Ph.D. Dissertation of Public Health

Association of Air Pollution with Neuropsychiatric Disease in Korea

한국에서 대기오염이 신경정신질환에 미치는 영향

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Abstract

Background: As one of the modern health risks, exposure to ambient air pollution has been associated with numerous health outcomes. Considering the increasing experimental evidence linking air pollution and neurological damage, a few epidemiological studies have been conducted to elucidate the association between air pollution and neuropsychiatric diseases in countries in the Europe and the North America, whereas very few have been conducted in Asian regions. Furthermore, previous results may not be generalized to other study areas considering various different characteristics among study areas and study populations. Hence, it is necessary to investigate this association in Korean population.

Objectives: This thesis aimed to examine the relation between ambient air pollution and neuropsychiatric diseases with three types of epidemiological data provided by public institutions. Short-term associations between selected neuropsychiatric diseases (Parkinson's disease, suicide, and migraine), which are of major health concerns in Korea, and air pollution exposure were assessed.

Methods: I studied the association of selected neuropsychiatric diseases

with short-term exposure to particles <10 μm (PM_{10}), particles <2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO), using a conditional logistic regression analysis with a time-stratified case-crossover design. According to data availability, potential effect modifications by socioeconomic factors (sex, age, education level, job, and marital status) and other related factors (method of suicide, migraine subtype, temperature, and season) were investigated. Further, two-pollutant models were analyzed to identify a pollutant that gives the strongest harmful effect on the neuropsychiatric system.

Results: For the association with Parkinson's disease (PD) aggravation, a unit increase in the 8-day moving average of concentrations of pollutants was significantly associated with PD aggravation. The association was consistent for $PM_{2.5}$ (odds ratio [95% confidence interval, CI]: 1.61 [1.14–2.29] per 10 $\mu g/m^3$), NO_2 (2.35 [1.39–3.97] per 10 ppb), SO_2 (1.54 [1.11–2.14] per 1 ppb), and CO (1.46 [1.05–2.04] per 0.1 ppm). The associations were stronger in women, patients aged 65–74 years, and cold season, but the differences between groups were not statistically significant. In two-pollutant models, NO_2 effect remained significant and strongest among all air pollutants.

For the association with completed suicide risk, NO_2 showed the strongest association across all lags among five pollutants (PM_{10}: 1.21% [95% CI, 0.15%, 2.29%]; NO_2: 4.30% [95% CI, 1.92%, 6.73%]; SO_2: 2.24% [95% CI, 0.70%, 3.80%]; O_3: 1.46% [95% CI, −0.26%, 3.21%]; and CO: 2.35% [95% CI, 0.94%, 3.78%] at lag0). In subgroup analyses by socioeconomic factors, stronger associations were observed in the male sex, the elderly, those with lower education status, the unemployed, white-collar workers, and the married; the largest association was an 11.04% increase (95% CI, 4.15%, 18.39%) by NO_2 among white-collar workers. Two-pollutant models also showed the highest NO_2 effect.

For the association with emergency department (ED) visits for migraine, higher air pollution levels were significantly associated with risk of migraine over various lag structures. In the best fitting lags, $PM_{2.5}$, PM_{10}, NO_2, O_3, and CO increased the risk of migraine by 3.1% (95% CI: 1.0%-5.3%), 3.2% (95% CI: 0.7%-5.7%), 5.3% (95% CI: 2.2%-8.5%), 3.4% (95% CI: 0.1%-6.7%), and 2.9% (95% CI: 0.5%-5.3%), respectively per interquartile range increase. PM effect was significantly stronger on high-temperature than on low-temperature days ($PM_{2.5}$, high: 6.8%, low: 2.1%, $P_{interact}$=0.03; PM_{10}, high: 6.6%, low: 1.4%, $P_{interact}$=0.02). NO_2 effect was largest in two-pollutant models.

Conclusion: In summary, short-term air pollution exposure increased risk of PD aggravation, risk of suicide completion, and risk of ED visits for migraine, and the largest association with NO_2 was consistently observed in all diseases. Ambien air pollution may cause neuropsychiatric disease progression in humans even in the short-time scale, and traffic-related air pollution may be closely associated with neuropsychiatric diseases, considering that NO_2 is regarded as a tracer of vehicle emissions. We present the first evidence of the association in Korean population, and of effect modification of the association by various factors. These findings can serve as the basis for future studies on short-term association between neuropsychiatric diseases and air pollution, and for policy-making to mitigate air pollution levels and reduce neuropsychiatric health effects.

Keyword: Ambient air pollution**,** neuropsychiatric diseases, Parkinson's disease, suicide, migraine, short-term association, case-crossover design

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Chapter 1. General Introduction

1.1 Study Background

As socioeconomic and health sectors in a society have improved, major risk factors for human health also have been shifted. Due to improvements in medical care system, public health interventions (vaccinations, provision of clean water and sanitations, etc.), and population aging, health risk transition occurred from traditional risk (undernutrition, unsafe water, and poor sanitation) to modern risk (tobacco, overweight, and urban air pollution). According to this transition, major health problems also changed from infectious diseases to non-communicable diseases such as cancer and cardiovascular diseases (WHO, 2009).

Outdoor air pollution, one of the modern risk factors, consists of various pollutants such as particles, gases, and metals which are induced from diverse anthropogenic (man-made) sources such as power plants and motor vehicles. This outdoor air pollution has been directly affecting human health causing various diseases (stroke, heart disease, lung cancer, and both chronic and acute respiratory diseases), or indirectly affecting human health through global warming, acid rain, eutrophication, effect on wildlife, and depletion of ozone layer.

Considering hazardous effects of air pollution, World Health Organization (WHO) has selected air pollution as a major environmental risk to health, and

established air quality guidelines for six criteria air pollutants, which are particles less than 2.5 micrometer, $PM_{2.5}$; particles less than 10 micrometer, PM_{10}; nitrogen dioxide, NO_2; sulfur dioxide, SO_2; ozone, O_3; and carbon monoxide, CO. According to WHO, however, 92% of the population all over the world was still living in places where the WHO air quality guidelines were not met in 2014, and WHO suggested that developing and implementing policies and investments which support cleaner transport, energy-efficient housing, power generation, industry and better municipal waste management will reduce key sources of urban outdoor air pollution.

As one of the most densely populated countries with 50 million citizens living in an area of 100,000 km^2, South Korea also has been confronted with severe outdoor air pollution caused by rapid urbanization and industrialization. The problem is that, unlike other modern risk factors including tobacco and obesity which can be reduced by individual-level efforts, reducing outdoor air pollution levels needs community- and country-level efforts. For example, implementing a transportation control policy such as an alternate-day driving for vehicle emission reduction needs the efforts of the government and citizens. However, the policy implementation would not be easy because vehicles provide benefits and citizens will not give up driving unless they realize air pollution as a big health problem. In this circumstance, scientific evidence of the harmful effect of air pollution should be fully provided to induce the community- and country-

level efforts.

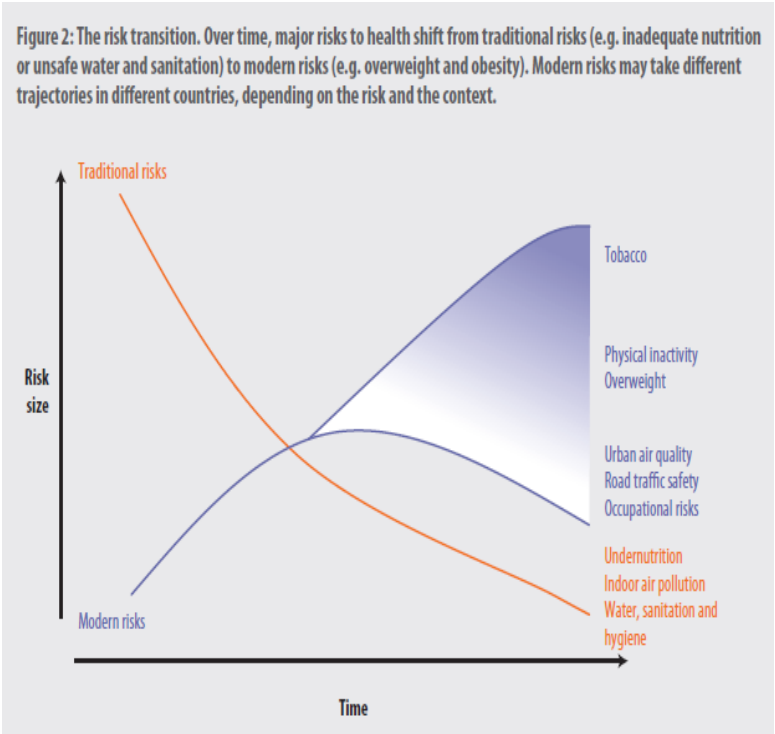

Figure 1. The risk transition. Source: Global Health Risks, World Health Organization, 2009

Recently, neuro-inflammation and oxidative stress have been increasingly considered causal factors in the pathology of central nervous system (CNS) diseases (Block et al. 2007). Although various environmental factors may be involved, air pollution has been identified as the most pervasive factor inducing inflammation and oxidative stress (Block and Calderón-Garcidueñas 2009). Air pollution has been consistently associated with cardiovascular and respiratory diseases (Dominici et al. 2006; Seaton et al. 1995), and is now considered an

emerging risk factor for neurological diseases. Recent experimental studies have shown that air pollutants cause neuro-inflammation, CNS oxidative stress, dopamine neuron damage, blood-brain barrier (BBB) damage, and cerebrovascular impairment (Block and Calderón-Garcidueñas 2009; Pereyra-Muñoz et al. 2006), which indicate potential biological pathways for neurological diseases. Considering the increasing experimental evidence linking air pollution and neurological damage, epidemiological studies have been conducted on the association between long-term exposure to air pollution and neurological diseases. However, the previous studies have mostly been conducted in Western countries in the Europe and the North America.

Therefore, this thesis aimed to investigate the short-term association between exposure to criterial air pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, and CO) and selected neurological diseases (Parkinson's disease, suicide, and migraine), which are major health problems in South Korea. I expect that these findings can serve as the basis for future studies on the relation between air pollution and neurological diseases, and contribute to policy-making for reducing air pollution levels and harmful health effects of air pollution by providing scientific evidence of neurological health effects and on more susceptible subgroups.

Ethics Statement

Before the study was performed, the Institutional Review Board of Seoul National University approved this thesis study protocol (no. E1710/002-004). The need for informed consent was waived because I analyzed the government data, which were provided after encryption to protect private information.

Chapter 2. Short-term air pollution exposure aggravates Parkinson's disease in a population-based cohort

2.1 Introduction

Parkinson's disease (PD) is the second-most prevalent neurodegenerative disease, following Alzheimer's disease (AD) worldwide; the socio-economic burden attributable to PD is expected to increase with the aging of the population(de Lau and Breteler 2006; Samii et al. 2004). In South Korea, the number of PD patients has been rapidly increasing (approximately 24,300 incidence cases between 2010 and 2014), and the total medical expenses for PD has more than doubled (to USD 222 million in 2014). Given the progression to a super-aged society, the number of PD patients in South Korea is expected to increase to 87–93 million by 2030 (Park 2015).

PD is caused by the loss of dopamine-generating cells in the substantia nigra (Malapani et al. 1994); however, the exact pathogenesis remains unclear (de Lau and Breteler 2006). Recently, neuro-inflammation and oxidative stress have been increasingly considered causal factors in the pathology of central nervous system (CNS) diseases (Block et al. 2007). Although various environmental factors may be involved, air pollution has been identified as the most pervasive factor inducing inflammation and oxidative stress (Block and Calderón-

Garcidueñas 2009). Air pollution has been consistently associated with cardiovascular and respiratory diseases (Dominici et al. 2006; Seaton et al. 1995), and is now considered an emerging risk factor for neurological diseases. Recent experimental studies have shown that air pollutants cause neuro-inflammation, CNS oxidative stress, dopamine neuron damage, blood-brain barrier (BBB) damage, and cerebrovascular impairment (Block and Calderón-Garcidueñas 2009; Pereyra-Muñoz et al. 2006), which indicate potential biological pathways for neurological diseases. Considering the increasing experimental evidence linking air pollution and neurological damage, epidemiological studies have been conducted on the association between long-term exposure to air pollution and neurological diseases. Decreased cognitive function in humans has been related to increasing annual concentrations of black carbon (BC) (Power et al. 2011), particles less than 10 μm in aerodynamic diameter (PM_{10}), and particles less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) (Tonne et al. 2014). PD incidence has been associated with annual increases in airborne metal concentrations(Palacios et al. 2014), very long-term exposure (over 20 years) to nitrogen dioxide (NO_2) (Ritz et al. 2016), and annual increases in PM_{10} and $PM_{2.5}$ among female never smokers (Liu et al. 2016); AD incidence has been associated with increasing annual exposure to nitrogen oxides (NO_x) (Oudin et al. 2015), NO_2, and carbon monoxide (CO) (Chang et al. 2014). A recent study focusing on $PM_{2.5}$ involvement in neurological disease progression found that long-term $PM_{2.5}$

exposure had significant effects on hospitalizations for dementia, AD, and PD (Kioumourtzoglou et al. 2015).

However, information on the association between short-term air pollution exposure (for days or weeks) and neurological diseases in humans is scarce, although short-term exposure to air pollution has been considered to aggravate neurological function. In the early 1970s, Lewis (1970) reported that mental efficiency in adults decreased after the breathing of polluted air from the streets in London. Recently, Wellenius et al. (2013) found that increasing mean $PM_{2.5}$ concentrations during 1–28 days before evaluation was associated with elevated cerebral vascular residence and reduced cerebral blood flow velocity in a community-dwelling senior cohort. Moreover, Zanobetti et al. (2014) reported that the average $PM_{2.5}$ concentrations over the 2 days before evaluation was related to an increased risk of hospitalization for PD. Here, we examine the effects of short-term exposure to 5 air pollutants on the aggravation of PD, defined as cases of emergency hospital admission that were primarily diagnosed with PD, using a time-stratified case-crossover design in Seoul, the largest metropolitan city, from a population-based cohort in South Korea.

2.2 Materials and Methods

2.2.1 Study population

The National Health Insurance Service (NHIS) is a health insurance system with

universal coverage in Korea, in which all citizens are registered. The NHIS established the National Health Information Database (NHID) that contains individual information, demographic data, and medical treatment information of Korean citizens since its formation in 2000. In 2015, the NHIS released data of the National Health Insurance Service-National Sample Cohort (NHIS-NSC), which is a representative, population-based cohort proportionally stratified by age, sex, and income level. The cohort includes 1,025,340 patients sampled from the target population of 46,605,433 individuals in the 2002 NHID, who were followed until 2013. Detailed information on the NHIS-NSC has been described elsewhere (Lee et al. 2016).

We obtained information on our study population from NHIS-NSC data for 2002 through 2013. We used information on patient demographics (sex, age, and district-level residential address) and medical treatment (date of visit, primary and accessory diagnosis, type of medical department, type of visits [outpatient or inpatient], and admission route). Before outcome ascertainment, we operationally defined PD aggravation, based on previous studies (Kioumourtzoglou et al. 2015; Zanobetti et al. 2014), as cases of emergency admission wherein PD was primarily diagnosed. We first collected data on the medical treatment of patients diagnosed with PD (International Classification of Disease, 10^{th} Revision code G20 for primary or accessory diagnosis) in 7 metropolitan cities in Korea (n = 191,012). Thereafter, we only assessed admission cases (n = 43,071). Among the

admission cases, we only selected patients residing in Seoul (n = 14,774). Seoul was chosen as the study area for our main analysis because regular measurement of $PM_{2.5}$ has been conducted only in Seoul. Furthermore, it is a suitable study location, considering the dense population and the heavy traffic; Seoul' population accounts for one-fifth of the entire population of Korea and its population density is 16,189 individuals/km^2. Finally, among the admission cases in Seoul, only emergency admission cases (n = 314) were selected, as scheduled admissions would not have been appropriate for assessing the short-term association (Figure 2.1).

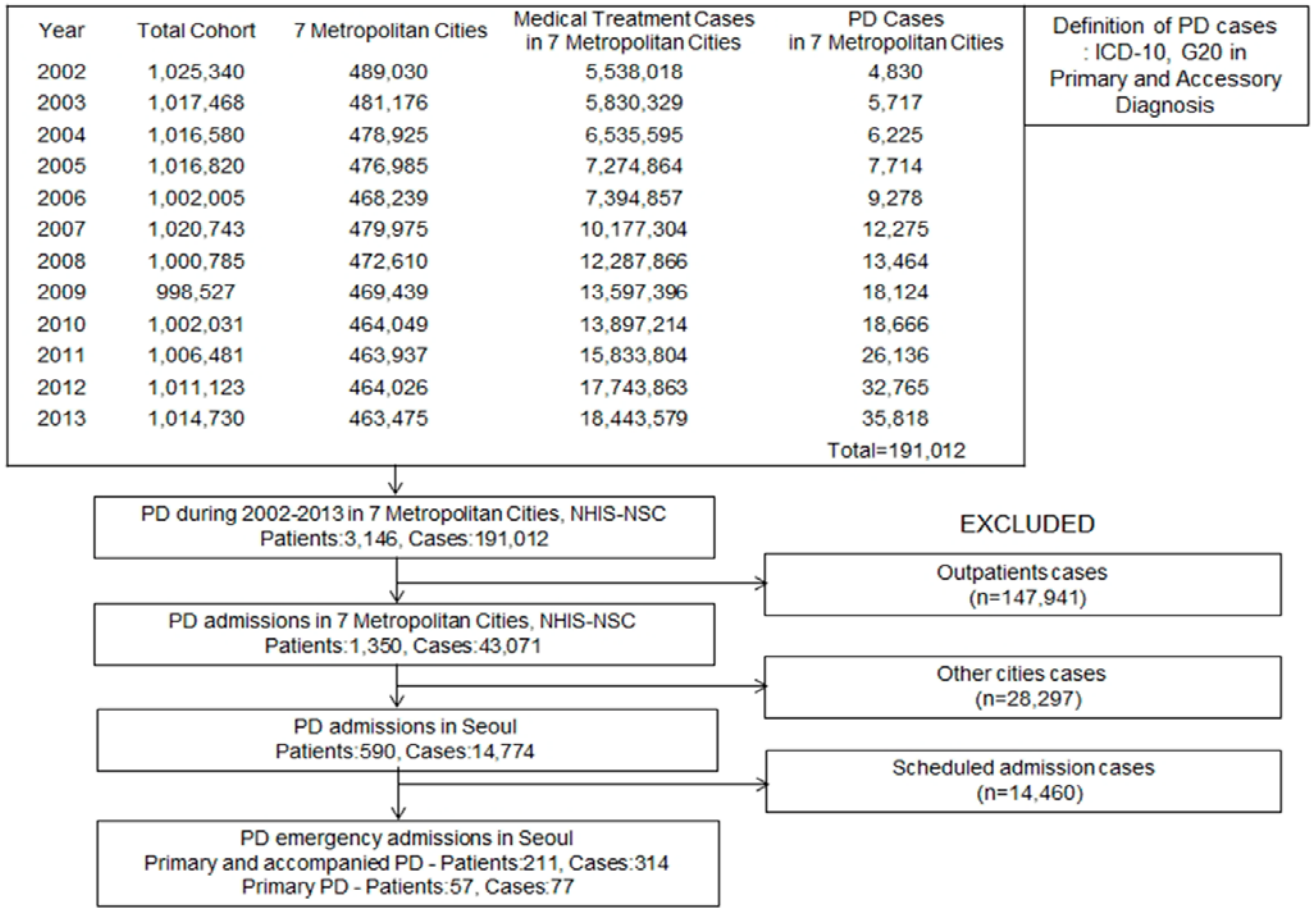

Figure 2.1. Flow chart of the study population from the NHIS-NSC, Seoul, Korea, 2002-2013.

Ethics statement. Ethical approval was obtained from the Institutional Review Board of Seoul National University (Approval Number: 1410/002-009). All methods were performed in accordance with the relevant guidelines and regulations. The NHIS provided the data after encryption to protect private information. Therefore, the need for informed consent was waived.

2.2.2 Air pollution and weather information

Seoul is composed of 25 districts ranging between 10 to 47 km^2. We obtained hourly concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO) from 27 monitoring sites operated by the Korean National Institute of Environmental Research, as well as those of particles <2.5 μm ($PM_{2.5}$) from 25 monitoring sites operated by the Seoul Research Institute of Public Health and Environment (only at 7 sites in 2002, which expanded gradually to 25) in Seoul. Each district has at least 1 monitoring site. During study period, there were substantial missing daily concentrations when daily exposure concentrations were constructed for each monitoring site, as mechanical failure at a monitoring site usually persists for a day (range: 18–1,822 missing values over a total of 4,383 days). Analysis with missing data can cause biased estimates (Demissie et al. 2003) and reduced power due to deletion of cases with missing exposures. To reduce the bias attributed to missing exposures, we constructed daily representative concentrations as follows: first, we calculated the

mean hourly concentrations by averaging the concentrations measured at each monitoring site. This method appropriately resolved the missing hourly values, as none of the cases had simultaneously missing hourly values across different sites at a certain hour. Second, the 24-h concentrations were averaged for $PM_{2.5}$, NO_2, and SO_2, whereas the daytime 8-h [09:00–17:00] concentrations were averaged for O_3 and CO. We chose daytime average of O_3 and CO concentrations to represent outdoor exposures better, considering that people are more likely to be active outdoors during the daytime. These city-specific concentrations as measures of short-term exposures solve the bias created by missing exposures. Although assigning averaged exposures measured via fixed monitoring sites to each individual causes a Berkson error, the error causes little or no bias in measurement and thus in risk estimates (Heid et al. 2004).

Hourly data on ambient temperature, relative humidity, and air pressure were obtained from the Korea Meteorological Administration; daily mean values were constructed to adjust for potential confounding by short-term variations in weather variables.

2.2.3 Study design

We applied a time-stratified case-crossover design to explore the short-term association between air pollution and PD aggravation. A case-crossover design is a variant of the case-control design for the evaluation of transient exposures and

rare acute-onset diseases that provides sufficient statistical power for fewer cases (Maclure 1991). As each patient serves as his own control, time-invariant individual factors, such as sex and genetic predisposition, are automatically controlled by perfect matching. Factors that vary gradually, such as seasonal patterns and long-term trends, can be controlled by choosing control days that are close to the case days (Zanobetti and Schwartz 2005). We selected 3 or 4 control days matched to the same day of the week within the same month and year as the admission day (case day) for each case (e.g., if admission occurred on a Monday in March 2002, then the remaining Mondays in that month were chosen as the control days). This time-stratified design has been shown to yield unbiased effect estimates, with an adequate conditional logistic likelihood (Schwartz et al. 2003).

2.2.4 Statistical analysis

The odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of PD aggravation, associated with short-term air pollution exposure, were estimated by using conditional logistic regression, which compares the air pollutants concentrations on the case and control days. We adjusted for moving average temperature of the same day and previous day (lag0–1) by using a regression spline (with 3 df) to control for potential nonlinear associations, and adjusted for relative humidity and air pressure on same day (lag0), influenza epidemics, holidays, and the first day of the month; the final adjustment was made to reduce

bias due to case misclassification, as the information of long-term in-patients is additionally recorded on every first day of each month because the NHIS provider submits claims to the Health Insurance Review Agency on the first day.

We entered each air pollutant linearly into the model with various lag structures in order to consider the immediate, delayed, and cumulative effects (single lag: same day and 1–7 days before admission [lag0 to lag7]; moving average lag: moving average of same day and 1–7 days before admission [lag0–1 to lag0–7]), and plotted the effect estimates of each pollutant at all lag structures to explore the lag pattern for different exposures. Among the lag structures, the lag that derived the strongest effect estimates was chosen as the main exposure for each air pollutant. This method has been recognized as an appropriate strategy for selecting lag structures when evaluating different exposures and outcome associations (Samoli et al. 2013; Stafoggia et al. 2010). For each pollutant, we tested for possible non-linearity in association with PD aggravation using a restricted natural cubic spline function with 3 knots (Desquilbet and Mariotti 2010). The placement of knots was selected based both on the distribution and air quality guidelines (EPA 2016; Organization 2006). The test for non-linearity is equivalent to testing the significance of the spline.

In the case-crossover design, the effects of time-invariant factors cannot be estimated due to perfect matching. We examined the potential effect modification by sex, age (<65 years, 65–74 years, ≥75 years), and seasons (warm:

April–September, cool: October–March), using the interaction terms of the modifiers and air pollutants maintaining statistical power.

2.2.5 Sensitivity analysis

We conducted several sensitivity analyses. First, we conducted co-pollutant analyses to investigate potential confounding by other pollutants. For the co-pollutants, both same-day (lag0) and 2-day average (lag0–1) concentrations were analyzed. Second, we tested alternate selection schemes for control days: a) every third day in the same month and year as the case day, and b) temperature-matched day in the same month and year as the case day (temperature rounded to the nearest degree in °C). The day of the week was further controlled in the alternate control models. Third, we conducted a district-level analysis by assigning district-specific averages to patients in order to investigate how the results using district-specific concentrations with missing values are different. Fourth, we only included patients' first admission case to confirm the sensitivity of the results to allow for multiple emergent admissions. Fifth, we included patients residing in the other 6 metropolitan cities (Incheon, Busan, Daegu, Daejeon, Gwangju, and Ulsan) in our study population for generalizability. We assigned city-level exposure variables to each patient and analyzed without any model stratification by city due to the small number of cases per city (range: 2–28). Lastly, we defined PD aggravation as either a primary or an accessory diagnosis.

All analyses were conducted using the PHREG method in SAS 9.4 (SAS Institute, Cary, NC). The results were reported as estimated ORs with 95% CIs per a unit increase in the concentrations of the 5 air pollutants; units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO.

2.3 Results

2.3.1 Confirmation of PD cases and air pollution

During 2002-2013, we identified 77 emergency admission cases with primarily diagnosed PD and 314 emergency admission cases with PD as a primary or an accessory diagnosis. Female patients (56%) and patients aged ≥75 years (53%) were predominant among the PD cases, and the season-specific case counts were similar (Table 2.1). Dementia, diabetes, and cerebral infarction were the most prevalent co-morbidities among the primary PD cases. While the 2-day moving average (lag0-2) concentrations of the pollutants were similar on case and control days, the 8-day moving average (lag0–7) concentrations were higher on case days than on control days, except for O_3 (Table 2.2). The difference in the lag0-7 concentrations between the case and control days ranged from 0.01 ppm for CO to 2.3 μg/m^3 for $PM_{2.5}$ among the cases who were primarily diagnosed with PD, and from 0 ppm for CO to 1.1 μg/m^3 for $PM_{2.5}$ among the cases with a primary or an accessory diagnosis of PD. All the air pollutants were highly inter-correlated with each other (correlation coefficient *r*: 0.54–0.76), except for O_3 (*r*: 0–0.44),

and were not or lowly correlated with the weather variables (*r*: 0–0.47; Table 2.3).

Table 2.1. Cases of emergency hospital admissions for Parkinson's disease (PD): Overall and according to sex, age, season, and co-disease in the NHIS-NSC, Seoul.

	Primary PD diagnosis		Primary and accessory PD diagnosis	
Variables	*n*	%	*n*	%
Overall	77		314	
Sex				
Male	34	44	151	48
Female	43	56	163	52
Age				
≤64	8	10	34	13
65–74	28	37	114	36
≥75	41	53	159	51
Season				
Warm (April–September)	36	47	159	51
Cool (October–March)	41	53	155	49
Accessory diagnosis				
Dementia	9	12		
Diabetes	9	12		
Cerebral infarction	7	9		
Primary diagnosis				
Respiratory			40	13
Cerebrovascular			33	11
Genitourinary			24	8

Table 2.2. Distribution (mean±standard deviation [SD]/interquartile range [IQR]) of the environmental variables during the case and control study periods.

	Primary PD diagnosis						Primary and accessory PD diagnosis					
	Case			Control			Case			Control		
Variables	N	Mean ± SD	IQR	N	Mean ± SD	IQR	N	Mean ± SD	IQR	N	Mean ± SD	IQR
$PM_{2.5}$ ($\mu g/m^3$)[a]	77	27.4 ± 12.7	16.6	268	27.5 ± 17.9	16.5	314	26.3 ± 14.1	15.3	1084	26.7 ± 15.3	17.4
NO_2 (ppb)[a]	77	36.2 ± 11.5	15.3	268	36.1 ± 11	16.5	314	36.1 ± 11.1	15.2	1084	35.9 ± 11	16.1
SO_2 (ppb)[a]	77	5.7 ± 2.6	1.9	268	5.3 ± 1.9	2.8	314	5.3 ± 2.1	2.2	1084	5.2 ± 2	2.5
O_3 (ppb)[a]	77	24.1 ± 12.4	16.3	268	22.9 ± 11.3	15.8	314	24.8 ± 12.6	17.5	1084	23.9 ± 12	17
CO (ppm)[a]	77	0.58 ± 0.22	0.2	268	0.57 ± 0.21	0.25	314	0.55 ± 0.21	0.21	1084	0.56 ± 0.22	0.24
$PM_{2.5}$ ($\mu g/m^3$)[b]	76	28.7 ± 14.9	13.5	268	26.4 ± 10.5	12.6	313	27.7 ± 12.4	13.8	1083	26.6 ± 10.4	12.4
NO_2 (ppb)[b]	76	37.2 ± 9.4	13.1	268	35.6 ± 7.5	11.3	313	36.4 ± 8.2	10.1	1083	35.8 ± 7.6	10.6
SO_2 (ppb)[b]	76	5.6 ± 2	3	268	5.3 ± 1.6	2.6	313	5.4 ± 1.7	2.3	1083	5.3 ± 1.7	2.2
O_3 (ppb)[b]	76	23 ± 10.1	15.4	268	23.2 ± 9.9	15.2	313	24.1 ± 10.4	16.5	1083	24.2 ± 10.4	16.7
CO (ppm)[b]	76	0.58 ± 0.18	0.25	268	0.57 ± 0.17	0.22	313	0.56 ± 0.17	0.21	1083	0.56 ± 0.17	0.2
Temperature (°C)	77	11.5 ± 12.1	23.1	268	12.1 ± 11.1	19.8	314	12.9 ± 11.1	18.9	1084	12.8 ± 10.5	18.6
Humidity (%)	77	48.4 ± 21.1	29.2	268	53 ± 22.9	30.3	314	50.3 ± 19.8	28.4	1084	52.9 ± 21	30.3
Air pressure (hPa)	77	766.8 ± 440.1	20.3	268	774.4 ± 433.1	19.9	314	764.7 ± 438.7	21	1084	771.2 ± 434	22.1

[a]The 2-day moving average (lag0–1) concentrations are described. [b]The 8-day moving average (lag0–7) concentrations are described.

Table 2.3. Correlations between exposure variables in Seoul, Korea, during 2002-2013.

	$PM_{2.5}$	NO_2	SO_2	O_3	CO	Temperature	Humidity	Air pressure
$PM_{2.5}$	1	0.56*	0.54*	0	0.60*	-0.08*	0.10*	0.13*
NO_2		1	0.69*	-0.2*	0.76*	-0.23*	-0.12*	0.02
SO_2			1	-0.19*	0.74*	-0.44*	-0.19*	0
O_3				1	-0.44*	0.47*	-0.15*	-0.07*
CO					1	-0.43*	0.02	0.05*
Temperature						1	0.36*	0
Humidity							1	0.68*
Air pressure								1

*Statistically significant correlation is indicated by $p<0.05$.

2.3.2 Short-term association between air pollution and PD aggravation

Figure 2.2 shows the ORs of PD aggravation associated with a unit increase in the concentrations of the 5 air pollutants, with various lag structures; units are 10 $\mu g/m^3$ for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO. We observed significant associations for all air pollutants except for O_3, and the estimated effects for each pollutant showed a similar lag pattern—i.e., a significant effect for lag3 concentrations (OR [95% CI] for $PM_{2.5}$: 1.29 [1.06–1.57], NO_2: 1.55 [1.19–2.03], CO: 1.22 [1.05–1.41]) for the single lag structure, and the largest significant effect for lag0–7 concentrations (OR [95% CI] for $PM_{2.5}$: 1.61 [1.14–2.29], NO_2: 2.35 [1.39–3.97], SO_2: 1.54 [1.11–2.14], CO: 1.46 [1.05–2.04]) for the moving average lag structure. Based on these results, the lag0–7 concentrations of all the pollutants were selected for further analyses, except for O_3 (same-day [lag0] concentrations). The ORs of emergency admission for PD including accessory diagnoses were smaller than those for PD aggravation (Figure 2.3). In the assessment of the possible non-linear associations, we did not find evidence of non-linearity; testing for linearity between short-term air pollution exposure and PD aggravation gave χ^2=0.06, df=1, P=0.80 for $PM_{2.5}$, χ^2=1.63, df=1, P=0.20 for NO_2, χ^2=0.15, df=1, P=0.70 for SO_2, χ^2=0.30, df=1, P=0.59 for O_3, and χ^2=0.52, df=1, P=0.47 for CO (Figure 2.4).

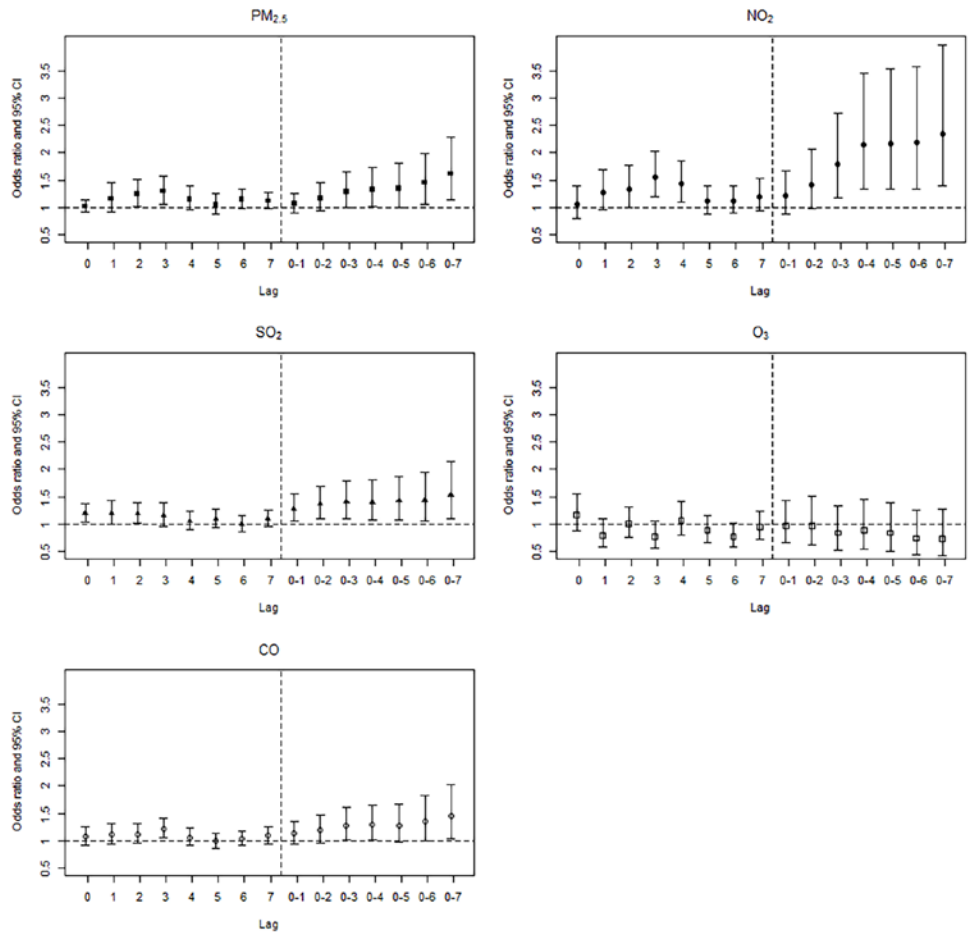

Figure 2.2. Odds ratios of Parkinson's disease aggravation associated with a unit[a] increase in the concentrations of 5 air pollutants with various lag structures (single lag on the same day [lag0] and on the previous 1−7 days [lag1−lag7], as well as moving average lag on the same day plus 1 day before [lag0−1] to 7 days before [lag0−7]). [a]Units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO.

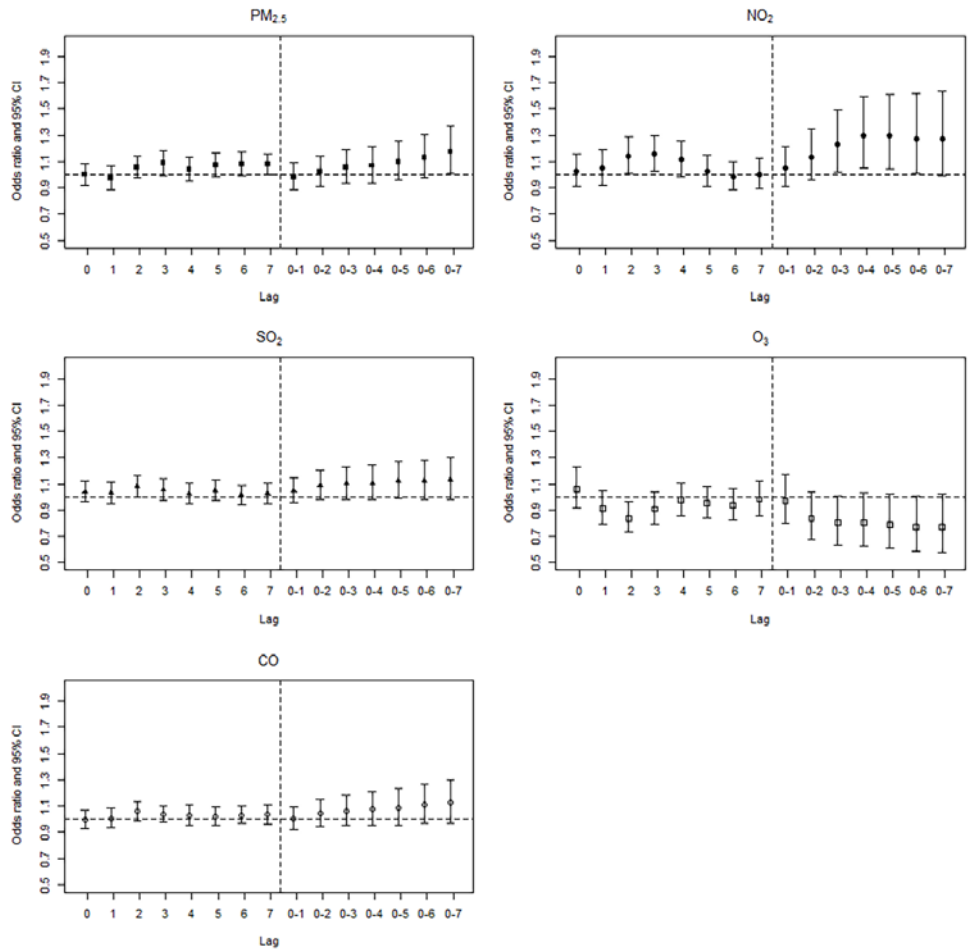

Figure 2.3. Odds ratios of emergency hospital admissions with Parkinson's disease as a primary or an accessory diagnosis associated with a unit[a] increase in the concentrations of 5 air pollutants with various lag structures (single lag on the same day [lag0] and on the previous 1−7 days [lag1−lag7], as well as moving average lag on the same day plus 1 day before [lag0−1] to 7 days before [lag0−7]). [a]Units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO.

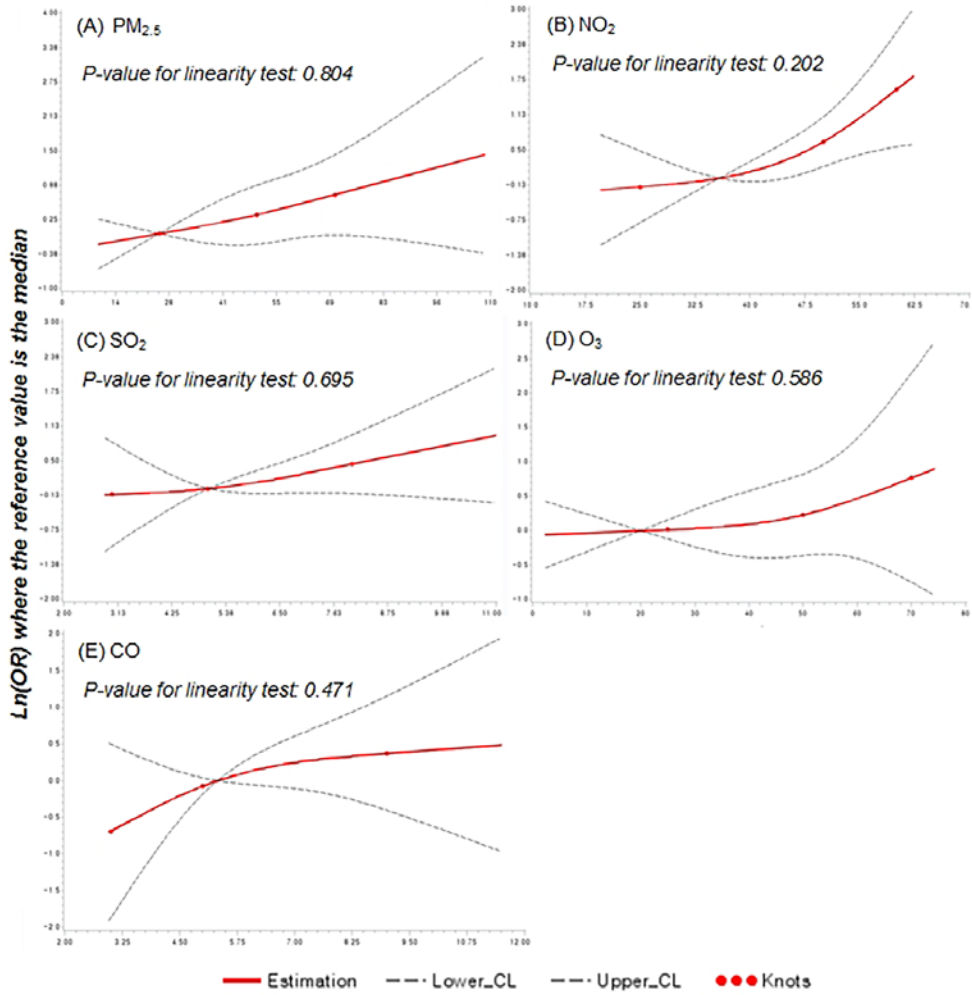

Figure 2.4. Concentration-response associations between air pollutants and Parkinson's disease aggravation using restricted cubic splines with 3 knots. [a]Knots were located at 25, 50, and 70 μg/m^3 for a 24-h average of $PM_{2.5}$; at 20, 40, and 60 ppb for a 24-h average of NO_2; at 3, 5, and 8 ppb for a 24-h average of SO_2; at 25, 50, and 70 ppb for an 8-h average of O_3; and at 0.3, 0.5, and 0.9 ppm for an 8-h average of CO. [b]Temperature, relative humidity, air pressure, influenza epidemics, holidays, and the first day of the month were adjusted. [c]The lag0−7 concentrations of all the pollutants, except for O_3, were analyzed (lag0 concentrations).

2.3.3 Effect modification by sex, age, and season

Table 2.4 presents the sex-, age-, and season-specific associations between air pollution and PD aggravation, estimated using interaction terms. In the sex-specific analysis, women showed slightly stronger associations (OR [95% CI] for $PM_{2.5}$: 1.66 [1.10–2.50], NO_2: 2.15 [1.16–3.99], SO_2: 1.64 [1.02–2.63], CO: 2.65 [1.05–6.68]) than men (OR [95% CI] for $PM_{2.5}$: 1.53 [0.86–2.72], NO_2: 2.81 [1.17–6.76], SO_2: 1.46 [0.94–2.25], CO: 1.34 [0.83–2.15]). Among the different age groups (<65, 65–74, and ≥75 years), the 65–74-year age group generally showed stronger associations (OR [95% CI] for $PM_{2.5}$: 1.95 [1.14–3.32], NO_2: 2.62 [1.27–5.4], CO: 1.74 [1.04–2.91]) than the other age groups. With regard to the season-specific results, all air pollutants, except for O_3, showed stronger association with PD in the cool season (OR [95% CI] for $PM_{2.5}$: 1.83 [1.17–2.87], NO_2: 2.77 [1.38–5.57], SO_2: 1.68 [1.13–2.51], CO: 1.48 [1.02–2.16]); however, these differences were not significant (*p* interaction=0.23–0.99). The group-specific results using single-lag concentrations also showed consistent results except in a case of a sex-specific result for SO_2, which revealed a significantly stronger association in women (*p* interaction=0.02) (Table 2.5).

Table 2.4. Odds ratios of Parkinson's disease aggravation associated with a unit[a] increase in the 8-day moving average (lag0−7) concentrations of air pollutants: effect modification by age, sex, and season.

	$PM_{2.5}$		NO_2		SO_2		O_3[c]		CO	
	OR (95% CI)	*p value*[b]	OR (95% CI)	*p value*	OR (95% CI)	*p value*	OR (95% CI)	*p value*	OR (95% CI)	*p value*
All	1.61 (1.14, 2.29)		2.35 (1.39, 3.97)		1.54 (1.11, 2.14)		1.17 (0.88, 1.55)		1.46 (1.05, 2.04)	
Sex										
Male	1.53 (0.86, 2.72)	0.82	2.81 (1.17, 6.76)	0.61	1.46 (0.94, 2.25)	0.72	1.08 (0.71, 1.65)	0.64	1.34 (0.83, 2.15)	0.62
Female	1.66 (1.10, 2.50)		2.15 (1.16, 3.99)		1.64 (1.02, 2.63)		1.23 (0.86, 1.78)		1.56 (1.02, 2.37)	
Age										
≤64	1.63 (0.66, 4.04)	0.58	3.15 (0.59, 16.9)	0.50	1.55 (0.70, 3.44)	0.99	1.10 (0.44, 2.77)	0.23	1.15 (0.59, 2.24)	0.60
65–74	1.95 (1.14, 3.32)		2.62 (1.27, 5.40)		1.49 (0.88, 2.52)		0.80 (0.47, 1.36)		1.74 (1.04, 2.91)	
≥75	1.32 (0.78, 2.24)		1.9 (0.86, 4.21)		1.57 (0.99, 2.50)		1.38 (0.96, 1.98)		1.39 (0.86, 2.26)	
Season										
Warm	1.34 (0.81, 2.23)	0.36	1.86 (0.48, 4.11)	0.45	1.27 (0.73, 2.21)	0.42	1.24 (0.90, 1.70)	0.39	1.38 (0.69, 2.77)	0.86
Cool	1.83 (1.17, 2.87)		2.77 (1.38, 5.57)		1.68 (1.13, 2.51)		0.92 (0.49, 1.70)		1.48 (1.02, 2.16)	

[a]Units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO.
[b]*p* value for the difference in the estimated effects of pollutants on the risk of Parkinson's disease aggravation between sex-, age-, and season-specific associations.
[c]The same-day (lag0) concentrations were used for O_3.

Table 2.5. Odds ratios of Parkinson's disease aggravation associated with a unit[a] increase in the 3-day lagged concentrations of air pollutants: effect modification by age, sex, and season.

	$PM_{2.5}$		NO_2		SO_2		O_3		CO	
	OR (95% CI)	*p value*[b]	OR (95% CI)	*p value*	OR (95% CI)	*p value*	OR (95% CI)	*p value*	OR (95% CI)	*p value*
All	1.29 (1.06, 1.57)		1.55 (1.19, 2.03)		1.15 (0.96, 1.39)		0.77 (0.57, 1.05)		1.22 (1.05, 1.41)	
Sex										
Male	1.10 (0.82, 1.47)	0.13	1.39 (0.92, 2.10)	0.49	0.94 (0.72, 1.22)	0.02	1.02 (0.63, 1.65)	0.14	1.12 (0.9, 1.39)	0.30
Female	1.48 (1.13, 1.94)		1.68 (1.18, 2.37)		1.49 (1.11, 2.00)		0.63 (0.41, 0.97)		1.31 (1.07, 1.61)	
Age										
≤64	1.10 (0.69, 1.75)	0.32	2.42 (0.89, 6.62)	0.24	1.00 (0.63, 1.60)	0.46	0.69 (0.26, 1.82)	0.87	1.25 (0.86, 1.83)	0.11
65–74	1.57 (1.13, 2.17)		1.92 (1.21, 3.07)		1.41 (0.96, 2.08)		0.85 (0.52, 1.40)		1.61 (1.17, 2.21)	
≥75	1.18 (0.89, 1.56)		1.27 (0.47, 3.31)		1.10 (0.86, 1.41)		0.73 (0.47, 1.12)		1.09 (0.90, 1.31)	
Season										
Warm	1.14 (0.82, 1.57)	0.32	1.41 (0.87, 2.27)	0.64	1.15 (0.80, 1.66)	0.98	0.92 (0.65, 1.31)	0.05	1.26 (0.91, 1.75)	0.82
Cool	1.39 (1.09, 1.78)		1.62 (1.18, 2.22)		1.16 (0.93, 1.44)		0.42 (0.21, 0.84)		1.21 (1.02, 1.43)	

[a]Units are 10 $\mu g/m^3$ for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO.
[b]*p* value for the difference in the estimated effects of pollutants on the risk of Parkinson's disease aggravation between sex-, age-, and season-specific associations.

2.3.4 Robustness of the air pollution effect

According to the co-pollutant analyses, our estimated ORs showed consistent, significant associations after adjusting for the lag0–1 concentrations of other pollutants, except in the case of CO while controlling for SO_2 (Figure 2.5). The findings were similar following the adjustment for lag0 concentrations (Figure 2.6). Figure 2.7 presents the results of other sensitivity analyses. Generally, the estimated effects of air pollution based on the sensitivity analyses were smaller than those of the main analysis; however, they were still significant or showed trends with an identical direction as the main results.

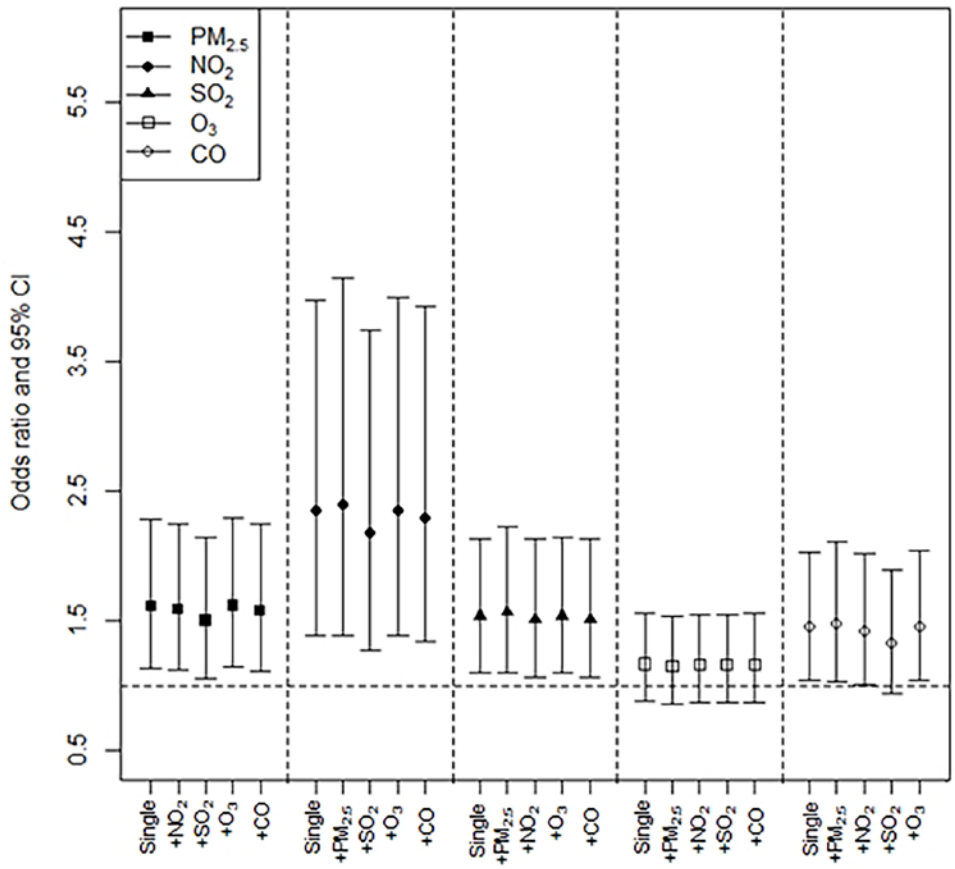

Figure 2.5. Odds ratios of Parkinson's disease aggravation associated with a unit[a] increase in the 8-day moving average (lag0−7) the concentrations of 5 air pollutants: one-and two-pollutant models adjusted for the 2-day average (lag0−1) concentrations. [a]Units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO. [b]The same-day (lag0) concentrations were used for O_3.

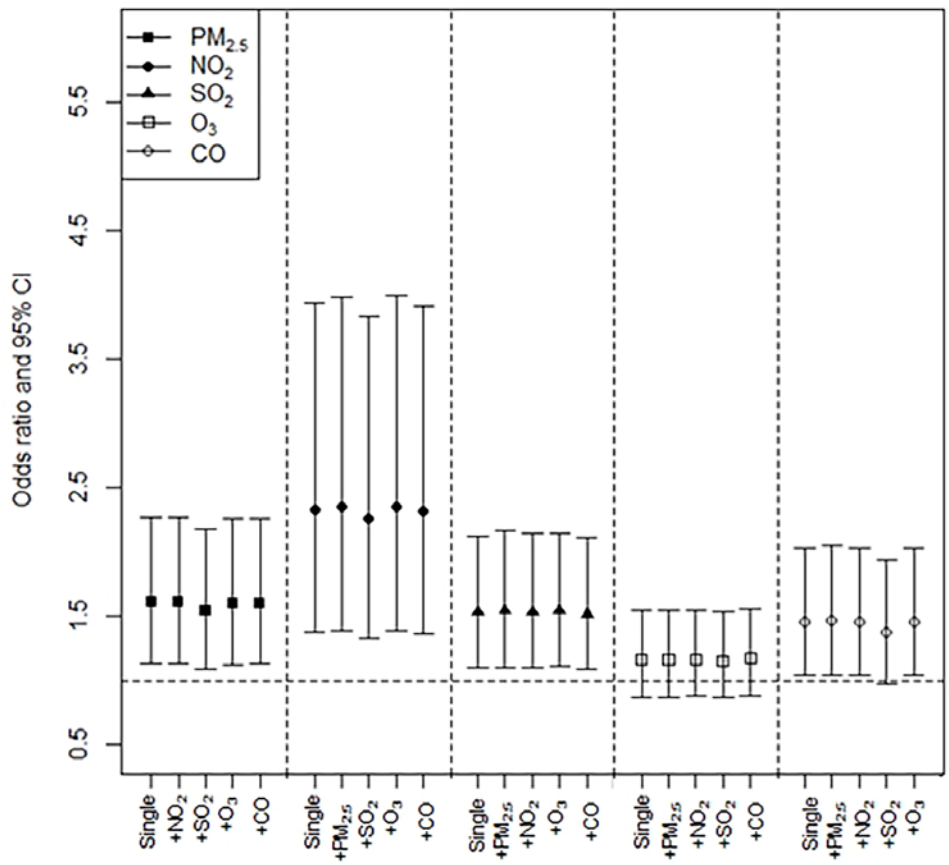

Figure 2.6. Odds ratios of Parkinson's disease aggravation associated with a unit[a] increase in the 8-day moving average (lag0−7) the concentrations of 5 air pollutants: one-and two-pollutant models adjusted for same day (lag0) concentrations. [a]Units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO. [b]The same-day (lag0) concentrations were used for O_3.

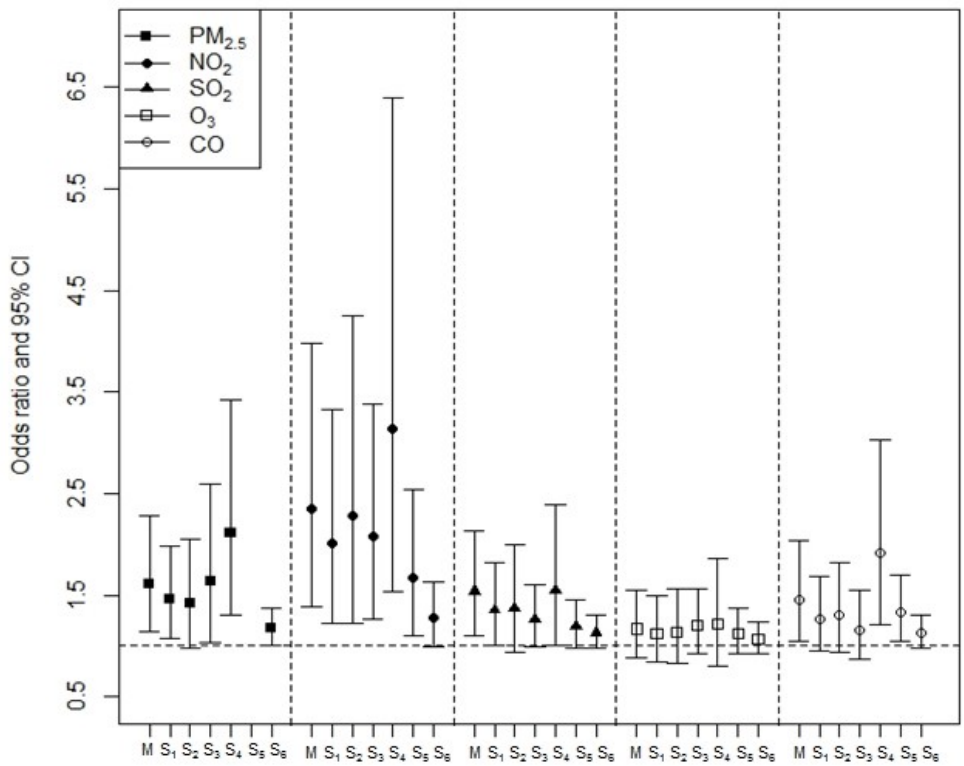

Figure 2.7. Odds ratios (95% confidence intervals) for emergency admissions for Parkinson's disease, associated with a unit[a] increase in the 8-day moving ave-age (lag0−7) the concentrations of 5 urban air pollutants: results of the main models and sensitivity analyses. [a]Units are 10 μg/m^3 for PM_{10}; 10 ppb for NO_2 and O_3; 1 ppb for SO_2; and 0.1 ppm for CO. [b]The same-day (lag0) concentrations were used for O_3. [c]The abbreviations of sensitivity analyses: M, main results; S_1, control chosen as every 3rd day; S_2, control chosen as a temperature-matched day; S_3, use of district-level concentrations; S_4, restriction of PD cases to patients' first emergent admissions; S_5, inclusion of the PD cases of 6 other metropolitan cities; and S_6, inclusion of patients with PD as the accompanying disease. [d]S_5 was not analyzed for $PM_{2.5}$ due to the unavailability of data.

2.4 Discussion

In this time-stratified case-crossover study involving a representative national sample cohort, the risk of PD aggravation, defined as emergency hospital admission for primarily diagnosed PD, significantly increased during exposure to higher short-term concentrations of air pollutants. This association was constantly observed for $PM_{2.5}$, NO_2, SO_2, and CO, and appeared to be robust to several sensitivity analyses. The group-specific results also showed a consistent pattern for each pollutant. To our knowledge, no study has explored the short-term associations between all 5 air pollutants and PD aggravation in humans, although the long-term associations have been evaluated previously (Kioumourtzoglou et al. 2015; Palacios et al. 2014). Our findings suggest that short-term exposure to air pollution may also affect neurological disease progression.

Our estimated OR for PD aggravation associated with a 10 $\mu g/m^3$ increase in the 2-day average concentrations of $PM_{2.5}$ was 1.06 (95% CI: 0.89–1.26; 6.18%), which is larger than the estimate of the only available study, which reported a 3.23% increase in emergency admissions for PD in association with a 10 $\mu g/m^3$ increase in the 2-day average concentrations (Zanobetti et al. 2014), although our result was not significant. The different effect estimates could be induced by various factors. Zanobetti et al. (2014) estimated the effect in the entire US; thus the exposure variability in the

study is likely much larger than in Seoul. In particular, the authors included cities with missing daily exposure information if the cities have at least 219 days' $PM_{2.5}$ data in 1 year, which would likely affect the effect estimate (Demissie et al. 2003). In addition, Zanobetti et al. (2014) only adjusted for day of the week and temperature in the regression analysis and selected control days as every third day in the same month and year; in contrast, we adjusted for additional possible confounders and selected control days matched to the same day of the week within the same month and year. We also confirmed that the effect estimates with every third day as control days were lower than our main results in a sensitivity analysis. Another possible factor might be different particle composition. A previous study analyzed the chemical composition of $PM_{2.5}$ in Seoul and compared the composition with that of the US (J-Y Son et al. 2012); the chemical composition of the US differed by regions and Seoul's chemical structure (Higher NO_3, Lower SO_4) was similar to that of the western US, but different from that of the eastern US. Additionally, a different topography may explain the different result; the topography of Seoul is a basin surrounded by mountains, so the atmospheric diffusion was not easily achieved, causing a build-up of pollutants. This would likely affect the larger effect estimate in Seoul. Other possible factors that can contribute to the different effect estimates are difference in climate, which not only affect chemical reaction of particles

but influence outdoor activity, and difference in distribution of potential modifiers of the association between $PM_{2.5}$ and PD aggravation.

We consistently observed the strongest effect estimates for the 8-day moving average (lag0–7) concentrations for $PM_{2.5}$, NO_2, SO_2, and CO. However, Zanobetti et al. (2014) reported a significant short-term association between $PM_{2.5}$ and PD admissions only for the immediate lag (lag0, lag1, lag0–1, and lag0–2) concentrations, but not for the cumulative lags (lag0–4, and lag0–5). A recent prospective, community-based cohort study found a significant reduction in cerebral blood flow velocity in the middle cerebral artery, that was related to an increase in the averaged $PM_{2.5}$ concentrations over the previous 1–28 days (Wellenius et al. 2013). The study found stronger associations for more cumulative concentrations (7–, 14–, 21–, 28–day average) than immediate concentrations (1–, 3–day average), similar to our study. Moreover, previous studies identified stronger effect estimates for the cumulative (lag0–5) concentrations of air pollutants than for the immediate (lag0–1) concentrations in terms of cardiovascular and respiratory mortality (Samoli et al. 2013; Stafoggia et al. 2010). Although it is likely that the cumulative concentrations of air pollutants have a stronger effect than the immediate concentrations on cardiovascular and respiratory diseases, future studies on short-term association between air pollution and neurological disease should

investigate the effect of both immediate and cumulative concentrations, considering the inconsistent results between the previous studies.

The estimated ORs for gaseous pollutants were larger than that of $PM_{2.5}$ when a same unit increase was applied. In particular, we found the strongest association between NO_2 and PD aggravation. A possible reason for the larger effect of gaseous pollutants might be that the gaseous pollutants are likely better tracers of specific air pollution sources than $PM_{2.5}$. For example, NO_2 is generally considered a tracer of traffic emissions and SO_2 is thought to be a tracer of power plant emissions. Particles, on the other hand, are more heterogeneous in origin, with multiple different sources contributing to their concentrations; therefore, if pollutants from a specific source are more biologically relevant, then tracers of that source would likely better capture the association. (e.g., the strongest association with NO_2 might imply that traffic-related pollution is particularly important in this association, even if NO_2 itself might not necessarily be the actual toxic agent). Although there has been no study on PD, the larger effect estimates of gaseous pollutants than particles were reported in studies on short-term association with non-accidental mortality and stroke mortality (Hong et al. 2002; Moolgavkar 2000). Further studies investigating association between neurological diseases and both gaseous pollutants and particles are warranted to establish more biologically relevant

pollution sources.

Although each air pollutant has distinct physical or chemical characteristics, and multiple pathways are involved in disease initiation and progression, an inflammatory reaction is the common mechanism through which pollutants cause damage to human organs, including the CNS (Block and Calderón-Garcidueñas 2009; Mills et al. 2009); this mechanism may have contributed to the consistent results observed for each pollutant in our study. Recent research suggested that microglia—cells of the immune system in the brain—play an important role in this mechanism (Block and Calderón-Garcidueñas 2009). Air pollutants may directly activate microglia, or cytokines from the peripheral systemic inflammatory response can induce microglial activation. Microglial activation may lead to the development and aggravation of alpha-synucleinopathy (Lim et al. 2016), a major component of PD pathogenesis. Additionally, changes in the BBB (Gray and Woulfe 2015) and the derivation of reactive oxygen species from air pollutants could induce the aggravation of CNS pathology (Block and Calderón-Garcidueñas 2009). Moreover, air pollution could indirectly influence emergency hospital admissions in PD patients with comorbidities associated with air pollution. For example, it has been reported that air pollution exposure aggravates respiratory disease, cardiovascular disease, and diabetes mellitus. These physical burdens could increase the risk of

admission in PD patients (Brunekreef and Holgate 2002). However, the significant results of the association between air pollution and emergent admission in patients with primarily diagnosed PD supported the hypothesis that the effect of air pollution on the aggravation of movement symptoms was substantial.

We firstly investigated potential non-linear association between short-term exposure to all 5 air pollutants and PD aggravation, and no found evidence of non-linearity for any pollutants. Although the biological process and time scale of neurological disease are likely different from those for non-accidental mortality, it is quite agreed that there is no “safe” threshold level for air pollutants except O_3 in short-term association with mortality (Chen et al. 2012; Schwartz et al. 2002). However, it has been controversial whether the O_3 and health association is linear (Bell et al. 2006; Kim et al. 2004). Several experimental studies have found that O_3 exposure causes BBB damage, dopamine neuron damage, and astrocyte death in the substantia nigra (Pereyra-Muñoz et al. 2006; Zhou et al. 2008). In particular, Zhou et al. (2008) found that only higher oxygen-O_3 concentrations (60 μg/ml for 2 and 4 h) induced damage to astrocytes in rats, as compared with lower concentrations (20 and 40 μg/ml) in vitro; this finding suggests that a specific threshold of O_3 may exist for neurological disease. The reason we did not find a significant O_3 effect is likely because the O_3 levels during the

study period may have been below a threshold level that induces damage to human neurological system. Also, it is likely that we did not find evidence of non-linear association for O_3, as our O_3 levels were distributed below a threshold. Additionally, an O_3 and mortality association study compared O_3 levels and their effect estimates across various cities, and found that the relative risk was <1 when the level was <25 ppb, and was >1 when the level was >25 ppb (Kim et al. 2004). Although threshold levels are likely different between outcome diseases, our O_3 levels (24 ppb) during the case days would be below a threshold for PD aggravation.

The sex-, age-, and season-specific results were consistent for each pollutant; stronger effect estimates were observed in women, aged 65-74 years, and cold season in general, but the differences among group-specific results were not statistically significant. Our age-specific results showed statistically significant effects in PD patients aged 65–74 years but not in PD patients aged ≥75 years, even though the cases aged ≥75 years were predominant and aging is the key risk factor in PD (Samii et al. 2004). We believe that PD patients aged ≥75 years in the present study likely stayed indoors, due to difficulty in movement as compared with younger patients. Therefore, their exposure to outdoor air pollution might be lower than that of younger patients. Moreover, the exposure measurement error would be greater in the elderly, because we assigned city-specific averages of

concentrations instead of individual exposures to all patients, which could bias the observed effect estimate more towards the null, and appear as effect modification. Although lower effect estimates were observed among the elderly, the CIs widely overlapped with those of the other age groups. The CIs of sex- and season-specific effect estimates also overlapped and group-specific sample sizes may not have been sufficiently large to detect statistical significance in this study; therefore, drawing a conclusion about the effect modification would not be desirable. A few previous studies have examined effect modifications by potential modifiers in studying the relationship between air pollution and PD. Zanobetti et al. (2014) conducted an age-specific analysis and found a higher effect in subjects aged 65–74 years than subjects ≥75 years, but the difference was not significant in terms of the short-term association between $PM_{2.5}$ and PD admissions. Liu et al. (2016) examined difference in sex-specific results in the long-term association between PM_{10} and PD, and reported a marginally significant higher effect in women (*p* interaction=0.06). Although previous studies, including the present study, do not support significant effect modifications by potential modifiers, future studies examining effect modifiers may be informative and may contribute to elucidating potential biological mechanisms that can explain how air pollution affects PD.

The main results were robust to various sensitivity analyses. The

effect estimates using alternate selection schemes for control days were slightly lower than those of main analysis. In the case-crossover analysis, selection of control period is one of the most important factors influencing effect estimation, and the results may differ markedly among selected controls. Several previous studies have proven that a time-stratified case-crossover design yields unbiased estimates among differently selected controls in air pollution epidemiology (Levy et al. 2001; Schwartz et al. 2003). Similarly, our main result used the most finely time-stratified case-crossover design, where the control days were matched up to day of the week, and is therefore likely to be unbiased. When using different control selections, using every third day as control may have yielded lower effects as these days are too close to be independent, and temperature may not be a key confounder in the association of air pollution and PD; nevertheless, the results were relatively robust. The district-level analysis also showed positive associations with PD aggravation. While the estimated effect of $PM_{2.5}$ was larger than that of the main analysis, the estimated effects of other pollutants were smaller than those of the main analysis. Additionally, the variation of $PM_{2.5}$ effect increased and the effects of SO_2 and CO became insignificant. This is likely due to missing information on district-specific averages, which causes biased estimates (Demissie et al. 2003) and reduced power due to deletion of cases with missing exposure data. The

results restricting PD aggravation cases to patients' first emergency admission showed the strongest association; including only data on the first admission of patients might better capture the association. However, the CIs of the results were considerably wide due to the smaller sample size (n=57), and hence future studies are warranted. The estimated effects of NO_2, SO_2, and CO decreased when PD cases in 6 other metropolitan cities were included. This would likely be due to differences in topography and urban environment among cities; Seoul is located in a basin, whereas some cities are located in plains, where more atmospheric diffusion of pollutants is likely to occur than in a basin. Moreover, the population size (1,147,000–3,538,500) and the population density (1,022–4,452 individuals/km^2) of other cities are much less than those of Seoul (size: 10,195,000 and density: 16,189 individuals/km^2), and the chemical composition of air pollutants may differ according to the dominant industrial activities of the region. The main results conducted in Seoul would not be generalized to other cities or countries that have different characteristics; nevertheless, when combining other cities' PD cases, the associations remained positive; this may indicate an association between short-term air pollution exposure and PD aggravation in other study areas. The analysis in which secondary PD admission cases were included revealed a positive, if less strong association. Although some diseases, such as cardiovascular and respiratory diseases,

known to be related to air pollution exposure, may increase the emergency admissions of PD patients, some primary causes of secondary PD may be unrelated to air pollution; accordingly the effect estimates became smaller due to unrelated primary causes of emergency admissions.

Our study had certain limitations. First, we operationally defined PD aggravation as emergency admissions for primarily diagnosed PD without direct measurement of aggravation of PD symptoms, due to limited data availability. To be recognized as PD aggravations, two things must be met: (1) the patients in our study should already be PD patients, and (2) the primary cause for the emergency admission of PD patients included in the main analysis (77 cases) actually needed to be PD. For the first thing, we confirmed that all 314 cases (primary and accessory diagnosed PD) had have visited or hospitalized with diagnosed PD prior to the emergency admissions. For the second thing, we utilized the fact that in South Korea, PD is one of the rare intractable diseases for which the government pays 90% of the total medical treatment cost; however, the patients need to receive a definite diagnosis of PD based on imaging examinations, such as positron emission tomography-computed tomography (PET-CT) to be eligible as beneficiaries. Thus, we checked whether the government paid 90% of the treatment cost for the 77 primary PD cases. If the 77 cases were beneficiaries, then they would receive a definite diagnosis of PD by imaging

examinations. We confirmed that almost every case only paid about 10% of the total treatment cost and every case paid less than 20% of the total cost, which is for ordinary inpatients without rare intractable diseases. Hence, the diagnosis of patients with PD in the NHIS-NSC was likely to be reliable. Second, our study population size seems small, as our PD cases were selected from the NHIS-NSC, comprising 2.2% of the total eligible population proportionally sampled in 18 age groups. However, there may be a larger number of PD patients at risk of developing PD aggravation due to air pollution in the entire population. Nevertheless, we found a consistent and significant association between short-term exposure to air pollution and PD aggravation by using a time-stratified, case-crossover analysis, in which each case had 3–4 controls; hence, the actual statistical analysis was conducted on a sample that was 3–4 times larger than the sample number. Such a case-crossover analysis is reportedly suitable for acute and rare outcomes, as it provides adequate statistical power (Maclure 1991); therefore, our results are likely unbiased with regard to sample size. Third, there is a possibility of exposure measurement error, as our daily representative concentrations of air pollutants may not be represent of each individual's actual exposure. Exposure measurement error may also occur if a family member who is not residing with the PD patient applied for medical insurance for the PD patient, as the residential address specified in

the NHIS-NSC form would be that of the insurant. However, the measurement error in exposure estimates tends to cause bias towards a null hypothesis and would hence underestimate the association, rather than cause a false-positive result (Armstrong 1998); therefore, our results are not likely to be exaggerated.

The strength of our study is that it is the first study to examine the short-term effects of 5 air pollutants on PD aggravation in humans, in a representative, population-based cohort. The NHIS-NSC provides comprehensive and detailed information on medical care utilization of citizens, based on claims data reflecting actual clinical practice. Thus, only the PD cases who received medical treatment in hospitals were included in our study. Although the exact pathogenesis of PD remains unclear, many risk factors, such as occupational exposure, smoking, coffee consumption, and genetic risk factors, have been suggested to be related to PD incidence and prevalence (Samii et al. 2004). We controlled for these individual confounding factors by using a case-crossover design with perfect matching, and confirmed the independent association between air pollution and PD aggravation. Moreover, we assessed potential effect modification by sex, age, and season, and these findings could contribute to the creation of public health policy for the prevention of PD deterioration by providing information on the highly susceptible group.

Overall, the findings of this study, involving a representative population-based cohort, suggest that short-term exposure to air pollution may increase the risk of PD aggravation. Our results can serve as the basis for further studies on the short-term association between air pollution and neurological diseases, and for policy-making to mitigate air pollution and reduce neurodegenerative health effects in our aging society.

Chapter 3. Suicide risk in association with short-term air pollution exposure: effect modification by socioeconomic status

3.1 Introduction

The World Health Organization (WHO) has estimated that over 800,000 people commit suicide annually and that suicide is the second leading cause of death among people aged 15–29 years worldwide (WHO 2016). Although WHO has recognized suicide as a public heath priority and encouraged countries to strengthen comprehensive prevention strategies (Organization 2016), the suicide rate in South Korea has remained high for decades. In 2013, the suicide rate in South Korea was 29.1 per 100,000 population, ranking first among developed countries (OECD 2015); furthermore, suicide was the fourth leading cause of death, following cancer, cardiovascular, and cerebrovascular diseases (KOSIS 2017).

To develop better suicide prevention strategies, it is important to investigate and understand risk factors for suicide. For decades, suicide has been related to multiple risk factors such as social, physical, and psychiatric status, as well as their synergetic effects(Nock et al. 2008; Qin et al. 2003); recently, environmental factors also have reportedly been regarded as an

emerging risk factors for suicide. While studies on the association of suicide risk with meteorological variables including sunshine and temperature have been widely conducted (Dixon et al. 2007; Page et al. 2007; Petridou et al. 2002), limited studies have been conducted to identify the association between completed suicide and air pollution, including data from just one year (Kim et al. 2010) and from a single county (Bakian et al. 2015); however, the biological plausibility has been reported through experimental studies (Allen et al. 2014; Block and Calderón-Garcidueñas 2009; Rich et al. 2012; Steiner et al. 2008). In addition, no study has examined the association of all criteria air pollutants (particles <10 μm, PM_{10}; nitrogen dioxide, NO_2; sulfur dioxide, SO_2; ozone, O_3; and carbon monoxide, CO) with suicide risk, considering potential confounding by each other although they are mostly coexisting in real world conditions, nor has there been an investigation regarding the potential effect modification by various socioeconomic factors despite their substantial roles on suicide risk (Qin et al. 2003).

Our goals were (1) to examine the association of completed suicide risk with short-term exposure to five air pollutants in 26 South Korean cities between 2002–2013, using a case-crossover design, where each case serves as its own control; (2) to analyze the associations stratified by socioeconomic factors as well as other related factors for investigation of

effect modification; and (3) to explore potential confounding by other air pollutants.

3.2 Materials and Methods

3.2.1 Study design

We applied a time-stratified case-crossover design, a variant of case-control design, where each case serves as its own control (Maclure 1991); hence, time-invariant individual characteristics such as sex and genetic predisposition are automatically controlled. Moreover, slowly varying characteristics such as age, marital/employment status, and seasonality can be controlled by selecting control days close to the case day (Zanobetti and Schwartz 2005); the case-crossover design is thus appropriate for the evaluation of transient exposures and acute onset outcomes. For our study, three or four control days matched to the day of the week were selected within the same month and year with the case day (e.g., if a person committed suicide on a Tuesday in May 2003, then the remaining Tuesdays in May 2003 were selected as the control days), and air pollutant concentrations during the case and control periods were compared. This time-stratified method provides unbiased estimates (Schwartz et al. 2003).

3.2.2 Study population

Data on completed suicide cases occurring in 26 South Korean cities (Table 3.2) between 2002 and 2013 were obtained from the Death Statistics Database of the Korean National Statistical Office (International Classification of Disease, 10th revision [ICD-10] codes X60 to X84). The Death Statistics Database includes the following information: district-level residential address, sex, age (years), education level (five categories), job (10 categories), marital status (unmarried/married/divorced/bereaved), date of death, and place of death (seven categories). The method of suicide was categorized based on ICD-10 codes in 15 categories. The variables were re-categorized for analysis except marital status as follows: age (<35, 35–64, or ≥65 years), education level (low: no education or elementary school graduation; middle: middle school or high school graduation; or high: college graduation or higher), job (white collar: administrator, expert, engineer, or office worker; sales or service worker; blue collar: farmer or fisherman, mechanic, or laborer; or unemployed: student, homemaker, or unemployed), place of death (in: house, hospital, or nursing home, worksite; out: death on arrival, street, or road), and method of suicide (Bakian et al. 2015) (non-violent: drug overdose, poisoning by drugs, alcohol, gas, and other noxious substances, or drowning; violent: all other intentional self-harm). A total of 73,445 suicide cases were analyzed.

3.2.3 Exposure assessment

Hourly concentrations of air pollutants (PM_{10}, NO_2, SO_2, O_3, and CO) measured at 131 monitoring sites located within the 26 cities were provided from the Korean National Institute of Environmental Research. The number of monitoring sites per city varied from 1 to 27 sites (Table 3.2). Daily city-specific concentrations were constructed as the short-term exposure measures as follows. First, hourly mean concentrations were calculated by averaging site-specific concentrations within same city. Second, the 24-hour mean values were averaged for PM_{10}, NO_2, and SO_2, and maximum 8-hour mean concentrations were constructed for O_3 and CO based on the WHO air quality guidelines (WHO 2016). In cities with one monitoring site, the 24-hour concentrations measured at the monitoring site were used. Data of air pollution exposure were 99.9% complete for all pollutants.

3.2.4 Potential confounders

Meteorological factors have been associated with suicide risk in previous studies (Nicholls et al. 2006; Page et al. 2007; Petridou et al. 2002). We obtained meteorological data on ambient temperature sunshine (hours of sunlight), relative humidity, rainfall, and air pressure measured at city-specific meteorological stations from the Korea Meteorological

Administration; we constructed daily mean values to adjust for confounding due to short-term variations.

3.2.5 Statistical Analysis

A two-stage analysis was conducted to calculate odds ratios (ORs) of suicide risk associated with short-term air pollution exposure. In the first stage, city-specific effect estimates were estimated using a conditional logistic regression analysis, which is the method applied to a matched case-control set. As the main exposure, air pollutant concentrations were linearly included in the model with single- or cumulative-lag structures to examine immediate, delayed, and cumulative effects of air pollution: (1) single-lag structures included concentrations on the day of suicide (lag0) or concentrations on 1, 2, …, 7 days prior to suicide (lag1 to lag7), and (2) cumulative-lag structures included moving average of concentrations on the day of suicide and on 1, 2, …, 7 days prior to suicide (lag0–1 to lag0–7). We adjusted for the 4-day moving average (lag0–3) temperature using a regression spline with 3 knots (degrees of freedom=3) to control for a possible non-linear association, and adjusted for lag0–3 sunshine, lag0–3 relative humidity, lag0–3 rainfall, lag0–3 air pressure, influenza epidemics, and holidays as linear terms. The selected lag structures for meteorological variables were based on previous studies (Bakian et al. 2015; Kim et al.

2010). To investigate the presence of effect modification in the association between air pollution exposure and suicide risk, subgroup analyses stratified by socioeconomic status (sex, age, education level, job, and marital status), place of death, method of suicide, and season were conducted in city-specific analyses of the first stage.

In the second stage of the analysis, the pooled effect estimates were derived through a random effect meta-analysis, which conservatively combined the city-specific estimates calculated form the first stage. This two-stage analysis provides the overall effect estimate across the cities, considering regional variations of air pollution effect.

As sensitivity analyses to assess robustness of the results, co-pollutant models were analyzed to examine potential confounding by other air pollutants (e.g., in PM_{10} effect estimation, we additionally adjusted for NO_2, SO_2, O_3, or CO respectively), and a fixed effect meta-analysis was conducted.

The first-stage analysis was conducted using the phreg procedure in SAS, version 9.4 (SAS Institute, Cary, NC), and the second-stage analysis was performed using the metafor package in R, version 3.3.2 (R Core Team, Vienna, Austria, 2016). All results are presented as percentage increase in estimated ORs with two-sided 95% confidence intervals (CIs) per IQR increase in the concentrations of each pollutant; IQRs were 31.5 $\mu g/m^3$ for

PM_{10}; 17 ppb for NO_2; 3.1 ppb for SO_2; 21.2 ppb for O_3; and 0.32 ppm for CO.

3.3 Results

3.3.1 Descriptive results

We identified 49,032 male suicide cases and 24,413 female suicide cases in the 26 cities during 2002-2013 (Table 3.1). Among the cases, age 35–64 years (men: 28,445 [58.0%], women: 10,647 [43.6%]), middle education level (men: 27,178 [55.4%], women: 11,383 [46.6%]), unemployment (men: 28,560 [58.2%], women: 19,314 [79.1%]), and married status (24,831 [50.6%], women 8,814 [36.1%]) were the most common categories. Death occurred more frequently in both sexes inside a house, a hospital, or a worksite. Suicide cases with violent methods were more common. The number of suicide cases did not differ by season.

Table 3.1. General characteristics of completed suicide cases in 26 South Korean cities* between 2002-2013.

	Male (N=49,032)		Female (N=24,413)	
	N	%	N	%
Age, years				
<35 years	9,636	19.7	7,428	30.4
35-64 years	28,445	58.0	10,647	43.6
≥65 years	10,951	22.3	6,338	26.0
Education				
Low	11,077	22.6	7,867	32.2
Middle	27,178	55.4	11,383	46.6
High	10,136	20.7	4,869	19.9
Unknown	641	1.3	294	1.2
Job				
White	6,962	14.2	2,209	9.1
Sales	5,361	10.9	1,677	6.9
Blue	6,581	13.4	620	2.5
Unemployed	28,560	58.2	19,314	79.1
Unknown	1,568	3.2	593	2.4
Marital status				
Unmarried	14,075	28.7	7,240	29.7
Married	24,831	50.6	8,814	36.1
Divorced	6, 779	13.8	2,818	11.5
Bereaved	3,048	6.2	5,412	22.2
Unknown	299	0.6	129	0.5
Death place				
Inside	37,452	76.4	19,388	79.4
Outside	5,342	10.9	2,864	11.7
ETC	6,133	12.5	2,113	8.7
Unknown	105	0.2	48	0.2
Method of death				
Violent	36, 340	74.1	18,968	77.7
Nonviolent	12, 692	25.9	5,445	22.3
Season				
Spring	13,611	27.8	6,798	27.9
Summer	12, 831	26.2	6,369	26.1
Fall	12,101	24.7	6,057	24.8
Winter	10,489	21.4	5,189	21.3

*For 19 cities except for 7 metropolitan cities among 26 cities, data from 2010-2013 were analyzed as the weather stations for those cities were established in 2010.

Suicide rates per city ranged from 16.3 in Suncheon to 43.1 in Jecheon per 100,000 population, and distributions of air pollutants (PM_{10}, NO_2, SO_2, O_3, and CO) concentrations differed by city (Table 3.2). Table 3.3 shows the differences in daily levels of air pollutants and meteorological variables between case and control periods at specific time lags. The concentrations of all air pollutants except O_3 were higher during case periods than during control periods for all immediate lags (lag0, lag1, and lag0–1). Sunshine levels were higher and rainfall levels were lower during case periods than those during control periods.

Table 3.2. City-specific descriptive information on the study period, suicide rate, and levels of air pollutants in 26 South Korean cities.

Cities	Study period	Population × 1000 (2010)	No. of suicide per year	Suicide rate per 100,000	No. of monitoring sites	PM_{10} (24-hr) percentiles		NO_2 (24-hr) percentiles		SO_2 (24-hr) percentiles		O_3 (8-hr) percentiles		CO (8-hr) percentiles	
						50	90	50	90	50	90	50	90	50	90
Seoul	2002~2013	9,794	2,161	22.1	27	49.1	96.4	34.8	53.5	4.7	8.3	25.1	49.4	6.2	11.4
Busan	2002~2013	3,415	964	28.2	16	47.3	84.5	21.2	34.6	5.7	9.2	32.9	50.8	4.9	7.8
Daegu	2002~2013	2,446	595	24.3	11	47	84.9	22.1	37.9	4.8	8.9	31.5	58.2	6.4	11.4
Incheon	2002~2013	2,663	709	26.6	11	52.3	95.2	27.1	44.6	6.7	10.7	29.4	51.2	6.4	11.6
Gwangju	2002~2013	1,476	314	21.3	5	40.2	77.5	19.2	33	3.6	6.2	31.3	54.1	5.9	10.5
Daejeon	2002~2013	1,502	359	23.9	6	40.4	76.4	19	32.3	3.8	7.3	29.5	53.9	6.2	11.8
Ulsan	2002~2013	1,083	234	21.6	13	43.4	77.6	19.4	31.1	6.2	10.1	32.8	52.9	5.3	8.4
Suwon	2010~2013	1,072	302	28.1	5	44.9	82	33.4	55.1	5.1	8.3	29.8	59.9	6.6	11.7
Chuncheon	2010~2013	276	89	32.3	2	46.5	85.4	14.3	30.6	3	7.1	34.6	63.8	5.4	12.1
Wonju	2010~2013	311	119	38.2	2	56.8	104.1	20.5	37	3.7	10.5	32.4	65.5	7.1	17.8
Gangneung	2010~2013	218	83	38.2	1	36.9	71.2	14.4	23	4.3	9.2	31.1	50.7	5.2	8.9
Cheongju	2010~2013	667	188	28.1	4	55.3	98.4	22.8	39.9	3.7	7.3	32.8	62.9	5.2	11.2
Chungju	2010~2013	203	84	41.5	1	39.8	74.2	19	36.6	4	13.6	36.3	67	5.6	18.4
Jecheon	2010~2013	135	58	43.1	1	51.5	97.3	22.8	36.9	4	13.4	31.6	61.3	7.2	20.1
Cheonan	2010~2013	575	184	32	2	42.6	77.3	21.8	35.8	4.2	7.1	29.1	56.3	6.6	10.3

Jeonju	2010~2013	650	152	23.4	3	48.4	84.4	17.7	30.8	4.2	6.9	28.6	51	5.2	8.3
Gunsan	2010~2013	261	93	35.4	3	43.5	80.6	14	24.5	4.3	7.8	35.4	55.6	5.3	8.3
Mokpo	2010~2013	250	72	28.8	1	32.3	58.4	15.3	35.6	5.3	9.1	33.3	59.5	5.7	10.2
Yeosu	2010~2013	270	74	27.3	3	32.6	62.8	18.8	31.8	7.4	12.8	36	56.5	5.5	8.9
Suncheon	2010~2013	259	42	16.3	1	35.2	64.7	14.3	26.3	4.6	7.4	33.9	54.7	4.4	7.9
Pohang	2010~2013	511	142	27.7	3	43.9	75.3	14.5	22.8	4.8	7.7	32.1	52.8	5.8	8.8
Andong	2010~2013	166	69	41.4	1	35.7	74.2	14.8	26.3	2.6	8.2	35.7	59.4	4	8.7
Gumi	2010~2013	403	111	27.5	3	41.9	76	16.2	27	3.9	6.5	36.5	62.3	5.8	9.2
Changwon	2010~2013	1058	269	25.4	3	41.9	74.7	19.1	35.9	4.2	6.5	39.7	66.1	5.4	8.8
Jinju	2010~2013	338	97	28.7	1	37.2	70.2	14	29.9	3.9	7.3	36.1	64.3	5.6	10
Jeju	2010~2013	532	126	23.7	2	35.3	75.5	10	17.7	2.3	5.3	42.3	59.6	4.4	6.8

Table 3.3. Differences in daily levels of air pollutants and meteorological variables between case and control periods and their distributions in 26 South Korean cities*, from 2002-2013.

	Case periods		Control periods		Mean difference	95% Confidence limit	Percentiles			p value for t-test
	Mean	SD	Mean	SD			10	50	90	
PM_{10} ($\mu g/m^3$)										
lag0	53.4	33.3	52.9	35.3	0.4	0.1, 0.7	22.3	43.5	82.7	0.003
lag1	53.1	33.7	52.8	35.7	0.3	0.0, 0.6	22.3	43.5	82.6	0.034
lag0−1	53.2	29.8	52.9	31.5	0.4	0.1, 0.6	23.8	44.4	80.3	0.004
NO_2 (ppb)										
lag0	27.9	12.8	27.6	12.8	0.2	0.1, 0.3	10.3	20	37.4	<.0001
lag1	27.7	12.8	27.5	12.8	0.2	0.1, 0.3	10.3	20	37.4	<.0001
lag0−1	27.8	12	27.6	11.9	0.2	0.1, 0.3	11	20.3	36.4	0.001
SO_2 (ppb)										
lag0	5.48	2.51	5.45	2.5)	0.03	0.01, 0.05	2.3	4.7	8.8	0.002
lag1	5.47	2.5	5.44	2.49	0.03	0.01, 0.05	2.3	4.7	8.8	0.005
lag0−1	5.47	2.33	5.44	2.32	0.03	0.01, 0.05	2.4	4.8	8.6	0.001
O_3 (ppb)										
lag0	32.9	15.7	32.8	15.7	0.1	0.0, 0.2	15.7	32.2	56.2	0.07
lag1	33	15.8	32.9	15.8	0.1	-0.1, 0.2	15.7	32.2	56.2	0.255
lag5†	33	15.8	32.9	15.8	0.1	0.0, 0.3	15.7	32.2	56.2	0.034
lag0−1	33	14.5	32.9	14.5	0.1	0.0, 0.2	17	32.3	54.8	0.115
CO (0.1ppm)										
lag0	6.5	2.94	6.45	2.91	0.05	0.02, 0.07	3.5	5.7	10.5	<.0001

lag1	6.49	2.93	6.44	2.9	0.05	0.02, 0.07	3.5	5.7	10.5	<.0001
lag0−1	6.49	2.73	6.45	2.7	0.05	0.03, 0.07	3.6	5.8	10.2	<.0001
Temperature (℃)										
lag0	14.1	9.5	14	9.6	0.1	0.0, 0.1	-0.5	14.3	25.8	0.141
lag0−3	14	9.4	14	9.5	0	-0.1, 0.1	-0.2	14.3	25.7	0.755
Sunshine (hr)										
lag0	5.91	3.95	5.89	3.96	0.03	-0.01, 0.06	0	6.7	10.7	0.113
lag0−3	5.91	2.6	5.88	2.6	0.02	0.0, 0.05	2.3	6.1	9.1	0.026
Humidity (%)										
lag0	63.09	16.07	63.2	16.19	-0.11	-0.24, 0.02	42.7	66.6	85.8	0.108
lag0−3	63.12	13.26	63.17	13.34	-0.06	-0.17, 0.05	47	66.2	82.1	0.32
Rainfall (mm)										
lag0	14	99.8	14.92	10.56	-0.88	-1.73, -0.02	0	0	19.5	0.039
lag0−3	14.6	59.9	15.09	60.96	-0.42	-0.92, 0.08	0	0.8	37.6	0.723
Air pressure (hPa)										
lag0	1015.5	7.68	1015.5	7.73	0.01	-0.05, 0.08	1005.8	1016.1	1026.2	0.723
lag0−3	1015.5	7.11	1015.5	7.12	0.02	-0.04, 0.08	1006.3	1016.5	1025.3	0.476

*For 19 cities except for 7 metropolitan cities among 26 cities, data from 2010-2013 were analyzed as the weather stations for those cities were established in 2010.

†O_3 concentration at lag5, only in which the difference between case and control periods was significant, was included.

3.3.2 Completed suicide risk linked to air pollution exposure

The Figure shows the random effect estimates combining 26 city-specific estimates for suicide risk associated with interquartile range (IQR) increase for each pollutant across various lag structures. Generally, significant associations were shown at immediate lags and became non-significant at delayed lags, except O_3. NO_2 showed the strongest association across all lags among the five air pollutants (percent change in adjusted odds, PM_{10}: 1.21% [95% CI, 0.15%, 2.29%]; NO_2: 4.30% [95% CI, 1.92%, 6.73%]; SO_2: 2.24% [95% CI, 0.70%, 3.80%]; O_3: 1.46% [95% CI, −0.26%, 3.21%]; and CO: 2.35% [95% CI, 0.94%, 3.78%] at lag0). The crude associations were consistent with the adjusted associations in both single and cumulative lag structures (Table 3.4 and 3.5).

Table 3.4. Random-effect estimates of percent increase in odds ratios of suicide risk associated with the interquartile range* increase in concentrations of five air pollutants across the single-lag structures†.

	% Increase in Odds (95% CI)							
Air pollutant	Lag0	Lag1	Lag2	Lag3	Lag4	Lag5	Lag6	Lag7
PM_{10}								
Crude Odds	1.55 (0.52, 2.59)	0.80 (-0.29, 1.90)	0.80 (0.01, 1.61)	-0.16 (-0.96, 0.65)	0.10 (-0.70, 0.91)	-0.02 (-0.83, 0.80)	0.69 (-0.58, 1.98)	-0.30 (-1.13, 0.54)
Adjusted Odds	1.21 (0.15, 2.29)	0.17 (-1.00, 1.35)	0.24 (-0.59, 1.06)	-0.71 (-1.53, 0.13)	-0.25 (-1.06, 0.57)	-0.17 (-0.99, 0.67)	0.63 (-0.90, 2.18)	0.36 (-1.27, 2.01)
NO_2								
Crude Odds	5.67 (2.54, 8.88)	3.68 (2.01, 5.38)	2.68 (1.11, 4.27)	1.65 (-1.85, 5.28)	-0.05 (-1.58, 1.50)	-0.27 (-1.80, 1.29)	0.20 (-1.38, 1.80)	0.32 (-2.65, 3.37)
Adjusted Odds	4.30 (1.92, 6.73)	2.35 (0.42, 4.32)	0.76 (-0.91, 2.45)	0.16 (-1.80, 2.16)	-1.39 (-3.24, 0.51)	-1.11 (-3.13, 0.96)	0.67 (-1.56, 2.95)	0.35 (-1.18, 1.91)
SO_2								
Crude Odds	2.29 (0.89, 3.71)	2.06 (0.43, 3.71)	1.96 (0.15, 3.80)	1.40 (-0.04, 2.85)	-0.21 (-1.59, 1.19)	-0.84 (-2.21, 0.55)	-0.18 (-1.56, 1.22)	-0.35 (-1.72, 1.04)
Adjusted Odds	2.24 (0.70, 3.80)	1.28 (-0.32, 2.92)	1.01 (-0.83, 2.90)	0.42 (-1.12, 1.99)	-0.72 (-2.18, 0.76)	0.95 (2.42, 0.53)	-0.02 (-1.42, 1.39)	0.10 (-1.30, 1.52)
O_3								
Crude Odds	2.07 (0.27, 3.91)	1.25 (-0.84, 3.39)	0.72 (-0.81, 2.27)	-0.33 (-2.79, 2.19)	1.66 (0.12, 3.22)	2.57 (1.01, 4.15)	0.50 (-1.99, 3.05)	0.58 (-2.12, 3.36)
Adjusted Odds	1.46 (-0.26, 3.21)	0.28 (-1.60, 2.20)	-0.69 (-2.41, 1.06)	-0.76 (-2.43, 0.95)	1.09 (-0.50, 2.70)	1.92 (0.34, 3.53)	0.18 (-1.87, 2.27)	0.18 (-2.50, 2.94)
CO								
Crude Odds	2.43 (1.23, 3.64)	2.31 (1.11, 3.53)	2.35 (1.14, 3.57)	1.18 (-0.98, 3.39)	0.26 (-0.92, 1.46)	0.13 (-1.05, 1.33)	0.48 (-0.80, 1.78)	0.33 (-0.85, 1.53)
Adjusted Odds	2.35 (0.94, 3.78)	1.44 (0.17, 2.73)	1.22 (-0.07, 2.51)	0.17 (-1.87, 2.25)	-0.43 (-1.64, 0.80)	-0.03 (-1.26, 1.22)	0.58 (-0.68, 1.86)	0.76 (-0.44, 1.98)

*Interquartile range of PM_{10}: 31.5 µg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm.
†Single lag on the same day [lag0] and on the previous 1–7 days [lag1–lag7] was considered.

Table 3.5. Random-effect estimates of percent increase in odds ratios of suicide risk associated with the interquartile range* increase in concentrations of five air pollutants across the cumulative-lag structures†.

	% Increase in Odds (95% CI)						
Air pollutant	Lag0-1	Lag0-2	Lag0-3	Lag0-4	Lag0-5	Lag0-6	Lag0-7
PM_{10}							
Crude Odds	1.56 (0.36, 2.77)	1.79 (0.75, 2.84)	1.56 (0.40, 2.73)	1.51 (0.25, 2.79)	1.47 (0.11, 2.85)	1.61 (0.14, 3.10)	1.49 (-0.09, 3.10)
Adjusted Odds	0.91 (-0.67, 2.53)	0.94 (-0.30, 2.20)	0.53 (-0.68, 1.76)	0.36 (-0.95, 1.69)	0.27 (-1.14, 1.70)	0.40 (-1.12, 1.94)	0.30 (-1.33, 1.96)
NO_2							
Crude Odds	5.87 (3.19, 8.62)	6.14 (3.67, 8.67)	6.90 (3.80, 10.09)	6.93 (2.07, 12.02)	6.37 (1.16, 11.84)	6.24 (2.72, 9.89)	5.93 (2.76, 9.21)
Adjusted Odds	4.68 (1.93, 7.51)	4.54 (1.48, 7.7)	4.49 (0.84, 8.27)	3.05 (-0.20, 6.41)	2.27 (-0.64, 5.26)	2.64 (-1.03, 6.44)	2.54 (-0.78, 5.98)
SO_2							
Crude Odds	2.83 (1.23, 4.46)	3.56 (1.74, 5.42)	3.95 (1.94, 5.99)	3.62 (1.39, 5.89)	3.09 (0.72, 5.51)	3.04 (0.55, 5.59)	2.88 (0.25, 5.57)
Adjusted Odds	2.33 (0.61, 4.08)	2.68 (0.61, 4.8)	2.68 (0.45, 4.95)	2.12 (-0.16, 4.46)	1.52 (-0.93, 4.04)	1.56 (-1.03, 4.22)	1.57 (-1.14, 4.36)
O_3							
Crude Odds	2.37 (0.29, 4.51)	2.31 (-0.01, 4.70)	2.02 (-0.70, 4.80)	3.1 (0.70, 5.55)	4.10 (1.53, 6.74)	4.52 (1.78, 7.33)	4.60 (1.68, 7.60)
Adjusted Odds	1.27 (-1.30, 3.91)	0.76 (-2.00, 3.60)	-0.21 (-3.59, 3.28)	1.02 (-1.94, 4.08)	2.17 (-0.93, 5.36)	2.34 (-0.87, 5.65)	2.11 (-1.22, 5.55)
CO							
Crude Odds	3.08 (1.70, 4.48)	3.83 (2.28, 5.39)	4.19 (2.40, 6.02)	4.42 (1.98, 6.92)	4.15 (1.86, 6.49)	4.26 (1.98, 6.59)	4.45 (2.06, 6.90)
Adjusted Odds	2.39 (0.92, 3.88)	2.74 (1.07, 4.43)	2.63 (0.78, 4.52)	2.35 (0.26, 4.48)	2.25 (-0.03, 4.58)	2.46 (0.12, 4.86)	2.82 (0.37, 5.32)

*Interquartile range of PM_{10}: 31.5 μg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm.
†Cumulative lag on the same day plus 1 day before [lag0–1] to 7 days before [lag0–7]) was considered.

3.3.3 Effect modification by socioeconomic factors and other factors

Table 3.6 and 3.7 present the adjusted and crude associations between suicide risk and short-term air pollution exposure by subgroup stratified by potential effect modifiers, including socioeconomic factors, place of death, method of suicide, and season. The subgroup-specific results were consistent across the five air pollutants in general; significant associations were observed for male sex, age 35–64 years, age >65 years, low education, white-collar job, unemployment, and married status in analyses stratified by socioeconomic factors. Furthermore, these associations were observed for death inside buildings, suicide by violent methods, and death during fall season in analyses stratified by other potential effect modifiers.

Table 3.6. Random-effect estimates of percent increase in adjusted odds ratios of suicide risk associated with the interquartile-range* increase in the same day (lag0) concentrations of five air pollutants in subgroup analyses by socioeconomic and other potential effect modifiers.

	% increase in adjusted odds (95% CI)				
	PM_{10}	NO_2	SO_2	O_3	CO
Sex					
Male	1.27 (0.26, 2.28)	4.49 (1.81, 7.24)	2.55 (0.74, 4.40)	2.68 (0.55, 4.86)	2.27 (0.73, 3.84)
Female	1.65 (-0.37, 3.71)	2.34 (-0.63, 5.4)	2.44 (-0.99, 5.99)	-0.89 (-4.45, 2.81)	1.74 (-0.48, 4.01)
Age, years					
<35 years	0.63 (-2.06, 3.40)	0.68 (-2.7, 4.19)	-1.63 (-5.15, 2.02)	1.69 (-2.99, 6.60)	-1.26 (-3.80, 1.34)
35-64 years	0.95 (-0.16, 2.07)	4.10 (1.04, 7.26)	3.15 (0.66, 5.69)	1.86 (-1.18, 5.00)	2.74 (0.99, 4.51)
≥65 years	3.21 (-0.44, 7.00)	6.10 (2.52, 9.81)	5.3 (-0.22, 11.11)	0.9 (-2.61, 4.54)	4.02 (1.36, 6.74)
Education					
Low	1.92 (-1.39, 5.33)	6.15 (1.11, 11.45)	4.53 (-0.99, 10.35)	1.64 (-2.06, 5.47)	3.49 (1.01, 6.04)
Middle	1.13 (0.00, 2.27)	2.65 (-0.3, 5.69)	0.71 (-1.32, 2.79)	1.51 (-0.87, 3.95)	1.80 (-0.30, 3.94)
High	0.72 (-1.19, 2.66)	4.52 (0.82, 8.36)	2.36 (-0.98, 5.82)	0.41 (-4.78, 5.87)	2.54 (-0.83, 6.02)
Job					
White	-1.17 (-7.19, 5.24)	11.04 (4.15, 18.39)	6.19 (1.78, 10.79)	-1.72 (-8.68, 5.78)	4.28 (0.59, 8.11)
Sales	2.09 (-2.90, 7.33)	4.64 (-1.61, 11.29)	5.93 (-0.06, 12.28)	5.31 (-0.53, 11.5)	3.43 (-0.69, 7.72)
Blue	0.81 (-4.91, 6.88)	1.61 (-4.63, 8.25)	3.38 (-1.36, 8.36)	0.36 (-5.12, 6.16)	0.98 (-3.04, 5.16)
Unemployed	1.65 (0.11, 3.21)	3.21 (0.52, 5.97)	1.81 (-0.90, 4.60)	1.55 (-2.24, 5.49)	1.78 (0.18, 3.40)
Marital status					
Unmarried	1.32 (-0.22, 2.88)	0.76 (-2.28, 3.88)	-1.05 (-3.75, 1.73)	4.74 (1.45, 8.13)	-0.16 (-2.45, 2.19)

Married	1.06 (-1.01, 3.17)	7.19 (3.95, 10.53)	4.37 (2.05, 6.75)	-0.52 (-3.20, 2.23)	4.11 (2.17, 6.09)
Divorced	0.73 (-1.60, 3.11)	0.87 (-3.71, 5.66)	1.52 (-4.36, 7.75)	1.22 (-3.48, 6.15)	1.98 (-1.56, 5.65)
Bereaved	2.59 (-0.89, 6.20)	-0.28 (-5.27, 4.98)	4.48 (-2.20, 11.62)	0.85 (-5.02, 7.09)	-0.07 (-3.70, 3.70)
Death place					
Inside	0.78 (-0.46, 2.04)	4.96 (2.10-7.91)	2.61 (0.27, 4.99)	2.12 (0.10, 4.18)	2.68 (0.58, 4.83)
Outside	2.67 (-0.69, 6.14)	0.34 (-4.27, 5.18)	2.34 (-2.70, 7.64)	-1.75 (-8.39, 5.37)	2.58 (-1.01, 6.30)
Method of death					
Violent	1.42 (0.47, 2.37)	3.31 (1.39, 5.26)	2.72 (0.94, 4.52)	2.14 (-0.60, 4.96)	3.39 (1.56, 5.24)
Nonviolent	0.29 (-1.54, 2.15)	5.33 (0.34, 10.56)	0.91 (-2.66, 4.61)	0.36 (-3.07, 3.91)	-0.05 (-2.59, 2.57)
Season					
Spring	-0.15 (-1.56, 1.27)	1.94 (-1.24, 5.22)	0.92 (-1.78, 3.69)	-1.72 (-5.66, 2.37)	0.33 (-3.63, 4.45)
Summer	3.59 (-0.56, 7.91)	2.14 (-2.64, 7.16)	1.91 (-2.60, 6.64)	3.56 (0.42, 6.81)	2.78 (-1.52, 7.28)
Fall	7.07 (2.67, 11.67)	8.75 (2.42, 15.47)	6.96 (2.78, 11.31)	1.77 (-3.02, 6.79)	6.27 (2.10, 0.62)
Winter	2.44 (0.16, 4.78)	3.33 (0.00, 6.78)	1.26 (-1.14, 3.72)	-0.31 (-6.40, 6.17)	0.98 (-0.96, 2.96)

*Interquartile range of PM_{10}: 31.5 μg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm.

Table 3.7. Random-effect estimates of percent increase in crude odds ratios of suicide risk associated with the interquartile-range* increase in the same day (lag0) concentrations of five air pollutants in subgroup analyses by socioeconomic and other potential effect modifiers.

	% Increase in Crude Odds (95% CI)				
	PM_{10}	NO_2	SO_2	O_3	CO
Sex					
Male	1.62 (0.65, 2.61)	5.19 (2.86, 7.58)	2.79 (1.09, 4.51)	3.08 (0.36, 5.87)	2.77 (1.27, 4.29)
Female	1.85 (-0.05, 3.79)	2.83 (0.00, 5.74)	1.41 (-1.09, 3.97)	-0.08 (-2.71, 2.61)	1.87 (-0.19, 3.97)
Age, years					
<35 years	1.13 (-1.63, 3.97)	1.73 (-1.43, 5.00)	-0.99 (-3.81, 1.90)	2.51 (-1.01, 6.17)	-0.61 (-3.03, 1.88)
35, 64 years	1.19 (0.12, 2.28)	4.12 (1.79, 6.50)	2.92 (0.85, 5.03)	1.66 (-0.74, 4.12)	3.13 (1.42, 4.88)
≥65 years	4.08 (0.83, 7.44)	7.20 (3.48, 11.05)	5.22 (0.15, 10.54)	2.52 (-0.66, 5.80)	4.13 (1.54, 6.79)
Education					
Low	2.59 (0.07, 5.17)	6.6. (3.25, 10.06)	5.04 (0.74, 9.52)	2.78 (-0.33, 5.98)	3.86 (1.5, 6.27)
Middle	1.19 (0.09, 2.30)	2.74 (-0.27, 5.85)	0.55 (-1.34, 2.47)	1.69 (-0.59, 4.02)	1.51 (-0.33, 3.4)
High	1.6 (-0.24, 3.48)	6.5. (3.01, 10.11)	3.36 (0.16, 6.66)	1.85 (-2.25, 6.12)	3.89 (1.22, 6.64)
Job					
White	1.06 (-1.86, 4.06)	11.9 (5.15, 19.12)	5.55 (0.8, 10.52)	-1.05 (-6.86, 5.12)	4.98 (1.49, 8.60)
Sales	1.42 (-3.78, 6.89)	3.38 (-2.88, 10.03)	2.80 (-3.34, 9.32)	4.28 (-1.58, 10.5)	2.96 (-0.87, 6.95)
Blue	1.39 (-1.71, 4.58)	0.34 (-4.81, 5.76)	2.37 (-1.98, 6.93)	-0.27 (-5.56, 5.32)	1.53 (-2.27, 5.48)
Unemployed	1.06 (-1.86, 4.06)	4.39 (1.88, 6.96)	1.73 (-0.13, 3.62)	2.70 (0.20, 5.26)	2.21 (0.73, 3.72)
Marital status					
Unmarried	1.52 (0.02, 3.05)	1.11 (-1.70, 4.01)	-1.02 (-3.54, 1.58)	5.51 (1.14, 10.07)	0.05 (-2.13, 2.28)

Married	1.84 (-0.57, 4.30)	8.40 (5.51, 11.37)	5.18 (3.09, 7.31)	0.77 (-2.42, 4.07)	4.87 (3.04, 6.74)
Divorced	0.32 (-1.92, 2.63)	0.76 (-4.23, 6.00)	-0.01 (-4.59, 4.78)	-0.70 (-4.81, 3.58)	1.76 (-1.62, 5.25)
Bereaved	3.33 (-0.05, 6.82)	1.68 (-3.42, 7.05)	3.94 (-2.26, 10.54)	2.77 (-2.37, 8.19)	0.29 (-3.15, 3.85)
Death place					
Inside	1.03 (-0.10, 2.17)	5.40 (2.32, 8.57)	1.97 (0.34, 3.62)	2.46 (0.11, 4.88)	2.38 (0.63, 4.17)
Outside	3.48 (-0.02, 7.10)	2.65 (-1.66, 7.15)	3.30 (-1.12, 7.92)	-0.32 (-6.74, 6.56)	3.74 (0.36, 7.25)
Method of suicide					
Violent	1.02 (-0.71, 2.78)	6.10 (2.25, 10.09)	1.60 (-1.23, 4.50)	2.50 (-0.60, 5.70)	1.06 (-1.39, 3.56)
Non, violent	1.64 (0.72, 2.57)	4.14 (1.43, 6.92)	2.56 (0.89, 4.25)	2.36 (-0.62, 5.42)	2.93 (1.51, 4.38)
Season					
Spring	-0.17 (-1.41, 1.08)	2.62 (-1.01, 6.38)	1.12 (-2.22, 4.57)	-0.93 (-4.81, 3.10)	1.17 (-3.47, 6.03)
Summer	3.28 (-0.26, 6.95)	3.31 (-1.23, 8.06)	1.96 (-2.21, 6.30)	3.12 (0.29, 6.02)	2.08 (-1.99, 6.31)
Fall	6.55 (3.17, 10.03)	6.16 (1.64, 10.88)	5.53 (2.00, 9.18)	4.72 (0.97, 8.62)	4.46 (1.40, 7.61)
Winter	3.93 (1.85, 6.06)	6.29 (2.51, 10.2)	1.81 (-0.35, 4.02)	-0.65 (-6.22, 5.25)	2.23 (0.53, 3.96)

*Interquartile range of PM_{10}: 31.5 μg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm.

3.3.4 Sensitivity analyses

Table 3.8 indicates that associations between suicide risk and short-term exposure to each air pollutant were robust when including other air pollutants in the model. While NO_2 showed the strongest significant associations in all two-pollutant models, the associations of other pollutants were attenuated after further adjustment for NO_2 or CO. Subgroup analyses with two-pollutant models also showed robust results (Figure 3.1).

The results of fixed effect meta-analyses for homogeneous city-specific estimates were consistent with the main findings both in overall and subgroup analyses (Figure 3.2 and 3.3).

Table 3.8. Random-effect estimates of percent increase in odds ratios of suicide risk associated with the interquartile-range* increase in the same day (lag0) concentrations of five air pollutants: single-and co-pollutant models adjusted for same day (lag0) concentrations.

	% increase in crude odds	95% CI	% increase in adjusted odds	95% CI
PM_{10}				
Single	1.55	0.52, 2.59	1.21	0.15, 2.29
+NO_2	0.72	-0.30, 1.76	0.51	-0.81, 1.85
+SO_2	1.14	0.20, 2.08	0.80	-0.13, 1.73
+O_3	1.35	0.37, 2.34	1.02	0.16, 1.89
+CO	0.92	-0.15, 2.00	0.64	-0.55, 1.84
NO_2				
Single	5.67	2.54, 8.88	4.30	1.92, 6.73
+PM_{10}	4.26	1.90, 6.67	3.96	1.36, 6.62
+SO_2	6.42	2.63, 10.3	5.00	1.63, 8.47
+O_3	4.84	2.50, 7.23	4.23	1.91, 6.60
+CO	4.95	1.85, 8.15	3.54	0.84, 6.31
SO_2				
Single	2.29	0.89, 3.71	2.24	0.70, 3.80
+PM_{10}	1.53	-0.02, 3.12	1.73	0.07, 3.43
+NO_2	-0.07	-2.57, 2.49	0.62	-2.04, 3.35
+O_3	2.12	0.68, 3.58	2.29	0.56, 4.05
+CO	0.62	-1.70, 3.00	0.98	-1.70, 3.73
O_3				
Single	2.07	0.27, 3.91	1.45	-0.26, 3.21
+PM_{10}	1.58	-0.33, 3.53	1.13	-0.61, 2.90
+NO_2	2.11	0.56, 3.68	1.52	-0.20, 3.28
+SO_2	1.77	-0.40, 4.00	1.27	-0.45, 3.0.
+CO	2.08	0.53, 3.66	1.37	-0.35, 3.12
CO				
Single	2.43	1.23, 3.64	2.35	0.94, 3.78
+PM_{10}	1.89	0.50, 3.31	1.97	0.37, 3.60
+NO_2	0.12	-1.71, 1.98	0.55	-1.36, 2.51
+SO_2	2.75	0.62, 4.93	1.93	0.09, 3.80
+O_3	2.48	1.28, 3.70	2.29	0.93, 3.66

*Interquartile range of PM_{10}: 31.5 µg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm.

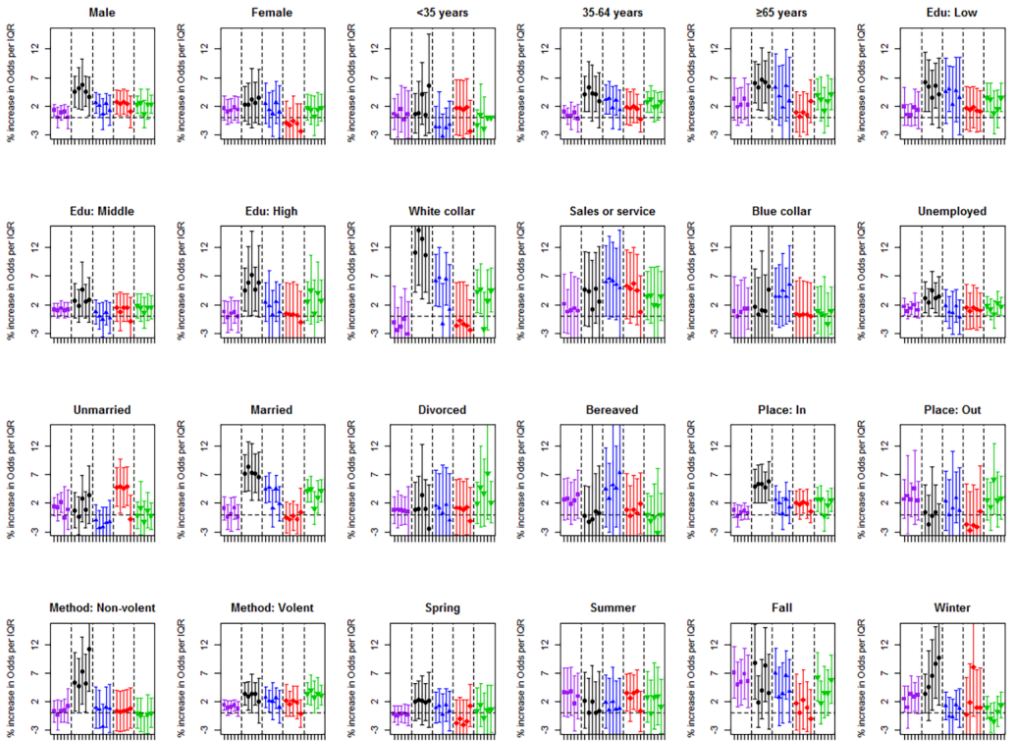

Figure 3.1. Random-effect estimates of percent increase in odds ratios of suicide risk associated with the interquartile-range* increase in the same day (lag0) concentrations of five air pollutants: single-and co-pollutant models adjusted for same day (lag0) concentrations in subgroup analyses by socioeconomic† and other potential effect modifiers‡.*Interquartile range of PM_{10}: 31.5 μg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm. †Socioeconomic effect modifiers include sex (male/female), age (<35/35-64/≥65 years), education level (low/middle/high), job (white collar/sales or service/blue collar/unemployed), and marital status (unmarried/ married/ divorced/ bereaved). ‡Other effect modifiers include place of death (in/out), method of suicide (non-violent/ violent), and season (spring/ summer/ fall/ winter)

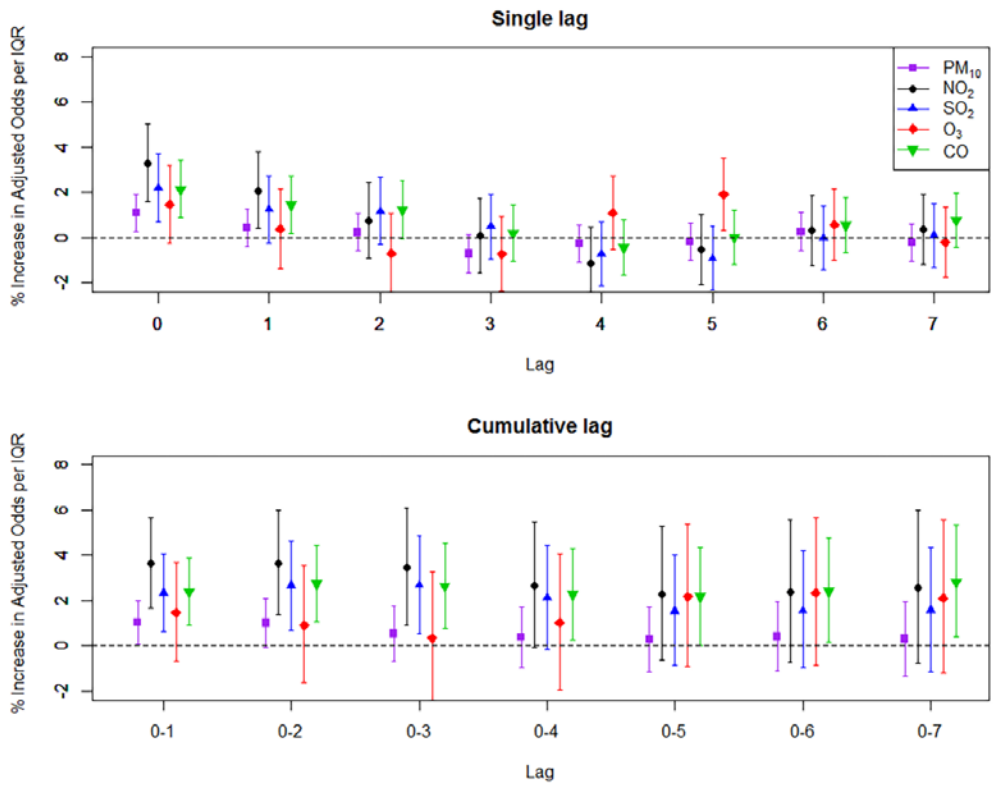

Figure 3.2. Fixed-effect estimates of percent increase in adjusted odds ratios of suicide risk associated with the interquartile range[*] increase in concentrations of five air pollutants across various lag structures[†]. [*]Interquartile range of PM_{10}: 31.5 µg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm. [†]Single lag on the same day [lag0] and on the previous 1−7 days [lag1−lag7], as well as cumulative lag on the same day plus 1 day before [lag0−1] to 7 days before [lag0−7]) were considered.

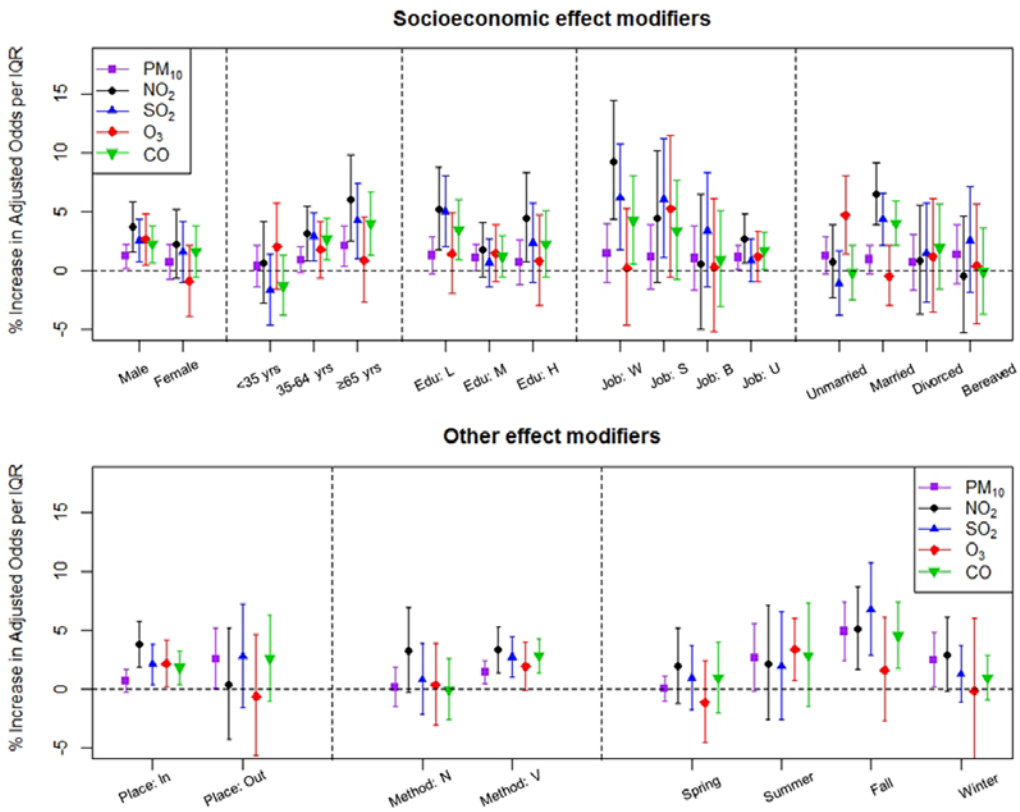

Figure 3.3. Fixed-effect estimates of percent increase in adjusted odds ratios of suicide risk associated with the interquartile-range[*] increase in the same day (lag0) concentrations of five air pollutants in subgroup analyses by socioeconomic[†] and other potential effect modifiers[‡]. [*]Interquartile range of PM_{10}: 31.5 μg/m^3, NO_2: 17 ppb, SO_2: 3.1 ppb, O_3: 21.2 ppb, and CO: 0.32 ppm. [†]Socioeconomic effect modifiers include sex (male/female), age (<35/35-64/≥65 years), education level (low/middle/high), job (white collar/ sales or service/ blue collar/ unemployed), and marital status (unmarried/ married/ divorced/ bereaved). [‡]Other effect modifiers include place of death (in/out), method of suicide (non-violent/ violent), and season (spring/ summer/ fall/ winter).

3.4 Discussion

Our time-stratified case-crossover study, including 73,445 completed suicide cases in 26 cities of South Korea, revealed increased suicide risk during short-term exposure to higher concentrations of air pollutants, independent of time-invariant demographic characteristics and slowly varying other factors such as morbidities and employment status of suicide completers, with sufficient power. The significant associations were consistently shown at immediate time lags (lag0, lag1, lag0–1, lag0–2, and lag0–3) for NO_2, SO_2, and CO, and at lag0 for PM_{10}. The association between suicide risk and short-term air pollution exposure was generally stronger among people with a certain socioeconomic status, including male sex, older age, low education, unemployment, white-collar employment, and married status in subgroup analyses by socioeconomic status. In stratified analyses by other effect modifiers, death inside buildings, suicide by violent methods, and death during the fall season showed stronger associations. Our findings were robust to several sensitivity analyses, including co-pollutant analyses, adjusting for their confounding by each other (Kim et al. 2006); the presence of confounders causes biased effect estimates (McNamee 2003).

Our findings are in line with previous studies from neuroscientific experiments and population studies. For instance, air pollutants can induce

inflammation, and it can impact on the central nervous system through proinflammatory cytokines (Block and Calderón-Garcidueñas 2009). The systemic inflammatory marker (C-reactive protein) that rapidly changed according to air pollution (Rich et al. 2012) was associated with suicide risk and psychological distress (Myung et al. 2016). Furthermore, exposure to air pollutants may induce epigenetic changes in the gene for inducible nitric oxide synthase that regulates inflammatory reactions (Madrigano et al. 2012) and may cause dysregulation of the hypothalamo-pituitary-adrenal axis (Thomson et al. 2013), which is associated with the pathobiology of suicide in mood disorders (Janelidze et al. 2011; Roy 1992).

The highest and consistent association of suicide risk with NO_2 in co-pollutant analyses may signify that traffic-related air pollution is more important in the association. NO_2 is regarded as a tracer of traffic emissions, and thus may better capture the effect of a specific component from traffic emissions even though NO_2 itself might not be actually toxic. A recent study on the association of Parkinson's disease aggravation with short-term air pollution exposure also showed the strongest association with NO_2 among five pollutants (Lee et al. 2017).

Previously, only two studies have examined the associations between completed suicide and air pollution by applying the appropriate study design, controlling for other risk factors for increased suicide risk

such as physical or mental health and seasonality by perfect matching (Bakian et al. 2015; Kim et al. 2010). An initial study (Kim et al. 2010), conducted with 4,341 suicide cases in seven south Korean cities in 2004, examined associations of suicide with PM_{10} and particles <2.5 μm ($PM_{2.5}$) and found the largest association with PM_{10} at lag0–2 (9.0% increase per 27.6 $\mu g/m^3$) and with $PM_{2.5}$ at lag1 (10.1% increase per 18.2 $\mu g/m^3$). A second study (Bakian et al. 2015), performed with 1,546 suicide cases in in the US in Salt Lake County, Utah during 2000–2010, investigated associations with PM_{10}, $PM_{2.5}$, NO_2, and SO_2, and confirmed significant associations with $PM_{2.5}$ (5% increase per 5.7–11.7 $\mu g/m^3$) and with NO_2 (20% increase per 32.7–44.8 ppb).

Despite a few discrepancies, our findings are in line with these prior findings and provide further support for the significant role of air pollutants in completed suicide risk, with sufficient suicide cases across 26 cities over 12 years. The discrepancies may be induced by several factors. First, our statistical model is different from those of previous studies; we additionally included rainfall variables in the model because rainfall was reportedly associated with suicide risk (Nicholls et al. 2006). Moreover, in previous studies, the levels of meteorological variables on the day of suicide (lag0) and the levels over the previous 3 days (lag1–3) were adjusted for separately, which could cause uncertain estimation of the associations due to

multicollinearity (Farrar and Glauber 1967), whereas our study adjusted for the levels of meteorological variables at lag0–4 to resolve multicollinearity. Second, the differences in study area and study period may lead to differences in concentrations and chemical compositions of air pollutants in accordance with natural environmental factors such as topography and climate as well as man-made environmental factors such as industrial activities and traffic volume. Third, there may be differences in demographic, socioeconomic, physical, and psychiatric status of the population at risk by different study areas and periods; these differences may explain some of the differing results among studies.

Consistent with previous findings (Bakian et al. 2015; Kim et al. 2010), the sex-specific analysis showed a significant suicide risk associated with air pollution among the male sex. In contrast with previous findings in which a significant association was found only for age 35–64 years, significant associations were shown for age 35–64 years and for age >65 years in the age-specific analysis. It is likely that these subgroups were more exposed to higher ambient concentrations of air pollutants and more sensitive to air pollution exposure. In South Korea, men take part in economic activities more frequently than women do, and thus men likely have a higher chance to be exposed while commuting or performing other activities. Higher effect estimates for those aged >65 years may reflect a

greater susceptibility to air pollution. The authors of previous studies (Bakian et al. 2015; Kim et al. 2010) suggested the positive but non-significant associations among the elderly, despite their greater susceptibility, might be due to insufficient sample sizes; we included a sufficiently large sample size of the elderly (n=17,289) and found a positively significant association.

To our knowledge, this is the first study to examine the effect modification of the association between suicide risk and short-term air pollution exposure by education level, employment, and marital status despite the crucial roles of these factors on suicide risk (Nock et al. 2008; Qin et al. 2003). We found significant associations among lower education level for NO_2 and CO; among the unemployed for PM_{10}, NO_2, and CO; and among the unmarried for O_3—these variables have generally been associated with higher suicide risk in previous studies (Nock et al. 2008; Qin et al. 2003). It is possible that those people with low social status were already at higher risk to commit suicide and thus more vulnerable to any added risk of air pollution exposure. Moreover, inflammatory responses induced by mental stress (Black and Garbutt 2002), one of the mechanisms by which air pollution damages human organs (Block and Calderón-Garcidueñas 2009), may accelerate the effect of air pollution. Significant associations were also found among higher education level for NO_2; among

white-collar employment for NO_2, SO_2, and CO; and among the married for NO_2, SO_2, and CO. These groups were likely more exposed to air pollution, especially exhaust gas from automobile emissions, which contains NO_2, SO_2, and CO (Elliott et al. 1955), during their daily economic activities. For instance, highly educated people more likely have their own cars (Blaug 1972) and thus have a greater chance to be exposed. The married may take part in economic activity more because they have family members to support. Regarding jobs, in most South Korean cities, workplaces for white-collar workers are concentrated in specific districts, and these workers usually commute to work in their own cars or by using public transportation. It is likely that both the biopsychosocial susceptibility of individuals as well as higher exposure to ambient air pollution play a substantial role in the association of suicide risk with air pollution.

This study also examined the association between the place, season, and method of the suicide. The results support a prior finding that the association between suicide and air pollution was significant only among people who committed suicide using violent methods (Bakian et al. 2015). A possible explanation is that air pollution exposure provokes impulsivity in this group by promoting serotonergic or dopaminergic abnormalities (Ryding et al. 2008; Yokota et al. 2013): previously, serotonergic dysfunction was found in violent suicide cases (Arora and Meltzer 1989;

Spreux-Varoquaux et al. 2001). In addition, our season-specific analysis indicated that suicide risk was associated with all air pollutants except O_3 during the fall, associated with PM_{10} and NO_2 during the winter, and associated with O_3 during the summer. The result is likely due to both higher concentrations of air pollutants during certain seasons (greater emissions from combustion for heating during fall and winter (JY Son et al. 2012) and higher ozone through high temperature and sunlight during summer (Krupa and Manning 1988)) and more outdoor activity in less extreme weather conditions. In contrast to our expectation, we did not find a significant association among with suicide cases occurring outside buildings. It may be that people attempted suicide outside, but that they died inside a hospital unless they were instantly killed. It is also possible that the sample size was insufficient (Künzli and Schindler 2005).

Our study had some limitations. First, there is a possibility of exposure measurement error because the daily representative concentrations of the air pollutants allocated to suicide cases may not represent actual individual exposure. However, the exposure measurement error causes bias towards a null hypothesis (Armstrong 1998), which underestimates the association; hence, the results are not likely to be exaggerated. Second, there is a chance of misclassification bias as we used information contained on the death certificate records; errors might arise during coding or recording

the records, causing non-differential misclassification bias; however, non-differential misclassification also tends to cause bias towards a null effect (Copeland et al. 1977). Third, we could not examine the effects of underlying diseases despite their reported roles (Kim et al. 2010) due to limited data availability. Finally, there may be potential confounders, which change in the short-term, that we were unable to control.

This study suggests that higher suicide risk is associated with greater short-term air pollution exposure. Especially, NO_2 had the highest association, remaining significant in co-pollutant analyses. Socioeconomic factors modified the relationship between higher air pollution exposure and suicide risk, indicating that both biopsychosocial susceptibility and extent of exposure to air pollution by daily activity patterns may have crucial roles in the association. These findings can serve as the basis for suicide prevention strategies by providing information regarding susceptible subgroups. Further studies are warranted to better understand the role of socioeconomic status in the association between suicide and air pollution.

Chapter 4. Association between air pollution exposure and emergency department visits for migraine: Synergistic effect with temperature

4.1 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 not only arises from economic perspectives through direct cost for health care utilization and indirect cost by loss of productivity and reduced performance at work, but also arises from quality-of-life perspectives (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 including diabetes and arthritis (Dahlöf 1993). In South Korea, the number of migraine patients has been dramatically increasing (from 479,000 in 2010 to 505,000 in 2015), and the medical expenses for migraine has also rapidly increased by 34.4% (from USD 39.6 million in 2010 to 53.2 million in 2015).

Activation and sensitization of the trigeminovascular system

(TVGS) have been identified as a central step in the migraine development, but the primary cause of migraine which induces the TVGS activation has remained unclear (Pietrobon and Striessnig 2003). Environmental factors including weather-related variables (temperature, humidity, and heat), noise, and odors as well as demographic factors such as sex and age have been considered risk factors for migraine (Prince et al. 2004; Wöber et al. 2006).

Little has been known, however, about the possible role of ambient air pollution on migraine although air pollution has been constantly associated with many health outcomes such as cardiovascular and respiratory diseases as a major environmental risk to health (Dominici et al. 2006; Seaton et al. 1995). Considering increasing experimental evidence linking air pollution and neurological damage (neuro-inflammation, the Central nervous system oxidative stress, and dopamine neuron damage etc.) (Block and Calderón-Garcidueñas 2009; Pereyra-Muñoz et al. 2006), and epidemiological studies supporting positive association between air pollution exposure and neurological diseases such as Parkinson's disease and stroke (Lee et al. 2017; Shah et al. 2015b), we hypothesize that exposure to ambient air pollution may trigger migraine. Although few studies have examined the association between 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 due to air pollution exposure (Szyszkowicz et al. 2009), this result was not replicated in a study performed in Boston, USA using a case-crossover design (Mukamal et al. 2009).

Furthermore, to the best of our knowledge, synergistic effects of air pollution and temperature on migraine has not been evaluated, although their joint effects on cardiovascular mortality have been reported.

Here, we studied the effects of 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 as well as possible factors including sex, age, and subtypes of migraine.

4.2 Materials and Methods

4.2.1 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-, local-emergency medical centers, and other local emergency medical facilities.

The NEDIS database consisted of all cases of ED visits which occurred since 2005 in regional- and local emergency medical center, and other local emergency medical facilities, accounting for approximate 76% of the national hospital-based ED visits data. NEDIS data contains 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 privacy of patients, physicians, and hospitals.

We obtained information on the study population from NEDIS data for 2008 through 2014 as the NEDIS data has been stabilized since 2008 regarding participating emergency medical centers. For case definition, the final diagnosis on discharge according to ICD-10 code was used. We collected data for patients who visited ED for migraine (having G43 code as a primary discharge diagnosis) which occurred in Seoul. As the capital city

of South Korea, its population accounts for one-fifth of the population and its population density is 16,189 individuals/km^2. Furthermore, regular monitoring system for $PM_{2.5}$ was established only in Seoul although the monitoring system 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 assessing this association by giving us adequate statistical power.

4.2.2 Assessment of air pollution exposure

Seoul consisted of 25 districts, which ranges 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 at least one monitoring site located centrally within the district, and each pollutant was measured by following methods: beta-ray absorption ($PM_{2.5}$, PM_{10}), chemo-luminescence (NO_2), ultraviolet fluorescence (SO_2), ultraviolet photometry (O_3), and nondispersive infrared photometry (CO). Because information on patient- or ED-specific addresses were not provided for privacy, we constructed city-level measures of air pollution exposure: first, we averaged hourly

concentrations from all monitoring sites for all pollutants. Then, we constructed daily representative values, the 24-hour means for $PM_{2.5}$, NO_2, and SO_2, and the maxim 8-hour means for O_3 and CO based on the WHO air quality guidelines (2006).

4.2.3 Meteorological factors

We obtained hourly data on ambient temperature, relative humidity, and air pressure, and data on sunlight hour and rainfall per day measured at a weather monitoring station for Seoul from the Korea Meteorological Administration. We calculated the 24-hour mean values for confounding adjustment and for evaluation of effect modification.

4.2.4 Study design

The odds ratios (ORs) for the risk of ED visits for migraine, associated with short-term air pollution exposure, were estimated by using the conditional logistic regression models for the matched dataset. In the main model, 2-day moving average of temperature on the same day and previous day (lag0–1) with a regression spline (with 3 df), 2-day moving averages of relative humidity, air pressure, sunlight, and rainfall, influenza epidemics, and holidays were adjusted for.

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 (single lag: same day and 1–7 days before admission [lag0 to lag7]; moving average lag: moving average of same day and 1–7 days before ED visits [lag0–1 to lag0–7]). Each air pollutant with different lag structures was included in the model separately. The lag structure which gives the smallest Akaike information criterion (AIC) value was chosen for further analyses.

In the case-crossover design, effect of time-invariant and slowly varying characteristics cannot be estimated due to 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), subtype (without aura/with aura/unspecified), and season and each pollutant. Furthermore, we evaluated 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 hour, and rainfall into low (lower 75th percentile) and high levels (upper 25th percentile levels of the distributions over all seasons during 2008–2014).

We conducted several sensitivity analyses to assess robustness of the main findings. First, co-pollutant models were evaluated to investigate potential confounding by other air pollutants (e.g., in estimating effect of $PM_{2.5}$, NO_2, SO_2, O_3, or CO was 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 checked whether the main results are changed by differing the temperature specification: a) differing the degrees of freedom for spline (from 3 to 4, 5, 6), and b) differing the knot locations (at from .5/.75 to .25/.75, .1/.9, .05/.95). Third, we performed subgroup analyses using stratification rather than interaction terms, for sex, age, subtype, and season. Lastly, we evaluated the effect modification by temperature under different definitions for high temperature (from 75th percentile to 50th, 90th, 95th percentiles).

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Results were presented as percent change in ORs with 2-sided 95% confidence intervals.

4.3 Results

4.3.1 Descriptive results

We identified 18,921 patients who visited emergency departments (ED) for migraine in Seoul during 2008–2014 (Table 4.1). Among the patients, women (72%), age under 40 years (57%), and unspecified subtype (67%) dominated the sample. The number of patients did not differ by season , and the patients more frequently visited ED for migraine on Sunday (18%).

Table 4.1. General characteristics of ED visit patients for migraine in Seoul, South Korea, between 2008 and 2014.

	Total (N=18,921)	
	N	%
Sex		
Male	5,315	28.1
Female	13,606	71.9
Age, years		
<40 years	10,695	56.5
40-64 years	6,866	36.3
≥65 years	1,360	7.2
Subtype		
Without aura	1,830	9.7
With aura	753	4
Unspecified	12,979	68.6
Season		
Spring	4,601	24.3
Summer	5,083	26.9
Fall	5,156	27.3
Winter	4,081	21.6
Day of week		
Sunday	3,464	18.3
Monday	2,839	15.0
Tuesday	2,533	13.4
Wednesday	2,354	12.4
Thursday	2,535	13.4
Friday	2,384	12.6
Saturday	2,812	14.9
Holiday	963	5.1

Table 4.2 shows daily levels of air pollutants and weather variables on case periods and on control periods. 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, 5.2 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. The levels of weather variables were not different between case and control periods. Air pollutants concentrations were highly inter-correlated (Pearson coefficient r=0.56–0.86) except O_3 (r=0.07-0.36), and lowly or moderately correlated with weather variables (r=-0.05–0.52) (Table 4.3).

Table 4.2. Differences in daily levels of air pollutants and meteorological variables between case and control periods and their distributions in Seoul, South Korea, from 2008-2014.

	Case periods (N=18,921)		Control periods (N=64,402)		Mean difference	95% Confidence limit	Percentiles			p value for t-test
	Mean	SD	Mean	SD			p25	p50	p75	
PM_{10} ($\mu g/m^3$)	24.25	13.56	23.86	13.21	0.39	0.17, 0.61	15.04	21.76	30.26	<0.001
PM_{10} ($\mu g/m^3$)	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 (0.1ppm)	6.48	2.66	6.42	2.62	0.06	0.01, 0.1	4.77	5.94	7.65	0.009
Temperature (℃)	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	0.13
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

Table 4.3. Pearson correlations between exposure variables in Seoul, Korea, during 2008−2014.

	$PM_{2.5}$	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*

4.3.2 Association between air pollution and migraine

Table 4.4 and Figure 4.1 present the estimated effect of ambient air pollution on ED visits for migraine per IQR increase at different lag structures. 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 4.5). In the best fitted models, $PM_{2.5}$, PM_{10}, NO_2, O_3, and CO were significantly associated with 3.1% (95% CI: 1.0%, 5.3%), 3.2% (95% CI: 0.7%, 5.7%), 5.3% (95% CI: 2.2%, 8.5%), 3.4% (95% CI: 0.1%, 6.7%), and 2.9% (95% CI: 0.5%, 5.3%) increase in risk of ED visits for migraine, respectively.

Table 4.4. Percent change in odds ratios of ED visits for migraine associated with an IQR increase in the concentrations of 6 air pollutants with various lag structures (single lag on the same day [lag0] and on the previous 1−7 days [lag1−lag7], as well as moving average lag on the same day plus 1 day before [lag0−1] to 7 days before [lag0−7]).

	% increase in adjusted odds (95% CI)					
	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
Single lag						
0	2.89 (0.81, 5.0)	1.43 (-0.47, 3.35)	5.27 (2.17, 8.46)	1.87 (-0.86, 4.67)	0.7 (-2.84, 4.38)	2.89 (0.54, 5.3)
1	2.59 (0.55, 4.67)	2.2 (0.31, 4.13)	1.28 (-1.76, 4.43)	0.58 (-2.08, 3.32)	2.91 (-0.7, 6.66)	0.86 (-1.51, 3.29)
2	1.92 (-0.04, 3.92)	1.42 (-0.41, 3.29)	-1.6 (-4.39, 1.27)	1.13 (-1.49, 3.83)	3.38 (0.14, 6.73)	0.58 (-1.67, 2.89)
3	1.35 (-0.6, 3.33)	1.61 (-0.22, 3.48)	0.49 (-2.23, 3.28)	0.44 (-2.18, 3.14)	-0.3 (-3.36, 2.85)	0.48 (-1.71, 2.71)
4	0.64 (-1.3, 2.62)	0.66 (-1.17, 2.52)	1.17 (-1.51, 3.92)	0.3 (-2.33, 2.99)	-1.18 (-4.15, 1.88)	0.98 (-1.19, 3.19)
5	1.21 (-0.76, 3.22)	1.03 (-0.81, 2.91)	0.83 (-1.84, 3.57)	0.83 (-1.83, 3.56)	-0.45 (-3.44, 2.63)	0.89 (-1.27, 3.1)
6	0.88 (-1.1, 2.89)	1.68 (-0.21, 3.6)	1.01 (-1.68, 3.76)	0.11 (-2.52, 2.8)	-1.14 (-4.11, 1.92)	0.94 (-1.23, 3.16)

7	0.24 (-1.73, 2.26)	0.61 (-1.24, 2.5)	1.01 (-1.69, 3.79)	1.36 (-1.38, 4.17)	-0.1 (-3.17, 3.07)	1.06 (-1.16, 3.33)
Moving average						
0-1	3.12 (1.02, 5.27)	2.13 (0.17, 4.12)	3.88 (0.78, 7.08)	1.5 (-1.41, 4.49)	2.89 (-1.54, 7.53)	2.39 (-0.17, 5.02)
0-2	3.12 (1.03, 5.26)	2.28 (0.25, 4.36)	2.07 (-0.91, 5.14)	1.76 (-1.36, 4.98)	4.85 (0.01, 9.91)	2.22 (-0.51, 5.01)
0-3	2.98 (0.92, 5.09)	2.62 (0.48, 4.81)	1.99 (-1.11, 5.19)	1.74 (-1.60, 5.20)	3.75 (-1.26, 9.01)	2.21 (-0.75, 5.26)
0-4	2.77 (0.7, 4.89)	2.6 (0.35, 4.89)	2.2 (-0.93, 5.42)	1.73 (-1.84, 5.43)	2.54 (-2.66, 8.03)	2.47 (-0.65, 5.7)
0-5	2.9 (0.76, 5.08)	2.78 (0.41, 5.2)	2.33 (-0.89, 5.65)	1.94 (-1.83, 5.86)	2.06 (-3.37, 7.79)	2.81 (-0.6, 6.33)
0-6	2.89 (0.74, 5.09)	3.2 (0.72, 5.74)	2.48 (-0.76, 5.83)	1.92 (-2.07, 6.07)	1.31 (-4.26, 7.2)	3.13 (-0.5, 6.89)
0-7	2.92 (0.67, 5.22)	3.41 (0.76, 6.14)	2.77 (-0.64, 6.3)	2.42 (-1.88, 6.9)	1.21 (-4.61, 7.38)	3.56 (-0.3, 7.57)

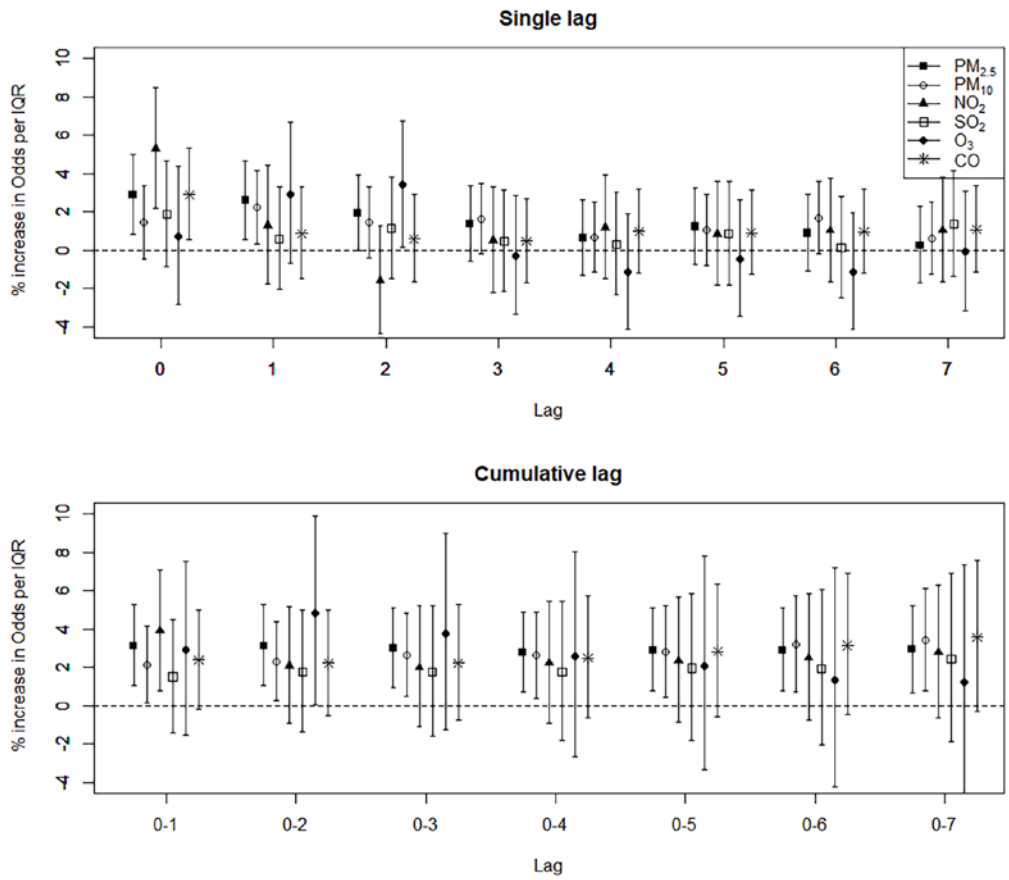

Figure 4.1. Percent change in odds ratios of ED visits for migraine associated with an IQR increase in the concentrations of 6 air pollutants with various lag structures (single lag on the same day [lag0] and on the previous 1−7 days [lag1−lag7], as well as moving average lag on the same day plus 1 day before [lag0−1] to 7 days before [lag0−7]).

Table 4.5. The Akaike information criterion (AIC) values in the main models with different lag structures.

	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
Single lag						
0	55822.14	55827.46	**55818.27**	**55827.84**	55829.48	**55823.82**
1	55823.46	55824.43	55828.95	55829.44	55827.13	55829.12
2	55825.96	55827.34	55828.41	55828.92	**55825.44**	55829.37
3	55827.80	55826.67	55829.50	55829.52	55829.59	55829.44
4	55829.21	55829.13	55828.91	55829.57	55829.04	55828.85
5	55828.18	55828.43	55829.26	55829.26	55829.54	55828.98
6	55828.87	55826.60	55829.09	55829.62	55829.08	55828.91
7	55829.57	55829.21	55829.09	55828.69	55829.62	55828.75
Moving average						
0-1	55821.09	55825.12	55823.59	55828.62	55828.01	55826.30
0-2	**55821.04**	55824.81	55827.80	55828.42	55825.74	55827.10
0-3	55821.59	55823.93	55828.07	55828.60	55827.50	55827.49
0-4	55822.74	55824.50	55827.74	55828.74	55828.72	55827.23
0-5	55822.60	55824.32	55827.64	55828.63	55829.09	55827.04
0-6	55822.64	**55823.22**	55827.39	55828.76	55829.42	55826.78
0-7	55823.11	55823.24	55827.09	55828.43	55829.46	55826.37

4.3.3 Evaluation of possible effect modification

Table 4.6 shows the estimated effect of air pollution on migraine by sex, age, subtype, and season. While slight differences between subgroups were observed, only the difference in $PM_{2.5}$ effect by season was statistically significant (warm: 5.7% [95% CI: 2.5%, 9.0%]; cool: 1.3% [95% CI: -1.4%, 4.1%]; $P_{interact}$=0.04). Figure 4.2 presents the modification of air pollution effect on ED visits for migraine by weather variables. The effect of air pollution was greater on high temperature days with statistical evidence for interaction for $PM_{2.5}$ (high: 6.8% [95% CI: 2.9%, 10.8%]; low: 2.1% [95% CI: -0.2%, 4.4%]; $P_{interact}$=0.03), PM_{10} (high: 6.6% [95% CI: 2.7%, 10.9%]; low: 1.4% [95% CI: -0.7%, 3.4%]; $P_{interact}$=0.02) SO_2 (high: 5.2% [95% CI: -0.1%, 10.8%]; low: 1.3% [95% CI: -1.7%, 4.3%]; $P_{interact}$=0.09), O_3 (high: 4.1% [95% CI: -0.6%, 9.1%]; low: 0.3% [95% CI: -4.8%, 507%]; $P_{interact}$=0.07), and CO (high: 6.1% [95% CI: 1.3%, 11.3%]; low: 2.0% [95% CI: -0.6%, 4.6%]; $P_{interact}$=0.08). Effect modification by other weather variables was not observed except for NO_2 effect by air pressure ($P_{interact}$=0.06). The effect modification by temperature was consistently observed when the patients were stratified by sex, age, and subtypes (Figure 4.3). Especially, strong interactions between air pollution and temperature were shown among female, patients aged under 40 years, and patients with migraine without aura.

Table 4.6. Effect modification of association between short-term exposure to six air pollutants and emergency department visits for migraine by sex, age, subtype, and season.

	OR (95% CI)					
	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
All	3.12 (1.03, 5.26)	3.2 (0.72, 5.74)	5.27 (2.17, 8.46)	1.87 (-0.86, 4.67)	3.38 (0.14, 6.73)	2.89 (0.54, 5.3)
Sex						
Male	2.73 (-0.95, 6.55)	2.87 (-1.63, 7.57)	5.82 (0.49, 11.44)	1.03 (-3.76, 6.06)	6.09 (0.08, 12.47)	2.28 (-1.84, 6.57)
Female	3.27 (0.84, 5.75)	3.32 (0.41, 6.31)	5.05 (1.51, 8.71)	2.22 (-0.98, 5.52)	2.35 (-1.39, 6.22)	3.14 (0.41, 5.93)
$P_{interact}$	0.81	0.87	0.81	0.17	0.3	0.73
Age						
≤40	3.19 (0.51, 5.94)	3.62 (0.37, 6.98)	6.87 (2.9, 11)	2.59 (-1.02, 6.34)	2 (-2.13, 6.29)	3.76 (0.7, 6.91)
40-65	3.33 (0, 6.77)	1.81 (-2.21, 5.99)	4.07 (-0.66, 9.03)	2.31 (-2.02, 6.84)	7.21 (1.79, 12.92)	2.48 (-1.2, 6.29)
≥65	1.53 (-5.52, 9.1)	6.59 (-2.3, 16.3)	-0.95 (-10.34, 9.42)	-4.92 (-13.41, 4.41)	-3.93 (-14.51, 7.97)	-1.26 (-8.6, 6.67)
$P_{interact}$	0.9	0.59	0.3	0.32	0.14	0.48
Subtype						
Without aura	3.88 (-2.19, 10.33)	5.99 (-1.37, 13.9)	0.81 (-7.42, 9.76)	-3.63 (-11.13, 4.49)	3.5 (-5.91, 13.84)	1.59 (-4.92, 8.54)
With aura	1.26 (-7.62, 10.99)	4.48 (-6.45, 16.67)	-4.17 (-16.27, 9.69)	6.39 (-6.54, 21.09)	-9.56 (-21.94, 4.78)	4.87 (-5.64, 16.56)
Unspecified	3.1 (0.61, 5.64)	3.34 (0.31, 6.46)	7.04 (3.38, 10.83)	2.69 (-0.62, 6.11)	3.63 (-0.28, 7.7)	3.13 (0.33, 6.02)
$P_{interact}$	0.21	0.81	0.15	0.28	0.21	0.87
Season						
Warm	5.67 (2.45, 9)	4.57 (1.16, 8.09)	5.99 (1.28, 10.92)	4.15 (-0.12, 8.6)	2.2 (-1.41, 5.94)	3.91 (-0.74, 8.79)
Cool	1.27 (-1.43, 4.05)	1.59 (-2.01, 5.33)	4.81 (0.94, 8.82)	0.32 (-3.15, 3.91)	7.52 (0.77, 14.71)	2.56 (-0.15, 5.33)
$P_{interact}$	0.04	0.25	0.7	0.18	0.17	0.62

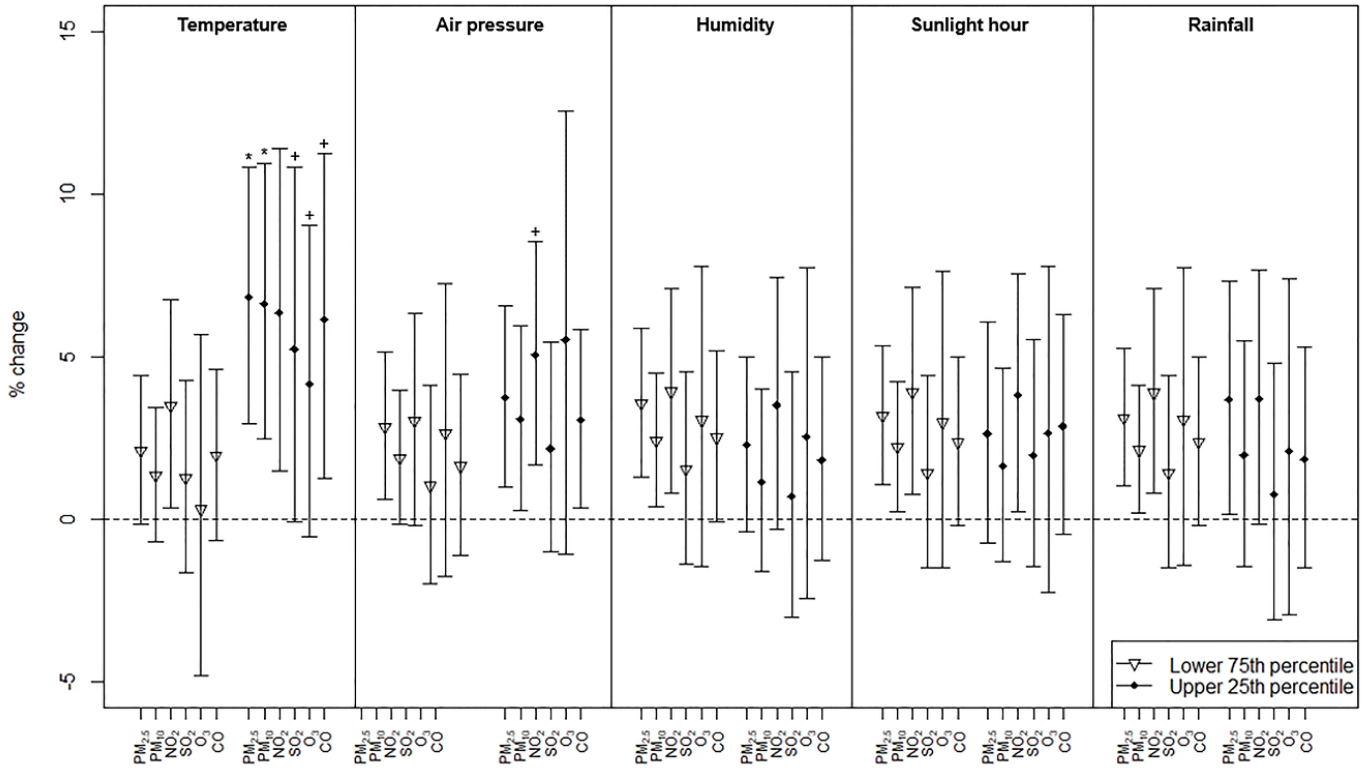

Figure 4.2. Effect modification of association between short-term exposure to six air pollutants and emergency department visits for migraine by weather variables.

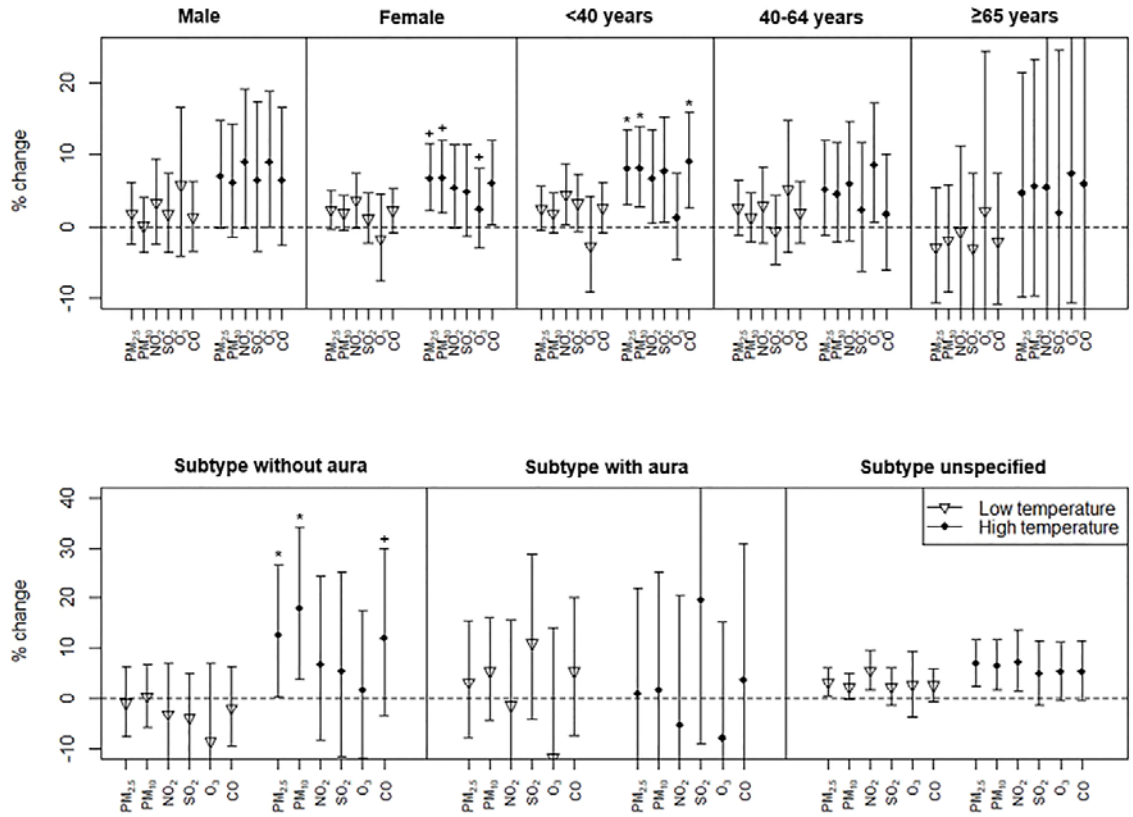

Figure 4.3. Effect modification of association between short-term exposure to six air pollutants and emergency department visits for migraine by temperature in stratified subgroups.

4.3.4 Results of sensitivity analyses

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 4.7). Significant effect of NO_2 was not changed after inclusion of any other pollutants at the best fitting lag days (Table 4.8). The differing temperature specifications little changed the main findings (Figure 4.4), and results of stratified subgroup analyses showed similar patterns with the analyses using interaction terms (Figure 4.5). The effect modification by temperature was consistently observed in different definition of high temperature days (Figure 4.6).

Table 4.8. Percent increase in odds ratios of ED visits for migraine associated with an IQR increase in the concentrations of six air pollutants: single-and two-pollutant models adjusted for concentrations of air pollutants at the best fitting lag days.

	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
Single pollutant	3.12 (1.03, 5.26)	3.20 (0.72, 5.74)	5.27 (2.17, 8.46)	1.87 (-0.86, 4.67)	3.38 (0.14, 6.73)	2.89 (0.54, 5.3)
Two pollutant						
+$PM_{2.5}$			3.93 (0.27, 7.72)	-0.95 (-4.29, 2.5)	2.71 (-0.55, 6.07)	1.03 (-2.02, 4.18)
+PM_{10}			4.73 (1.27, 8.32)	0.38 (-2.8, 3.67)	3.07 (-0.18, 6.42)	2.13 (-0.67, 5.01)
+NO_2	2.41 (-0.18, 5.06)	2.42 (-0.18, 5.1)		-0.22 (-3.52, 3.19)	2.95 (-0.3, 6.31)	1.54 (-2.00, 5.21)
+SO_2	4.24 (1.46, 7.09)	3.15 (0.5, 5.87)	6.27 (2.57, 10.11)		3.32 (0.07, 6.67)	3.51 (0.49, 6.62)
+O_3	2.99 (0.79, 5.24)	3.03 (0.53, 5.59)	5.25 (2.15, 8.44)	1.74 (-0.99, 4.55)		2.86 (0.50, 5.28)
+CO	3.49 (0.53, 6.54)	2.7 (0.05, 5.43)	6.27 (2.00, 10.72)	0.46 (-2.97, 4.01)	3.27 (0.03, 6.62)	

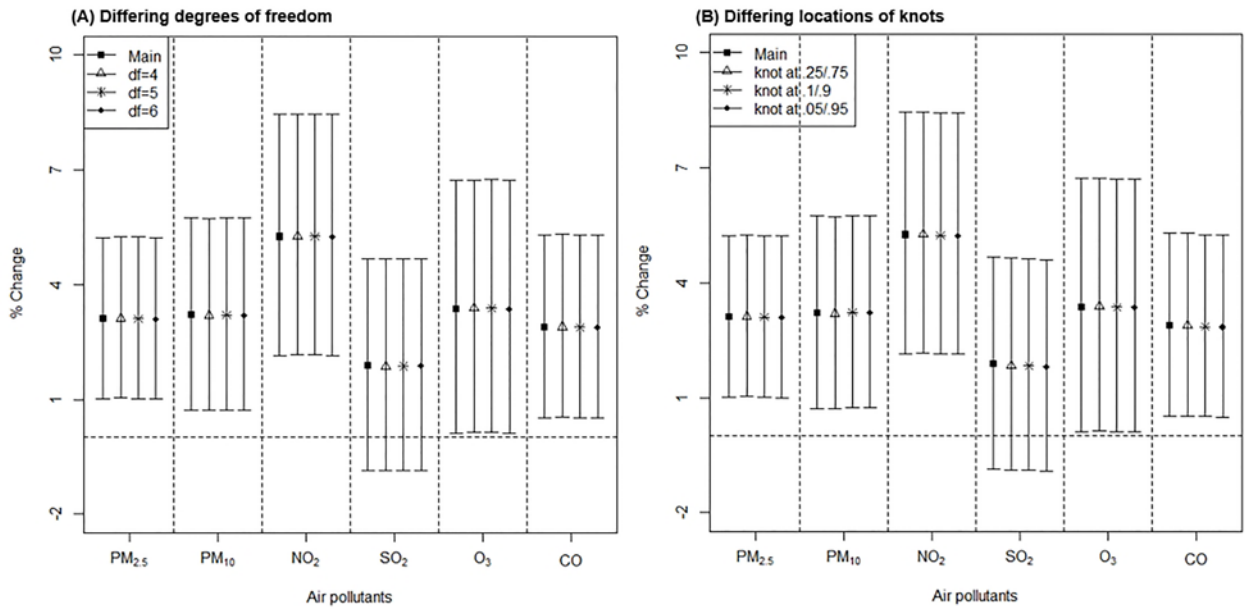

Figure 4.4. Sensitivity analysis: Differing temperature specification.

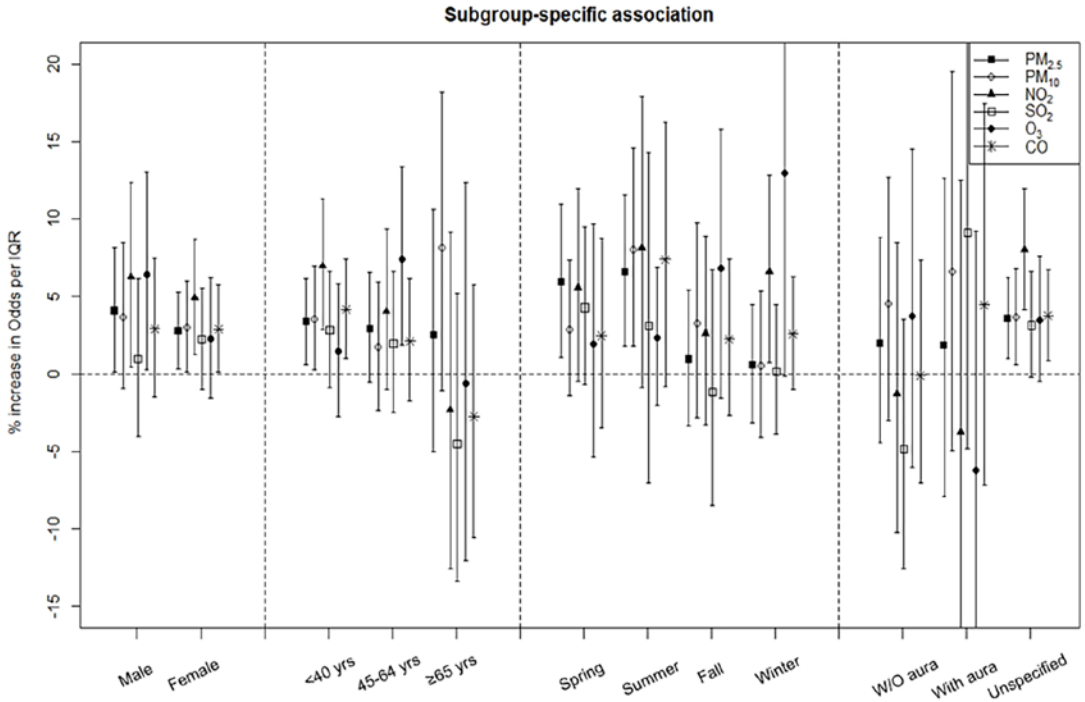

Figure 4.5. Sensitivity analysis: Subgroup analysis stratified rather than interaction terms.

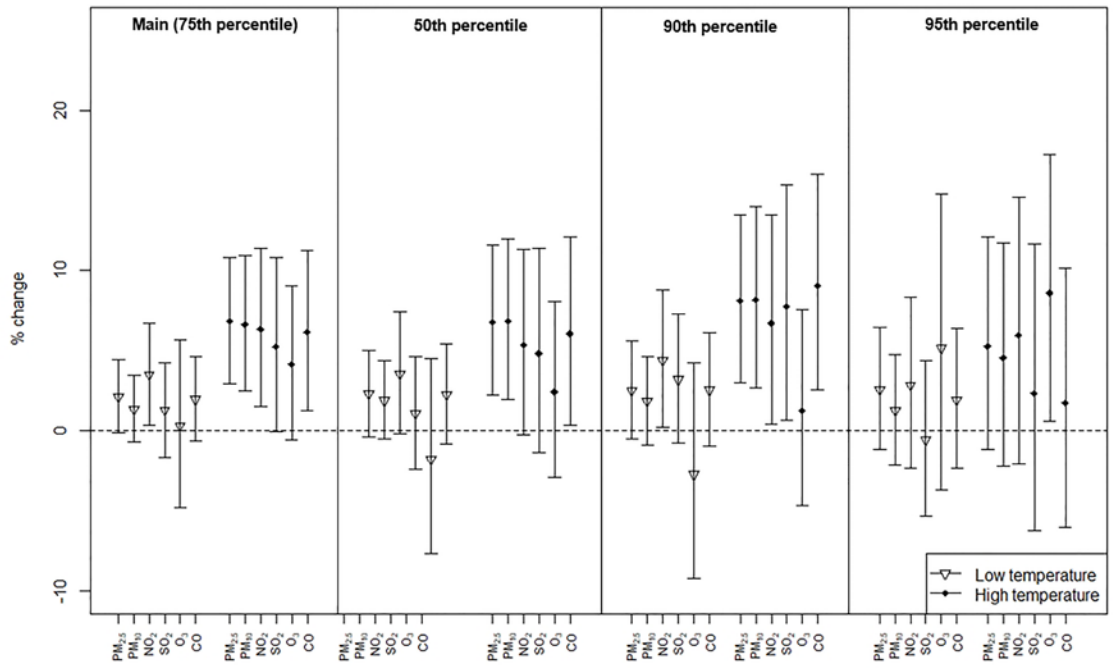

Figure 4.6. Sensitivity analysis: Differing definition of high temperature days.

4.4 Discussion

In the over 18,000 patients who visited ED 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 and slowly-varying risk factors. Among the pollutants, the NO_2 effect 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. 2015a; Wu et al. 2015), and the results are 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 per IQR increase in generalized lineal mixed models, whereas, a study in Boston (MA) 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 analysis. However, a recent study using the case-crossover method reported a significant association between air pollution and clinic visits for migraine in

Taipei (Taiwan). Despite a few discrepancies, our findings contribute to the limited available evidence on the effect of air pollution on triggering 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), 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 pollutants (WHO 2006). PM and CO, whose major components are also emitted from traffic combustion processes, were highly correlated with NO_2.

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 nerve 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.

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 co-morbidities 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, 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 towards the null effect (Copeland et al. 1977). Finally, potential confounders, which vary in the short term and we were unable to consider may still be present.

This 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.

Chapter 5. General Discussion

Key findings

In this thesis, I investigated the relationship between short-term exposure to higher air pollution levels and risk of the three types of neuropsychiatric diseases, which are Parkinson's disease aggravation, suicide completion, and emergency department visits for migraine in South Korea. I found that short-term exposure to ambient air pollution was significantly associated with all three diseases, although the lag structures that gave the best fit to each data showing the strongest effect estimate, differed by each disease. In the analysis on aggravation of Parkinson's disease, significant effects of air pollutants were observed at cumulative lags such as 8-day moving average concentrations, whereas air pollution effect on suicide completion and emergency department visits for migraine, was more pronounced at immediate lags such as 1-day or 2-day moving average concentrations. This may imply that major biological mechanisms through which air pollution affects each neuropsychiatric disease are somewhat different by sub types of neuropsychiatric diseases.

Interestingly, however, NO_2 showed the largest effect in all three studies among all criteria air pollutants. This strong association was constantly shown in all two-pollutant models. It has been known that NO_2 is

a tracer of traffic emissions. Hence, it is likely that neuropsychiatric diseases are more closely associated with traffic-related air pollution. Further, other pollutants such as PM and CO were highly correlated with NO_2, whose major components are also emitted from traffic emissions. However, it should be noted that two pollutants models including highly correlated two variables should be interpreted with caution.

Previous studies on effect of NO_2 on health outcomes

As one of the hazardous air pollutants, WHO suggested that levels of NO_2 should be managed both in short- and long-term scales (WHO, 2005). NO_2 is considered as a mixture pollutant of combustion-related pollutants, especially, those from traffic and indoor combustion sources. Other pollutants such as PM and nitrous oxide also emitted from combustion processes. Hence, effects of other pollutants on the association between NO_2 and health outcomes have been difficult to rule out (WHO, 2005).

Previous epidemiological studies have investigated the association between NO_2 and various health outcomes including natural mortality, asthma, cardiovascular disease, and recently neurological diseases (Table 5).

Table 5. Previous studies on NO_2 effect on health outcomes.

Country	Period	Outcome	Method	Result	Covariates	Reference
30 European cities	1990-1997	Total non-accidental mortality, cardiovascular mortality, respiratory mortality	Time-series analysis with Poisson distribution/meta-analysis	Total: 0.30% (0.22%, 0.38%) / Cardiovascular: 0.40% (0.29%, 0.52%) / Respiratory: 0.38% (0.17%, 0.58%) per 10 $\mu g/m^3$	Seasonality, long-term trends and meteorological variables (mean daily temperature and mean daily relative humidity), the day-of-the week effect, holidays and influenza epidemics.	Samoli et al. 2006
12 Canadian cities	1981-1999	Total non-accidental mortality	Random-effects regression model for count data/meta-analysis	2.25 % increase (t=4.45) per 22.4 ppb	Temporal trends in mortality and weather factors (humidex)	Burnett et al. 2004
10 Italian cities	2001-2005	Natural, cardiac, cerebrovascular, and respiratory mortality	Time-stratified case-crossover analysis	Natural mortality [2.09% for lag 0–5; 95% C), 0.96–3.24]/ Cardiac mortality (2.63% for lag 0–5; 95% CI, 1.53–3.75)/ Respiratory mortality (3.48% for lag 1–5; 95% CI, 0.75–6.29) per 10-$\mu g/m^3$	Population decrease, holidays, influenza epidemics, barometric pressure, and apparent temperature. Day of the week and long-term and seasonal trends were adjusted for by design	Chiusolo et al. 2011
Barcelona, Spain	1985-1995	Morality among patients with severe asthma	Time-stratified case-crossover analysis	All causes mortality (Odds ratio: 1.50, 95% CI: 1.09–2.64) Respiratory mortality (Odds ratio: 1.63, 95% CI: 0.93–2.86)	Asthma epidemics, temperature, humidity, hot days, and influenza epidemics	Sunyer et al. 2002

10 communities in California	2000	Childhood asthma	Logistic regression analysis	Odds ratio: 1.83 (1.04 –3.22) per 5.7 ppb	Sex, race, Hispanic ethnicity, cohort (whether the subject was enrolled in 1993 or 1996), and indicator variables for study community	James et al. 2005
Southampton, UK	1994	Severity of Virus-induced asthma in Children	Generalized Estimating Equations	Significant increases in the severity of lower respiratory-tract symptom scores across the three tertiles (0.6 for all viruses [p=0.05] and >2 for respiratory syncytial virus [p=0.01]) and a reduction in PEF of more than 12 L/min for picornavirus (p=0.04) for high compared with low NO_2 exposure before the start of the virus-induced exacerbation.	Age, sex, social class, atopy, and use at baseline of inhaled 2 agonists, inhaled corticosteroids, or oral corticosteroids	Chauhan et al. 2003
Taipei, Taiwan	2001-2002	Heart rate variability in Chronic heart disease patients	Linear mixed-effects regressions	Increase in 10 ppb NO_2 at 4-h to 8-h moving averages was associated with 1.5–2.4% decreases in the standard deviation of all normal-to-normal intervals (SDNN) in participants. For every 10 ppb NO_2 at 5 and 7-h moving averages, the participants' low frequency was decreased by 2.2 and 2.5%, respectively.	Sex, age, body mass index, health status (CHD versus non-CHD), smoking status (current versus never), medication use, and the hour of day	Chan et al. 2005

				In contrast, HRV was not associated with PM_{10}, CO, SO_2, or O_3.		
Copenhagen, and Aarhus, Denmark	1993-2006	Incident stroke	Cox regression analysis	Borderline significant associations between mean nitrogen dioxide levels at residence since 1971 and incident stroke (hazard ratio, 1.05; 95% CI, 0.99 −1.11, per interquartile range increase) and stroke hospitalization followed by death within 30 days (1.22; 1.00 −1.50).	Age, sex, smoking status, smoking duration, smoking intensity, indicator for environmental tobacco smoke at home or work for minimum 4 hours/day, body mass index, educational level (<8/8 − 10/≥10 years), indicator of sports activity in leisure time, intensity of sports activity (hours/week), indicator of alcohol consumption, alcohol consumption (g/day), fruit and vegetable intake (g/day), and fat intake (g/day); indicator of having diagnoses or taking medication for hypertension, hypercholesterolemia, or diabetes.	Anderson et al. 2012

Taiwan	2000-2010	Dementia	Cox regression analysis	Adjusted hazard ratios of dementia for all participants in Q2, Q3, and Q4 compared to Q1 were 1.10 (95% confidence interval (CI), 0.96−1.26), 1.01 (95% CI, 0.87−1.17), and 1.54 (95% CI, 1.34−1.77)	Age, sex, monthly income, DM, HT, IHD, COPD, alcoholism, and urbanization	Chang et al. 2014
Ontario, Canada	2001-2013	Incidence of Dementia	Random-effects Cox regression analysis	NO_2 was associated with increased incidence of dementia (HR = 1.10; 95% CI: 1.08−1.12)	Age, sex, preexisting comorbidities, urban residency, a North/South indicator, and neighborhood SES	Chen et al. 2017

Comparison with the current study

Table 5 shows the summaries of the previous epidemiologic studies on health effects of NO_2. The health outcomes include mortality, respiratory diseases, cardiovascular diseases, and neurological diseases.

In the present study, NO_2 increased the risk of Parkinson's disease aggravation by 2.4 (95% CI, 1.4–3.9) per 10 ppb in the 8-day moving average; the risk of suicide completion by 4.3% (95% CI, 1.9%, 6.7%) per IQR increase in same day concentrations; and the risk of ED visits for migraine by 5.3% (95% CI: 2.2%-8.5%) per IQR increase in same day concentrations. These effect estimates are larger than those estimated form the mentioned previous studies. First, in the assessment of short-term association, the effect estimates for mortality (all causes, cardiovascular, respiratory) ranged from 0.30% to 3.48%; the estimated odds ratio for mortality in patients with severe asthma was 1.50, and that for childhood asthma was 1.83; in the assessment of heart rate variability, NO_2 was the only pollutant that showed the significant negative effect (2.4%). Second, in the assessment of long-term association, NO_2 increased the risk of stroke incidence by 1.05, and the risk of dementia incidence by 1.54 in Taiwan, and by 1.10 in Ontario, Canada.

Overall, while all studies found the significant hazardous effects of NO_2, the magnitude of the effect was different between studies. The

differences may be attributable to interregional differences in baseline concentrations according to major industries and traffic volume, different atmospheric conditions, different populations at risk, different study designs, different outcomes examined, different selections of exposure windows, and different statistical models.

Biological mechanism of NO_2

On cardiovascular and respiratory diseases

The authors of previous studies cannot conclude that whether NO_2 independently produced adverse health effects in humans, or is just a marker for combustion or its oxidation products through epidemiological observational studies. While some studies suggested that NO_2 is a surrogate of other pollutants (Chiusolo et al. 2011; Seaton and Dennekamp 2003), several other studies mentioned that effect of NO_2 on human health is likely independent from other air pollutants (Samoli et al. 2006).

Chiusolo et al. (2011) found the independent effect of NO_2 on mortality from PM_{10}, but suggested that NO_2 might act a role as a surrogate of unmeasured pollutants that cannot be ruled out. During the presence of high levels of traffic, PM is composed of a mixture of carbon particles (including PM in the ultrafine range) that are mainly produced by diesel engines (diesel soot). He mentioned that because diesel engines are the main

sources of both NO_2 and ultrafine particles, and that the ultrafine particles are sulfated and nitrogenized, which may explain the high correlation observed among PM, NO_2, and sulfur dioxide, NO_2 should be considered a surrogate of ultrafine particles.

However, several experimental studies have demonstrated that NO_2 inhalation can induce pulmonary inflammation by causing damage of epithelial cells and inflammation of the airway epithelium. Bousquet and Davies (1993) showed in an in-vitro study that the human bronchial epithelial cells exposure to 0.4–0.8 ppm NO_2 exposure for 6 hours were associated with the synthesis of proinflammatory cytokines such as granulocyte–macrophage colony-stimulating factor, interleukin-8 (IL-8), and tumor necrosis factor-a. The other experimental study on the airways of healthy subjects found that NO_2 exposure induced neutrophilic inflammation in the airways of healthy subjects that was detectable in bronchial washing at 6 hours after 2 ppm NO_2 exposure (BLOMBERG et al. 1997). This increase in neutrophils may be related to the enhanced IL-8 secretion observed at 1.5 hours after exposure. The experimental findings support that NO_2-induced pulmonary inflammation is a plausible mechanism responsible for adverse health outcomes.

On neuropsychiatric diseases

Scientific evidence for neuropsychiatric effects of NO_2 is limited but increasing in recent years. An experimental study on the guinea-pig reported that exposure to 5-10 ppm NO_2 for 2 hours daily for 5 weeks induced significant depletion of the total lipids and phospholipids content as well as the cholesterol diminution content of the cerebral hemisphere, cerebellum, and midbrain (Farahani 1990). The lipids are essential components of all cellular elements of the central nervous system. The peroxidation changes induced by free radicals in the brain lipids might be of importance in the development of brain cell damage.

Morales et al. (2009) performed an epidemiological study on association between exposure to indoor NO_2 and neuropsychological development in preschool children, and found the significant decrease in cognitive function and inattention symptoms. They found the higher effect of NO_2 on the executive function which is related to cognitive tasks performed by a predominant activation of the prefrontal cortex, and this neurologic area is innervated by the monoamines dopamine, noradrenaline, and serotonin (Morales et al. 2009). The authors also mention that NO_2 may impair dopaminergic neuron functioning by triggering oxidative stress and inhibiting dopamine biosynthesis, which in turn causes the poor executive function.

An experimental study with model rats of ischemic stroke and

healthy rats investigated the effect of NO_2 exposure on synaptic mechanisms, which is the foundation of neuronal function and viability (Li and Xin 2013). In this study, 5 $\mu g/m^3$ NO_2 exposure exacerbated the ultrastructural impairment of synapses in stroke model rats and also caused neuronal damage in healthy rats. It is known that the structural and functional status of synaptic connections are closely correlated with overall neuronal health. Previous studies reported that synaptic pathology precedes cell death in dementia and is a clinical characteristic of neurodegeneration diseases (Costain et al., 2008). The results implied that NO_2 exposure could increase the risk of vascular dementia through inducing excitotoxicity in healthy rats but weakening synaptic plasticity directly in stroke model rats.

While the main disease of interest in above mentioned previous studies are slightly different, the diseases all belong to neuropsychiatric disease. They found the consistent hazardous effect of NO_2 on parts of neuropsychiatric system including lipids depletion in the brain and synaptic mechanisms.

Public Health Implications

This epidemiologic study is firstly conducted in Asian regions as well as in South Korea, in the circumstances where the direct epidemiologic evidence linking air pollutants exposures to neurological diseases is sparse. In Korea,

the issues of the aging population have been increasing with the growing number of the neurodegenerative diseases. Traffic-related air pollutants has been rapidly increasing according to increasing vehicle ownership. Between 2000 and 2010, vehicle ownership increased from 8 million to 11 million and the number of households with more than three vehicles increased from 0.11 million to 0.28 million (KOSIS, 2010). The number of vehicles on the roads per day (traffic volume) increased from 70,000 to 76,000 (KOSIS, 2016). Consequently, most citizens have been exposed to traffic-related air pollution, and tackling vehicle emissions has become an urgent problem for South Korea.

The air pollution warning system in Korea also should be improved more properly in Korean population. The warning system is not based on scientific evidence from Korean epidemiological study, but the interim level of WHO guidelines. Susceptible group specified in warning system are limited to kids, elderly, patients with cardiovascular and respiratory diseases, although there may be more vulnerable people to air pollution other than those groups.

In this circumstance, I provide a direct scientific evidence from Korean population, and this result can play a role in persuading people to develop, implement, and follow the policies for air quality improvement, in establishing air pollution warning system suitable to Korean population, and

in listing up patients with neuropsychiatric diseases as a vulnerable group, so that their exposure to outdoor air pollution can be minimized.

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Abstract in Korean

연구배경

국가가 발전함에 따라 인구집단의 건강에 영향을 미치는 위험요소가 변화하고 있다. 현대사회의 주요 건강 위험요소 중 하나로써, 대기오염은 많은 질병들과 연관이 있는 것으로 밝혀졌다. 최근 실험연구를 통해 대기오염이 신경손상에 미치는 영향에 대한 증거들이 점차 증가하면서 몇몇 역학연구들도 대기오염과 인간의 신경정신질환 간의 관계를 밝히기 위해 북아메리카와 유럽 지역에서 수행되었지만, 아시아 지역에서는 거의 연구되지 않았다. 더욱이 이러한 선행연구들의 결과는 지역마다, 인구마다 다른 여러 가지 특성들을 고려했을 때 다른 지역으로 일반화하기 어렵다. 따라서 대기오염과 신경정신질환 간 관계에 대한 연구가 한국인을 대상으로 수행되어야 할 필요가 있다.

연구목표

본 학위논문은 한국에서 대기오염에의 노출이 신경정신질환의 위험을 증가시킬 것이라는 가설을 한국의 세가지 역학자료를 가지고 연구하는 것을 목표로 한다. 신경정신질환 중 한국에서의 유병률, 연구가 진행된 정도, 원인이 밝혀진 정도를 고려하여 세가지 (파킨슨병,

자살, 편두통)를 선정하였으며, 이 세 신경정신질환과 단기 대기오염 노출 간의 관련성에 대해 평가하였다.

연구방법

대기오염 가이드라인의 기준이 되는 6개의 대기오염물질 [particles <10 μm (PM_{10}), particles <2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO)]과 신경정신질환 간의 관계를 시간-층화 환자-교차 연구 디자인을 가지는 조건부 로지스틱 회귀분석을 통해 평가하였다. 자료의 가용성에 따라, 사회경제적 요인, 자살 방법, 편두통의 하부유형, 계절 등 다른 관련 요인에 의한 관계의 수정효과가 있는지 평가하였다. 더욱이, 두 물질 모형 (two-pollutant models)을 분석하여 가장 큰 연관성이 있는 대기오염물질을 탐색하였다.

연구결과

파킨슨병 악화와의 연구에서, 8일 평균 노출이 한 단위 증가할 때 마다 파킨슨병 악화 위험률이 다음과 같이 증가하였다: $PM_{2.5}$ - odds ratio [95% confidence interval]: 1.61 [1.14– 2.29] per 10 $\mu g/m^3$; NO_2 - odds ratio 2.35 [1.39– 3.97] per 10 ppb; SO_2 - odds ratio 1.54 [1.11– 2.14]

per 1 ppb; and CO - odds ratio 1.46 [1.05– 2.04] per 0.1 ppm. 이 관련성은 여성, 65-74세 연령층, 추운 계절 (9~2월)에서 더 크게 나타났으나 그룹별 차이가 통계적으로 유의하지는 않았다. 두 물질 모형 분석 결과, NO_2의 영향이 가장 큰 유의한 결과를 도출하였다.

자살과의 연구에서, NO_2가 전체 래그에 걸쳐 모든 대기오염 물질 중 가장 큰 영향을 미치는 것으로 나타났다 (PM_{10}: 1.21% [95% CI, 0.15%, 2.29%]; NO_2: 4.30% [95% CI, 1.92%, 6.73%]; SO_2: 2.24% [95% CI, 0.70%, 3.80%]; O_3: 1.46% [95% CI, − 0.26%, 3.21%]; and CO: 2.35% [95% CI, 0.94%, 3.78%] at lag0). 사회경제적 요인에 따른 하부 그룹별 분석에서, 남성, 노인층, 교육수준이 낮은 집단, 비고용자, 사무직, 그리고 혼인집단에서 더 큰 관련성을 보였다. 가장 큰 관련성은 사무직 집단에서 NO_2의 영향이었다 (11.04%; 95% CI, 4.15%, 18.39%). 두 물질 모형 분석 결과 역시 NO_2의 영향이 가장 컸다.

편두통으로 인한 응급실 방문과의 연구에서, SO_2를 제외한 모든 대기오염 물질이 통계적으로 유의한 관련성을 보였다 ($PM_{2.5}$: 3.12% [95% CI, 1.03%, 5.26%]; PM_{10}: 3.2% [95% CI, 0.72%, 5.74%]; NO_2: 5.27% [95% CI, 2.17%, 8.46%]; O_3: 3.38 [95% CI, 0.14%, 6.73%]; and CO: 2.89% [95% CI, 0.54%, 5.3%]). 기온이 높은 날에 PM이 편두통에 미치는 영향이, 기온이 낮은 날 PM의 영향보다 통계적으로 유

의하게 강하였다 ($PM_{2.5}$, high: 6.8%, low: 2.1%, $P_{interact}$=0.03; PM_{10}, high: 6.6%, low: 1.4%, $P_{interact}$=0.02). NO_2가 두 물질 모형에서 가장 큰 연관성을 보였다.

고찰

본 학위논문 연구 결과, 대기오염에의 단기 노출은 파킨슨병 악화의 위험, 자살의 위험, 편두통으로 인한 응급실 방문의 위험을 모두 증가시키는 것으로 나타났으며, 특히 모든 질환에서 NO_2의 영향이 일관성 있게 가장 큰 것으로 나타났다. 대기오염에의 단기간 노출은 인간의 신경정신질환 진행에 영향을 미칠 수 있다고 생각되며, NO_2가 자동차 배기가스의 추적물질로써 간주되는 것을 고려해볼 때, 특히 교통관련 대기오염이 신경정신질환과 더 밀접한 영향이 있는 것으로 생각된다.

한국은 인구밀집현상, 자동차수 증가 및 교통량 증가에 따라 대기오염문제가 지속되고 있는데 이러한 상황에서 차량2부제 등 정책을 수행하는 것이 필요하지만 정책의 이점이 정책으로 인한 손실을 능가하는지에 대해서는 여전히 논쟁이 되고 있다. 또한 현재 국내에서 실시하고 있는 대기오염경보제의 농도기준은 한국의 역학연구로부터의 과학적 근거를 기반으로 한 것이 아니고 WHO 가이드라

인의 중간수준을 차용한 것이며, 명시되어 있는 취약계층도 영유아, 노인, 심혈관 및 호흡기질환자 뿐이다. 본 연구는 한국인구를 대상으로 한 직접적 근거를 제공하였으며 이 결과는 대기 질 향상을 위한 정책을 개발, 수행, 및 충실히 이행하도록 사람들을 설득하는 역할을 하고, 한국에 적합한 대기오염경보제를 수립하는데 역할을 하며, 신경정신질환자도 취약계층으로써 명시될 수 있는 근거를 제공하여 노출 최소화 및 신경정신질환 예방 정책 개발에 기여할 수 있다. 또한 본 연구 결과는 향후 진행될 대기오염-신경정신질환 연구에도 기반이 될 것이다.

주요어: 대기오염, 신경정신질환, 파킨슨병, 자살, 편두통, 단기노출 관련성, 환자-교차연구 디자인

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