Association between Air Pollutants and Initial Hospital Admission for Ischemic Stroke in Korea from 2002 to 2013

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Objectives: There is limited information regarding the association between air pollution exposure and stroke incidence. Therefore, this study aimed to assess the associations between short-term exposure to ambient air pollutants and initial hospital admission for ischemic stroke. *Materials and Methods:* From the Korea National Health Insurance Service−National Sample Cohort 2002−2013 database in South Korea, 55,852 first hospital admissions for ischemic stroke were identified. A generalized additive Poisson model was used to explore the association between air pollutants, including particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide and admissions for ischemic stroke. *Results:* All air pollutant models showed significant associations with ischemic stroke in the single lag model. In all air pollutant models excluding particulate matter 10 μm, a significant association was found between nitrogen dioxide exposure and initial admission for ischemic stroke after adjusting for other pollutants. An increment of 10 $\mu g/m^3$ in nitrogen dioxide concentration at lag 0 and 14 days corresponded to a 0.259% (95% confidence interval, 0.231−0.287%) and 0.110% (95% confidence interval, 0.097−0.124) increase in initial admission for ischemic stroke, respectively. *Conclusions:* The exposure-response relationship between nitrogen dioxide and initial admissions for ischemic stroke was approximately linear, with a sharper response at higher concentrations. Short-term exposure to nitrogen dioxide was positively associated with initial hospital admission for ischemic stroke.

Key Words: Ischemic stroke—Air pollution—Hospital admission—Nitrogen dioxide

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Introduction

Stroke is the second most common cause of death and the third leading cause of long-term disability worldwide.[1,2] In 2010, approximately 16.9 million new cases of stroke were diagnosed, and 5.9 million stroke-related deaths occurred worldwide.[3] In Korea, stroke is the third most common cause of death[4,5]; each year, almost 105,000 Koreans experience a new or recurrent stroke. Despite major improvements in primary and secondary prevention of stroke over the last several decades, the global incidence of stroke continues to increase because of rapid population growth, increased life expectancy, and various environmental and lifestyle changes, particularly in economically transitioning countries[3] Additionally, stroke is responsible for patient suffering, and it imposes a substantial economic burden on society.[6,7] Therefore, it is of great significance to identify modifiable risk factors for stroke from the public health perspective.

Several epidemiological studies, including pooled analyses, have demonstrated that cardiac rather than pulmonary disease is the primary cause of morbidity and mortality associated with exposure to air pollution.[8] Studies on long-term air pollution exposure have shown a strong association between air pollution and stroke.[9-11] While the short-term effects of air pollution on cardiovascular disease have received much attention, it is less certain whether acute exposure to air pollution is a trigger for cerebrovascular disease, especially stroke.[12-14] This is partly because the results of many studies on short-term exposure evaluating the effect of air pollution on stroke have been inconclusive, reflecting both the nature of the condition and the size of individual studies.[8] Recent meta-analyses[15] have reported an association between exposure to air pollution and hospital admissions for stroke or death caused by stroke.[16-19] Considering stroke as a heterogeneous disorder, with its subtypes depending on the underlying vascular risk factors and acute phase triggers,[20,21] the effect of air pollution on stroke may differ according to the subtype. Previous experimental and epidemiological studies have described the deleterious effects of air pollution on endothelial dysfunction, cardiac arrhythmia, and dysfunctional heart rate modulation.[22,23] Hence, this may suggest that air pollution may be associated with ischemic stroke (IS).

Despite the high incidence of stroke, no large-scale study based on the National Sample Cohort (NSC) data has been published on the relationship between air pollutants and initial admissions for IS in South Korea. This study aimed to determine the association between short-term exposure to air pollutants and admissions for IS using the National Inpatients Sample database in Korea from 2002 to 2013. The study also aimed to evaluate the effects of age, sex, season, and temperature on this association.

Materials and methods

National health insurance database

Data on the initial diagnosis of IS were extracted using a nationwide representative sample from the Korea National Health Insurance Service (KNHIS) National Sample Cohort (NSC) 2002−2013 database in South Korea. This nationwide population-based database provides the entire medical service utilization history for more than 1 million South Koreans. In the KNHIS, the Korean Classification of Diseases (KCD), a system similar to the International Classification of Diseases, is used as a system of diagnostic practice codes. The database comprises 1,025,340 nationally representative random individuals, accounting for approximately 2.2% of the South Korean population in 2002. Stratified random sampling was performed using 1476 strata by age (18 groups), sex (two groups), and income level (41 groups: 40 for health insurance beneficiaries and one for medical aid) of 46 million South Koreans in 2002.[24] This study used the KNHIS-NSC database (NHIS-2018-2-253), created by the KNHIS.

Study population

This study consisted of all patients who received inpatient and outpatient care for an initial diagnosis of IS (KCD code, I63.x) between January 1, 2002, and December 31, 2013. IS defined as KCD code of I63.x including cerebral infarction due to thrombosis (I63.0 and I63.3), cerebral infarction due to embolism (I63.1 and I63.4), cerebral infarction due to unspecified occlusion or stenosis (I63.2 and I63.5), cerebral infarction due to cerebral venous thrombosis, nonpyogenic (I63.6), other cerebral infarction (I63.8) or cerebral infarction, unspecified site (I63.9). Overall, 55,852 patients were included.

Air pollutant and weather database

Air pollution data, including daily average fine particulate matter (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO) from January 1, 2002, to December 31, 2013, were obtained using open public information released by the Ministry of Environment.[25] Regarding the effects of weather conditions, meteorological data on daily average temperature (°C) and relative humidity (%) were extracted from the Korea Meteorological Administration.[26]

Statistical analysis

The time series analysis was based on daily counts of IS diagnoses from the KNHIS-NSC 2002−2013 database. To calculate the diagnosis number, a time series of the number of patients with their initial diagnosis of IS was constructed for each day. Air pollutant and weather data were connected to IS population data by date for time series analysis.

A generalized additive Poisson model was used to explore the association between air pollutants and IS. The time, day of the week, public holidays, daily mean temperature, and relative humidity were adjusted in our model. For the time, the smoothing spline function with 10 degrees of freedom (df) per year was applied to adjust for seasonality and long-term trends.[27] The temperature (df = 6) and relative humidity (df = 3) on the same day were also incorporated in the model using smoothing splines because of the potential confounding effects of the weather.[28] In addition, the day of the week and public holidays were included in the model to control for differences in the number of IS diagnoses for each day. The final model used is as follows:

$Y_t \sim \text{Poisson}(\mu_t)$

$\log(\mu_t) = \alpha + \beta(air\ pollutant)_{t-l} + DOW + public\ holiday + s(time,\ df = 10) + s(temperature_0,\ df = 6) + s(relative\ humidity_0,\ df = 3)$ where t refers to the day of the observation; Y_t is the number of IS diagnoses at day t; α is the model intercept; β represents the regression coefficient, which is the log-relative risk of IS associated with the unit increase in air pollutants; $(air\ pollutant)_{t-l}$ is the mean air pollutant (i.e., PM_{10}, SO_2, NO_2, CO) concentration on day t and l is the day lag; DOW is the day of the week; public holidays were binary variables indicating a public holiday at day t; s() indicates the smoothing spline function; $temperature_0$ and $relative\ humidity_0$ indicate the daily average temperature and relative humidity on the current day, respectively.

The time series analyses were performed in two stages. The first analysis was performed to estimate the association between PM_{10} and the initial diagnosis of IS. Models were established around PM_{10}. The single-pollutant model included only PM_{10} without other air pollutants, and multi-pollutant models were adjusted for other air pollutants. Using the same procedure as the first analysis, the second analysis was performed to identify the association between the other air pollutants, excluding PM_{10}, and the initial diagnosis of IS.

To investigate the temporal association of air pollutants with IS diagnosis, models with different lag structures were used. Based on the results of the correlation test with the current day and lag days between air pollutants and IS, single-day models, lag 0 and lag 14, were selected. In addition, 2-week moving averages of air pollutant concentrations were applied to identify cumulative effects, considering that single-day lag models might underestimate the associations.[28] In addition, for temperature and relative humidity, two meteorological variables on the current day were adjusted in single-day models, and their 2-week means were included in 2-week lag models. Covariates of air pollutants were also incorporated in the model with 2-week means.

The results are presented as the percentage change and 95% confidence interval (CI) in the daily IS diagnosis number per 10 $\mu g/m^3$ increase in air pollutant concentrations. The percent increase in the diagnosis of IS per unit increase in the pollutant equals a relative risk minus 1 multiplied by 100. The smoothing function was used to graphically analyze the exposure-response relationship between the log-relative risk of IS and the air pollutant concentration.

All statistical analyses were performed using R version 3.4.3 (R Foundation for Statistical Computing) with “mgcv” and “tsModel” packages. The statistical significance was set at $p<.05$.

Ethics

This study was approved by the Institutional Review Board of Hallym Medical University Chuncheon Sacred Hospital (IRB No. 2018-09-005), and the need for written informed consent was waived because the KNHIS-NSC data set consists of de-identified secondary data for research purposes.

Results

Environmental data

The summary statistics for daily incidence of IS, air pollution, and weather conditions between January 1, 2002, and December 31, 2013, are shown in Table 1. On average, there were 12.7 ± 7.5 IS occurrences per day. The overall mean daily NO_2 concentration was 43.3 $\mu g/m^3$ (range 11.0−101.3). The means (standard deviation) of temperature and relative humidity were 12.6°C (10.4°C) and 61.0% (15%), respectively. During the 4383 days, the mean daily PM_{10} concentration was 50.0 $\mu g/m^3$ (range, 11.6−625.7). Only 3.08% (135 days) of the daily PM_{10} concentrations met the target of South Korea’s Ambient Air Quality Standards (100 $\mu g/m^3$), 0.66% (29 days) met the target of the US National Ambient Air Quality Standards (150 $\mu g/m^3$), and 39.97% (1752 days) met the target of WHO Air Quality Guidelines (50 $\mu g/m^3$).

Basic characteristics

Table 2 summarizes the general characteristics. Overall, 55,852 IS occurrences were identified during the study period. Of those, 46.4% were men, and 63.4% were aged <65 years. Of all the IS cases, 59% occurred in Seoul, the capital of South Korea, and 42.9% occurred in 30% of those in the lower-income brackets.

Modeling

Air pollutants including PM_{10}

Table 3 shows the association between initial admission for IS and air pollutants, mainly PM_{10}, for different lag structures. Significant associations were observed between the initial hospital admission for IS and PM_{10}

Table 1. *Distribution of daily data on air pollutants and weather conditions in Korea from 2002 to 2013.*

Variables	Mean	SD	Minimum	percentile 25	50	75	Maximum
Daily ischemic stroke patients	12.7	7.5	0.0	8.0	12.0	17.0	89.0
PM_{10} ($\mu g/m^3$)	50.0	28.5	11.6	33.8	45.2	59.3	625.7
SO_2 ($\mu g/m^3$)	15.3	5.1	7.5	11.7	14.0	17.7	53.4
NO_2 ($\mu g/m^3$)	43.3	14.3	11.0	32.4	40.9	52.7	101.3
CO ($\mu g/m^3$)	1104.3	366.6	450.1	839.2	1014.2	1283.3	2998.9
Temperature (˚C)	12.7	10.4	-14.5	4.0	14.2	22.1	31.8
Relative humidity (%)	61.0	15.0	19.9	49.8	61.0	71.8	96.5

PM_{10}, particulate matter 10μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; SD, standard deviation.

Table 2. *General characteristics of ischemic stroke patients in Korea from 2002 to 2013.*

	Number	%
Total	55,852	100
Sex		
Male	25,911	46.4
Female	29,941	53.6
Age group		
<45 years old	3514	6.3
45–64 years old	31,880	57.1
≥65 years old	20,458	36.6
Residence		
Seoul	32,952	59.0
Other metropolitan	12,237	21.9
Do	10,663	19.1
Income		
0–30%	14,910	26.7
30–70%	17,001	30.4
70–100%	23,941	42.9
Comorbidity		
Hypertension	39,874	71.4
Diabetes mellitus	27,508	49.3
Ischemic heart disease	18,581	33.3
Chronic kidney disease	1347	2.4
Asthma	16,949	30.3
Chronic obstructive pulmonary disease	7430	13.3
Alcohol-related disorders	1066	1.9
Osteoarthritis	29,103	52.1
Rheumatoid arthritis	8903	15.9
Cancer	7168	12.8
Acquired immune deficiency syndrome	33	0.1

concentrations on the current day (lag 0) and lag 14 days after adjustments for calendar time, day of the week, public holidays, and weather conditions. A 10 $\mu g/m^3$ increase in the PM_{10} concentration at lag 0 and 14 days corresponded to a 0.011% (95% CI, 0.007–0.016) and 0.009% (95% CI, 0.004–0.013) increase in the initial hospital admission for IS, respectively. All air pollutant models showed significant associations with IS in the single lag model. A 10 $\mu g/m^3$ increase in the concentration of all air pollutants at lag 0 and lag 14 days corresponded to 0.012% (95% CI, 0.005–0.019) and 0.011% (95% CI, 0.005–0.017) increase in the initial hospital admission for IS, respectively.

Air pollutants excluding PM_{10}

Excluding PM_{10}, the associations between the different types of air pollutants and the initial admission for IS at lag 0 and lag 14 days were significant, except for the SO_2+CO model. A significant lag association was found between the initial admission for IS and NO_2 concentrations at lag 0 and lag 14 days, after adjustments for calendar time, day of the week, public holidays, and weather conditions. In the single-pollutant model, an increment of 10 $\mu g/m^3$ in NO_2 concentration at lag 0 and lag 14 days corresponded to a 0.164% (95% CI, 0.147–0.181) and 0.100% (95% CI, 0.087–0.112) increase in initial hospital admissions for IS, respectively. In the all air pollutant models, a significant association was found between NO_2 and the initial admission for IS after adjusting for other pollutants (SO_2, CO). An increment of 10 $\mu g/m^3$ in NO_2 concentration at lag 0 and lag 14 days corresponded to a 0.259% (95% CI, 0.231–0.287) and 0.110% (95% CI, 0.097–0.124) increase in the initial admission for IS, respectively (see Table 4). There was a clear dose-response relationship between the NO_2 concentration and the count of daily admissions for IS (see Fig. 1). The relationship was approximately linear, with a sharper response at higher concentrations.

Discussion

This study shows that the initial admission for IS was positively associated with NO_2 levels in South Korea. Short-term exposure to NO_2 was found to be significantly associated with the initial admission for IS after adjusting for temperature, relative humidity, day of the week, public holiday, long-term trends, and seasonality of stroke events. Currently, this is the first nation-level investigation of the relationship between air pollutants and the initial admission for IS. Although the risk of IS due to NO_2 exposure was relatively small, the number of IS events attributable to NO_2 might be high owing to the high incidence of IS and the fact that most people are exposed to ambient fine PM_{10}, suggesting potentially large public health implications.

Several epidemiological and experimental studies suggested a possible link between air pollution and a higher risk of IS.[14] Several potential mechanisms have been suggested to explain the short-term effect of particulate air pollution on cardiovascular diseases, including inflammatory processes, oxidative stress, and alterations in the autonomic nervous control of the heart.[29] A previous study has demonstrated an increase in the levels of inflammatory markers such as interleukin-12 and C-reactive protein in the blood of individuals exposed to air pollution. These inflammatory processes can lead to destabilization and rupture of atheromatous plaques, vasoconstriction of arteries causing increased blood pressure, and an increase in blood viscosity, which may enhance the formation of a thrombus.[29] Another potential effect of air pollution is the increased risk of heart rhythm disorders.[25,30,31] The biological mechanisms of the onset of heart rhythm disorders caused by air pollution may include an alteration in the autonomic nervous system, causing repolarization disorders. Another mechanism involves the pollutants entering the bloodstream, causing high blood pressure and endothelial dysfunction. This latter mechanism has been demonstrated for ultrafine particles.[32]

Table 3. *Association between initial admission for ischemic stroke and a 10 μg/m³ increase in PM_{10} based on single-pollutant models and multi-pollutant models for different lag structures.*

Models with pollutants	Single lag model				lag 0−13 model (14 days)	
	lag 0		lag 13			
Single-pollutant models	% change (95% CI)	*p*-value	% change (95% CI)	*p*-value	% change (95% CI)	*p*-value
PM_{10}	0.011 (0.007−0.016)	0.000	0.009 (0.004−0.013)	0.000	-0.002 (-0.015−0.011)	0.768
Double-pollutant models						
PM_{10}+SO_2	0.004 (-0.001−0.010)	0.130	0.010 (0.005−0.015)	0.000	0.005 (-0.010−0.020)	0.527
PM_{10}+NO_2	-0.001 (-0.008−0.005)	0.699	0.012 (0.006−0.018)	0.000	0.000 (-0.014−0.015)	0.995
PM_{10}+CO	0.001 (-0.005−0.007)	0.769	0.011 (0.006−0.016)	0.000	-0.007 (-0.022−0.008)	0.371
Triple-pollutant models						
PM_{10}+SO_2+NO_2	0.004 (-0.003−0.011)	0.204	0.011 (0.005−0.017)	0.000	0.004 (-0.011−0.019)	0.581
PM_{10}+SO_2+CO	0.000 (-0.006−0.006)	0.928	0.011 (0.006−0.016)	0.000	-0.003 (-0.018−0.013)	0.739
PM_{10}+NO_2+CO	0.011 (0.004−0.018)	0.002	0.011 (0.005−0.017)	0.000	-0.007 (-0.023−0.008)	0.336
All air pollutant models						
PM_{10}+SO_2+NO_2+CO	0.012 (0.005−0.019)	0.001	0.011 (0.005−0.017)	0.000	-0.003 (-0.019−0.012)	0.656

PM_{10}, particulate matter 10μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; CI, confidence interval.

This study analyzed the association of NO_2 exposure with the risk of hospitalization among patients who received inpatient and outpatient care after an initial diagnosis of IS during the study period. The association between exposure to fine particles or NO_2 and the onset of acute coronary disorder has been described on numerous occasions.[12] Unlike fine particles, NO_2 does not appear to have a direct effect on cardiovascular pathologies.[21] Conversely, this pollutant is a good proxy for particulate air pollution (i.e., PM_{10} and $PM_{2.5}$) generated by road traffic.[22] Cardiovascular disease had a stronger association with NO_2 than it did with the exposure to fine particles.[23] Andersen et al. also reported an increased risk of hospitalization due to stroke followed by death in relation to residential NO_2 exposure.[33] These associations were observed for IS but not for hemorrhagic stroke. Another study presented a ratio of 1.13 for the highest (457.7 μg/m³ NO_2) relative to the lowest (49.6 μg/m³ NO_2) exposed subjects aged 45 years and above.[34] Identification of the dose-response relationship between IS and air pollutant concentration is of public health and regulatory interest. As previous studies were primarily conducted in Western countries with NO_2 pollution, they reported exposure-response relationships in real settings. In this study, a dose-response analysis was conducted to explore the pattern and scope of the adverse response. An approximately linear exposure-response relationship was observed, which is consistent with a study conducted in Belgium that reported a relationship between NO_2 and risk of cardiovascular disease.[35]

This study has several limitations. First, there is a risk of ecological bias, as the factors associated with disease rates at the geographical level may not be associated with the disease at the individual level. Ecological bias is caused by regional differences in disease rates due to the variation in confounding factors across regions. However, evaluation of the extent of bias is usually difficult; therefore, further exploration of the exposure-health relationship using individual data is required.[36] Second, there is no monitoring data on $PM_{2.5}$, which is currently a major interest. Therefore, these findings should be interpreted with caution, and further research examining the independent effect of $PM_{2.5}$ on the initial hospital admission for IS is warranted. Finally, the retrospective data collection may bring about a bias in diagnostic and coding accuracy. However, both the International Classification of Disease-10 codes and corresponding Korean diagnoses were used to identify eligible IS hospitalizations, which significantly reduced bias from coding inaccuracy.[37,38] Given the robustness of the association in all lag models, in the stratified and sensitivity analyses, as well as in the large sample size, these potential limitations are unlikely to have compromised the results.

This study has several strengths. Several air pollutants associated with an increased risk of hospital admissions for IS in a large population were assessed using novel

Table 4. *Association between initial admission for ischemic stroke and a 10 μg/m³ increase in single-pollutant models and multi-pollutant models, excluding PM_{10}, for different lag structures.*

Models with pollutants	Single lag model				lag 0–14 model (15 days)	
	lag 0		lag 14			
Single-pollutant models	% change (95% CI)	*p*-value	% change (95% CI)	*p*-value	% change (95% CI)	*p*-value
SO_2	0.169 (0.132–0.206)	0.000	0.100 (0.067-0.133)	0.000	-0.109 (-0.201–0.017)	0.018
NO_2	0.164 (0.147–0.181)	0.000	0.100 (0.087–0.112)	0.000	-0.042 (-0.078–0.006)	0.021
CO	0.003 (0.003–0.004)	0.000	0.002 (0.002-0.002)	0.000	0.001 (-0.001–0.002)	0.412
Double-pollutant models						
SO_2+NO_2	-0.163 (-0.225–0.100)	0.000	0.121 (0.079–0.164)	0.000	-0.068 (-0.202–0.066)	0.309
SO_2+CO	0.052 (-0.005–0.109)	0.066	0.113 (0.076–0.150)	0.000	-0.341 (-0.485–0.196)	0.000
NO_2+SO_2	0.202 (0.180–0.224)	0.000	0.107 (0.094–0.121)	0.000	-0.022 (-0.074–0.029)	0.389
NO_2+CO	0.255 (0.227–0.283)	0.000	0.110 (0.096–0.124)	0.000	-0.164 (-0.228–0.101)	0.000
CO+SO_2	0.003 (0.002–0.004)	0.000	0.002 (0.002–0.003)	0.000	0.005 (0.002–0.007)	0.000
CO+NO_2	-0.005 (-0.006–0.004)	0.000	0.002 (0.002–0.003)	0.000	0.006 (0.003–0.008)	0.000
All air pollutant models						
SO_2+NO_2+CO	-0.060 (-0.132-0.013)	0.098	0.120 (0.076-0.163)	0.000	-0.269 (-0.423–0.115)	0.000
NO_2+SO_2+CO	0.259 (0.231–0.287)	0.000	0.110 (0.097–0.124)	0.000	-0.134 (-0.200–0.068)	0.000
CO+SO_2+NO_2	0.00 (-0.01–0.00)	0.000	0.002 (0.002–0.003)	0.000	0.008 (0.005–0.011)	0.000

PM_{10}, particulate matter 10μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; CI, confidence interval.

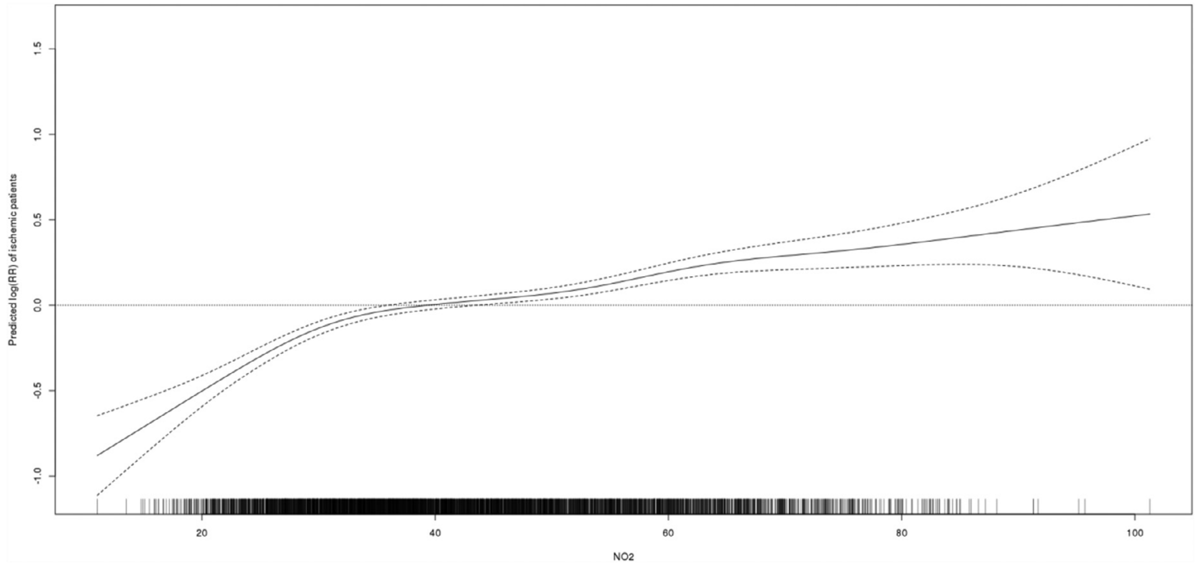

Fig. 1. *The smoothed exposure-response curves of daily average nitrogen dioxide (NO_2) concentrations at current day against the initial admission for ischemic stroke after adjusting for calendar time, day of the week, public holiday, current-day temperature, relative humidity, and other air pollutants (sulfur dioxide+carbon monoxide). The X-axis indicates the current day (lag 0 day) NO_2 concentrations ($\mu g/m^3$). The Y-axis indicates the predicted log (relative risk) shown using the solid line; the dotted lines represent the 95% confidence interval.*

frame-distributed lag linear and non-linear models for the assessed parameters. This is the first study conducted in Korea that focused on admissions for IS. Additionally, a relatively large sample size of 55,852 subjects admitted for IS from 2002 to 2013 was used. Potential confounding factors were also controlled, particularly air pollution in Korea, which could exert a greater impact on admissions for stroke.

Conclusions

The results of this study suggest that a short-term increase in NO_2 concentration is associated with an increased risk of IS among the Korean population. This finding has potential public health and clinical significance. It may provide the necessary evidence to advise policy makers on environmental laws that will reduce environmental pollution and hospital admissions for stroke due to extremely high concentrations of air pollutants. These results also contribute to the limited scientific literature on the short-term effects of PM air pollution on IS in developing countries. Additional research on this topic is warranted.

Declaration of Competing Interest

None.

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