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Air Pollution and Risk of Stroke

Underestimation of Effect Due to Misclassification of Time of Event Onset

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Background: Epidemiologic studies linking ambient air pollution to the onset of acute cardiovascular events often rely on date of hospital admission for exposure assessment.

Methods: We investigated the extent of exposure misclassification resulting from assigning exposure to particulate matter based on (1) date of hospital admission, or (2) time of hospital presentation compared with particulate matter exposure based on time of stroke symptom onset. We performed computer simulations to evaluate the impact of this source of exposure misclassification on estimates of air pollution health effects in the context of a time-stratified case-crossover study.

Results: Among 1101 patients admitted for a confirmed acute ischemic stroke to a Boston area hospital, symptom onset occurred a median of 1 calendar day before hospital admission (range = 0–30 days). The difference between ambient particulate matter exposure based on the calendar day of admission versus time of symptom onset ranged from -47 to $36 \mu\text{g}/\text{m}^3$ ($-0.1 \pm 7.1 \mu\text{g}/\text{m}^3$; mean \pm SD). The simulation study indicated that for nonnull associations, exposure assessment based on hospitalization date led to estimates that were biased toward the null by 60%–66%, whereas assessment based on time of hospital presentation yielded estimates that were biased toward the null by 37%–42%.

Conclusions: Epidemiologic studies of air pollution–related risk of acute cardiovascular events that assess exposure based on date of hospitalization likely underestimate the strength of associations.

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Using data on time of hospital presentation would marginally attenuate, but not eliminate, this important source of bias.

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Epidemiologic studies suggest an association between short-term fluctuations in ambient air pollution levels and risk of hospitalization for acute cardiovascular events, including ischemic stroke,¹ myocardial infarction,^{2,3} and acute decompensated heart failure.⁴ Time-series studies using generalized additive models or generalized linear models represent a widely used approach to evaluating the acute health effects of ambient air pollution.⁵ More recently, case-crossover methods have been applied to time-series data yielding theoretically equivalent results under certain assumptions.⁶

Regardless of the analytic approach, the majority of previous time-series studies have used data from administrative databases in which the date of hospitalization is the only information available on the timing of the event. Accordingly, pollution exposure just before the index event is necessarily defined as the average exposure over a fixed period before the calendar day of admission. For example, to evaluate the association between ambient fine particulate matter (PM_{2.5}) and risk of same-day hospitalization for acute ischemic stroke, each case is commonly assigned the mean daily (eg, midnight–midnight) PM_{2.5} level on the date of hospital admission. Such studies are limited by the fact that hospital admission may occur at any time of day and that the true onset of the event may occur hours or days before hospital admission (Fig. 1).

The impact of misclassification of the time of event onset on the estimated association between ambient air pollution and the risk of acute cardiovascular events has not been evaluated. Accordingly, the aims of this study were to (1) investigate whether significant exposure misclassification may result from using the hospitalization date to estimate air pollution exposure at the true onset time of an acute cardiovascular event, and (2) evaluate the impact of the resulting exposure misclassification on the estimated association between ambient air pollution and the risk of acute cardiovas-

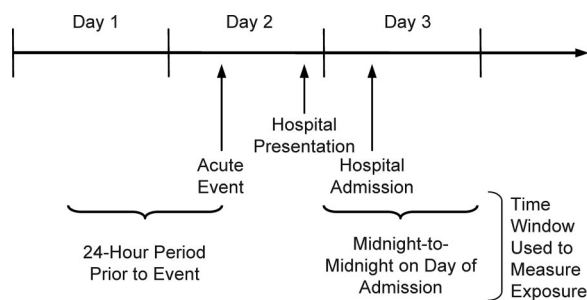


FIGURE 1. An illustration of how measurement error in the onset time of an acute cardiovascular event may give rise to exposure misclassification. Most time-series studies of ambient air pollution and acute cardiovascular events have used fixed time periods (eg, midnight–midnight) based on the calendar day of hospital admission to assess pollution exposure before the event. The onset of the event necessarily occurs before hospital admission and may be associated with a different exposure level.

cular events. We used data collected in the Boston metropolitan region as part of an ongoing study of ambient air pollution and the risk of acute ischemic stroke to accomplish the first aim and performed computer simulations to accomplish the second aim.

METHODS

Assessment of Exposure Misclassification

This study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center. First, we investigated whether substantial exposure misclassification may result from using hospitalization date to estimate $PM_{2.5}$ exposure at the true onset time of an acute cardiovascular event, using hospitalizations for acute ischemic stroke as an example. Data on delay times between stroke onset time and hospital presentation were obtained from an ongoing study in the Boston metropolitan area of ambient air pollution and the risk of acute ischemic stroke. Specifically, we reviewed charts and electronic medical records of all patients aged 21 years and older admitted to the Beth Israel Deaconess Medical Center between 1 April 1999 and 31 December 2004 with a primary discharge diagnosis related to ischemic cerebrovascular disease (ICD-9 codes 433–438). Patients who were admitted for a neurologist-confirmed acute ischemic stroke were identified. Trained abstractors, using standardized forms, estimated stroke symptom onset times as previously described.^{7,8} Patients with in-hospital strokes or transient ischemic attacks were excluded. Stroke symptom onset times could not be estimated from medical records for less than 1% of patients (7 of 1101) because of conflicting information.

We obtained hourly measures of ambient particles with aerodynamic diameter of $2.5 \mu m$ or less ($PM_{2.5}$) from the Boston/Harvard Countway Library PM Center, located less than 1 km from the study site. $PM_{2.5}$ was measured contin-

uously (TEOM Model 1400A, Rupprecht and Patashnick; Albany, NY) and calibrated against colocated integrated 24-hour Teflon filter (Teflon, Pall-Gelman, Ann Arbor, MI) gravimetric measurements, as previously described.⁹ We calculated 24-hour mean values when 75% or more of hourly measurements were available. Patient addresses were obtained from the medical record and geocoded using ArcGIS 9.0 (ESRI, Redlands, CA). To reduce exposure misclassification, we excluded patients who lived more than 40 km from this central monitor, as in previous studies.¹⁰

For each case, we calculated exposure to $PM_{2.5}$ by using 3 different exposure assessment strategies. First, we defined exposure based on the 24-hour mean $PM_{2.5}$ levels on the calendar day of admission (midnight–midnight). This is equivalent to the exposure assessment approach used in most of published time-series studies in which only the date of hospitalization is available. Second, we defined exposure based on the mean $PM_{2.5}$ levels over the 24 hours preceding the time of hospital presentation. This approach might be used in future studies with more detailed administrative data. Third, we defined exposure based on the mean $PM_{2.5}$ levels over the 24 hours preceding the estimated time of stroke symptom onset. This approach assesses exposure over the most etiologically relevant period and has been used in certain previous studies of the transient effects of ambient particles on the risk of acute cardiovascular events.^{11,12} Because hospitalization necessarily follows onset of stroke symptoms, the first 2 exposure assessment strategies would be expected to result in more exposure misclassification compared with the strategy based on time of stroke symptom onset.

We used the intraclass correlation coefficient estimated by 1-way analysis of variance^{13,14} to assess the agreement between each of the first 2 exposure assessment strategies and the approach based on symptom onset times. We used Bland-Altman plots^{15,16} to evaluate whether the exposure misclassification under the first 2 approaches was nondifferential, and formally tested this hypothesis with paired *t*-tests. Analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

Impact of Exposure Misclassification on Estimated Regression Coefficients

We performed computer simulations to evaluate the impact of this source of exposure misclassification on the estimated association between $PM_{2.5}$ and risk of acute ischemic stroke. For simplicity, we assumed that $PM_{2.5}$ exposure based on the time of onset of stroke symptoms represents the true personal exposure to $PM_{2.5}$. We compared exposure estimates based on calendar day of hospital admission or date and time of admission to this “true” exposure. These simulations explicitly do not account for any other sources of exposure misclassification.

To mimic the conditions actually observed in the ongoing stroke study, we assume that about 1100 cases of acute ischemic stroke were identified over a 5-year period. First, we simulated the number of cases observed each hour (Y_t) during this period as a Poisson random variable:

$$Y_t \sim \text{Pois}(\ln(\lambda_t) = \beta_0 + \beta_1 * PM_t),$$

where, PM_t represents the 24-hour moving average for $PM_{2.5}$ (time = t-24-time = t) and β_1 is the hypothesized linear effect of a $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ 24-hour moving average on the log rate of hospitalization for stroke. The observed $PM_{2.5}$ time-series from the ongoing stroke study was used for PM_t . Next, for each simulated case we assigned a random delay time between time of symptom onset and hospital presentation, based on the distribution of delay times observed in the ongoing stroke study. Third, we assessed exposure based on date of hospitalization, time of hospital presentation, and time of symptom onset. Finally, for each exposure assessment strategy we evaluated the association between exposure and rate of hospitalization for stroke ($\hat{\beta}_1$) by using the time-stratified case-crossover design.¹⁷ Referents were all days in the same year, month, day-of-week, and time-of-day as the simulated case, excluding the case day. For each simulation, this process was repeated 500 times and the properties of $\hat{\beta}_1$ summarized. Relative bias was defined as $\frac{\beta_1 - \hat{\beta}_1}{\beta_1} \times 100$. A separate simulation was performed for values of $\exp(\beta_1)$ of 1.00, 1.10, 1.20, and 1.30, consistent with the range of values observed in previous studies of $PM_{2.5}$ and risk of acute ischemic stroke.^{1,18} Simulations were performed in R v2.1.1.¹⁹

RESULTS

Assessment of Exposure Misclassification

There were 1101 patients admitted to the Beth Israel Deaconess Medical Center for a neurologist-confirmed acute ischemic stroke who lived within 40 km of the central ambient particle monitor (Table 1). The mean daily ambient $PM_{2.5}$ concentration over the study period was $11.3 \mu\text{g}/\text{m}^3$ (SD = $6.6 \mu\text{g}/\text{m}^3$; Table 2). The mean distance between patient residential address and the central monitoring site was 9.6 km (SD = 8.0 km), with the majority of patients (89%) living within 20 km of the central monitor. The 25th, 50th, and 75th percentiles for distance were 3.9, 7.3, and 12.4 km, respectively.

Stroke onset occurred at least 1 calendar day before hospital admission among 53% of patients (median delay = 1 day, range = 0–30 days; Fig. 2A). The difference in $PM_{2.5}$ exposure based on date of hospitalization versus time of stroke onset ranged from -47 to $36 \mu\text{g}/\text{m}^3$ (mean difference \pm SD = $-0.1 \pm 7.1 \mu\text{g}/\text{m}^3$; 5th–95th percentile = -11.7 – $9.9 \mu\text{g}/\text{m}^3$; Fig. 2B). The intraclass correlation coefficient be-

TABLE 1. Characteristics of 1101 Confirmed Cases of Acute Ischemic Stroke With a Residential Address Within Forty Kilometer From the Ambient Particle Monitoring Site

Characteristic	%
Age (y)	
<65	25
65–75	24
>75	51
Sex	
Male	45
Female	55
Race/ethnicity	
White	63
African American	11
Hispanic/Latino	3
Asian/Pacific islander	2
American Indian/Alaskan native	0
Multiple/other	2
Unknown	23

TABLE 2. Summary of Mean Daily $PM_{2.5}$ Concentrations During Period of Study

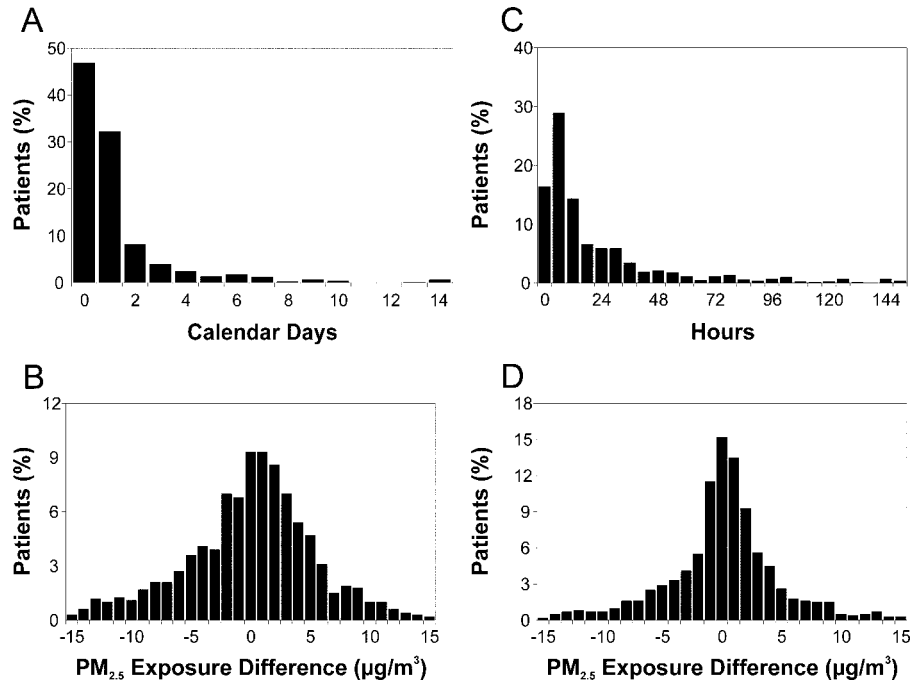
Daily Mean $PM_{2.5}$ Concentrations ($\mu\text{g}/\text{m}^3$)	
Percentiles	
5th	3.5
25th	6.6
50th	9.5
75th	14.2
95th	23.8
IQR	7.6
Mean (SD)	11.2 (6.7)

IQR indicates interquartile range.

tween these 2 $PM_{2.5}$ measurements was 0.45. There was no evidence that the exposure misclassification was systematically differential ($P = 0.68$ from paired t test of $\delta = 0$). A plot of the differences between each pair of $PM_{2.5}$ measurements against their averages was symmetric around $0 \mu\text{g}/\text{m}^3$ (not shown). Limiting the analysis to patients living less than 20 km from the monitoring site, did not materially alter the results.

The median delay between time of symptom onset and time of hospital presentation was 13 hours (Fig. 2C). The difference in $PM_{2.5}$ assessed based on time of hospital presentation versus time of stroke symptom onset ranged from -46 to $32 \mu\text{g}/\text{m}^3$ (mean difference \pm SD = $0.1 \pm 6.0 \mu\text{g}/\text{m}^3$; 5th–95th percentile = -9.8 – $9.0 \mu\text{g}/\text{m}^3$; Fig. 2D). The intraclass correlation coefficient between the 2 measurements was 0.60. There was no evidence of systematic differential misclassification ($P = 0.74$ from paired t test of $\delta = 0$). A plot of the differences between each pair of $PM_{2.5}$ measurements

FIGURE 2. A, Time in calendar days between ischemic stroke onset and hospital admission (full range = 0–30 days). B, The difference between the mean PM_{2.5} level (midnight–midnight) on the day of hospital admission and the mean over the 24 hour period before stroke onset (full range = –47.1 to 36.3 μg/m³). C, Time in hours between stroke onset and hospital admission (full range = 0–742 hours). D, The difference between the mean PM_{2.5} levels over the 24 hours before hospital presentation and the mean over the 24 hours before symptom onset (full range = –45.9–31.7 μg/m³).



against their averages was symmetric around 0 μg/m³ (not shown). Limiting the analysis to patients living less than 20 km from the monitoring site did not materially alter the results.

Impact of Exposure Misclassification on Estimated Regression Coefficients

We performed computer simulations to evaluate the impact of this exposure misclassification on the estimated association between PM_{2.5} and risk of acute ischemic stroke. Under the null hypothesis of no effect of PM_{2.5} [ie, β₁ = ln(1.0)], all 3 exposure assessment strategies yielded similar unbiased results (Fig. 3). However, under the alternative hypotheses of a positive association between PM_{2.5} and risk of acute ischemic stroke [β₁ = ln(1.1), ln(1.2), ln(1.3)], using an exposure assessment strategy based on date of hospitalization resulted in attenuation of β₁ by 60%–66% compared with assessing exposure based on time of stroke onset, whereas using an exposure assessment strategy based on time of hospitalization presentation resulted in attenuation of β₁ by 37%–42%.

DISCUSSION

Epidemiologic studies of the short-term effects of ambient air pollution on the risk of acute cardiovascular events often use data from administrative databases in which only the date of hospitalization is known. However, because true time of event onset may precede hospitalization by hours or days, using an exposure assessment strategy based on the date of hospitalization may lead to substantial exposure misclassification. In this study we estimated the degree of exposure

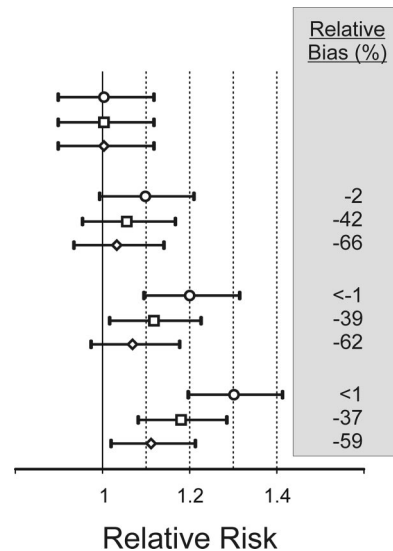


FIGURE 3. Simulated effect of measurement error in the onset time of acute ischemic stroke on the estimated association between ambient PM_{2.5} levels and risk of stroke. Relative risk estimates are shown for a 10-μg/m³ increase in the 24-hour moving average of PM_{2.5} based on stroke onset time (○), time of hospital presentation (□), and date of hospital admission (◇).

misclassification by using as an example data from an ongoing study of the effects of ambient PM_{2.5} on the risk of hospitalization for acute ischemic stroke. We found that among 1101 patients hospitalized for acute ischemic stroke, date of hospitalization, and time of hospital presentation were associated with varying degrees of misclassification of stroke

onset time. Specifically, stroke symptoms began a median of 13 hours before hospital admission and occurred on a different calendar day from hospital admission among more than half of all patients. Furthermore, our simulation studies show that an exposure assessment strategy based on date of hospitalization can attenuate estimates of PM_{2.5} health effects by about 60% compared with using stroke onset times.

The difference between the average PM_{2.5} levels on the date of hospitalization versus the 24-hour period before symptom onset had a range of 83 $\mu\text{g}/\text{m}^3$ and SD of 7.1 $\mu\text{g}/\text{m}^3$. The range between the 5th and 95th percentiles of differences between measurements was 22 $\mu\text{g}/\text{m}^3$, demonstrating that more than 10% of exposure measurements were extremely misclassified. The observed intraclass correlation coefficient of 0.45 indicates that more than half of the variance in exposure is attributable to misclassification of the onset time, rather than between-day differences in exposure. Moreover, an exposure assessment strategy based on the time of hospital presentation—as might be available in administrative databases with more detailed data—performed only somewhat better. The difference between the mean PM_{2.5} levels over the 24-hour period before the time of hospital presentation versus the 24-hour period before stroke onset had a range of 78 $\mu\text{g}/\text{m}^3$ and the intraclass correlation coefficient of 0.60. Importantly, misclassification of the onset time resulted in exposure misclassification that was nondifferential.

The exposure misclassification quantified in this study is consistent with the classic error model,^{20,21} in which the observed exposure x^* (here, exposure based on the date of hospitalization) is randomly distributed around the true exposure x (here, exposure based on stroke onset time). Although x^* is an unbiased estimate of x [ie, $E(x^*|x) = x$], the use of x^* in regression analyses is expected to attenuate associations between exposure and the outcome y . In a simple linear regression model with 1 explanatory variable, such that $E(y|x) = \alpha + \beta_x x$, if population exposure and measurement error are normally distributed, it has been shown that the regression coefficient β_x is attenuated by a factor that ranges between 0 and 1 and is given by $c = \text{var}(x)/[\text{var}(x) + \text{var}(x^* - x)]$. Thus, the degree of attenuation increases with the variance of exposure measurement error ($x^* - x$). In this simple model, the exposure misclassification observed in the current study would be predicted to reduce the association between daily PM_{2.5} levels and the risk of acute ischemic stroke by about 50%. In reality, however, the problem is more complex, and a simple linear regression model would be inappropriate. Because of the discrete nature of the outcome and the choice of study design, the data are analyzed using conditional logistic regression.

Accordingly, to evaluate the impact of the exposure misclassification in this setting, we conducted a simulation study. We observed a similar degree of attenuation empiri-

cally through computer simulations based on the degree of exposure misclassification observed in the ongoing stroke study. Under hypotheses of a positive association between PM_{2.5} and risk of acute ischemic stroke, using an exposure assessment strategy based on date of hospitalization or time of hospital presentation, the observed association was attenuated by 40%–60% compared with exposure based on time of stroke symptom onset. When simulations were run under the null hypothesis of no association between PM_{2.5} and hospitalization, all exposure assessment strategies led to unbiased results. Therefore, misclassification of onset time is unlikely to have contributed to positive associations in previous studies.

Results from a few published studies provide anecdotal evidence consistent with the notion that the use of misclassified onset times of acute events may bias health effect estimates toward the null. For example, Rich et al¹² evaluated the association between ambient levels of PM_{2.5} and the risk of ventricular arrhythmias as recorded by implanted cardioverter defibrillators and found an 8% (95% CI = -6%–24%) increased risk per interquartile range increase in PM_{2.5} when using the midnight-to-midnight mean PM_{2.5} levels on the same day, but a 19% (2%–38%) increase in risk when using the mean PM_{2.5} exposure over the 24-hour preceding event onset. Although the impact of onset time misclassification is substantial in this example, the impact may be even more substantial in the context of studies of hospital admissions in which the date of event onset is less precisely known than in the case of ventricular arrhythmias recorded by implanted cardioverter defibrillators.

Limitations

We used the example of acute ischemic stroke in the Boston metropolitan area to describe onset time and exposure misclassification in typical time-series studies of daily air pollution and acute cardiovascular events. The magnitude of the impact of onset time misclassification observed in this study may not be generalizable to studies in other locations, or of acute events other than acute ischemic stroke. Specifically, we expect that the amount of attenuation of the pollutant–health effect association is influenced by the distribution of prehospital delay times and the temporal characteristics of the pollution time-series being considered.

Our study has other potential limitations. First, we assessed only the exposure misclassification due to misinformation on timing of event onset and did not account for other known sources of exposure misclassification. Second, stroke onset times were estimated based on neurologists' notes in patient medical records and are likely misclassified with respect to true stroke onset times. However, this residual error is expected to be nondifferential with respect to air pollution levels and would not materially alter the conclusions of this analysis.

Epidemiologic studies of PM-related risk of acute cardiovascular events based on date of hospitalization can substantially underestimate the strength of associations with health effects. Using data on time of hospital presentation rather than date of hospitalization would only marginally attenuate this important source of bias. Whenever possible, investigators should consider collecting detailed data on time of event onset in studies of the effect of environmental exposures on acute events.

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