values on OHCA were then presented together with the cumulative effect over lag days 0–6. Change in risk for specific temperature was calculated for low temperature (first centile), medium (50th centile), moderately warm (75th centile) and extremely warm (99th centile).

We did sensitivity analyses to assess the impact of model choices:

1. Different time lags of the explanatory variables were tested.
2. We used the apparent temperature instead of temperature adjusted for dew-point temperature. We calculated the apparent temperature (At), as the measure of the perceived temperature in degrees Celsius derived from a combination of temperature and humidity, according to the following formula: $At = -2.653 + 0.994 \cdot T + 0.0153 * (DEW)^2$, where the dew point ($DEW$) is defined as $DEW = (H/100)^{(1/8)} \cdot (112 + (0.9 \cdot T)) + 0.1 \cdot T - 112)$.[14]
3. We used the relative humidity, instead of adjustment for dew-point temperature.

Analyses were performed with SAS software (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 5761 OHCAs were included in the study. Mean incidence over the two-year study period was 7.9 cases per day. The number of cases was higher for males (55.4%), and mean age at occurrence was 77.3 years. Figure 1 shows a map with mean PM_{10} during the study period for each municipality involved in the catchment area (Figure 1(a)) and the geographic location of each OHCA event (Figure 1(b)). The distribution of mean $PM_{2.5}$ and PM_{10} across days preceding the OHCA event, and temperature distribution, are reported in Figure 2. As previously reported by studies performed in the same geographic area,[15] the correlation between $PM_{2.5}$ and PM_{10} was extremely high ($R^2 = 0.97$). For the analyses described below, we used PM_{10} instead of $PM_{2.5}$ to improve coverage and spatial resolution of PM_{10} data available. Characteristics of the study population, PM and temperature levels across seasons, are reported in Table 1. An inverse correlation was observed between PM_{10} and temperature ($r = -0.56$).

A higher risk of OHCA was associated with exposure to PM_{10} during several time intervals. Figure 3 presents the relationship between PM exposure at different lag days and the risk of OHCA. The association at single day lags were essentially null up to two days before the event and increased in magnitude from three to five days before, declining on the sixth day. The strongest association was experienced three days before the cardiac event with an increase of 1.7% (95% confidence interval (CI): 0.5–2.9%) (Supplementary Material Table 1 online). The cumulative exposure risk over the lags 0–6 was 8.5% (95% CI: 0.0–17.9%). Figure 4 shows the risk of OHCA evaluated at four selected levels of temperature (1° centile, median value, 75°, 99° centiles). The association between PM_{10} and OHCA risk grew stronger at higher temperatures. The lag specific associations at different temperatures showed a null effect for low temperatures and the largest increase associated with the highest temperatures. A slight increase in risk was observed at medium temperatures (14°C) from three to five days before the event, with a change ranging from 1.35% to 1.70%. Moderate and extremely warm temperatures showed a non-significant risk at the day of the cardiac arrest (lag 0) and a strong and significant increase risk from two to six days before the event. The strongest association with OHCA was

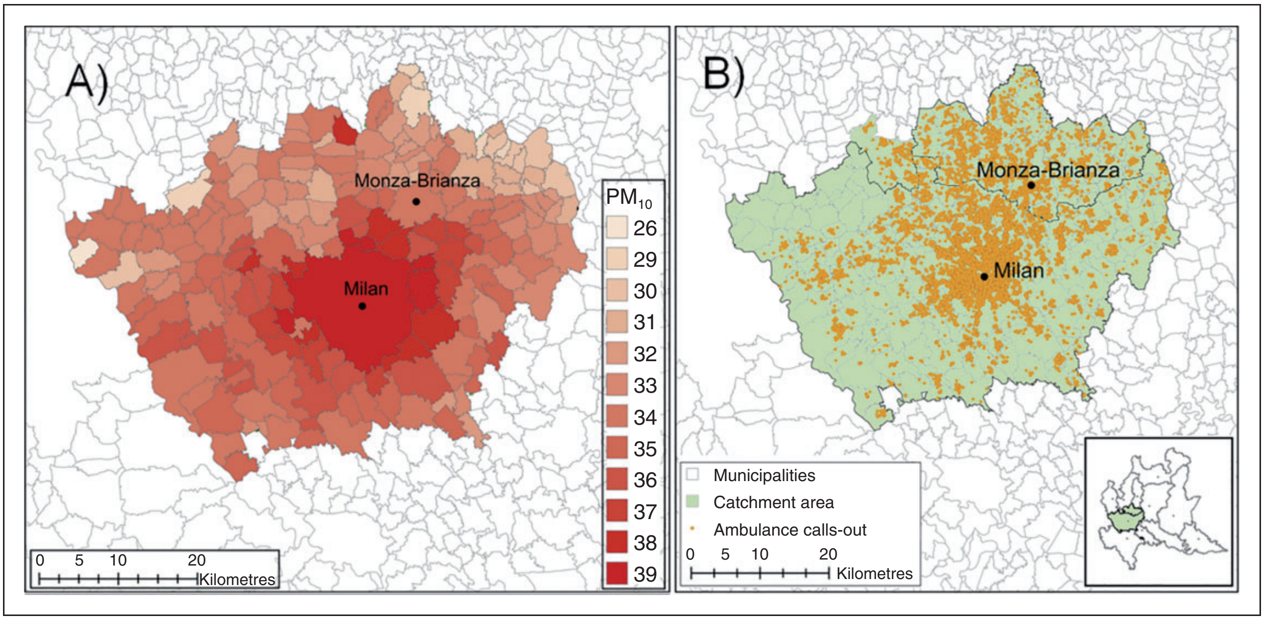

Figure 1. (a) Graphical representation of PM_{10} concentration levels predicted by the Flexible Air quality Regional Model for the mean of the two-year study period 2015–2016 and (b) location of each OHCA event.
PM: particulate matter; OHCA: out-of-hospital cardiac arrest

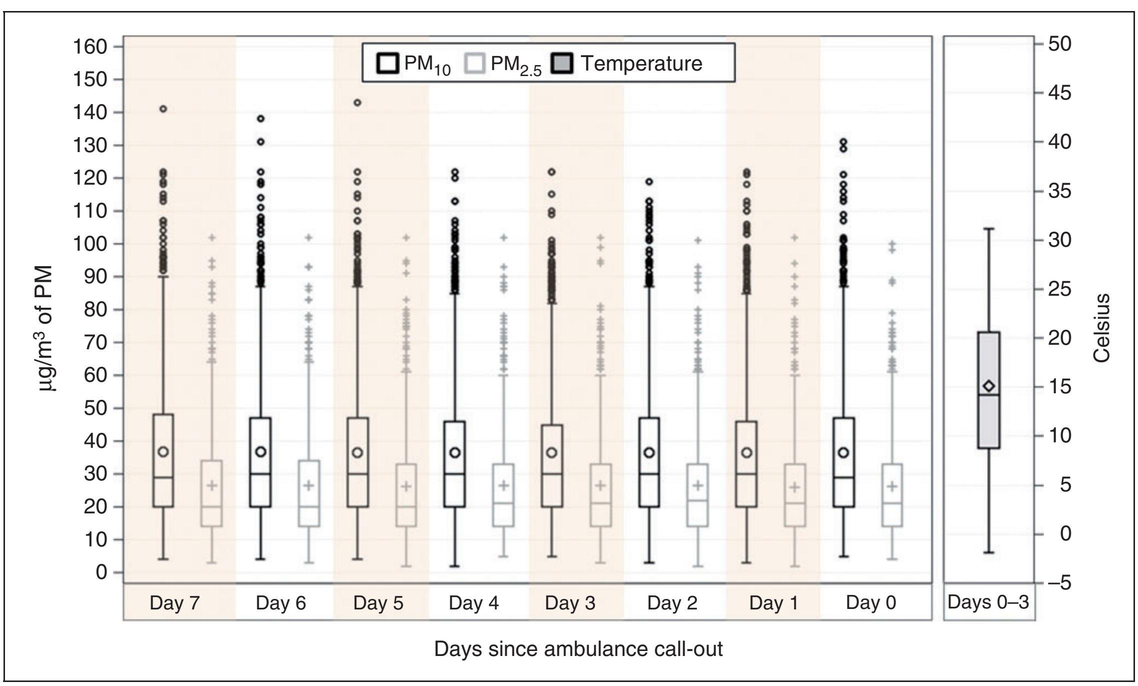

Figure 2. Distribution of $PM_{2.5}$, $PM_{10,}$ the day of the out-of-hospital cardiac arrest event and across the preceding days and temperature averaged over lag 0–3.
PM: particulate matter

experienced three days before the event, which showed an increased risk of 8.2% with moderately warm (23°C) and of 14% with extremely warm (31°C) temperatures (Supplementary Table 2). A plot showing the changes in OHCA risk along the range of temperature and PM for the day of exposure strongly associated with ambulance call-outs (lag 3) is also presented (Figure 5). Other models included in the sensitivity analyses (detailed in

Table 1. Description of the study population.

	OHCA $N = 5761$
Cases per day, mean (min–max, ±SD)	7.9 (1–31; ±3.3)
Year, *n* (%)	
2015	2991 (51.9)
2016	2770 (48.1)
Sex, *n* (%)	
Female	2569 (44.6)
Male	3192 (55.4)
Age, year, mean (SD)	77.3 (14.5)
Registered cases of seasonal Influenza in Lombardy, $N = 33{,}898$, %	
Winter	84.4%
Spring	0.5%
Summer	0.0%
Autumn	15.1%
PM_{10} at OHCA µg/m^3, median (IQR)	
Overall	29.0 (27.0)
Winter	45.0 (34.0)
Spring	23.0 (15.0)
Summer	22.0 (10.0)
Autumn	45.5 (42.0)
$PM_{2.5}$ at OHCA, µg/m^3, median (IQR)	
Overall	21.0 (19.0)
Winter	31.5 (24.0)
Spring	16.0 (9.0)
Summer	15.0 (8.0)
Autumn	31.5 (27.0)
Temperature (average lag 0–3), Celsius, median (IQR)	
Overall	14.0 (12.8)
Winter	7.4 (3.5)
Spring	18.2 (5.9)
Summer	26.8 (4.1)
Autumn	12.0 (7.0)

OHCA: out-of-hospital cardiac arrest; IQR: interquartile range

the Methods section) gave similar results to the main analysis.

Discussion

This study shows for the first time a joint effect of PM and temperature in triggering OHCA. The maximum effect, obtained by a bidirectional case-crossover approach, was observed for high levels of PM in the presence of high temperatures. We found a potentially synergistic effect, which may have a tremendous impact on future public health. In fact, the two environmental conditions described are becoming more and more frequent because of global warming, which may

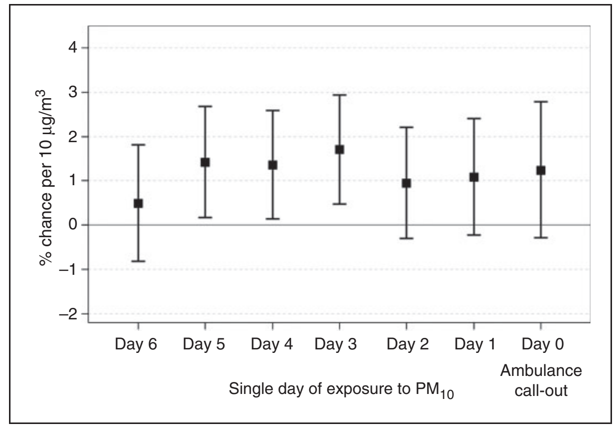

Figure 3. Estimated percentage change of out-of-hospital cardiac arrest risk according to 10 µg/m^3 increase in the daily mean concentration of PM_{10}.
Adjusted percentage change is calculated from conditional logistic regression models and presented by the change in 10 µg/m^3. PM_{10} was fitted from a distributed lag non-linear model over lags 0 to 6 days adding a natural cubic spline with 3 df at equally spaced quantiles for the PM at lag 0–6. Models were adjusted for temperature (average lag 0–3), dew-point temperature, the interaction between PM as a function of lag times 0–6 and temperature, influenza-like illness. Out-of-hospital cardiac arrest risk estimates are evaluated at a temperature of 14°C (median value). PM: particulate matter.

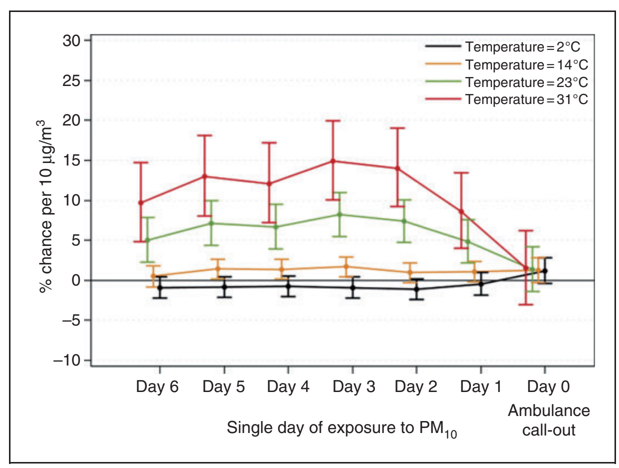

Figure 4. Estimated percentage change of out-of-hospital cardiac arrest risk according to 10 µg/m^3 increase in the daily mean concentration of PM_{10}.
Out-of-hospital cardiac arrest (OHCA) percentage change was estimated from a distributed lag non-linear model over lags 0 to 6 days of exposure adding a natural cubic spline with 3 df at equally spaced quantiles for the particulate matter (PM) at lag 0–6. Models were adjusted for temperature (average lag 0–3), dew-point temperature, the interaction between PM as a function of lag times 0–6 and temperature, influenza-like illness. OHCA risk estimates are evaluated at different temperatures defined as low (2°C), medium (14°C), moderately warm (23°C) and extremely warm (31°C).

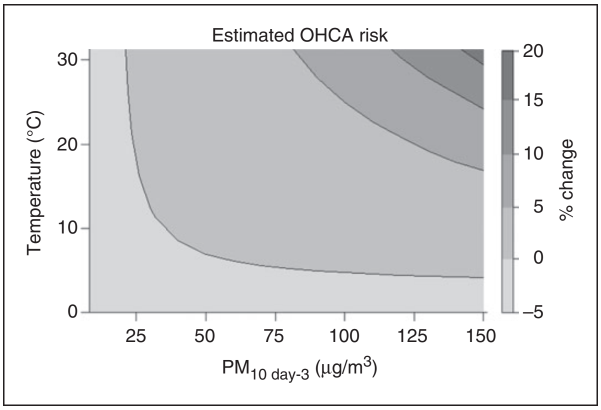

Figure 5. Estimated percentage change in risk of out-of-hospital cardiac arrest across levels of PM_{10} day 3 and temperature. PM_{10} was fitted from a distributed lag non-linear model over lags 0 to 6 days adding a natural cubic spline with 3 df at equally spaced quantiles for the particulate matter (PM) at lag 0–6. Models were adjusted for temperature (average lag 0–3), dew-point temperature, the interaction between PM as a function of lag times 0–6 and temperature, influenza-like illness. Out-of-hospital cardiac arrest risk estimates are evaluated at different temperatures defined as low (2°C), medium (14°C), moderately warm (23°C) and extremely warm (31°C).

exacerbate the detrimental effects of air pollution on human health.[16,17]

Our findings indicate that risk of ambulance calls for cardiac arrest was higher in periods with elevated PM levels and that three days prior the level was the most effective, in term of risk estimate, with a significant cumulative percentage change over the three days before the occurrence of OHCA. This does not necessarily mean that the day of the ambulance call was characterized by low PM levels (Figure 2 shows the mean levels of PM across days). The observed lag between the environmental trigger (PM exposure) and cardiovascular event (OHCA) is not uncommon and has a strong biological explanation. Particulate air pollutants produce a strong inflammatory reaction in the lungs, but only a very small fraction of these particles are able to travel and reach peripheral tissues such as the heart. Thus, the most accredited hypothesis is that the exposure occurring at the pulmonary level is only the first event of a cascade involving a strong 'cross-talk' between the pulmonary and cardiovascular systems.

Previous papers[17] reported similar findings, with increased mortality in cardiovascular events associated with the exposure experienced three days before. Moreover, also conspicuous items in the literature focused on biomarkers measured in peripheral blood, consistently showing a maximum effect of PM levels measured three days before the blood draw.

Altogether, these findings gave us a robust rationale to infer that the observed effect is not likely to be due to chance.

This study has several strengths. First, our study is based on an extremely large number of cases, covering an area with approximately four million inhabitants, which is characterized by the highest PM levels in Western Europe. Second, we validated OHCA after evaluation of the ambulance call-outs, which yielded a limited selection of OHCA events. Moreover, our study covers two years in an area characterized not only by high PM levels but also by large seasonal variations in temperature, which optimized exposure contrast for PM levels and temperature.

Nonetheless, the study does have certain limitations. The personal level of PM exposure was determined on the basis of the address where each case experienced OHCA; this address may have differed from the residential address. On one hand, this approach prevented exposure misclassification of people living (and having an OHCA) outside their residential address. On the other hand, this approach may have led to improper measurements of individual exposure for subjects who had OHCA in a municipality differing from the place they had been just days earlier. However, our analysis based risk estimates on temporal variability, which, in our region, showed high collinearity across municipalities. This high collinearity of PM levels over time throughout the entire catchment area derives mainly from meteorological factors.

In addition, by using ambulance call-out records, we were able to examine a relatively large number of events ($N = 5761$). This approach, however, suffers from the lack of personal data of each subject, such as socioeconomic status, previous cardiovascular disease, or other known risk factors. For example, it is possible that we have underestimated the contribution of several chronic comorbidities in defining susceptibility to PM and temperature exposures.

The present study helps to clarify the controversial role of PM as an OHCA determinant and helps to identify the role of increased temperature as a key interactive factor in triggering OHCA. These findings support the concept that tackling air pollution and climate change may have relevant effects in terms of public health.[18]

Moreover, our study results suggest that the out-of-hospital emergency system may forecast an increase in emergency calls during days with high levels of PM and higher temperatures, which would allow institutions to dedicate human and technical resources to out-of-hospital emergency calls. Future ad hoc studies are needed in order to clarify the pathophysiological pathways that underlie the observed effects.

Author contribution

ET and SI equally contributed to the manuscript. ET, SI, RB, AB, GS, VB and NM contributed to the conception or design of the work. RB and MB contributed to the acquisition of data for the work, ET, SI, MB, VB and NM contributed to the interpretation of data for the work. SI contributed to the analysis of data for the work. ET, SI, MB, VB and NM drafted the manuscript. ET, SI, RB, MB, AB, GS, VB and NM critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

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