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Original Contribution

A Case-Crossover Study of Fine Particulate Matter Air Pollution and Onset of Congestive Heart Failure Symptom Exacerbation Leading to Hospitalization

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Persons with congestive heart failure may be susceptible to ambient air pollution. The authors evaluated the association between exposure to particulate matter with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) and onset of symptom exacerbation leading to hospital admission in Baltimore, Maryland. They used a case-crossover design for 135 case events occurring among 125 persons with prevalent congestive heart failure who were admitted to a single hospital through the emergency department during 2002. The case period was assigned using three index times: 8-hour and 24-hour periods of symptom onset and date of hospital admission. Controlling for weather, the authors detected a modest relative increase in risk for cases defined by 8-hour symptom onset for an interquartile-range increase in $PM_{2.5}$ at a 2-day lag (odds ratio = 1.09, 95% confidence interval: 0.91, 1.30). A corresponding increase in risk was not observed when admission date was used to define the case period. A series of simulations based on study data indicated that the study had adequate statistical power to detect odds ratios of 1.2 or higher. Although overall findings were not statistically significant, the identification of case events defined by an 8-hour onset period may be more relevant than either a 24-hour onset period or the admission date for estimating harmful effects of air pollutant exposure on cardiovascular health.

air pollutants; disease susceptibility; dyspnea; environmental exposure; heart failure, congestive; hospitalization

Abbreviations: BMCA, Bayview Medical Center admission date; CHF, congestive heart failure; CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of <10 μm; TOS, time of onset for symptom exacerbation.

Editor's note: *An invited commentary on this article appears on page 434.*

Fine-particle air pollution, defined as particulate matter with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$), is associated with increased all-cause and cause-specific mortality (1, 2) and with increased respiratory and cardiovascular morbidity (3–5). While mechanisms through which inhaled particulate matter injures the pulmonary system have been documented (6, 7), understanding of the biologic processes by which particulate matter may affect the cardiovascular system remains incomplete (8). Epidemiologic research has identified adverse physiologic effects associated with increased particulate matter exposure in persons with cardiovascular disease, including reduced heart rate variability

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(9, 10), increased blood pressure (11), cardiac arrhythmias (12), increased oxidative stress and inflammation (13), and progression of atherosclerosis (14, 15).

Among persons with cardiovascular disease, those with congestive heart failure (CHF) may be especially sensitive to ambient air pollutants, principally $PM_{2.5}$ (16, 17). In general, the rising incidence of chronic heart failure has led to an increased number of persons who are potentially susceptible to adverse health effects associated with particulate matter (18). CHF, a clinical syndrome resulting from pump failure of the cardiac muscle (19), is characterized by symptoms that include shortness of breath, fatigue, and edema resulting in weight gain and swelling of lower body extremities. As heart failure worsens, patients typically experience acute, severe symptom exacerbations that require medical care, usually through a hospital emergency department (20). Worsening CHF is responsible for over one million hospital admissions annually, representing one of the largest categories of annual Medicare expenditures (21).

The present pilot investigation focuses on the onset of dyspnea as a cardinal indicator of CHF decompensation; its timing should be more directly related to particulate matter exposure than hospital admission date. In this analysis, we sought to determine the relation between ambient $PM_{2.5}$ exposure and development of symptoms sufficiently severe to lead to hospital admission through the emergency department. Specifically, we identified onset times for exacerbation of heart failure symptoms in relation to subsequent emergency hospital admission; evaluated the association between onset time for exacerbation of heart failure symptoms and ambient particulate matter exposure levels; and assessed the ability of the case-crossover analytic method to detect specific effect estimates using simulated case data and empirical particulate matter measurements.

MATERIALS AND METHODS

Recruitment of the study population

Study participants were patients diagnosed with CHF who were admitted to Johns Hopkins Bayview Medical Center in Baltimore, Maryland, through the emergency department. Bayview Medical Center was selected because it was located adjacent to the Baltimore Particulate Matter Supersite, an air quality monitoring station that conducted intensive monitoring of $PM_{2.5}$ (22, 23). Participant recruitment occurred from April to December of 2002, coinciding with the data collection period of the Baltimore Supersite. Eligible participants were identified through daily review of emergency department admission logs by a hospitalist who examined patient charts to verify the diagnosis of CHF. Trained interviewers screened potentially eligible patients and obtained informed consent for participation prior to conducting an in-hospital interview. Patients were excluded at the interview stage if they were cognitively impaired, could not verbally communicate, or could not speak English. The study was approved by the institutional review board of the Johns Hopkins Bloomberg School of Public Health.

Data collection

Hospitalized persons were interviewed after admission through the emergency department during their stays in overnight wards of the hospital. All participants responded to an interviewer-administered questionnaire that covered awareness and self-evaluation of symptoms occurring prior to admission. The questionnaire was designed to collect relevant information regarding symptom onset, health conditions, and factors related to air pollution exposure. Interviews conducted using the questionnaire were intended to take no more than 20 minutes, in order to minimize time demands on participants during their hospitalization. Participants were asked to assess the onset of exacerbation of heart failure decompensation by identifying the day on which "breathing became more difficult than usual" and their symptoms necessitated emergency medical attention. This time of onset for symptom exacerbation (TOS) was used as the decompensation event time for the period associated with particulate matter exposure and risk of emergency admission. If possible, participants further specified an 8-hour period of the day for shortness-of-breath onset.

Air pollutant and weather measurement

$PM_{2.5}$ mass concentration and copollutant data, including levels of nitrogen dioxide and carbon monoxide, were provided by researchers at the Baltimore Supersite (22, 23). Additional data recorded at monitoring sites located near the recruitment hospital, including ozone and meteorologic measurements, were obtained from the Maryland Department of the Environment. All air pollutant measurements were reported for 1-hour intervals. All weather data were measured at 5-minute intervals and averaged for 8-hour and 24-hour periods.

The main exposure metric used for this analysis was ambient $PM_{2.5}$ mass concentration. The original study design assumed that all $PM_{2.5}$ data would be provided by researchers at the Baltimore Supersite; however, because of an instrument malfunction, data were unavailable from May 23, 2002, to July 4, 2002—approximately 17 percent of the study period. Subsequently, we obtained mass concentration data from seven other monitoring stations maintained by the Maryland Department of the Environment in Baltimore City to estimate the $PM_{2.5}$ series for the study period. Table 1 lists these eight monitoring stations, as well as measurement methods, sampling intervals, and pairwise correlation coefficients for the $PM_{2.5}$ concentrations.

To estimate average $PM_{2.5}$ concentrations, we fitted a generalized linear model with an autoregressive measurement error term of the first order, AR(1) (24). The estimation model is expressed as $Z_{tj} = \Theta_t + \varepsilon_{tj}$, $\varepsilon_{tj} \sim \mathrm{AR}(1)$, where Z_{tj} is the $PM_{2.5}$ mass concentration at time t measured at monitoring station j, Θ_t is the "true" $PM_{2.5}$ mass concentration at time t, and ε_{tj} is the measurement error at time t at monitoring station j. Inputs for daily estimates came from all monitoring stations, while inputs for hourly estimates were obtained from only the Baltimore Supersite and the Old Town site, using tapered element oscillating microbalances (Rupprecht and Pataschnick, Albany, New York). A larger

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TABLE 1. Locations of $PM_{2.5}$* monitoring stations, sampling methods, and correlation coefficients for collection of data on 24-hour average $PM_{2.5}$ concentrations, Baltimore, Maryland, 2002

$PM_{2.5}$ monitoring site	Sampling method	Sampling interval†	Baltimore Supersite	FMC*	Old Town	Old Town TEOM*	Northeast	Northwest	Westport	Southeast
Baltimore Supersite	TEOM	Hourly	1	0.97	0.97	0.97	0.97	0.98	0.98	0.98
FMC	FRM*	Daily		1	0.96	0.97	0.98	0.98	0.99	0.97
Old Town	FRM	Daily			1	0.96	0.97	0.97	0.98	0.96
Old Town TEOM	TEOM	Hourly				1	0.96	0.97	0.97	0.93
Northeast	FRM	Third day					1	0.99	0.98	0.96
Northwest	FRM	Third day						1	0.99	0.98
Westport	FRM	Third day							1	0.98
Southeast	FRM	Third day								1

* $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm; FMC, FMC Corporation; TEOM, tapered element oscillating microbalance; FRM, federal reference method.

† Frequency of monitor operation during the study period.

estimated standard error was applied to hourly concentration estimates for the time period with missing Baltimore Supersite data. Hourly estimates of $PM_{2.5}$ concentrations were averaged to obtain an 8-hour exposure measurement.

Study design

A case-crossover design was used to assess the risk of CHF symptom exacerbation and ensuing emergency admission in relation to ambient $PM_{2.5}$ levels. In this design, a specified referent window is identified for each subject that includes the case event matched to a set of control, or nonevent, periods for the same individual. The analytic approach compares exposures occurring during case events, defined as the "hazard" or "at-risk" period, with exposures for control periods, in which the outcome of interest did not occur (25). By making within-person comparisons, the case-crossover design eliminates confounding by fixed personal characteristics, such as age and gender (26). For this study, selection of the case period was assigned to two index dates: the participant-identified day of symptom onset (TOS) and the day of emergency department admission (Bayview Medical Center admission date (BMCA)). To control for time-varying factors and remove potential overlap bias, we used a time-stratified referent selection approach (27–29). We matched control periods by day of the week in the same calendar month as the case period in order to account for potential time trends in the exposure series (30, 31). For 8-hour averaged exposures, case and control periods were assigned to one of three 8-hour onset periods (morning = 4 a.m. to <12 p.m.; afternoon = 12 p.m. to <8 p.m.; night = 8 p.m. to <4 a.m.). If the participant was unable to identify an 8-hour period of the day for TOS, we assigned the period using a random process with the probabilities of morning (40 percent), afternoon (30 percent), and evening (30 percent) onset based on the distribution of times for participant-identified TOS periods.

Statistical methods

To assess the relation between $PM_{2.5}$ exposure and defined case events, we fitted a conditional logistic regression model that estimated the relative risk associated with interquartile-range increases in exposure to ambient $PM_{2.5}$ and gaseous pollutants for 8-hour and 24-hour averaged mass concentrations. Models were fitted for three case periods: 1) the participant's onset period (TOS_{8h}), 2) the participant's onset date (TOS_{24h}), and 3) BMCA. Since the induction time for symptom exacerbation related to fine particulate matter exposure was assumed to be limited to an acute period, we investigated single and cumulative lagged exposure periods ranging from 0 days to 3 days (32). Analyses were performed for both single-pollutant models ($PM_{2.5}$, carbon monoxide, nitrogen dioxide, and ozone) and two-pollutant models ($PM_{2.5}$ with a copollutant), unadjusted and adjusted for temperature and humidity (33, 34). All analyses were performed using the statistical software packages SAS (version 8.1; SAS Institute, Inc., Cary, North Carolina) and S-PLUS (version 6.1; Insightful Corporation, Seattle, Washington).

Simulation study

To assess the lower bound of detectable effects using this study design, we conducted a simulation study with 135 case events distributed over the 244-day study period. For the conditional logistic regression model, the probability that an event occurs at time t is taken from the proportional hazards model (28). The resulting probability function after removal of the baseline hazard rate used to randomly assign case events is $P_t = \exp(\beta X_t)/\sum_{j=1}^{T}\exp(\beta X_j)$, where X_t represents the series of daily average pollutant levels measured on day t and the coefficient β represents the known or "true" effect estimate. We applied the observed 24-hour average $PM_{2.5}$ measurements to three sets of simulations for β equal to 0.01, 0.02, and 0.05, with 500 data sets being randomly generated for each fixed estimate (35, 36). These values were chosen to be consistent with odds ratio estimates for interquartile-range differences in 24-hour $PM_{2.5}$ of 1.10, 1.20, and 1.58, respectively. Simulated case data sets were analyzed using the same conditional logistic regression model, adjusted for temperature and humidity, as that used in the empirical analysis with no exposure lag period.

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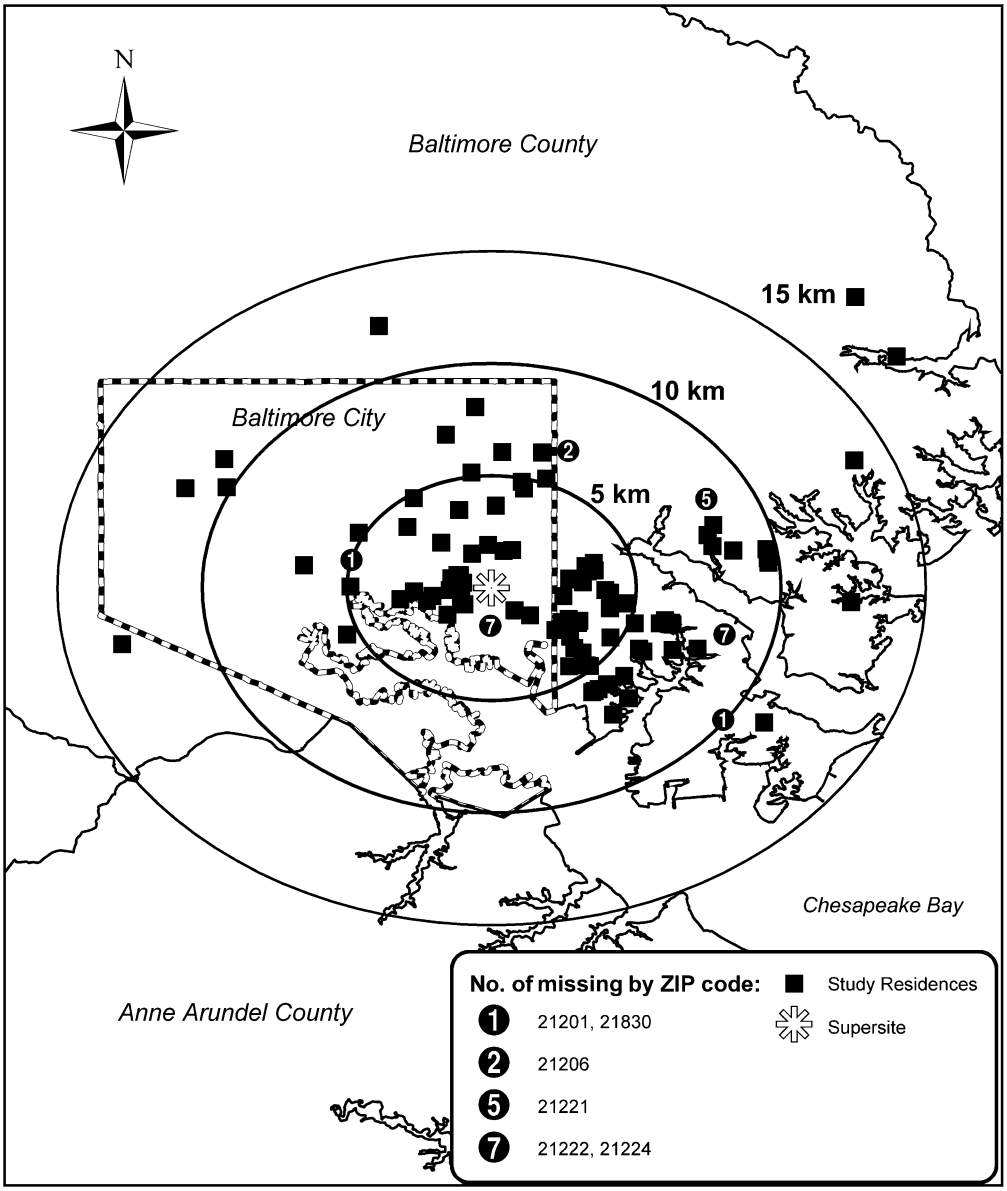

FIGURE 1. Residence locations for participants ($n = 101$) in a study of exacerbation of congestive heart failure symptoms by fine particulate air pollution, Baltimore, Maryland, 2002. Participants without street address information ($n = 23$) are enumerated in six residential ZIP codes, indicated by black circles. One participant residing in ZIP code 20724 is not shown on the figure.

RESULTS

From April through November of 2002, we identified 398 admissions of patients to Bayview Medical Center for overnight stays following CHF symptom exacerbation. Overall, 127 persons completed 137 interviews conducted a median of 2 days after admission (range, 0–16 days). In addition to the exclusions listed above ($n = 62$), some patients were not interviewed because of lack of consent ($n = 86$) or our inability to contact them during their hospitalization (e.g., they were not in the room during interviewer visits; $n = 113$). Two persons with primary residences outside the state of Maryland were excluded. Therefore, the final sample comprised 125 persons, of whom eight were interviewed twice and one was interviewed three times. This resulted in a total of 135 case events of hospital admission due to exacerbation of CHF symptoms. All repeat cases occurred during separate calendar months of the study period; therefore, they were assumed to be independent events for this analysis (35). Figure 1 shows the geographic distribution of participants in the study area defined around the primary air pollutant monitoring site, the Baltimore Supersite.

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TABLE 2. Characteristics of participants in a study of exacerbation of congestive heart failure symptoms by fine particulate air pollution ($n = 125$), Baltimore, Maryland, 2002

Characteristic	No. of participants	%
Female gender	76	60.8
Age (years)		
<50	9	7.2
50–59	24	19.2
60–69	31	24.8
70–79	34	27.2
≥80	27	21.6
Race		
White	99	79.2
Black	22	17.6
Other	4	3.2
High school education or more	63	50.4
Annual household income		
<$15,000	58	46.4
$15,000–$30,000	29	23.2
$30,001–$50,000	19	15.2
>$50,000	9	7.2
Not reported	10	8
Employed	16	12.8
Current smoker	18	14.4
Other smoker in household	46	36.8
Comorbid chronic condition(s) (diagnosis in medical chart)		
Asthma	5	4.0
Chronic obstructive pulmonary disease	36	28.8
Pneumonia	11	8.8
Hypertension	85	68.0
Prior myocardial infarction	26	20.8
Coronary heart disease	62	49.6
Diabetes	68	54.4
Other kidney or renal disease	35	28.0
Confirmatory chest radiograph consistent with congestive heart failure present in medical chart	112	89.6

Addresses for 101 participants are plotted, while 24 participants with missing information on street address were enumerated by residential ZIP code only.

The median age of study participants was 70 years. Participants were more likely to be female (61 percent) and White (79 percent) than nonparticipants (table 2). Although few participants were current smokers (14 percent), almost 40 percent had experienced passive exposure to tobacco smoke in their homes. A substantial proportion of participants had indications of comorbid disease in their medical charts, including high levels of hypertension (68 percent), diabetes (54 percent), and coronary heart disease (50 percent), as well as other chronic cardiovascular and respiratory conditions.

TOS for shortness of breath

Figure 2 displays case periods based on the identified day of TOS with further assignment of the 8-hour period for onset prior to admission day. Participants varied in interval from symptom exacerbation onset to emergency admission, with most participants (88 percent) visiting the emergency department within 1 day of TOS (range, 0–7 days). Participants identified an 8-hour period of the day for symptom exacerbation (TOS_{8h}) in 97 interviews. For 38 cases without an 8-hour TOS time, we assigned this period using a random process based on proportions of identified 8-hour TOS periods. Overall, 56 case events (41 percent) had morning onset, 39 (29 percent) had afternoon onset, and 40 (30 percent) had evening onset.

Summary of exposure measures

Figure 3 illustrates the temporal series of daily measures for each monitoring site and the averaged time-series results for daily $PM_{2.5}$ concentrations as estimated by the AR(1) model. Each series represents the 24-hour averaged concentrations for the eight monitoring stations listed in table 1. Measurements of $PM_{2.5}$ provided evidence of a strong correlation between monitoring stations (Pearson's $r > 0.9$ for all two-way comparisons). The overall time series at the bottom of the figure represents the estimated $PM_{2.5}$ daily average for Baltimore City. Sensitivity analyses found that the generalized linear model results were robust to the specification of more complex autoregressive structures than AR(1).

Table 3 summarizes the distributions of 8-hour and 24-hour averaged mean values for air pollutants and weather variables. Ambient $PM_{2.5}$ was moderately correlated with nitrogen dioxide ($r = 0.53$), ozone ($r = 0.48$), and temperature ($r = 0.51$) and was weakly correlated with carbon monoxide ($r = 0.18$) and relative humidity ($r = -0.08$). Table 4 shows the distribution of differences in $PM_{2.5}$ concentrations between case and control periods by lag time (37). For referent windows using 8-hour averaged periods, exposure concentrations for control periods are higher than those for case periods at a lag time of 0, while at a lag of 2 days, average case period exposures differ by 2.2 $\mu g/m^3$ from corresponding control periods. For each case definition and lag period, 75 percent of referent windows differ by less than the interquartile range of time-averaged $PM_{2.5}$ for the study period.

Analytic results

Table 5 presents estimates of the odds ratio from single-pollutant analyses. Generally, point estimates were near 1.0, with 95 percent confidence intervals extending below and above this null value. For single-lag analyses, the odds ratios for $PM_{2.5}$ for TOS_{8h} increased from a lag of 0 to a lag of 3 days. Only a single association for TOS_{8h} reached statistical significance ($p < 0.05$): that for carbon monoxide at a 2-day lag (odds ratio = 1.23, 95 percent confidence interval (CI): 1.01, 1.51). For both 24-hour averaged outcomes, odds ratio estimates were consistently below the null value of 1.0 in single-pollutant models for $PM_{2.5}$, carbon monoxide, and

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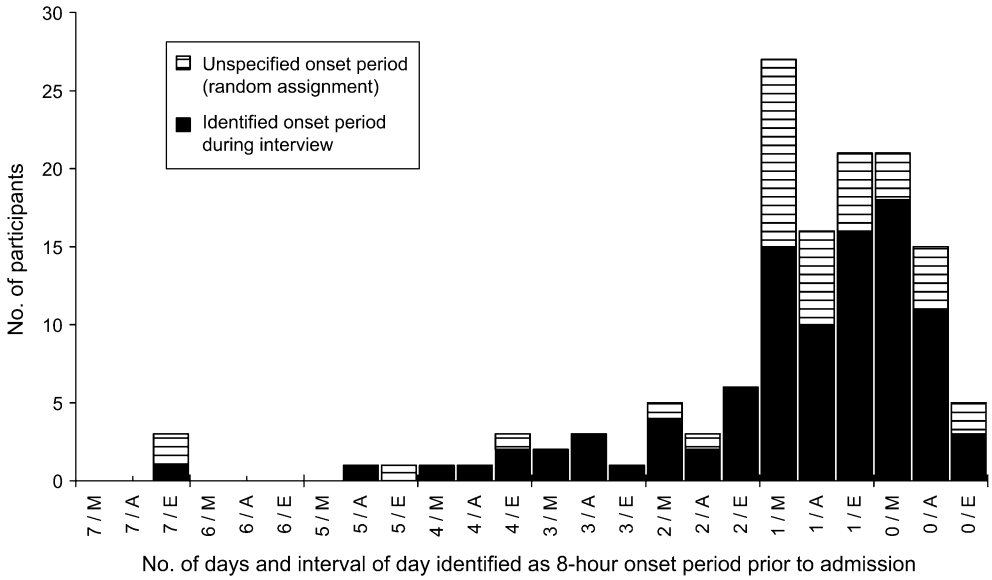

FIGURE 2. Distribution of participant-identified 8-hour periods of onset of congestive heart failure symptom exacerbation preceding hospital admission (135 admissions), Baltimore, Maryland, 2002. M, morning period (4 a.m. to <12 p.m.); A, afternoon period (12 p.m. to <8 p.m.); E, evening period (8 p.m. to <4 a.m.).

nitrogen dioxide. In single-pollutant models for ozone, odds ratio estimates above unity were observed for TOS_{24h} in association with lagged exposures at 2 and 3 days and with BMCA at a lag of 1 day.

We also assessed the effect of $PM_{2.5}$ with adjustment for other pollutants in two-pollutant models. Similar to the findings from single-pollutant models, $PM_{2.5}$ risk estimates were generally below the null value and did not attain statistical significance. A trend of increased odds ratios with lengthening lag was observed for TOS_{8h} after adjustment for copollutants and weather variables. Risk estimates for this outcome, though close to the null, were maximized at 2-day exposure lags for each set of model estimates (adjusted for ozone, odds ratio = 1.09, 95 percent CI: 0.91, 1.31 (displayed in figure 4); adjusted for carbon monoxide, odds ratio = 1.03, 95 percent CI: 0.86, 1.25 (results not shown); and adjusted for nitrogen dioxide, odds ratio = 1.04, 95 percent CI: 0.85, 1.27 (results not shown)). A similar pattern was not observed for TOS_{24h} or BMCA case events with adjustment for gaseous copollutants and weather variables (figure 4).

Simulation results

Figure 5 illustrates the distribution of regression coefficient estimates (β) provided by the conditional logistic regression model for 500 iterations of data simulated for the three fixed β values. The results indicated that our study design was sufficiently powerful to detect statistically significant effects for odds ratios greater than 1.20 for an interquartile-range difference in 24-hour averaged $PM_{2.5}$. However, uncertainty increased for estimates when we tried to detect a smaller fixed effect of β equal to 0.01 that was consistent with an odds ratio of 1.10.

DISCUSSION

Our study provides new insights into the temporal dynamics of symptom onset in persons with CHF that may be useful for future research. Although the primary results did not demonstrate a statistically significant association between case events and exposure to $PM_{2.5}$, a trend of increased risk estimates at lengthening lagged exposures was observed when we used the 8-hour symptom onset period to define case events. This relation was not seen when 24-hour exposure periods were evaluated using either onset day or hospital admission date to define case events.

In this case-crossover study, we found that a more precise definition of disease and exposure timing allowed for the potential detection of a more specific association between exposure to air pollutants, specifically $PM_{2.5}$, and exacerbation of CHF symptoms. We developed an interview approach that described the timing of CHF decompensation and were able to explore the impact of $PM_{2.5}$ exposure for clinically important periods prior to hospitalization. We hypothesized that this approach would enhance detection of a more relevant exposure period for $PM_{2.5}$ associated with cardiovascular effects. The use of a case-crossover design allowed for the control of confounding due to time-fixed characteristics for persons with CHF (38), and the choice of time-stratified referent sampling minimized bias due to seasonal and weekly trends in $PM_{2.5}$ levels (27, 29).

Previous studies have explored the relation between CHF morbidity and exposure to air pollutants (17, 39–44). The majority of these studies have demonstrated positive and significant associations with at least one of the pollutants examined. For example, in a study carried out in Detroit, Michigan, Schwartz and Morris (42) found a significant

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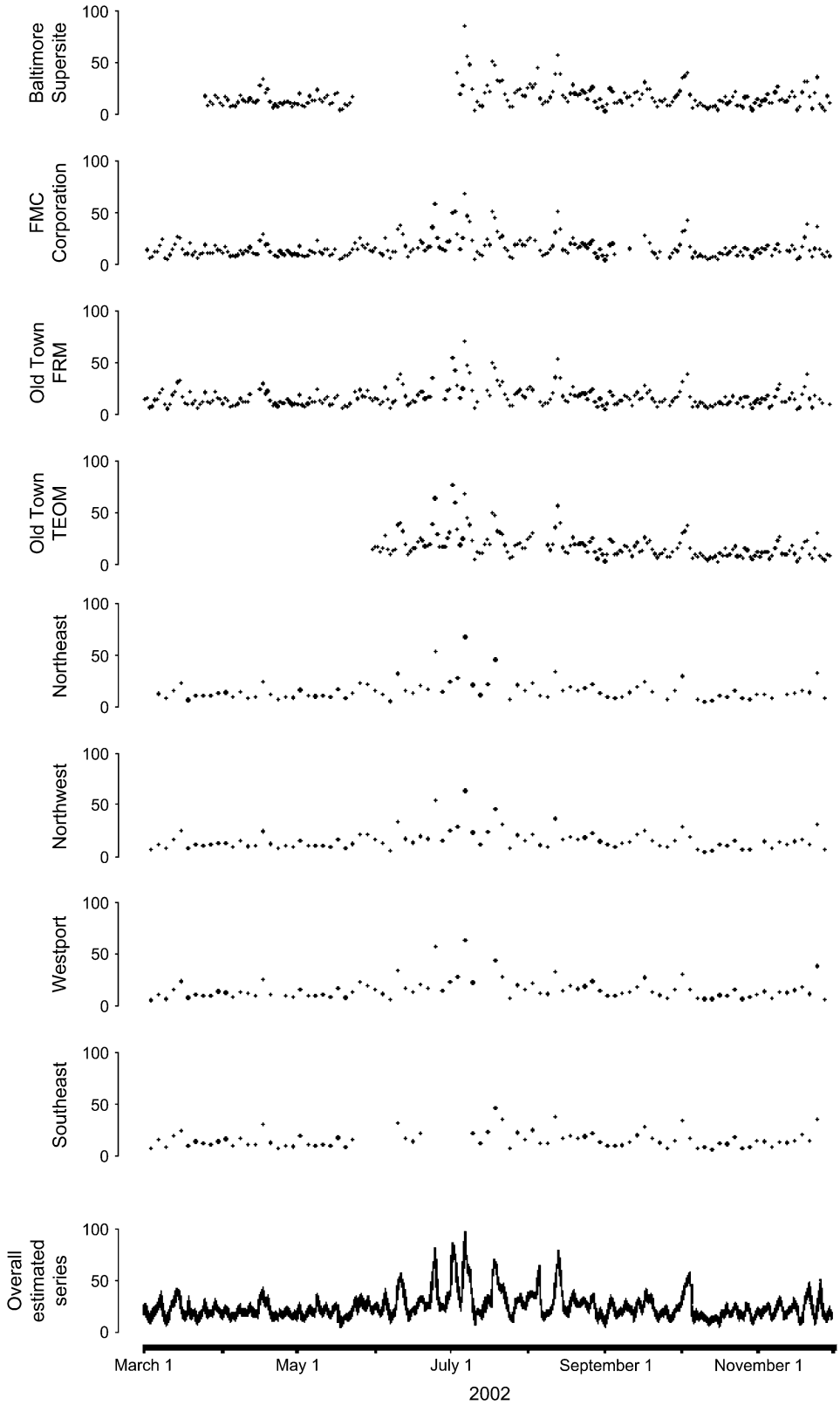

FIGURE 3. Time-series estimates of daily average and overall concentrations ($\mu g/m^3$) of particulate matter with an aerodynamic diameter of <2.5 μm from eight monitoring stations, Baltimore, Maryland, 2002. FRM, federal reference method; TEOM, tapered element oscillating microbalance.

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TABLE 3. Exposure variables included in a study of exacerbation of congestive heart failure symptoms by fine particulate air pollution, by averaging period, Baltimore, Maryland, 2002

Variable	8-hour average			24-hour average		
	Mean (SD*)	IQR*	Range	Mean (SD)	IQR	Range
$PM_{2.5}$* (μg/m^3)	17.0 (12.7)	12.1	0.1–111.9	16.0 (10.0)	9.2	3.5–69.2
Carbon monoxide (ppm)	0.4 (0.2)	0.3	0.0–2.3	0.4 (0.2)	0.2	0.1–1.0
Nitrogen dioxide (ppb)	26 (11)	13	4–78	26 (9)	11	8–52
Ozone (ppb)	31 (20)	26	3–120	31 (14)	19	3–72
Temperature (°C)	18.5 (8.6)	14.3	−5.3 to 36.4	18.6 (8.2)	13.7	−1.5 to 33.0
Humidity (%)	61.4 (18.9)	27.2	17.0–99.3	61.3 (15.6)	21.6	28.3–98.6

* SD, standard deviation; IQR, interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm.

association between heart failure hospital admission and concentrations of carbon monoxide and particulate matter with an aerodynamic diameter of <10 μm (PM_{10}) (for carbon monoxide, relative risk = 1.02, 95 percent CI: 1.01, 1.03; for PM_{10}, relative risk = 1.02, 95 percent CI: 1.00, 1.04). In a study carried out in Denver, Colorado, Koken et al.

TABLE 4. Differences between case and control $PM_{2.5}$* exposure concentrations by case event referent window, Baltimore, Maryland, 2002

Referent window	Mean difference (μg/m^3) (SD*)	Percentile				
		5th	25th	50th	75th	95th
8-hour average TOS* (TOS_{8h})						
Lag 0	−0.4 (12.4)	−22.0	−7.5	−0.6	6.7	20.7
Lag 1	0.5 (15.7)	−21.8	−6.9	−2.5	7.1	20.9
Lag 2	2.2 (16.8)	−23.8	−5.5	−0.2	7.2	33.0
Lag 3	0.8 (12.8)	−14.8	−7.7	−1.5	7.3	30.8
Cum. lag 1†	0.1 (12.2)	−17.7	−6.8	−1.5	6.2	20.1
Cum. lag 2	0.8 (11.6)	−17.7	−5.2	−0.3	6.3	21.8
Cum. lag 3	0.8 (10.2)	−16.3	−5.4	0.2	6.3	21.1
24-hour average TOS (TOS_{24h})						
Lag 0	−0.5 (11.2)	−16.9	−7.6	−1.3	4.6	24.1
Lag 1	−0.2 (12.0)	−24.5	−5.8	−0.2	5.2	22.2
Lag 2	1.1 (11.7)	−16.5	−5.4	−0.1	5.5	32.5
Lag 3	0.0 (9.3)	−11.2	−5.4	−1.5	3.8	16.5
Cum. lag 1	−0.4 (10.4)	−19.6	−6.8	−1.5	4.6	20.9
Cum. lag 2	0.1 (9.3)	−16.8	−4.8	−0.6	4.5	19.0
Cum. lag 3	0.1 (8.0)	−14.7	−4.5	−0.6	3.9	15.4
Bayview Medical Center admission date (BMCA) (24-hour average)						
Lag 0	−1.1 (11.8)	−17.6	−7.7	−3.3	4.8	24.1
Lag 1	−0.2 (11.1)	−16.9	−5.8	−1.0	4.6	23.5
Lag 2	−0.6 (10.1)	−16.0	−5.6	−0.7	3.9	15.7
Lag 3	−0.7 (11.2)	−17.7	−6.0	−2.2	3.8	21.6
Cum. lag 1	−0.7 (10.6)	−17.3	−6.9	−1.9	3.5	21.9
Cum. lag 2	−0.6 (9.1)	−13.6	−6.3	−0.7	2.6	19.4
Cum. lag 3	−0.6 (8.1)	−14.5	−5.1	−1.4	2.5	14.7

* $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm; SD, standard deviation; TOS, time of onset for symptom exacerbation.

† Cum. lag, cumulative lagged exposure (the average of concentrations on the numerically specified day and all days following).

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TABLE 5. Odds ratio estimates for defined case events associated with an interquartile-range increase in pollutant concentrations in single-pollutant models, Baltimore, Maryland, 2002*

Case event	$PM_{2.5}$†		Carbon monoxide		Nitrogen dioxide		Ozone	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI
8-hour average TOS† (TOS_{8h})								
Lag 0	0.87	0.69, 1.09	0.99	0.80, 1.23	1.06	0.80, 1.41	0.69	0.46, 1.05
Lag 1	0.96	0.78, 1.18	0.86	0.67, 1.12	0.99	0.74, 1.33	1.18	0.78, 1.79
Lag 2	1.09	0.91, 1.30	1.23	1.01, 1.51	1.21	0.91, 1.61	0.99	0.66, 1.50
Lag 3	0.99	0.79, 1.23	0.99	0.78, 1.26	1.03	0.77, 1.37	1.29	0.83, 2.00
Cum. lag 1‡	0.89	0.67, 1.16	0.88	0.64, 1.21	1.06	0.73, 1.54	0.88	0.52, 1.50
Cum. lag 2	0.99	0.74, 1.33	1.06	0.75, 1.51	1.21	0.79, 1.86	0.96	0.52, 1.78
Cum. lag 3	0.98	0.70, 1.36	1.03	0.69, 1.55	1.20	0.75, 1.93	1.16	0.58, 2.32
24-hour average TOS (TOS_{24h})								
Lag 0	0.84	0.67, 1.05	0.82	0.62, 1.09	0.88	0.64, 1.20	0.78	0.51, 1.19
Lag 1	0.91	0.74, 1.11	0.90	0.69, 1.18	0.94	0.69, 1.29	0.98	0.64, 1.50
Lag 2	1.01	0.83, 1.23	0.99	0.76, 1.29	1.04	0.76, 1.42	1.23	0.80, 1.88
Lag 3	0.92	0.73, 1.15	0.86	0.65, 1.14	0.94	0.69, 1.28	1.40	0.91, 2.16
Cum. lag 1	0.83	0.64, 1.07	0.79	0.55, 1.12	0.89	0.62, 1.28	0.84	0.51, 1.39
Cum. lag 2	0.88	0.66, 1.16	0.78	0.51, 1.19	0.93	0.61, 1.43	0.99	0.56, 1.76
Cum. lag 3	0.85	0.62, 1.16	0.71	0.44, 1.13	0.91	0.57, 1.46	1.20	0.64, 2.22
Bayview Medical Center admission date (BMCA) (24-hour average)								
Lag 0	0.81	0.65, 1.01	0.86	0.67, 1.11	0.88	0.65, 1.19	0.73	0.48, 1.11
Lag 1	0.90	0.74, 1.11	0.90	0.70, 1.17	0.86	0.62, 1.17	1.03	0.66, 1.60
Lag 2	0.85	0.68, 1.07	0.96	0.73, 1.26	0.91	0.67, 1.24	0.78	0.49, 1.23
Lag 3	0.86	0.70, 1.05	0.88	0.67, 1.16	0.91	0.67, 1.22	0.91	0.60, 1.39
Cum. lag 1	0.82	0.64, 1.04	0.82	0.60, 1.13	0.83	0.58, 1.20	0.82	0.50, 1.34
Cum. lag 2	0.76	0.57, 1.01	0.80	0.54, 1.17	0.80	0.53, 1.23	0.74	0.42, 1.31
Cum. lag 3	0.70	0.51, 0.97	0.72	0.46, 1.14	0.77	0.48, 1.24	0.72	0.38, 1.37

* Results were controlled for temperature and humidity in all models.

† $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm; OR, odds ratio; CI, confidence interval; TOS, time of onset for symptom exacerbation.

‡ Cum. lag, cumulative lagged exposure (the average of concentrations on the specified day and all days following).

(43) verified a significant association with CHF admission only for carbon monoxide at a 3-day lag (relative risk = 1.10, 95 percent CI: 1.00, 1.22). In contrast, in a study carried out in London, United Kingdom, Poloniecki et al. (44) found no statistically significant relation between any pollutant and hospital admission for heart failure.

In most of these studies, the primary outcome was hospital admission, with disease status being determined by *International Classification of Diseases*, Ninth Revision, codes. Previous research has indicated that reliance on *International Classification of Diseases*, Ninth Revision, codes may result in undercounting of hospitalizations of persons with clinical evidence of CHF by as much as 33 percent (45). The potential miscoding or exclusion of significant numbers of CHF patients in large studies where disease is identified solely through discharge codes may result in outcome misclassification arising from hospital administrative decisions (46). In addition, exposure in the referenced studies was estimated on the basis of lag structures defined by time of admission, which may not be biologically relevant to onset of symptom exacerbation.

We did find carbon monoxide to be significantly associated with onset of heart failure symptom exacerbation for 8-hour exposures at a 2-day lag. Our positive finding for this pollutant is consistent with other studies of heart failure morbidity and air pollution exposure. In these studies, carbon monoxide, of all the pollutants considered, has been most consistently found to be related to CHF (17, 39–44). Carbon monoxide reduces oxygen delivery and has been linked to myocardial ischemia at low concentrations (47, 48).

We also observed maximum effect estimates at a 2-day lagged exposure in analyses evaluating participant-identified 8-hour TOS as the case period. This result is similar to that of studies which have detected associations for elevated levels of fine particulate matter 2 days prior to specific adverse cardiovascular events with identifiable acute onset times, such as primary cardiac arrest (49) and automated implantable cardiac defibrillator firings (12). However, our findings

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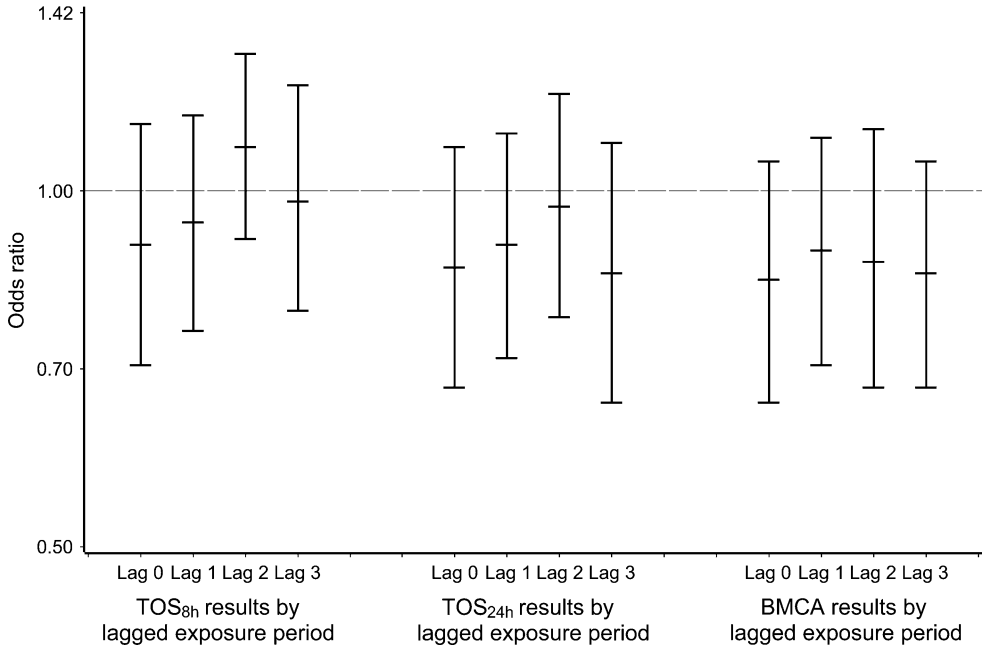

FIGURE 4. Adjusted odds ratios for the relation between exposure to particulate matter with an aerodynamic diameter of <2.5 μm and exacerbation of congestive heart failure symptoms leading to hospitalization, by lag period (days), for three case definitions (8-hour time of onset for symptom exacerbation (TOS_{8h}), 24-hour time of onset for symptom exacerbation (TOS_{24h}), and Bayview Medical Center admission date (BMCA)), Baltimore, Maryland, 2002. Results were adjusted for ozone level, temperature, and humidity in all models. Bars, 95% confidence interval.

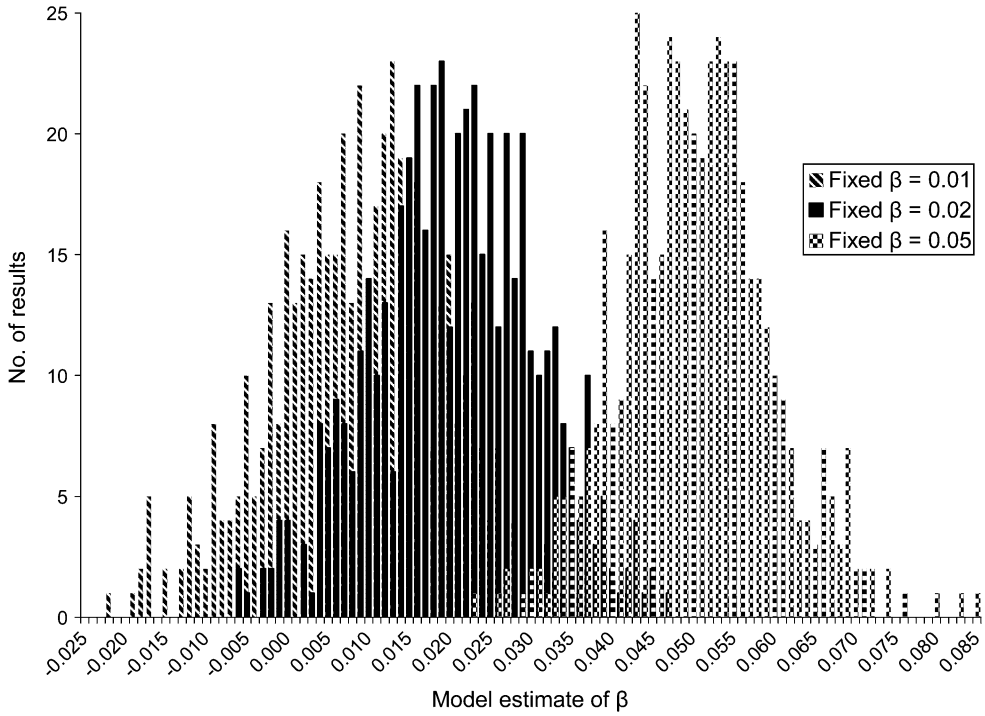

FIGURE 5. Estimated results from 500 simulations each for three fixed values of β (beta coefficient from conditional logistic regression model).

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differ from those of large time-series studies in which investigators reported stronger associations between CHF admission and $PM_{2.5}$ level on the day of hospital admission (50).

One explanation for this discrepancy may be differences between outcomes defined for individual-based case-crossover studies and those identified from larger admissions databases. In this study, each participant was recruited on the basis of a CHF diagnosis confirmed by a physician, using information obtained from hospital admission charts. This approach may be more specific for case-finding in comparison with studies that rely on discharge diagnoses coded by hospital billing departments. Moreover, persons with CHF are a clinically heterogeneous group with a high proportion of comorbid diseases, such as chronic obstructive pulmonary disease, hypertension, and diabetes, that may be potential sources of outcome misclassification (51). High rates of these conditions were observed among participants in our study, illustrating the complicated nature of medical classification of persons with CHF.

There are several potential limitations to our findings. As with other studies of ambient air pollution, exposure measurement error may have led us to incorrectly estimate the true pollutant exposures for study participants (52). The use of multiple monitors to complete the measurement series of $PM_{2.5}$ demonstrated a high level of homogeneity for ambient $PM_{2.5}$ concentrations estimated throughout the study area. Previous research has demonstrated that personal and ambient concentrations of $PM_{2.5}$ are highly correlated in populations similar to the one in this study (53, 54). Additionally, some participants, mostly at the beginning of the study, were unable to specify an 8-hour period for TOS. During the course of the study, refinements in the interview allowed us to improve patients' identification of TOS for 8-hour onset periods. A comparative analysis found little bias in using this random assignment process. Finally, time-varying risks such as individual compliance with physician recommendations concerning diet, activity, and medications were not assessed because of concerns about the length of the interview. These factors may exert an acute effect on the ability to assess hospitalization risk for persons with CHF either independently of or as modified by elevated fine particulate matter exposures (55).

In planning this study, we recognized that statistical power might be limited by the sample size, that is, the number of persons who could be feasibly recruited. Our empirical analyses detected an increasing trend in risk but lacked statistical significance. To better interpret our findings, we conducted three simulation analyses using 135 case events assigned to the observed daily $PM_{2.5}$ concentrations for our study period. The results indicated that if the ''true'' odds ratio were 1.20 or higher for an interquartile-range difference in observed $PM_{2.5}$ ambient concentration, our study design was sufficiently powerful to detect this level of increased risk.

The generally null findings of our empirical analysis weigh against strong effect estimates for risk of symptom exacerbation due to $PM_{2.5}$ exposures. The results of the simulations conducted for a fixed β equal to 0.01 (equivalent to an odds ratio of 1.10) indicate that our design was able to detect this smaller effect, though many individual model estimates lacked statistical significance. This simulated value is similar to our maximum estimate of association between 8-hour averaged ambient $PM_{2.5}$ and symptom onset detected at an exposure lag of 2 days. Findings from the simulation study suggest that the absence of statistical evidence does not necessarily represent evidence for the absence of an effect. Rather, it is likely that the small magnitude of $PM_{2.5}$ effects requires a larger number of cases in order to obtain sufficient power for detection using this design. Furthermore, comparison of exposure differences between case and control periods indicates that our null findings may also have resulted from relatively small absolute differences in exposure concentrations within referent windows (37).

If $PM_{2.5}$ has a causal effect in worsening the health of persons with chronic illnesses such as CHF, a potentially large number of excess hospitalizations can be attributed to this ubiquitous exposure (56). Exacerbations of CHF symptoms have been associated with increased ambient $PM_{2.5}$ levels; however, individual variation in the severity and timing of responses may be due to differing physiologic mechanisms (57). Evidence from studies of shortness of breath and other heart failure decompensation symptoms demonstrates that exacerbations may progress over a period of several days following a triggering exposure (58, 59). Assigning case periods by individual onset time may provide a useful model for estimating the risk of hospitalization associated with increased levels of ambient $PM_{2.5}$. Although our findings are inconclusive, they suggest that exposures sufficient to affect health may be occurring earlier than would be inferred from studies based only on date of hospital admission. The understanding of induction time is a key element for determining which biologic mechanisms that adversely affect the health of susceptible persons are influenced by fine particulate matter exposure.

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