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Ambient air pollution and out-of-hospital cardiac arrest

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ABSTRACT

Background: Sudden cardiac arrest is a leading cause of cardiovascular death. This study aimed at investigating the impact of short-term exposure to air pollutants on the incidence of OHCA.
Methods: We identified OHCA cases that occurred in Seoul between 2006 and 2013 from the nationwide emergency medical service database. The association of the daily incidence of OHCA with air pollutants including $PM_{2.5}$ (particles ≤2.5 μm in aerodynamic diameter), PM_{10}, CO, O_3, NO_2, and SO_2 was analyzed with the use of time-series and case-crossover analyses.
Results: A total of 21,509 OHCAs of presumed cardiac origin were identified. An elevation in $PM_{2.5}$ by 10 μg/m^3 at a moving average of lag 1 and 2 days was shown to increase the risk of OHCA by 1.30% (95% confidence intervals, 0.20–2.41%). An exposure–response relationship was present: the risk of OHCA increased significantly with even a mild elevation of $PM_{2.5}$ (10–15 μg/m^3) and further increased with higher levels. While PM_{10}, NO_2, CO, and SO_2 also showed significant associations with OHCA in single-pollutant models, only $PM_{2.5}$ remained significant after adjustment for other pollutants. Subgroup analyses showed male sex, advanced age, hypertension, diabetes, heart disease, and history of stroke were risk factors for OHCA in response to elevations in $PM_{2.5}$.
Conclusions: This study showed that increased ambient levels of $PM_{2.5}$ were significantly associated with increased risk of OHCA within 1 to 2 days of exposure, which had a dose–response relationship. Subjects with conventional cardiovascular risk factors were more susceptible to harm of $PM_{2.5}$.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide. It accounts for up to 50% of all cardiovascular deaths [1]. In the United States, 424,000 people each year experience non-traumatic OHCA, and about 90% of them fail to survive to hospital discharge [2]. The burden of OHCA is surging in Korea: the incidence rate increased from 37.5 in 2006 to 46.8 in 2010 per 100,000 person-years, while the survival rate was reported to be as low as 3.0% [3]. As OHCA is typically associated with high mortality rates, predicting the incidence and screening subjects at risk are of the utmost importance.

Recent studies have sought to find a link between short-term exposure to air pollutants and OHCA. It is well established that ambient air pollution triggers cardiovascular fatal and nonfatal events [4]. However, its impact on OHCA has been controversial [5–16]. Most studies on this subject were performed in developed countries with only a paucity of data from Asia, where air pollution is increasingly becoming a major healthcare issue [17].

The objective of this study was to investigate the impact of short-term exposure to outdoor air pollutants on the incidence of OHCA in Seoul, Korea. We also sought to identify high risk individuals that are most susceptible to harm from ambient air pollution.

2. Methods

Seoul is a megacity in Korea. As of 2013, Seoul had more than 10 million residents, making it the most highly populated city in Asia and second worldwide following Paris [18]. It has a temperate climate with four distinct seasons. Air quality in Seoul is relatively poor compared to western cities [19]. Air pollution in Korea is not only determined by local emissions, but also affected significantly

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by long-range transport of emissions from adjacent countries, such as China [20].

2.1. Study population

Study subjects were patients who experienced an OHCA in Seoul, Korea between January 2006 and December 2013, who were extracted from the cardiovascular disease surveillance database, a nationwide population-based retrospective observational database. Details of the database have been described elsewhere [3]. In brief, the database contains information about emergency medical service (EMS)-assessed OHCAs across the country. Korea has a single-tiered EMS system provided by the government, and ambulance run sheets are electronically stored in each province's EMS headquarters. Trained medical record reviewers visited the hospitals and reviewed the hospital records to compile information related to the risks and outcomes using the Utstein guidelines for reporting cardiac arrest and resuscitation data [21]. Patients were classified as having an arrest of cardiac origin when there were no previous symptoms or known non-cardiac etiologies (Supplementary Fig. 1). The reviewers recorded the patients' pertinent medical history, such as hypertension, diabetes, heart disease, history of stroke, renal disorder, and respiratory disorder, although these data were not available for patients prior to January 2009. All information was recorded in a manner that protected the subjects' identities. This study was exempt from review by the Seoul National University Hospital Institutional Review Board (1505-087-673).

2.2. Air pollution and meteorological data

Weather data, including daily mean temperature (°C), relative humidity (%), and air pressure (hPa), were obtained from the Korean Meteorological Administration. Air pollutant monitoring data were obtained from the Korea National Institute of Environmental Research. Hourly concentrations of particulate matter (PM) ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$) (μg/m^3), PM ≤10 μm (PM_{10}) (μg/m^3), CO (ppm), O_3 (ppb), NO_2 (ppb), and SO_2 (ppb) were collected from 27 monitoring stations in Seoul, from which daily averages were calculated after omitting 5% of the data points from the top and bottom of the distributions. SO_2 was measured by pulse ultraviolet fluorescence, NO_2 by chemiluminescence, CO by non-dispersive infrared method, O_3 by ultraviolet photometry, and both $PM_{2.5}$ and PM_{10} by beta-ray absorption method.

2.3. Statistical analysis

Both time series and case-crossover analyses were performed to address the sensitivity of the results and to model uncertainty. The main analysis employed was the time series analysis, a quasi-Poisson generalized additive model with penalized cubic regression splines. 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. Seven degrees of freedom per year were selected for smoothing the time trends based on a sensitivity analysis using 1 to 15 degrees of freedom (Supplementary Fig. 2). We examined concentrations of individual lag days 0 through 5 (lag 0 represents the air pollution level on the day of OHCA, lag 1 on the previous day, and so on). Based on the lag day model, moving averages of lag days 1 and 2 were used for $PM_{2.5}$ throughout the manuscript. Two-pollutant models were also constructed utilizing all possible pairs of pollutants. The calculated coefficients were compared with those obtained from the single-pollutant models.

To evaluate the sensitivity of the results, a case-crossover analysis was done. Two methods were used for matching control days for a case: 1) matching on the day of week, and 2) matching on the temperature within 0.5 °C. Then, conditional logistic regression was performed. The same smoothing terms for temperature and humidity as described in the time-series model were used in the case-crossover analysis. Subgroup analyses were performed to identify those at high risk for OHCA upon exposure to air pollution. Subjects with missing values were excluded from the analysis.

Statistical analyses were performed with the R statistical software [22]. Results were presented as the percentage of excess risk (ER) with 95% confidence interval. A p value <0.05 was considered significant.

3. Results

3.1. Cohort characteristics

A total of 28,315 OHCAs were identified in Seoul from January 2006 to December 2013 (2922 days). After excluding cases from clearly non-cardiac etiologies, 21,509 OHCAs with presumably cardiac origin were analyzed in this study (Supplementary Fig. 1). The mean age of the study population was 66.4 ± 19.9, and approximately half of the events occurred in the advanced age group (≥70 years) (Table 1). Male patients accounted for about two thirds of the population.

Summary statistics for the average daily pollutant levels and meteorological variables during the study period are shown in Table 2. Fig. 1 shows the histogram for the distribution of ambient $PM_{2.5}$ concentrations. The daily average $PM_{2.5}$ was ≤15 μg/m^3, a level classified as "good" by the Korean Meteorological Administration, on 683 days corresponding to the 23rd percentile. Meanwhile, the daily average $PM_{2.5}$ was >50 μg/m^3, a "bad" level, on 205 days corresponding to the upper 7th percentile. Correlations between air pollutants, temperature, and relative humidity are detailed in Supplementary Table 1. $PM_{2.5}$ correlated highly with PM_{10}, and moderately with NO_2, CO, and SO_2.

3.2. Air pollutants and incidence of OHCA

$PM_{2.5}$ was found to increase the risk of OHCA marginally at lag day 1 (percent ER, 0.94% per 10 μg/m^3 increase; 95% confidence intervals [CI], −0.05–1.94%; $P = 0.062$) and significantly at lag day 2 (percent ER, 1.13%; 95% CI, 0.16–2.11%; $P = 0.023$) (Fig. 2). The ER was attenuated with increasing days of lag. An increase in the risk of OHCA by 1.30% (95% CI, 0.20–2.41%; $P = 0.020$) was observed after a 10-μg/m^3 elevation of $PM_{2.5}$ measured in a moving average of lag days 1 and 2.

PM_{10} at lag day 2 was associated with an increased risk of OHCA. However, coarse PM, which is calculated by subtracting $PM_{2.5}$ from PM_{10} ($PM_{2.5-10} = PM_{10} - PM_{2.5}$), was shown to have no statistically significant association with OHCA. Positive associations with OHCA were also present for other pollutants: NO_2 at lag day 1 (1.31% per 10 ppb), CO at lag days 1 and 2 (0.91% and 0.76%, respectively, per 10 ppm), and SO_2 at lag days 1, 2, and 3 (0.98%, 0.97%, and 0.82%, respectively, per 1 ppb). In terms of O_3, no significant association was found with the lag day models using either daily maximal 8-hour average or daily 24-hour average.

An exposure–response relationship was observed between $PM_{2.5}$ levels and the risk of OHCA. Fig. 3 shows even a mild elevation of $PM_{2.5}$ levels within the "good" category according the Korean Meteorological Administration standards (10–15 μg/m^3) was significantly associated with an increased risk of OHCA compared to the lower levels (≤10 μg/m^3). Exposure to a level classified as "bad" ($PM_{2.5} > 50$ μg/m^3) was associated with a 13.4% increase in the risk of OHCA ($P < 0.001$).

3.3. Sensitivity analysis and two-pollutant models

Estimates derived from case-crossover models are shown in Supplementary Table 2. For a $PM_{2.5}$ increase of 10 μg/m^3 at lag day 2, the ER of OHCA was 0.94% ($P = 0.126$) for the model matching on day of the week and 2.23% ($P = 0.002$) for that matching on mean temperature within 0.5 °C degrees. Otherwise, the estimates were similar to those obtained with time series analyses.

Table 1
Summary statistics for study population with out-of-hospital cardiac arrests in Seoul, 2006–2013.

		Number	(%)
All		21,509	(100.0%)
Age, years			
<16		326	(1.5%)
16–39		1169	(5.4%)
40–69		9280	(43.1%)
≥70		10,734	(49.9%)
Sex			
Male		14,101	(65.6%)
Female		7406	(34.4%)
Unknown		2	(0.0%)
Initial rhythm			
Ventricular fibrillation		1999	(9.2%)
Pulseless ventricular tachycardia		207	(1.0%)
Pulseless electrical activity		1788	(8.3%)
Asystole		13,285	(61.8%)
Bradycardia		38	(0.2%)
Unknown		4192	(19.5%)
Underlying disease*			
Hypertension	Yes	5264	(34.1%)
	No	6121	(39.7%)
	Unknown	4044	(26.2%)
Diabetes mellitus	Yes	3410	(22.1%)
	No	7460	(48.4%)
	Unknown	4559	(29.5%)
Heart disease	Yes	2147	(13.9%)
	No	7139	(46.3%)
	Unknown	6143	(39.8%)
Renal disorder	Yes	694	(4.5%)
	No	7846	(50.9%)
	Unknown	6889	(44.6%)
Respiratory disorder	Yes	716	(4.6%)
	No	7977	(51.7%)
	Unknown	6736	(43.7%)
Stroke	Yes	1145	(9.4%)
	No	7448	(48.3%)
	Unknown	6536	(42.4%)

CPC denotes cerebral performance category scale.
* Information on underlying diseases was not available until January 01, 2008.

Two-pollutant models were constructed to estimate the independent effects of $PM_{2.5}$ among other pollutants. The ER of OHCA for an increase in $PM_{2.5}$ (lag days 1 and 2) was unchanged when analyzed with the two-pollutant models (Fig. 4). The hazardous effects of other pollutants observed in the single-pollutant model were mostly attenuated in the two-pollutant model.

3.4. Subgroup analysis

Fig. 5 shows the analyses for various subgroups per an increase in $PM_{2.5}$ concentrations by 10 μg/m^3 (moving average for lag days 1 and 2). Men, patients 60 years of age or older, and those with hypertension or diabetes were more susceptible to the harmful effects of $PM_{2.5}$. The interaction was significant for the hypertension subgroup and marginal for the diabetes subgroup. Although statistically insignificant, the incidence of OHCA in patients with heart disease or a history of stroke was higher after exposure to $PM_{2.5}$ than those without.

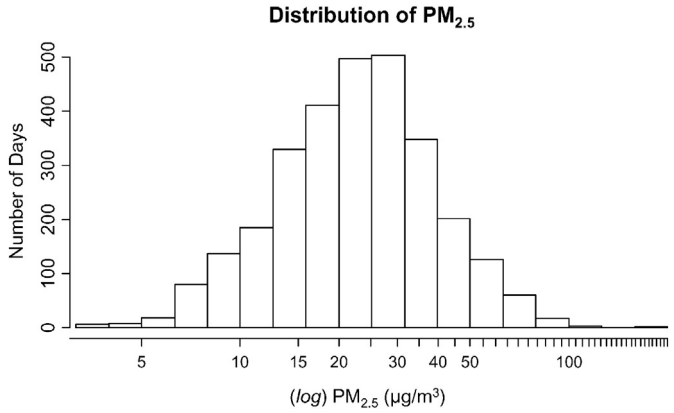

Fig. 1. Distribution of ambient $PM_{2.5}$ levels in Seoul, 2006–2013. The X-axis was presented in a logarithmic scale.

4. Discussion

By analyzing the incidence of OHCA in Seoul from 2006 to 2013, we found OHCAs were significantly associated with short-term exposure to ambient air pollution. Of all the pollutant exposures included in the analysis, $PM_{2.5}$ exposure was most strongly associated with OHCA. $PM_{2.5}$ and OHCA had an exposure–response relationship: an increase in ambient $PM_{2.5}$ concentrations by 10 μg/m^3 was associated a 1.3% increased risk of OHCA 1 to 2 days later. The risk of OHCA following $PM_{2.5}$ exposure was greater in men, the elderly, and those with hypertension, diabetes, heart disease, or a history of stroke.

OHCA is a major cause of cardiovascular mortality [23]. More than a half of cardiovascular deaths present as sudden cardiac arrest, and most cardiac arrests occur outside of hospitals [24]. Conventional cardiovascular risk factors, including coronary heart disease, explain the majority of the risk for sudden cardiac arrest. However, many patients with coronary heart disease are not even aware that they have the disease until the development of cardiac arrest. In addition, the occurrence of cardiac arrest is not random but triggered by short-term factors [25]. Circadian and seasonal variations in cardiac arrest occurrence rates have been reported [26,27]. Only recently has ambient air pollution gained attention as a possible short-term triggering factor [5–16].

While outdoor air pollution is an established environmental factor in cardiovascular mortality, its impact on OHCA remains unclear. The World Health Organization estimates 3.7 million premature deaths

Table 2
Summary statistics for number of out-of-hospital cardiac arrest events, meteorology, and air pollution in Seoul, 2006–2013.

	Daily mean (SD)	Quantiles					Interquartile range
		Min	25%	50%	75%	Max	
Number of cardiac arrests	7.3 (3.3)	0	5	7	9	23	4
Meteorology							
Temperature, °C	12.7 (10.6)	−14.5	3.8	14.1	22.3	31.8	18.5
Humidity, %	60.4 (15.0)	20	49	60	71	97	22
Pressure, hPa	1016.0 (8.2)	993.1	1010.0	1016.0	1022.0	1038.0	12.8
Air pollutants							
$PM_{2.5}$, μg/m^3	25.8 (14.7)	3.3	15.6	22.6	32.0	190.6	16.4
PM_{10}, μg/m^3	52.7 (35.3)	6.1	31.9	46.5	63.7	864.1	31.8
O_3, ppb	29.9 (16.1)	2.2	18.0	27.5	39.0	109.5	20.9
NO_2, ppb	37.9 (12.7)	9.7	28.0	36.5	46.7	92.4	18.6
CO, ppm	0.61 (0.24)	0.23	0.45	0.55	0.71	1.81	25.7
SO_2, ppb	5.6 (2.3)	2.5	4.0	5.0	6.6	21.2	2.6

For O_3, the 8-hour maximum per day was analyzed. SD denotes standard deviation; min, minimum; max, maximum; ppb, parts-per-billion, 10^{-6}; ppm, parts-per-million, 10^{-6}.

worldwide were attributable to ambient air pollution in 2012 [28]. Elevations in air pollutant levels lead to a greater absolute mortality risk from cardiovascular diseases than from other causes: 69% of the premature deaths are estimated to be caused by cardiovascular diseases such as ischemic heart disease and stroke, whereas pulmonary diseases account for only 28% [4]. However, studies on the relationship between air pollution and OHCA have yielded inconsistent results. Some studies found a significant association [7,9,11,12,16] whereas others did not [5,6]. A study with large sample size in Stockholm found a significant association with O_3 but not with $PM_{2.5}$ [15].

This study showed short-term exposure to outdoor air pollutants significantly increases the risk of OHCA. While PM_{10}, NO_2, CO, SO_2

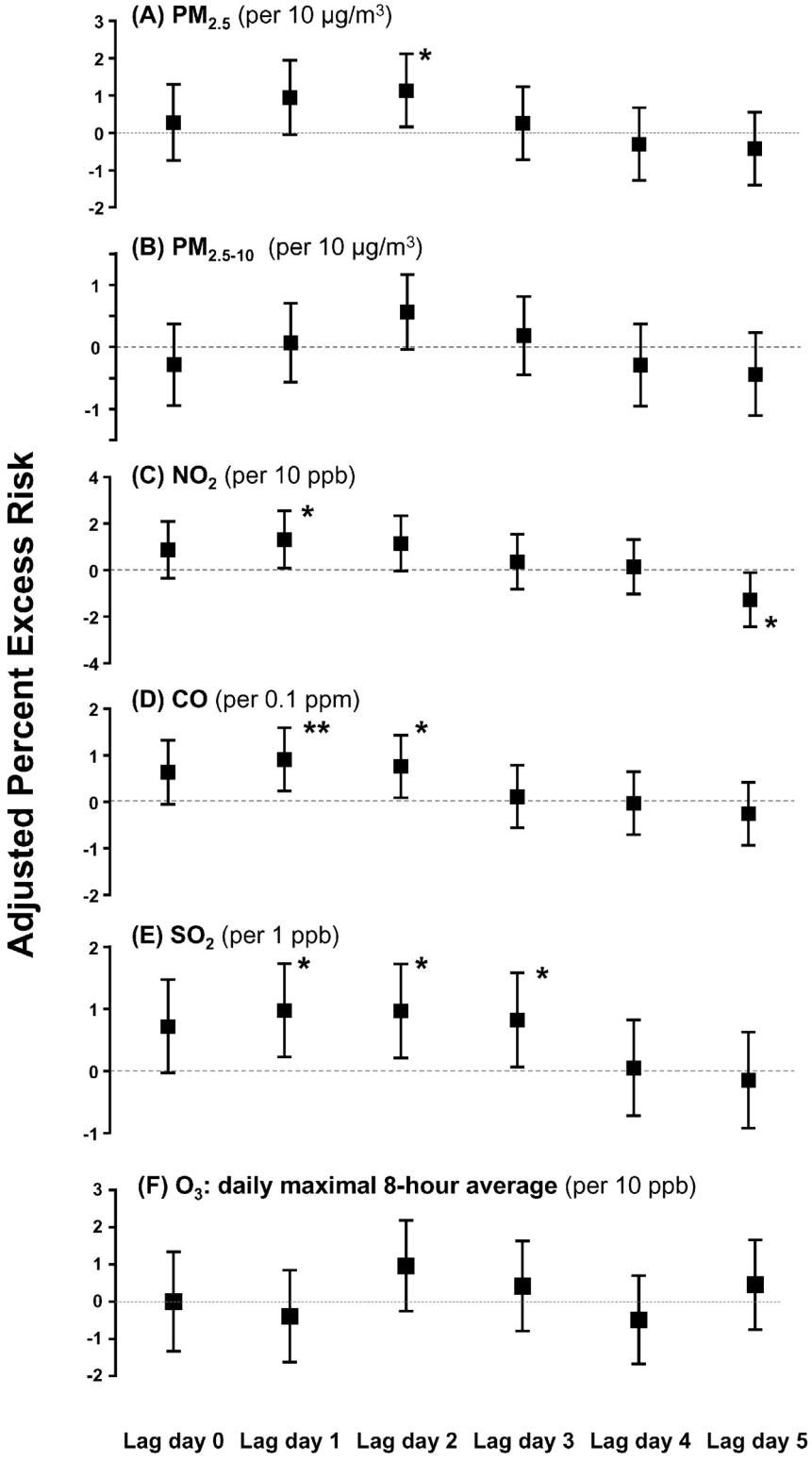

Fig. 2. Level of air pollutants and the adjusted risk of out-of-hospital cardiac arrests: (A) $PM_{2.5}$, (B) coarse PM, (C) NO_2, (D) CO, (E) SO_2 and (F) O_3 (daily maximal 8-hour averages). The Y-axis represents percentage of excess risk with 95% confidence intervals. *$P < 0.05$. **$P < 0.01$.

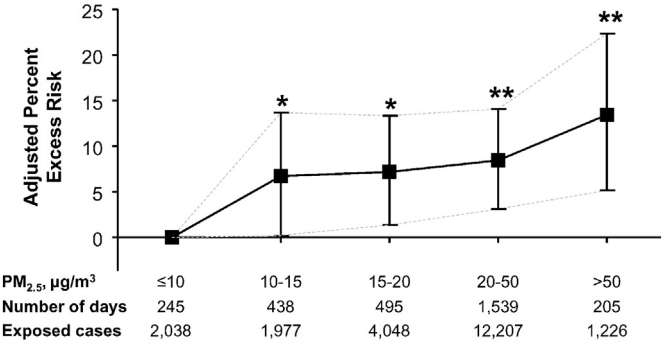

Fig. 3. Adjusted risk of out-of-hospital cardiac arrests according to ambient $PM_{2.5}$ levels. The Y-axis represents percentage of excess risk with 95% confidence intervals. *$P < 0.05$. **$P < 0.01$.

were all significantly associated with OHCA, $PM_{2.5}$ was most strongly associated. $PM_{2.5}$ is a complex and heterogeneous mixture of hundreds of chemical species, semi-volatile and solid particles originating from various sources and produced via atmospheric photochemical processes. The small size of $PM_{2.5}$ makes it possible for these particles to reach the small airways and alveoli. Studies have suggested short-term exposure to PM increases blood levels of proinflammatory mediators, induces a hypercoagulability state, and inhibits fibrinolytic capacity [29,30]. Alterations in the systemic autonomic balance, which may result in life-threatening arrhythmias, in response to PM exposure have also been postulated [31]. This study demonstrated that $PM_{2.5}$ exposure is associated with OHCA 2 to 3 days after exposure in a dose–response manner and mainly in susceptible individuals with prior risk factors for cardiovascular disease.

Notably, the increased risk of OHCA associated with an elevation of $PM_{2.5}$ levels found in this study was relatively small compared to those in previous studies: ER of 1.3% per 10 μg/m^3 increase in $PM_{2.5}$ concentration in this study contrasts to 3.6% (per 4.26 μg/m^3) in Melbourne [9], 4–6% (per 10 μg/m^3) in New York [10], 4.6% (per 6 μg/m^3) in Houston [11], 4.4–5.2% (per 5.9 μg/m^3) in Copenhagen [13], and 10.6–13.6% (per 5.08 μg/m^3) in Perth [16]. This discrepancy may be due to the low prevalence of cardiovascular disease, including ischemic heart disease, in Korea compared to western countries [32]. As also shown in this study, the association between $PM_{2.5}$ exposure and OHCA occurs primarily in susceptible individuals, such as elderly persons and those with pre-existing coronary artery disease [4]. A low proportion of susceptible people in the general population could translate to a low net effect of air pollution in the general population. On the other hand, the ER for cardiovascular mortality per a 10-μg/m^3 increase of $PM_{2.5}$ concentration is generally thought to be between 0.4% and 1.0% [4]. Assuming OHCA comprises a half of cardiovascular deaths [1], the ER of 1.3% is consistent with the results reported in other studies. Whether there exists a difference in the effects of air pollution based on the ethnicity of the individual warrants further investigation. A study performed in Japan investigating the effects of air pollution on OHCA examined PM of a different size, making a direct comparison impossible [14]. Previous studies did not detect significant discrepancies between ethnicities, although Asian ethnicity was not adequately represented in these studies [8,11].

Although the ER of 1.3% per 10-μg/m^3 increase in the $PM_{2.5}$ concentration may appear small, this result can translate to a significant public health impact. As an example, implantable cardioverter-defibrillator is the single most efficacious tool in preventing sudden cardiac death. Studies have shown it reduces the risk of cardiovascular death by approximately 20% to 30% [33,34]. However, the benefit is limited to a small fraction of patients who are at high risk of cardiac arrest and thus indicated for the implantable device. As the majority of OHCA victims come from the general population, the so-called "Myerburg's paradox", the gain of implantable cardioverter-defibrillator is limited when projected to the whole cardiac arrest population [35]. This study showed the risk of OHCA increased as much as 13% after exposure to high levels of $PM_{2.5}$ (>50 μg/m^3). A 1.8% of risk reduction is expected when the annual concentration of $PM_{2.5}$ is reduced from the mean of 25.8 μg/m^3 to <12 μg/m^3, the standard proposed by the Environmental Protection Agency [36]. This reduction in risk would have a major impact on public health.

This study had several strengths. First, the sample size of 21,509 OHCAs is the largest ever studied. Second, the patients' diseases were identified by retrospective medical record reviews. Based on this information, we could identify baseline factors that increased susceptibility to OHCA upon exposure to $PM_{2.5}$. The risk factors that heightened the susceptibility to harm from air pollution (i.e., hypertension, diabetes, male sex, old age, heart disease, stroke) corresponded to conventional cardiovascular risk factors. We confirmed that short-term exposure to high levels of $PM_{2.5}$ triggers fatal cascades in subjects who already have vulnerable substrates for cardiac arrest. Those with multiple risk factors may benefit from becoming informed of air pollution levels and staying indoors when the air quality is poor. Last, this is the first study in Asia showing the relationship between $PM_{2.5}$ and OHCA. This region is rapidly industrializing and suffers from poor air quality, as also shown in this study. The median of $PM_{2.5}$ in Seoul during this study period was 22.6 μg/m^3 in contrast to 4.8 μg/m^3, 12 μg/m^3, 10.3 μg/m^3, 8.7 μg/m^3, and 6.8 μg/m^3 in Melbourne, New York, Houston, Copenhagen, and Perth, respectively [9–11,13,16]. Air pollution, especially $PM_{2.5}$ concentrations, in Korea, China, and Japan is transboundary rather than local [20]. Thus, these countries must coordinate their efforts against air pollution to be most effective.

Limitations of this study include the lack of detailed information on the etiology of the cardiac arrests. Second, other clinical variables including body weight and smoking status were not available in this cohort. Third, the proportion of missing values of underlying diseases was also high. OHCA is a sudden, unexpected event and is typically associated with high mortality rates. Thus, it is not always possible to obtain all

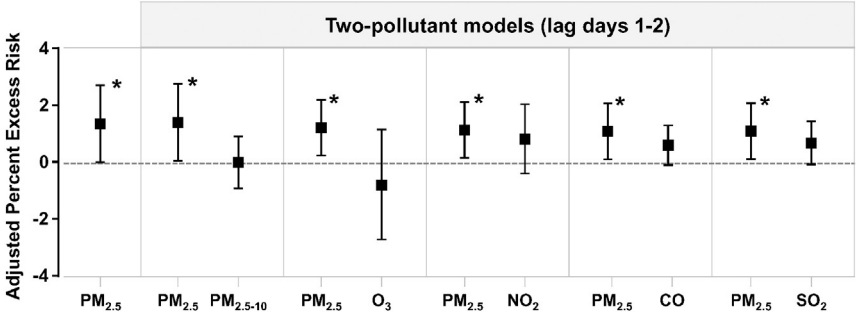

Fig. 4. Two-pollutant models with $PM_{2.5}$: adjusted percentage of excess risk (95% CI) in the incidence of out-of-hospital cardiac arrests (OHCA) with an increase of air pollutants for average lag days 1–2. The Y-axis represents percentage of excess risk with 95% confidence intervals. *$P < 0.05$.

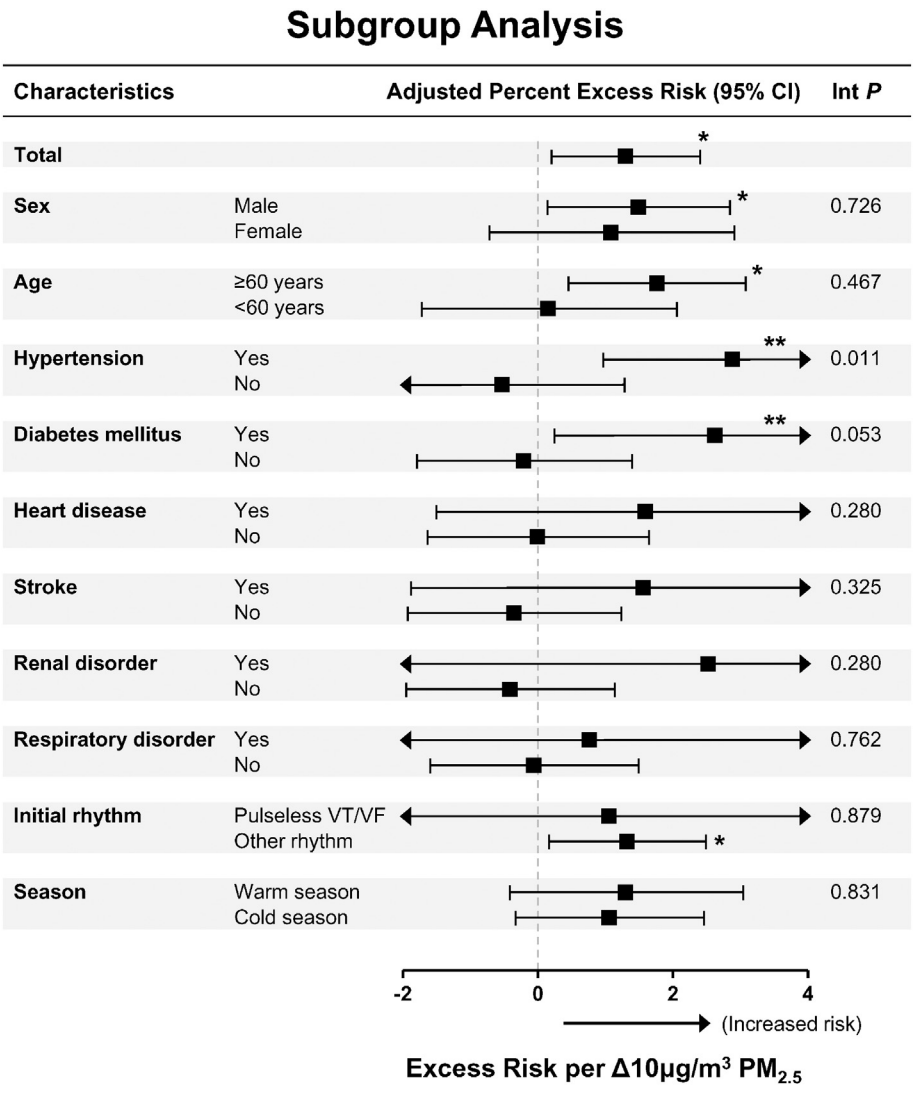

Fig. 5. Subgroup analysis for $PM_{2.5}$ (per 10 μg/m^3), 1–2 lag day running mean model. The X-axis represents percentage of excess risk with 95% confidence intervals. Warm season was defined as March through August; cold season, September through February. Abbreviations: CI, confidence intervals; Int *P*, interaction *P* value; VT, ventricular tachycardia; VF, ventricular fibrillation. $^*P < 0.05$. $^{**}P < 0.01$.

the patient information. Fourth, the incidence of OHCA was derived from the records of the EMS system. Although a single-tiered EMS system is provided by the government in Korea helping to ensure that this study included all OHCA to which EMS responded, there could have been unwitnessed cases. Lastly, although the models were adjusted for multiple meteorological variables, we cannot exclude the possibility that there were confounding factors for which we did not adjust.

5. Conclusion

Increased ambient levels of $PM_{2.5}$ were significantly associated with increased risk of OHCA within 1 to 2 days of exposure. $PM_{2.5}$ was the most important pollutant among those included in the analysis. An exposure–response relationship was present between $PM_{2.5}$ and OHCA. Those with conventional cardiovascular risk factors were more vulnerable to the adverse effects of $PM_{2.5}$. The results of this study suggest a causal relationship between short-term exposure to outdoor air pollution and OHCAs.

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.2015.11.100.

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