Cardiovascular Emergency Hospital Visits and Hourly Changes in Air Pollution

Takashi Yorifuji, MD; Etsuji Suzuki, MD; Saori Kashima, PhD

Background and Purpose—Few studies have examined the effect of hourly changes in air pollution on cardiovascular disease morbidity. We evaluated the associations between hourly changes in air pollution and the risks of several types of cardiovascular disease.

Methods—We used a time-stratified case-crossover design. Study participants were 10,949 residents of the city of Okayama, Japan, aged ≥65 years who were taken to hospital emergency rooms between January 2006 and December 2010 for onset of cardiovascular disease. We calculated city representative hourly average concentrations of air pollutants from several monitoring stations and examined the associations between air pollution exposure before the case event, focusing mainly on suspended particulate matter, and disease onset.

Results—Suspended particulate matter exposure 0 to <6 hours before the case events was associated with risks of onset of cardiovascular and cerebrovascular disease; odds ratios after 1 interquartile range increase in suspended particulate matter exposure were 1.04 (95% confidence interval, 1.01–1.06) for cardiovascular disease and 1.04 (95% confidence interval, 1.00–1.08) for cerebrovascular disease. We observed an elevated risk of hemorrhagic as well as ischemic stroke, but the risk was slightly higher for hemorrhagic stroke, and this elevation was persistent. Women tended to have higher effect estimates.

Conclusions—This study provides further evidence that particulate matter exposure increases the risks of onset of cardiovascular and cerebrovascular disease (including hemorrhagic stroke) shortly after exposure. (Stroke. 2014;45:1264-1268.)

Key Words: air pollution ■ cardiovascular diseases ■ particulate matter ■ stroke

Several studies have shown associations between short-term exposure to air pollution and cardiovascular disease. Specific cardiovascular events considered to be associated with air pollution include ischemic heart disease,1 heart failure,2 cardiac arrhythmia/arrest,3 and ischemic stroke.4 However, the findings for hemorrhagic stroke remain inconsistent. Most such studies in Western countries have linked the levels of air pollutants to ischemic but not hemorrhagic stroke.4-6 Several studies in Asian countries, where the incidence of hemorrhagic stroke is high,7 have suggested an association between air pollutant levels and this type of stroke.8-13

In addition, most studies to date have evaluated the association between daily time scale of air pollution and cardiovascular outcomes. Only a small number of epidemiological studies have examined the effect of hourly variations in air pollution on ischemic heart disease,1,14 cardiac arrest,1 or ischemic stroke5,6 and demonstrated possible adverse effects. Although 1 study in Japan suggested that suspended particulate matter (SPM) exposure 2 hours before death was associated with the risk of intracerebral hemorrhage mortality in warmer seasons,11 no study thus far has examined the effect of hourly changes in air pollution on hemorrhagic stroke morbidity. Because of the findings of 1 experimental study, in which inhalation of diesel exhaust was shown to impair the regulation of vascular tone 2 hours after exposure and that the impairment was persistent at 6 hours,15 it is plausible that hemorrhagic stroke may also be induced shortly after air pollution exposure.

We, therefore, evaluated the associations between hourly changes in air pollution and the risk of cardiovascular disease onset, focusing mainly on types of cerebrovascular disease, in the residents of Okayama, Japan, who had visited emergency rooms between January 2006 and December 2010.

Material and Methods

Study Design and Subjects

We used a time-stratified, case-crossover design. Case-crossover design can be considered as a case–control version of crossover study and is an approach for studying acute effects of exposure.16 The design uses cases only; for each individual case, exposure before the event (case period) is compared with exposure at other control (or referent) periods. By making within-subject comparisons, time-invariant confounders (eg, demographic factors, past history of disease, chronic conditions) are not confounded.

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Air Pollution Data and Meteorologic Data
We obtained hourly concentrations of SPM, NO$_2$, SO$_2$, ozone, and CO, measured at monitoring stations in the city of Okayama during the study period, from the Okayama Prefectural Government. PM is measured as SPM in Japan and accounts for PM with an aerodynamic diameter <7 μm (PM$_{10}$). During the study period, 11 stations were used for SPM measurements, 11 for NO$_2$, 7 for SO$_2$, 8 for ozone, and 2 for CO. The entire area of the city is covered by 30-km buffers from at least 2 monitoring stations. We then calculated city representative hourly average concentrations of each air pollutant from hourly concentrations at each monitoring station. Although there were no missing data for city representative hourly average concentrations for SPM, NO$_2$, and SO$_2$ during the study period, we lacked 502 hourly concentrations for ozone (1.15% of eligible hours) and 26 for CO (0.06% of eligible hours).

We also obtained hourly temperature and relative humidity during the study period from 1 weather station in the city of Okayama managed by the Japan Meteorological Agency. There were no missing data for temperature and relative humidity.

Health Outcomes
Type of disease was diagnosed by physicians at the hospitals to which the patients were transported and coded in accordance with the International Classification of Diseases, 10th edition (ICD-10). We used the following diseases as main outcomes: cardiovascular disease (ICD-10: I10–I70 and G45.9), cerebrovascular disease (I60–I69), transient ischemic attack (TIA; G45.9), and cardiovascular disease (I44–I49) cases for reference. The Ambulance Division of the Fire Bureau in the city of Okayama (the towns of Takebe and Mitsu) so that the study area could be covered by 20-km buffers from each monitoring station. We then repeated the analyses. Second, because influenza infection can be a risk factor for cardiovascular disease, we included weekly numbers of reported influenza cases in patients aged ≥60 years among monitoring medical institutions in the city. We obtained these data from the Website of the public health center in the city. Third, we tested the linearity assumption between air pollution exposure and health outcomes by replacing the continuous exposure variables by a natural spline with 3 degrees of freedom and compared the model fit by the likelihood ratio test.

Results
Table 1 presents the characteristics of the participants. More than 15% of the patients had a history of hypertension or cerebrovascular disease, and the most common type of emergency room visit was for cerebrovascular disease.

During the study period, means (SDs) of air pollutants were 26.8 (18.3) μg/m$^3$ for SPM, 17.1 (8.1) ppb for NO$_2$, 3.0 (2.5) ppb for SO$_2$, 25.9 (17.9) ppb for ozone, and 0.6 (0.3) ppm for CO.

We conducted conditional logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between air pollution exposure and each health outcome. We used exposure data as continuous variables based on the previous studies showing linear relationships between acute exposure to air pollution and health outcomes and estimated adjusted ORs for an interquartile range increase in each air pollutant during the study period. In all analyses, we adjusted for hourly ambient temperature using a natural spline with 6 degrees of freedom and hourly relative humidity with 3 degrees of freedom. We used meteorologic data at the time of case event.

We first assessed the effects of exposure to each air pollutant, averaged during the period 0 to <6 hours before the case events (ie, emergency calls), on the onset of cardiovascular and cerebrovascular disease. We next evaluated the effect of SPM, averaged during 6 different periods before the case event (0 to <6, 0 to <12, 0 to <24, 24 to <48, 48 to <72, and 72 to <96 hours), on both outcomes (cardiovascular and cerebrovascular disease) as well as more detailed outcomes (hemorrhagic stroke, ischemic stroke, and TIA). To evaluate the effect of shorter exposure in more detail, we also evaluated the effect of SPM averaged for 2-hour increments before the case event (ie, 0 to <2 through 22 to <24 hours).

In additional analyses, we evaluated the effects of SPM, averaged for the period 0 to <6 hours before the case event, on onset of cardiovascular and cerebrovascular disease by each subgroup of patients: age (<75 versus ≥75 years), sex, season of onset (April to September versus October to March), history of hypertension, history of diabetes mellitus, history of arrhythmia, history of coronary heart disease, and history of cerebrovascular disease. P values for statistical interaction <0.05 (2-sided) were considered significant.

When we examined the effect of SPM averaged at 6 different periods before the case event, the latest exposure (ie, 0 to <6 hours) was associated more strongly than other exposure periods with health outcomes other than hemorrhagic stroke (Table 2). After 1 interquartile range increase in SPM averaged at 0 to <6 hours before the case events, ORs were 1.04 (95% CI, 1.01–1.06) for cardiovascular disease, 1.04 (95% CI, 1.00–1.08) for cerebrovascular disease, 1.04 (95% CI, 0.98–1.09) for ischemic stroke, and 1.04 (95% CI, 0.95–1.13) for TIA. For hemorrhagic stroke, the highest OR was observed for the exposure 48 to <72 hours before onset (OR, 1.08; 95% CI, 1.00–1.16), and we observed elevated ORs across various exposure periods (ie, up to 96 hours before onset). In contrast, the effect estimates for ischemic stroke and TIA were in the protective direction at longer lags (eg, 24–72 hours before onset).
Table 1. Characteristics of Emergency Hospital Visits for Patients >65 Years With Cardiovascular Disease and Residing in Okayama City, Japan, 2006 to 2010 (n=10949)

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>80 (8.1)</td>
</tr>
<tr>
<td>Patients ≥75 y*</td>
<td>7930 (72.4)</td>
</tr>
<tr>
<td>Women*</td>
<td>5801 (53)</td>
</tr>
<tr>
<td>Medical history*</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1933 (18)</td>
</tr>
<tr>
<td>Arhythmia</td>
<td>245 (2.2)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>965 (8.8)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1829 (17)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>726 (6.6)</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>274 (2.5)</td>
</tr>
<tr>
<td>Types of cardiovascular disease*</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1597 (15)</td>
</tr>
<tr>
<td>Arhythmia</td>
<td>813 (7.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5851 (54)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1452 (13)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2726 (25)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1047 (9.6)</td>
</tr>
</tbody>
</table>

*No. (%) of participants is shown. Percentages may not sum to 100% due to rounding.

We examined the effect of exposure <24 hours of onset of disease in more detail (Figure): SPM exposure 0 to 6 hours before onset was more highly correlated with elevated risks of cardiovascular and cerebrovascular disease onset. SPM exposure 4 to <6 hours before the case event was most strongly associated with an elevated risk of hemorrhagic stroke (OR, 1.06; 95% CI, 0.99–1.14), whereas SPM exposure 2 to <4 hours before the case event was most strongly associated with an elevated risk of ischemic stroke (OR, 1.04; 95% CI, 0.99–1.09). However, the effect estimates for ischemic stroke were in the protective direction a greater number of hours before onset (eg, 10–20 hours). The results for TIA were equivocal (Figure I in the online-only Data Supplement).

In stratified analyses by subgroups of patients (Table I in the online-only Data Supplement), we observed a statistically significant interaction only for stratification by sex. Women had higher effect estimates for both cardiovascular and cerebrovascular disease compared with men.

In sensitivity analyses, the exclusion of the towns of Takebe and Mitsu from the analyses provided similar results: ORs for exposure 0 to <6 hours before the case events were 1.04 (95% CI, 1.01–1.06) for cardiovascular disease and 1.04 (95% CI, 1.00–1.08) for cerebrovascular disease. Even after adjusting for weekly number of influenza cases, the results did not change substantially; ORs for exposure 0 to <6 hours before the case events were 1.03 (95% CI, 1.01–1.06) for cardiovascular disease and 1.04 (95% CI, 1.00–1.08) for cerebrovascular disease. Finally, the comparison of linear models and spline models showed that the association of SPM exposure 0 to <6 hours before the case events with cardiovascular and cerebrovascular disease did not deviate significantly from linearity (P=0.55 and 0.98, respectively).

### Table 2. Adjusted ORs* and 95% CIs After an Intergroup Range (IQR) Increase in Each Pollutant in the 6 h Preceding Emergency Call for Cardiovascular Hospital Visits

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Cardiovascular Disease</th>
<th>Cerebrovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPM</td>
<td>0.6 μg/m³</td>
<td>1.04 (1.01–1.06)</td>
</tr>
<tr>
<td>NO₂</td>
<td>11.1 ppb</td>
<td>1.04 (0.99–1.08)</td>
</tr>
<tr>
<td>SO₂</td>
<td>2.3 ppb</td>
<td>1.03 (1.00–1.06)</td>
</tr>
<tr>
<td>Ozone</td>
<td>25.8 ppb</td>
<td>1.00 (0.93–1.05)</td>
</tr>
<tr>
<td>CO</td>
<td>0.3 ppm</td>
<td>1.03 (1.00–1.07)</td>
</tr>
</tbody>
</table>

*Adjusted for ambient temperature (degrees of freedom=6) and humidity (degrees of freedom=3).

Discussion

In the present study, we evaluated the associations between hourly changes in air pollution, in particular SPM, and the risk of cardiovascular disease onset, focusing mainly on the types of cerebrovascular disease in Okayama, Japan. We found that SPM exposure 0 to <6 hours before the case events was positively associated with the risk of cardiovascular and cerebrovascular disease onsets. We also observed elevated risk for hemorrhagic as well as ischemic stroke, but the risk was slightly higher for hemorrhagic stroke, and the elevated risk persisted for several days. Increased risk of ischemic stroke was followed by reduced risk at longer lags. Women tended to have higher effect estimates for both cardiovascular and cerebrovascular disease.

The observed cardiovascular effect of intraday levels of SPM exposure was consistent with that of previous studies. Peters et al found that PM concentrations 1 and 2 hours before onset were associated with an elevated risk of myocardial infarction in the United States. Bhaskaran et al also demonstrated that PM and NO₂ levels were associated with transiently increased risk of myocardial infarction 1 to 6 hours after exposure in England and Wales. Moreover, the effect of hourly changes in PM in the United States on ischemic stroke was evaluated by Wellenius et al, and the risk of stroke onset increased immediately after exposure and peaked 12 to 14 hours before onset. These transient increases in risk immediately after PM exposure are supported by experimental studies demonstrating that inhalation of diesel exhaust caused vascular dysfunction, ischemia, and thrombotic dysfunction within few hours after exposure.

The elevated risk of hemorrhagic stroke (ie, 2 to <4 hours as well as 48 to <72 hours before the event) is consistent with previous studies in Asian countries and may be explained by the high frequency of hemorrhagic stroke in these countries, including Japan. The present finding of slightly higher and persistently elevated risk of hemorrhagic stroke compared with ischemic stroke or TIA may be attributable to differences in the mechanisms of hemorrhagic stroke and ischemic stroke/TIA.

We also observed that women were at greater risk for both cardiovascular and cerebrovascular disease onset, and the findings are consistent with previous studies. The increased
risk may be attributable to biological or exposure differences between men and women.

The strength of the present study is that we could obtain hourly data on both air pollution and emergency visits, which enabled us to examine the effects of hourly changes in air pollution on the risk of cardiovascular onsets. Previous mortality studies\(^{12,13}\) were not able to determine whether air pollution could trigger new stroke events or precipitate death of patients with pre-existing stroke, and their use of daily time scale prevented the determination of exact temporal relationship between air pollution exposure and disease onset. In addition, we were able to obtain patient information (eg, pre-existing disease) and thus could evaluate effect modifications of these individual characteristics. Finally, we were able to examine the effect of air pollution on the risk of hemorrhagic stroke in Japan, where the incidence of this type of stroke is high.

However, several limitations should be noted. First, this study is a retrospective study using an administrative data set not designed for research purpose. Second, because we did not have the exact times of disease onset, we used the time of emergency call as the time of disease onset for each case. We think, however, that the lag between time of disease onset and time of emergency call is negligible. In Japan, there is good access to medical care, for example, a universal health insurance system that covers all of its citizens, and ambulance transport is free of charge.

### Table 3. Adjusted OR* per Interquartile Range Increase in SPM by Exposure Period Before Emergency Call

<table>
<thead>
<tr>
<th>SPM</th>
<th>Cardiovascular Disease</th>
<th>Cerebrovascular Disease</th>
<th>Hemorrhagic Stroke</th>
<th>Ischemic Stroke</th>
<th>TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 h</td>
<td>1.04 (1.01–1.06)</td>
<td>1.04 (1.00–1.08)</td>
<td>1.05 (0.97–1.13)</td>
<td>1.04 (0.98–1.09)</td>
<td>1.04 (0.95–1.13)</td>
</tr>
<tr>
<td>0–12 h</td>
<td>1.02 (0.99–1.05)</td>
<td>1.03 (0.99–1.07)</td>
<td>1.05 (0.97–1.13)</td>
<td>1.02 (0.96–1.08)</td>
<td>1.01 (0.92–1.11)</td>
</tr>
<tr>
<td>0–24 h</td>
<td>1.00 (0.97–1.04)</td>
<td>1.01 (0.96–1.05)</td>
<td>1.03 (0.95–1.12)</td>
<td>0.99 (0.92–1.06)</td>
<td>1.00 (0.90–1.10)</td>
</tr>
<tr>
<td>24–48 h</td>
<td>0.97 (0.94–1.00)</td>
<td>0.96 (0.92–1.00)</td>
<td>1.03 (0.95–1.12)</td>
<td>0.92 (0.86–0.98)</td>
<td>0.88 (0.79–0.98)</td>
</tr>
<tr>
<td>48–72 h</td>
<td>1.00 (0.97–1.03)</td>
<td>0.99 (0.95–1.03)</td>
<td>1.08 (1.00–1.16)</td>
<td>0.95 (0.89–1.01)</td>
<td>0.92 (0.83–1.01)</td>
</tr>
<tr>
<td>72–96 h</td>
<td>0.97 (0.95–1.00)</td>
<td>1.00 (0.96–1.04)</td>
<td>1.05 (0.97–1.13)</td>
<td>0.97 (0.91–1.03)</td>
<td>0.94 (0.85–1.03)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; SPM, suspended particulate matter; and TIA, transient ischemic attack.

*Adjusted for ambient temperature (degrees of freedom=6) and humidity (degrees of freedom=3). Interquartile range=20.6 μg/m\(^3\).

### Figure

Odds ratio of cardiovascular disease onset for an interquartile range increase in suspended particulate matter (20.6 μg/m\(^3\)) in the hours before disease onset. Vertical bars indicate 95% confidence intervals: (A) cardiovascular disease, (B) cerebrovascular disease, (C) hemorrhagic stroke, and (D) ischemic stroke.
Although we did not have data on time lags in the city of Okayama, the median lags and the proportion of lags <1 hour in the Tokyo metropolitan area in 2010 were reported as follows: 46 minutes and 52.4% for ischemic stroke, 38 minutes and 63.8% for intracerebral hemorrhage, and 30 minutes and 57.1% for subarachnoid hemorrhage. The shorter lag for hemorrhagic stroke than for ischemic stroke may partially explain the differences between peaks in effect estimates for the diseases, but the lags for each type of stroke would not affect the observed results substantially.

Third, disease diagnosis was made by physicians at the hospitals to which the patients were transported. Diagnostic technique is, however, considered standardized in these hospitals. Thus, misclassification would be nondifferential and relatively rare.

Fourth, we assumed that all residents were exposed to the same concentration without considering spatial distribution. This exposure measurement error may widen confidence intervals but may lead to little or no bias (ie, Berkson error). In support of this, the analyses restricted to 20-km buffers from each monitoring station provided similar effect estimates.

Finally, we did not include patients who arrived at hospitals by their private vehicles. Therefore, we might not be able to generalize the present findings to all emergency hospital visits. Moreover, we could not differentiate each patient on the data; thus, we might have counted the same participants more than once. However, we still observed elevated risks among those without history of cardiovascular diseases (Table I in the online-only Data Supplement); the present findings, thus, could be generalized to the first-onset cases.

In conclusion, the present study provides additional evidence that PM exposure increases the risks of cardiovascular and cerebrovascular disease onset shortly after exposure. In addition, the exposure increases the risk of hemorrhagic stroke as well as ischemic stroke, but the elevated risk of ischemic stroke is followed by reduced risk. These findings, derived from finer temporal resolution of air pollution, provide additional insights into the physiological mechanisms of air pollution health effects as well as air pollution regulations.

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