European Heart Journal (2014) **35**, 861–867
doi:10.1093/eurheartj/eht489

Short-term effects of air pollution on out-of-hospital cardiac arrest in Stockholm

Auriba Raza[1], Tom Bellander[1,2]*, Getahun Bero-Bedada[1], Marcus Dahlquist[1], Jacob Hollenberg[3], Martin Jonsson[3], Tomas Lind[1,2], Mårten Rosenqvist[4], Leif Svensson[3], and Petter L.S. Ljungman[1,5]

[1]Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, SE-17177 Stockholm, Sweden; [2]Department of Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden; [3]Department of Cardiology, Karolinska Institutet, Stockholm South General Hospital, Stockholm, Sweden; [4]Department of Cardiology, Karolinska Institutet, Danderyds Sjukhus, Stockholm, Sweden; and [5]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Received 15 July 2013; revised 4 November 2013; accepted 4 November 2013; online publish-ahead-of-print 2 December 2013

Background Although ozone (O_3) and other pollutants have been associated with cardiovascular morbidity and mortality, the effects of O_3 on out-of-hospital cardiac arrest (OHCA) have rarely been addressed and existing studies have presented inconsistent findings. The objective of this study was to determine the effects of short-term exposure to air pollution including O_3 on the occurrence of OHCA, and assess effect modification by season, age, and gender.

Methods and results A total of 5973 Emergency Medical Service-assessed OHCA cases in Stockholm County 2000–10 were obtained from the Swedish cardiac arrest register. A time-stratified case-crossover design was used to analyse exposure to air pollution and the risk of OHCA. Exposure to O_3, $PM_{2.5}$, PM_{10}, NO_2, and NO_x was defined as the mean urban background level during 0–2, 0–24, and 0–72 h before the event and control time points. We adjusted for temperature and relative humidity. Ozone in urban background was associated with an increased risk of OHCA for all time windows. The respective odds ratio (confidence interval) for a 10 $\mu g/m^3$ increase was 1.02 (1.01–1.05) for a 2-h window, 1.04 (1.01–1.07) for 24-h, and 1.05 (1.01–1.09) for 3 day. The association with 2-h O_3 was stronger for events that occurred outdoors: 1.13 (1.06–1.21). We observed no effects for other pollutants and no effect modification by age, gender, or season.

Conclusion Short-term exposure to moderate levels of O_3 is associated with an increased risk of OHCA.

Keywords Out-of-hospital cardiac arrest • Ozone • Air pollution • Stockholm

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health problem. Survival after an incident of OHCA is low and it is a leading cause of death in the USA and Europe.[1,2] Recent estimates in USA suggest that 295 000 emergency medical service-treated (EMS) cardiac arrests (CA) occur annually, with only 8% survival to hospital discharge.[3] In Europe an estimated 275 000 all-rhythms, CAs are treated by EMS annually with 10.7% surviving to hospital discharge.[1] In Sweden, ~5000–10 000[4] CAs occur each year with ~3–16% survival to 1 month.[5]

Although there is ample evidence of negative health effects from air pollution,[6,7] only a handful of studies with inconsistent results have focused on the harmful effects of air pollution exposure on OHCA.[8–15] Studies have used small data sets or calendar day averages for exposure, which carry a risk of exposure misclassification. In our previous study, 2-h exposure to particles was associated with an increased risk of ventricular arrhythmias in patients with implantable cardioverter devices,[16] pointing to the possible importance of shorter exposure periods. Larger OHCA studies with hourly pollutant averages are lacking and a convincing link with air pollution has not yet been established.

We aimed to investigate short-term exposure to air pollution and the risk of OHCA, using a well-defined prospective OHCA registry and high temporal resolution of exposure.

Methods

Study area and outcome data

Our study population included all EMS-assessed cases of OHCA that occurred in Stockholm County between 2000 and 2010, and included in the

* Corresponding author. Tel: +46 852480003, Fax: +46 8304571, Email: tom.bellander@ki.se

Swedish Cardiac Arrest register,[17] that uses the Utstein criteria[18] for reporting. This register is supported by the Swedish National Board of Health and Welfare and started operation in 1990 covering 80% of all OHCA patients in Sweden. It comprises information about age, gender, time and location of event, the patient's status at EMS arrival, and plausible cause as assessed by the EMS personnel.

We defined CA as sudden cessation of cardiac mechanical activity in the absence of non-cardiac cause of CA. The ambulance crew classified the probable cause of CA based on clinical assessment and bystander information.

We excluded cases that had been assessed as non-cardiac (*Figure 1*) and to avoid temporal misclassification of exposure, those who were dead on the arrival (rigor mortis) of EMS personnel, and all patients with missing time data. The stated time of the CA was obtained from the time of the call to the dispatch centre (42.7%) or the communication between the emergency dispatch and the ambulance (56%). For 1.3% of cases, this information was not available and the earliest available secondary time data were used, e.g. the time of the ambulance arrival.

This study was approved by the regional ethical review board and complied with the Declaration of Helsinki.

Air pollution and meteorological data

Exposure data were provided by the Stockholm-Uppsala County Air Quality Management Association and the Swedish Environmental Research Institute. Hourly means of Nitrogen dioxide (NO_2), Nitrogen oxides (NO_x), Ozone (O_3) and particles with aerodynamic diameter smaller than 2.5 and 10 μm ($PM_{2.5}$ and PM_{10}) were obtained from roof-level monitors within central Stockholm. To estimate the coarse fraction of particles, we calculated the difference between $PM_{2.5}$ PM_{10} from the same station. Additional O_3 data were obtained from a rural station 80 km southwest of Stockholm.[19] Meteorological data including hourly values of temperature and relative humidity were obtained from a suburban station. Air pollution levels were collected independently and blindly of health outcome data and then merged. Averaging periods were constructed blindly according to the pre-defined time-stratified protocol described below.

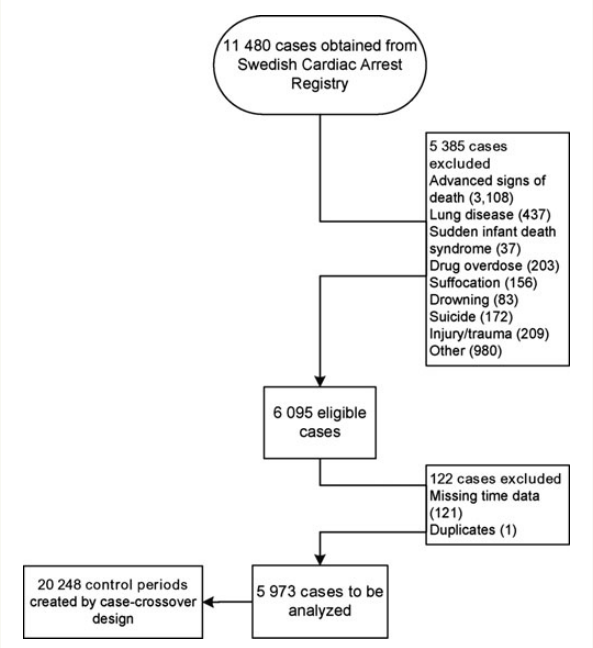

Figure 1 Flow chart of inclusion of cases of out-of-hospital cardiac arrest.

Statistical analysis

Spearman correlation coefficients were calculated for the relationship between air pollutants and meteorological variables.

A case-crossover design with time-stratified referent selection was used to analyse air pollution and the risk of OHCA. The period instantaneously proceeding the time of event was the case period and all other comparable time intervals within the same time stratum were control periods. Since each patient serves as their own control slowly changing personal characteristics cannot confound the association.

The reported time of the event was rounded back to the preceding hour. We used control periods for the same hour intervals for all same days of the week within the same calendar month (leading to three to four controls per case). The effect of exposure was analysed with conditional logistic regression.

Two-, 24-, and 72-h means of all pollutants, and for O_3 the maximum 8-h mean within the previous 24-h, were constructed from hourly means. Complete data were required for the 2-h averages and the maximum 8-h O_3. For longer exposure windows, at least 75% coverage was required.

The specific associations of exposure in different time windows, with adjustment for other time windows, were obtained by distributed lag models including adjacent lags in the model (all 24-h windows up until 7-days).

The crude models were extended with adjustment for temperature and relative humidity, using the same exposure periods as for air pollution, except for the 2-h lags where 24-h average was used. Temperature was modelled as piece-wise linear splines with one knot at the temperature threshold (12°C). The temperature threshold was identified as the 24-h temperature associated with the lowest odds ratio (OR) for OHCA (Marcus Dahlquist, unpublished data, 2013).

For pollutants demonstrating effects, we constructed two-pollutant models including both pollutants as linear terms in the model. The influence of season on O_3 effects was explored using separate analyses for warm (April-September) and cold season (October-March). Temperature was modelled as for the whole year but with the knot set at the minimum risk temperature of 10°C for summer and 14°C for winter.

Possible effect modification of the association between OHCA and air pollution by age (categorized below the median or median plus above) and gender was investigated by constructing multiplicative interaction terms.

To test if our exposure classification performed better for events occurring outdoors, as a sensitivity analyses, we modelled an interaction between 2-h air pollution exposure and OHCA by event location. Events that were reported to have occurred outdoors or in the street, public transport, taxis, cars, public transport stations or terminals, and in sports facilities were coded as outdoors, and those events that occurred at home, nursing homes, and workplace were classified as indoors. Events at other locations were classified as unknown with respect to indoors or outdoors. In addition, we conducted an interaction analysis using bystander information to explore the possibility that witnessed OHCAs would imply a better temporal estimation of time of OHCA.

For comparison with the air quality guideline (AQG) set at 100 $\mu g/m^3$ maximum 8-h daily mean for O_3 set by the World Health Organization (WHO), we explored the exposure–response relationship between for O_3 exposure and risk of OHCA by categories of 20 $\mu g/m^3$ of exposure with the lowest exposure category as a reference.

The estimates are expressed as OR per 10 $\mu g/m^3$ with 95% confidence interval (CI). A *P*-value of 0.1 was considered significant for interaction.

Data management, descriptive statistics, and analysis were performed using STATA version 12 (StataCorp, College Station, USA).

Results

Study population and exposure characteristics

Out of 11 480 EMS-assessed cases during the study period, 5973 met the inclusion criteria. A flow chart of inclusion is provided in *Figure 1*.

The mean incidence of included CA was 1.5 cases per day over the 11 years study period. A majority of cases was men (67%) and the average age in years at which the CA occurred in women was 74, whereas in men it was 70. Approximately two-thirds of the OHCA occurred at home and were witnessed. Other characteristics of the study population are presented in *Table 1*.

The distribution of the air pollutants and meteorological measurements during the study period are summarized in *Table 2*. The means for the 24-h case and control periods show very small differences in the air pollution levels. Ozone measured at the regional station was somewhat higher than that from the urban background station, but the two are highly correlated (*Table 3*). NO_2 and NO_x were strongly correlated to each other and negatively correlated to O_3. There was no correlation between temperature and any fraction of particulate matter (PM).

Ozone demonstrated a clear seasonal pattern with higher levels in warmer months but no clear long-term trend over the entire study period (*Figure 2*).

Associations between air pollution and out-of-hospital cardiac arrest

Urban background O_3 demonstrated statistically significant positive associations for 2-h and 24-h exposures and with larger estimates for the latter (*Figure 3*). No associations were observed for any of the PM fractions and OHCA. NO_2 and NO_x exposure was negatively associated with both 2- and 24-h average exposures.

Table 1 Study population characteristics

Category	Men (%)	Women (%)
Age		
≤40 years	152 (3.8)	69 (3.5)
41–60 years	730 (18.2)	262 (13.4)
61–80 years	1928 (48.0)	767 (39.3)
>80 years	1015 (25.2)	804 (41.2)
Missing	195 (4.9)	49 (2.5)
Place of cardiac arrest		
Home	2424 (60.3)	1431 (73.3)
Outdoors/street	251 (6.2)	59 (3.0)
Nursing home	53 (1.3)	63 (3.2)
Workplace	103 (2.6)	10 (0.5)
Ambulance	152 (3.8)	82 (4.2)
Primary healthcare centre	23 (0.6)	8 (0.4)
Public transportation and taxi	16 (0.4)	5 (0.3)
Public transportation station/terminal	29 (0.7)	7 (0.4)
Car	42 (1.0)	6 (0.3)
Airport	12 (0.3)	4 (0.2)
Sports facility/fitness centre/golf course/public bath	19 (0.5)	2 (0.1)
Public facility	624 (15.5)	139 (7.1)
Shopping mall/store	29 (0.7)	10 (0.5)
Other place	192 (4.8)	111 (5.7)
Unclear	30 (0.7)	11 (0.6)
Missing	21 (0.5)	3 (0.2)
Plausible aetiology		
Cardiac aetiology	3043 (75.7)	1366 (70.0)
Missing	977 (24.3)	585 (30.0)
Whether the OHCA was witnessed		
Witnessed	2585 (64.3)	1198 (61.4)
Unwitnessed	1146 (28.5)	566 (29.0)
Missing	289 (7.2)	187 (9.6)

Table 2 Distribution of 24-h mean for air pollution levels and meteorological parameters during 2000–10

Parameter ($\mu g/m^3$)	Coverage (%) (all year)	Mean			Min (all year)	Max (all year)	IQR (all year)	Mean for cases	Mean for controls
		All year	Warm	Cold					
$PM_{2.5}$	96.0	8.1	8.2	8.0	0.14	161.7	4.81	7.88	7.90
PM_{coarse}	96.0	7.2	8.0	6.5	−6.0	78.1	5.34	7.20	7.21
NO_2	99.3	15.7	13.2	18.2	1.5	78.1	9.71	15.40	15.55
NO_x	99.2	20.2	16.2	24.2	1.7	254.5	13.05	19.63	19.92
O_3 (rural)	97.3	60.0	66.5	53.4	0	154.6	26.44	59.21	58.73
O_3 (urban)	99.8	51.2	60.5	42.0	2.3	131.9	26.18	50.55	49.96
O_3urban 8 h-max	98.5	62.2	72.9	51.6	3.01	143.4	27.44	61.34	60.80
Temperature(°C)	99.7	7.1	13.1	1.1	−18.2	25.2	12.51	6.45	6.61
Relative humidity (%)	95.0	77.0	71.4	83.2	30.8	99.9	17.87	77.12	77.26

IQR, Inter-quartile range.

Table 3 Correlation among air pollutants and meteorological parameters

	O_3 urban	O_3 rural	O_3 urban 8 h-max	$PM_{2.5}$	PM_{coarse}	NO_x	NO_2|	Temp	Rh
O_3 urban	1.00								
O_3 rural	0.89	1.00							
O_3 urban 8 h-max	0.95	0.84	1.00						
$PM_{2.5}$	0.17	0.25	0.22	1.00					
PM_{coarse}	0.37	0.41	0.40	0.19	1.00				
NO_x	−0.47	−0.26	−0.36	0.23	0.11	1.00			
NO_2	−0.44	−0.20	−0.32	0.24	0.12	0.93	1.00		
Temperature	0.34	0.17	0.39	0.05	0.01	−0.33	−0.39	1.00	
Relative humidity	−0.62	−0.52	−0.63	0.06	−0.43	0.18	0.19	−0.36	1.00

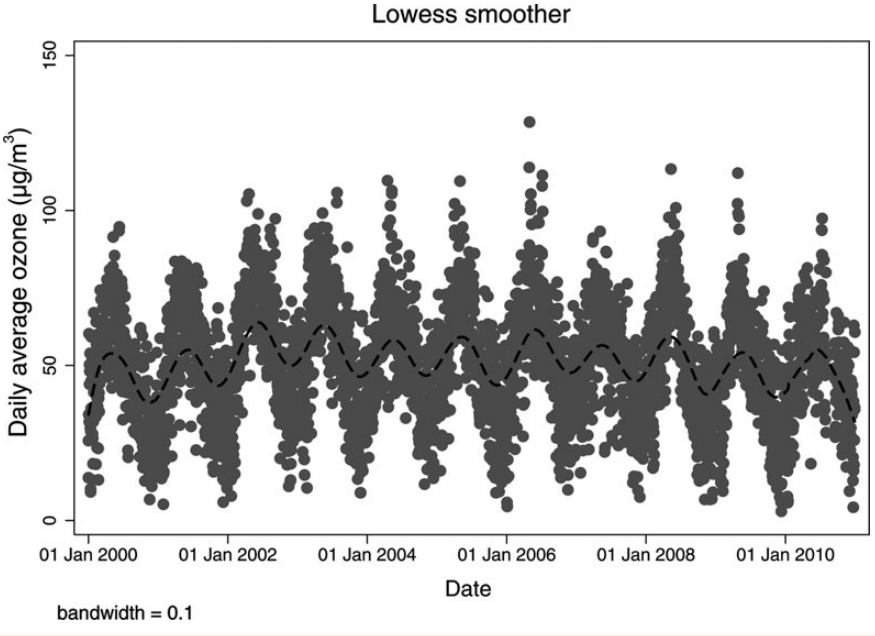

Figure 2 Cyclic seasonal pattern of ozone over the study period (2000–10).

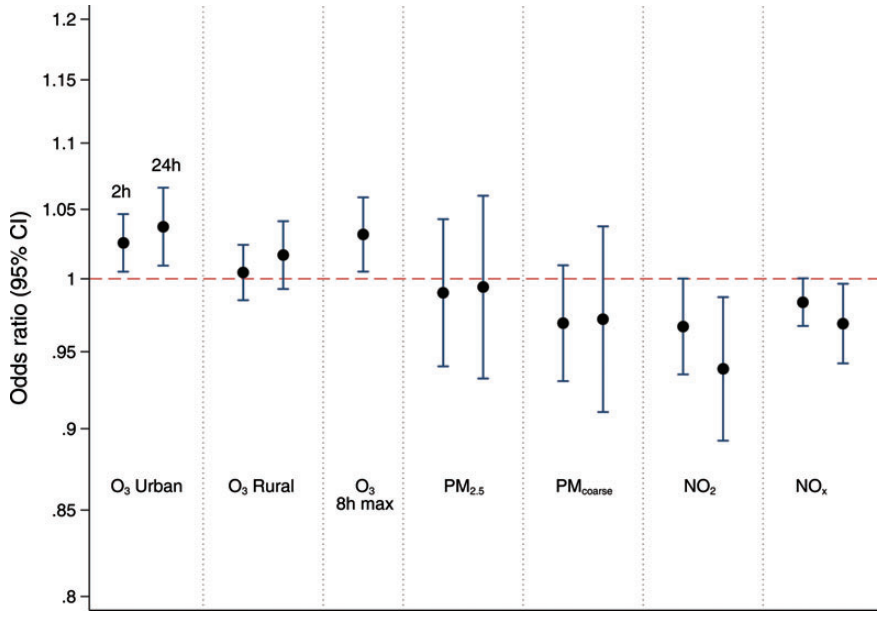

Figure 3 Associations of 2-h and 24-h exposure to air pollutants with out-of-hospital cardiac arrest, per 10 μg/m^3, adjusted for temperature, and relative humidity.

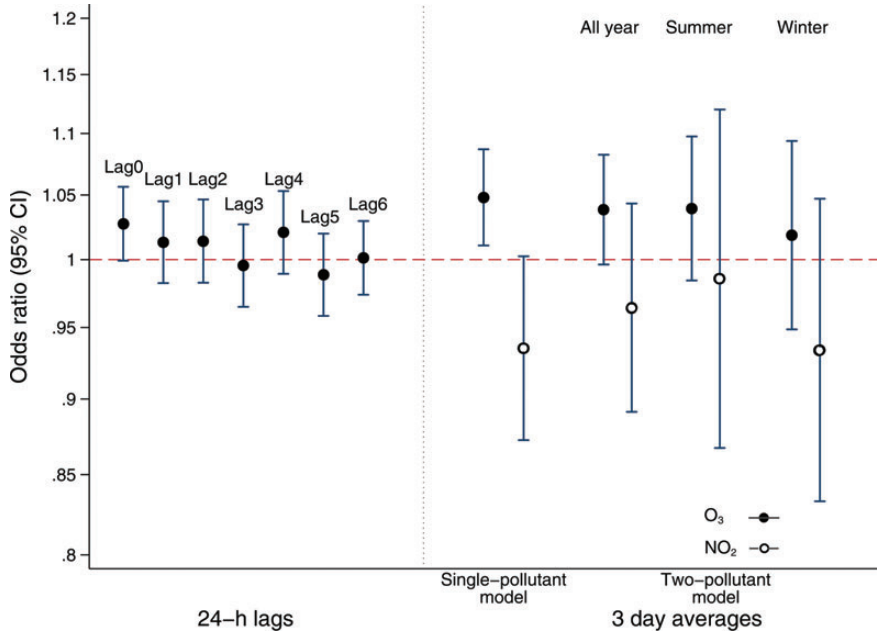

Figure 4 Odds ratios for out-of-hospital cardiac arrest per 10 μg/m^3 increase in ozone and nitrogen dioxide. Distributed 24-h lags, and 3-day average in single and two-pollutant model including nitrogen dioxide and stratified by season.

In the distributed lag model for O_3 with 24-h consecutive lags up until 168-h (Lag6), independent associations were observed between O_3 and OHCA for lag0, and positive non-significant associations for lag1, lag2, and lag4 (*Figure 4*). The average of 3-day exposure to O_3 (72-h prior to the event) demonstrated an OR of 1.05 (CI: 1.01–1.09; *P*-value: 0.01) for a 10 μg/m^3 increase. To compare our results with other studies, we calculated a 48-h average and observed an OR of 1.04 (CI: 1.01–1.08; *P*-value: 0.008). In view of the negative correlation between O_3 and NO_2, we included both pollutants in the same model and the association of NO_2 diminished (*Figure 3*).

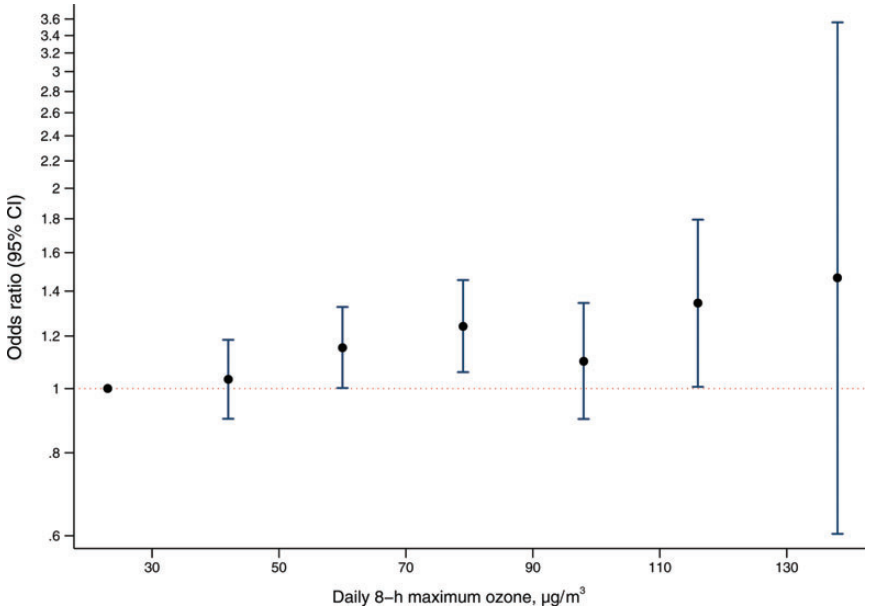

Figure 5 Exposure–response relationship for O_3 and out-of-hospital cardiac arrest. Preceding 8-h max O_3 and OHCA by 20 μg/m^3 categories with the mid-point of lowest category (23 μg/m^3) as a reference. The first and last categories were categorized as min to 30 and 130 to max (143), respectively. The odd ratio is plotted on the log-scale.

None of the PM fractions were found to modify the association of O_3 with OHCA in two-pollutant models (data not shown).

Seasonal analysis

Our results showed stronger associations of 24-h O_3 exposure with OHCA in the cold season (OR: 1.05; CI: 1.01–1.10) compared with the warm season (OR: 1.01; CI: 0.97–1.05) and this interaction was marginally significant (interaction *P*-value = 0.1). However, for 72-h O_3 exposure, we did not observe any seasonal difference in risk (interaction *P*-value = 0.6). The two-pollutant model was also subject to seasonal stratification in warm and cold with results similar to those for the whole year (*Figure 4*).

Subgroup analyses

Events occurring outdoors demonstrated a significantly higher O_3-related risk of OHCA (OR: 1.13; CI: 1.05–1.21) than events occurring indoors (OR: 1.02; CI: 0.99–1.05; interaction *P*-value = 0.001), for 2-h exposure. Interaction analyses by gender, age, or witnessed events showed no differences in association between 24-h exposure window of O_3 and OHCA (interaction *P*-value; gender = 0.4, age = 0.9, witnessed = 0.4).

Exposure–response between ozone exposure and out-of-hospital cardiac arrest

The exposure–response suggests a sustained risk of OHCA on exposure to O_3 concentrations below the WHO guideline of 100 μg/m^3 (*Figure 5*).

Discussion

We found associations between short-term exposure to elevated urban background levels of O_3 and the risk of OHCA. Statistically significant associations were found for 2-, 24-, and 72-h average exposures, as well as for 8-h maximum in the preceding 24-h. The association appeared stronger for events occurring outdoors and our data do not support a biological threshold of effect for O_3. We did not observe any associations between OHCA and other pollutants, and no effect modification by age or gender.

Ozone, a toxic component of the photochemical air pollution mixture, has been associated with cardiovascular morbidity and mortality in many epidemiological studies.[20–22] A few studies have specifically examined out-of-hospital coronary events, including OHCA. Among eight OHCA studies, four studies investigated the association between O_3 exposure, along with other pollutants, and the risk of OHCA. In Melbourne[11] and New York,[12] O_3 exposure was not associated with OHCA. Both studies included roughly 8000 OHCAs, but Melbourne had lower levels of O_3 (mean: 13 ppb, IQR: 8 ppb) than New York (median: 28 ppb, IQR: 22 ppb). In a smaller study from Helsinki (n = 2134),[14] the results were inconsistent but with an indication of a 2-day lagged effect driven by OHCAs of cardiac aetiologies other than myocardial infarction. Recently in a large study in Houston (n = 11 677), O_3 exposure was associated with OHCA, for averages of up to 3-h and for an 8-h maximum of O_3 on the day of the event but not for longer exposure periods.[13] Compared with the results from Houston, we found stronger associations for the 2-h average and 8-h daily maximum O_3 (OR for 8-hour maximum per 20 ppb: 1.13; CI: 1.02–1.26 in Stockholm vs 1.039 CI: 1.005–1.073 in Houston) as well as for averages upto 3 days.

Ozone shows seasonal variations with higher levels in the warm season when there is more sunlight. Previous studies have reported stronger associations between cardiovascular outcomes and O_3 in the warm season.[22,23] Cold season levels of O_3 were relatively high in our study and we did not observe any consistent seasonal difference.

We observed stronger associations to 2-h air pollution exposure for events coded as outdoors or in traffic, when compared with events coded as indoors, indicating that better exposure classification may uncover very short-term effects. However, the outdoor/indoor status of the reference periods was unknown, why this analysis should be seen as suggestive only.

Owing to correlation with other pollutants, studies have demonstrated that associations with O_3 can be confounded by some of these pollutants, especially particles.[24] However, in our study the effect of O_3 was unaltered when we added $PM_{2.5}$ or PM_{coarse} to the model, consistent with other OHCA studies.[11,14] When O_3 was adjusted for NO_2 in the two-pollutant model, the O_3 estimates remained similar (but non-significant), whereas the association between NO_2 and OHCA approached the null.

Alteration in the balance of autonomic components is an important underlying mechanism of cardiovascular diseases including OHCA.[25] Exposure to ambient O_3 was related to autonomic imbalance with the withdrawal of cardiac parasympathetic nervous activity and prominence of sympathetic nervous activity in healthy elderly,[26] and with alterations in heart rate variability indices in healthy young adults.[27] Several other mechanisms, such as myocardial infarction, alteration in vascular tone, arterial pressure control, inflammation, oxidative stress, and coagulation, have also been associated with O_3 exposure.[21,27,28]

In Northern Europe, high O_3 levels are mostly attributed to long-range transport of O_3 and its precursors from multiple sources in South and Central Europe.[29,30] According to European environmental agency, $<$95% of the total EU urban population are exposed to O_3 levels exceeding the WHO AQG.[31] In our study the WHO AQG of 100 $\mu g/m^3$ (as a daily 8-h maximum)[32] was exceeded only for 7% of the days, indicating that the AQG not be fully protective.[32] We had limited power to identify a threshold, but our data suggest possible health benefits of decreasing exposure to very low levels.

We found no associations with any of the PM studied. Previous studies of air pollution and OHCA reported inconsistent findings for particulates. $PM_{2.5}$ exposure was associated with an increased OCHA risk in Melbourne,[11] New York,[12] Indianapolis,[10] Helsinki,[14] Copenhagen,[15] and Houston,[13] but not in Seattle[8,33] and in western Washington State.[9] Particle number concentration, PM_{10}, and carbon monoxide were significantly associated with out-of-hospital coronary deaths in Rome.[34] Our results for PM therefore are consistent with studies from Washington State but not with studies from other cities. In Stockholm, PM concentrations were relatively low compared with previously studied cities, possibly underpowering our study.

There are several reasons that might explain discrepancies of observed associations between the different pollutants investigated in the separate studies, including differences in methodology, study outcomes, and the characteristics of the local pollution. Furthermore, local climatic, environmental and socioeconomic conditions, and different geographical settings might affect the association.[35] Another explanation could be difference in demographic features, for instance, the higher proportion of elderly residents[35] in our study. Finally, for O_3, the personal exposure could differ by the time spent indoors, and by ventilation characteristics.[36]

This study has several strengths. The most important is the large sample of a well-defined outcome, regarding both aetiology and timing. We used the Swedish Cardiac Arrest Register, which was specifically designed to accurately record OHCA handling times and quality of the EMS. The register provides highly accurate information about the time of CA.[17] The use of data from this registry reduced the risk of selection bias. We had a high coverage of hourly pollutant means collected independently of health outcomes and in contrast to previous studies using calendar day averages we constructed moving averages preceding the OHCA event, minimizing temporal misclassification.

There are also some limitations in our study. Like most studies of this type, we used central urban monitoring station as an exposure estimate for the entire population, assuming that the exposure is homogenous across the whole area. While possibly introducing non-differential misclassification of personal exposure this would underestimate any association.[37] Moreover, information regarding potentially important risk modifiers, as previous hospitalization, disease history, and personal risk factors was not available. However, no bias is expected from such temporally stable individual risk factors, since cases serve as their own controls in the case-crossover design. Another limitation is the unavailability of information about physical activity of the cases before they had OHCA, for instance whether they were clearing snow on sunny spring days, as studies have associated myocardial infarction and sudden cardiac death with snow shoveling.[38] Triggering activities such as these may conceivably be correlated to days with high O_3 levels, however, the degree of confounding is expected to be limited.

Conclusion

The results of our study suggest that short-term elevations of O_3 urban background levels are associated with an increased risk of OHCA with no indication of a threshold level, in a region with $\sim$50 $\mu g/m^3$ annual O_3 levels. Exposure to particulate air pollutants and to NO_2, and NO_x was not associated with OHCA in our study.

Conflict of interest: none declared.

Funding

Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet. This project was further supported through funding from the Swedish Transport Agency. A.R. is supported by Karolinska Institutet's fund for doctoral students (KID).

References

1. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation* 2005;**67**:75–80.
2. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* 2001;**104**:2158–2163.
3. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK,

Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013;**127**:143–152.
4. Hollenberg J. Out-of-hospital cardiac arrest. Karolinska Institutet Clinical Science and Educations 2008.
5. Axelsson C, Claesson A, Engdahl J, Herlitz J, Hollenberg J, Lindqvist J, Rosenqvist M, Svensson L. Outcome after out-of-hospital cardiac arrest witnessed by EMS: Changes over time and factors of importance for outcome in Sweden. *Resuscitation* 2012;**83**:1253–1258.
6. Beckerman BS, Jerrett M, Finkelstein M, Kanaroglou P, Brook JR, Arain MA, Sears MR, Stieb D, Balmes J, Chapman K. The association between chronic exposure to traffic-related air pollution and ischemic heart disease. *J Toxicol Environ Health A* 2012;**75**:402–411.
7. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;**109**:71–77.
8. Levy D, Sheppard L, Checkoway H, Kaufman J, Lumley T, Koenig J, Siscovick D. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. *Epidemiology* 2001;**12**:193–199.
9. Sullivan J, Ishikawa N, Sheppard L, Siscovick D, Checkoway H, Kaufman J. Exposure to ambient fine particulate matter and primary cardiac arrest among persons with and without clinically recognized heart disease. *Am J Epidemiol* 2003;**157**:501–509.
10. Rosenthal FS, Carney JP, Olinger ML. Out-of-hospital cardiac arrest and airborne fine particulate matter: a case-crossover analysis of emergency medical services data in Indianapolis, Indiana. *Environ Health Perspect* 2008;**116**:631–636.
11. Dennekamp M, Akram M, Abramson MJ, Tonkin A, Sim MR, Fridman M, Erbas B. Outdoor air pollution as a trigger for out-of-hospital cardiac arrests. *Epidemiology* 2010;**21**:494–500.
12. Silverman RA, Ito K, Freese J, Kaufman BJ, De Claro D, Braun J, Prezant DJ. Association of ambient fine particles with out-of-hospital cardiac arrests in New York City. *Am J Epidemiol* 2010;**172**:917–923.
13. Ensor KB, Raun LH, Persse D. A Case-Crossover Analysis of Out-of-Hospital Cardiac Arrest and Air Pollution. *Circulation* 2013;**127**:1192–1199.
14. Rosenthal FS, Kuisma M, Lanki T, Hussein T, Boyd J, Halonen JI, Pekkanen J. Association of ozone and particulate air pollution with out-of-hospital cardiac arrest in Helsinki, Finland: evidence for two different etiologies. *J Expo Sci Environ Epidemiol* 2013; **23**:281–288.
15. Wichmann J, Folke F, Torp-Pedersen C, Lippert F, Ketzel M, Ellermann T, Loft S. Out-of-hospital cardiac arrests and outdoor air pollution exposure in Copenhagen, Denmark. *PLoS One* 2013;**8**:e53684.
16. Ljungman PL, Berglind N, Holmgren C, Gadler F, Edvardsson N, Pershagen G, Rosenqvist M, Sjogren B, Bellander T. Rapid effects of air pollution on ventricular arrhythmias. *Eur Heart J* 2008;**29**:2894–2901.
17. Hollenberg J, Bang A, Lindqvist J, Herlitz J, Nordlander R, Svensson L, Rosenqvist M. Difference in survival after out-of-hospital cardiac arrest between the two largest cities in Sweden: a matter of time? *J Intern Med* 2005;**257**:247–254.
18. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, Cassan P, Coovadia A, D'Este K, Finn J, Halperin H, Handley A, Herlitz J, Hickey R, Idris A, Kloeck W, Larkin GL, Mancini ME, Mason P, Mears G, Monsieurs K, Montgomery W, Morley P, Nichol G, Nolan J, Okada K, Perlman J, Shuster M, Steen PA, Sterz F, Tibballs J, Timerman S, Truitt T, Zideman D. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation* 2004; **63**:233–249.
19. Clapp LJ, Jenkin ME. Analysis of the relationship between ambient levels of O_3, NO_2 and NO as a function of NOx in the UK. *Atmos Environ* 2001;**35**:6391–6405.
20. Hampel R, Breitner S, Zareba W, Kraus U, Pitz M, Geruschkat U, Belcredi P, Peters A, Schneider A. Immediate ozone effects on heart rate and repolarisation parameters in potentially susceptible individuals. *Occup Environ Med* 2012;**69**:428–436.
21. Ruidavets JB, Cournot M, Cassadou S, Giroux M, Meybeck M, Ferrieres J. Ozone air pollution is associated with acute myocardial infarction. *Circulation* 2005;**111**: 563–569.
22. Almeida SPd, Casimiro E, Calheiros J. Short-term association between exposure to ozone and mortality in Oporto, Portugal. *Environ Res* 2011;**111**:406–410.
23. Bejot Y, Henrotin JB, Osseby GV, Zeller M, Cottin Y, Giroud M. 280 Impact of ozone air pollution on ischemic cerebral and cardiac events in Dijon, France. *Arch Cardiovasc Dis Suppl* 2011;**3**:93.
24. Borja-Aburto VH, Castillejos M, Gold DR, Bierzwinski S, Loomis D. Mortality and ambient fine particles in southwest Mexico City, 1993–1995. *Environ Health Perspect* 1998;**106**:849–855.
25. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi PG, Traversi E, Cobelli F. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003;**107**:565–570.
26. Jia X, Song X, Shima M, Tamura K, Deng F, Guo X. Acute effect of ambient ozone on heart rate variability in healthy elderly subjects. *J Expo Sci Environ Epidemiol* 2011;**21**: 541–547.
27. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med* 2007;**176**:370–376.
28. Henrotin JB, Zeller M, Lorgis L, Cottin Y, Giroud M, Bejot Y. Evidence of the role of short-term exposure to ozone on ischaemic cerebral and cardiac events: the Dijon Vascular Project (DIVA). *Heart* 2010;**96**:1990–1996.
29. Solberg S, Bergström R, Langner J, Laurila T, Lindskog A. Changes in Nordic surface ozone episodes due to European emission reductions in the 1990s. *Atmos Environ* 2005;**39**:179–192.
30. Tang L, Karlsson PE, Gu Y, Chen D, Grennfelt P. Synoptic weather types and long-range transport patterns for ozone precursors during high-ozone events in Southern Sweden. *Ambio* 2009;**38**:459–464.
31. European Environmental Agency E. Air Quality in Europe—2011 report. 2011.
32. Krzyzanowski M, Cohen A. Update of WHO air quality guidelines. *Air Qual Atmos Health* 2008;**1**:7–13.
33. Checkoway H, Levy D, Sheppard L, Kaufman J, Koenig J, Siscovick D. A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. *Res Rep Health Eff Inst* 2000;**99**:5–28; discussion 29–32.
34. Forastiere F, Stafoggia M, Picciotto S, Bellander T, D'Ippoliti D, Lanki T, von Klot S, Nyberg F, Paatero P, Peters A, Pekkanen J, Sunyer J, Perucci CA. A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. *Am J Respir Crit Care Med* 2005;**172**:1549–1555.
35. Parodi S, Vercelli M, Garrone E, Fontana V, Izzotti A. Ozone air pollution and daily mortality in Genoa, Italy between 1993 and 1996. *Public Health* 2005;**119**:844–850.
36. Saez M, Ballester F, Barcelo MA, Perez-Hoyos S, Bellido J, Tenias JM, Ocana R, Figueiras A, Arribas F, Aragones N, Tobias A, Cirera L, Canada A. A combined analysis of the short-term effects of photochemical air pollutants on mortality within the EMECAM project. *Environ Health Perspect* 2002;**110**:221–228.
37. Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, Cohen A. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect* 2000;**108**:419–426.
38. Franklin BA, Bonzheim K, Gordon S, Timmis GC. Snow shoveling: a trigger for acute myocardial infarction and sudden coronary death. *Am J Cardiol* 1996;**77**:855–858.