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Ambient air pollution exposure and risk of migraine: Synergistic effect with high temperature

Hyewon Lee[a,b], Woojae Myung[b,*,1], Hae-Kwan Cheong[c], Seung-Muk Yi[d], Yun-Chul Hong[e], Sung-Il Cho[f], Ho Kim[a,g,**,1]

[a] Institute of Health and Environment, Seoul National University, Seoul, Republic of Korea
[b] Department of Neuropsychiatry, Pain Center, Seoul National University Bundang Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea
[c] Department of Social and Preventive Medicine, Sungkyunkwan University School of Medicine, Suwon-si, Gyeonggi-do, Republic of Korea
[d] Department of Air Pollution and Climate Change, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[e] Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea
[f] Department of Chronic Disease Epidemiology, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[g] Department of Public Health Sciences, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea

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ABSTRACT

Background: Migraine is a chronic and agonizing neurological disorder prevalent worldwide. Although its pathogenesis remains unclear, limited evidence exists on the role of air pollution.

Objective: We aimed to assess the association of short-term air pollution exposure with migraine in conjunction with the synergistic effect of temperature.

Methods: We identified 18,921 patients who visited emergency departments (EDs) for migraine as a primary disease in Seoul from the national emergency database between 2008 and 2014. We conducted a time-stratified, case-crossover analysis to compare levels of particles < 2.5 μm ($PM_{2.5}$), particles < 10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) on ED visit days and those on the control days matched to day of the week, month, and year. We evaluated the synergistic effects of air pollution and temperature using an interaction term.

Results: Higher air pollution levels were significantly associated with risk of migraine over various lag structures. In the best fitting lags, the odds ratio (OR) associated with an interquartile range increase of $PM_{2.5}$, PM_{10}, NO_2, O_3, and CO was 1.031 (95% CI: 1.010–1.053), 1.032 (95% CI: 1.007–1.057), 1.053 (95% CI: 1.022–1.085), 1.034 (95% CI: 1.001–1.067), and 1.029 (95% CI: 1.005–1.053), respectively. The SO_2 effect was positive but not significant (OR 1.019 [95% CI: 0.991–1.047]). The PM effect was significantly stronger on high-temperature days (above the 75th percentile) than on low-temperature days ($PM_{2.5}$, high: OR 1.068, low: OR 1.021, $P_{interact}$ = 0.03; PM_{10}, high: OR 1.066, low: OR 1.014, $P_{interact}$ = 0.02).

Conclusion: Our study provides new evidence that air pollution exposure may trigger migraine especially on high-temperature days, and this finding may contribute in establishing preventive measures against migraine.

1. Introduction

Migraine is a common, chronic, and agonizing neurological disorder, characterized by recurrent attacks of intense headache and other related symptoms such as nausea (Goadsby et al., 2002; Lipton and Bigal, 2005). The burden of migraine arises from both economic perspectives and the perspective of quality of life (Lipton and Bigal, 2005). A study on health-related quality of life (HRQoL) reported that the effect of migraine on HRQoL corresponded to that of depression and was more severe than that of other chronic diseases such as diabetes and arthritis (Dahlöf, 1993). In South Korea, the number of patients with migraine has been dramatically increasing (from 479,000 in 2010 to 505,000 in 2015), and the medical expenses for migraine have also increased by 34.4% (from USD 39.6 million to 53.2 million).

* Correspondence to: W. Myung, Department of Neuropsychiatry, Pain Center, Seoul National University Bundang Hospital 29, Gumi-ro 173beon-gil Bundang-gu, Seongnam-si, Gyeonggi-do, 13619, Republic of Korea.
** Correspondence to: H. Kim, Graduate School of Public Health, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea.
E-mail addresses: wjmyung@snubh.org (W. Myung), hokim@snu.ac.kr (H. Kim).
[1] These authors contributed equally to this study and should be considered as co-corresponding authors.

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Abbreviations

ED	emergency department
HRQoL	health-related quality of life
NEMC	National Emergency Medical Center
NEDIS	National Emergency Department Information System
NI	neurogenic inflammation

Identifying risk factors of migraine is necessary to reduce its increasing burden. Activation of the trigeminovascular system has been identified as a central step in migraine development, but the primary cause has remained unclear (Pietrobon and Striessnig, 2003). Environmental factors including weather conditions, noise, and odors, as well as demographic factors have been considered as risk factors of migraine (Prince et al., 2004; Wöber et al., 2006).

Little is known, however, about the possible role of ambient air pollution on migraine, despite increasing experimental evidence linking air pollution and neurological damage, including neuro-inflammation, neuronal damage, and neurotransmitter changes (Block and Calderón-Garcidueñas, 2009; Pereyra-Muñoz et al., 2006) and epidemiological studies supporting a positive association between air pollution exposure and neurological disease such as Parkinson's disease and stroke (Lee et al., 2017; Shah et al., 2015). Although limited studies have examined the association between ambient air pollution and migraine, the findings have been mixed in this regard. While a study conducted in Edmonton, Canada using a generalized linear mixed model reported a significantly increased risk of migraine associated with exposure to ambient air pollution (Szyszkowicz et al., 2009), this association was not replicated in a study performed in Boston, USA using a case-crossover design (Mukamal et al., 2009).

Furthermore, the synergistic effect of air pollution and temperature on migraine has not been evaluated, although it is biologically possible that they have a joint effect (Gordon, 2003; Ren et al., 2011). A few studies have provided evidence of the synergism between high air pollution levels and high temperature, mainly on risk of mortality by cardiovascular or respiratory diseases (Qian et al., 2008; Stafoggia et al., 2008). The interaction between air pollution and high temperature is of public health interest given the increasing temperatures associated with climate change (Patz et al., 2005).

We therefore studied the effects of short-term exposure to six criteria air pollutants on the risk of migraine in Seoul, South Korea using a time-stratified case-crossover design. We further assessed potential effect modification by temperature.

2. Methods

2.1. Study population

The National Emergency Department Information System (NEDIS) is the largest database for emergency department (ED) information in South Korea, developed by the National Emergency Medical Center (NEMC). The NEMC was established on July 31, 2001 by the Ministry of Health and Welfare in order to coordinate regional and local emergency medical centers and other local emergency medical facilities.

The NEDIS database consists of all cases of ED visits that occurred since 2005 in regional and local emergency medical centers and other local emergency medical facilities, accounting for approximate 76% of the national hospital-based ED visit data. NEDIS data contain individual demographic information (sex, age, type of insurance, and region to which the emergency medical center belongs), ED visit information (ED visit date/time, ED visit route, reason for ED visit [disease, other reason], symptom onset date/time, mechanism of injury [car accident, fall, burn, etc.], patient state on ED arrival [alert, unresponsive], medical information (initial diagnosis [Unified Medical Language System code], results of ED treatment [discharge, transfer, admission, death], and discharge/admission information [final diagnosis on discharge/admission, date and time of discharge/admission]). The data from different emergency medical centers are standardized and combined by NEMC and encrypted for the privacy of patients, physicians, and hospitals.

We obtained information on the study population from NEDIS data for 2008 through 2014, as the NEDIS data have been stabilized since 2008, regarding the participating emergency medical centers. For case definition, the final diagnosis on discharge according to the ICD-10 was used. We collected data from patients who visited the ED for migraine (having the G43 ICD-10 code as a primary discharge diagnosis) that occurred in Seoul. As the largest and capital city of South Korea, Seoul's population accounts for one-fifth of the total population of South Korea, and its population density is 16,189 individuals/km^2. Furthermore, a regular monitoring system for $PM_{2.5}$ was originally established only in Seoul, although monitoring systems in other cities have been developed in recent years. Given the heavy traffic volume and the high population density, Seoul is a suitable city for examining the association between air pollution and the risk of migraine by affording adequate statistical power.

The Institutional Review Board of Seoul National University approved the study protocol (no. E1710/002-004). The need for informed consent was waived because encrypted NEDIS data were provided to protect private information.

2.2. Assessment of air pollution exposure

Seoul consists of 25 districts, which range from 10 to 47 km^2 (mean, 24 km^2). We obtained hourly concentrations of particles < 2.5 μm ($PM_{2.5}$) from 25 monitoring sites, and particles < 10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) from 27 monitoring sites operated by the Seoul Research Institute of Public Health and Environment. Each district has one monitoring site located centrally within the district (two districts have two monitoring sites for five pollutants except $PM_{2.5}$), and each pollutant was measured with the following methods every 15 min: gravimetry ($PM_{2.5}$), beta-ray absorption (PM_{10}), chemo-luminescence (NO_2), ultraviolet fluorescence (SO_2), ultraviolet photometry (O_3), and nondispersive infrared photometry (CO). These measurements followed the standard protocols established by the Korean Ministry of Environment (MOE, 2011). Because information on patient or ED-specific addresses was not provided for privacy, we constructed city-level measures of air pollution exposure; first, we averaged the hourly concentrations from all monitoring sites for all pollutants. Then, we constructed daily representative values, the 24-hour means for $PM_{2.5}$, PM_{10}, NO_2, and SO_2, and the maximum 8-hour means for O_3 and CO based on the World Health Organization (2006) air quality guidelines.

We calculated paired Pearson's correlations ($N = {}_{25}C_2 = 300$, $N = {}_{27}C_2 = 351$) among site-specific daily concentrations of air pollutants from 25 monitoring sites for $PM_{2.5}$ and 27 monitoring sites for the other pollutants during the study period. All site-specific concentrations were highly correlated with each other from mean 0.725 (SD = 0.079) in SO_2 to mean 0.953 (SD = 0.020) in PM_{10}, showing unimodal distributions, suggesting homogeneity in air pollution levels in the 25 districts within Seoul. Therefore, we decided to use the constructed daily measures of air pollutants as the representatives of ambient air pollution exposure in Seoul.

2.3. Meteorological variables

Seoul is located in the west central part of the Korean Peninsula and has four distinct seasons with a maximum temperature of approximately 32 °C in August and a rainy season during July to August in the temperate zone. Seoul has one weather monitoring station with an automated synoptic observing system, which is located slightly north of

the center of the city, operated by the Korea Meteorological Administration (KMA). Various meteorological variables including ambient temperature, relative humidity, rainfall, wind speed, and air pressure are measured every minute and constructed as hourly data. We obtained hourly data on ambient temperature, relative humidity, and air pressure and data on sunlight hours and rainfall per day measured at the weather monitoring station by the KMA. We calculated the 24-hour mean values for confounding adjustment and for evaluation of effect modification.

2.4. Study design

A time-stratified, case-crossover design was used to investigate the association between short-term exposure to air pollution and ED visits for migraine. The case-crossover design is a variant form of a case-control design in which patients serve as their own control (Maclure, 1991); hence, time-invariant characteristics, such as genetic predisposition, are automatically controlled for through the design itself. Furthermore, time-dependent factors that vary slowly, such as morbid states, can be adjusted for by selecting control periods close to the case (ED visit) day. We selected 3 or 4 control days that were matched to the day of the week, month, and year with the case day (e.g., if a patient visited an ED for migraine on a Sunday in April 2008, then all other Sundays in April 2008 were the control days). This time-stratified method has been proven to provide unbiased estimates (Janes et al., 2005).

2.5. Statistical analysis

We compared air pollution levels on case and control periods using 2-tailed *t*-tests. We used conditional logistic regression models to estimate the association of short-term air pollution exposure with ED visits for migraine. In the main model, we adjusted for the 2-day moving average of temperature on the same and previous days (lag0–1) with a regression spline (with 3 degrees of freedom), 2-day moving averages of relative humidity, air pressure, sunlight, and rainfall; influenza epidemics, and holidays.

To assess whether the air pollution effect on migraine is immediate, delayed, or cumulative, we constructed single-day lag and moving-average lag structures up to 7 days prior to the ED visit (single lag: same day and 1–7 days prior to the ED visit [lag0 to lag7]; moving-average lag: moving average of same day and 1–7 days prior to the ED visit [lag0–1 to lag0–7]). Each air pollutant with different lag structures was included in the model separately. The lag structure that provided the smallest Akaike information criterion value was chosen for further analyses.

In the case-crossover design, the effect of time-invariant and slowly-varying characteristics cannot be estimated due to quasi-perfect matching. To examine possible effect modification by those factors, we ran the models including interaction terms between sex, age (< 40/40–64/≥65 years), migraine subtype (without aura/with aura/unspecified), and season (warm: March–August/cold: September–February) and each pollutant. Furthermore, we evaluated the modifying roles of weather variables using interaction terms between air pollutants (with lag0–1 structures) and the dummy variables dividing the levels (2-day moving average) of temperature, air pressure, relative humidity, sunlight hours, and rainfall into low (below the 75th percentile) and high levels (above the 75th percentile levels of the distributions over all seasons during 2008–2014).

We conducted several sensitivity analyses to assess the robustness of the main findings. First, co-pollutant models were evaluated to investigate potential confounding by other air pollutants (e.g., in $PM_{2.5}$ effect estimation, NO_2, SO_2, O_3, or CO were additionally included, respectively): a) adjustment for 2-day moving average (lag0–1) concentrations of other pollutants, and b) adjustment for concentrations of other pollutants on the best fitting lag days. Second, we examined whether the main results were changed by differing the temperature specification: a) differing the lag structures (using distributed lag nonlinear functions with a lag up to 5, 7, and 10 days prior to ED visit), b) differing the degrees of freedom for spline (from 3 to 4, 5, 6), and c) differing the knot locations (from 0.5/0.75 to 0.25/0.75, 0.1/0.9, 0.05/0.95). Third, we performed subgroup analyses using stratification rather than interaction terms, for sex, age, subtype, and season. Last, we evaluated the effect modification by temperature under different definitions for high temperature (from the 75th percentile [22.7 °C] to the 50th, 95th, 99th percentiles [14.3 °C, 26.8 °C, 28.7 °C]).

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Results are presented as odds ratios (ORs) with 2-sided 95% CIs per interquartile range (IQR) increase (Table S1).

3. Results

We identified 18,921 patients who visited EDs for migraine in Seoul during 2008–2014 (Table S2). Among the patients, women (72%), those aged under 40 years (57%), and those with the unspecified migraine subtype (67%) dominated the sample. The number of patients did not differ by season, and the patients more frequently visited EDs for migraine on Sundays (18%).

Table 1 shows daily levels of air pollutants and weather variables on case and on control periods. The concentrations of all air pollutants on the day of ED visits ($PM_{2.5}$, 24.3 μg/m^3; PM_{10}, 48.0 μg/m^3; NO_2, 35.9 ppb; SO_2, 5.23 ppb; O_3, 30.9 ppb; CO, 0.65 ppm) were higher than those on control periods. Especially, the differences of $PM_{2.5}$, PM_{10}, NO_2, and CO were significant in *t*-tests (p = 0.049–0.001). The levels of weather variables were not different between the case and control periods. Air pollutants concentrations were highly inter-correlated

Table 1
Differences in daily levels of air pollutants and meteorological variables between case and control periods and their distributions in Seoul, South Korea, during 2008–2014.

	Case periods (N = 18,921)		Control periods (N = 64,402)		Mean difference	95% Confidence limit	Percentiles (Total period)			p value for t-test
Variables	Mean	SD	Mean	SD			p25	p50	p75	
$PM_{2.5}$ (μg/m^3)	24.25	13.56	23.86	13.21	0.39	0.17, 0.61	15.04	21.76	30.26	< 0.001
PM_{10} (μg/m^3)	48.01	28.25	47.55	28.02	0.46	0, 0.91	30.67	43.92	59.9	0.049
NO_2 (ppb)	35.85	12.25	35.53	12.14	0.33	0.13, 0.52	26.89	34.67	44.47	0.001
SO_2 (ppb)	5.23	1.91	5.21	1.9	0.02	−0.01, 0.05	3.93	4.87	6.3	0.137
O_3 (ppb)	30.94	16.52	30.86	16.4	0.09	−0.18, 0.35	18.03	27.55	39.93	0.528
CO (0.1 ppm)	6.48	2.66	6.42	2.62	0.06	0.01, 0.1	4.77	5.94	7.65	0.009
Temperature (°C)	13.66	10.53	13.63	10.61	0.03	−0.15, 0.2	3.54	14.3	22.65	0.767
Sunshine (hr)	6.03	3.99	6.08	3.99	−0.05	−0.11, 0.01	2.1	6.9	9.3	0.130
Humidity (%)	61.18	14.84	61.17	14.87	0.01	−0.23, 0.25	49.25	60.25	71.13	0.929
Rainfall (mm)	23.23	148.2	22.39	140.3	0.87	−1.53, 3.22	0	0	0.8	0.487
Air pressure (hPa)	1015.6	7.98	1015.5	8.05	0.06	−0.07, 0.19	1009.7	1016.3	1022.5	0.339

(Pearson coefficient r = 0.56–0.86) except for O_3 (r = 0.07–0.36) and weakly or moderately correlated with weather variables (r = −0.05–0.52) (Table 2).

3.1. Association between air pollution and migraine

Fig. 1 presents the estimated effect of ambient air pollution on ED visits for migraine per IQR increase at different lag structures. The air pollution effect was most pronounced at immediate lags (lag0, lag0–1, lag0–2) and declined at delayed lags, in general. The best fitting lag days were lag0 days for NO_2, SO_2, and CO, lag0–2 days for $PM_{2.5}$, lag2 days for O_3, and lag0–6 days for PM_{10} (Table S3). In the best fitted models, the OR of the risk of ED visits for migraine was 1.031 (95% CI: 1.010–1.053) for $PM_{2.5}$, 1.032 (95% CI: 1.007–1.057) for PM_{10}, 1.053 (95% CI: 1.022–1.085) for NO_2, 1.019 (95% CI: 0.991–1.047) for SO_2, 1.034 (95% CI: 1.001–1.067) for O_3, and 1.029 (95% CI: 1.005–1.053) for CO.

3.2. Effect modifiers of the association between air pollution and migraine

Table S4 shows the estimated effect of air pollution on migraine by sex, age, migraine subtype, and season using interaction terms. While slight differences between subgroups were observed, only the difference in the $PM_{2.5}$ effect by season was statistically significant (warm: OR 1.057 [95% CI: 1.024–1.090]; cold: OR 1.013 [95% CI: 0.986–1.040]; $P_{interact}$ = 0.04).

Fig. 2 presents the association between air pollution and migraine by high/low levels of weather variables (temperature, air pressure, relative humidity, sunlight hours, and rainfall) using interaction terms. The air pollution effect was greater on high-temperature days with statistical evidence of interaction for $PM_{2.5}$ (high: OR 1.068 [95% CI: 1.029–1.108]; low: OR 1.021 [95% CI: 0.999–1.044]; $P_{interact}$ = 0.03) and PM_{10} (high: OR 1.066 [95% CI: 1.025–1.109]; low: OR 1.013 [95% CI: 0.993–1.034]; $P_{interact}$ = 0.02). The associations for other pollutants showed similar patterns, but the differences were not significant (SO_2 [high: OR 1.052; low: OR 1.013; $P_{interact}$ = 0.09], O_3 [high: OR 1.041; low: OR 1.003; $P_{interact}$ = 0.07], and CO [high: OR 1.061; low: OR 1.020; $P_{interact}$ = 0.08]). Effect modification by other weather variables was not observed. The effect modification by temperature was consistently observed when the patients were stratified by sex, age, and migraine subtype (Fig. 3). Especially, strong interactions between air pollution and temperature were shown among women ($P_{interact}$ for $PM_{2.5}$ = 0.07; PM_{10} = 0.05; O_3 = 0.09), patients aged under 40 years ($P_{interact}$ for $PM_{2.5}$ = 0.04; PM_{10} = 0.03; CO = 0.04), and patients with migraine without aura ($P_{interact}$ for $PM_{2.5}$ = 0.04; PM_{10} = 0.02; O_3 = 0.06).

3.3. Sensitivity analysis

Two-pollutant models revealed the robustness of the main results, although inclusion of NO_2 for all other pollutants and inclusion of PM for O_3 and CO weakened the statistical significance (Table 3). The significant NO_2 effect was not changed after inclusion of any other pollutants at the best fitting lag days (Table S5). Among the results of changing temperature specifications, adjustment of temperature with longer lag structures yielded a slightly diminished air pollution effect (Fig. S1A). While the estimated effect of $PM_{2.5}$, PM_{10}, and NO_2 remained significant, that of O_3 and CO became non-significant. Changing degrees of freedom and locations of knots had no significant effect on the main findings (Fig. S1B and S1C). The results of stratified subgroup analyses showed similar patterns with the analyses using interaction terms (Fig. S2). The associations between air pollution and migraine on high-temperature days using a 50th percentile value ($PM_{2.5}$: OR 1.043; PM_{10}: OR 1.036; NO_2: OR 1.037) were weaker than those using the 75th percentile value ($PM_{2.5}$: OR 1.068; PM_{10}: OR 1.066; NO_2: OR 1.063), whereas higher effect estimates were produced using a 95th percentile value ($PM_{2.5}$: OR 1.087; PM_{10}: OR 1.083; NO_2: OR 1.081) than those found in the main results (Fig. 4). However, use of a 99th percentile value derived no significant associations probably due to the very small sample size (Fig. 4).

4. Discussion

Here, we conducted a time-stratified case-crossover study to assess the association between exposure to transient higher levels of ambient air pollution and risk of migraine. In the over 18,000 patients who visited EDs for migraine, we found that short-term exposure to higher concentrations of $PM_{2.5}$, PM_{10}, NO_2, O_3, and CO immediately increased the risk of ED visits for migraine. The association was independent of time-invariant factors including sex and genetic predisposition and slowly-varying risk factors such as chronic morbidities and seasonality. Among the pollutants, the association of NO_2 was the strongest and was not confounded by other pollutants. To our knowledge, this is the first study to evaluate the synergistic effect of air pollution and temperature on migraine that found significantly greater air pollution effects on triggering migraine on high temperature days.

Studies on the association of air pollution with migraine have been fewer compared to those concerning other neurological diseases (Oudin et al., 2016; Shah et al., 2015; Wu et al., 2015), and the results have been inconsistent. In Edmonton (Canada), SO_2 during the warm season (2.3%), $PM_{2.5}$ during the cold season (2.8%), and PM_{10} (2.2%) among women during the cold season were associated with ED visits for migraine in generalized linear mixed models per IQR increase (Szyszkowicz et al., 2009). However, a study in Boston (USA) did not find significant associations between ED visits for migraine and air pollution ($PM_{2.5}$, black carbon, NO_2, and SO_2) using a case-crossover

Table 2
Pearson correlation coefficients among air pollutants and meteorological variables in Seoul, South Korea, during 2008–2014.

	Rho (ρ)										
Variables	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO	Temperature	Humidity	Air pressure	Sunshine	Rainfall
$PM_{2.5}$	1	0.86*	0.66*	0.69*	0.08*	0.72*	−0.13*	0.03	0.14*	−0.05*	−0.12*
PM_{10}		1	0.56*	0.64*	0.07*	0.61*	−0.2*	−0.12*	0.16*	0.03	−0.13*
NO_2			1	0.66*	−0.18*	0.79*	−0.21*	−0.13*	0.34*	−0.02	−0.11*
SO_2				1	−0.17*	0.74*	−0.47*	−0.26*	0.43*	0.09*	−0.13*
O_3					1	−0.36*	0.52*	−0.12*	−0.47*	0.4*	−0.06*
CO						1	−0.42*	−0.04	0.41*	−0.11*	−0.08*
Temperature							1	0.42*	−0.78*	−0.08*	0.11*
Humidity								1	−0.52*	−0.64*	0.22*
Air pressure									1	0.22*	−0.16*
Sunshine										1	−0.19*

* Denotes statistically significant correlations at the 0.05 level.

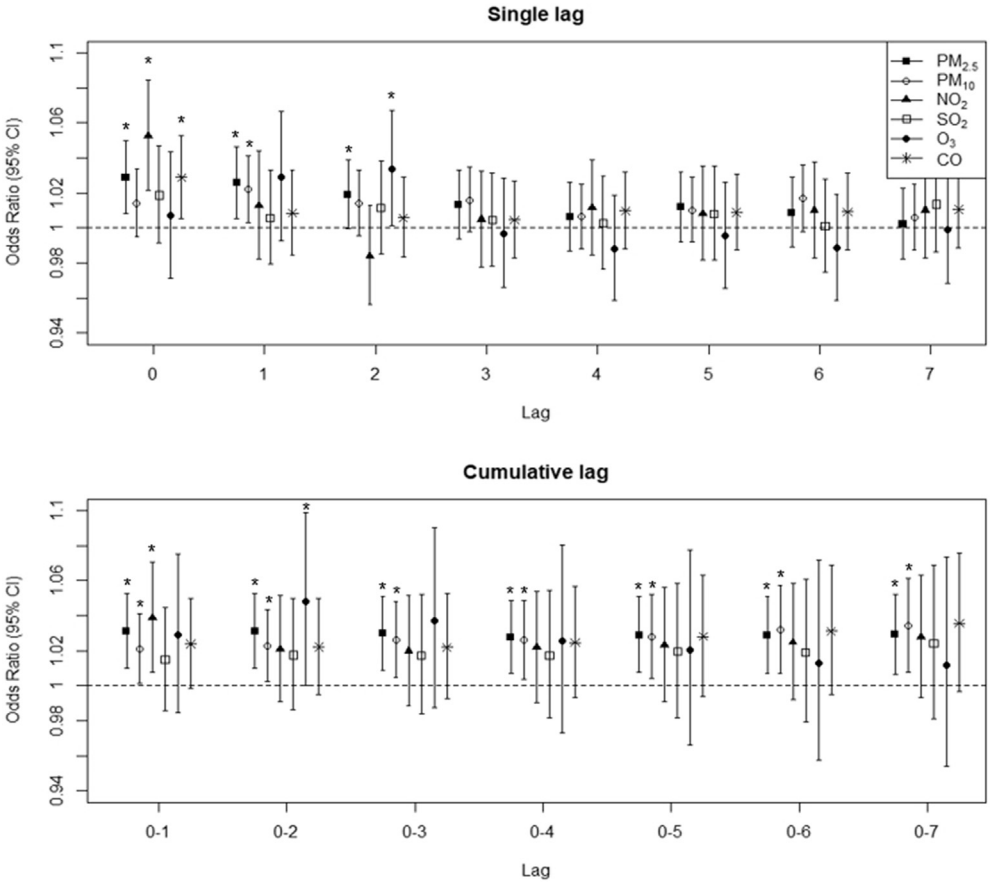

Fig. 1. Association between emergency department (ED) visits for migraine and short-term exposure to six air pollutants per interquartile range increase at various lag structures (single lag on the same day [lag0] and on the 1–7 days prior to the ED visit [lag1–lag7], as well as moving-average lag on the same day plus 1 day before [lag0–1] to 7 days before [lag0–7]) the ED visit. Interquartile range of $PM_{2.5}$ (lag0–2): 12.65 μg/m^3; PM_{10} (lag0–6): 22.81 μg/m^3, NO_2 (lag0): 17.58 ppb, SO_2 (lag0): 2.37 ppb, O_3 (lag2): 21.90 ppb, and CO (lag0): 0.29 ppm. *denotes statistical significance at the 0.05 level.

analysis per IQR increase (Mukamal et al., 2009). More recently, a study using the case-crossover method reported a significant association between air pollution and clinic visits for migraine in Taipei (Taiwan) (Chiu and Yang, 2015). Our findings contribute to the limited available evidence on the effect of air pollution on triggering migraine despite a few discrepancies; while we found a higher association between $PM_{2.5}$ and migraine during the warm season, Szyszkowicz et al. (2009) found a significant association of $PM_{2.5}$ only in the cold season. Moreover, we

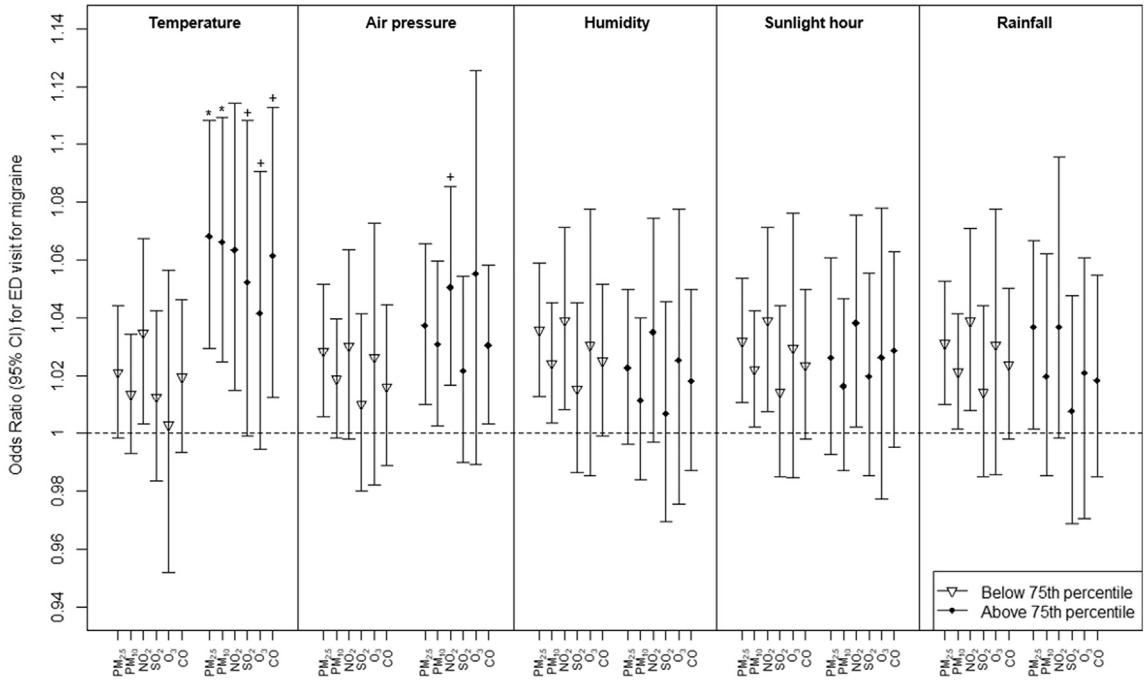

Fig. 2. Effect modification of the association between short-term exposure to six air pollutants and emergency department visits for migraine by weather variables. *denotes statistically significant interactions at the 0.05 level. $^+$denotes statistically significant interactions at the 0.1 level.

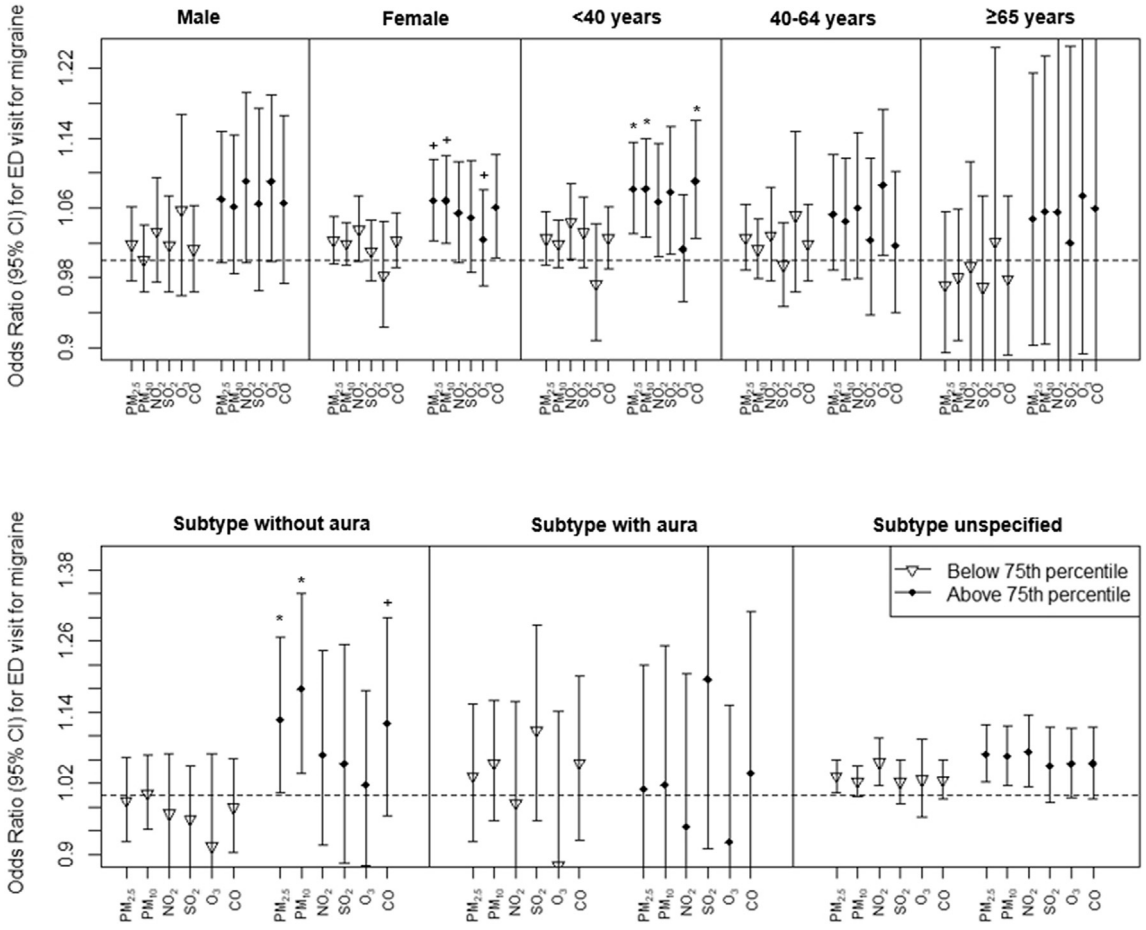

Fig. 3. Effect modification of the association between short-term exposure to six air pollutants and emergency department visits for migraine by temperature in stratified subgroups.*denotes statistically significant interactions at the 0.05 level. $^{+}$denotes statistically significant interactions at the 0.1 level.

Table 3
Association between emergency department visits for migraine and six air pollutants per an interquartile range increase: two-pollutant models adjusted for 2-day moving-average (lag0–1) concentrations.

	Odds Ratio (95% CI)					
Model	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
Single pollutant	1.031 (1.010, 1.053)	1.032 (1.007, 1.057)	1.053 (1.022, 1.085)	1.019 (0.991, 1.047)	1.034 (1.001, 1.067)	1.029 (1.005, 1.053)
Two pollutant						
+ $PM_{2.5}$			1.039 (1.003, 1.077)	0.990 (0.957, 1.025)	1.027 (0.994, 1.061)	1.010 (0.980, 1.042)
+ PM_{10}			1.047 (1.013, 1.083)	1.004 (0.972, 1.037)	1.031 (0.998, 1.064)	1.021 (0.993, 1.050)
+ NO_2	1.024 (0.998, 1.051)	1.024 (0.998, 1.051)		0.998 (0.965, 1.032)	1.030 (0.997, 1.063)	1.015 (0.980, 1.052)
+ SO_2	1.042 (1.015, 1.071)	1.032 (1.005, 1.059)	1.063 (1.026, 1.101)		1.033 (1.001, 1.067)	1.035 (1.005, 1.066)
+ O_3	1.030 (1.008, 1.052)	1.030 (1.005, 1.056)	1.052 (1.022, 1.084)	1.017 (0.990, 1.045)		1.029 (1.005, 1.053)
+ CO	1.035 (1.005, 1.065)	1.027 (1.000, 1.054)	1.063 (1.020, 1.107)	1.005 (0.970, 1.040)	1.033 (1.000, 1.066)	

found significant associations with all pollutants except SO_2, whereas Szyszkowicz et al. (2009) and Chiu and Yang (2015) reported a significant association of SO_2 with migraine. The discrepancies may be attributable to interregional differences in the chemical composition and concentration of air pollutants according to major industries and traffic volume, different atmospheric conditions including temperature, and different populations at risk. Further, study designs, outcome selections (ED visit/clinic visit), outcome definitions (ICD-9/ICD-10 code), selections of exposure windows, and statistical models may have contributed to the inconsistencies. For example, we exhaustively controlled for possible confounding factors, such as sunlight hours and holidays, which vary in the short term.

Although the exact pathogenesis of migraine has not been well established, plausible mechanisms have been suggested. A dominant possible mechanism is explained by the neurogenic inflammation (NI) theory (Peroutka, 2005). NI is the physiological process that reacts to chemical, thermal, or electrical stimulants (stressors) on sensory nerves. During the NI process, peripheral blood flow, vascular permeability, and neurogenic vasodilation mediated by the release of neuropeptides, such as substance P and calcitonin gene-related peptide, from trigeminal neurons may trigger migraine attacks (Moskowitz, 1984; Peroutka, 2005). Air pollutants may induce the release of the neuropeptides involved in the NI reaction by stimulating sensory nerves, including the trigeminal nerves (Calderón-Garcidueñas et al., 2010; Meggs, 1993; Oberdörster et al., 2004).

The strongest association with NO_2 among six pollutants may indicate that air pollution from traffic combustion sources likely affects migraine most, considering that NO_2 is a tracer of combustion-related

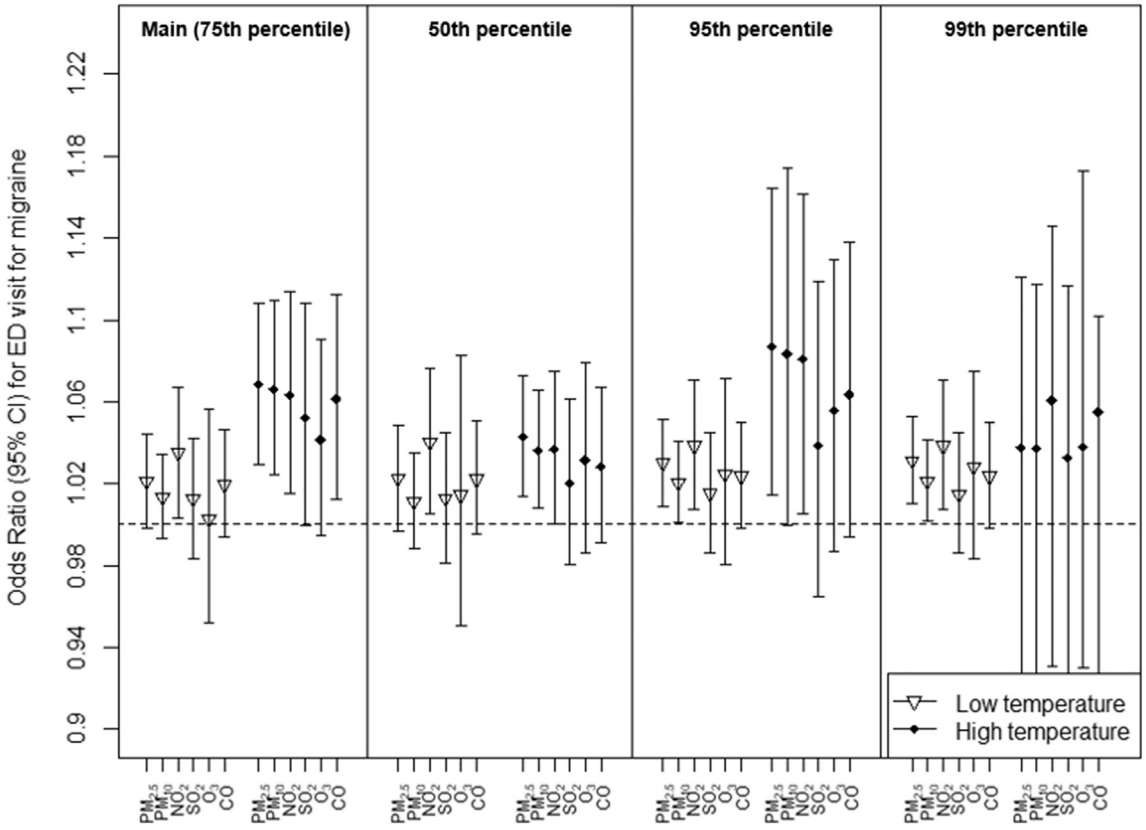

Fig. 4. Results of the sensitivity analysis: differing definition of high-temperature days. The definition of high-temperature days was changed from the 75th percentile to the 50th, 95th, and 99th percentiles over all seasons during 2008–2014.

pollutants (WHO, 2006). PM and CO, whose major components are also emitted from traffic combustion processes, were highly correlated with NO_2. Despite high correlations with other pollutants (r = 0.64–0.74), however, SO_2 did not show a significant association with ED visits for migraine. There has been controversy whether SO_2 is a hazardous pollutant contributing to adverse health outcomes or a surrogate for other pollutants such as ultrafine particles (WHO, 2006). Our finding suggests that SO_2 likely act as a proxy of other hazardous pollutants.

We found a significant synergism between air pollution and high temperature. The findings are in line with those of previous studies on the joint effects of air pollution and temperature on natural mortality (Analitis et al., 2014; Katsouyanni et al., 1993; Qian et al., 2008; Stafoggia et al., 2008). A possible mechanism involved in this synergism is the thermoregulatory system that responds to heat stress (Gordon, 2003); three major systems, the cardiovascular, respiratory, and sudomotor, are activated to dissipate excess heat. This activation has direct or indirect effects on the entry of toxicants into the body through the respiratory and gastrointestinal tracts and the skin. Hence, this mechanism during exposure to high temperature may augment the total absorption of air pollutants. In addition, numerous studies have shown that the hypothalamus, a key brain structure of thermoregulation, is implicated in the pathophysiology of migraine (Alstadhaug, 2009; Denuelle et al., 2007). Activation of the sympathetic nervous system by hypothalamic inflammation, induced by air pollution exposure (Ying et al., 2014) is likely more harmful during high temperature days because lowering body temperature requires the suppression of sympathetic nerves. Further, high temperature itself may induce migraine attacks through arteriolar vasodilation during the thermoregulatory process. Another possible explanation is that our exposure measures, based on monitoring sites, likely better reflected the true exposure of patients during the warm season (to which most of high-temperature days belong) because people spend more time outdoors and keep windows open during the warm season; hence, the true association between air pollution and migraine might be better captured during high-temperature days. However, on hotter days (e.g., above 28 °C), people would keep windows closed during air-conditioning use (Kondo et al., 2013). This might be another reason for the diminished, non-significant association between air pollution and migraine on high-temperature days when we defined high-temperature days using a 99th percentile temperature (28.7 °C) (Fig. 4).

Previous studies have found that reduced regional cerebral blood flow is prominent in patients with aura, but not in patients without aura (Olesen et al., 1981a; Olesen et al., 1981b). A clinical study has found different effectiveness of pharmacotherapy according to subtype of migraine (with and without aura) (Hansen et al., 2015). Moreover, epidemiological studies have found that comorbidities and precipitating factors were different between the two subtypes of migraine (Russell et al., 1996; Wang et al., 2010). In our study, a significant and strong synergistic effect of air pollution and high temperature was only found in patients with migraine without aura (~18% increase). Along with those of previous studies, our findings suggest that the pathophysiology involved may differ depending on migraine subtype (Olesen, 2016).

This study has several limitations. First, there is a possible exposure measurement error as our exposure measures estimated from fixed monitoring sites may not represent true individual exposure. However, this exposure measurement error tends to cause bias toward the null hypothesis (Armstrong, 1998), rather than overestimation. Further, we used the city-level exposure measures because patient or ED-specific addresses were not provided to protect privacy. The use of averaged exposures measured from several fixed monitoring sites causes a Berkson error, which causes large variation, but no or little bias in measurement and thus in risk estimates (Heid et al., 2004). Second, misclassification bias may exist because we relied on recorded

information; however, the results are unlikely exaggerated because the misclassification arises at the same degree in both case and control periods, causing non-differential misclassification, which also causes bias toward the null effect (Copeland et al., 1977). Third, because our outcome definition was based on the day of an ED visit rather than the time of actual symptom onset, we could not account for the variable duration of time that patients experienced migraine headaches before evaluation. Furthermore, because the outcome was ED visits requiring immediate/emergency evaluation, it is impossible to distinguish whether observed increases in risk associated with air pollution exposure reflect changes in the incidence of migraines or severity of migraines. Fourth, we could not consider patients' other health conditions that might be associated with migraine due to limited data availability, although some health conditions which do not change within a month were automatically adjusted for. Fifth, we could not discriminate recurrent cases of migraine because no personal identifiable information was provided; every ED visit case was treated as a new case. Sixth, since many episodes of migraine do not result in an ED visit, our findings based on ED visits are not generalizable to all migraine headaches. Finally, potential confounders, which vary in the short term and we were unable to consider may still be present.

5. Conclusions

In summary, short-term exposure to ambient air pollution was associated with increased risk of migraine, and the association was especially pronounced on high temperature days. Our study adds to evidence of the synergistic effect of air pollution and high temperature on triggering migraine. Despite the modest effect size of air pollution, a prevention measure based on our findings may contribute to the reduction of migraine risk in the population.

Declarations of interest

None.

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Appendix A. Supplementary data

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