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Heat, heat waves, and out-of-hospital cardiac arrest

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A B S T R A C T

Objective: Cardiac arrest is one of the common presentations of cardiovascular disorders and a leading cause of death. There are limited data on the relationship between out-of-hospital cardiac arrest (OHCA) and ambient temperatures, specifically extreme heat. This study investigated how heat and heat waves affect the occurrence of OHCA.
Methods: Seven major cities in Korea with more than 1 million residents were included in this study. A heat wave was defined as a daily mean temperature above the 98th percentile of the yearly distribution for at least two consecutive days.
Results: A total of 50,318 OHCAs of presumed cardiac origin were identified from the nationwide emergency medical service database between 2006 and 2013. Ambient temperature and OHCA had a J-shaped relationship with a trough at 28 °C. Heat waves were shown to be associated with a 14-% increase in the risk of OHCA. Adverse effects were apparent from the beginning of each heat wave period and slightly increased during its continuation. Excess OHCA events during heat waves occurred between 3 PM and 5 PM. Subgroup analysis showed that those 65 years or older were significantly more susceptible to heat waves.
Conclusions: Ambient temperature and OHCA had a J-shaped relationship. The risk of OHCA was significantly increased with heat waves. Excess OHCA events primarily occurred during the afternoon when the temperature was high. We found that the elderly were more susceptible to the deleterious effects of heat waves.

1. Introduction

Extreme heat is associated with an increased risk of mortality and morbidity [1–4]. Previous studies have found remarkable ill-health effects from heat waves, which are defined as prolonged periods of extremely hot weather. The European heat wave in 2003 was shown to be responsible for approximately 70,000 premature deaths [5]. The heat wave in Korea in 1994 was also shown to have caused more than 3000 excess deaths [6]. Health impacts from extreme heat are attracting increasing interest with concerns about climate change [7].

Cardiovascular mortality comprises more than one-half of excess deaths due to heat waves [8–10]. In addition, cardiovascular deaths are reported to be more sensitive to extreme heat than other causes of death [11,12]. Sudden cardiac arrest can arise from a variety of cardiovascular disorders and is frequently associated with fatal outcomes. Most cardiac arrests occur suddenly and unexpectedly before the victim presents to the hospital with preceding symptoms, also known as out-of-hospital cardiac arrest (OHCA). More than 400,000 people develop OHCA annually in the United States [13]. Korea is also seeing an increase in the rate of OHCA: The annual incidence rate increased from 37.5 in 2006 to 46.8 per 100,000 in 2010 [14]. With its high incidence and low survival rate, OHCA is a leading cause of death worldwide [15]. Studies have shown that up to 50% of cardiovascular deaths can be attributed to OHCA.

While previous studies have consistently shown that cardiac arrest occurs more frequently at low ambient temperature [15–18], there are limited studies on the association of OHCA and high temperature. A previous study compared the incidence of OHCA during the 2003 European heat wave with the adjacent 5 years [19]. However, recent studies have tried to estimate the effects of heat as continuous risk variables over time, incorporating nonlinear relationships rather than single distinct episodes [20,21]. Statistical methods such as time-series and case-

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crossover models have been used to assess the short-term effects of exposure to heat or heat waves on health outcomes [22–24], which may also help in the assessment of the effects of heat on OHCA. This study aimed to evaluate the effects of heat on the occurrence of OHCA using a nationwide population-based database in Korea. We also tried to validate the definition of heat waves and to assess the interactions between heat waves and air pollution.

2. Methods

2.1. Study data

This study included OHCA cases in seven major cities in Korea between January 2006 and December 2013. Cities with more than 1 million residents as of 2013 were chosen for this study. Study cities included Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan (Supplementary Fig. 1). All cities have a temperate climate but a variety of temperature ranges and population densities (Table 1).

Study subjects were obtained from the cardiovascular disease surveillance database, a nationwide population-based, retrospective observational database. Details of the database have been described elsewhere [14,25]. Briefly, OHCAs assessed by emergency medical services were collected across the country. Trained medical record reviewers visited the hospitals and reviewed medical records to confirm the etiology of the arrest and to gather information related to the risks and outcomes of individuals using Utstein criteria [26]. An arrest was assumed to be of cardiac origin when there were neither previous symptoms nor known noncardiac etiologies (Supplementary Fig. 2). This study protocol was exempt from review by the Seoul National University Hospital Institutional Review Board (1505-087-673). Informed consent was not obtained because of the retrospective nature of the cohort. Individual patient records were anonymized prior to analysis.

Weather data such as daily mean temperature (°C), relative humidity (%), and air pressure (hPa) were obtained from the Korean Meteorological Administration. Ambient levels of air pollutants including particulate matter (PM) ≤10 μm in aerodynamic diameter (PM_{10}) (μg/m^3), CO (ppm), O_3 (ppb), NO_2 (ppb), and SO_2 (ppb) were obtained from the Korea National Institute of Environmental Research. Daily averages were calculated based on hourly concentrations of each pollutant after omitting 5% of the data points from the top and bottom of the distributions. For ozone, a maximum 8-hour moving average was calculated.

2.2. Statistical analysis

We defined exposure variables as follows: For heat effects, we selected a threshold temperature from the plot of the results of the generalized additive models. Heat effects were then estimated by assessing the impact of a 1 °C increase in the ambient temperature above the threshold level on the incidence of OHCA. Although there is no standard definition, heat waves are usually defined by an absolute or relative temperature threshold within consecutive days. To assess the effects of heat waves, we first decomposed the "main effect" due to the independent effects of the daily high temperature and the "added effect" due to the sustained duration of the heat waves [20]. Heat waves were defined as a daily mean temperature above the 98th percentile of the yearly distribution for at least two consecutive days throughout the study period.

The associations between heat or heat waves and OHCA were investigated using a two-stage analysis. In the first stage, we performed a time-series analysis with the generalized additive models separately for each city assuming a quasi-Poisson distribution, allowing for nonlinearity and delayed effects. The models were controlled for mean temperature, relative humidity, and mean air pressure, which were treated as continuous variables, as well as for the day of the week. The model structure was as follows:

$$\begin{aligned}\ln[E(Y_t{}^c)] &= a^c + \beta^c \boldsymbol{I}(HW_t{}^c) + s(Temperature_t{}^c, df=6) + s(Humidity_t{}^c, df=4)\\ &+ s(Pressure_t{}^c, df=4) + s(Time_t, df=7/\text{year}) + \boldsymbol{I}(DOW_t)\end{aligned}$$

where $E(Y_t^c)$ was the expected daily number of OHCA events on day t in city c; a^c was the intercept of city c; β^c represented the regression coefficient for the risk of OHCA events associated with a heat wave in city c; $\boldsymbol{I}(HW_t^c)$ was the indicator variable for the heat wave (0 if day t is a non-heat wave day, and 1 if day t is a heat-wave day) in city c; $s^c(\cdot)$ was the smooth function using penalized splines to control for non-linear relationships with daily OHCA events from confounding variables (temperature, humidity, and air pressure), seasonality, and time trends. Specifically, we adjusted for ambient temperature on day t with 6 degrees of freedom (*df*) based on a sensitivity analysis using 1–9 *df* for Seoul (Supplementary Fig. 3), 4 *df* for relative humidity and air pressure, and 7 *df* for time trends per year based on previous study results [25]; and $\boldsymbol{I}(DOW_t)$ was the indicator variable for day of the week. For heat effects as defined as high temperature effects, we conducted a segmented regression analysis on the maximal temperature over 28 °C and a mean temperature over 22.5 °C using the same model. In the second stage, city-specific effect estimates were pooled with the use of a random-effects model by the restricted maximum likelihood method. Heterogeneity was assessed using Cochran Q test and I^2 statistics.

Multiple sensitivity analyses were performed to confirm the robustness of the heat wave effects on OHCA. First, a time-stratified, case-crossover analysis was conducted as a sensitivity analysis. As in the time-series model, heat waves were coded as an indicator variable. Control days were chosen such that cases and controls were matched for calendar year, calendar month, and day of the week. Conditional logistic regression was then performed with the same smoothing terms for temperature and humidity as described for the time-series model. Second, we performed sensitivity analyses without adjusting for daily mean temperature but with a study period restriction for warm seasons (from May to September). Finally, interactions between heat waves and air pollution were examined. Heat wave effects were estimated first without adjustments for air pollutants, and then after adjustments for each pollutant in order to assess the magnitude of confounding. Interaction terms between heat waves and each pollutant were introduced in the model. For air pollutant levels, adjustments were made for 1) concentrations on the day of heat waves, 2) moving averages of lag days 1 and 2, and 3) levels on lag day 2.

Statistical analyses were performed using R statistical software [27]. Results were presented as the rate ratio (RR) and odds ratio (OR) with 95% confidence intervals (CI). A P value less than 0.05 was considered significant.

3. Results

3.1. Characteristics of study subjects and cities

A total of 50,318 OHCAs of presumed cardiac origin were identified in seven cities in Korea from January 2006 to December 2013 (2922 days) (Supplementary Fig. 2). The mean age of the study population was 66.1 ± 21.7 years, and about two-thirds were male (Supplementary Table 1). Table 1 summarizes the population number and density, daily mean number of OHCA events, and meteorological characteristics of each study city during the study period. The mean temperatures were between 12 and 15 °C, and the range was widest in Seoul. Highest quantiles of the mean and maximal temperatures in the study cities are detailed in Supplementary Table 2. Correlations between temperature, relative humidity, and air pollutants are detailed in Supplementary Table 3.

3.2. Heat effects on OHCA

Ambient temperature and OHCA had a J-shaped relationship. The lowest risk of cardiac arrest was observed around a daily maximal temperature of 28 °C especially in Seoul, Busan, and Gwangju (Fig. 1, Supplementary Fig. 4). The daily mean temperature of 22.5 °C was associated with the minimum risk of OHCA, corresponding approximately to the 75th percentile (Supplementary Fig. 5). Table 2 shows the pooled effects of heat. A 1-°C increase in maximal temperature was associated with a 1.3% excess risk of OHCA ($P = 0.022$), whereas mean temperature had no significant relationship on OHCA risk.

Table 1
Summary statistics for the number of out-of-hospital cardiac arrest (OHCA) events, meteorological characteristics, and air pollution in seven Korean cities from 2006 to 2013.

City	Size, km^2	Population, thousands	Population density, per km^2	Daily number of OHCAs	Daily mean temperature, °C						Humidity, %	Pressure, hPa
					Mean (SD)	Min	25%	50%	75%	Max		
Seoul	605.52	9926	16,402	7.4 (3.3)	12.7 (10.6)	−14.5	3.8	14.1	22.3	31.8	60.4 (15.0)	1016.0 (8.2)
Busan	758.21	3426	4450	2.8 (1.8)	15.0 (8.3)	−6.9	8.1	16.0	21.8	30.1	60.8 (18.1)	1015.5 (7.1)
Deagu	885.61	2465	2790	1.8 (1.5)	14.6 (9.7)	−8.7	6.2	15.7	22.9	32.9	56.5 (16.3)	1016.1 (7.7)
Incheon	958.61	2826	2715	2.3 (1.7)	12.4 (9.9)	−12.2	4.3	13.7	21.5	31.1	68.8 (15.5)	1016.0 (8.1)
Gwangju	501.41	1514	3021	1.0 (1.1)	14.3 (9.6)	−7.9	5.9	15.3	22.8	31.4	67.3 (13.1)	1016.4 (7.9)
Daejeon	539.73	1540	2851	1.2 (1.1)	12.9 (10.1)	−11.7	4.3	14.0	22.0	31.9	66.7 (14.3)	1016.0 (8.1)
Ulsan	1056.09	1129	1064	0.7 (0.9)	14.3 (8.9)	−7.9	6.8	15.2	21.5	33.1	64.2 (17.0)	1015.5 (7.3)

Data are presented as the mean (standard deviation).

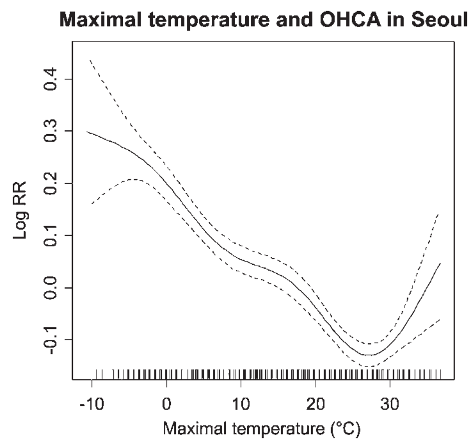

Fig. 1. Generalized additive models for the risk of out-of-hospital cardiac arrest (OHCA) and daily maximal temperature in Seoul. The figure shows estimates (black bold line) and 95% confidence intervals (black dashed lines). The *x*-axis represents daily maximal temperature (°C); the *y*-axis shows the rate ratio for OHCA.

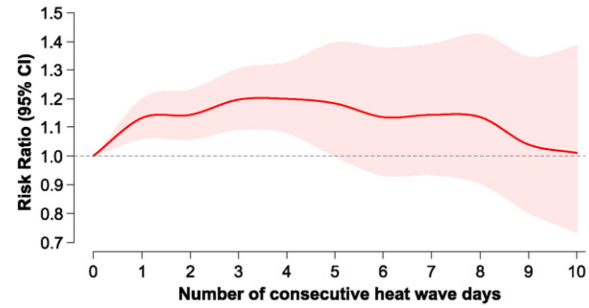

Fig. 2. Relative risk of heat waves according to the duration of consecutive heat wave days (≥98th percentile) with 95% confidence intervals (CI).

Next, we separated the main and added effects of heat waves under a variety of definitions of heat waves (Supplementary Tables 4 and 5). Daily mean temperature had a better discriminative function than maximal temperature, whereas the main effects were stronger than the added effects. Based on these analyses, a mean or maximal temperature above the 98th percentile for 2 days or more was chosen for the definition of heat waves (Table 2). Using the definition, a 14% increase in the risk of OHCA was observed with heat waves for both mean and maximal temperatures ($I^2 = 0\%$ for both models). The effects of heat waves began from the beginning of a heat wave period (Fig. 2). Although the risk further increased over time up to four consecutive days, the added effects were small.

The excess risk of cardiac arrest precipitated by heat waves primarily occurred in the afternoon when the outdoor temperature is at its highest. Fig. 3 shows the distribution of OHCA by the hour of the day during heat wave versus non-heat wave days. During non-heat wave days, the morning hours from 7 to 10 AM were the peak times with a secondary peak at early evening around 5–8 PM. However, during heat waves, the peak was during the late afternoon from 3 to 5 PM (Supplementary Fig. 6).

Heat waves defined using absolute temperature criteria were validated. The Korean Meteorological Administration issues a “heat wave advisory” and a “heat wave alert” when an absolute daily maximal temperature is at or above 33 °C and 35 °C, respectively, for at least two consecutive days. A heat wave defined as ≥33 °C showed only a weak association with OHCA, whereas one as at least 35 °C was associated with a 16-% increased risk of OHCA (Supplementary Table 6). However, heat waves by the latter definition were rare and experienced only in five of the seven study cities during the study period.

3.3. Sensitivity analysis, subgroup analysis, and interactions with air pollution

A sensitivity analysis using case-crossover models showed similar effect estimates (Supplementary Table 7). The case-crossover models showed that heat waves were associated with a 19% increase in the risk of OHCA. Secondary sensitivity models were constructed without adjusting for mean temperature (Supplementary Table 8A). Although the effect estimates were smaller than those from the main analysis, heat waves were statistically associated with increased risk of OHCA. Additional sensitivity analyses were performed by restricting the study period to warm seasons from May to September (Supplementary Table 8B). The OR of heat waves was 1.10, which was similar to that from the main analysis. However, the association was not significant, mainly due to a reduction in statistical power.

Subgroup analysis showed that men and the elderly were more susceptible to developing cardiac arrest during heat waves (Fig. 4). Cardiac arrests with initial shockable rhythms were unaffected by heat waves, whereas arrests with other rhythms increased during heat waves. Interactions were significant only in the age subgroups. We also explored interactions between heat wave effects and air pollution (Fig. 5). The effect estimates of heat waves did not change significantly after adjustments for air pollutants, such as particulate matter ≤10 μm in aerodynamic diameter, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide. No interaction terms were significant for any pollutants with any distributed lag models.

Table 2
Effects of high temperature on out-of-hospital cardiac arrest according to the definition of heat waves.

	1 °C increase of maximal temperature over 28 °C		1 °C increase of mean temperature over 22.5 °C		Heat wave 1 T_{mean} ≥ 98th (≥2 days)			Heat wave 2 T_{max} ≥ 98th (≥2 days)		
	RR (95% CI)	P	RR (95% CI)	P	No. of HW	RR (95% CI)	P	No. of HW	RR (95% CI)	P
Seoul	1.019 (1.004–1.034)	0.012	1.016 (1.003–1.029)	0.017	41	1.12 (0.99–1.26)	0.070	30	1.13 (0.98–1.30)	0.086
Busan	1.026 (0.999–1.055)	0.061	1.015 (0.996–1.034)	0.132	42	1.21 (1.00–1.47)	0.054	36	1.15 (0.93–1.43)	0.190
Daegu	0.999 (0.977–1.020)	0.893	0.998 (0.976–1.020)	0.850	42	0.93 (0.72–1.20)	0.585	36	0.96 (0.74–1.25)	0.770
Incheon	1.005 (0.967–1.045)	0.797	0.993 (0.967–1.019)	0.589	38	1.11 (0.90–1.38)	0.327	33	1.05 (0.82–1.34)	0.695
Gwangju	1.069 (1.006–1.136)	0.032	1.043 (0.925–1.176)	0.490	44	1.31 (0.93–1.83)	0.121	43	1.41 (1.04–1.91)	0.026
Daejeon	1.009 (0.976–1.042)	0.612	1.008 (0.980–1.037)	0.577	38	1.26 (0.96–1.67)	0.100	37	1.43 (1.08–1.88)	0.012
Ulsan	0.991 (0.957–1.026)	0.601	0.992 (0.960–1.025)	0.628	41	1.20 (0.83–1.73)	0.328	38	1.27 (0.88–1.85)	0.200
Pooled	1.013 (1.002–1.024)	0.022	1.008 (0.999–1.017)	0.081	286	1.13 (1.05–1.23)	0.001	253	1.16 (1.06–1.26)	<0.001

The left two columns show the results of segmented regression for the effects of heat, and the right two columns show the results of the heat wave effects as an indicator variable.
Models were adjusted for mean humidity, mean pressure, day of the week, and time trends.
Heat wave 1 was defined as at least two consecutive days with a daily mean temperature at or above the 98th percentile for each city.
Heat wave 2 was defined as at least two consecutive days with a daily maximal temperature at or above the 98th percentile for each city.
RR denotes rate ratio; CI, confidence interval.

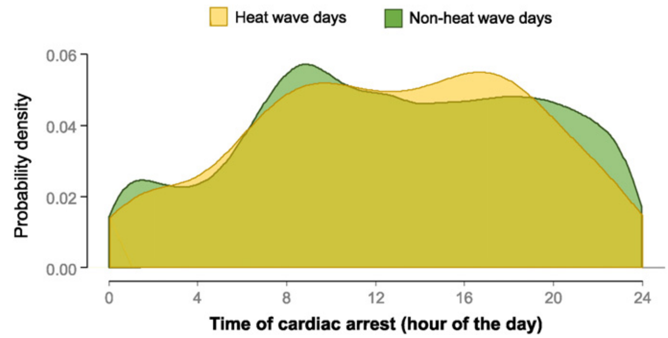

Fig. 3. Kernal density estimation of the distribution of out-of-hospital cardiac arrest by hour of the day. Yellow represents heat wave days; green shows non-heat wave days.

4. Discussion

In this study, we found that the relationship between ambient temperature and OHCA was nonlinear and J-shaped. The risk of OHCA was lowest at a daily maximal temperature of approximately 28 °C. Heat waves, defined by temperatures above the 98th percentile lasting at least two uninterrupted days, were associated with a 14-% increased risk of OHCA. Excess OHCAs during heat waves were shown to occur during the afternoon when the temperature is highest. The elderly were shown to be more susceptible to the effects of heat waves, whereas cardiac arrests with ventricular tachycardia or fibrillation were unaffected by heat waves. No significant interactions were observed between heat waves and air pollution.

The cardiovascular system plays a pivotal role in thermoregulation. Cutaneous vasodilation increases blood flow to the skin at the expense of blood supply to other major organs [28]. Increased skin blood flow and volume depletion due to sweating in response to passive heat stress results in decreased cardiac preload and afterload [29]. Heart rate and cardiac contractility are elevated, which in turn results in increased cardiac output. In contrast to the increase in myocardial oxygen consumption, blood flow to the myocardium has been shown to be reduced [30]. Disruptions in the autonomic nervous system may also pose a threat of fatal arrhythmias [31].

Studies have shown that thermoregulatory mechanisms are impaired in the elderly, as well as those with diabetes, hypertension, and congestive heart failure [32–35]. In addition, the inability to increase cardiac output or adapt to altered hemodynamics may result in cardiovascular failure and eventual death [36]. An increased propensity for thrombosis, electrolyte imbalance due to excessive perspiration, changes in renal function, inability to increase skin blood flow due to peripheral vascular disease, and impaired upregulation of cardiac output due to cardiovascular medications have also been proposed as possible mechanisms of the increase risk of OHCA [36,37]. This study findings that the elderly have a higher susceptibility to heat waves are in line with previous studies [32–35].

The health effects of heat waves are gaining attention with increasing concerns about global warming. A recent study found that an increase in global temperatures of 0.85 °C raises the probability of heat waves four or five fold [38]. Studies have consistently shown high temperature effects on mortality and a number of adverse health outcomes [1–4]. More than 50% of such excess events are cardiovascular, whereas heat-related illnesses such as heat stroke or heat exhaustion contribute only a small proportion of the total [11,12]. Cardiac arrest is one of the presentations of cardiovascular disorders and is closely linked with cardiovascular mortality. The case fatality rate of OHCA amounts to 97% in Korea [14]. Previous studies have shown that cardiac arrest explains more than one-half of cardiovascular deaths [15]. In this study, we found that heat waves significantly raise the risk of OHCA.

To our knowledge, this is the first study to show an association between extreme hot weather and OHCA using a systematic approach.

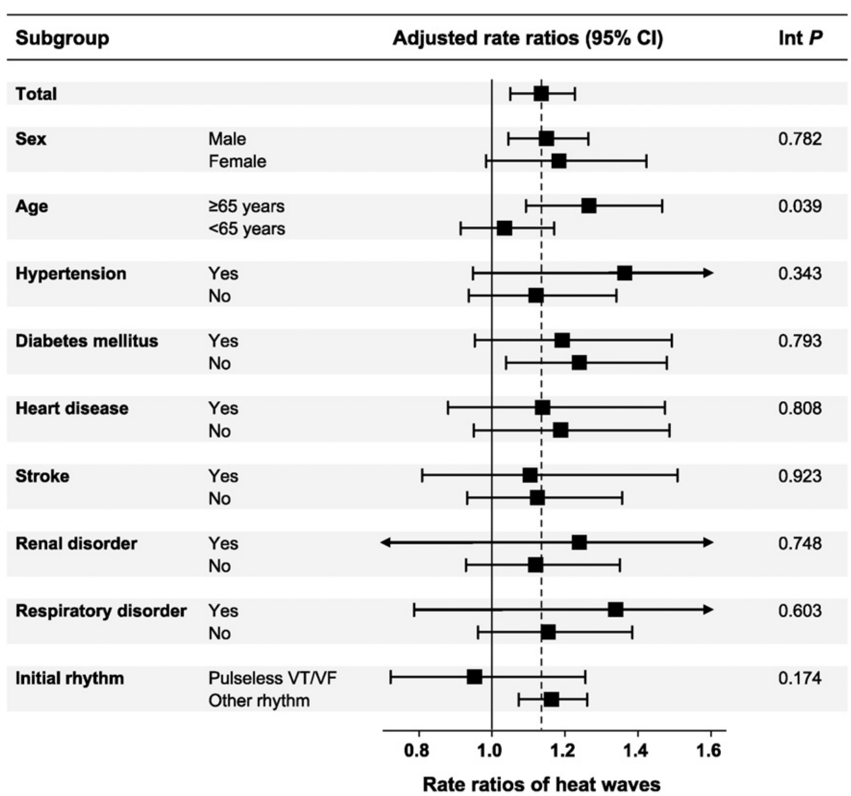

Fig. 4. Subgroup analysis The *x*-axis represents relative risk with 95% confidence intervals. Abbreviations: CI, confidence interval; *Int* P, interaction P value; VT, ventricular tachycardia; VF, ventricular fibrillation.

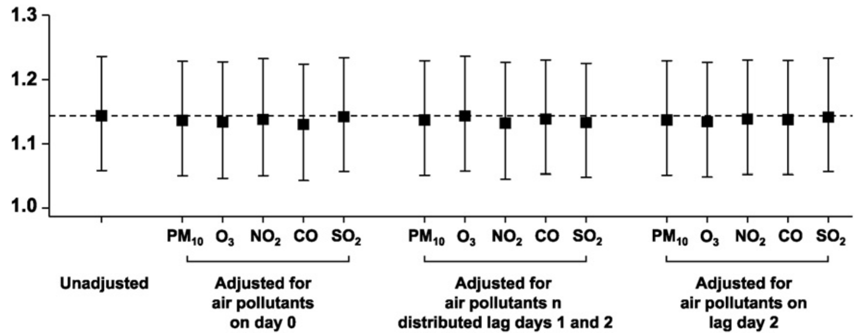

Fig. 5. Heat wave effects after adjusting for air pollution. The *y*-axis represents relative risk with 95% confidence intervals. Abbreviations: PM, particulate matter ≤10 μm in aerodynamic diameter; CO, carbon monoxide; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulfur dioxide.

While it is well known that cardiac arrest occurs more frequently at low ambient temperature [16,18], there are limited data on the association of OHCA and high temperature. A previous study showed a 2.5-fold increase in the risk of sudden cardiac death during the 2003 heat wave in Paris using an absolute definition of heat waves [19]. Dahlquist et al. showed a V-shaped relationship between mean temperature and the occurrence of OHCA [39]. As health effects of temperature vary by region, heat wave definitions using relative temperature criteria from the region's yearly distribution have advantages over using absolute cutoff values [2,20,40]. This study also showed that relative definitions have improved predictive value for OHCA risk. Interestingly, the trough of OHCA risk lies at a mean temperature of 22.5 °C in Seoul (38°N latitude) but at 12 °C in Stockholm (59°N). This study not only investigated the effects of heat in a relative sense but also showed the impact of heat waves defined by a prolonged duration of extremely hot weather. In addition, the novel findings of this study include relatively small "added effects" compared to the main effects and the distribution of excess risk mainly during the daytime.

Previous studies have shown that, in contrast to cardiovascular mortality, hospital admissions for cardiovascular causes such as myocardial infarction, cardiac dysrhythmia, and congestive heart failure were unaffected by heat waves [3,41,42]. The results of this study could explain these apparently paradoxical findings. Cardiovascular mortality occurs not only within in-hospital settings but also in the community. Out-of-hospital mortality is typically sudden and unexpected, which is also known as OHCA. As OHCA is linked with extremely high case fatality rates [14], an increase in OHCA may result in excess mortality while negligibly contributing to the total number of hospital admissions.

Son et al. recently examined the impact of heat waves on mortality in Korea [43]. Common findings of their study and ours included a significant effect of heat waves, varied estimates across cities, and increased susceptibility in the elderly. Interestingly, they also found that deaths occurring out of hospitals were more strongly related with heat waves than those in hospitals, supporting this study's findings. However, estimated heat wave effects on cardiovascular mortality were insignificant. Future studies should determine how heat waves affect various cardiovascular events.

This study has several limitations. First, some of the study cities had small numbers of cardiac arrests. Second, there could have been a sampling bias. As OHCA cases were collected from the records of the emergency management service, there could have been unwitnessed cases. Third, previous studies consistently showed PM less than 10 μm in diameter and ozone may confound the impact of heat waves on mortality [1,44,45]. We found no significant interactions between heat waves and air pollution, which requires further investigation. Fourth, details on activities before the events, which were unavailable in this study, would provide better insight into the health effects of heat waves. For example, Nishiyama et al. showed that OHCA during bathing increased with decreasing temperature, but OHCA during work or exercise had no associations with temperature [46]. Lastly, although the models were adjusted for multiple meteorological characteristics, we cannot exclude the possibility that there were confounding factors for which we did not adjust.

5. Conclusion

This study showed a J-shaped relationship between ambient temperature and risk of OHCA. Heat waves were significantly associated with increased risk of OHCA. Excess OHCA events primarily occurred during the afternoon when the temperature is high. We found that the elderly were more susceptible to the adverse effects of heat waves.

Conflict of interest disclosures

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.07.071.

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