Air Pollution and Hospital Admissions for Ischemic and Hemorrhagic Stroke Among Medicare Beneficiaries

Gregory A. Wellenius, ScD; Joel Schwartz, PhD; Murray A. Mittleman, MD, DrPH

Background and Purpose—The association between short-term elevations in ambient air particles and increased cardiovascular morbidity and mortality is well documented. Ambient particles may similarly increase the risk of stroke.

Methods—We evaluated the association between daily levels of respirable particulate matter (aerodynamic diameter ≤10 μm, PM₁₀) and hospital admission for ischemic and hemorrhagic stroke among Medicare recipients (age ≥65 years) in 9 US cities using a 2-stage hierarchical model. In the first stage, we applied the time-stratified case-crossover design to estimate the effect of PM₁₀ in each city. We used a 3-day unconstrained, distributed lag model to simultaneously estimate the effect of PM₁₀ 0 to 2 days before the admission day and controlled for meteorological covariates in all of the models. In the second stage, we used random-effects metaanalytic techniques to combine the city-specific effect estimates.

Results—Ischemic (n = 155 503) and hemorrhagic (19 314) stroke admissions were examined separately. For ischemic stroke, an interquartile range increase in PM₁₀ was associated with a 1.03% (95% CI, 0.04% to 2.04%) increase in admissions on the same day only. Similar results were observed with CO, NO₂, and SO₂. For hemorrhagic stroke, no association was observed with any pollutant 0 to 2 days before admission.

Conclusions—These results suggest that elevations in ambient particles may transiently increase the risk of ischemic, but not hemorrhagic, stroke. Studies with more accurate assessment of timing of stroke onset are necessary to confirm or refute these findings. (Stroke. 2005;36:2549-2553.)

Key Words: ischemic stroke ■ hemorrhagic stroke ■ air pollution ■ environmental exposure ■ epidemiology

Epidemiological studies have demonstrated a consistent increased risk for cardiac morbidity and mortality associated with acute exposure to ambient air particles, including triggering of acute myocardial infarction,¹,² discharge of implanted cardioverter defibrillators,³ and hospital admission for acute decompensation of patients with congestive heart failure.⁴ Although the mechanisms have not been fully elucidated, current evidence suggests that alterations in hemodynamics,⁵,⁶ hemostatic factors,⁷–⁹ and autonomic function¹⁰,¹¹ may underlie the cardiovascular effects of particulate air pollution.

Exposure to particulate air pollution may similarly increase the risk of stroke. Studies of small-area variation have found a positive association between stroke mortality rates and living in areas of high-ambient pollution.¹² Time series studies using hospital discharge summaries report a statistically significant positive association between daily measures of respirable particles (particulate matter with aerodynamic diameter <10 μm, PM₁₀) and cerebrovascular hospitalizations,¹³–¹⁶ but the results have been inconsistent.¹⁷–¹⁹ Moreover, few studies have distinguished between ischemic and hemorrhagic strokes.¹⁵,¹⁶,²⁰ Given the putative mechanisms of particulate-related cardiovascular effects, we hypothesized that short-term elevations in PM₁₀ would be associated with increased hospitalizations for ischemic but not hemorrhagic stroke. We evaluated this hypothesis among Medicare beneficiaries ≥65 years of age in 9 US cities with daily PM₁₀ monitoring.

Methods

Study Population

This study was approved by the Institutional Review Boards of the Harvard School of Public Health and Beth Israel Deaconess Medical Center. We evaluated the association between mean daily PM₁₀ levels and the rate of admission for stroke among Medicare beneficiaries in 9 cities chosen a priori based on their large populations, many years of daily PM₁₀ monitoring, and geographic diversity (Table 1). The observation period in each city was limited by the range of dates for which both hospital admissions and daily PM₁₀ data were available.

We obtained information on hospital admissions from the Centers for Medicare and Medicaid Services. Ischemic stroke cases were defined as persons admitted from the emergency room with a primary discharge diagnosis of acute but ill-defined cerebrovascular...
disease or occlusion of cerebral arteries, excluding those without cerebral infarction. In a sensitivity analysis, we limited the definition of ischemic stroke to patients admitted from the emergency room with a primary discharge diagnosis of occlusion of cerebral arteries. Hemorrhagic stroke cases were defined as persons admitted from the emergency room with a primary discharge diagnosis of intracerebral hemorrhage.

### Exposure Information

We obtained daily measures of PM$_{10}$ and hourly measures of CO, NO$_2$, and SO$_2$ from the US Environmental Protection Agency and computed daily mean concentrations in each city. To evaluate the effect of PM$_{10}$ within the range of exposure deemed acceptable in the United States under current regulations, we excluded from analysis 31 days (of 37 203 possible) on which PM$_{10}$ levels exceeded 150 g/m$^3$, the current 24-hour US Environmental Protection Agency standard. We considered pollutant data unavailable for a given city if >10% of days in the observation period had missing values. Using this criterion, data on CO was missing in New Haven, Conn; NO$_2$ in Salt Lake City, Utah, and Seattle, Wash; and SO$_2$ in Birmingham, Ala. We obtained National Weather Service data on climatologic variables (National Climatic Data Center) and calculated the apparent temperature (an index of human discomfort that incorporates ambient temperature and relative humidity) as described previously.

Data on PM$_{10}$ were missing on 4.0% of the days. In a sensitivity analysis, we used city-specific prediction models to impute single missing values. Specifically, we modeled PM$_{10}$ as smooth functions of PM$_{10}$ on the previous and following day, available copollutants, and climatologic variables. City-specific model $R^2$ values ranged from 0.50 to 0.85 (mean, 0.71). We imputed missing values of PM$_{10}$ for days preceded and followed by nonmissing days. This time-series, referred to as “PM$_{10}$ with imputed values,” had missing values on 1.7% of days.

### Data Analysis

We used a 2-stage hierarchical model to evaluate the association between ambient pollution and the rate of hospital admission, as described previously. In the first stage, we used the time-stratified case-crossover study design to separately estimate the effect of air pollution in each city. In this design, each subject’s exposure before a case-defining event (case period) is compared with his or her own exposure experience during $\geq 1$ control period when the subject did not become a case. Control periods were chosen such that exposures during the case period were compared with exposures occurring on other days of the same month falling on the same day of the week as the case period. Exposure during the case period was defined as pollutant concentrations 0 to 2 days before admission (lags 0 to 2 days). This design has been shown to be effective in controlling for seasonality, time trends, and chronic and slowly varying potential confounders.

We performed conditional logistic regression, stratifying on each day, to obtain estimates of odds ratios and 95% CIs. We report effect estimates as the percentage of change in the rate of hospitalization associated with an interquartile range increase in mean daily pollutant levels. For each pollutant, we simultaneously evaluated the effect at lags of 0 to 2 days using unconstrained distributed lag models and controlled for meteorological covariates. We modeled the mean apparent temperature at lag 0 as a quadratic function and mean apparent temperature at lags 1 and 2, mean barometric pressure at lags 0 and 1, and pollutants at lags 0 to 2 as linear functions of continuous variables.

### Table 1: Summary of Mean Daily Concentrations of Air Pollutants and Climatologic Variables in 9 US Cities

<table>
<thead>
<tr>
<th>Variable</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>Correlation With PM$_{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{10}$, $\mu g/m^3$</td>
<td>12.91</td>
<td>18.88</td>
<td>28.36</td>
<td>41.84</td>
<td>57.89</td>
<td>…</td>
</tr>
<tr>
<td>PM$_{10}$ with imputed values, $\mu g/m^3$</td>
<td>12.94</td>
<td>18.95</td>
<td>28.44</td>
<td>41.83</td>
<td>58.00</td>
<td>…</td>
</tr>
<tr>
<td>CO, ppm</td>
<td>0.54</td>
<td>0.73</td>
<td>1.02</td>
<td>1.44</td>
<td>1.98</td>
<td>0.43</td>
</tr>
<tr>
<td>NO$_2$, ppb</td>
<td>13.71</td>
<td>18.05</td>
<td>23.54</td>
<td>29.98</td>
<td>36.54</td>
<td>0.53</td>
</tr>
<tr>
<td>SO$_2$, ppb</td>
<td>2.17</td>
<td>3.57</td>
<td>6.22</td>
<td>10.26</td>
<td>16.17</td>
<td>0.39</td>
</tr>
<tr>
<td>Apparent temperature, °C</td>
<td>−3.93</td>
<td>0.95</td>
<td>9.47</td>
<td>19.33</td>
<td>25.42</td>
<td>0.22</td>
</tr>
</tbody>
</table>
In the second stage, we obtained a combined random-effects estimate from the city-specific effect estimates using standard random-effects meta-analysis methods. All of the reported P values are based on 2-sided tests at the α=0.05 level. Analyses were performed using SAS V9 and the R statistical package.

Results

Ischemic Stroke Admissions

There were 155,503 hospital admissions from the emergency department with a primary discharge diagnosis of ischemic stroke among Medicare beneficiaries ≥65 years of age in 9 US cities (Table 1). The overall mean PM$_{10}$ level was 32.69 μg/m$^3$ (SD±19.75; Table 2). Age on admission ranged from 65 to 117 years with a mean of 78.6±7.7 years. Cases were mostly white (75.4%) and female (60.7%).

We simultaneously estimated the effect of PM$_{10}$ at lags of 0 to 2 days in each city and then obtained summary estimates using standard random-effects meta-analysis techniques. A positive association between PM$_{10}$ and hospital admissions on the same day was observed in 7 of the 9 cities examined ($P_{heterogeneity}=0.71$; Figure, A). Overall, an interquartile range increase in PM$_{10}$ on the day of admission was associated with a 1.03% (95% CI, 0.04% to 2.04%) increase in the rate of hospital admission for ischemic stroke. PM$_{10}$ levels 1 or 2 days before admission were not associated with increased risk. Using the alternate definition of ischemic stroke yielded a 1.39% (95% CI, 0.26% to 2.52%) increase for an interquartile range increase in PM$_{10}$ on the admission day and no significant increase associated with PM$_{10}$ levels 1 or 2 days before admission. Using PM$_{10}$ with imputed values as the exposure did not materially alter the results.

Ambient measures of CO, NO$_2$, and SO$_2$ were correlated with ambient PM$_{10}$ levels (Table 2). An interquartile range increase in each pollutant was associated with a qualitatively similar increase in admissions on the same day (Table 3). No association was observed with any pollutant 1 or 2 days before the admission date.

Hemorrhagic Stroke Admissions

There were 19,314 hospital admissions with a primary discharge diagnosis of hemorrhagic stroke (Table 1). Compared with patients admitted for ischemic stroke, these patients tended to be younger (mean age, 77.9±7.6 years), more likely to be white (78.2%), and less likely to be female (58.8%).

PM$_{10}$ levels on the day of admission were not associated with hemorrhagic stroke admissions although there was evidence of statistical heterogeneity between cities ($P_{heterogeneity}=0.013$; Figure, B). PM$_{10}$ levels 1 to 2 days before admission were also not associated with increased risk. Likewise, no association was observed between hemorrhagic stroke admissions and PM$_{10}$ with imputed values, CO, NO$_2$, or SO$_2$ (Table 3).

Discussion

Previous studies using administrative data from 1 to 3 cities suggest an association between daily fluctuations in PM$_{10}$ and cerebrovascular hospital admissions. We evaluated the association between PM$_{10}$ and hospital admissions for ischemic and hemorrhagic stroke among Medicare beneficiaries ≥65 years of age in 9 US cities and found that a transient increase in ambient particles was associated with an increased risk of hospital admission for ischemic but not hemorrhagic stroke. Specifically, for ischemic stroke, we found that an interquartile range increase in PM$_{10}$ was associated with a 1.03% (95% CI, 0.04% to 2.04%) increase in the risk of admission on the same day. In contrast, for hemorrhagic stroke, we found no evidence of an association with PM$_{10}$ or any other pollutant examined.

Few published studies have examined the effects of ambient particles specifically on ischemic or hemorrhagic stroke. Using hospital admission records from Taiwan,
C-reactive protein.9 Second, particulate-related changes in he-
ination and thrombosis. This could be mediated by a combination
of ischemic stroke by promoting atherosclerotic plaque disrup-
studies.

population characteristics between the current and previous
definitions, analytic methods, average pollutant levels, or
hemorrhagic strokes. The discrepant results in relation to
hemorrhagic strokes. The discrepant results in relation to
hospitalization rates for ischemic stroke in metropolitan Los Angeles, but did not consider
hemorrhagic strokes. The discrepant results in relation to
hemorrhagic stroke may be explained by differences in case
definitions, analytic methods, average pollutant levels, or
population characteristics between the current and previous
studies.

Exposure to ambient particles may plausibly increase the risk
of ischemic stroke by promoting atherosclerotic plaque disruption
and thrombosis. This could be mediated by a combination of
≥3 different mechanisms. First, particulate exposure can induce
an acute systemic inflammatory response with an increased
number of circulating neutrophils28 and increased levels of
C-reactive protein.9 Second, particulate-related changes in he-
mostatic factors have been reported, including increased levels
of fibrinogen7,8 and von Willebrand factor9 and enhanced pe-
ripheral arterial thrombosis.29 Third, particulate-related changes
in autonomic nervous system activity, as assessed by heart rate
variability, are well documented and are consistent with relative
sympathoexcitation.10,11

The observed association between ischemic stroke and air
pollution was similar for all of the pollutants considered.
Likewise, we consistently failed to find evidence of an
association between hemorrhagic stroke and any pollutant
considered. Because ambient measures are correlated, sepa-
rating the effects of individual pollutants is problematic.
However, PM10 is relatively spatially homogenous within a
metropolitan area,30 and ambient measures at a central site are
well correlated with personal exposure measures.31 In con-
trast, personal exposures to CO, NO2, and SO2 are relatively
poorly predicted by ambient measures.32 For example, ambient
measures of NO2 are likely more strongly correlated with
personal exposure to particulate matter than to personal NO2
exposure.32 Thus, the present study is consistent with the
interpretation that sources of pollution that lead to concurrent
elevation of these pollutants may be responsible for the
observed associations.

Tsai et al16 found a statistically significant positive association
between PM10 and both ischemic and hemorrhagic
strokes after excluding days with mean daily temperature
<20°C. Similarly, Hong et al20 analyzed death certificates in
Seoul, Korea, with similar statistically significant results for
ischemic and hemorrhagic stroke. Linn et al15 also found a
significant increase in hospitalization rates for ischemic stroke
in metropolitan Los Angeles, but did not consider
hemorrhagic strokes. The discrepant results in relation to
hemorrhagic stroke may be explained by differences in case
definitions, analytic methods, average pollutant levels, or
population characteristics between the current and previous
studies.

The health effects of exposure to air pollution from indoor
sources (eg, from tobacco smoke or cooking) are also of
interest, but evaluating these effects requires a different study
design and indoor, as well as ambient, pollutant monitors.
Although ambient particles have been shown to penetrate
indoors, there is little correlation between exposure to parti-
cles originating from indoor sources and those from outdoor
sources.33

This study has several potential limitations. First, misclas-
sification of the outcome is expected as a result of diagnostic
or coding errors. However, these errors are likely unrelated to
pollutant levels and are expected to reduce the precision of
our estimates and potentially bias the relative risk toward the
null. In fact, using the alternate definition of ischemic stroke,
which is likely to be more specific, albeit less sensitive, than
the primary definition,34,35 we found a stronger association
with PM10. Similarly, we expect that the incidence of clinic-
ally unrecognized or nonhospitalized stroke is unrelated to
pollutant levels after adjusting for meteorological covariates
and month-of-year and day-of-week effects. Therefore, ex-
clusion of these cases is expected to reduce the precision of
our estimates but not otherwise bias our results. Second, the
use of ambient rather than personal exposure measures is
expected to result in exposure misclassification. However,
this misclassification is expected to lead one to underestimate
the relative risk.36 Third, the date of symptom onset likely
preceded the date of admission in a proportion of cases,
leading to nondifferential exposure misclassification and bias
of the relative risk toward the null. Fourth, residual confound-
ing by short-term respiratory epidemics remains a possibility.
However, the time-stratified case-crossover design used in
this study has been shown to effectively control for confound-
ing by time trends in both exposure and outcomes.24 In
particular, this approach provides effective control for time
trends that occur over periods longer than 1 calendar month.
Additionally, studies directly examining this possibility sug-
gest that respiratory epidemics are not important confound-
ers of the association between particulate matter and all-cause
or cardiovascular mortality.37

Conclusions

In the current study, we found that a transient increase in
ambient particles was associated with an increased risk of
hospital admission for ischemic but not hemorrhagic stroke.
Although the relative increase in risk was small, given the large number of people simultaneously at risk for ischemic stroke and exposed to urban pollution, even a small relative risk may be of significant public health interest. Additional studies with more detailed data on the clinical characteristics of subjects and more accurate assessment of the timing of symptom onset are needed to confirm or refute these findings.

Acknowledgments
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References

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