

## Air Pollution

### A New Risk Factor in Ischemic Stroke Mortality

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**Background and Purpose**—Air pollution is known to be associated with cardiovascular disease, but little is known about the occurrence of stroke in relation to air pollution. We investigated the association between acute stroke mortality and air pollution over a 7-year period (January 1991 through December 1997) in Seoul, Korea.

**Methods**—A generalized additive model was used to regress daily stroke death counts for each air pollutant, controlling for time trends, day of the week, and meteorological influences such as temperature, relative humidity, and atmospheric pressure. Ischemic and hemorrhagic stroke deaths were examined separately.

**Results**—The effects of air pollutants on ischemic stroke mortality were statistically significant, whereas this was not the case for hemorrhagic stroke mortality. We observed estimated relative risks of 1.03 (95% CI, 1.00 to 1.06) and 1.04 (95% CI, 1.01 to 1.08) for ischemic stroke mortality for each interquartile range increase in total suspended particulates and sulfur dioxide concentrations on the same day. We also found significantly increased relative risks of 1.04 (95% CI, 1.01 to 1.07) for nitrogen dioxide with a 1-day lag, of 1.06 (95% CI, 1.02 to 1.09) for carbon monoxide with a 1-day lag, and of 1.06 (95% CI, 1.02 to 1.10) for ozone with a 3-day lag for each interquartile range increase.

**Conclusions**—These findings indicate that air pollutants are significantly associated with ischemic stroke mortality, which suggests an acute pathogenetic process in the cerebrovascular system induced by air pollution. (*Stroke*. 2002;33:2165-2169.)

**Key Words:** air pollution ■ mortality ■ stroke, hemorrhagic ■ stroke, ischemic

Epidemiological studies incorporating time-series analyses have demonstrated an association between short-term exposure to air pollution and increased mortality after adjustment for confounding factors.<sup>1,2</sup> Meta-analysis of epidemiological data has provided evidence that the relative risk of mortality is consistently increased by rising pollutant levels.<sup>3</sup> Past studies have shown an association between air pollution and not only respiratory mortality but also cardiovascular mortality. The involvement of cardiovascular disease is strongly supported by analyses showing associations between air pollution and hospital admissions for cardiovascular disease.<sup>4-8</sup> Given these results, it is reasonable to hypothesize that a similar situation might exist for stroke.

Recently, potential mechanisms of pollutants in cardiovascular disease have been proposed, and increasing heart rates and changes in heart rate variability have been associated with elevated levels of air pollutants.<sup>9-12</sup> In addition, particulate air pollution has been associated with day-to-day changes in plasma viscosity.<sup>13</sup> These findings suggest hemodynamic disturbances that may lead to the increased risk of cardiovascular disease and that may lead to an increased risk of other types of circulatory disease such as stroke.

Little is known, however, about the nature of the association between air pollution and stroke despite the health burden placed on the middle-aged and elderly. We hypothesize that air pollutants may have significant effects on mortality through acute stroke events. In this analysis, we examined the association between air pollutants and ischemic and hemorrhagic stroke mortality. To investigate the nature of this relationship, we conducted a time-series study in Seoul, Korea, which has experienced a rapid rise in the number of motor vehicle. Seoul is an attractive location for such a study because stroke is a leading cause of death and because the proportion of stroke death is higher than that in most western cities, giving us greater power to examine this outcome. We also investigated the lag times and exposure-response relationships between exposure to air pollutants and cause-specific stroke mortality.

## Materials and Methods

### Mortality and Air Pollution Data

Daily stroke deaths in the Seoul area were obtained from the annual mortality records of the Korean National Statistical Office between January 1, 1991, and December 31, 1997. This analysis includes

Received October 17, 2001; final revision received January 25, 2002; accepted February 11, 2002.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000026865.52610.5B

**TABLE 1. Mean Values of the Variables Related to Daily Circulatory Mortality in Seoul, Korea, From 1991 to 1997**

Variables	Mean (SD)	Min	Q1	Med	Q3	Max
<b>Mortality, deaths/d</b>						
Ischemic stroke	2.8	1.0	2.0	3.0	4.0	12.0
Hemorrhagic stroke	4.6	1.0	3.0	4.0	6.0	12.0
<b>Meteorology</b>						
Temperature, °C	12.6 (10.1)	-11.1	3.7	13.7	21.7	33.0
Relative humidity, %	64.4 (14.7)	18.8	54.1	64.6	75.5	97.4
Air pressure, hPa	1016.5 (8.2)	984.3	1009.9	1016.6	1023.0	1040.8
<b>Pollutants</b>						
TSP, $\mu\text{g}/\text{m}^3$	87.6 (41.1)	17.0	57.7	81.1	109.4	323.4
SO <sub>2</sub> , ppb	21.8 (18.8)	3.4	9.2	15.4	26.7	135.3
NO <sub>2</sub> , ppb	32.2 (9.9)	9.7	25.0	31.1	38.9	68.5
O <sub>3</sub> , ppb	22.0 (12.4)	2.8	12.3	20.1	29.6	75.3
CO, 100 ppb*	14.4 (7.0)	4.3	9.4	12.0	17.0	51.4

Min indicates minimal value; Q1, first quartile value; Med, median value; Q3, third quartile value; and Max, maximum value.

\*CO data are for the period of 1992 to 1997.

hemorrhagic and ischemic stroke deaths coded according to the *International Classification of Diseases* (ICD; World Health Organization, Geneva, Switzerland). The causes of death were coded according to ICD-9 before 1995 and according to ICD-10 (431 and 434 by ICD-9, I61 and I63 by ICD-10) since then.

Seoul, located centrally in the Korean peninsula, is the biggest metropolitan city in the country. Mean population size during the study period was 10.6 million, and the major air pollution source was automobile exhaust emission. Seoul has a 4-season climate and an annual temperature range of  $-11.1^{\circ}\text{C}$  to  $30.0^{\circ}\text{C}$ . Data on 24-hour average temperature and relative humidity were obtained from the National Meteorological Office.

Air pollution data were provided by the Department of the Environment (Seoul). Exposure measurements during the study period were taken from 20 monitoring sites, which provide hourly measurements of total suspended particles (TSP; by  $\beta$ -ray absorption) and gaseous pollutants: sulfur dioxide (SO<sub>2</sub>; by ultraviolet fluorescence), nitrogen dioxide (NO<sub>2</sub>; by chemiluminescence), ozone (O<sub>3</sub>; by ultraviolet photometry), and carbon monoxide (CO; by nondispersive infrared photometry). All pollutant data were available during the whole study period except the CO data, which were available from January 1, 1992. We calculated the hourly mean of each pollutant from the 20 stations and then computed their 24-hour averages. For ozone, a daytime 8-hour average instead of a 24-hour average was used.

### Statistical Analysis

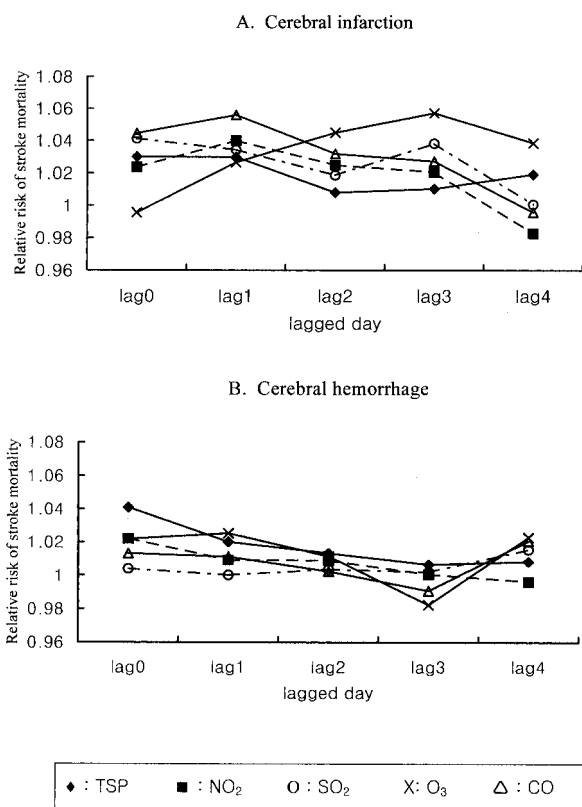
A generalized additive model<sup>14</sup> was used to regress daily stroke death counts for each pollutant, controlling for time trends, day of the week, and meteorological influences such as same-day and previous-day temperature, relative humidity, and atmospheric pressure.<sup>15</sup> Daily stroke mortality figures were fitted to the generalized additive model, which included the locally weighted running-line smoother (loess) function of time, to capture seasonal and long-term trends. Autoregressive terms were inserted into the model to remove serial correlations of residuals. Smoothing parameters that minimized Akaike's information criteria were chosen to capture short-term variations for day of the week and weather variables.<sup>16</sup> Robust regression with M estimation was used to reduce the influence of extreme observations on daily death counts.<sup>17</sup> To minimize the influence of pollutant concentration outliers, we excluded air pollutant exposures  $>6$  SD above the mean. Because of the likelihood that air pollutants affect mortality after some time delay, lagged-day exposures of up to 4 days were examined. The lag effects on the

relative risks of ischemic and hemorrhagic stroke mortality were plotted for each air pollutant. The associations between the levels of air pollutants singly and in combination and daily stroke mortality were evaluated. Although our hypothesis testing for the pollutants used linear terms in the regression, we explored the shape of the dose-response relationship by fitting smooth functions of the pollutants.

### Results

The distributions of stroke mortality, meteorological measurements, and air pollution from January 1, 1991, until December 31, 1997, for the Seoul metropolitan area are shown in Table 1. An average of 2.8 and 4.6 people died of ischemic and hemorrhagic stroke, respectively, in the city each day over the study period. The overall numbers of ischemic and hemorrhagic stroke deaths were 7137 and 11 868. The number of deaths from ischemic stroke showed a slightly increasing trend, but deaths resulting from hemorrhagic stroke showed a decreasing trend with seasonal fluctuation (data not shown). Same-day concentrations of primary pollutants (TSP, SO<sub>2</sub>, NO<sub>2</sub>, CO) were moderately to strongly correlated with each other; Pearson's correlation coefficients ranged from 0.50 to 0.90. O<sub>3</sub> and temperature correlated negatively with the other pollutants.

The Poisson regression model included time trends, day of the week, and weather variables. To determine the lag effects of air pollutants on stroke mortality, the relative risks of different lag models, with a maximum lag of 4 days, were compared (Figure 1). The effects of air pollutants on ischemic stroke mortality were found to be statistically significant, whereas those on hemorrhagic stroke mortality were not statistically significant, except for TSP of the same day (relative risk, 1.04; 95% CI, 1.02 to 1.07). The associations between TSP and SO<sub>2</sub> and ischemic stroke mortality were highest on the same day, whereas 1-day lagged concentrations of NO<sub>2</sub> and CO and 3-day lagged concentrations of O<sub>3</sub> showed the highest risk of ischemic stroke mortality.



**Figure 1.** Relative risks of ischemic and hemorrhagic stroke mortality attributed to each interquartile change in pollutant level for different lag periods with a maximum lag of 4 days.

Table 2 shows the estimated relative risks of ischemic stroke mortality attributable to each interquartile change in pollutant concentration after controlling for temporal trends, meteorological variables, and days of the week in single- and 2-pollutant models. We observed estimated relative risks of 1.03 (95% CI, 1.00 to 1.06) and 1.04 (95% CI, 1.01 to 1.08) for ischemic stroke mortality for each interquartile range increase in TSP and SO<sub>2</sub> concentrations on the same day. We also found significantly increased relative risks of 1.04 (95% CI, 1.01 to 1.07) for NO<sub>2</sub> with a 1-day lag, 1.06 (95% CI, 1.02 to 1.09) for CO with a 1-day lag, and 1.06 (95% CI, 1.02 to 1.10) for O<sub>3</sub> with a 3-day lag for each interquartile range increase in single-pollutant models. To consider the interre-

lationship between pollutants, we analyzed regression models for combinations of 2 pollutants. The associations of gaseous pollutants with ischemic stroke mortality were robust in 2-pollutant models, and the relative risk of ischemic stroke mortality with respect to TSP changed but was without statistical significance, except in combination with O<sub>3</sub>.

The estimated log relative risk of ischemic stroke mortality for gaseous pollutants showed the exposure-response relationships in the generalized additive model plot (Figure 2).

### Discussion

We found that air pollution was statistically significantly associated with ischemic stroke mortality after taking into account time trends, day of the week, and meteorological variables. Relative risks for the pollutant increases were greater for ischemic stroke mortality than for hemorrhagic stroke mortality, except for TSP on the same day.

Stroke is a very common cause of death and confers a great health risk on the middle-aged and elderly, especially in association with risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, excessive alcohol consumption, and atherosclerosis.<sup>18</sup> However, if stroke is also associated with air pollution, lowering the level of exposure could considerably reduce the associated health burden without relying on behavioral change.

Despite its great public importance, little is known about the association between air pollution and stroke. When daily mortality resulting from cerebrovascular causes (ICD-9 430 to 436) was evaluated in the Netherlands recently,<sup>19</sup> gaseous air pollutants were found to be significantly associated with stroke. However, no study has been conducted to show the difference between ischemic and hemorrhagic stroke in terms of their association with air pollution.

Time-series analysis has shown that a large proportion of deaths associated with high pollution levels are due to cardiovascular disorders.<sup>3,20</sup> Recently, investigation was done into the short-term effects of air pollution on mortality or on hospital admissions in a small number of Asian studies.<sup>7,21–23</sup> In these studies, circulatory mortality, which included ischemic and hemorrhagic stroke, was found to be significantly associated with air pollutants.<sup>21</sup>

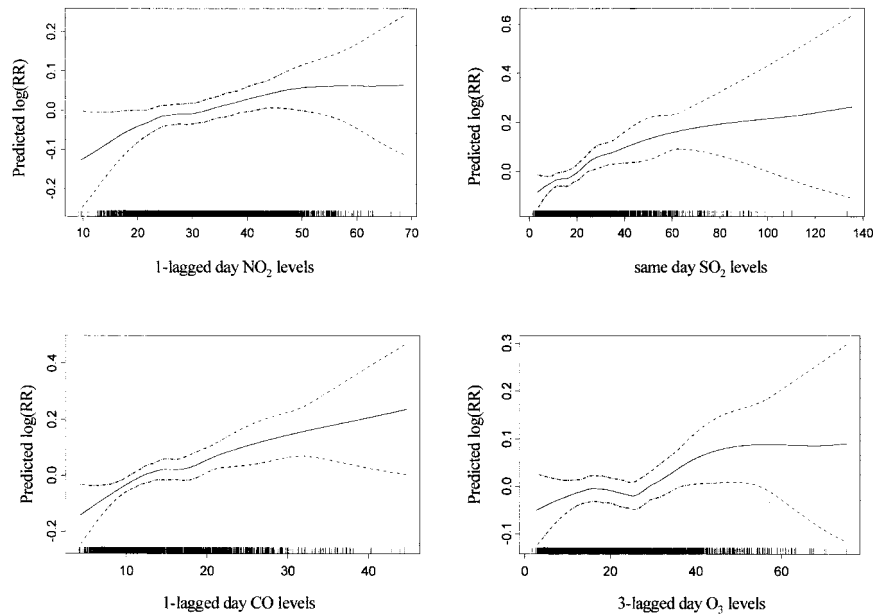
In our study, the influence of air pollutants on ischemic and hemorrhagic stroke mortality differed in terms of effect size

**TABLE 2. Estimated Relative Risk of Ischemic Stroke Mortality for Each Interquartile Range Increase in TSP (51.69 μg/m<sup>3</sup>), NO<sub>2</sub> (13.94 ppb), SO<sub>2</sub> (17.43 ppb), CO (0.76 ppm), and O<sub>3</sub> (17.32 ppb) in Single- and 2-Pollutant Models,\* Seoul, Korea, 1991 to 1997**

Pollutants	Two-Pollutant Model																	
	1-Pollutant Model			Adjusted for TSP			Adjusted for NO <sub>2</sub>			Adjusted for SO <sub>2</sub>			Adjusted for CO			Adjusted for O <sub>3</sub>		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
TSP	1.03	1.00–1.06	0.074				1.02	0.98–1.06	0.462	1.00	0.96–1.04	0.971	1.01	0.97–1.05	0.714	1.03	1.00–1.07	0.060
NO <sub>2</sub>	1.04	1.01–1.07	0.013	1.04	1.00–1.08	0.062				1.03	0.99–1.06	0.104	1.02	0.97–1.07	0.505	1.05	1.02–1.08	0.004
SO <sub>2</sub>	1.04	1.01–1.08	0.013	1.06	1.02–1.11	0.010	1.06	1.02–1.10	0.005				1.06	1.00–1.12	0.044	1.08	1.04–1.12	<0.001
CO	1.06	1.02–1.09	0.001	1.07	1.03–1.11	0.001	1.06	1.00–1.11	0.040	1.05	1.01–1.10	0.015				1.09	1.05–1.13	<0.001
O <sub>3</sub>	1.06	1.02–1.10	0.003	1.04	1.00–1.08	0.048	1.03	0.99–1.07	0.111	1.04	1.00–1.08	0.035	1.05	1.01–1.09	0.024			

RR indicates relative risk.

\*Confounding factors used in the analysis are temporal trends, day of the week, same-day and previous-day temperature, relative humidity, and atmospheric pressure.



**Figure 2.** Estimated log relative risks (RR) of ischemic stroke mortality for concentrations of gaseous pollutants; 1-day lagged concentrations of NO<sub>2</sub> and CO, same-day concentrations of SO<sub>2</sub>, and 3-day lagged concentrations of O<sub>3</sub> were used.

and time-lag distribution effects. Statistically significant associations were found between gaseous air pollutants and ischemic stroke mortality, whereas the risk of hemorrhagic stroke mortality was elevated for only TSP on the day of exposure. Given that there are >11 000 deaths from hemorrhagic stroke, the lack of association between hemorrhagic stroke and air pollutants is unlikely to be due to inadequate sample size.

The increase of relative risk of dying from ischemic stroke with increased air pollution is on the order of 3% to 6%, depending on the air pollutant being investigated. This relative risk increase is potentially important, given that the mortality of ischemic stroke is 2.8 per day in this city, which indicates that 214 to 428 ischemic stroke deaths were due to air pollution in the study period.

It is noteworthy that gaseous pollutants showed robust associations with ischemic stroke mortality in the 2-pollutant models. However, TSP may not work well as a surrogate for fine particles, which are believed to be a risk factor of premature mortality.<sup>24</sup> TSP measurements include large coarse particles that exceed the inhalable range; therefore, it is reasonably expected to provide biased estimates of exposure-effect relationships. Because fine particles can form as a result of chemical reactions between gases in the atmosphere and because these particles dominate the inhalable particulate fraction, gaseous pollutants such as SO<sub>2</sub> and NO<sub>2</sub> may be good markers for such particles.<sup>25</sup>

Despite the consistency of the associations between air pollution and mortality in many locations around the world, an explanation for the biological plausibility of these relationships is still required. We suspect that such a mechanism exists, perhaps via some effect on blood coagulability, that would increase the susceptibility of individuals to acute stroke events. Free radicals produced by air pollutants may cause inflammatory responses and enhanced blood coagulation and plasma viscosity and therefore add to the risk of ischemic stroke but not to the risk of hemorrhagic stroke.<sup>13,26</sup>

The association between gaseous pollutants and ischemic stroke mortality shows an exposure-response relationship with no specific pollution threshold, except in the case of O<sub>3</sub> with a suggested threshold of around 25 ppb for an 8-hour (9 AM to 5 PM) average exposure.

This study is limited because it uses environmental monitoring data to represent ambient concentrations, and these data do not necessarily represent individual exposures. Measurement errors resulting from differences between the population-average exposure and ambient levels also cannot be avoided. However, this kind of measurement error is known to cause a bias toward the null and underestimates the pollution effects.<sup>27</sup> Another measurement error resulting from a difference between the measured and true ambient levels was minimized or circumvented by the use of data from 20 air-monitoring stations evenly located within the study area. Many individual risk factors such as smoking, diet, cholesterol level, and obesity either do not vary significantly over time or vary slowly. In addition, there is no reason to believe that daily variations in the individual risk factors are correlated with daily changes in air pollution; therefore, they are unlikely to be confounding factors in this time-series study.<sup>5</sup> There is a possibility of error in the classification of stroke death, and the misclassification could cause an underestimation of the risks if such errors occurred nondifferentially. However, this misclassification error is not believed to be great because the classification into hemorrhagic and ischemic stroke was supported by a high CT or MRI rate in Korea because of the diagnostic criteria for stroke, including brain imaging workup.<sup>28,29</sup>

We do not know whether air pollution is a causative factor or only a precipitating factor of ischemic stroke because we analyzed only the date of death rather than the onset date. Therefore, there is a possibility that patients who have suffered ischemic strokes recently are susceptible to air pollution, which may precipitate the fatal outcome.

In summary, air pollution was significantly associated with ischemic stroke mortality in Seoul. These associations were



observed after taking into account time trends, day of the week, and meteorological variables. These findings support the possibility that acute pathogenetic processes in the cerebrovascular system could be induced by the air pollution.

### Acknowledgment

This work was supported by the Post-doc Program of Korea Science and Engineering Foundation (1999).

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*Stroke*. 2002;33:2165-2169

doi: 10.1161/01.STR.0000026865.52610.5B

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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