

# Effects of Air Pollutants on Acute Stroke Mortality

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The relationship between stroke and air pollution has not been adequately studied. We conducted a time-series study to examine the evidence of an association between air pollutants and stroke over 4 years (January 1995–December 1998) in Seoul, Korea. We used a generalized additive model to regress daily stroke death counts for each pollutant, controlling for seasonal and long-term trends and meteorologic influences, such as temperature, relative humidity, and barometric pressure. We observed an estimated increase of 1.5% [95% confidence interval (CI), 1.3–1.8%] and 2.9% (95% CI, 0.3–5.5%) in stroke mortality for each interquartile range increase in particulate matter < 10  $\mu\text{m}$  aerodynamic diameter (PM<sub>10</sub>) and ozone concentrations in the same day. Stroke mortality also increased 3.1% (95% CI, 1.1–5.1%) for nitrogen dioxide, 2.9% (95% CI, 0.8–5.0%) for sulfur dioxide, and 4.1% (95% CI, 1.1–7.2%) for carbon monoxide in a 2-day lag for each interquartile range increase in single-pollutant models. When we examined the associations among PM<sub>10</sub> levels stratified by the level of gaseous pollutants and vice versa, we found that these pollutants are interactive with respect to their effects on the risk of stroke mortality. We also observed that the effects of PM<sub>10</sub> on stroke mortality differ significantly in subgroups by age and sex. We conclude that PM<sub>10</sub> and gaseous pollutants are significant risk factors for acute stroke death and that the elderly and women are more susceptible to the effect of particulate pollutants. **Key words:** air pollution, mortality, stroke. *Environ Health Perspect* 110:187–191 (2002). [Online 17 January 2002]

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Stroke is a common cause of death and a leading cause of long-term severe disability. Despite widespread concern and the great health burden imposed on the middle-aged and elderly, the relationship between stroke and environmental risk factors such as air pollution has not been studied adequately. Recent reviews on the effect of particulate matter of aerodynamic diameter < 10  $\mu\text{m}$  (PM<sub>10</sub>) on mortality suggest that a rise of 10  $\mu\text{g}/\text{m}^3$  in PM<sub>10</sub> is associated with an increase in the daily total mortality of 1% (1,2). Some epidemiologic studies have also reported associations between gaseous pollutants, such as SO<sub>2</sub>, NO<sub>2</sub>, and CO, and mortality (3–5). However, relatively few studies have attempted to quantify the specific effects of air pollution on stroke mortality, although a number of studies have demonstrated an increased risk of cardiovascular mortality associated with air pollution (6–8). Because air pollution is a potentially modifiable risk factor that does not rely on behavioral change, we thought it worthwhile to explore the relationship between air pollution and stroke. By focusing on the preventive aspects of stroke, we can reduce stroke-related health problems more significantly than by the acute management of stroke patients after stroke occurs (9).

Pollution is composed of various mixtures from diverse emitting sources. Because it is very difficult to separate one pollutant effect from another and because the effect

of one pollutant may be influenced by those of others, interactions among pollutants should be considered rather than the effects of just single pollutant.

Seoul, Korea, presents a useful model for studying effects of air pollutants on stroke because of the high concentrations of particulate pollutants and the high stroke mortality (72.9 per 100,000 population annually). It is the biggest Korean metropolitan area and is located centrally on the Korean peninsula. Mean population size during this study period (1995–1998) was 10.6 million and the major air pollution source was automobile exhaust emissions. Korea has a four-season climate and an annual temperature range of –11.9 to 33°C.

We used a time-series study to examine the association between air pollutants and stroke. Although our main objective was to determine the presence and magnitude of any association between ambient concentrations of PM<sub>10</sub> and daily stroke mortality in Seoul, we also considered the relative importance of gaseous pollutants with respect to stroke mortality risk. To assess the relationships among the pollutants, we focused on the effects of interactions between PM<sub>10</sub> and other gaseous pollutants on the risk of stroke mortality. In addition, we analyzed effect modifications caused by age and sex on the relationship between PM<sub>10</sub> concentrations and daily stroke mortality.

Our results show that PM<sub>10</sub> and gaseous pollutants are significant risk factors of acute stroke mortality, after controlling for confounding factors, such as long-term trends, seasonal changes, day-of-the-week effects, and meteorologic influences. When we examined the associations among PM<sub>10</sub> levels stratified by the level of gaseous pollutants and vice versa, we found that pollutant effects are interactive in terms of stroke mortality risk. We also report statistically significant modification of stroke mortality risk from the exposure to PM<sub>10</sub> by age and sex.

## Methods

**Data sources.** We obtained information on daily circulatory deaths in the Seoul area between 1 January 1995 and 31 December 1998 from the annual mortality records of the Korean National Statistical Office, and we extracted data concerning the number of daily deaths due to stroke (*International Classification of Diseases*, 10th revision [ICD-10] code 160–169) (10). The data on Seoul death certificates can be considered reliable because over than 95% of the data were reported by physicians.

We obtained information on air quality in Seoul from 20 automated air quality monitoring stations. Exposure measurements of PM<sub>10</sub> (by  $\beta$ -ray absorption) and the gaseous pollutants sulfur dioxide (by ultraviolet fluorescence), nitrogen dioxide (by chemoluminescence), ozone (by ultraviolet photometry), and carbon monoxide (by nondispersive infrared photometry) were taken hourly during the study period. Daily 24-hr mean concentrations of air pollutants, midnight to midnight, were constructed. In the case of ozone, a daytime 8-hr average was used instead of a 24-hr average. Meteorologic information from a station in central Seoul was obtained from the National Meteorological Office (Seoul, Korea). This included 24-hr average temperature, relative humidity, and barometric pressure.

**Data analysis.** We used a generalized additive model (GAM) (11) to regress daily

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stroke death counts for each pollutant, while controlling for seasonal and long-term trends, day of the week and meteorologic influences (temperature, relative humidity, and barometric pressure) (12). Because there was a systematic difference in daily mortality among weekdays, we included terms for days of the week in the models. We inserted autoregressive terms into the model to remove serial correlations of residuals, in an effort to control for any confounding effect caused by omitted time-dependent covariates (13). We considered air pollution variables to be linear in the models to obtain estimates of relative risk easily. However, the assumption of the linearity between the log of stroke mortality and air pollution may not be accurate. Therefore, we added the effect of each pollutant to the basic model using a smoothing function when we graphically analyzed the relationship between air pollution and stroke mortality. We used the locally weighted running-line smoother (loess) for the smoothing function (14). To identify the appropriate span of smoothing functions to predict stroke mortality, we used a stepwise regression procedure. The selection criterion of goodness of fit was assessed using Akaike's information criterion (AIC) (15).

We excluded air pollutant levels exceeding 6 standard deviations above the mean to minimize the effects of pollutant extremes. We used robust regression by M-estimation to reduce the influence of extreme observations on daily death counts (16). We then evaluated the associations between the levels of air pollutants singly and in combination and daily stroke mortality. We express the relative risks as a percentage increase in stroke mortality for an interquartile increase in air pollutant concentrations. To explore the susceptibility of groups to the influence of PM<sub>10</sub>, we assessed the effect of age and sex on the relationship between stroke mortality

and PM<sub>10</sub> concentrations. We analyzed each subgroup stratified by age and sex to determine if the effects of PM<sub>10</sub> differ in this respect.

We also explored the sensitivities of our results to extreme concentrations of pollutants, to inclusion or exclusion of autoregressive terms in the model, and to a change of smooth function of time (windows of 175 to 700 days).

## Results

Table 1 shows the distribution of variables with respect to daily stroke mortality, meteorologic variables, and air pollutants in Seoul from 1995 to 1998. On average, 15.3 stroke deaths occurred per day during this period, which represents 15.7% of all nonexternally caused deaths. The concentration of PM<sub>10</sub> in Seoul is relatively high compared with those of other major world cities. Stroke mortality and pollution concentrations varied according to the day of the week (data not shown).

To determine lag effects of air pollutants upon stroke mortality, we compared the relative risks of different lag models with a maximum lag of 5 days (Figure 1). The associations between PM<sub>10</sub> and O<sub>3</sub> and stroke mortality were highest on the same day, whereas 2-day lagged concentrations of NO<sub>2</sub>, SO<sub>2</sub>, and CO showed the highest risk of stroke mortality. The correlations between same-day levels of PM<sub>10</sub> and O<sub>3</sub> and levels of NO<sub>2</sub>, SO<sub>2</sub>, and CO at a lag of 2 days are given in Table 2. Tables 3 and 4 show the estimated percentage increases in stroke mortality attributable to each interquartile change in pollutant concentrations after controlling for temporal trends, meteorologic variables, and days of the week. We observed an estimated increase of 1.5% (95% CI, 1.3–1.8%) and 2.9% (95% CI, 0.3–5.5%) in stroke mortality for each interquartile range increase in PM<sub>10</sub> and O<sub>3</sub> concentrations in the same day. Stroke

mortality also increased 3.1% (95% CI, 1.1–5.1%) for NO<sub>2</sub>, 2.9% (95% CI, 0.8–5.0%) for SO<sub>2</sub>, and 2.2% (95% CI, 0.4–4.1%) for CO in the 2-day lag for each interquartile range increase in single pollutant models.

We also evaluated changes in the relative risk of stroke mortality for one pollutant after stratifying the concentrations of another pollutant to determine whether there is any interaction between PM<sub>10</sub> and the other gaseous pollutants (Tables 3 and 4). The relative risk for PM<sub>10</sub> decreased from 4.8% to –1.5% when we changed NO<sub>2</sub> concentrations from below to above the median level in the model. The relative risk for PM<sub>10</sub> also depended on the different concentrations of SO<sub>2</sub>, CO, and O<sub>3</sub>. This risk increased at lower concentrations of SO<sub>2</sub> and CO and at the higher concentrations of O<sub>3</sub>. The gaseous pollutants were significantly associated with stroke mortality, and the magnitude of the increase in the relative risk of gaseous pollutants was greater than that of PM<sub>10</sub> for each interquartile range increase. Gaseous pollutants also showed changes of the relative risk when examined after stratifying PM<sub>10</sub> concentrations.

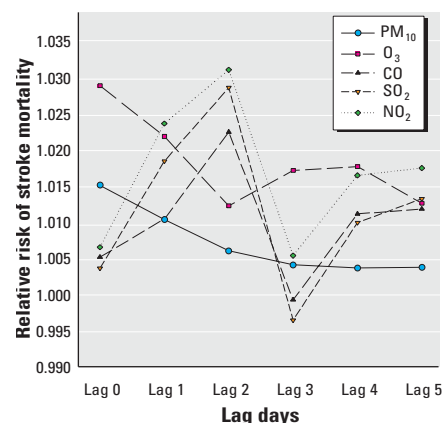
We found significant associations between stroke mortality and sex as well as age. The relative risk for females was 1.12 (95% CI, 1.09–1.15) and that for the elderly (≥ 65 years) was 2.05 (95% CI, 1.99–2.11). We also found significant interactions between the PM<sub>10</sub> concentrations and sex as well as age (Figures 2 and 3). For females and the elderly, we found linear exposure–response relationships, whereas for males and the younger age group, the exposure–response relationships were not evident.

The sensitivity analysis showed that the inclusion of extreme observation, use of autoregressive terms in the model, and

**Table 1.** Mean values of variables related to daily stroke mortality in Seoul, 1995–1998

Variables	Mean (SD)	Min	Med	Q1	Q3	Max
Stroke mortality (deaths/day)						
Male	7.3 (2.8)	1	5	7	9	17
Female	8.0 (3.0)	1	6	8	10	19
< 65 years old	5.0 (2.2)	1	3	5	6	13
≥ 65 years old	10.3 (3.5)	2	8	10	12	25
Meteorology						
Temperature (°C)	12.8 (10.1)	–11.8	3.9	14.3	22.0	30.4
Relative humidity (%)	62.7 (14.8)	18.8	52.1	63.1	73.6	96.1
Barometric pressure (hPa)	1016.3 (7.9)	994.8	1010.0	1016.4	1022.4	1036.5
Pollutants						
PM <sub>10</sub> (µg/m <sup>3</sup> )	71.1 (30.8)	18.4	47.4	67.6	89.3	236.9
NO <sub>2</sub> (ppb)	32.5 (10.2)	10.2	25.0	31.4	39.7	65.1
SO <sub>2</sub> (ppb)	12.1 (7.4)	3.0	6.8	9.8	15.5	46.0
O <sub>3</sub> (ppb)	22.6 (12.4)	3.1	13.3	20.7	30.0	75.3
CO (ppm)	1.2 (0.5)	0.4	0.9	1.1	1.4	3.4

Abbreviations: Max, maximum value; Med, median value; Min, minimum value; Q1, first quartile value; Q3 third quartile value.



**Figure 1.** The relative risks of stroke mortality attributable to each interquartile change in pollutant levels for different lag models with a maximum lag of 5 days.

change in the window span had little effect upon the model estimates.

## Discussion

Pollution-related health effects are results of exposure to mixed—particulate and gaseous—pollutants. Even though our study focuses on the effects of PM<sub>10</sub> concentrations on the relative risk of stroke mortality, we also found that gaseous pollutants were significant predictors of acute stroke death after controlling for obvious causes of confounding, including long-term trends, seasonal change, day-of-the-week effects, and meteorologic influence.

Some monitored pollutants, such as PM<sub>10</sub>, may be directly involved in the adverse health outcome, but it is more plausible that the pollutants are simply indicators of the pollutant mixtures that are actually associated with the adverse health effects (17). However, it is very difficult to separate one pollutant's effect from another's because the various pollutant levels tend to be interrelated. Collinearity among pollutants is a common problem in a time-series study, especially in multipollutant models (18). In this study, we tried to evaluate the effect of pollutant interactions on stroke mortality to understand better the effects of the pollution mix.

Because of the possible confounding effects of time-varying variables, we took into account various confounding factors, such as long-term trends, seasonality, and

meteorologic conditions. We also considered the day of the week because it was associated with remarkable changes in stroke mortality.

Through single-pollutant analyses and interaction models, our results demonstrated statistically significant associations between stroke mortality and PM<sub>10</sub> as well as all other gaseous pollutants. The strongest associations between stroke mortality and PM<sub>10</sub> and O<sub>3</sub> were seen in the same day, whereas for NO<sub>2</sub>, SO<sub>2</sub>, and CO the strongest associations were seen in 2-day lag. Interestingly, the effect sizes of the gaseous pollutants were greater than that of PM<sub>10</sub>, which is compatible with Moolgavkar's suggestion that gaseous pollutants are more strongly associated with various mortalities including stroke (17). Given that these lag times are pollutant dependent, the use of the same lag day to estimate pollutant effects would be likely to cause misinterpretation of any relationship. The estimated risks of stroke mortality for NO<sub>2</sub>, SO<sub>2</sub>, and CO were much lower and not significant when the same day's concentrations were used instead of concentrations of 2-day lag in the single-pollutant analyses. The reason why the three gaseous pollutants have their maximum effects at a lag of 2 days is not evident. Perhaps because the three pollutants are highly correlated at a lag of 2 days, one has an effect at a lag of 2 days and the others are simply collinear. The physiologic reason for this lag would be that it takes

some time for gaseous pollutants to convert into or adhere to fine particles that actually cause acute strokes.

We analyzed various pollutant models in an attempt to estimate the independent effect of PM<sub>10</sub> and the possible interaction between PM<sub>10</sub> and the gaseous pollutants present in a mixture rather than separately in the air. The relative risk for PM<sub>10</sub> varied with different concentrations of the gaseous pollutants. Gaseous pollutants also showed changes of relative risk when considered after stratifying PM<sub>10</sub> concentrations. However, certain combinations of PM<sub>10</sub> with the pollutants may be under-represented because the distributions of the pollutant variables are frequently not independent. For example, there were few days when both PM<sub>10</sub> and O<sub>3</sub> were in the highest quartiles of their respective ranges. This makes the interpretation of this stratified analysis limited to a certain range of pollutant concentrations.

There is a strong consensus that a significant and consistent association exists between mortality and PM<sub>10</sub> (19). The relationship between particulate air pollutants and mortality seems to continue well below current ambient air quality standards, and the exposure-response relationship is nearly linear with no evidence of a threshold (20,21). The shape of the exposure-response relationship between air pollutant concentrations and stroke mortality risk is also important for understanding the characteristics of pollutant effects, such as the linearity of the relationship or the presence of a stroke mortality threshold. Our findings suggest that the relationship is relatively linear without definite evidence of a threshold in a sensitive subgroup of the population.

A thorough identification of high-risk groups for target diseases would be useful to appropriate air quality management (18). If the epidemiologic association between

**Table 2.** Pearson's pairwise correlation coefficients of air pollutants.

Air pollutants	PM <sub>10</sub>	NO <sub>2</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>
PM <sub>10</sub>	1				
NO <sub>2</sub>	0.19	1			
SO <sub>2</sub>	0.26	0.50	1		
CO	0.22	0.64	0.90	1	
O <sub>3</sub>	-0.03	-0.13	-0.31	-0.35	1

Same-day concentrations are used for PM<sub>10</sub> and O<sub>3</sub>, whereas the 2-day lagged concentrations are used for NO<sub>2</sub>, SO<sub>2</sub>, and CO.

**Table 3.** Percent increase of the estimated relative risk of stroke mortality for each interquartile range increase in PM<sub>10</sub> in the single-pollutant model and change of the estimated percentage increases of relative risk when stratified by the median concentration of the gaseous pollutants.

Single-pollutant model for PM <sub>10</sub>	Percent change of relative risk for PM <sub>10</sub> stratified by gaseous pollutant concentrations							
	NO <sub>2</sub>		SO <sub>2</sub>		CO		O <sub>3</sub>	
	< Med	≥ Med	< Med	≥ Med	< Med	≥ Med	< Med	≥ Med
1.5 (1.3–1.8)	4.8	-1.5	1.7	0.5	2.6	0.0	-1.2	2.7

Med, median. Same-day concentrations are used for PM<sub>10</sub> and O<sub>3</sub>, whereas the 2-day lagged concentrations are used for NO<sub>2</sub>, SO<sub>2</sub>, and CO.

**Table 4.** Percent increase of the estimated relative risk of stroke mortality for each interquartile range increase in gaseous pollutants in the single-pollutant model and change of the estimated percentage increases of relative risk when stratified by the median concentration of PM<sub>10</sub>.

Single-pollutant model for gaseous pollutants	Percent change of relative risk for gaseous pollutants stratified by PM <sub>10</sub> concentration							
	PM <sub>10</sub>		PM <sub>10</sub>		PM <sub>10</sub>		PM <sub>10</sub>	
	< Med	≥ Med	< Med	≥ Med	< Med	≥ Med	< Med	≥ Med
NO <sub>2</sub>	3.1 (1.1–5.1)	2.8	3.2					
SO <sub>2</sub>	2.9 (0.8–5.0)			1.3	3.8			
CO	2.2 (0.4–4.1)					1.1	3.6	
O <sub>3</sub>	2.9 (0.3–5.5)							5.5
								-2.5

Med, median. Same-day concentrations are used for PM<sub>10</sub> and O<sub>3</sub>, whereas the 2-day lagged concentrations are used for NO<sub>2</sub>, SO<sub>2</sub>, and CO.

PM<sub>10</sub> and stroke is causal, it is likely that a frail subgroup is more affected by air pollution than a healthy group. Even though little is known of the characteristics of persons who are susceptible to adverse health effects related to air pollution, some studies suggest that some subgroups within the population are sensitive to air pollution, such as the elderly or pre-morbid people (22–25). We examined whether the effect of PM<sub>10</sub> on the risk of stroke death differed depending on age and sex. Even though the mean effect size of PM<sub>10</sub> is small, representing only a 1.5% increase in stroke mortality risk for a 41.9 µg/m<sup>3</sup> increase in PM<sub>10</sub> as an interquartile change, the significant interaction found between the effects of PM<sub>10</sub> and age as well as sex suggests that the elderly and women carry greater risks of stroke death due to PM<sub>10</sub>. The reasons for stronger effects in women are not clear, but it is notable that there are more stroke deaths in women in Seoul, whereas in the United States the rate among men is higher.

Biologic mechanisms for these associations have not been fully established and the characteristics of pollutant particulates are not understood well. The extent of the

effects of particulate pollutants vary and depend upon compositions and sources; therefore, estimates based on one location may not apply to other locations directly, without consideration of the particulates' characteristics. On the other hand, associations between particle concentrations and health effects have been found consistently in locations with widely varying emission sources, which indicates that there may be common pathways mediated by chemical species despite the diversity of exogenous chemicals (26).

It has been hypothesized that alveolar inflammation, induced by exposure to particulate air pollution, causes acute cardiovascular events in susceptible individuals (27). Metal components adsorbed onto air pollution particulates contribute significantly to the particles' ability to cause oxidant stress and cytokine production in alveolar macrophages (28). Therefore, production of free radicals induced by particulate pollutants might cause an inflammatory response, enhancing blood coagulation and increasing the risk of stroke deaths, especially in persons with pre-existing circulatory disease (27,29). The increase of plasma viscosity

associated with the inflammatory reactions might explain the pathogenesis linking air pollution to increased stroke mortality and cardiovascular disease mortality. This proposed biologic mechanism is supported by the findings that particulate air pollution is associated with day-to-day changes in plasma viscosity (30).

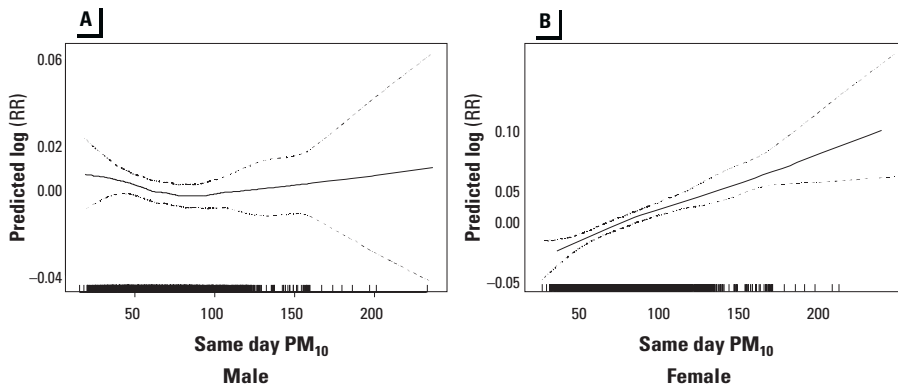
Individual-level studies are superior for assessing the effects of specific pollutants among individuals (31). However, like other time-series air pollution epidemiologic studies, this study is limited by its use of environmental monitoring data to represent ambient concentrations, which do not necessarily represent individual exposure. Therefore, measurement errors from difference between population-average exposures and ambient levels cannot be avoided completely. We also have unknown amounts of measurement error in other covariates (32). These kinds of measurement errors could bias our estimates of regression coefficients for air pollutants, but frequently they bias the result toward the null and underestimate the effects of pollution (31). Another source of measurement error from the difference between measured and true ambient level was minimized by using data from 20 air monitoring stations, which represented 80% of the Seoul administrative areas.

We do not know whether the pollution-related increase of stroke mortality truly represents an increase of stroke mortality or represents only an earlier death, by a few days or weeks, of those already about to die from previous strokes or other causes (33). Stroke mortality can represent stroke incidence because stroke is highly fatal and often takes an acute course. However, harvesting cannot be excluded as an explanation for at least some of the observed association.

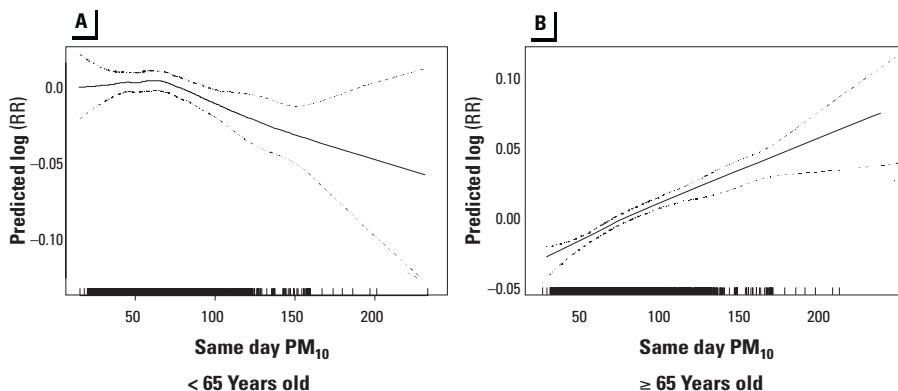
In summary, this study demonstrates an association between exposure to air pollutants and stroke mortality. In addition, we have seen evidence for interactions among air pollutants on the risk of stroke mortality. Our analysis indicates that the elderly and women carry greater risks of stroke mortality due to the effect of particulate pollutants.

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**Figure 2.** Change of the relationship between exposure to PM<sub>10</sub> and stroke mortality by sex. RR, relative risk. Percent increases of stroke mortality for each interquartile range increase of PM<sub>10</sub> for (A) males and for (B) females are –0.1 (95% CI, –3.2 to 3.1) and 2.4 (95% CI, –0.6 to 5.5).



**Figure 3.** Change of the relationship between exposure to PM<sub>10</sub> and stroke mortality by age. RR, relative risk. Percent increases of stroke mortality for each interquartile range increase of PM<sub>10</sub> for the age group (A) < 65 years old and for (B) ≥ 65 years old are –0.1 (95% CI, –3.6 to 3.5) and 2.1 (95% CI, –0.6 to 4.9).

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