Ambient air pollution and emergency department visits for stroke

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ABSTRACT

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Background: Many epidemiological studies have shown short-term effects of ambient air pollution on cardiovascular diseases. Several studies have investigated the relationship between air pollutant exposure and stroke but the findings have been inconsistent.

Objective: We conducted a time-series study to assess the association between ambient air pollution and emergency department (ED) visits for stroke in Seoul, Republic of Korea.

Materials and methods: The ED data from 2005 to 2009 were obtained from the Health Insurance Review and Assessment Service, and the number of ED visits for stroke was 94,539. We used a generalized additive model with Poisson distribution, adjusting for temperature (cubic spline, df=6), relative humidity (cubic spline, df=3), day of the week, and national holidays. The risk was expressed as a RR with one standard deviation increase and its 95% CI. We explored the lag effects with cumulative lag models (lag0-1 to lag0-3). Stratification of age and gender to analyze the differences was conducted and the RRs were estimated.

Results: In the same day exposure, the RRs of ED visits for stroke were 1.017 (95% CI, 1.011-1.024) per 12.04 ppb increment of NO_2 and 1.013 (1.006-1.020) per 0.24 ppm increment of CO. In lag0-3, the RRs for stroke were 1.006 (1.000-1.013) per 36.70 μg/m3 increment of PM_{10}, 1.012 (1.004-1.020) per 10.04 ppb increment of O_3 and 1.009 (1.002-1.016) for CO. In oldest elderly group, significantly positive correlation was found for hemorrhagic stroke in contrast to other age groups and the RR was 1.044 (1.011-1.077) per 10.04 ppb increment of O_3 in lag1.

Conclusion: Ambient air pollutants are significantly correlated with ED visits for stroke.

Keywords: air pollution, emergency department, stroke

I. INTRODUCTION

Stroke is a common cause of death and a leading cause of long-term severe disability in both developed and developing countries (Johnston et al. 2009). Despite the great disease burden imposed on the middle-aged and elderly, the relationship between stroke and environmental risk factors has not been studied adequately. Several prior epidemiological studies have demonstrated a consistent increased risk for cardiovascular diseases associated with acute exposure to ambient air pollutants, including triggering of acute myocardial infarction (Peters et al. 2001) and emergency admissions for acute decompensation of patients with congestive heart failure (Wellenius et al. 2005). Although the mechanisms have not been fully elucidated, current evidence suggests that alterations in hemodynamics (Zanobetti et al. 2004), hemostatic factors (Schwartz 2001), and autonomic function (Gold et al. 2000) may underlie the cardiovascular effects of ambient air pollutants.

Exposure to ambient air pollution may similarly increase the risk of stroke. Several studies have found a positive association between stroke mortality rates and living in areas of high ambient air pollution (Maheswaran et al. 2005). Also, time-series studies using hospital discharge data report a statistically significant positive association between daily measures of PM_{10} (particulate matter with aerodynamic diameter 10 μm) and cerebrovascular hospitalizations (Linn et al. 2000), but the inconsistent results have been obtained from studies that have examined the relationship between air pollution and hospital visits for stroke. Moreover, few studies have distinguished between ischemic and hemorrhagic strokes (Hong et al. 2002b).

This study is based on 5 years' daily counted numbers of emergency department (ED) visits for ischemic and hemorrhagic stroke. Such parameters as exposure to air pollutants and meteorological factors were considered. ED data were linked to the concentrations of ambient air pollutants and weather variables and models for SO_2, PM_{10}, O_3, NO_2, and CO were constructed. Given the possible mechanisms of air pollution-related effects, we hypothesized that short-term elevations in air pollutants would be associated with increased ED visits for ischemic and hemorrhagic stroke.

II. OBJECTIVES

The purpose of this study was to verify a hypothesis that exposure to ambient air pollutants including sulfur dioxide (SO_2), coarse particulate matter (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2) and carbon monoxide (CO) may be associated with ED visits for ischemic and hemorrhagic stroke in Seoul, Republic of Korea. The risk for stroke was evaluated by the following steps:

1) The first step involved the whole ED visits for any strokes.
2) The second step included two stroke categories (ischemic and hemorrhagic stroke) which were defined among any strokes and analyzed separately.
3) Finally, patients who had ED visits for stroke were stratified by gender and age group to investigate the gender and age differences.

III. METHODS

1. Study population

Health data on daily emergency department (ED) visits for stroke were collected from the Health Insurance Review and Assessment Service (HIRA), a part of the National Health Insurance program of the Republic of Korea. The data used in this study targeted the whole ED visits for stroke that occurred in Seoul between 2005 and 2009. The diagnosis codes based on the International Classification for Diseases 10th Revision (ICD-10) were used to categorize the cases for stroke; all strokes (I60-I69), hemorrhagic strokes (I60, I61, I62), ischemic strokes (I63, I65, I66). The subarachnoid, intracerebral, and other non-traumatic hemorrhages were assorted as hemorrhagic stroke and other specified cerebral infarctions were grouped as ischemic stroke.

The information of demographic variables such as age and gender was also obtained from HIRA. To analyze the gender and age differences, patients who had ED visits for stroke were stratified by gender and age group. The age groups selected for this study were less than 65, 65-79, and 80 or greater.

2. Air pollutants and meteorological data

Daily mean values of air pollutants including particulate matter <10 μm in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) were considered in this study. The daily average ambient concentrations were calculated using hourly measured concentrations obtained from 27 continuous monitoring stations in Seoul by the Ministry of Environment. The methods of measurement are as follows: beta-ray absorption method (PM_{10}), pulse Ultra-Violet fluorescence method (SO_2), chemiluminescent method (NO_2), UV photometric method (O_3) and non-dispersive infrared method (CO).

Meteorological data to adjust for the effect of average temperature and relative humidity were obtained from the National Meteorological Office, which are collected hourly in one station (Jongro-gu, Seoul).

3. Statistical Analysis

To examine the short-term effect of ambient air pollutants on stroke, we applied generalized additive models (GAM) with Poisson regression that use nonparametric functions of the variable to allow for flexible fits for time and weather conditions, thus reducing any potential confounding due to these variables (Hastie et al. 1995). We incorporated a smoothing function of calendar time to explain the variations of ED visits during the period. Furthermore, we included natural smooth functions with 6 *df* per year for temperature and 3 *df* per year for humidity. Because there are some difficulties of arbitrariness by researchers in specifying the number of degrees of freedom of the smoothed nonparametric function (Carracedo-Martinez et al. 2010), our time-series model and the selection of *df* were based on previous studies (Yorifuji et al. 2011, Chen et al. 2013). We also included dummy variables, day of the week and public holidays as an indicator variable.

After establishing the basic model, lagged-day exposures with a maximum lag of 3 days were examined, and lag models were considered to evaluate the lag effects on the relative risks of stroke. In addition to single day lag relation, we analyzed the cumulative lag between air pollutants and stroke to investigate the lag effect over time. The risk was expressed as a relative risk (RR) per increment in one standard deviation of each air pollutant and its 95% confidence interval (95% CI).

All analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC) using "PROC GAM" with GCV smoothing parameter estimation, and probability values of <0.05 were considered statistically significant.

IV. RESULTS

1. General characteristics of emergency department visits for stroke

Total study period is composed of 1,826 days for 5 years (2005-2009) and the number of total emergency department visits for any stroke is 94,539 cases in Seoul, Republic of Korea. The numbers of men and women were 50,654 (53.58%) and 43,885 (46.42%), respectively. In stratification of age group, 30,189 (31.93%) patients less than 65-year age, 38,235 (40.44%) of 65- to 80-year age and 26,115 (27.63%) patients greater than 80 year age visited emergency department for stroke. In categories of stroke, the numbers in hemorrhagic and ischemic stroke were 27,987 (29.60%) and 57,108 (60.41%), respectively.

Table 1. Characteristics of the emergency department visits for stroke

	Emergency department visits, N(%)
Total visits (I60-I69)	94,539 (100.0)
Gender	
Male	50,654 (53.58)
Female	43,885 (46.42)
Age	
<65	30,189 (31.93)
65-79	38,235 (40.44)
80≥	26,115 (27.63)
Subtypes	
Hemorrhagic (I60-I62)	27,987 (29.60)
Ischemic (I63, I65, I66)	57,108 (60.41)

2. Average concentration of air pollutants

Table 2 shows the average concentrations of air pollutants, which were expressed as median, interquartile range (IQR), 10^{th} percentile and 90^{th} percentile. During the study period from 2005 to 2009, median concentrations of SO_2, PM_{10}, O_3, NO_2, and CO were 0.005 ppm (IQR. 0.003), 47.28 μg/m^3 (IQR, 33.44), 0.016 ppm (IQR, 0.015), 0.033 ppm (IQR, 0.017), and 0.512 ppm (IQR, 0.259), respectively. Standard deviations of air pollutants are 2.33 ppb for SO_2, 36.70 μg/m^3 for PM_{10}, 10.04 ppb for O_3, 12.04 ppb for NO_2, and 0.24 ppm for CO (data not shown).

Table 2. Average concentration of air pollutants from 2005 to 2009 in Seoul, Republic of Korea

	Median	IQR	10 percentile	90 percentile
SO_2 (ppm)	0.005	0.003	0.003	0.009
PM_{10} ($\mu g/m^3$)	47.28	33.44	22.01	93.29
O_3 (ppm)	0.016	0.015	0.006	0.031
NO_2 (ppm)	0.033	0.017	0.02	0.051
CO (ppm)	0.512	0.259	0.339	0.886
Temperature (℃)	14.51	17.73	-1.50	25.14
Relative humidity (%)	61.6	21.54	41.42	79.63

3. Air pollutants and ED visits for stroke in total study population

In Table 3, the relative risk of emergency department visits for any strokes was 1.017 (95% confidence interval, 1.011-1.024) per 12.04 ppb increment of NO_2 and 1.013 (95% CI, 1.006-1.020) per 0.24 ppm increment of CO in the same day exposure. In single lag models, O_3 in lag1 (RR=1.018; 95% confidence interval, 1.011-1.026) and O_3 in lag2 (RR=1.010; 95% CI, 1.002-1.017) were positively correlated with emergency department visits for any strokes and all of the pollutants showed the positive correlation in lag3. In cumulative lag model, PM_{10}, O_3 and CO were partially correlated in lag0-3 and other models showed no significant correlation.

In subgroup analysis, no positive correlation was found for hemorrhagic stroke except SO_2 in lag3 (RR=1.013; 95% CI, 1.000-1.026) and PM_{10} in lag 3 (RR=1.012; 95% CI, 1.001-1.023). The general aspect of the ischemic stroke showed similar patterns of relative risk in the both lag models. The trends of relative risk with each pollutant on multiple lag days were depicted in Figure 1.

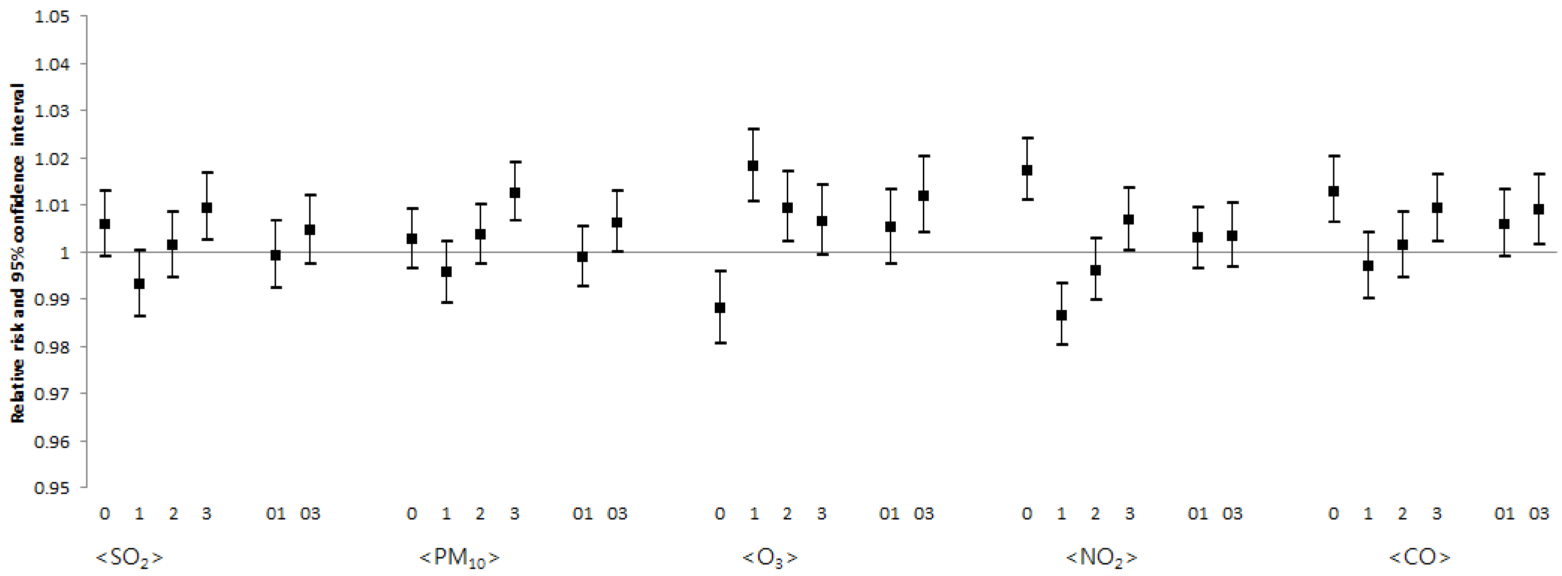
Table 3. Adjusted relative risks (RR) and their 95% confidence intervals

	Lag0	Lag1	Lag2	Lag3	*Lag0-1	Lag0-3
Any stroke						
SO_2	1.006 (0.999 1.013)	0.993 (0.986 1.000)	1.001 (0.994 1.009)	1.010 (1.002 1.017)	0.999 (0.992 1.006)	1.005 (0.997 1.012)
PM_{10}	1.003 (0.996 1.009)	0.996 (0.989 1.002)	1.004 (0.997 1.010)	1.013 (1.006 1.019)	0.999 (0.993 1.005)	1.006 (1.000 1.013)
O_3	0.988 (0.981 0.996)	1.018 (1.011 1.026)	1.010 (1.002 1.017)	1.007 (1.000 1.014)	1.005 (0.997 1.013)	1.012 (1.004 1.020)
NO_2	1.017 (1.011 1.024)	0.987 (0.980 0.993)	0.996 (0.990 1.003)	1.007 (1.000 1.014)	1.003 (0.996 1.010)	1.004 (0.997 1.010)
CO	1.013 (1.006 1.020)	0.997 (0.990 1.004)	1.001 (0.994 1.008)	1.009 (1.002 1.017)	1.006 (0.999 1.013)	1.009 (1.002 1.016)
Hemorrhagic stroke						
SO_2	0.986 (0.974 0.999)	0.984 (0.972 0.997)	0.998 (0.985 1.011)	1.013 (1.000 1.026)	0.982 (0.969 0.995)	0.993 (0.980 1.007)
PM_{10}	0.997 (0.985 1.009)	0.992 (0.980 1.004)	1.004 (0.992 1.015)	1.012 (1.001 1.023)	0.993 (0.981 1.005)	1.002 (0.990 1.014)
O_3	0.992 (0.978 1.006)	1.006 (0.992 1.020)	0.992 (0.979 1.006)	1.007 (0.993 1.021)	0.999 (0.984 1.013)	0.999 (0.984 1.014)
NO_2	1.010 (0.998 1.022)	0.996 (0.985 1.008)	1.000 (0.988 1.012)	1.006 (0.994 1.018)	1.004 (0.992 1.016)	1.005 (0.993 1.018)
CO	1.003 (0.990 1.015)	1.001 (0.989 1.014)	0.998 (0.985 1.011)	1.006 (0.993 1.019)	1.002 (0.990 1.015)	1.003 (0.990 1.017)
Ischemic stroke						
SO_2	1.012 (1.003 1.021)	0.996 (0.987 1.005)	1.002 (0.993 1.011)	1.005 (0.995 1.014)	1.004 (0.995 1.014)	1.006 (0.996 1.015)
PM_{10}	1.002 (0.994 1.011)	0.998 (0.989 1.006)	1.003 (0.995 1.011)	1.012 (1.004 1.020)	1.000 (0.992 1.008)	1.006 (0.998 1.015)
O_3	0.990 (0.980 1.000)	1.023 (1.014 1.033)	1.020 (1.010 1.029)	1.010 (1.001 1.020)	1.010 (1.000 1.021)	1.023 (1.012 1.033)
NO_2	1.019 (1.010 1.027)	0.983 (0.974 0.991)	0.993 (0.984 1.001)	1.005 (0.997 1.014)	1.001 (0.993 1.009)	1.000 (0.991 1.008)
CO	1.015 (1.006 1.024)	0.993 (0.984 1.002)	1.000 (0.991 1.009)	1.008 (0.999 1.017)	1.005 (0.996 1.014)	1.007 (0.997 1.016)

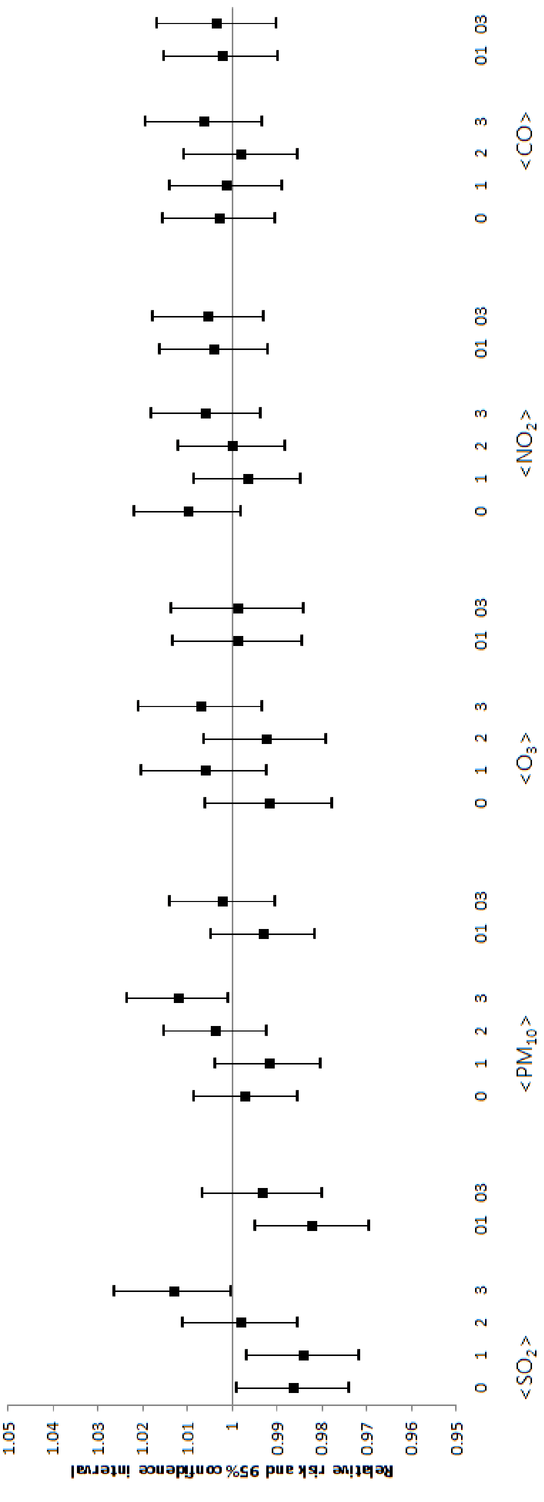
* Cumulative lag model

Figure 1. Adjusted relative risks per increment in one standard deviation of air pollutants using single lag and cumulative lag models

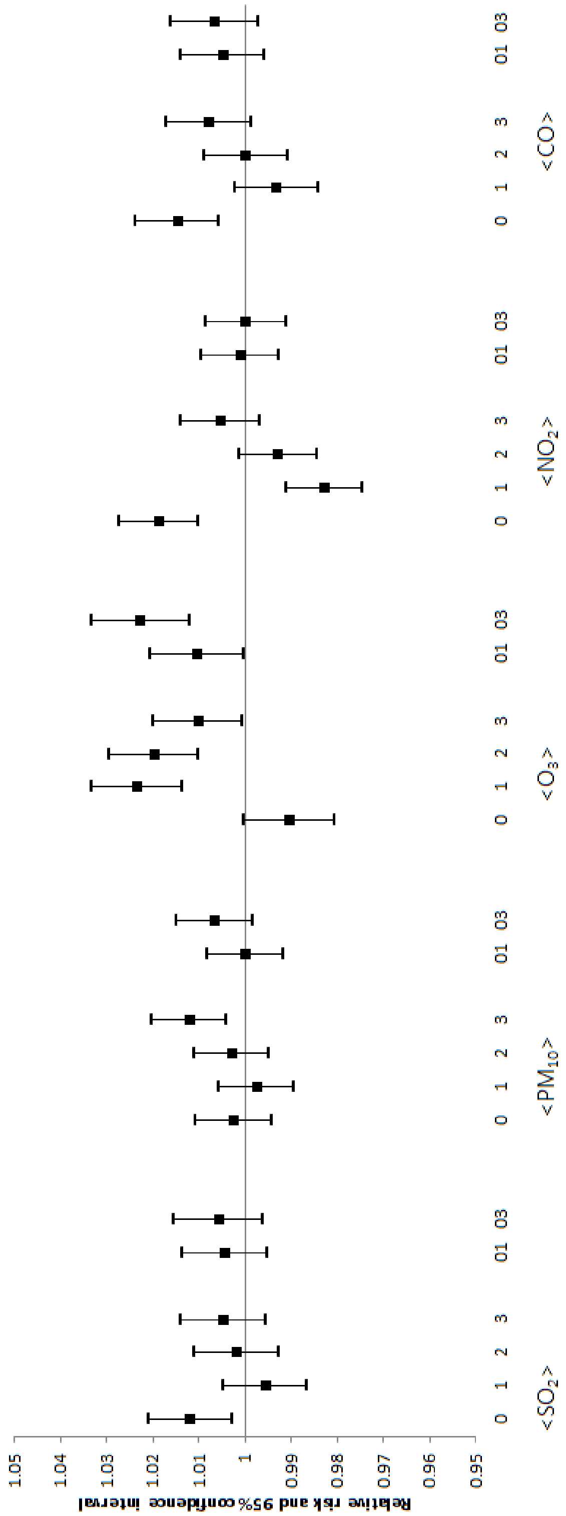
a) Any strokes



b) Hemorrhagic stroke



c) Ischemic stroke



4. Air pollutants and ED visits for stroke in men

To investigate the gender difference in stroke, the relative risks of emergency department visits for any strokes in men are shown in Table 4. In single lag models, SO_2 in lag3 (RR=1.009; 95% CI, 1.000-1.019), PM_{10} in lag3 (RR=1.016; 95% CI, 1.007-1.024), O_3 in lag1 (RR=1.017; 95% CI, 1.007-1.028) and lag2 (RR=1.010; 95% CI, 1.000-1.0280, NO_2 in lag0 (RR=1.019; 95% CI, 1.010-1.028) and CO in lag0 (RR=1.014; 95% CI, 1.005-1.024) and lag3 (RR=1.010; 95% CI, 1.000-1.020) were positively correlated with emergency department visits for any strokes in men. In cumulative lag model, there was no difference with total population in patterns of relative risks.

In subgroup analysis, no positive correlation was found in hemorrhagic stroke except NO_2 in lag0 (RR=1.019; 95% CI, 1.002-1.036) and CO in lag1 (RR=1.018; 95% CI, 1.000-1.036). The trends of relative risk with each pollutant on multiple lag days in men were depicted in Figure 2.

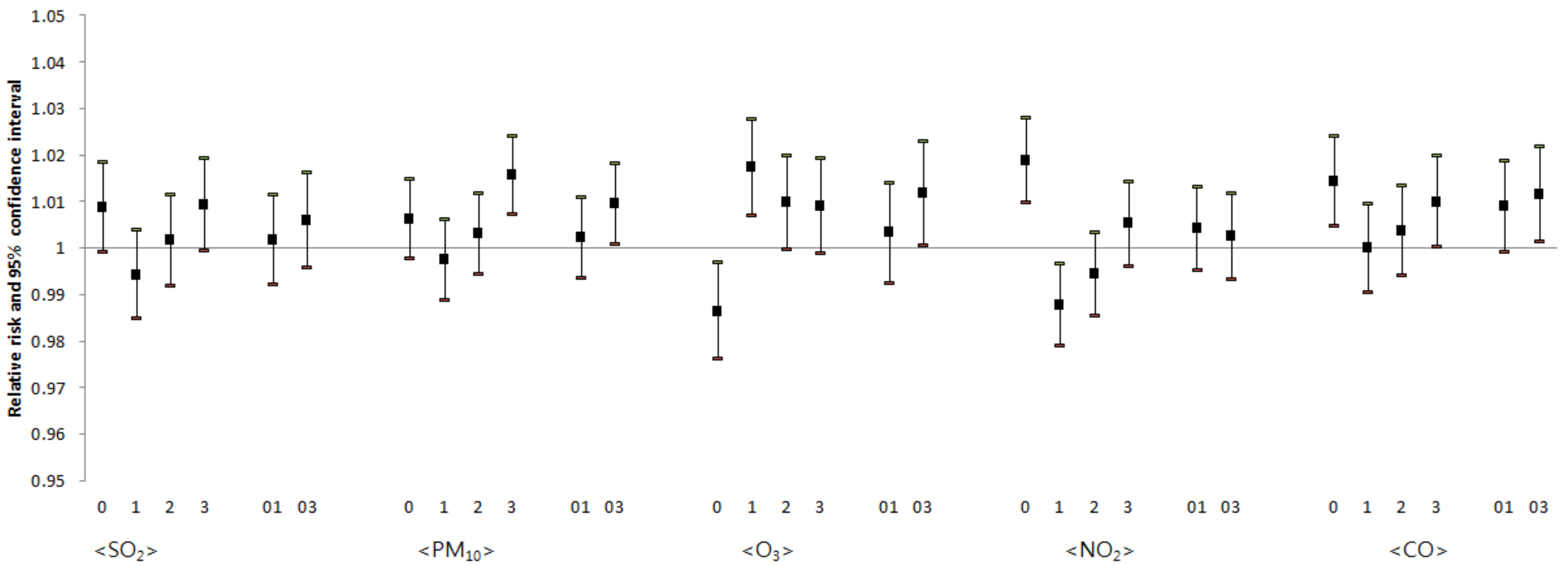
Table 4. Adjusted relative risks (RR) and their 95% confidence intervals in men

	Lag0	Lag1	Lag2	Lag3	*Lag0-1	Lag0-3
Any stroke						
SO_2	1.009 (0.999 1.018)	0.994 (0.985 1.004)	1.002 (0.992 1.011)	1.009 (1.000 1.019)	1.002 (0.992 1.011)	1.006 (0.996 1.016)
PM_{10}	1.006 (0.998 1.015)	0.997 (0.989 1.006)	1.003 (0.995 1.012)	1.016 (1.007 1.024)	1.002 (0.993 1.011)	1.010 (1.001 1.018)
O_3	0.986 (0.976 0.997)	1.017 (1.007 1.028)	1.010 (1.000 1.020)	1.009 (0.999 1.019)	1.003 (0.993 1.014)	1.012 (1.001 1.023)
NO_2	1.019 (1.010 1.028)	0.988 (0.979 0.997)	0.994 (0.986 1.003)	1.005 (0.996 1.014)	1.004 (0.995 1.013)	1.003 (0.993 1.012)
CO	1.014 (1.005 1.024)	1.000 (0.991 1.010)	1.004 (0.994 1.013)	1.010 (1.000 1.020)	1.009 (0.999 1.019)	1.012 (1.001 1.022)
Hemorrhagic stroke						
SO_2	1.001 (0.984 1.018)	1.000 (0.983 1.017)	1.006 (0.988 1.024)	1.008 (0.990 1.026)	1.000 (0.983 1.018)	1.006 (0.987 1.025)
PM_{10}	1.009 (0.994 1.025)	1.004 (0.988 1.020)	1.009 (0.994 1.025)	1.009 (0.993 1.025)	1.008 (0.992 1.024)	1.013 (0.997 1.029)
O_3	0.990 (0.971 1.010)	1.002 (0.983 1.021)	0.999 (0.980 1.018)	1.009 (0.990 1.028)	0.995 (0.975 1.015)	1.000 (0.980 1.021)
NO_2	1.019 (1.002 1.036)	1.007 (0.991 1.024)	1.001 (0.984 1.017)	1.002 (0.985 1.019)	1.016 (1.000 1.033)	1.011 (0.994 1.028)
CO	1.015 (0.998 1.033)	1.018 (1.000 1.036)	1.008 (0.991 1.026)	1.005 (0.988 1.023)	1.020 (1.002 1.038)	1.017 (0.999 1.036)
Ischemic stroke						
SO_2	1.013 (1.001 1.025)	0.992 (0.980 1.004)	1.001 (0.989 1.014)	1.010 (0.997 1.023)	1.002 (0.990 1.015)	1.006 (0.993 1.019)
PM_{10}	1.003 (0.992 1.014)	0.995 (0.984 1.006)	1.001 (0.990 1.012)	1.017 (1.007 1.028)	0.998 (0.987 1.010)	1.007 (0.996 1.018)
O_3	0.988 (0.975 1.001)	1.022 (1.009 1.035)	1.014 (1.001 1.026)	1.008 (0.996 1.021)	1.007 (0.994 1.021)	1.016 (1.002 1.030)
NO_2	1.017 (1.006 1.029)	0.979 (0.968 0.990)	0.993 (0.982 1.005)	1.007 (0.996 1.019)	0.997 (0.986 1.009)	0.999 (0.987 1.010)
CO	1.012 (1.000 1.024)	0.991 (0.979 1.003)	1.002 (0.990 1.014)	1.011 (0.999 1.024)	1.001 (0.989 1.014)	1.007 (0.994 1.020)

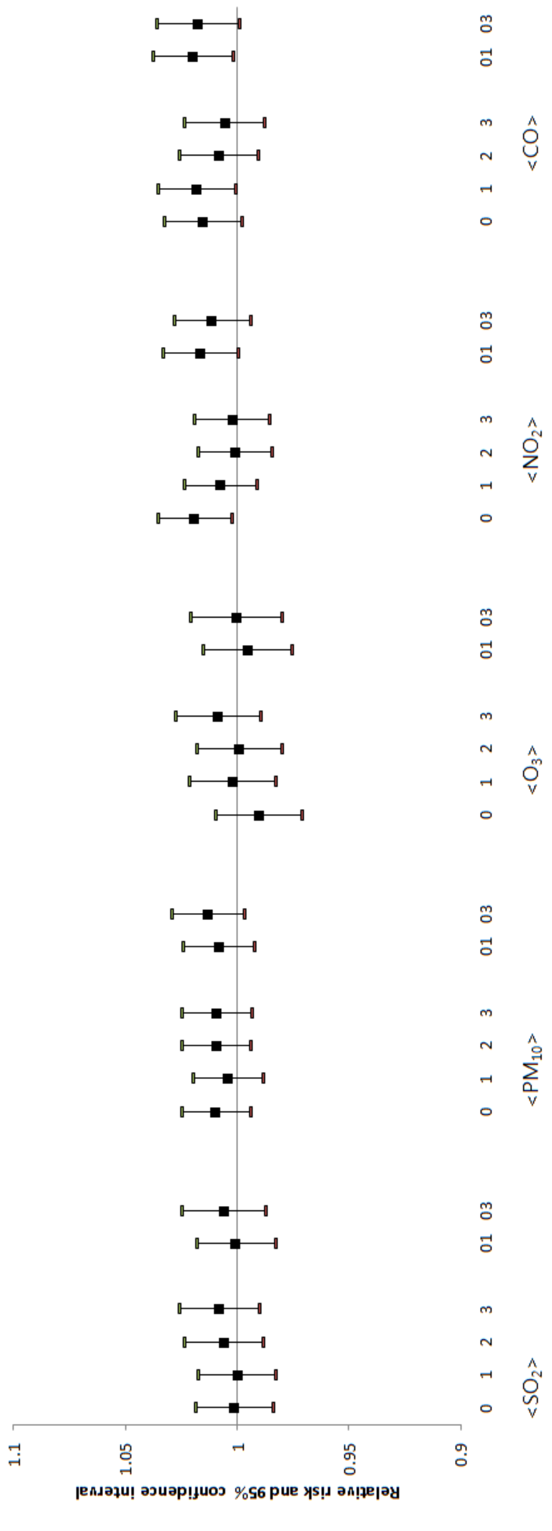
* Cumulative lag model

Figure 2. Adjusted relative risks per increment in one standard deviation of air pollutants using single lag and cumulative lag models in men

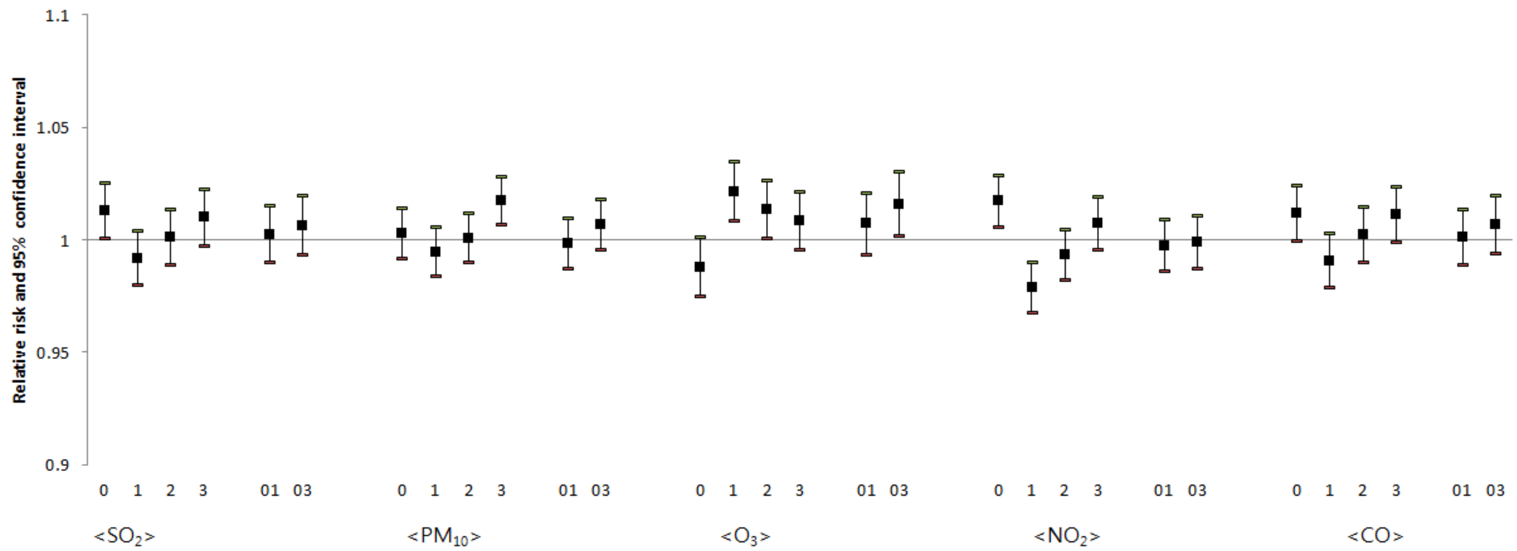
a) Any strokes



b) Hemorrhagic stroke



c) Ischemic stroke



5. Air pollutants and ED visits for stroke in women

The relative risks of emergency department visits for any strokes in women are shown in Table 5. In single lag models, the positive correlations were estimated in O_3 in lag1 (RR=1.018; 95% CI, 1.007-1.030), NO_2 in lag0 (RR=1.015; 95% CI, 1.005-1.025) and CO in lag0 (RR=1.011; 95% CI, 1.001-1.021) and there was no significant correlation in cumulative lag models. In hemorrhagic stroke, there was also no statistically significant result in the both lag models. Likewise, the trends of relative risk with each pollutant on multiple lag days in women were depicted in Figure 3.

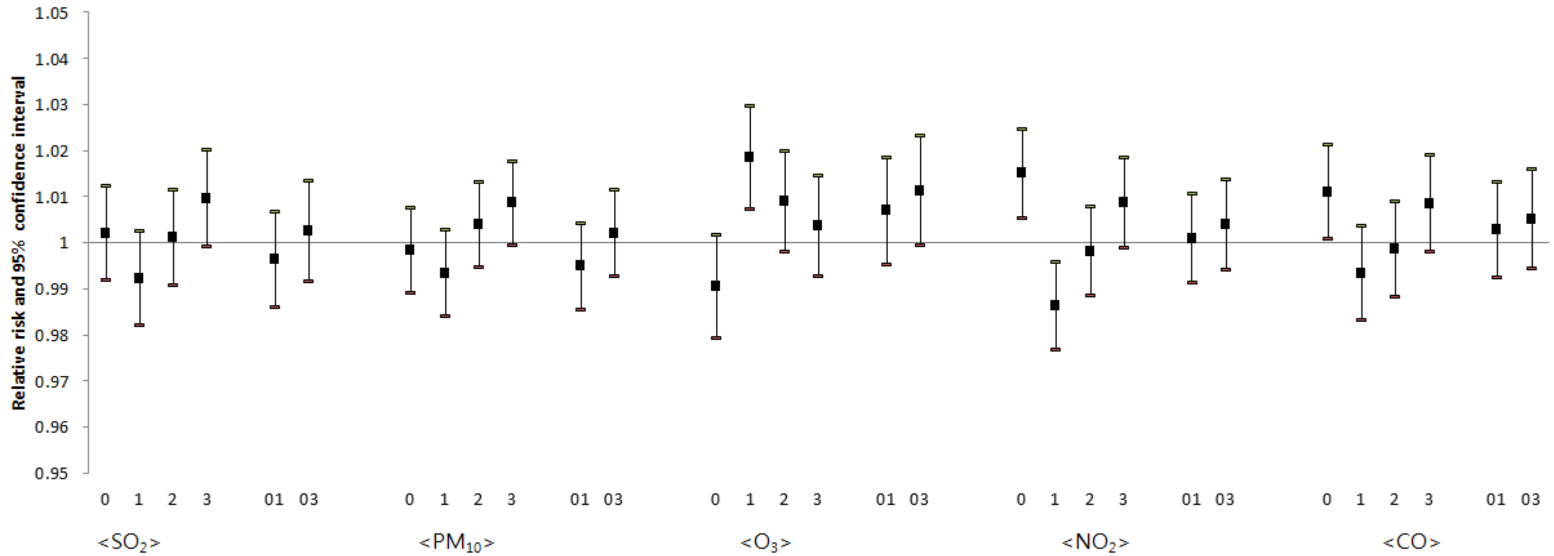
Table 5. Adjusted relative risks (RR) and their 95% confidence intervals in women

	Lag0	Lag1	Lag2	Lag3	*Lag0-1	Lag0-3
Any stroke						
SO_2	1.002 (0.992 1.012)	0.992 (0.982 1.002)	1.001 (0.991 1.011)	1.010 (0.999 1.020)	0.996 (0.986 1.007)	1.002 (0.992 1.013)
PM_{10}	0.998 (0.989 1.008)	0.993 (0.984 1.003)	1.004 (0.995 1.013)	1.009 (0.999 1.018)	0.995 (0.986 1.004)	1.002 (0.993 1.012)
O_3	0.990 (0.979 1.002)	1.018 (1.007 1.030)	1.009 (0.998 1.020)	1.004 (0.993 1.015)	1.007 (0.995 1.019)	1.011 (0.999 1.023)
NO_2	1.015 (1.005 1.025)	0.986 (0.977 0.996)	0.998 (0.989 1.008)	1.009 (0.999 1.018)	1.001 (0.991 1.011)	1.004 (0.994 1.014)
CO	1.011 (1.001 1.021)	0.993 (0.983 1.004)	0.999 (0.988 1.009)	1.008 (0.998 1.019)	1.003 (0.992 1.013)	1.005 (0.994 1.016)
Hemorrhagic stroke						
SO_2	0.970 (0.952 0.988)	0.967 (0.949 0.985)	0.989 (0.971 1.008)	1.018 (0.999 1.037)	0.963 (0.945 0.981)	0.979 (0.960 0.999)
PM_{10}	0.980 (0.963 0.998)	0.976 (0.959 0.994)	0.996 (0.979 1.013)	1.013 (0.997 1.030)	0.974 (0.957 0.992)	0.987 (0.970 1.005)
O_3	1.003 (0.983 1.024)	1.019 (0.998 1.040)	0.994 (0.974 1.014)	1.011 (0.991 1.032)	1.016 (0.994 1.037)	1.012 (0.991 1.034)
NO_2	0.996 (0.978 1.013)	0.983 (0.966 1.000)	0.999 (0.982 1.017)	1.011 (0.993 1.029)	0.987 (0.970 1.004)	0.996 (0.979 1.014)
CO	0.984 (0.966 1.002)	0.978 (0.960 0.996)	0.985 (0.967 1.004)	1.006 (0.987 1.025)	0.977 (0.959 0.996)	0.983 (0.965 1.002)
Ischemic stroke						
SO_2	1.010 (0.996 1.023)	0.999 (0.986 1.013)	1.001 (0.988 1.015)	0.997 (0.983 1.011)	1.005 (0.992 1.019)	1.003 (0.989 1.018)
PM_{10}	1.001 (0.989 1.014)	1.000 (0.988 1.013)	1.005 (0.993 1.017)	1.005 (0.993 1.017)	1.001 (0.989 1.013)	1.005 (0.993 1.018)
O_3	0.993 (0.978 1.008)	1.025 (1.010 1.039)	1.027 (1.012 1.041)	1.012 (0.997 1.026)	1.013 (0.998 1.029)	1.030 (1.014 1.046)
NO_2	1.019 (1.006 1.031)	0.987 (0.975 1.000)	0.991 (0.979 1.004)	1.001 (0.989 1.014)	1.004 (0.991 1.017)	0.999 (0.986 1.012)
CO	1.017 (1.003 1.031)	0.996 (0.982 1.009)	0.996 (0.983 1.010)	1.003 (0.989 1.017)	1.008 (0.995 1.022)	1.005 (0.990 1.019)

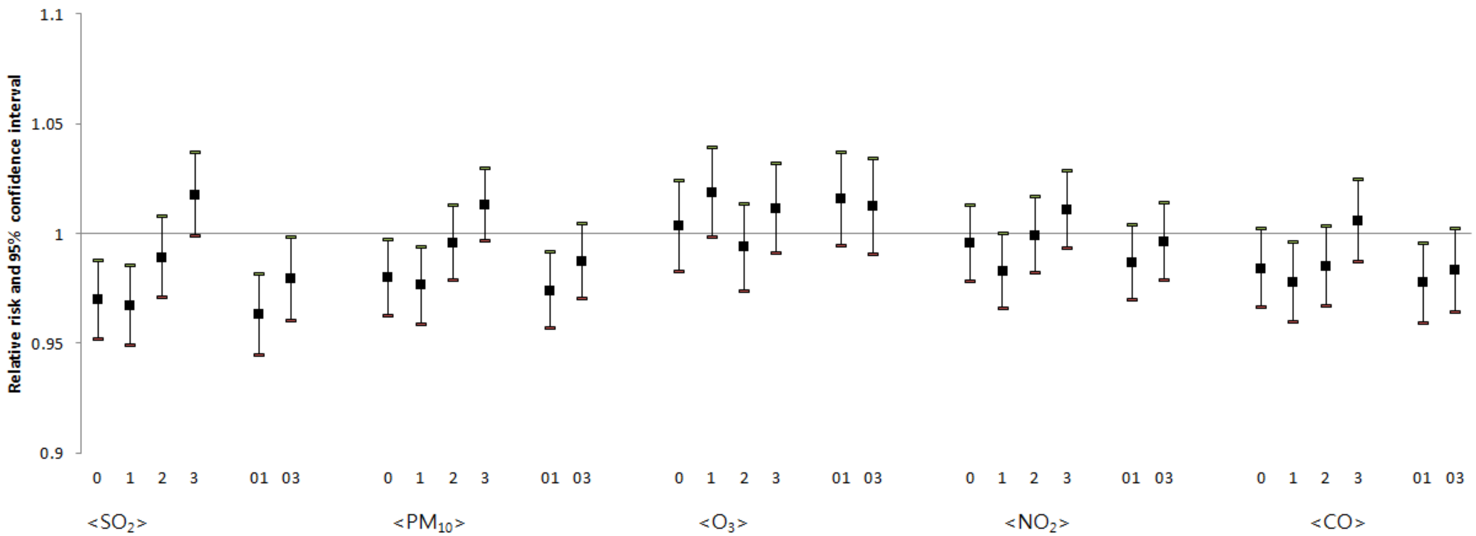
* Cumulative lag model

Figure 3. Adjusted relative risks per increment in one standard deviation of air pollutants using single lag and cumulative lag models in women

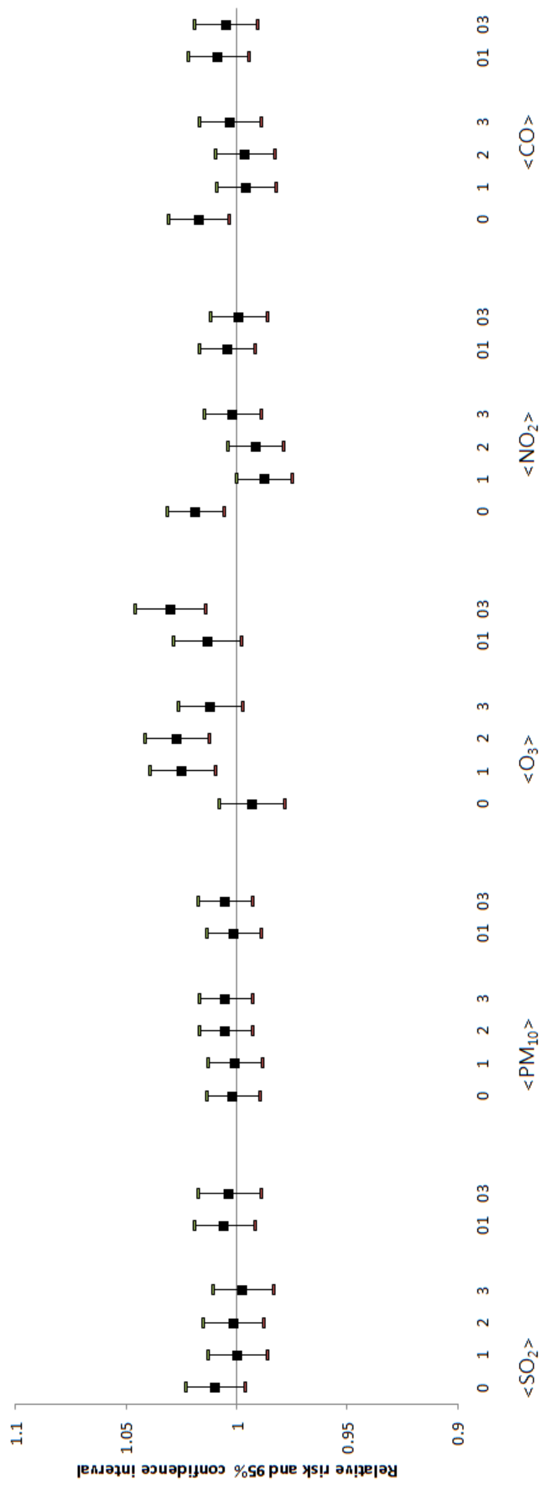
a) Any strokes



b) Hemorrhagic stroke



c) Ischemic stroke



6. Air pollutants and ED visits for stroke in less than 65 years of age

To explore the age difference, age stratification was conducted by 3 groups (less than 65, 65-79, 80 or greater) and the relative risks of emergency department visits for any strokes in youngest group are shown in Table 6. In single lag models, SO_2 in lag3 (RR=1.016; 95% CI, 1.004-1.029), PM_{10} in lag3 (RR=1.019; 95% CI, 1.009-1.030), O_3 in lag1 (RR=1.018; 95% CI, 1.005-1.031), NO_2 in lag0 (RR=1.017; 95% CI, 1.006-1.029) and lag3 (RR=1.014; 95% CI, 1.002-1.026) and CO in lag0 (RR=1.013; 95% CI, 1.001-1.025) were positively correlated with emergency department visits for any strokes. For hemorrhagic stroke, only SO_2 and PM_{10} showed significantly positive correlation in lag3 models (Figure 4).

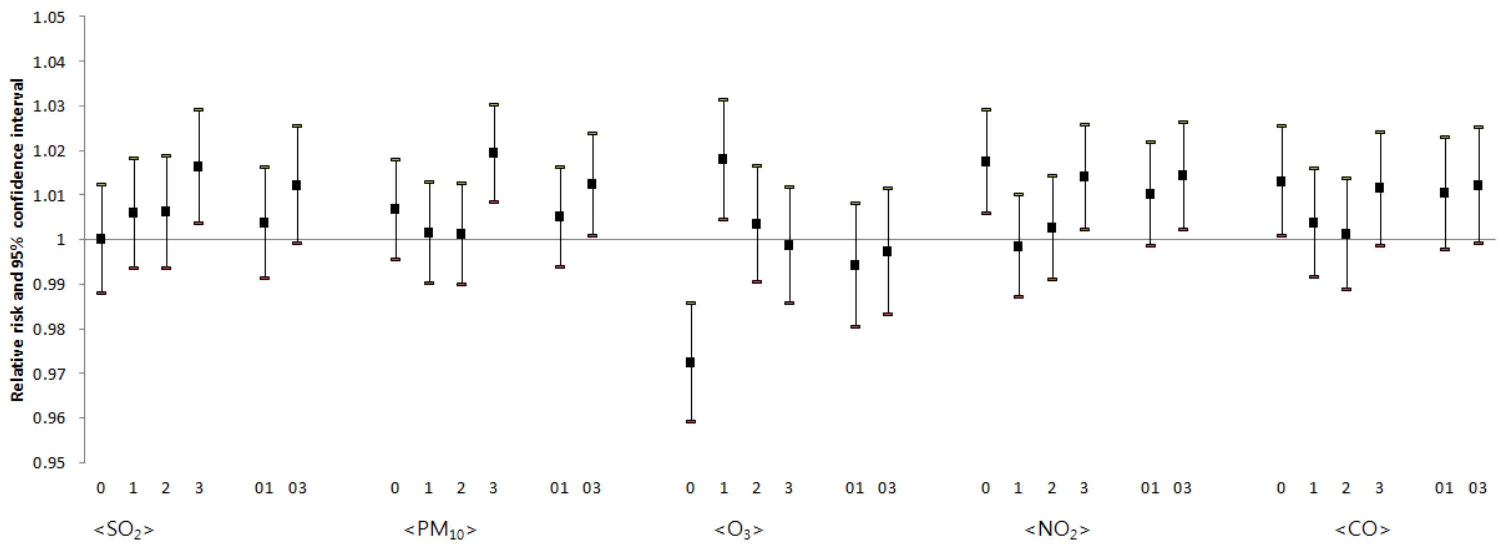
Table 6. Adjusted relative risks (RR) and their 95% confidence intervals in less than 65 years of age

	Lag0	Lag1	Lag2	Lag3	*Lag0-1	Lag0-3
Any stroke						
SO_2	1.000 (0.988 1.012)	1.006 (0.994 1.018)	1.006 (0.994 1.019)	1.016 (1.004 1.029)	1.004 (0.991 1.016)	1.012 (0.999 1.025)
PM_{10}	1.007 (0.996 1.018)	1.001 (0.990 1.013)	1.001 (0.990 1.013)	1.019 (1.009 1.030)	1.005 (0.994 1.016)	1.012 (1.001 1.024)
O_3	0.972 (0.959 0.986)	1.018 (1.005 1.031)	1.003 (0.991 1.017)	0.999 (0.986 1.012)	0.994 (0.980 1.008)	0.997 (0.983 1.012)
NO_2	1.017 (1.006 1.029)	0.998 (0.987 1.010)	1.003 (0.991 1.014)	1.014 (1.002 1.026)	1.010 (0.999 1.022)	1.014 (1.002 1.026)
CO	1.013 (1.001 1.025)	1.004 (0.992 1.016)	1.001 (0.989 1.014)	1.011 (0.999 1.024)	1.010 (0.998 1.023)	1.012 (0.999 1.025)
Hemorrhagic stroke						
SO_2	0.980 (0.962 0.998)	0.985 (0.967 1.003)	1.004 (0.985 1.023)	1.023 (1.004 1.042)	0.979 (0.960 0.997)	0.998 (0.978 1.018)
PM_{10}	0.996 (0.980 1.013)	0.993 (0.976 1.011)	1.000 (0.983 1.018)	1.018 (1.002 1.034)	0.994 (0.977 1.011)	1.004 (0.987 1.021)
O_3	0.980 (0.960 1.000)	1.004 (0.984 1.025)	0.986 (0.966 1.006)	1.008 (0.988 1.028)	0.990 (0.969 1.011)	0.990 (0.969 1.012)
NO_2	1.008 (0.991 1.026)	1.002 (0.985 1.019)	1.004 (0.986 1.021)	1.014 (0.996 1.032)	1.006 (0.989 1.024)	1.012 (0.994 1.030)
CO	1.001 (0.983 1.020)	0.998 (0.980 1.016)	0.999 (0.981 1.018)	1.011 (0.992 1.030)	0.999 (0.981 1.018)	1.004 (0.985 1.024)
Ischemic stroke						
SO_2	1.002 (0.983 1.020)	1.017 (0.998 1.036)	1.003 (0.985 1.023)	1.011 (0.992 1.030)	1.012 (0.993 1.031)	1.014 (0.994 1.034)
PM_{10}	1.004 (0.987 1.021)	1.006 (0.990 1.023)	1.000 (0.983 1.017)	1.025 (1.009 1.041)	1.006 (0.989 1.024)	1.015 (0.998 1.032)
O_3	0.961 (0.942 0.981)	1.032 (1.012 1.052)	1.029 (1.010 1.049)	1.001 (0.982 1.021)	0.997 (0.976 1.018)	1.014 (0.993 1.036)
NO_2	1.021 (1.004 1.039)	0.995 (0.978 1.012)	0.997 (0.980 1.014)	1.010 (0.993 1.028)	1.010 (0.993 1.028)	1.010 (0.992 1.028)
CO	1.014 (0.996 1.033)	1.000 (0.981 1.018)	0.993 (0.975 1.012)	1.011 (0.992 1.031)	1.009 (0.990 1.028)	1.008 (0.988 1.028)

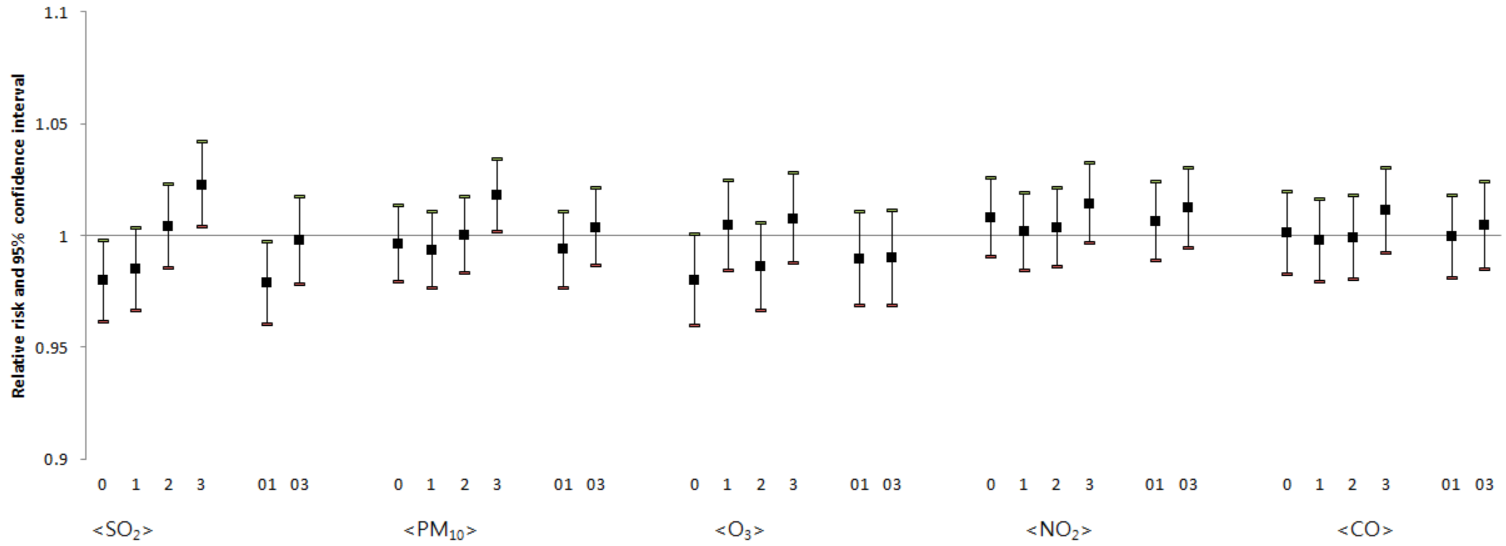
* Cumulative lag model

Figure 4. Adjusted relative risks per increment in one standard deviation of air pollutants using single lag and cumulative lag models in age<65

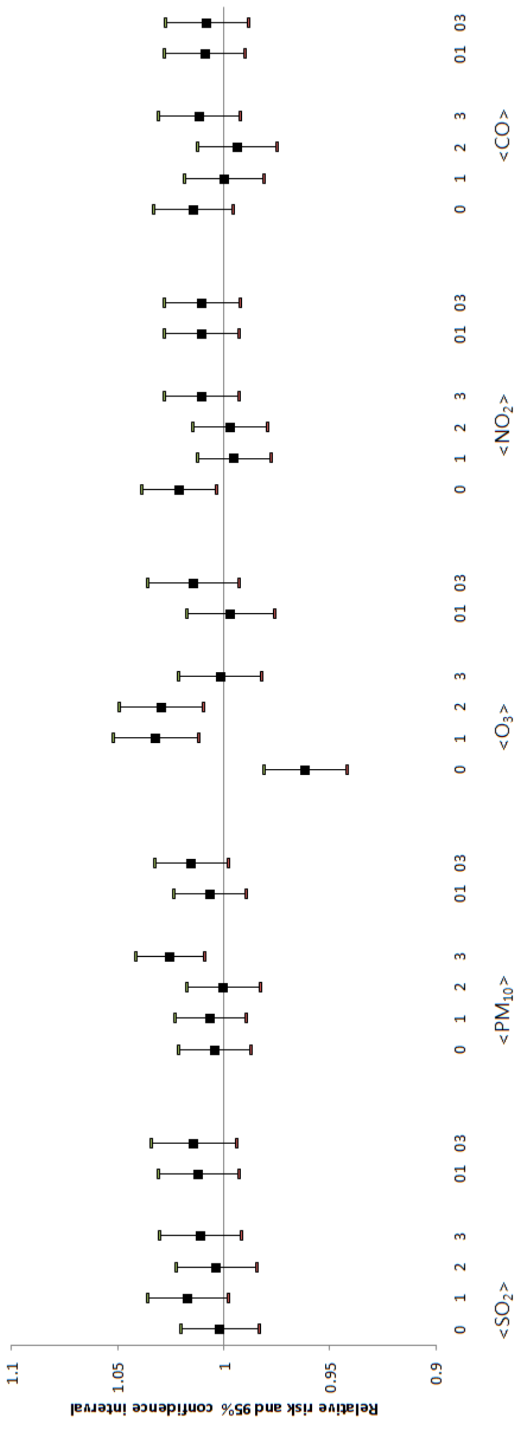
a) Any strokes



b) Hemorrhagic stroke



c) Ischemic stroke



7. Air pollutants and ED visits for stroke in 65 to 79 years of age

The relative risks of emergency department visits for any strokes in 65 to 79 years of age group are shown in Table 7. In single lag models, SO_2 in lag0 (RR=1.014; 95% CI, 1.003-1.025), O_3 in lag1 (RR=1.014; 95% CI, 1.002-1.026), NO_2 in lag0 (RR=1.017; 95% CI, 1.007-1.028) and CO in lag0 (RR=1.014; 95% CI, 1.003-1.025) were positively correlated with emergency department visits for any strokes. In general, similar patterns of relative risk were shown for ischemic stroke and there was no significantly positive correlation for hemorrhagic stroke in the both lag models (Figure 5).

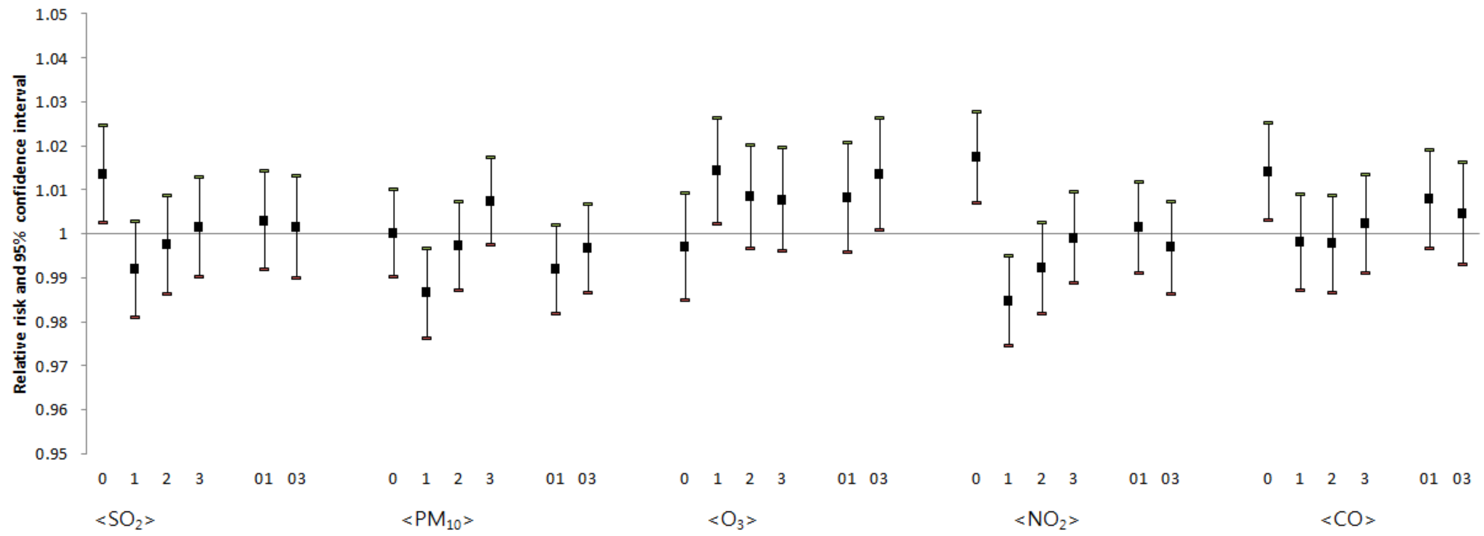
Table 7. Adjusted relative risks (RR) and their 95% confidence intervals in age 65-79 year group

	Lag0	Lag1	Lag2	Lag3	*Lag0-1	Lag0-3
Any stroke						
SO_2	1.014 (1.003 1.025)	0.992 (0.981 1.003)	0.997 (0.986 1.009)	1.002 (0.990 1.013)	1.003 (0.992 1.014)	1.002 (0.990 1.013)
PM_{10}	1.000 (0.990 1.010)	0.987 (0.976 0.997)	0.997 (0.987 1.007)	1.007 (0.998 1.017)	0.992 (0.982 1.002)	0.997 (0.987 1.007)
O_3	0.997 (0.985 1.009)	1.014 (1.002 1.026)	1.008 (0.997 1.020)	1.008 (0.996 1.020)	1.008 (0.996 1.021)	1.014 (1.001 1.026)
NO_2	1.017 (1.007 1.028)	0.985 (0.975 0.995)	0.992 (0.982 1.003)	0.999 (0.989 1.010)	1.001 (0.991 1.012)	0.997 (0.986 1.007)
CO	1.014 (1.003 1.025)	0.998 (0.987 1.009)	0.998 (0.987 1.009)	1.002 (0.991 1.014)	1.008 (0.997 1.019)	1.005 (0.993 1.016)
Hemorrhagic stroke						
SO_2	0.990 (0.969 1.012)	0.991 (0.970 1.013)	0.994 (0.972 1.016)	1.001 (0.979 1.024)	0.988 (0.967 1.010)	0.990 (0.968 1.013)
PM_{10}	0.991 (0.971 1.012)	0.984 (0.964 1.005)	1.001 (0.982 1.021)	1.002 (0.982 1.022)	0.985 (0.965 1.006)	0.992 (0.972 1.012)
O_3	1.009 (0.985 1.034)	1.002 (0.978 1.026)	0.995 (0.972 1.018)	1.011 (0.987 1.035)	1.007 (0.982 1.032)	1.007 (0.981 1.033)
NO_2	1.005 (0.985 1.026)	0.994 (0.974 1.014)	0.994 (0.974 1.015)	0.987 (0.967 1.008)	0.999 (0.979 1.020)	0.992 (0.972 1.013)
CO	0.994 (0.973 1.015)	0.998 (0.977 1.020)	0.986 (0.964 1.007)	0.989 (0.967 1.011)	0.995 (0.974 1.017)	0.987 (0.965 1.010)
Ischemic stroke						
SO_2	1.024 (1.010 1.037)	0.993 (0.980 1.007)	0.996 (0.982 1.010)	0.995 (0.981 1.009)	1.010 (0.996 1.024)	1.002 (0.988 1.017)
PM_{10}	1.004 (0.992 1.016)	0.989 (0.976 1.001)	0.993 (0.981 1.006)	1.004 (0.992 1.016)	0.996 (0.983 1.008)	0.996 (0.983 1.008)
O_3	0.998 (0.983 1.013)	1.018 (1.004 1.033)	1.012 (0.998 1.026)	1.007 (0.992 1.021)	1.012 (0.996 1.027)	1.017 (1.002 1.033)
NO_2	1.019 (1.006 1.032)	0.982 (0.969 0.994)	0.989 (0.977 1.002)	1.001 (0.988 1.014)	1.001 (0.988 1.013)	0.996 (0.983 1.009)
CO	1.022 (1.008 1.036)	0.998 (0.984 1.012)	1.000 (0.986 1.014)	1.003 (0.989 1.017)	1.012 (0.998 1.026)	1.009 (0.994 1.023)

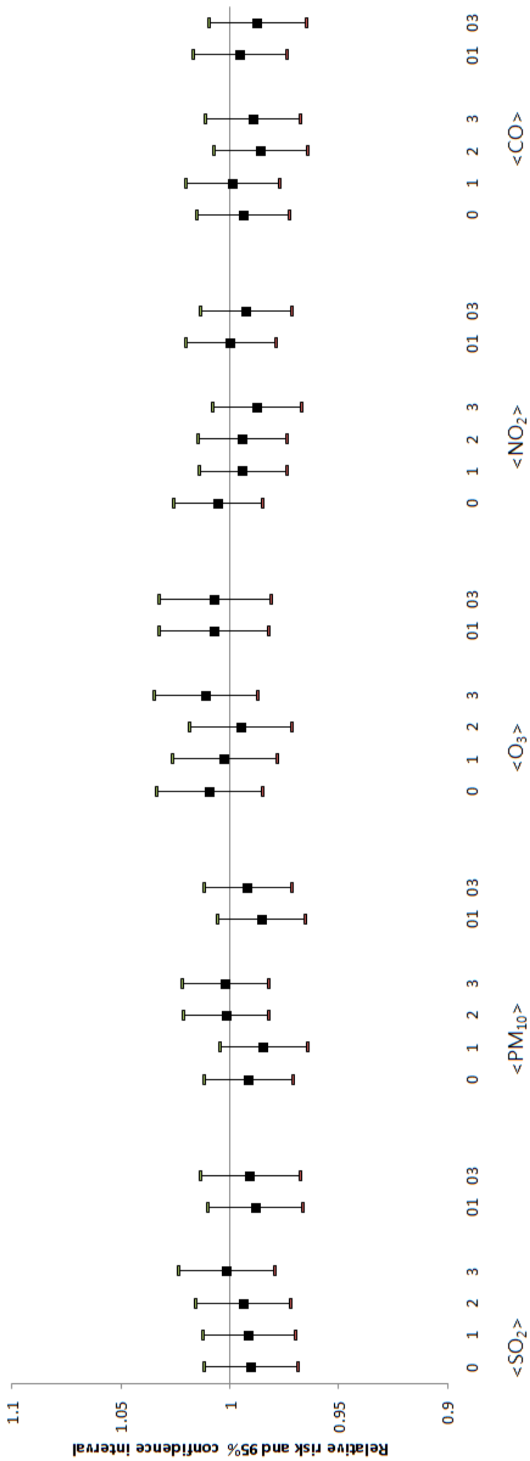
* Cumulative lag model

Figure 5. Adjusted relative risks per increment in one standard deviation of air pollutants using single lag and cumulative lag models in age 65-79

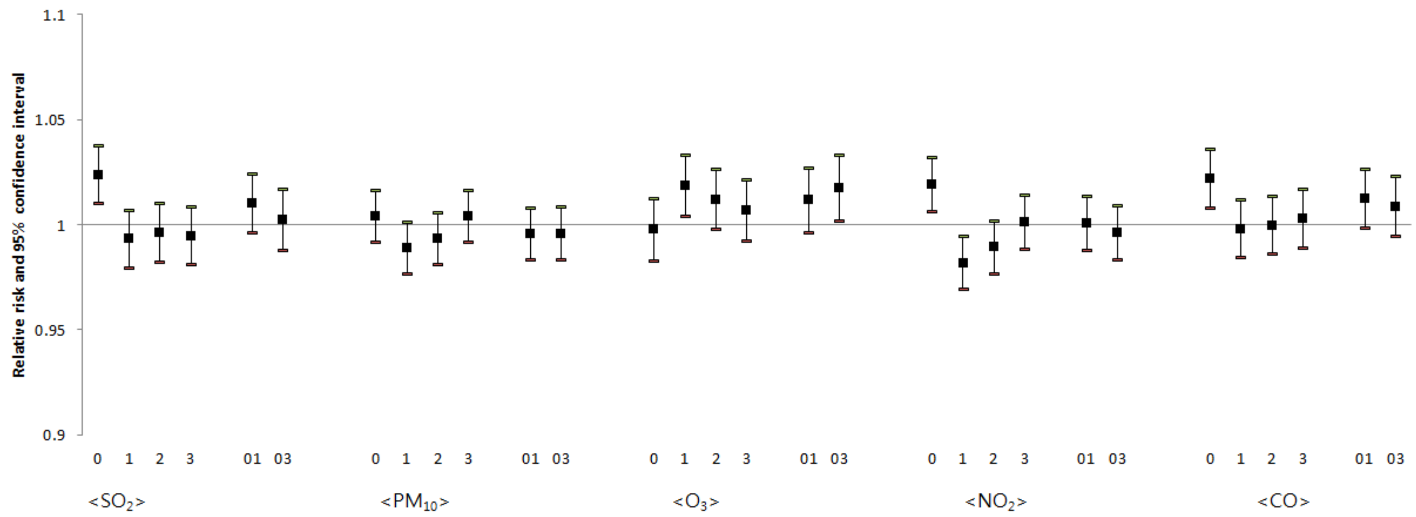
a) Any strokes



b) Hemorrhagic stroke



c) Ischemic stroke



8. Air pollutants and ED visits for stroke in greater than 79 years of age

In Table 8, the relative risks of emergency department visits for any strokes in oldest group are shown. In single lag models, SO_2 in lag3 (RR=1.014; 95% CI, 1.000-1.028), PM_{10} in lag2 (RR=1.015; 95% CI, 1.003-1.026) and lag3 (RR=1.012; 95% CI, 1.000-1.023), O_3 in lag1 (RR=1.025; 95% CI, 1.011-1.040), lag2 (RR=1.020; 95% CI, 1.006-1.034) and lag3 (RR=1.017; 95% CI, 1.002-1.031), NO_2 in lag0 (RR=1.016; 95% CI, 1.003-1.028) and CO in lag3 (RR=1.017; 95% CI, 1.004-1.031) were positively correlated with emergency department visits for any strokes. In contrast to other age groups, significantly positive correlation was found in O_3 in lag1 (RR=1.044; 95% CI, 1.011-1.077) and all cumulative lag models for hemorrhagic stroke (Figure 6).

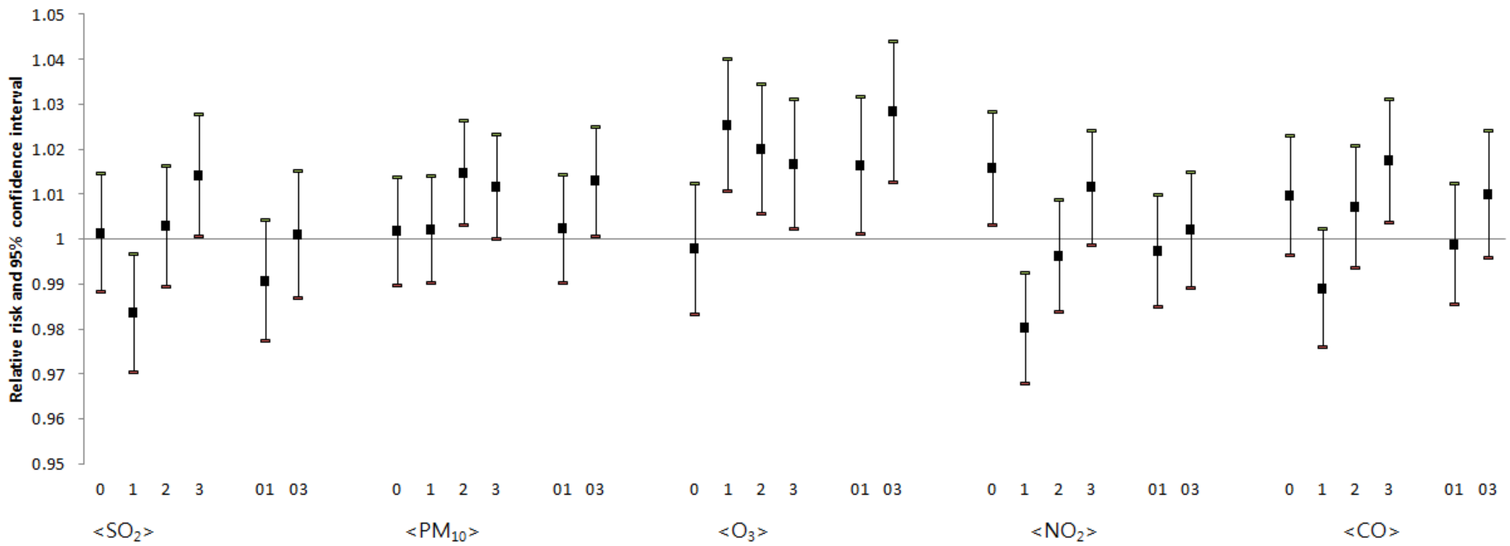
Table 8. Adjusted relative risks (RR) and their 95% confidence intervals in age 80 or greater year group

	Lag0	Lag1	Lag2	Lag3	*Lag0-1	Lag0-3
Any stroke						
SO_2	1.001 (0.988 1.015)	0.983 (0.970 0.997)	1.003 (0.989 1.016)	1.014 (1.000 1.028)	0.991 (0.977 1.004)	1.001 (0.987 1.015)
PM_{10}	1.002 (0.990 1.014)	1.002 (0.990 1.014)	1.015 (1.003 1.026)	1.012 (1.000 1.023)	1.002 (0.990 1.014)	1.013 (1.001 1.025)
O_3	0.998 (0.983 1.012)	1.025 (1.011 1.040)	1.020 (1.006 1.034)	1.017 (1.002 1.031)	1.016 (1.001 1.032)	1.028 (1.013 1.044)
NO_2	1.016 (1.003 1.028)	0.980 (0.968 0.992)	0.996 (0.984 1.009)	1.011 (0.999 1.024)	0.997 (0.985 1.010)	1.002 (0.989 1.015)
CO	1.010 (0.996 1.023)	0.989 (0.976 1.002)	1.007 (0.994 1.021)	1.017 (1.004 1.031)	0.999 (0.985 1.012)	1.010 (0.996 1.024)
Hemorrhagic stroke						
SO_2	0.997 (0.969 1.026)	0.974 (0.946 1.003)	0.995 (0.967 1.025)	1.015 (0.985 1.045)	0.982 (0.954 1.012)	0.993 (0.963 1.024)
PM_{10}	1.007 (0.981 1.033)	1.002 (0.976 1.029)	1.015 (0.989 1.041)	1.014 (0.990 1.040)	1.005 (0.979 1.032)	1.016 (0.989 1.043)
O_3	1.015 (0.983 1.049)	1.044 (1.011 1.077)	1.028 (0.996 1.061)	1.019 (0.987 1.052)	1.040 (1.006 1.075)	1.045 (1.010 1.082)
NO_2	1.017 (0.990 1.045)	0.987 (0.961 1.015)	1.004 (0.977 1.032)	1.023 (0.995 1.051)	1.003 (0.975 1.031)	1.013 (0.985 1.042)
CO	1.014 (0.986 1.044)	1.005 (0.976 1.034)	1.014 (0.986 1.044)	1.024 (0.995 1.054)	1.011 (0.982 1.041)	1.022 (0.992 1.053)
Ischemic stroke						
SO_2	1.002 (0.987 1.018)	0.986 (0.970 1.002)	1.008 (0.992 1.024)	1.014 (0.997 1.030)	0.993 (0.977 1.009)	1.005 (0.988 1.022)
PM_{10}	1.000 (0.985 1.014)	1.003 (0.989 1.017)	1.017 (1.003 1.030)	1.013 (1.000 1.027)	1.002 (0.987 1.016)	1.014 (1.000 1.028)
O_3	1.004 (0.986 1.021)	1.023 (1.005 1.040)	1.023 (1.006 1.040)	1.021 (1.004 1.038)	1.018 (1.000 1.036)	1.033 (1.014 1.052)
NO_2	1.014 (0.999 1.029)	0.979 (0.965 0.994)	0.996 (0.981 1.011)	1.007 (0.992 1.022)	0.996 (0.981 1.011)	0.999 (0.984 1.014)
CO	1.004 (0.988 1.020)	0.984 (0.969 1.000)	1.005 (0.989 1.021)	1.012 (0.995 1.028)	0.993 (0.977 1.009)	1.003 (0.986 1.020)

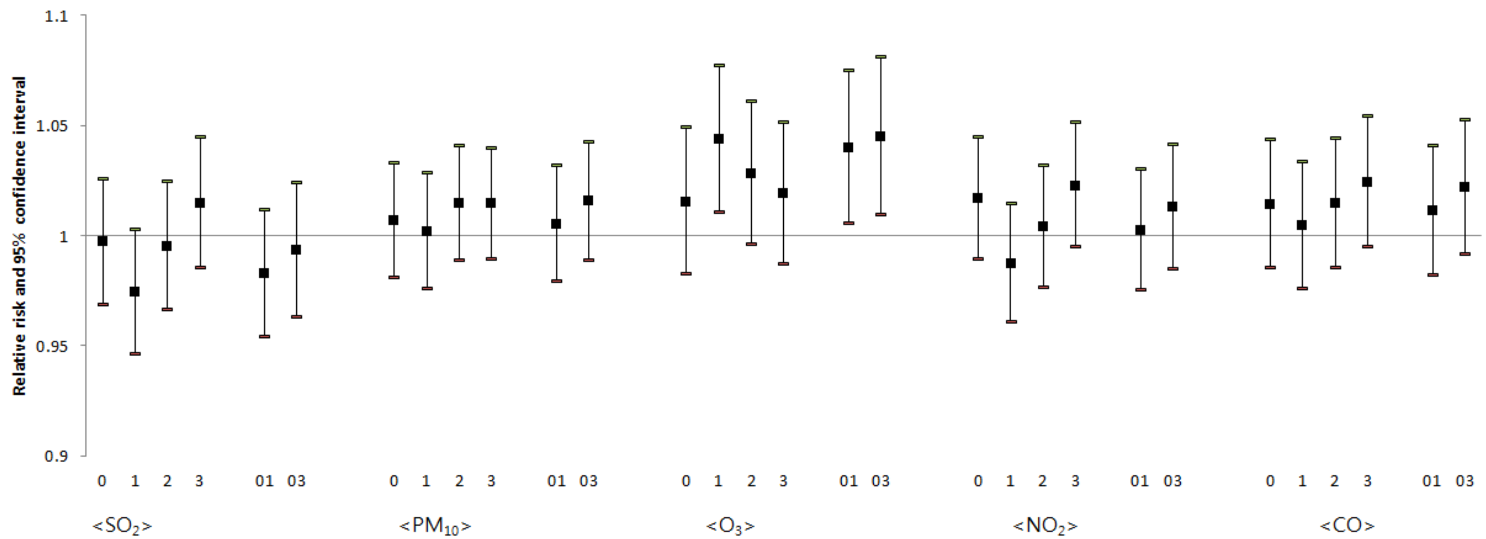
* Cumulative lag model

Figure 6. Adjusted relative risks per increment in one standard deviation of air pollutants using single lag and cumulative lag models in age>79

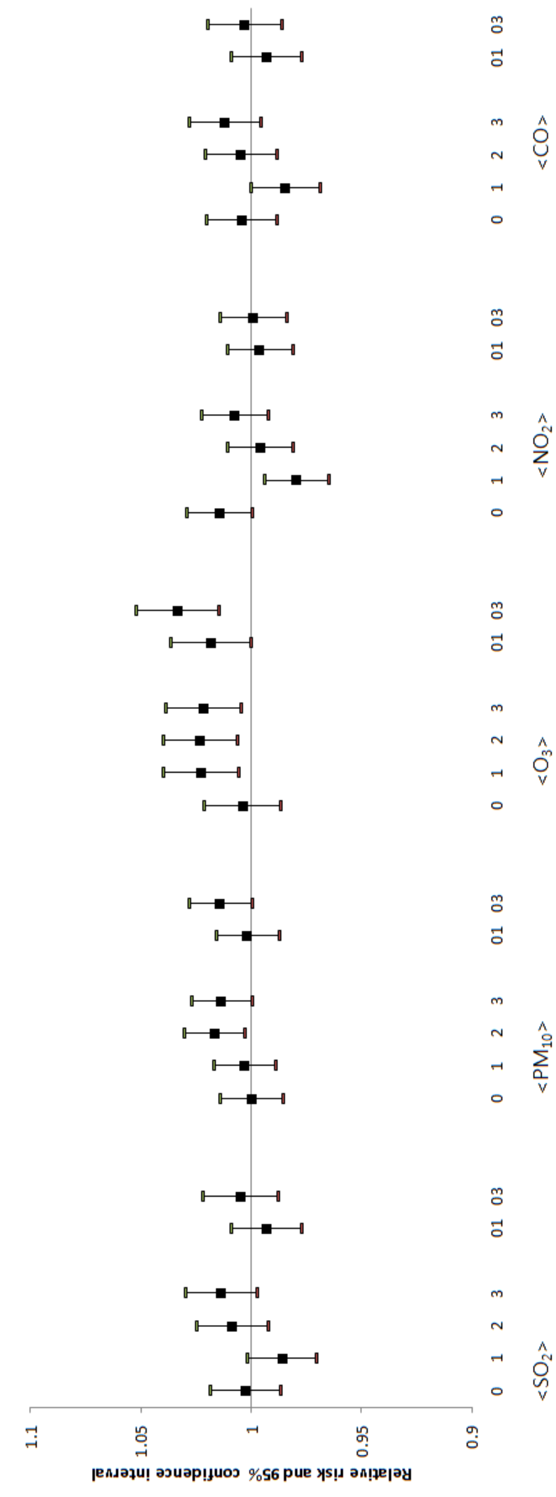
a) Any strokes



b) Hemorrhagic stroke



c) Ischemic stroke



V. DISCUSSION

We investigated short-term effects of air pollution on emergency department visits for stroke in Seoul, Republic of Korea. The major findings in this study are converged into the following: 1) the correlation of air pollutants with emergency department for any strokes; and 2) the correlation of air pollution with emergency department visits for hemorrhagic stroke in elderly (80 years of age or greater) group.

1. Air pollution and stroke (including hemorrhagic and ischemic stroke)

First, we found that ambient air pollutants including ozone are positively correlated with emergency department visits for any strokes on not only the same day, but multiple lag days. This finding is consistent with the results of other studies reporting an association between O_3 concentration and stroke occurrence. Previous study reported an estimated increase of 2.9% (95% CI; 0.3 to 5.5%) and 6% (95% CI; 2 to 10%) in stroke mortality for each interquartile range increase in O_3 concentrations respectively with 0-day lag and 3-day lag in Seoul, Republic of Korea (Hong et al. 2002a). With a case-crossover design, a positive association was reported between ischemic stroke hospital admissions and O_3 (OR 1.15, 95% CI 1.07 to 1.23) in the single-pollutant models (Tsai et al. 2003). Emergency admissions for cerebrovascular diseases among adults were positively associated with increasing air pollution levels of O_3 lagged 0 days in Taipei, Taiwan (Chan et al. 2006). Also, a French study reports an association between atherosclerotic diseases including myocardial infarction and O_3 pollution with 0-day lag and 1-day lag (Ruidavets et al. 2005).

Some pathophysiological hypotheses can explain our findings. Several studies have been suggested that there are possible associations between atherosclerotic disease and pollutants (Brook et al. 2004). Our findings might be explained by experimental data similar to the cardiovascular effects. Brook et al found that short-term inhalation of O_3 and particulate matter at concentrations in the urban environment might cause acute artery vasoconstriction in even healthy adults (Brook et al. 2002). This vasoconstrictor effects might trigger rupture of unstable atherosclerosis plaque and induce obstruction in artery, consequently causing ischemic stroke. Experimental data also show ozone inhalation can induce epithelial injury with acute inflammatory response in upper and lower airways (Kelly 2003). Oxidative stress exists with an excess of free radicals over antioxidant defense mechanisms. As a consequence, free radicals and other cell components lead to tissue injury and influx of inflammatory cells to injury sites (Kelly 2003). Several authors also suggest that, following air pollutant exposure, delayed indirect effects (several hours to days) mediated through pulmonary oxidative stress and systemic inflammatory response may occur (Brook et al. 2004). Moreover following activation of those biological processes, delayed indirect effects occur, which may also ultimately activate a thrombotic phenomenon or induce rupture of unstable atherosclerosis plaque (Brook et al. 2004). However, all these inferences mainly rely on the experimental data, so there should be further studies on biological mechanisms.

2. Air pollution and hemorrhagic stroke in elderly group

Our study further demonstrated that emergency department visits of different age groups for hemorrhagic stroke varied in their susceptibility to the effects of ozone. We found that ozone concentration was positively associated with hemorrhagic stroke emergency department visits among patients aged 81 years or older. In the single lag model, the relative risk of emergency department visits for hemorrhagic stroke increased by 4.4% as O_3 increased by 10.04 ppb. In cumulative lag models, the positive correlations between ozone and any strokes including hemorrhagic stroke were showed in the all lag models, lag 0-1 to lag 0-3, which is consistent with previous studies.

The earlier studies have suggested that the elderly with comorbid diseases was more susceptible to air pollution-related adverse health effects (Zanobetti et al. 2000, Hong et al. 2002a). The higher risk of ischemic stroke was observed for the elderly (65- to 80-year age) group in a small-area level ecological study (Maheswaran et al. 2012). A combined analysis of acute exposure studies performed in European and North American cities found that higher proportions of older people in study populations were associated with increased air pollutants risk estimates (Katsouyanni et al. 2009).

These results suggest that older people may be more susceptible to adverse effects of pollution. A numerous potential explanations have been proposed for this vulnerability, including impaired homeostasis, altered immune response, and concurrent cardiorespiratory diseases (Sandstrom et al. 2003). Elderly individuals have been reported to show less marked acute phase responses, reduced cytotoxic cell activity, increased apoptosis and less systemic responses compared to younger people, which is likely that immune and inflammatory responses to air pollutants may be less appropriate to protect the elderly individual, consequently (Eilat et al. 1999). Another potential explanation may be that because atheroma formation is a chronic process and elderly people are less likely to move frequently, those living in polluted areas are more likely to have been exposed to activated atherosclerotic processes for longer periods of time. However, the association between air pollutants and hemorrhagic stroke in elderly people need further studies to explain the difference with other biologically plausible mechanisms.

3. Strength and limitation

Our study used national record data covering almost all Korean people, and air pollutants and meteorological data had no missing values during the entire study period. However, this study has several potential limitations. First, misclassification of the outcome is expected as a result of diagnostic or coding errors. However, these errors are likely unrelated to pollutant levels and are expected to reduce the precision of our estimates and potentially bias the relative risk toward the null. Similarly, we expect that the incidence of clinically unrecognized or non-hospitalized stroke is unrelated to pollutant levels after adjusting for meteorological covariates and month-of-year and day-of-week effects. Therefore, exclusion of these cases is expected to reduce the precision of our estimates but not otherwise bias our results. Second, the use of ambient rather than personal exposure measures is expected to result in exposure misclassification. However, this misclassification is expected to lead one to underestimate the relative risk (Zeger et al. 2000). Third, the date of symptom onset likely preceded the date of emergency department visit in a proportion of cases, leading to nondifferential exposure misclassification and bias of the relative risk toward the null. Fourth, residual confounding by short-term respiratory epidemics remains a possibility. However, the time-series generalized additive models used in this study have been shown to effectively control for confounding by time trends in both exposure and outcomes (Carracedo-Martinez et al. 2010). Finally, as an issue derived from the study design, we cannot establish the causal relationship, and we could only demonstrate the correlation. In spite of diminutive change of risks, previous epidemiological studies consistent with the present study and several studies related to biological mechanisms could support the relationships this study suggested and further studies will be needed to evaluate the effects of the various pollutants on cerebrovascular health.

VI. CONCLUSION

The present study suggested that ambient air pollutants were significantly correlated with emergency department visits for any strokes. The relative risk of hemorrhagic stroke was positively correlated with O_3 concentration only in elderly group, which suggest that old people are more sensitive to air pollution. However, these underlying biological mechanisms still need to be further studied.

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ABSTRACT (IN KOREAN)

대기오염과 뇌졸중으로 인한 응급실 방문

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손정우

서론: 대기오염은 최근 많은 역학 연구들에서 심혈관질환의 발생에 단기적인 영향을 미치는 것으로 밝혀진 바 있다. 대기오염과 뇌졸중의 관계 역시 최근 들어 많은 연구들이 보고되고 있으나, 그 결과는 일관적이지 않았다. 이번 연구는 대한민국 서울에서 대기오염이 미치는 급성 영향에 대한 것으로, 시계열 분석을 이용하여 대기오염과 뇌졸중으로 인한 응급실 방문의 연관성을 살펴보고자 한다.

방법: 연구 기간은 2005 년에서 2009 년까지의 5 년간으로, 응급실 방문 자료는 건강보험심사평가원을 통해 획득하였으며 연구에 포함된 SO_2, PM_{10}, O_3, NO_2, CO 등 5 개 대기오염 물질 자료는 환경부에서, 일일 평균 기온, 상대습도 등 기상자료는 기상청을 통해 확보하였다. 시계열 분석을 위해 포아송 분포를 가정한 일반화부가모형 (Generalized additive model)이 사용되었으며 방문 날짜, 일일 평균 온도 및 상대 습도는 3 차원 스플라인 (cubic spline) 변수로, 요일과 휴일은 모수적

(parametric) 변수로 각각 모형에 삽입하였다. 또한 출혈성 뇌졸중과 허혈성 뇌졸중은 발생기전이 상이하므로 하위 분류하여 추가 분석하였으며, 연령과 성별에 따른 연관성의 차이를 살펴보기 위하여 분석 대상을 연령과 성별로 층화하여 동일한 모형을 이용한 분석을 시행하였다. 모든 분석에서 시차 (time lag) 분석을 함께 시행하였으며 그 결과는 각 대기오염 물질 농도의 1 표준편차 증가 당 상대위험도 (relative risk)와 그 95% 신뢰구간 값으로 제시하였다.

결과: 뇌졸중으로 인한 전체 응급실 방문 건수는 총 94,539 건 이었다. 전체 1,826 일의 연구기간을 대상으로 시계열 분석을 시행한 결과 NO_2 12.04 ppb 증가당 응급실 내원의 상대위험도는 1.017 (95% 신뢰구간, 1.011-1.024), CO 0.24 ppm 증가당 상대위험도는 1.013 (1.006-1.020)로 유의한 관련성을 확인할 수 있었다. 또한, 고연령군에서 오존과 출혈성 뇌졸중의 유의한 관련성을 발견하였다.

고찰: 이번 연구에서 분석에 포함된 모든 대기오염물질이 뇌졸중에 대한 유의한 연관성을 보였으며, 고연령군 등 취약인구집단에서 출혈성 뇌졸중과의 유의한 연관성이 또한 확인되었다. 추후 대기오염에 대한 관리 정책 및 발생 기전과 관련한 추가적인 연구가 뒤따라야 할 것이다.

핵심 되는 말: 대기오염, 응급실, 뇌졸중