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Original Contribution

Seasonal and Regional Short-term Effects of Fine Particles on Hospital Admissions in 202 US Counties, 1999–2005

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The authors investigated whether short-term effects of fine particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) on risk of cardiovascular and respiratory hospitalizations among the elderly varied by region and season in 202 US counties for 1999–2005. They fit 3 types of time-series models to provide evidence for 1) consistent particulate matter effects across the year, 2) different particulate matter effects by season, and 3) smoothly varying particulate matter effects throughout the year. The authors found statistically significant evidence of seasonal and regional variation in estimates of particulate matter effect. Respiratory disease effect estimates were highest in winter, with a 1.05% (95% posterior interval: 0.29, 1.82) increase in hospitalizations per 10-μg/m^3 increase in same-day $PM_{2.5}$. Cardiovascular diseases estimates were also highest in winter, with a 1.49% (95% confidence interval: 1.09, 1.89) increase in hospitalizations per 10-μg/m^3 increase in same-day $PM_{2.5}$, with associations also observed in other seasons. The strongest evidence of a relation between $PM_{2.5}$ and hospitalizations was in the Northeast for both respiratory and cardiovascular diseases. Heterogeneity of $PM_{2.5}$ effects on hospitalizations may reflect seasonal and regional differences in emissions and in particles' chemical constituents. Results can help guide development of hypotheses and further epidemiologic studies on potential heterogeneity in the toxicity of constituents of the particulate matter mixture.

air pollution; hospitalization; Medicare; particulate matter; seasons

Abbreviations: ICD-9, *International Classification of Diseases*, Ninth Revision; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm.

Numerous studies have demonstrated increased risk of cardiovascular and respiratory hospitalizations in relation to airborne particles, including particulate matter with an aerodynamic diameter ≤10 μm or ≤2.5 μm (PM_{10} or $PM_{2.5}$) (1). Previous research identified associations between $PM_{2.5}$ and chronic obstructive pulmonary disease hospital admissions (2) and between coarse particulate matter ($PM_{10–2.5}$) and respiratory hospitalizations (3). PM_{10} has been associated with admissions for adult asthma (4), cardiopulmonary causes (5), and cardiovascular disease (6) and with emergency admissions for childhood asthma (7) and cardiovascular causes (8).

Recent studies suggest that particulate matter effects vary by region and season. A study of cause-specific cardiovascular and respiratory hospital admissions and daily $PM_{2.5}$ levels among Medicare enrollees found strong regional patterns of effect across 204 US counties (9). Effect estimates for some cardiovascular causes, including ischemic heart and peripheral vascular diseases, were statistically significant in the eastern but not the western United States. For chronic obstructive pulmonary disease and respiratory tract infection, effects were observed in both eastern and western regions, but they were larger in the latter. Short-term effects of PM_{10} on mortality were larger in the Northeast and in summer, whereas evidence for seasonal variation was not found in the southern United States (10). In the Air Pollution and Health: A European Approach (APHEA) study, effect estimates for particles and mortality were lower for central-eastern Europe than western Europe (11), although more recent work suggests these differences are explained in part

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by statistical modeling choices (12). Other work shows spatial differences in PM_{10}–mortality associations in the United States (13) and seasonal variation in coarse particulate matter effects on lung inflammation (14).

In addition to seasonal variation, time trends of effect have been examined. Methods developed in the National Morbidity, Mortality and Air Pollution Study were applied to evaluate change in short-term PM_{10} effects over a period of increasingly stringent regulation that might have altered particulate matter composition and toxicity (15–17). There was weak evidence that the effects declined over the period 1987–2000, primarily in the eastern United States.

Regional and temporal differences in effect estimates may relate to heterogeneity in the particulate matter mixture. In the United States, we found substantial spatial and temporal variability in $PM_{2.5}$ chemical composition (18). However, differences in effect estimates across locations could also reflect differences in exposure patterns, such as indoor versus outdoor activity patterns, and community characteristics, including the presence of susceptible subpopulations. Heterogeneity in effect estimates across seasons could reflect seasonal variation in particulate matter toxicity or confounding by a seasonally varying factor, such as ozone pollution. In addition, evidence that health effect estimates have different seasonal and regional patterns by cause would be indicative of multiple mechanisms of toxicity.

This study quantified evidence of spatial and temporal heterogeneity in the health effects of short-term exposure to particles. We applied 3 statistical approaches to investigate the short-term effects of $PM_{2.5}$ on cardiovascular or respiratory hospitalizations among Medicare enrollees by season and geographic region of the United States. We also identified $PM_{2.5}$ chemical components with higher levels for regions and seasons with higher effect estimates compared with regions and seasons with lower effect estimates.

MATERIALS AND METHODS

We used a national database of hospital admissions for 1999–2005 based on Medicare enrollees aged ≥65 years for 202 US counties with populations ≥200,000. Each Medicare claim includes age and place of residence. The number of hospitalizations for a given cause on a given day and for a specific community was calculated as the sum of all claims for that cause based on primary diagnosis. The number of individuals at risk was defined as the number of Medicare enrollees on a given day for that community.

We considered urgent hospitalizations for cardiovascular and respiratory causes, excluding scheduled visits that by definition are not pollution related. Cardiovascular admissions were calculated as the sum of hospitalizations for heart failure (*International Classification of Diseases*, Ninth Revision (ICD-9) code 428), heart rhythm disturbances (ICD-9 codes 426–427), cerebrovascular events (ICD-9 codes 430–438), ischemic heart disease (ICD-9 codes 410–414 and 429), and peripheral vascular disease (ICD-9 codes 440–449); and we determined respiratory admissions as the sum of admissions for chronic obstructive pulmonary disease (ICD-9 codes 490–492) and respiratory tract infections (ICD-9 codes 464–466, 480–487). These ICD codes were used in earlier work, which enhances comparability across studies including research on hospitalizations and $PM_{2.5}$ (9) and $PM_{10-2.5}$ (19).

$PM_{2.5}$ data were obtained from the US Environmental Protection Agency. While some communities measured $PM_{2.5}$ daily, most measured every 3 days. We used a 10% trimmed mean to average across monitors after correction for yearly monitor averages, protecting against outlier values and as applied in earlier studies (9). Daily temperature and dew point temperatures were obtained from the National Climatic Data Center.

We applied a 2-stage Bayesian hierarchical model to estimate the association between the daily $PM_{2.5}$ and hospitalization rates on average across the 202 US counties. The first stage estimated this association within a single county, accounting for several time-varying confounders; the second stage combined county-specific estimates, accounting for their statistical uncertainty to generate an overall effect. At the first stage, we fitted a "main" model that assumes that the short-term $PM_{2.5}$ effect on hospitalizations is constant throughout the year and a "seasonal" model allowing the effect to vary by season. As a sensitivity analysis, we applied a third approach of using a "harmonic" model allowing the $PM_{2.5}$ effect to vary smoothly throughout the year (10).

The main-effect model can be defined as

$$\begin{aligned}\ln\left(E\left[h_t^c\right]\right) = {} & \beta^c x_{t-l}^c + \alpha^c DOW_t + ns(T_t^c, \mathrm{df}_T) \\ & + ns(D_t^c, \mathrm{df}_D) + ns(Ta_t^c, \mathrm{df}_{Ta}) \\ & + ns(Da_t^c, \mathrm{df}_{Da}) + ns(t, \mathrm{df}_t) \\ & + A_t ns(t, \mathrm{df}_{A_t}) + \ln(N_t^c),\end{aligned} \tag{1}$$

where

- h_t^c = hospitalization rate in county c, day t
- β^c = regression coefficient relating $PM_{2.5}$ to hospitalization rates in county c
- x_{t-l}^c = $PM_{2.5}$ level in county c, day t, at lag of l days (e.g., $l = 0$ is the same day)
- α^c = regression coefficient relating day of the week to hospitalization rates in county c
- DOW_t = day of the week on day t
- $ns\left(T_t^c, df_T\right)$ = natural cubic spline of temperature in county c, day t with df_T (six) degrees of freedom
- $ns\left(D_t^c, \mathrm{df}_D\right)$ = natural cubic spline of dew point temperature in county c, day t with df_D (three) degrees of freedom
- $ns\left(Ta_t^c, \mathrm{df}_{Ta}\right)$ = natural cubic spline with df_{Ta} (six) degrees of freedom for the average of the 3 previous days' temperature in county c, day t, adjusted for current day temperature and dew point temperature
- $ns\left(Da_t^c, \mathrm{df}_{Da}\right)$ = natural cubic spline with df_{Da} (three) degrees of freedom for the average of the 3 previous days' dew point temperature in county c, day t, adjusted for current day temperature and dew point temperature
- $ns(t, \mathrm{df}_t)$ = natural cubic spline of time with df_t (eight/year) degrees of freedom
- $ns\left(t, \mathrm{df}_{A_t}\right)$ = natural cubic spline of time with df_{A_t} (one/year) degrees of freedom

A_t = indicator for persons aged ≥75 years
N_t^c = size of the population at risk in county c, day t.

The above model was fitted separately for each county and hospitalization cause (cardiovascular or respiratory). The nonlinear relation between health and weather was modeled by using natural splines of temperature and dew point temperature, including variables for previous days' conditions. We accounted for temporal trends through a nonlinear function of time. Differential temporal trends by age category were modeled through an interaction term between age and the nonlinear temporal function. A version of this model was used previously to investigate $PM_{2.5}$ and cause-specific hospitalizations (9).

The first-stage seasonal interaction model allows effect estimates to differ by season, replacing the pollution term in equation 1, $\beta^c x_{t-l}^c$, with

$$\beta_w I_w x_{t-l}^c + \beta_{Sp} I_{Sp} x_{t-l}^c + \beta_{Su} I_{Su} x_{t-l}^c + \beta_A I_A x_{t-l}^c, \qquad (2)$$

where

I_w, I_{Sp}, I_{Su}, I_A = 0/1 indicator variables representing winter, spring, summer, and autumn, respectively
β_w, β_{Sp}, β_{Su}, β_A = regression coefficients regarding the relation between $PM_{2.5}$ and hospitalization rates for a given season.

We also allowed temporal trend to differ by season, replacing the temporal trend term in equation 1, $ns(T_t^c, \mathrm{df}_T)$, with

$$I_w ns(t, \mathrm{df}_t) + I_{Sp} ns(t, \mathrm{df}_t) + I_{Su} ns(t, \mathrm{df}_t) + I_A ns(t, \mathrm{df}_t). \quad (3)$$

The other terms of equation 1 were maintained in the seasonal interaction model. For the seasonal interaction model, seasons were defined as 3-month periods (e.g., summer as June–August). This model provides seasonal estimates of the relation between $PM_{2.5}$ and cause-specific hospitalizations by county, and it assumes no temporal variation in $PM_{2.5}$ effects by season. The harmonic model relaxes this assumption by allowing $PM_{2.5}$ effects to vary smoothly throughout the year and was initially developed to investigate seasonality in PM_{10} mortality effects (10). The harmonic model is analogous to equation 1, replacing the pollution term with

$$\beta_1^c \sin(2\pi t/365) x_{t-l}^c + \beta_2^c \cos(2\pi t/365) x_{t-l}^c + \beta_3^c x_{t-l}^c. \quad (4)$$

All nonpollution terms from equation 1 were maintained in the harmonic model.

These 3 model structures incorporate different assumptions about the relation between $PM_{2.5}$ and hospitalizations. The main-effect model assumes constant effects throughout the year. The seasonal interaction model improves upon the main-effect model by allowing the association to differ by season. The harmonic model is not subject to the specifications of seasons or the condition that the effect be constant throughout the year or in a given season. Main-effect and seasonal interaction models were applied for cardiovascular and respiratory admissions and $PM_{2.5}$ at lags 0, 1, and 2 days. The harmonic model was applied for cardiovascular and respiratory admissions at the lag with the strongest effect, as reported by the main-effect and seasonal interaction models.

The main-effect, first-stage model provides an estimate of the relation between $PM_{2.5}$ and hospitalizations for a given county ($\hat{\beta}^c$)and its estimated variance, whereas the seasonal interaction, first-stage model provides an estimate of the relation between $PM_{2.5}$ and hospitalizations for a given county (4-dimensional vector $\hat{\beta}^c$) and its estimated covariance matrix (V^c) for each season. The second-stage model assumes that the true relation in a given county (β^c) has a multivariate normal distribution with mean (μ) and the between-community variance (Σ). We applied this model by using 2-level normal independent sampling estimation (TLNise) with uniform priors (20) as

$$\hat{\beta}^c \mid \beta^c \sim N_4(\beta^c, V^c)$$
$$\beta^c \mid \mu, \sum \sim N_4(\mu, \sum). \qquad (5)$$

A similar version of the second-stage modeling structure described in equation 5 was applied to the first-stage, county-specific estimates of the main and harmonic models (21–23). Sensitivity of the risk estimates to the smooth function of time and the models for temperature and dew point have been explored previously, indicating that national average estimates obtained from hierarchical models are robust to a wide variety of modeling approaches (24–26).

We fitted all 3 models (main, seasonal, and harmonic) separately within geographic regions. Noncontinental counties in the national analysis were excluded from regional analyses (Honolulu, Hawaii; Anchorage, Alaska). We divided the remaining 200 counties into 4 regions: Northeast (n = 108), Southeast (n = 58), Northwest (n = 9), and Southwest (n = 25). Regions were based on spatial divisions applied previously in the National Morbidity, Mortality and Air Pollution Study and studies investigating hospital admissions (9, 10, 27).

We tested for evidence of seasonal and regional heterogeneity in the short-term effects of $PM_{2.5}$ on hospitalizations for the lags with the strongest effects for each hospitalization cause. Specifically, we used the Wald test statistic to assess whether there is evidence of heterogeneity in 1) national average effects across seasons, and 2) regional average effects across regions for both cardiovascular and respiratory admissions. The Wald test statistic was compared with a chi-square distribution with appropriate degrees of freedom to obtain corresponding significance levels. A significance level of $P < 0.05$ was used; we did not include multiple testing correction for the 4 simultaneous tests.

RESULTS

Respiratory admissions rates showed a seasonal pattern with higher admissions in winter, whereas cardiovascular

Table 1. National Estimates of the Percentage Increase in Hospital Admission Rates per 10-μg/m^3 Increase in $PM_{2.5}$ for 202 US Counties for 1999–2005, by Lag and by Season

	Main Model		Seasonal Interaction Model							
	Yearly		Winter		Spring		Summer		Autumn	
	Central Effect	95% PI	Central Effect	95% PI	Central Effect	95% PI	Central Effect	95% PI	Central Effect	95% PI
Cardiovascular admissions										
Lag 0	0.80[a]	0.59, 1.01	1.49[a]	1.09, 1.89	0.91[a]	0.47, 1.35	0.18	−0.23, 0.58	0.68[a]	0.29, 1.07
Lag 1	0.07	−0.12, 0.26	0.56[a]	0.16, 0.96	−0.10	−0.58, 0.39	−0.16	−0.54, 0.22	0.04	−0.28, 0.35
Lag 2	0.06	−0.12, 0.23	0.27	−0.12, 0.65	0.19	−0.23, 0.60	−0.12	−0.50, 0.26	0.02	−0.30, 0.34
Respiratory admissions										
Lag 0	0.22	−0.12, 0.56	1.05[a]	0.29, 1.82	0.31	−0.47, 1.11	−0.62	−1.33, 0.09	0.02	−0.63, 0.67
Lag 1	0.05	−0.29, 0.39	0.50	−0.27, 1.27	−0.24	−1.01, 0.53	0.28	−0.39, 0.95	0.15	−0.49, 0.79
Lag 2	0.41[a]	0.09, 0.74	0.72[a]	0.01, 1.43	0.35	−0.29, 0.99	0.57	−0.07, 1.23	0.39	−0.22, 1.01

Abbreviations: PI, posterior interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm.
[a] Statistically significant effect.

admission rates were more similar across seasons. Figure S1 provides box plots of hospitalization rates by region and season, and Figure S2 shows analogous plots of $PM_{2.5}$ and weather variables (these 2 supplementary figures and other supplementary information are posted on the *Journal*'s website (http://aje.oupjournals.org/)).

Table 1 summarizes national average estimates of the association between $PM_{2.5}$ and hospitalizations by lag for

Table 2. Estimates of the Percentage Increase in Hospital Admission Rates per 10-μg/m^3 Increase in $PM_{2.5}$ for 202 US Counties, by Season and Region

	Main Model		Seasonal Interaction Model							
	Yearly		Winter		Spring		Summer		Autumn	
	Central Effect	95% PI	Central Effect	95% PI	Central Effect	95% PI	Central Effect	95% PI	Central Effect	95% PI
Cardiovascular admissions (lag 0)										
National ($n = 202$)	0.80[a]	0.59, 1.01	1.49[a]	1.09, 1.89	0.91[a]	0.47, 1.35	0.18	−0.23, 0.58	0.68[a]	0.29, 1.07
Northeast ($n = 108$)	1.08[a]	0.79, 1.37	2.01[a]	1.39, 2.63	0.95[a]	0.32, 1.58	0.55[a]	0.08, 1.02	1.03[a]	0.48, 1.58
Southeast ($n = 58$)	0.29	−0.19, 0.77	1.06	−0.07, 2.21	0.75	−0.26, 1.78	−0.67	−1.60, 0.26	0.17	−0.72, 1.07
Northwest ($n = 9$)	0.74	−1.74, 3.29	0.85	−4.11, 6.07	−0.07	−12.40, 13.98	−1.55	−15.22, 14.31	−0.67	−6.96, 6.05
Southwest ($n = 25$)	0.53	0.00, 1.05	0.76	−0.25, 1.79	1.78	−0.87, 4.51	−1.20	−4.90, 2.65	0.30	−0.98, 1.59
Respiratory admissions (lag 0)										
National	0.22	−0.12, 0.56	1.05[a]	0.29, 1.82	0.31	−0.47, 1.11	−0.62	−1.33, 0.09	0.02	−0.63, 0.67
Northeast	0.32	−0.18, 0.83	1.76[a]	0.60, 2.93	0.34	−0.66, 1.34	−0.8	−1.65, 0.07	−0.01	−0.87, 0.85
Southeast	0.2	−0.57, 0.97	0.59	−1.35, 2.58	−0.06	−1.77, 1.68	−0.15	−1.88, 1.61	−0.58	−2.06, 0.91
Northwest	−0.29	−3.59, 3.11	−0.07	−6.74, 7.08	−8.52	−25.62, 12.51	0.25	−21.46, 27.96	−1.38	−11.84, 10.32
Southwest	−0.02	−0.78, 0.74	0.03	−1.25, 1.34	1.87	−2.00, 5.90	0.64	−5.38, 7.04	1.77	−0.73, 4.33
Respiratory admissions (lag 2)										
National	0.41[a]	0.09, 0.74	0.72[a]	0.01, 1.43	0.35	−0.29, 0.99	0.57	−0.07, 1.23	0.39	−0.22, 1.01
Northeast	0.28	−0.17, 0.72	0.79	−0.21, 1.80	0.04	−0.88, 0.97	0.77	−0.01, 1.56	0.12	−0.82, 1.07
Southeast	0.35	−0.44, 1.14	0.4	−1.45, 2.27	0.75	−0.82, 2.34	−0.52	−2.07, 1.06	0.14	−1.29, 1.59
Northwest	0.19	−2.52, 2.98	−0.06	−6.52, 6.85	2.29	−14.26, 22.03	0.74	−18.73, 24.86	−0.74	−10.08, 9.58
Southwest	0.94[a]	0.22, 1.67	1.2	−0.10, 2.52	1.05	−2.18, 4.39	2.41	−2.61, 7.69	0.97	−1.36, 3.36

Abbreviations: PI, posterior interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm.
[a] Statistically significant effect.

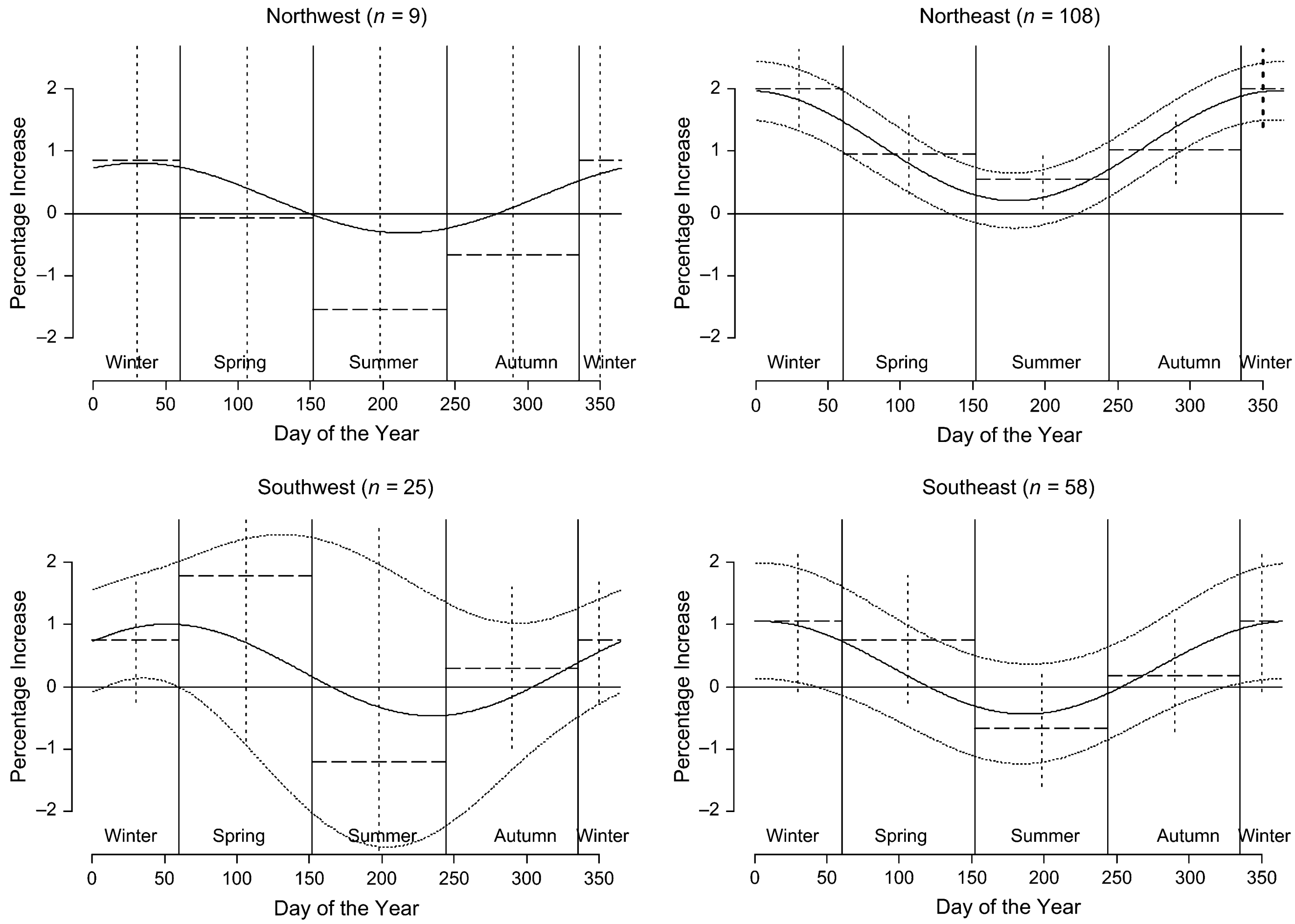

Figure 1. Percentage increase in total cardiovascular hospital admissions (1999–2005) per 10-μg/m^3 increase in same-day (lag 0) particulate matter with an aerodynamic diameter ≤2.5 μm, by US region, for results from the harmonic model (curved lines) and seasonal interaction model (straight lines). Vertical lines mark the divisions among seasons as defined by the seasonal interaction model. For the harmonic model (curved lines), solid lines represent the central estimate and dashed lines the 95% posterior interval. For the seasonal interaction model (straight lines), horizontal dashed lines represent the central estimate and vertical dotted lines the 95% posterior interval. The number in parentheses (*n*) represents the number of US counties included in each region. Note that the *y*-axis scale is identical across regions. The 95% intervals for some regions are too large to fit on this scale (e.g., Northwest region for the harmonic model); a color version of this figure is available as supplemental Figure S3 (posted on the *Journal*'s website (http://aje.oupjournals.org/)).

the yearly estimates (main-effect model) and by season (seasonal interaction model). Results are presented as the percentage increase in hospital admission rates per 10-μg/m^3 increase in $PM_{2.5}$. The value of 10 μg/m^3 is close to the interquartile range of overall $PM_{2.5}$ levels (8.7 μg/m^3).

For the main model, $PM_{2.5}$ was associated with cardiovascular admissions on the same day (lag 0) and with respiratory admissions at lag 2. These lags were also identified as those with the strongest effects in earlier work using analysis similar to that for the main-effect model (9). For cardiovascular admissions, associations at lag 0 were observed for all seasons except summer, with the strongest effect in winter at lag 0. For respiratory admissions, associations were observed in winter only, at lags 0 and 2. Again, the strongest effect is in winter at lag 0.

Table 2 provides regional average estimates by season at lag 0 for cardiovascular admissions and lags 0 and 2 for respiratory admissions for the full year (main-effect model) and by season (seasonal interaction model). For lag-0 cardiovascular admissions, the largest effects occurred in the Northeast in winter, and significant effects were also observed in all other seasons in this region. For lag-0 respiratory admissions, the largest effect also occurred in the Northeast in winter. For lag-2 respiratory admissions, the yearly estimate was largest in the Southwest.

We tested for evidence of regional and seasonal heterogeneity in the short-term effects of $PM_{2.5}$ on hospital admissions for lag-0 cardiovascular and respiratory admissions. We found strong evidence of variability across seasons in national average effects of $PM_{2.5}$ for cardiovascular ($P < 0.01$) and respiratory ($P < 0.01$) admissions. Cardiovascular effect estimates were also heterogeneous across regions ($P = 0.03$), whereas respiratory effects did not exhibit statistically significant evidence of heterogeneity.

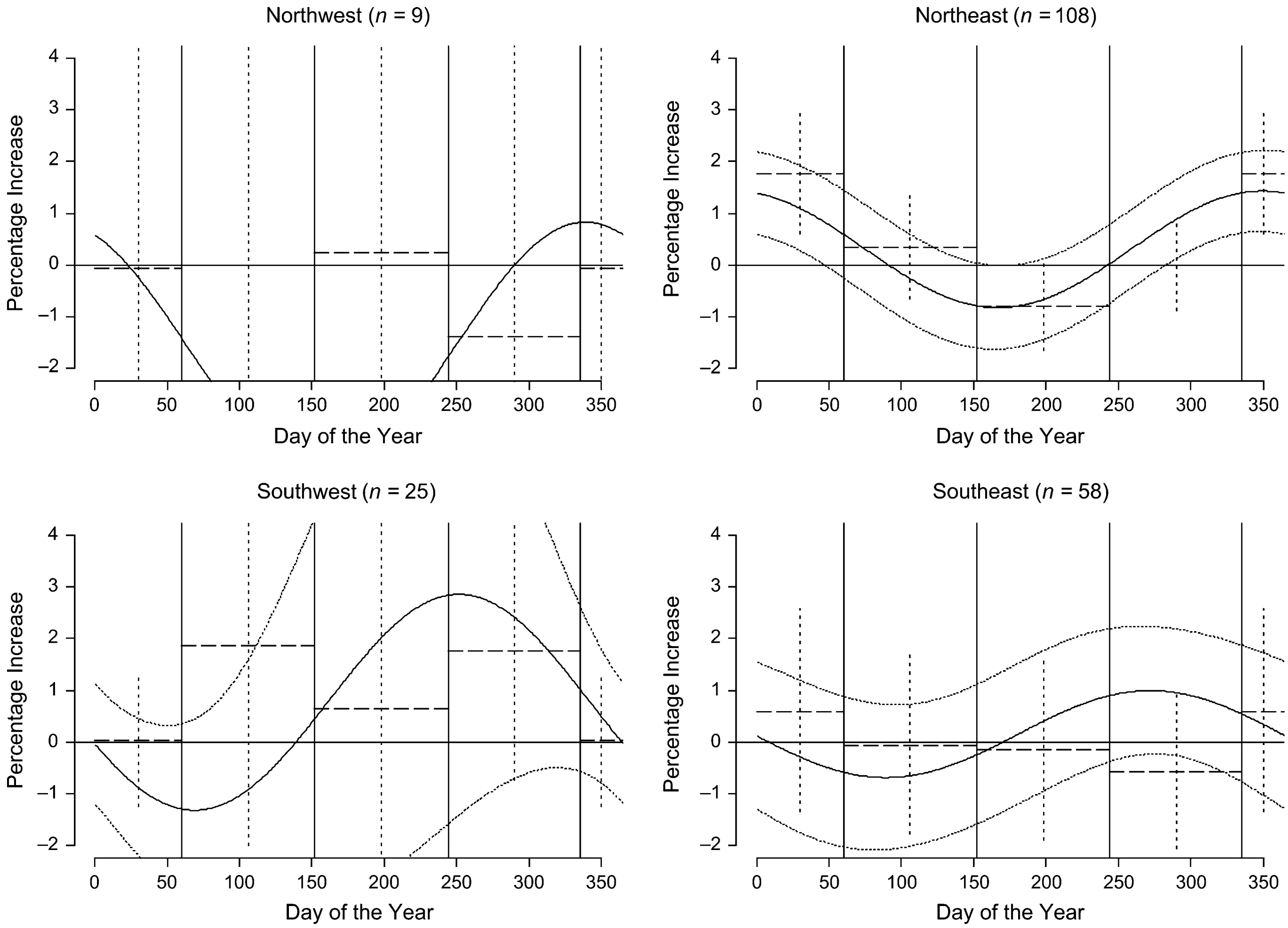

Figure 2. Percentage increase in total respiratory hospital admissions (1999–2005) per 10-μg/m^3 increase in same-day (lag 0) particulate matter with an aerodynamic diameter ≤2.5 μm, by US region, for results from the harmonic model (curved lines) and seasonal interaction model (straight lines). Vertical lines mark the divisions among seasons as defined by the seasonal interaction model. For the harmonic model (curved lines), solid lines represent the central estimate and dashed lines the 95% posterior interval. For the seasonal interaction model (straight lines), horizontal dashed lines represent the central estimate and vertical dotted lines the 95% posterior interval. The number in parentheses (*n*) represents the number of US counties included in each region. Note that the *y*-axis scale is identical across regions. The 95% intervals for some regions are too large to fit on this scale (e.g., Northwest region for the harmonic model); a color version of this figure is available as supplemental Figure S4 (posted on the *Journal*'s website (http://aje.oupjournals.org/)).

Results from the sensitivity analysis using the harmonic model support those from the seasonal interaction model, as shown in Figures 1 (cardiovascular) and 2 (respiratory). These findings indicate that the seasonal patterns identified by the seasonal interaction model are not an artifact of the choice of seasonal division (e.g., summer as June–August) because the harmonic model allows smooth variation in effect estimates throughout the year by location. Supplemental Figures S3 and S4 are color versions of Figures 1 and 2. Figures 1 and 2 apply the same scale to the health effect estimates, although some 95% posterior intervals are too large to fit on this scale. Supplemental Figures S5 and S6 are alternative versions of Figures 1 and 2, with scales allowing a full view of the 95% posterior intervals.

Variation in seasonal and regional effect estimates may result from differences in the chemical composition of particulate matter. The chemical component database currently is not sufficiently large to estimate the short-term effects of $PM_{2.5}$ chemical components on hospital admissions by season and region. As a descriptive analysis, we identified the chemical components of $PM_{2.5}$ that are higher for the regions and seasons with higher effect estimates than for the regions and seasons with lower effect estimates. First, we identified the regions and seasons with higher effect estimates for $PM_{2.5}$ and hospital admissions based on overall trends. Then, for each chemical component, we calculated ratios between the average concentration for the region or season with the largest effect estimate divided by the average concentration for all other regions and seasons combined. In this paper, results are presented for the $PM_{2.5}$ chemical components with >20% levels in the places or time periods with higher effect estimates.

County-level component averages were based on a database of 52 $PM_{2.5}$ chemical components from 2000–2005, previously developed from the US Environmental Protection Agency's monitoring network (18). Chemical composition data were available for 106 counties and were used to estimate long-term levels and seasonal averages for each region and for the United States. For the main-effect model, associations between cardiovascular admissions and $PM_{2.5}$ were strongest in the Northeast regarding both magnitude of effect and degree of statistical significance. Figure 3A presents components that were $\geq$20% higher in the Northeast than in other regions, and it provides box plots for the Northeast (gray boxes) and other regions (white boxes). National effect estimates for respiratory admissions were higher in winter than in other seasons. Levels of sulfate, selenium, ammonium, nitrate, nickel, zinc, and lead were higher in this region than elsewhere. Results from the seasonal interaction model for respiratory admissions based on all 202 counties exhibited higher effects in winter than in other seasons. For nitrate, elemental carbon, nickel, bromine, zinc, and chlorine, national averages were $\geq$20% higher in winter than in other seasons (Figure 3B).

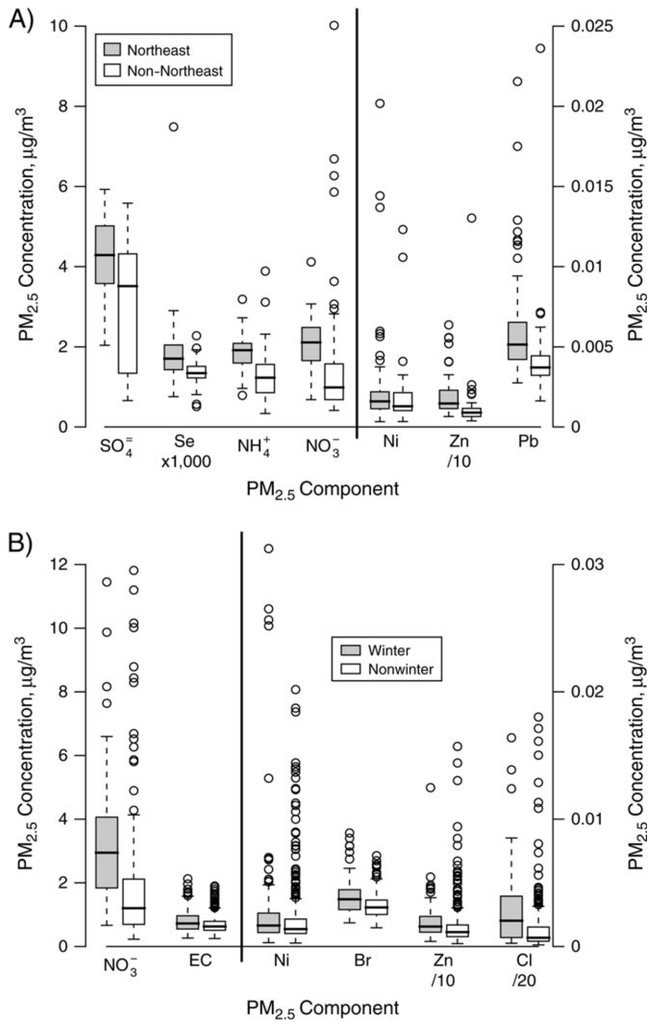

Figure 3. Comparison of concentrations of chemical components of particulate matter with an aerodynamic diameter $\leq$2.5 µm ($PM_{2.5}$) (µg/m^3), by US region and season, 1999–2005. A) Concentrations of specific components that were $\geq$20% higher in the Northeast than in other regions; B) concentrations of specific components that were $\geq$20% higher in winter than in other seasons. Each part uses 2 *y*-axis scales. Components to the left of the vertical line use the left-side *y*-axis scale; components to the right of the vertical line use the right-side *y*-axis scale. $SO_4^{=}$, sulfate; Se, selenium; NH_4^{+}, ammonium; NO_3^{-}, nitrate; Ni, nickel; Zn, zinc; Pb, lead; EC, elemental carbon; Br, bromine; Cl, chlorine.

DISCUSSION

Efforts to protect human health from ambient particulate matter are limited by scientific understanding of the toxicity of various components of the particulate matter mixture and the sources that contribute injurious particles (28). The components of the particle mixture vary seasonally and regionally with source use patterns and weather (18). If the chemical composition of particles affects toxicity, we would expect to find evidence of seasonal and regional heterogeneity in the short-term risks associated with $PM_{2.5}$ total mass. A lack of spatial and temporal heterogeneity would provide evidence for the hypothesis that particulate matter risk is not related to chemical composition. The presence of heterogeneity could result from variation in the toxicity of particulate matter chemical constituents, the nature of the air pollution mixture and the presence of other pollutants, or differences in populations' susceptibility. Characterization of spatial and temporal heterogeneity in risks associated with particulate matter provides an opportunity to test hypotheses regarding the significance of particle characteristics for human health and to develop focused hypotheses based on variation in risks by time period and region.

We conducted a multisite time-series analysis to investigate whether regional and seasonal heterogeneity exists in the short-term effects of $PM_{2.5}$ on cardiovascular and respiratory hospital admissions. Both cardiovascular and respiratory disease effect estimates exhibited spatial and temporal differences, although the patterns differed by disease outcome. This pattern might indicate that the particle component or set of components most strongly associated with the adverse health response may vary by health outcome. However, for both outcomes, $PM_{2.5}$ had the largest effects in winter and the Northeast.

Components with higher concentrations in the seasons and regions with the largest short-term effects of $PM_{2.5}$ total mass on hospitalization (Figure 3) relate to several source categories. In particular, these components correspond to several combustion sources as well as metals and sea salt (1). As additional chemical component measurements become available, further analysis is warranted, such as multisite time-series studies investigating whether the health effects of particular components or set of components also vary seasonally and spatially.

To date, findings from several epidemiologic studies indicate that certain particulate matter components may be more harmful than others with respect to mortality (29, 30). Daily mortality in 6 California counties was associated with various $PM_{2.5}$ chemical components and source categories, including metals (zinc, lead, vanadium), combustion-related products (sulfate), crustal components (silicon, calcium), chlorine, and carbon (organic carbon, elemental carbon) (30). Combustion-related $PM_{2.5}$ (sulfate, elemental carbon) was associated with cardiovascular mortality in Phoenix, Arizona (31). Sulfate and metals (iron, nickel, zinc) were linked to mortality in 8 Canadian cities (32). Combustion and traffic-related $PM_{2.5}$ sources, but not crustal $PM_{2.5}$, were associated with mortality in 6 US eastern cities (33). Higher effect estimates for PM_{10} on mortality were observed in communities with a higher percentage of primary PM_{10} from traffic sources (34). Other studies have linked individual components to health responses (29), such as sulfate and organic carbon $PM_{2.5}$, and heart rate variability in cardiovascular disease patients.

$PM_{2.5}$ in the Northeast, the region with the largest effect estimates in this study, contains higher sulfate $PM_{2.5}$ levels than elsewhere (Figure 3) (18). In this region, $PM_{2.5}$ levels are linked to emissions of sulfur oxides and nitrogen oxides from power-generation point sources in the Midwest, and sulfate levels are particularly related to sulfur oxide emissions (35, 36). In addition to coal combustion for electricity production, local sources of residual oil combustion contribute to particulate matter in the Northeast (37).

The observed regional heterogeneity in the short-term effects of $PM_{2.5}$ may also be explained by differences in population susceptibility, access to health care, and socioeconomic status. US maps of chronic obstructive pulmonary disease and heart disease mortality rates show substantial regional variation, although rates are not consistently higher in the Northeast, the area with the highest effect estimates in this study (38). Short-term effects of PM_{10} on mortality were greater in communities with higher population densities (34), while short-term effects of PM_{10} on hospital admissions were greater in communities in which a lower percentage of the population used air conditioning (39, 40). Thus, although our results indicate that the impact of chemical composition on toxicity is important, other factors may also be relevant.

Seasonal and regional variation in effect estimates could also be explained by variation in exposure patterns. Studies of persons aged >64 years in Baltimore, Maryland, and Boston, Massachusetts, identified different personal $PM_{2.5}$ exposures, varied activity patterns, and differing use of gas stoves by season (41, 42). The relation between ambient and personal $PM_{2.5}$ exposure for an older population can also differ by season (43). A study of 3 retirement communities found that housing factors, such as open versus closed windows and use of heating, ventilation, and air conditioning systems, influence the relation between ambient and personal $PM_{2.5}$ exposure (44).

Disentangling effects of multiple pollutants can be challenging, especially because of the different measurement frequencies for various pollutants as well as common sources producing multiple pollutants in the overall air pollution mixture. For example, traffic contributes to particles and ozone precursors. Analysis directed at separating the risk from $PM_{2.5}$ and from gaseous pollutants, such as nitrogen dioxide and sulfur dioxide that contribute to secondary particle formation, is subject to substantial uncertainty.

This study demonstrated regional and temporal patterns in the association between $PM_{2.5}$ and cardiovascular and respiratory hospitalizations, with the strongest evidence in the Northeast and in winter for both causes. The clear finding of heterogeneity provides a rationale for further work to understand its basis. The higher effect estimates in the Northeast, previously observed for mortality (10), need further explanation and testing of hypotheses related to pollution sources for this region, such as power plants.

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