

# Evidence for an Association Between Air Pollution and Daily Stroke Admissions in Kaohsiung, Taiwan

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**Background and Purpose**—Many studies have reported increases in daily cardiovascular mortality and hospital admissions associated with increases in levels of air pollutants. However, little is known about the relationship between hospital admissions for stroke and air pollution. This study was undertaken to determine whether there is an association between air pollution and hospital admissions for stroke in Kaohsiung, Taiwan.

**Methods**—Data on a total of 23 179 stroke admissions were obtained for the period 1997 through 2000. The relative risk of hospital admissions was estimated with a case-crossover approach.

**Results**—In the single-pollutant models, on warm days ( $\geq 20^{\circ}\text{C}$ ), significant positive associations were found between levels of  $\text{PM}_{10}$ ,  $\text{NO}_2$ ,  $\text{SO}_2$ ,  $\text{CO}$ , and  $\text{O}_3$  and both primary intracerebral hemorrhage and ischemic stroke admissions. On cool days ( $< 20^{\circ}\text{C}$ ), only  $\text{CO}$  levels and ischemic stroke admissions were significantly associated. For the 2-pollutant models,  $\text{PM}_{10}$  and  $\text{NO}_2$  remained consistently and significantly associated with admissions for both types of stroke on warm days. We observed estimated relative risks of 1.54 (95% confidence interval [95%], 1.31 to 1.81) and 1.56 (95% CI, 1.32 to 1.84) for primary intracerebral hemorrhage for each interquartile range increase in  $\text{PM}_{10}$  and  $\text{NO}_2$ . The values for ischemic stroke were 1.46 (95% CI, 1.32 to 1.61) and 1.55 (95% CI, 1.40 to 1.71), respectively. The effects of  $\text{CO}$ ,  $\text{SO}_2$ , and  $\text{O}_3$  were mostly nonsignificant when either  $\text{NO}_2$  or  $\text{PM}_{10}$  was controlled for.

**Conclusions**—This study provides an association between exposure to air pollution and hospital admissions for stroke. (*Stroke*. 2003;34:2612-2616.)

**Key Words:** air pollution ■ crossover studies ■ patient admissions ■ stroke

In the last decade, many studies have applied time-series methods to look for associations between air pollution and daily mortality.<sup>1,2</sup> However, most studies have been conducted in North American and European cities, with only a few done in Asia.<sup>3-6</sup> Most studies have reported associations between air pollution and daily deaths resulting from either respiratory or cardiovascular mortality.<sup>7,8</sup>

If air pollution is responsible for the observed increased mortality, one would expect to see it affect hospitalization rates. However, less attention has been focused on hospitalization compared with mortality during the past decade. Although mortality studies are still useful in cities with air pollution problems, studies on hospital admissions have become more important as the levels of air pollutants have decreased.<sup>9</sup> There is increasing interest in the use of hospital admission data in studies of short-term effects of air pollution. A number of studies have reported associations between air pollution and hospital admissions for respiratory<sup>9-17</sup> and cardiovascular ailments.<sup>9,12,16-21</sup>

Relatively few studies have examined the association between air pollution and stroke mortality. Two studies conducted in Seoul, Korea, have shown that commonly

measured pollutants ( $\text{O}_3$ ,  $\text{SO}_2$ ,  $\text{NO}_2$ ,  $\text{CO}$ ,  $\text{PM}_{10}$ ) are all significantly associated with stroke mortality.<sup>22,23</sup> In a study conducted in the Netherlands,<sup>24</sup> gaseous air pollutants ( $\text{O}_3$ ,  $\text{CO}$ ,  $\text{SO}_2$ ) were found to be significantly associated with stroke mortality. In Hong Kong, however, none of 4 pollutants ( $\text{SO}_2$ ,  $\text{NO}_2$ ,  $\text{O}_3$ ,  $\text{PM}_{10}$ ) studied were found to be significantly associated with stroke mortality.<sup>6</sup>

Several studies have also found associations between air pollution and stroke admissions. Significant associations were found between stroke admissions and  $\text{PM}_{10}$ <sup>12,21</sup> and  $\text{NO}_2$ .<sup>21</sup> However, several studies have also reported a lack of association between air pollution and stroke admission.<sup>16,20,25</sup> Taken overall, existing studies lack consistency as to the presence of effects or, where effects have been observed, the type of pollutant most responsible.

This study was undertaken to investigate the relationship between stroke admissions and the concentrations of air pollutants in Kaohsiung, Taiwan, over the 4-year period of 1997 through 2000.

## Materials and Methods

Kaohsiung is situated on the southwest coast of Taiwan. It is Taiwan's biggest commercial harbor and second largest city, with a

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**TABLE 1. Distribution of Daily Hospital Admission Counts, Weather, and Air Pollution Variables**

Variable	Minimum	25%	50%	75%	Maximum	Mean
PM <sub>10</sub> , µg/m <sup>3</sup>	20.50	42.00	77.63	108.33	217.33	78.82
SO <sub>2</sub> , ppb	1.25	6.83	9.76	13.00	26.80	10.08
NO <sub>2</sub> , ppb	6.25	19.25	28.67	36.33	63.40	28.17
CO, ppm	0.24	0.64	0.79	0.93	1.72	0.79
O <sub>3</sub> , ppb	1.25	13.20	23.80	34.40	83.00	25.02
Temperature, °C	10.50	22.80	26.20	28.20	31.10	25.28
Humidity, %	50.00	74.00	78.00	82.00	99.00	78.17
Stroke	2	12	16	19	50	15.87
SHS	0	0	0	1	9	0.59
PIH	0	2	3	5	40	3.55
IS	0	6	8	11	33	8.73
Others	0	2	3	4	11	2.99

population of ≈1.46 million. It is the chief center of Taiwan's heavy industry, including China Steel Corp, China Shipbuilding Corp, and the petrochemical industry.

The National Health Insurance Program, which provides compulsory universal health insurance, was implemented in Taiwan on March 1, 1995, and covers most of the population (coverage was 96.16% in 2000).<sup>26</sup> Computerized records of daily clinic visits or hospital admissions are available for each contracted medical institution. All medical institutions must submit standard claim documents for medical expenses on a computerized form that includes the dates of admission and discharge, identification number, sex, birthday, and diagnostic code of each admission from the *International Classification of Diseases*, 9th revision (ICD-9). We abstracted data on the number of daily admissions for cases in which the principal diagnosis was cerebrovascular diseases (ICD-9 codes 430 to 438) from the medical insurance file. For this report, stroke subtypes were categorized as subarachnoid hemorrhagic stroke (SHS; ICD-9 code 430), primary intracerebral hemorrhage (PIH; ICD-9 codes 431 to 432), ischemic stroke (IS; ICD-9 codes 433 to 435), and others (ICD-9 codes 436 to 438). Information regarding how the stroke subtypes were categorized was not available. However, the classification of stroke types appears to be sufficiently accurate for use in epidemiological studies because CT and/or MRI are performed in almost all stroke patients.<sup>27,28</sup>

Six air-quality monitoring stations were established in Kaohsiung by the Environmental Protection Administration. The monitoring stations are fully automated and provide readings of SO<sub>2</sub>, PM<sub>10</sub>, NO<sub>2</sub>, CO, and O<sub>3</sub>. For each day, air pollution data were extracted for all of the monitoring stations and averaged. When data were missing for a particular monitoring station on a given day, the values from the remaining monitors were used to compute the average. Daily information on mean temperature and mean humidity was provided by the Central Weather Bureau from a station located on the coastline of Kaohsiung Harbor.

Data were analyzed with the case-crossover technique.<sup>29,30</sup> This design is an alternative to time-series regression models for studying the short-term effects of air pollution.<sup>31</sup> In general, the case-crossover design and the time-series approach have produced almost identical results.<sup>32,33</sup>

The number of stroke admissions varied significantly according to the day of the week (data not shown). This day-of-the-week effect was controlled for by comparing air pollution levels on the dates of hospital admissions with air pollution levels 1 week before and 1 week after the date of admission.<sup>34</sup> Results of previous studies indicated that the increased mortality or hospital admissions were associated with high air pollution levels on the same day or the previous 2 days.<sup>35</sup> Longer lag times have rarely been described. Thus, we used the cumulative lag up to 2 previous days. The associations between hospital admissions and levels of air pollutants

were estimated by use of odds ratios (ORs) and their 95% confidence intervals (CIs), which were produced through conditional logistic regression with weights equal to the number of admissions on that day. SAS software was used for statistical analysis. Exposure to air pollutants and meteorologic variables were entered into the models as continuous variables. ORs were calculated for the interquartile range (IQR; between the 25th and 75th percentiles) of each pollutant as observed during the study period.

## Results

There were a total of 23 179 stroke admissions (864 for SHS, 5193 for PIH, 12 758 for IS, and 4364 for others) for the 63 hospitals in Kaohsiung. The distribution of air pollutants, meteorologic variables, and daily number of stroke admissions are shown in Table 1. There were an average of 16 stroke admissions. The current level of pollutants was quite low compared with Taiwan's current standard.<sup>36</sup>

The associations between various air pollutants and stroke admissions are shown in Table 2. For the single-pollutant models, both PIH and IS admissions were significantly associated with all pollutants except SO<sub>2</sub> on warm days. However, for cool days, only IS admissions and CO levels were significantly associated. We observed estimated ORs of 1.54 (95% CI, 1.31 to 1.81) and 1.56 (95% CI, 1.32 to 1.84) for PIH for each IQR increase in PM<sub>10</sub> and NO<sub>2</sub>. The estimated ORs for IS were 1.46 (95% CI, 1.32 to 1.61) and 1.55 (95% CI, 1.40 to 1.71), respectively. The patterns are similar when we analyzed the data combining IS and PIH (data not shown).

Two-pollutant models were examined to obtain insight into which individual pollutants might influence stroke admissions independently of the effects of others. These analyses were confined to warm days. Again, SO<sub>2</sub> was not significant. We draw attention to those analyses in which the effect of a particular pollutant remained significant after each of the other 4 pollutants was included in the model. PM<sub>10</sub> and NO<sub>2</sub> were all significant in combination with each of the other 4 pollutants. CO remained significant after the inclusion of SO<sub>2</sub> or O<sub>3</sub>. O<sub>3</sub> remained significant after SO<sub>2</sub> or CO was included in the model (Table 3).

**TABLE 2. ORs (95% CIs) of Stroke Admissions for Each IQR Increase\* in Single-Pollutant Models†**

Temperature, °C	OR (95% CI)	
	PIH	IS
≥20	(n=4539)	(n=11528)
PM <sub>10</sub>	1.54 (1.31–1.81)‡	1.46 (1.32–1.61)‡
SO <sub>2</sub>	1.06 (0.95–1.18)	1.06 (1.00–1.13)
NO <sub>2</sub>	1.56 (1.32–1.84)‡	1.55 (1.40–1.71)‡
CO	1.21 (1.09–1.34)‡	1.21 (1.14–1.28)‡
O <sub>3</sub>	1.20 (1.06–1.35)‡	1.15 (1.07–1.23)‡
<20	(n=654)	(n=1230)
PM <sub>10</sub>	0.82 (0.48–1.40)	0.97 (0.65–1.44)
SO <sub>2</sub>	0.85 (0.58–1.26)	1.11 (0.83–1.48)
NO <sub>2</sub>	0.81 (0.50–1.31)	1.16 (0.81–1.68)
CO	1.18 (0.80–1.72)	1.77 (1.31–2.39)‡
O <sub>3</sub>	0.57 (0.24–1.34)	0.88 (0.50–1.53)

\*An IQR increase in PM<sub>10</sub> (66.33 μg/m<sup>3</sup>), SO<sub>2</sub> (6.17 ppb), NO<sub>2</sub> (17.08 ppb), CO (0.29 ppm), and O<sub>3</sub> (21.20 ppb).

†Adjusted for temperature and humidity.

‡P<0.01.

## Discussion

This is one of the few investigations of daily stroke admissions reported so far and is one of the few studies on short-term effects of air pollution on mortality or hospital admissions performed in Asia. This study has shown for the first time an association between concentrations of PM<sub>10</sub> and NO<sub>2</sub> and IS and PIH admissions on warm days. The associations were generally stronger for PIH admissions than for IS admissions. The reasons for stronger associations in PIH admissions are not clear, but it is notable that the range of daily stroke admissions for PIH is greater than that for IS.

The case-crossover study design offers the ability to control confounders by design rather than by modeling. This design is an adaptation of the case-control study in which each case serves as his or her own referent. Therefore, time-invariant subject-specific variables such as sex and age do not act as confounders. Also, by choosing 1 week before and 1 week after the date of stroke admission as the controls, this approach could avoid possible confounding resulting from the effects of day of the week, seasonability, or long-term trends.<sup>32–34</sup> We do not think that our findings can be attributed to the approach used because this approach is now accepted for studying the short-term effects of air pollution.<sup>32,33,37–39</sup>

For a factor to confound the relationship between air pollution and stroke admissions, it has to be correlated with both of those variables. It is unlikely that smoking and other indoor pollutants confound the present associations because day-to-day variations in indoor emissions, including smoking, are not correlated with outdoor air pollution.

Seasonal interactions between daily mortality or hospital admissions and air pollutants have often been reported, and various explanations have been postulated.<sup>16</sup> In the present study, we found that on cool days only IS admissions and CO levels were significantly associated. Because multiple significance tests were performed, the likelihood of this finding being the result of chance is considerable. The absence of an association on cool days could be related to the relatively mild winters in Kaohsiung, where the mean monthly temperatures from December to February ranged from 18.8°C to 22.1°C and the mean daily temperature rarely drops below 15°C. Also, there may not have been enough power to detect associations resulting from the small daily number of stroke admissions on cool days.

**TABLE 3. ORs (95% CIs)\* of Stroke Admissions for Each IQR Change† in 2-Pollutant Models**

	OR (95% CI)				
	Adjusted for PM <sub>10</sub>	Adjusted for SO <sub>2</sub>	Adjusted for NO <sub>2</sub>	Adjusted for CO	Adjusted for O <sub>3</sub>
PM <sub>10</sub>					
PIH	...	1.55 (1.31–1.83)§	1.28 (1.01–1.61)§	1.45 (1.20–1.74)§	1.56 (1.27–1.91)§
IS	...	1.46 (1.32–1.61)§	1.16 (1.01–1.34)§	1.35 (1.21–1.51)§	1.51 (1.34–1.71)§
SO <sub>2</sub>					
PIH	0.99 (0.88–1.11)	...	0.91 (0.80–1.03)	0.94 (0.83–1.06)	1.08 (0.96–1.20)
IS	1.01 (0.95–1.08)	...	0.93 (0.87–1.00)	0.94 (0.88–1.02)	1.08 (1.01–1.15)§
NO <sub>2</sub>					
PIH	1.31 (1.03–1.66)‡	1.66 (1.38–2.00)§	...	1.60 (1.25–2.05)§	1.51 (1.26–1.80)§
IS	1.39 (1.20–1.60)§	1.62 (1.45–1.81)§	...	1.54 (1.33–1.79)§	1.53 (1.37–1.71)§
CO					
PIH	1.08 (0.97–1.22)	1.25 (1.11–1.40)§	0.98 (0.84–1.14)	...	1.19 (1.08–1.32)§
IS	1.11 (1.04–1.19)§	1.24 (1.16–1.33)§	1.00 (0.92–1.09)	...	1.19 (1.12–1.26)§
O <sub>3</sub>					
PIH	0.98 (0.85–1.14)	1.21 (1.07–1.36)§	1.07 (0.94–1.22)	1.17 (1.03–1.32)‡	...
IS	0.96 (0.88–1.05)	1.16 (1.08–1.24)§	1.02 (0.94–1.10)	1.12 (1.04–1.20)§	...

\*Adjusted for temperature and humidity.

†An IQR increase in PM<sub>10</sub> (66.33 μg/m<sup>3</sup>), SO<sub>2</sub> (6.17 ppb), NO<sub>2</sub> (17.08 ppb), CO (0.29 ppm), and O<sub>3</sub> (21.20 ppb).

‡P<0.05; §P<0.01.

There is now strong consensus that a significant association exists between mortality and PM<sub>10</sub> levels. Lipfert,<sup>40</sup> in a review of several studies on hospital admissions, suggests a consistent association between hospital admissions for respiratory conditions and PM<sub>10</sub>. The impact of PM<sub>10</sub> on admissions for stroke is less well documented.<sup>12,16,20,21,25</sup> We found evidence of an association between PM<sub>10</sub> and stroke admissions that is in agreement with the findings of Ponka and Virtanen<sup>21</sup> and Wordley et al.<sup>12</sup> Our results further suggest that increased stroke admissions are associated with NO<sub>2</sub> levels and not merely with PM<sub>10</sub> levels, which are highly correlated with NO<sub>2</sub> concentrations. This finding is in agreement with that of Ponka and Virtanen.<sup>21</sup> The importance of NO<sub>2</sub> as a cause of increased mortality or hospital admissions is not sufficiently understood. However, we cannot rule out the possibility that NO<sub>2</sub> was acting, at least in part, as a surrogate for some other unmeasured end products of reaction sequences initiated by NO<sub>2</sub>.

In most recent studies, particles have been indicated to have a possible causal effect on cardiovascular mortality. Several potential mechanisms have been proposed. It has been hypothesized that exposure to particles could provoke alveolar inflammation, causing exacerbations of existing lung disease and increased blood coagulation.<sup>41</sup> It has also been suggested that elevated levels of particulates are associated with increased plasma viscosity,<sup>42</sup> increased risks of raised heart rate,<sup>43</sup> and changes in heart rate variability.<sup>44</sup> In addition, studies have reported an association between plasma fibrinogen and both particles and NO<sub>2</sub>.<sup>45,46</sup> These findings suggest hemodynamic disturbances that may lead to an increased risk of cardiovascular events and an increased risk of other types of circulatory events such as stroke.<sup>22</sup> Exposure to high temperatures has also been found to increase plasma viscosity and serum cholesterol levels.<sup>47,48</sup> During the onset of heat stroke in experimental animals exposed to very high temperatures, increased intracranial hypertension and cerebral ischemia have been reported.<sup>48</sup> It is not clear whether these conditions might explain the increased risk of stroke admissions found in this study on hot days.

Our study has several limitations. First, there is potential for selection bias because we were unable to include clinically unrecognized stroke cases or cases treated at home. Second, we assigned air pollutant levels from fixed outdoor monitoring stations to individuals to estimate their exposure. Measurement errors resulting from the differences between the population-average exposure and ambient levels cannot be avoided. However, this kind of measurement error is of the Berkson type and is known to cause a bias toward the null and an underestimate of the association.<sup>35,49</sup> Third, data on influenza epidemics were not available and could not be controlled for in this study. The present work, however, focused on determining whether daily air pollution fluctuation is associated with stroke admissions. Influenza epidemics can produce respiratory diseases, but the presence of influenza epidemics may not promote stroke epidemics. We therefore think that influenza epidemics are unlikely to be a true confounder. Fourth, this study was conducted in a tropical city, and this fact may restrict somewhat the generalizability of these findings to other locations with different meteorological characteristics.

Fifth, findings may have been influenced by the “seasonally” stratified analyses. A potential disadvantage is the loss of statistical power.

A major argument in favor of causality is the consistency of results obtained from a wide variety of cities throughout the world. Our work provides evidence that the associations found in other countries are present in a city in Taiwan, even under different climatic conditions. The possibility that this consistency results from publication bias cannot be excluded.

In summary, this study provides an association between exposure to air pollution and hospital admissions for stroke. PM<sub>10</sub> and NO<sub>2</sub> seem to be the most important pollutants, and the effects appear to be stronger on warm days. The ecological design of the study precludes the inference of cause and effect. However, these findings support the possibility that there are acute pathogenetic processes in the cerebrovascular system that are induced by air pollution.

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