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Assessment of the Health Impacts of Particulate Matter Characteristics

Michelle L. Bell

Includes a Commentary by the Institute's Health Review Committee

Assessment of the Health Impacts of Particulate Matter Characteristics

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with a Commentary by the HEI Health Review Committee

Research Report 161

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives half of its core funds from the U.S. Environmental Protection Agency and half from the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 280 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in the peer-reviewed literature and in more than 200 comprehensive reports published by HEI.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 161, *Assessment of the Health Impacts of Particulate Matter Characteristics*, presents a research project funded by the Health Effects Institute and conducted by Dr. Michelle L. Bell of the School of Forestry & Environmental Studies and School of Public Health, Yale University, New Haven, Connecticut. This research was funded under HEI's Walter A. Rosenblith New Investigator Award Program, which provides support to promising scientists in the early stages of their careers. The report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Health Review Committee's comments on the study.

The Investigator's Report, prepared by Bell, describes the scientific background, aims, methods, results, and conclusions of the study.

The Commentary is prepared by members of the Health Review Committee with the assistance of HEI staff; it places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Health Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

HEI STATEMENT

Synopsis of Research Report 161

Assessment of the Health Impacts of Particulate Matter Characteristics

BACKGROUND

Over the past several decades, epidemiologic studies in diverse locations across the United States and other parts of the world have reported associations between daily increases in low levels of ambient particulate matter (PM) mass and daily increases in morbidity and mortality. On the basis of these and other findings, many governmental agencies have set regulatory standards or guidelines for PM based on the concentration of its mass in ambient air.

However, scientists have long known that ambient PM is actually a complex mixture of solid and liquid airborne particles whose size, chemical composition, and other physical and biological properties vary with location and time. They have hypothesized that if the chemical components of PM most responsible for its associated health effects could be identified, it might then be possible to target their sources more cost effectively.

Until relatively recently, the large-scale epidemiologic studies necessary to explore associations between PM composition and health effects have not been possible. Data on particle composition were not collected systematically across the United States until 1999, when the U.S. Environmental Protection Agency began monitoring components of PM $\leq$ 2.5 µm in aerodynamic diameter ($PM_{2.5}$) in what has come to be known as the Chemical Speciation Network. Dr. Michelle L. Bell of Yale University sought to take advantage of this new source of composition data and proposed to evaluate the effects of short-term (that is, daily) exposures to various components of the $PM_{2.5}$ mixture on short-term morbidity and mortality, building on statistical methods established by the National Morbidity, Mortality, and Air Pollution Study and related research. The HEI Research Committee recommended funding her work under HEI's Walter A. Rosenblith New Investigator Award.

APPROACH

Bell's approach to investigating the relationship between the chemical components of PM and human health involved three broad steps. She began by characterizing how the chemical composition of $PM_{2.5}$ varies regionally and seasonally in the United States. Next, she evaluated whether the associations between short-term exposure to PM total mass and health effects followed regional and seasonal patterns. Finally, she evaluated whether the observed regional and seasonal variation in the health effects associated with PM total mass could in turn be explained by regional and seasonal variations in the chemical composition of $PM_{2.5}$.

The investigator obtained data on $PM_{2.5}$ total mass and on the mass of 52 chemical components of $PM_{2.5}$ for 187 counties in the continental United States for the period 2000 through 2005. She collected data on daily admissions to hospitals for cardiovascular- and respiratory-related illnesses for the period 1999 through 2005 for Medicare enrollees aged 65 years or older. Her analysis of the influence of $PM_{2.5}$ composition on associations between PM $\leq$ 10 µm in aerodynamic diameter (PM_{10}) and total nonaccidental mortality had to rely on associations reported from a previous study using earlier mortality data (from 1987 through 2000).

Bell focused her analysis of the regional and seasonal variation of components on seven components that made up 1% or more, on average, of $PM_{2.5}$ total mass on an annual or seasonal basis: ammonium, elemental carbon, organic carbon matter, nitrate, silicon, sodium, and sulfate. Together, these seven components made up more than 80% of annual average $PM_{2.5}$ mass.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Michelle L. Bell of the School of Forestry & Environmental Studies and School of Public Health, Yale University, New Haven, Connecticut. Research Report 161 contains both the detailed Investigator's Report and a Commentary on the study prepared by the Institute's Health Review Committee.

Bell explored variations in the statistical associations between exposures to $PM_{2.5}$ mass and hospital admissions across regions and seasons using three different, but related, statistical models:

- The main model is based on the approach used in the National Morbidity, Mortality, and Air Pollution Study, in which a regression model is used to predict the percentage change in the daily rate of hospitalizations (from cardiovascular or respiratory disease) as a function of $PM_{2.5}$ concentrations on the same day, the previous day, or two days before. The relationship is assumed to be constant throughout the year.
- The seasonal model has essentially the same structure as the main model, with the exception that the relationship is allowed to vary by season — defined as four discrete 3-month periods — but to be constant within each season.
- The harmonic model essentially allows the $PM_{2.5}$ and hospitalization association to vary smoothly and continuously throughout the year.

Relationships between PM_{10} and mortality were estimated using only the main model. Each of the models included common approaches to controlling for other factors that might also influence rates of hospitalizations or mortality.

The last step of the analysis was to explore whether differences in levels of $PM_{2.5}$ components could explain any regional and seasonal variations in health effects associated with PM total mass. In addition to the seven key chemical components of $PM_{2.5}$ evaluated in the first part of her study, Bell examined 13 other components that either covaried with $PM_{2.5}$ or had been associated with adverse health outcomes in previous studies: aluminum, arsenic, calcium, chlorine, copper, iron, lead, magnesium, nickel, potassium, titanium, vanadium, and zinc. Note that her approach does not estimate the direct effect of individual component mass concentrations on rates of hospitalizations or mortality as is done for $PM_{2.5}$ or PM_{10}; instead, it evaluates how much the PM total mass–related health effect estimates change for each unit of variation, expressed as the interquartile range, in each component's fraction of PM in ambient air.

Finally, Bell explored the sensitivity of her main findings about the effects of individual components to some key variables in her model. She evaluated the sensitivity of the elemental carbon, nickel, and vanadium effects on the associations of PM total mass with hospital admissions and mortality to removal of individual counties from the data set, to adjustment for the presence of one or more of the other components, and to various characteristics of the communities (socioeconomic status and education level of its residents, racial composition, and degree of urbanization). She also assessed whether rates of hospitalization or of mortality could be partly explained by the prevalence of air conditioning.

RESULTS AND INTERPRETATION

In this study, Bell has shown persuasively that concentrations of $PM_{2.5}$ components vary across counties and regions of the United States as well as over seasons. Her analysis of the seven components making up most of $PM_{2.5}$ mass found patterns similar to those in other studies. Organic carbon matter, nitrate, and elemental carbon were generally higher in the West than in the East, with some seasonal differences; sulfate was higher in the East, particularly in summer; and sodium ion appeared most prominently along the coasts.

Similarly, she has demonstrated that relationships between daily $PM_{2.5}$ total mass concentrations and hospitalizations for cardiovascular and respiratory disease also vary over season and region. Using the main model, statistically significant increases in cardiovascular admissions associated with same-day exposures to $PM_{2.5}$ total mass were observed in spring and fall, but were largest in winter. These increases were greatest across the 108 Northeast counties, followed by the 25 Southwest counties. With the seasonal model, positive and statistically significant increases in cardiovascular admissions were observed only for the Northeast region and in all seasons. Results from the harmonic model were similar to those of the seasonal model.

When hospitalizations for respiratory disease were examined, the main model results showed a pattern of increases in rates of hospitalization that were most pronounced on the second day after exposure to $PM_{2.5}$ total mass. With the seasonal model, the percentage increases nationwide in respiratory hospital admissions were largest in the

winter with same-day $PM_{2.5}$ exposures. In her analysis of the influence of air conditioning prevalence, Bell found that counties with higher levels of central air conditioning had lower $PM_{2.5}$ total mass effects on cardiovascular hospital admissions, particularly in summer. PM_{10} total mass effects on mortality were unaffected by air conditioning.

The main question Bell's report set out to answer was whether or not the variation in the $PM_{2.5}$ components could explain any variation in the health effects associated with $PM_{2.5}$ or with PM_{10} total mass. Her results show that the observed variations in relationships between PM and health effects could only partly be explained by variation in the chemical composition of $PM_{2.5}$. Of the components that made up the largest fractions of $PM_{2.5}$ total mass, only variability in elemental carbon explained variation in $PM_{2.5}$ mass effect estimates for hospitalization. For the remaining components studied, Bell reported that greater content of nickel and vanadium in $PM_{2.5}$ was associated with larger $PM_{2.5}$ total mass health effect estimates for both cardiovascular and respiratory hospitalizations. PM_{10} mass associations with total nonaccidental mortality were also larger in regions and seasons with higher fractions of vanadium and particularly nickel in $PM_{2.5}$. These relationships showed some sensitivity to the removal of either New York County or Queens County from the analysis, by declining in size and, in some cases, significance. They did not appear to be sensitive to socioeconomic status, race, or how urbanized the counties were.

In its independent review, the HEI Health Review Committee commented that Bell's well-conducted study had taken a careful and logical approach to the exploration of both $PM_{2.5}$ chemical speciation data and their implications for human health in the United States. Her work represents one of the largest efforts to take advantage of the $PM_{2.5}$ speciation data available for 52 chemical species and to analyze them in conjunction with data on hospital admissions and nonaccidental mortality from throughout the continental United States. In the spirit of the Rosenblith Award, her work bodes well for her development as an investigator.

However, the Committee concluded that a causal interpretation of the relationships between $PM_{2.5}$ composition and PM mass health effects observed in this study would be premature and agreed with Bell that more research is needed. Although some alternative explanations for spatial variation were considered (e.g., county, region, socioeconomic status, race, and degree of urbanization), the study ultimately could not rule out the possibility that other explanations might account for the observed influence of components on PM total mass health effects. No alternative explanations were considered for temporal variation. In view of these and other limitations discussed in the report (e.g., the absence of basic details about and evaluation of the implications of minimum detection limits for individual chemical species), the Committee concluded that the evidence from Bell's study implicating elemental carbon, nickel, and vanadium in the $PM_{2.5}$ impacts on hospitalizations and nickel and vanadium on mortality associated with PM_{10} should be considered only suggestive at this time. The Committee also thought that suggestions about specific sources for the influential components identified — whether in this report (e.g., traffic) or in Bell's related publications (e.g., power-generation, coal combustion, and residual oil, as in Bell 2008) — should also be viewed cautiously. That Bell's study has not led to more than very tentative and partial conclusions about the toxicity of PM components reflects the considerable complexity of the task, rather than deficiencies of her approach, which indeed offers important insights for future studies.

Bell's work now sits within a broader, rapidly growing body of epidemiologic literature that reports on associations between PM components and a range of health outcomes. Studies differ along many more dimensions — design, regional coverage, time period covered, study-population characteristics, PM size fraction, number of particles, components measured, copollutants measured, monitoring methods, health endpoints, and statistical methods applied. This current situation makes both simple comparisons and systematic reviews challenging. Bell's study, however, represents an early step in HEI's larger National Particle Component Toxicity initiative. The systematic toxicologic and epidemiologic studies in that multicenter effort are nearing completion and may help bring more consistent, comparable approaches to these important investigations going forward.

INVESTIGATOR'S REPORT

Assessment of the Health Impacts of Particulate Matter Characteristics

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ABSTRACT

While numerous studies have demonstrated that short-term exposure to particulate matter (PM*) is associated with adverse health effects, the characteristics of PM that cause harm are not well understood, and PM toxicity may vary by its chemical composition. This study investigates whether spatial and temporal patterns in PM health effect estimates based on total mass can be explained by spatial and temporal heterogeneity in the chemical composition of the particles.

A database of 52 chemical components of PM with an aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$) was constructed for 187 U.S. counties, for 2000 through 2005, based on data from U.S. Environmental Protection Agency (U.S. EPA) monitoring networks. Components that covary with $PM_{2.5}$ total mass and/or are large contributors to $PM_{2.5}$ total mass were identified using actual and seasonally detrended data. Using Bayesian hierarchical modeling, seasonal and temporal variation in $PM_{2.5}$ and the risk of total, cardiovascular, and respiratory hospital admissions were investigated for persons ≥ 65 years in 202 U.S. counties for 1999 through 2005. Seasonal variation was investigated using three model structures with different underlying assumptions about the relationship between $PM_{2.5}$ and hospitalizations.

Data from the chemical component database and season- and county-specific $PM_{2.5}$ total mass effect estimates for hospitalizations were combined to investigate whether the chemical composition of particles can partially explain spatial and seasonal heterogeneity in the relative rates. Long-term, county-specific seasonal averages of component concentrations were generated for the subset of counties for which there were chemical composition data. The components selected for analysis were those that contribute substantially to or covary with $PM_{2.5}$ total mass or that were implicated as potentially toxic in previous research. Alternative hypotheses to explain the between-community variability of health effect estimates were also explored using community-level indicators of socioeconomic status, racial composition, urbanicity, and air conditioning (AC) prevalence.

The chemical composition of $PM_{2.5}$ exhibited strong seasonal and regional patterns, especially for some components, such as sulfate ($SO_4^=$). The components most highly correlated with $PM_{2.5}$ total mass were ammonium (NH_4^+), for the yearly averages; organic carbon matter (OCM), especially in winter; nitrate (NO_3^-) in winter; and $SO_4^=$, for the yearly averages and across most seasons. Of the 52 components in the database, only 7 contributed ≥ 1% to total mass for yearly or seasonal averages: $SO_4^=$, NO_3^-, NH_4^+, silicon (Si), sodium ion (Na^+), OCM, and elemental carbon (EC). These components were selected for subsequent analysis; however, that does not imply that other components or sets of components are not potentially harmful to human health. Rather, these components were used as a starting point of analysis.

Day-to-day variation in $PM_{2.5}$ total mass was associated with day-to-day variation in hospital admissions. A 10-µg/m^3 increase in lag-0 (same-day) $PM_{2.5}$ was associated with a 0.80% (95% posterior interval [PI], 0.59–1.01) increase in cardiovascular admissions, whereas the same increment of lag-2 (two days previous) $PM_{2.5}$ was associated with a 0.41% (PI, 0.09–0.74) increase in the risk of respiratory admissions. These estimates, however, obscure regional and seasonal heterogeneity in health effect estimates as demonstrated by the results of seasonal and harmonic models.

This Investigator's Report is one part of Health Effects Institute Research Report 161, which also includes a Commentary by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigator's Report may be addressed to Dr. Michelle L. Bell, School of Forestry & Environmental Studies and School of Public Health, Yale University, 195 Prospect St., New Haven, CT 06511, email: *michelle.bell@yale.edu.*

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83234701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations and other terms appears at the end of the Investigator's Report.

The findings of this study indicate higher effects in winter for both causes of hospitalization, and higher effects in the Northeast for cardiovascular admissions, although 53% of the counties were in this region.

Higher $PM_{2.5}$ effect estimates for cardiovascular or respiratory hospitalizations were observed in seasons and counties with a higher $PM_{2.5}$ content of nickel (Ni), vanadium (V), or EC. Mortality effect estimates for PM with an aerodynamic diameter ≤ 10 µm (PM_{10}) were higher in seasons and counties with higher $PM_{2.5}$ Ni content. The association between the Ni content of $PM_{2.5}$ and effect estimates for cardiovascular hospitalization was robust to adjustment by EC, V, or both EC and V. An interquartile range (IQR) increase in the fraction of $PM_{2.5}$ that is Ni was associated with a 14.9% (PI, 3.4–26.4) increase in the relative rates of cardiovascular hospital admissions associated with $PM_{2.5}$ total mass adjusted for EC and V. No associations were observed between PM total mass health effect estimates and community-level variables for socioeconomic status, racial composition, or urbanicity. Communities with a higher prevalence of central AC had lower $PM_{2.5}$ effect estimates for cardiovascular hospital admissions.

The findings of this study indicate strong spatial and temporal variation in the chemical composition of the particle mixture and in the regional and seasonal variation in health effect estimates for $PM_{2.5}$ total mass. The chemical composition of particles partially explained the heterogeneity of effect estimates. Observed associations could be related to the components themselves, to other components, or to a combination of components that share similar sources. The findings do not exclude the possibility that other components or characteristics of PM are harmful.

The limitations of this study include the use of community-level aggregated data for exposure and for the variables used to investigate alternate hypotheses. Also, particle components and chemical forms (e.g., ammonium sulfate) not measured in the U.S. EPA database were not included. PM_{10} results in particular should be viewed with caution as the time frame of measurement and PM size fraction are different for the chemical composition and health effects data. A better understanding of the particular chemical components or sources that are most harmful to health can help decision-makers develop more targeted air pollution regulations and can aid in understanding the biological mechanisms by which air pollution–related health effects occur, thereby informing future research.

INTRODUCTION

The health effects of airborne particles have been vigorously investigated for several decades (U.S. EPA 2004, Pope and Dockery 2006), although the specific characteristics of PM that are harmful are not well understood. PM has been linked to numerous adverse human health effects including increased hospital admissions and emergency room visits, respiratory symptoms, exacerbation of chronic respiratory and cardiovascular diseases, decreased lung function, and premature mortality (e.g., Dockery et al. 1993; Pope et al. 2002; Dominici et al. 2003; Laden et al. 2006; Peng et al. 2008; Samoli et al. 2008).

Studies on the health effects of PM have used a variety of metrics for PM concentration, including total suspended particles (TSP), coefficient of haze, black smoke, British Smoke, measures of particulate optical reflectance, PM_{10}, $PM_{2.5}$, coarse PM particles greater than 2.5 µm and less than 10 µm in aerodynamic diameter ($PM_{10-2.5}$), and ultrafine PM with an aerodynamic diameter ≤ 0.1 µm ($PM_{0.1}$). Various size fractions of PM have been associated with health effects. However, the impact of PM on health may be related to specific characteristics of the PM mixture other than particle size. A growing body of literature explores the specific characteristics and sources of PM that are harmful (e.g., Ito and Thurston 1989; Laden et al. 2000; Lippmann et al. 2006; Franklin et al. 2008).

Spatial differences in the relationship between PM total mass and health have been observed for mortality and morbidity. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) used consistent methodology to investigate how PM_{10} affected mortality in 90 large U.S. cities and found the largest effect in the northeastern U.S. and also a large effect in southern California (Samet et al. 2000; Dominici et al. 2003). The association between PM and mortality was higher in the western part of Europe than in Eastern Europe in the study Air Pollution and Health: A European Approach (APHEA) (Katsouyanni et al. 1997). However, later work provides evidence that the choice of statistical models may have contributed to these differences (Samoli et al. 2001). $PM_{2.5}$ effect estimates for hospitalizations have differed between the eastern and western portions of the United States (Dominici et al. 2006).

PM composition and concentrations can also vary in space and time, which could explain the spatial differences in the health effects observed. For example, in the eastern United States, the largest component of $PM_{2.5}$ is $SO_4^{=}$, whereas organics comprise the largest component in the Pacific Northwest, and nitrates in southern California (Malm 2000). In addition to spatial variability, levels of PM constituents can display seasonal patterns, with NO_3^-

concentrations typically highest in winter or spring and sulfates and organic carbon (OC) highest in summer (Malm 2000). Other factors may also affect temporal and spatial heterogeneity in PM total mass health effects estimates, such as differences in community-level demographics and levels of copollutants. The specific characteristics of PM that damage health have not been fully identified. The characteristics of PM that might be detrimental to health include particle size; acidity; the presence of components such as metals (e.g., iron [Fe], V, Ni, copper), organic compounds that adsorb onto particles or form particles themselves, biologic components (e.g., viruses, fungal spores, pollens), $SO_4^{=}$, NO_3^{-}, carbonaceous material, or an unknown component; and a combination of factors (HEI 2002).

Knowledge of the toxicity of various PM components is vital to the effective regulation of airborne particles. Whereas most air pollutants are defined by a particular chemical composition (e.g., ozone as O_3), PM comprises a range of chemical species. However, it is currently regulated according to size (PM_{10} or $PM_{2.5}$) without regard to chemical composition. It is the only major pollutant regulated under Section 109 of the Clean Air Act that is defined without consideration of its chemical form. In response to human health studies that had demonstrated a health effect for smaller particles, the U.S. EPA revised the ambient air quality standard for PM with respect to particle size, moving from a TSP standard to a PM_{10} standard in 1987 and adding a $PM_{2.5}$ standard in 1997 (Greenbaum et al. 2001).

In addition to the presence of varying chemical components in PM, other factors may explain the between-community variability in PM health effect estimates. AC may lower an individual's exposure to particles by changing a home or building's ventilation rate and thus altering the indoor–outdoor ratio of pollution. Differences in socioeconomic status, racial composition, preexisting health conditions, or urbanicity may affect health effect estimates because they may affect such factors as baseline health status, access to health care, and exposure profiles (O'Neill et al. 2003; Bateson and Schwartz 2004; Bell et al. 2005; Zeka et al. 2006; Franklin et al. 2007).

Numerous researchers and agencies have identified a greater comprehension of the toxic characteristics of PM as a critical area of research (NRC 1998, 1999, 2001, 2004; HEI 2002; Pope and Dockery 2006; Lippmann 2009). A better understanding of the role of various PM characteristics in eliciting adverse health responses would allow decision-makers to target the most harmful components or sources, rather than having to regulate PM by size distribution alone. Similarly, the implementation of air quality standards could focus on the sources that are of the greatest concern. Evidence of which PM components or set of components are most harmful can also provide insight into the biological mechanisms through which PM affects health and could thereby guide future studies.

In this study, we examined the relationship between airborne particles and health, with a particular emphasis on the role of the chemical composition of PM. First, we investigated the spatial and temporal variation in $PM_{2.5}$ chemical components in the United States using a database based on U.S. EPA monitoring data. Then, we generated $PM_{2.5}$ total mass effect estimates for the risk of hospitalizations on a national scale. We explored a variety of modeling structures to determine whether effect estimates vary by location or season. Finally, we evaluated whether spatial and temporal patterns in the chemical composition of $PM_{2.5}$ can, in part, explain any spatial and temporal heterogeneity in PM total mass health effect estimates.

This HEI-funded project is part of larger efforts of our collaborative research team to study the health impacts of particles, including the impacts of particle size, the chemical composition of particles, and the settings in which multiple pollutants are present. Related recent work includes a study finding no statistically significant associations between $PM_{10-2.5}$ and the risk of cardiovascular or respiratory hospitalization (Peng et al. 2008) and another showing that ambient levels of $PM_{2.5}$, EC, and OCM are associated with the risk of hospital admissions for the Medicare population (Peng et al. 2009). Large portions of the research presented here have been previously published elsewhere (Bell et al. 2007, 2008, 2009a,b); however, in this report, we aim to provide a broader perspective based on a synthesis of the individual study results from our research program.

SPECIFIC AIMS

This goal of this study is to investigate the relationship between the chemical components of PM and human health, using national databases of pollution, weather, and health outcomes. In particular, this work investigates the hypothesis that spatial and temporal variation exists in the health effect estimates for PM total mass and that such variation relates to heterogeneity in the chemical composition of the particle mixture. The specific aims are as follows:

1. Investigate the spatial and temporal variation in $PM_{2.5}$ chemical composition in the United States.
2. Determine whether the associations between short-term exposure to $PM_{2.5}$ and hospital admissions follow spatial and temporal patterns.

3. Evaluate whether spatial and temporal variation in the PM total mass effect estimates for mortality and morbidity (hospital admissions) can be partially explained by spatial and temporal heterogeneity in $PM_{2.5}$ chemical composition.

To date, most studies of PM and health have focused on defining exposure by particle size distribution, although several studies have examined particular chemical components or sources, and these approaches to defining exposure continue to be the focus of active research.

METHODS

SPATIAL AND TEMPORAL VARIATION IN $PM_{2.5}$ CHEMICAL COMPOSITION

The U.S. EPA established a national monitoring network to determine the chemical composition of $PM_{2.5}$. Data from this network has played a considerable role in much of the research on PM chemical composition and health to date. The first stage of this research project involved utilizing the U.S. EPA measurements to develop a database of the chemical components of $PM_{2.5}$ reported for the United States from 2000 to 2005. This section describes how the database was developed and how specific $PM_{2.5}$ components were selected for subsequent analysis (Bell et al. 2007).

We used data obtained from the U.S. EPA's Office of Air Quality Planning and Standards (U.S. EPA 2006) to generate a database of 52 $PM_{2.5}$ chemical components for 187 continental U.S. counties. Most monitoring stations measured data at a frequency of once every 6 days, although the frequency of measurement varied across monitors and at single monitors. The average frequency of measurement ranged from 1 in 3.1 days to 1 in 11.9 days. We also obtained data for $PM_{2.5}$ total mass. Data were not corrected for minimum detection limit (MDL). Although this analysis focused on components with large contributions to $PM_{2.5}$ total mass, questions related to MDL will become more relevant in future research as components (e.g., gallium) with low levels in $PM_{2.5}$ are studied.

The database development protocol specified that observations coded by the U.S. EPA as suspect, such as those believed to be based on faulty equipment, be removed from the database. Because a key focus of this study is the spatial and temporal distribution of PM chemical composition and health effects within the continental United States, data from monitors from the noncontinental states were omitted. Fifteen of the 259 monitoring sites included multiple monitors. Measurements from colocated monitors were treated as duplicate samples and were averaged to generate a single time series for each monitoring location.

The health outcome datasets for this project were based on county- or community-level aggregation (e.g., the number or rate of hospitalizations within a given county for a given day). Given the structure of the different health datasets used for this analysis, some exposure values were generated at the county level and others were generated at the community level. A "community" is a county or contiguous set of counties selected to represent a specific city. County-level estimates for daily exposures were generated for each component by averaging the monitor values within each county for each day. Community-level exposure estimates were generated on a daily basis for each component by averaging the monitor values within each community for each day. Analysis of PM_{10} effect estimates for mortality was based on community data, whereas other analyses were based on county data.

For some counties, data were available for only a small portion of the study period. Counties with data for less than 6 months or with less than 30 observations (days) were not included, resulting in a loss of 11.4% of counties and 2.7% of observation days. The database protocol omitted extreme values, defined as those over three times higher than the second highest value, which resulted in the deletion of two observation days.

Estimated levels of OCM for each day and monitor were based on measured values of OC adjusted for field blanks and to account for elements such as oxygen and hydrogen that are associated with OC. Daily county- or community-level values for OCM were estimated as

$$OCM = k(OC_m - OC_b) \quad (1)$$

where OCM represents organic carbon matter, k is the adjustment factor to account for noncarbon organic matter, OC_m is the measured value of OC as reported by the U.S. EPA (2006), and OC_b is the OC blank filter value. U.S. EPA data were used for OC_b values (U.S. EPA 2006). A value of 1.4 was used for the k adjustment value.

The OC blank values exhibited a temporal trend, with the values of some samples increasing and others decreasing for the period 2001 to 2005 (Frank 2006). A second set of OCM values, based on the blank correction values specific to the sampler and year, were calculated as a sensitivity analysis. This alternate measure of OCM is referred to in this report as OCM2.

Yearly and seasonal concentrations of each component for each county were calculated. Seasons were defined as three-month periods: June through August as summer, September through November as autumn, December through

February as winter, and March through May as spring. For a particular component or set of components to explain the health effects observed in time-series studies based on PM total mass, the levels of such components (or set of components) would need to vary with the levels of PM total mass. However, not all components are measured with identical accuracy, and not all potentially relevant components are measured in the U.S. EPA monitoring network. Thus, this criterion (covariance with PM total mass) should not be considered as the basis for excluding other potentially toxic components or set of components. To identify a subset of the components for subsequent analysis, we selected key components as those that covaried with $PM_{2.5}$ total mass, or those that contributed a substantial fraction of $PM_{2.5}$ total mass. As a sensitivity analysis, covariance was also calculated with seasonally detrended values. We also considered components that were identified as potentially harmful to human health in earlier work. Our intent was to select a narrower list of components for further study but not to imply that other components are not harmful to human health or that the identified components are the most toxic.

Seasonally detrended values were calculated as

$$\tilde{X}^{c}_{p,t} = X^{c}_{p,t} - \frac{1}{n^{c}_{p,t}} \sum_{l \in t \pm 45} X^{c}_{p,l} \qquad (2)$$

where $X^{c}_{p,t}$ is the concentration of component p at time t for county c; $\frac{1}{n^{c}_{p,t}} \sum_{l \in t \pm 45} X^{c}_{p,l}$ is the 91-day moving average of component p for county c centered at time t, and $n^{c}_{p,t}$ represents the number of days with observations for component p for county c for a 91-day moving average centered at time t. The analysis based on the detrended data included only counties with data for a full year or more.

EVALUATION OF SPATIAL AND TEMPORAL PATTERNS IN THE ASSOCIATION BETWEEN SHORT-TERM EXPOSURE TO $PM_{2.5}$ AND HOSPITAL ADMISSIONS

This phase of the project estimated the association between day-to-day variation in $PM_{2.5}$ total mass and the risks of cause-specific (cardiovascular, respiratory) hospitalizations for an older population, and investigated whether such estimates exhibited spatial and/or temporal heterogeneity (Bell et al. 2008).

The health data were based on hospital admission rates for the years 1999 through 2005 for Medicare enrollees aged 65 or older living in 202 U.S. counties. We restricted the counties to those with populations of 200,000 or more, and they therefore represented areas that were more urban. We based the cause of hospitalization on the primary diagnosis and omitted nonurgent hospitalizations (e.g., scheduled visits). Cardiovascular-related hospitalizations were calculated as the sum of hospitalizations for the following International Classification of Diseases, Ninth Revision (ICD-9) codes: heart failure ICD-9 code 428; heart rhythm disturbances ICD-9 codes 426–427; cerebrovascular ICD-9 codes 430–438; ischemic heart disease ICD-9 codes 410–414 and 429; and peripheral vascular disease ICD-9 codes 440–449. Respiratory admissions were calculated as the sum of hospitalizations for the following causes: chronic obstructive pulmonary disease ICD-9 codes 490–492 and respiratory tract infections ICD-9 codes 464–466 and 480–487. These ICD-9 categorizations for cardiovascular- and respiratory-related causes of hospitalization have been used in earlier work (Dominici et al. 2006; Peng et al. 2008).

Weather data for temperature and dew point temperature for each county were based on existing monitoring data acquired from the National Climatic Data Center. Daily county-level exposure estimates for $PM_{2.5}$ were based on data from U.S. EPA monitors. The use of the term "daily" in reference to data does not indicate that data were available for every day in each county throughout the study period. Most counties measured $PM_{2.5}$ once every three days. To address outliers, we applied a 10% trimmed mean after correction for yearly monitor averages, as has been done in previous work (Dominici et al. 2006).

A two-stage Bayesian hierarchical model (Everson 2000) was used to estimate the association between short-term exposure to $PM_{2.5}$ total mass and cause-specific hospitalizations. First, estimates were generated for each county; then, estimates were combined to generate an overall effect. This approach accounts for the statistical uncertainty of each county-specific estimate; county-specific results with more certainty have a larger influence on the overall result.

We used three statistical approaches to generate county-specific estimates for the association between $PM_{2.5}$ and the risk of cardiovascular or respiratory hospitalizations. The first model, the "main model," generates an estimate that is not permitted to vary throughout the course of a year. In other words, this model assumes that the association between $PM_{2.5}$ and the risk of hospital admissions does not vary by season. The second model, the "seasonal model," allows a separate association between $PM_{2.5}$ and hospitalizations for each season, but assumes a constant effect within each individual season. The third model, the "harmonic model," allows a varying association between $PM_{2.5}$ and hospitalizations throughout the year. A similar approach was previously used to investigate seasonal patterns in the relationship between PM_{10} levels and the risk

of mortality (Peng et al. 2005). All models accounted for long-term trends, day of the week, and a nonlinear association between weather and hospital admissions on a county-specific basis. The models were fit separately for each county and cause of hospitalization (cardiovascular, respiratory).

Each of these models takes the form of

$$\begin{aligned}\ln(E[h_t^c]) = {} & \alpha^c DOW_t + ns(T_t^c, df_T) \\ & + ns(D_t^c, df_D) + ns(Ta_t^c, df_{Ta}) \\ & + ns(Da_t^c, df_{Da}) + ns(t, df_t) \\ & + A_t ns(t, df_{A_t}) + \ln(N_t^c) \\ & + \textit{pollution term}\end{aligned} \tag{3}$$

where $E[h_t^c]$ is the expected hospitalization rate in county c on day t, α^c is the regression coefficient relating the day of the week to hospitalization rates in county c, DOW_t represents categorical variables for the day of the week on day t, $ns(T_t^c, df_T)$ represents a natural cubic spline of temperature in county c on day t with df_T degrees of freedom, $ns(D_t^c, df_D)$ represents a natural cubic spline of dew point temperature in county c on day t with df_D degrees of freedom, $ns(Ta_t^c, df_{Ta})$ represents a natural cubic spline with df_{Ta} degrees of freedom for the average temperature for the three previous days in county c on day t adjusted for current-day temperature and dew point temperature, $ns(Da_t^c, df_{Da})$ represents a natural cubic spline with df_{Da} degrees of freedom for the average dew point temperature for the three previous days in county c on day t adjusted for current-day temperature and dew point temperature, $ns(t, df_t)$ represents a natural cubic spline of time with df_t degrees of freedom, $ns(t, df_{A_t})$ represents a natural cubic spline of time with df_{A_t} degrees of freedom, A_t is an indicator for persons of ≥ 75 years of age, and N_t^c is the size of the population at risk in county c on day t. The splines of temperature used six degrees of freedom. The splines of dew point temperature used three degrees of freedom. The spline of time used eight degrees of freedom per year, and, in the A_t interaction term, the spline of time used one degree of freedom per year.

The *pollution term* in equation 2 varies by model structure. For the main model, in which effect estimates are assumed to have no temporal variation, the *pollution term* is $\beta^c x_{t-l}^c$, in which β^c is the regression coefficient relating $PM_{2.5}$ to hospitalization rates in county c, and x_{t-l}^c is the $PM_{2.5}$ level in county c on day t at lag of l days (e.g., $l = 0$ is same day).

For the seasonal model, the *pollution term* is

$$\beta_w^c I_w x_{t-l}^c + \beta_{Sp}^c I_{Sp} x_{t-l}^c + \beta_{Su}^c I_{Su} x_{t-l}^c + \beta_A^c I_A x_{t-l}^c \tag{4}$$

where the terms I_w, I_{Sp}, I_{Su}, and I_A are binary indicator variables representing winter, spring, summer, and autumn, respectively, and β_w^c, β_{Sp}^c, β_{Su}^c, β_A^c are regression coefficients relating $PM_{2.5}$ and hospitalization rates for each season. For this model, the temporal trend was permitted to differ by season, so the temporal trend term in equation 3, $ns(T_t^c, df_T)$, was replaced with $I_w ns(t, df_t) + I_{Sp} ns(t, df_t) + I_{Su} ns(t, df_t) + I_A ns(t, df_t)$. These variables are interaction terms between season and the natural cubic spline of time.

For the harmonic model, which allows the association between $PM_{2.5}$ and hospitalizations to vary smoothly throughout the year, the *pollution term* is

$$\begin{aligned}& \beta_1^c \sin(2\pi t / 365) x_{t-l}^c \\ & + \beta_2^c \cos(2\pi t / 365) x_{t-l}^c \\ & + \beta_3^c x_{t-l}^c.\end{aligned} \tag{5}$$

Each of the above three models provides different estimates of the association between $PM_{2.5}$ and hospitalizations, based on the differing underlying assumptions in each model structure. For example, the main model provides a single estimate for each county $\left(\hat{\beta}^c\right)$ and an estimate of its variance. The seasonal model provides county-specific estimates for each season $\left(\hat{\beta}_w^c, \hat{\beta}_{Sp}^c, \hat{\beta}_{Su}^c, \hat{\beta}_A^c\right)$ and an estimated covariance matrix for each season.

With each of these models, we investigated different single-day lag structures. We examined the associations between the risk of hospitalizations and lag-0, lag-1 (previous day) and lag-2 $PM_{2.5}$ exposure. The application of a distributed lag model structure, accounting for multiple days of exposure, was prohibited by the frequency of $PM_{2.5}$ measurement.

We used a second-stage model to combine the county-specific estimates, to generate an overall association; this model structure assumes that the true association between $PM_{2.5}$ and the risk of hospitalizations in county c has a multivariate normal distribution with mean μ and the between-community variance Σ. We used the second-stage model through two-level normal independent sampling estimation (TLNise) (Everson 2000) with uniform priors for the seasonal models:

$$\hat{\beta}^c \mid \beta^c \sim N_4(\beta^c, V^c)$$
$$\beta^c \mid \mu, \Sigma \sim N_4(\mu, \Sigma) \quad (6)$$

where $\hat{\beta}^c$ and β^c represent the estimated and true association between $PM_{2.5}$ and the risk of hospitalizations in county *c*, respectively. We used second-stage models similar to those in equation 6 to generate overall estimates of the main and harmonic models. Previous work provides evidence that this modeling approach is robust to the smooth function of time and various specifications for weather (Welty et al. 2005; Peng et al. 2006; Touloumi et al. 2006), although the investigations considered different pollutants (PM total mass) than those studied here. Additional research could evaluate whether the models used here are also robust to alternate specifications.

Whereas the above three models explore seasonal variation in health effect estimates using all counties within the continental United States, we also investigated spatial variation by generating regional estimates for the subsets of counties in a specified region (i.e., by including only a subset of the counties for analysis in equation 6). The regions were defined based on the NMMAPS research and related studies (Samet et al. 2000; Peng et al. 2005; Dominici et al. 2006). Two counties were included in overall estimates of $PM_{2.5}$ total mass and hospital admissions, but were excluded from the regional analysis because they are not part of the continental United States. The United States was divided into four regions: Northeast, Southeast, Southwest, and Northwest. The number of counties varied among regions, with only 9 counties in the Northwest and 108 in the Northeast. The southeastern region had 58 counties, and the Southwest had 25. The Wald test statistic was used to evaluate whether $PM_{2.5}$ effect estimates for hospitalization were heterogeneous across seasons and regions.

EVALUATION OF WHETHER SPATIAL AND TEMPORAL PATTERNS IN PM TOTAL MASS HEALTH EFFECT ESTIMATES ARE RELATED TO SPATIAL AND TEMPORAL PATTERNS IN PM CHEMICAL COMPOSITION

This portion of the project examined whether the seasonal and regional variation in PM total mass health effect estimates can be explained by heterogeneity in the $PM_{2.5}$ chemical composition (Bell et al. 2009a,b). Three types of health effects estimates were examined: (1) $PM_{2.5}$ and the risk of cardiovascular hospitalizations for persons 65 years and older, from 1999 through 2005; (2) $PM_{2.5}$ and the risk of respiratory hospitalizations for persons 65 years and older, from 1999 through 2005; and (3) PM_{10} and the risk of total nonaccidental mortality, from 1987 through 2000. Estimates for the association between PM_{10} and mortality were generated in previous work (Peng et al. 2005). The mortality estimates were calculated using similar methods, including community-specific models with adjustment for the day of the week, long-term trends, and weather. In addition to the health outcomes, the effect estimates for hospitalization and mortality differ in three areas: the time frames of the study period, size fractions of PM, and spatial units of analysis used. The hospitalization effect estimates are based on data from a time frame similar to that of the data in the $PM_{2.5}$ chemical component database, and the PM size distribution is the same ($PM_{2.5}$), whereas the mortality effect estimates were generated for an earlier time frame and for PM_{10}. The effect estimates for hospitalization are county specific. The mortality health effect estimates are based on a community, which consists of a single county or set of adjacent counties. At the time of this report, national mortality effect estimates based on $PM_{2.5}$ exposure were not available, so the mortality estimates based on PM_{10} exposure were used as an approximation; therefore, results from this portion of the analysis should be interpreted in the context of this important limitation.

The chemical composition database generated for the first phase of the project was combined with the PM effect estimates for hospital admissions and mortality to estimate how the chemical composition of fine particles affected the PM total mass health effect estimates. We used a hypothesis-driven approach to select the chemical components for analysis. The chemical components in the database (> 50) were narrowed to a list of those identified to contribute a substantial fraction of $PM_{2.5}$ total mass, to covary with $PM_{2.5}$ total mass, or to have been linked with health responses in previously conducted studies (Lippmann et al. 2006; Dominici et al. 2007; Ostro et al. 2007, 2008; Franklin et al. 2008).

Data for the chemical composition of $PM_{2.5}$ were not available for all counties or communities included in the health effects analysis. For the effect estimates for hospital admissions, data for the chemical components of $PM_{2.5}$ were available for 106 continental counties. They were also available for 64 of the communities included in the health effects analysis for mortality. Long-term season-specific averages for each of the selected $PM_{2.5}$ chemical components were calculated for each county or community. The fraction of $PM_{2.5}$ total mass represented by each component was calculated on a season- and county- (or community-) specific basis. The level of a given component divided by the $PM_{2.5}$ total mass was first calculated for a given day, and these daily values were then used to generate long-term averages for each season for each county.

We used Bayesian hierarchical modeling (Everson 2000) to evaluate whether county- (or community-) and season-specific PM total mass health effect estimates are associated

with the chemical composition of county- (or community-) and season-specific $PM_{2.5}$, assuming a linear model. Future research could investigate other model forms, such as nonlinear models. The results are presented as the percentage increase in the health effect estimates (relative rate) associated with an IQR increment in the fraction of $PM_{2.5}$ total mass represented by the specified $PM_{2.5}$ chemical component. We used sensitivity analysis to investigate whether identified associations were robust to adjustment by additional chemical components or exclusion of any single community.

Using yearly health effect estimates, we investigated an alternative hypothesis to examine whether the between-county or between-community variability in health effect estimates was associated with socioeconomic conditions, the racial composition of the counties or communities, or their degree of urbanization. Socioeconomic conditions were assessed with two variables: the percentage of those aged 25 or older with a high school degree or equivalent and the median household income. Racial composition was assessed as the percentage of the population self-identifying as black or African-American. Degree of urbanization was examined with two variables: the percentage of the population living in an urban setting and the total population. These values were based on the 2000 U.S. Census (U.S. Census 2000a,b) for the effect estimates for hospitalizations. Because the effect estimates for mortality span a different time frame than those for hospitalizations, weighted values from the 1990 and 2000 U.S. Censuses were used (U.S. Census 1990a,b, 2000a,b).

We also investigated whether the prevalence of AC, determined at a community level, could explain between-community heterogeneity of PM total mass health effect estimates. The lags investigated were those with the strongest effect in yearly models: lag 1 for PM_{10} and mortality, lag 0 for $PM_{2.5}$ and cardiovascular hospitalizations, and lag 2 for $PM_{2.5}$ and respiratory hospitalizations. The prevalence of AC was based on U.S. Census data from the American Housing Survey. These data are not available for every community and are measured every few years for select communities. Time-weighted averages of census data were used to generate a long-term average for the prevalence of AC that was aligned with the time period of study used to generate the health effect estimates (1987 through 2000 for mortality, 1999 through 2005 for hospital admissions). AC prevalence was included as a second-stage variable in a way analogous to the methods described in the preceding section, Evaluation of Spatial and Temporal Patterns in the Association Between Short-Term Exposure to $PM_{2.5}$ and Hospital Admissions. Because AC use would be more common in the summer, separate models were applied for yearly and summertime health effect estimates.

RESULTS

SPATIAL AND TEMPORAL VARIATION IN $PM_{2.5}$ CHEMICAL COMPOSITION

This portion of the project examined spatial and temporal patterns in the chemical composition of $PM_{2.5}$ (Bell et al. 2007). The protocol for development of the database resulted in 48,591 observation days for 187 counties, based on an original dataset of 62,690 observation days (monitor-days of data). Not all monitors provided data for the entire study period. The average number of observation days per county for $PM_{2.5}$ total mass was 260 days, with a range of 41 to 676 observation days. The number of observation days varied by component. The least amount of data was available for Na^+, with an average of 248 observation days per county; the most for OC, with an average of 260 days per county.

Data were available for each season for all counties. The distribution of data for $PM_{2.5}$ total mass was 26.3% from summer, 26.5% from autumn, 22.7% from winter, and 24.6% from spring. Figure C.1 (see Appendix C, which includes the figures discussed in this and the next four paragraphs, available on the HEI Web site) provides the average $SO_4^=$ levels in $PM_{2.5}$ total mass for 2000 through 2005 by county, and Figure C.2 provides similar estimates by season. Figures C.3 through C.14 are analogous figures for other key $PM_{2.5}$ components (NO_3^-, Na^+, Si, EC, NH_4^+, and OCM), and Figures C.15 and C.16 are equivalent figures for $PM_{2.5}$ total mass.

A strong regional pattern was exhibited in the level of $PM_{2.5}$ $SO_4^=$, which was higher in the eastern United States and peaked during the summer (Figures C.1 and C.2). Levels of NO_3^- were higher in the western United States compared to the eastern United States, but levels were also higher in parts of the northeastern United States, with lower levels in the southeastern region of the country (Figure C.3). This north–south pattern was present during all seasons (Figure C.4). EC peaked in winter and autumn (Figure C.10). Levels of Na^+ were higher in the coastal regions, which was anticipated due to its contribution from sea salt (Figures C.5 and C.6). The highest levels of NO_3^- occurred in the winter in the eastern United States and in the winter and autumn in the western United States. The spatial pattern of EC was similar to that of NO_3^- (Figure C.9). OCM levels were highest on the western coast region, possibly because of traffic sources (Figures C.13 and C.14).

The estimated values for OCM were similar to the OCM2 values calculated for the sensitivity analysis. The correlation between OCM and OCM2 values was 0.99 on average across the counties. The lowest correlation between values for any single county was 0.97, and the highest 1.00. Subsequent analyses discussed in this report use the OCM values.

In general, the eastern United States and California had higher levels of $PM_{2.5}$ total mass (Figure C.15); however, the concentrations exhibited strong seasonal variation (Figure C.16). $PM_{2.5}$ total mass concentrations were highest in winter and autumn on the west coast, especially in northern California. Summer peaks were observed in the eastern United States, and low levels were observed in the central region of the country for all seasons.

Summary statistics for each component and $PM_{2.5}$ total mass, on average across the counties, are provided in Table 1. Note that the values in Table 1 and any other summary measures providing a national average obscure the heterogeneity among smaller spatial domains, as shown in Figures C.1 through C.16 (available online on the HEI Web site) and as demonstrated by the standard deviation and IQR values in Table 1. Similarly, the use of a yearly value

Table 1. Yearly, Summer, and Winter Summary Statistics for $PM_{2.5}$ Chemical Components for 187 U.S. Counties, 2000–2005[a,b]

	Yearly		Summer		Winter	
$PM_{2.5}$ Components	Average (SD)	IQR (Minimum to Maximum)	Average (SD)	IQR (Minimum to Maximum)	Average (SD)	IQR (Minimum to Maximum)
Al	29.2 (1.48)	11.4 (10.2 to 171)	43.6 (2.98)	27.6 (11.5 to 391)	17.3 (0.80)	6.22 (2.18 to 71.5)
NH_4^+	1543 (42.6)	729 (227 to 3889)	1699 (61.1)	1198 (121 to 5028)	1591 (43.4)	772 (196 to 3965)
Sb	11.1 (0.23)	2.41 (3.4 to 17.7)	11.2 (0.23)	2.87 (2.96 to 17.6)	11.2 (0.23)	3.24 (2.96 to 18.9)
As	1.70 (0.04)	0.58 (0.6 to 4.46)	1.7 (0.06)	0.62 (0.57 to 7.89)	1.65 (0.04)	0.53 (0.50 to 4.07)
Ba	24.2 (0.48)	7.34 (9.98 to 39.4)	24.9 (0.52)	8.73 (9.11 to 41.1)	23.5 (0.53)	8.23 (7.51 to 41.0)
Br	3.14 (0.09)	1.10 (1.34 to 13.9)	2.61 (0.07)	0.91 (1.11 to 8.82)	3.71 (0.14)	1.68 (1.32 to 22.3)
Cd	5.51 (0.11)	0.71 (2.16 to 7.18)	5.4 (0.11)	0.73 (2.23 to 9.50)	5.62 (0.11)	0.92 (2.11 to 8.03)
Ca	57.0 (3.57)	36.5 (12.4 to 450)	63.3 (3.68)	39.1 (14.3 to 428)	45.6 (3.42)	30.4 (9.19 to 478)
Ce	29.5 (0.6)	9.81 (8.86 to 44.5)	30.4 (0.65)	12.1 (9.6 to 51.6)	27.6 (0.62)	9.26 (4.87 to 45.2)
Cs	13.4 (0.27)	3.41 (4.03 to 19.1)	13.8 (0.29)	4.1 (5.11 to 22.8)	12.8 (0.29)	3.61 (2.53 to 22.4)
Cl	24.8 (2.32)	21.3 (3.25 to 300)	14.0 (2.16)	4.91 (2.73 to 322)	44.4 (4.02)	47.2 (4.47 to 414)
Cr	2.03 (0.12)	0.92 (0.42 to 19.13)	2.04 (0.1)	1.06 (0.45 to 11.4)	2.16 (0.23)	0.97 (0.38 to 39.5)
Co	0.71 (0.01)	0.06 (0.28 to 1.41)	0.71 (0.01)	0.07 (0.28 to 1.4)	0.72 (0.02)	0.06 (0.28 to 1.49)
Cu	3.98 (0.22)	2.46 (1.00 to 23.5)	4.54 (0.28)	2.71 (1.13 to 36.8)	4.16 (0.23)	2.74 (0.64 to 24.6)
EC	629 (19.6)	283 (166 to 1742)	540 (18.5)	264 (143.6 to 1899)	721 (27.3)	406 (156.3 to 2126)
Eu	4.56 (0.09)	1.21 (1.72 to 7.75)	4.64 (0.1)	1.14 (1.74 to 10.9)	4.40 (0.1)	1.09 (1.13 to 8.97)
Ga	1.63 (0.03)	0.22 (0.59 to 2.25)	1.66 (0.03)	0.33 (0.55 to 2.35)	1.60 (0.03)	0.23 (0.59 to 2.19)
Au	2.74 (0.06)	0.44 (1.07 to 3.87)	2.92 (0.06)	0.71 (1.01 to 4.39)	2.66 (0.06)	0.50 (0.89 to 3.66)
Hf	11.3 (0.22)	1.19 (4.29 to 14.1)	11.3 (0.22)	1.93 (3.92 to 16.3)	11.5 (0.22)	1.61 (4.87 to 15.4)
In	6.27 (0.12)	0.91 (2.33 to 8.22)	6.29 (0.13)	0.97 (2.43 to 10.6)	6.38 (0.13)	1.17 (2.26 to 9.11)
Ir	3.16 (0.06)	0.44 (1.07 to 4.57)	3.29 (0.07)	0.79 (1.01 to 4.56)	3.04 (0.06)	0.62 (1.03 to 4.25)
Fe	85.7 (3.91)	44.4 (15.39 to 437)	93.0 (4.09)	39.9 (18.5 to 455)	77.7 (4.59)	44.3 (11.0 to 635)
La	23.3 (0.47)	7.92 (6.79 to 35.1)	23.9 (0.51)	9.5 (8.91 to 42.6)	22.1 (0.49)	7.4 (3.7 to 34.7)
Pb	4.89 (0.21)	1.82 (1.63 to 23.6)	4.74 (0.32)	1.81 (1.33 to 51.0)	5.01 (0.19)	2.21 (1.5 to 22.4)
Mg	15.3 (0.43)	3.28 (7.17 to 67.6)	18.6 (0.60)	6.83 (4.46 to 76.3)	12.6 (0.39)	3.12 (3.69 to 62.62)
Mn	3.00 (0.22)	1.41 (0.71 to 32.2)	2.84 (0.18)	1.32 (0.72 to 22.3)	3.08 (0.27)	1.53 (0.77 to 39.8)
Hg	2.39 (0.04)	0.28 (0.91 to 3.94)	2.34 (0.04)	0.38 (0.88 to 3.31)	2.42 (0.05)	0.44 (0.88 to 5.01)
Mo	3.1 (0.06)	0.49 (1.14 to 6.21)	3.14 (0.07)	0.61 (1.03 to 8.61)	3.18 (0.07)	0.52 (0.96 to 5.79)
Ni	1.85 (0.17)	0.86 (0.33 to 20.2)	1.67 (0.12)	0.82 (0.33 to 13.9)	2.4 (0.33)	1.02 (0.3 to 31.3)
Nb	1.98 (0.04)	0.18 (0.78 to 2.48)	2.00 (0.04)	0.32 (0.74 to 2.59)	1.95 (0.04)	0.21 (0.74 to 2.45)

Table continues next page

[a] All units are in ng/m^3, except for $PM_{2.5}$ total mass, which is in $\mu g/m^3$.

[b] Bell et al. 2007.

obscures variation by season, as demonstrated by the maps of seasonal concentrations in Appendix C.

Figure 1 shows the ratios of long-term summer averages to winter averages, and vice versa, for each $PM_{2.5}$ component, averaged over the counties. The components with the highest summer levels, compared to winter levels, were aluminum, Si, $SO_4^=$, and titanium. The components with the highest winter levels, compared to summer levels, were NO_3^-, chlorine (Cl), and zinc (Zn).

We identified the components that comprised a substantial portion of $PM_{2.5}$ total mass and those that covaried with $PM_{2.5}$ total mass. Only seven of the components contributed 1% or more to the $PM_{2.5}$ total mass averaged across the counties, using either yearly or seasonal values. These components were NH_4^+, NO_3^-, EC, OCM, Si, Na^+, and $SO_4^=$, and collectively they comprised approximately 80% of the $PM_{2.5}$ total mass. Table 2 provides the percentage of $PM_{2.5}$ total mass that these components contributed to the yearly and seasonal averages, for the United States and for the eastern and western regions of the country. In the winter, OCM and NO_3^- were the largest contributors to $PM_{2.5}$ total mass, whereas in the summer OCM and $SO_4^=$ provided over 50% of the total mass. $SO_4^=$ was a larger contributor to $PM_{2.5}$ total mass in the eastern United States than in the western United States, and NO_3^- was a larger contributor in the western United States than in the eastern United States.

Table 1 (*Continued*). Yearly, Summer, and Winter Summary Statistics for $PM_{2.5}$ Chemical Components for 187 U.S. Counties, 2000–2005[a,b]

	Yearly		Summer		Winter	
$PM_{2.5}$ Components	Average (SD)	IQR (Minimum to Maximum)	Average (SD)	IQR (Minimum to Maximum)	Average (SD)	IQR (Minimum to Maximum)
NO_3^-	1733 (84.9)	1298 (327 to 10017)	836 (76.3)	567 (119 to 11814)	2990 (122)	2059 (657 to 11451)
OCM	3823 (100.9)	1373 (967 to 12120)	4413 (77.1)	1432 (1910 to 7604)	3995 (185)	2150 (152 to 24332)
P	4.80 (0.09)	0.82 (1.26 to 7.9)	5.07 (0.12)	1.46 (1.26 to 11.8)	4.49 (0.11)	0.73 (1.26 to 15.5)
K	72.9 (2.41)	27.4 (23.1 to 275)	85.4 (3.13)	43.8 (22.9 to 309)	73.2 (2.64)	31.1 (20.9 to 274)
Rb	0.99 (0.02)	0.07 (0.41 to 1.33)	1.00 (0.02)	0.16 (0.41 to 1.27)	0.96 (0.02)	0.13 (0.32 to 1.40)
Sm	3.00 (0.05)	0.3 (1.24 to 5.48)	3.17 (0.07)	0.5 (1.24 to 11.9)	2.82 (0.05)	0.38 (1.09 to 4.56)
Sc	2.10 (0.06)	0.67 (0.49 to 5.39)	1.76 (0.06)	0.69 (0.38 to 5.52)	2.38 (0.07)	0.82 (0.48 to 6.01)
Se	1.62 (0.05)	0.44 (0.51 to 7.49)	1.59 (0.05)	0.46 (0.53 to 7.11)	1.73 (0.05)	0.68 (0.52 to 5.91)
Si	105 (4.70)	49.6 (35.1 to 454)	147 (7.10)	87.0 (30.5 to 795)	65.0 (3.38)	25.1 (19.5 to 352)
Ag	5.06 (0.1)	0.36 (2.11 to 6.44)	5.02 (0.10)	0.66 (2.05 to 7.10)	5.00 (0.10)	0.66 (1.94 to 6.76)
Na^+	128 (5.10)	58.15 (37.2 to 509)	130 (6.30)	60.3 (24.8 to 620)	142 (4.70)	70.1 (45.8 to 606)
Sr	1.49 (0.03)	0.23 (0.57 to 4.11)	1.77 (0.05)	0.53 (0.56 to 6.22)	1.41 (0.04)	0.24 (0.51 to 4.82)
$SO_4^=$	3698 (102.4)	2020 (658 to 6604)	5256 (172)	3527 (523 to 9304)	2524 (62)	1026 (446 to 5925)
Ta	8.67 (0.19)	3.26 (2.43 to 14.8)	9.06 (0.22)	3.87 (2.85 to 18.4)	8.07 (0.19)	2.54 (1.73 to 15.3)
Tb	3.85 (0.11)	0.64 (1.48 to 17.6)	3.93 (0.13)	0.86 (1.37 to 21.5)	3.72 (0.11)	0.78 (1.36 to 19.4)
Sn	10.18 (0.19)	1.15 (4.34 to 15.7)	10.49 (0.2)	1.99 (3.86 to 14.8)	9.91 (0.19)	1.69 (3.92 to 13.4)
Ti	5.33 (0.16)	1.87 (1.69 to 16.2)	6.96 (0.23)	2.82 (2.25 to 22.3)	4.18 (0.17)	1.55 (1.18 to 18.5)
W	2.15 (0.12)	0.81 (0.62 to 10.6)	2.17 (0.13)	0.65 (0.6 to 12.4)	2.31 (0.13)	1.11 (0.54 to 9.80)
V	5.64 (0.11)	1.23 (1.96 to 7.4)	5.76 (0.12)	1.42 (2.01 to 8.01)	5.51 (0.11)	1.23 (1.79 to 8.11)
Y	1.40 (0.03)	0.14 (0.56 to 1.71)	1.42 (0.03)	0.23 (0.56 to 1.88)	1.38 (0.03)	0.13 (0.47 to 1.84)
Zn	14.0 (0.98)	7.67 (1.59 to 130)	11.21 (1.00)	7.39 (1.29 to 144)	17.2 (0.97)	9.13 (1.84 to 125)
Zr	1.9 (0.04)	0.23 (0.74 to 3.03)	1.94 (0.04)	0.32 (0.74 to 4.71)	1.86 (0.04)	0.26 (0.72 to 3.25)
$PM_{2.5}$(μg/m^3)	14.0 (0.22)	4.09 (5.04 to 26.0)	16.19 (0.34)	7.29 (5.59 to 28.5)	13.9 (0.27)	3.5 (5.06 to 32.8)

[a] All units are in ng/m^3, except for $PM_{2.5}$ total mass, which is in μg/m^3.

[b] Bell et al. 2007.

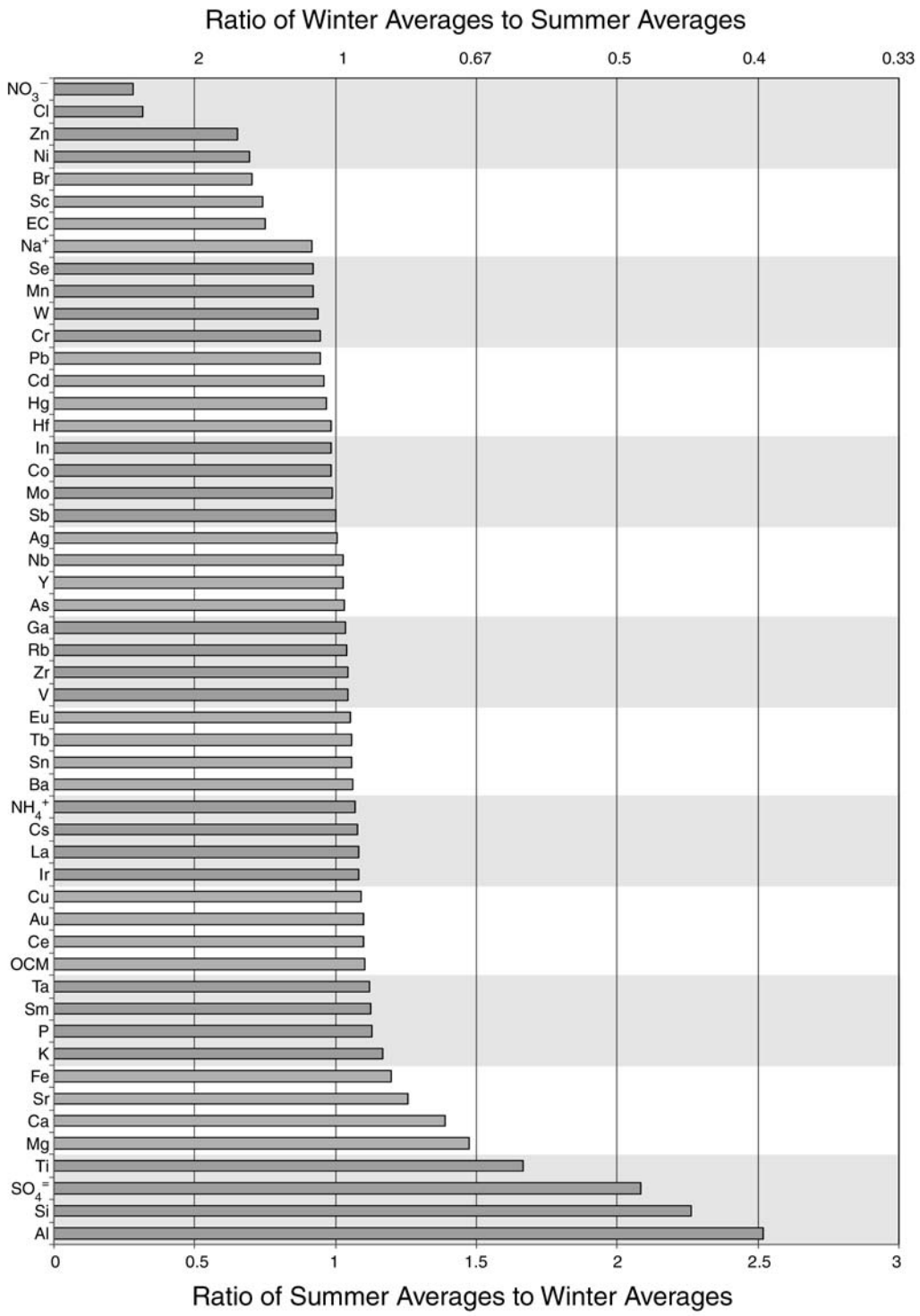

Figure 1. Ratios of long-term seasonal averages by $PM_{2.5}$ component.

Table 2. Average (Minimum to Maximum) Percentage of $PM_{2.5}$ Total Mass Composition by Component for Yearly and Seasonal Averages, for the U.S. and by Region[a]

	Yearly	Winter	Spring	Summer	Autumn
National (*n*[b] = 187)					
OCM	27.5 (14.0 to 78.6)	27.7 (3.0 to 82.8)	24.4 (9.2 to 71.8)	29.0 (14.2 to 77.2)	28.6 (11.8 to 78.1)
$SO_4^=$	25.8 (4.3 to 36.2)	18.9 (2.5 to 36.8)	26.1 (6.8 to 36.9)	30.7 (6.6 to 43.7)	25.8 (3.6 to 38.7)
NO_3^-	12.3 (2.7 to 38.6)	21.1 (3.8 to 39.2)	14.6 (2.7 to 43.4)	5.1 (1.2 to 41.5)	10.7 (2.1 to 37.5)
NH_4^+	10.7 (1.7 to 16.2)	11.4 (1.5 to 17.4)	11.6 (2.4 to 17.5)	9.9 (1.6 to 17.6)	10.2 (1.5 to 16.5)
EC	4.6 (2.1 to 15.2)	5.2 (1.6 to 15.2)	4.6 (2.3 to 13.0)	3.5 (1.3 to 14.4)	5.4 (2.3 to 18.0)
Na^+	1.0 (0.4 to 5.3)	1.1 (0.3 to 5.2)	1.2 (0.3 to 10.6)	0.9 (0.2 to 6.0)	0.8 (0.3 to 3.4)
Si	0.8 (0.3 to 4.8)	0.5 (0.1 to 3.4)	1.0 (0.3 to 6.9)	1.1 (0.2 to 6.2)	0.7 (0.3 to 3.7)
Eastern U.S. (*n* = 155)					
OCM	24.9 (14.0 to 38.5)	25.2 (9.4 to 55.9)	22.7 (9.2 to 42.3)	26.0 (14.2 to 41.2)	26.8 (11.8 to 41.8)
$SO_4^=$	28.6 (18.0 to 36.2)	21.1 (12.1 to 36.8)	28.5 (16.7 to 36.9)	33.6 (17.6 to 43.7)	28.8 (17.3 to 38.7)
NO_3^-	11.3 (2.7 to 25.2)	20.7 (4.3 to 38.5)	14.2 (2.7 to 30.5)	4.3 (1.2 to 12.0)	9.5 (2.1 to 22.0)
NH_4^+	11.4 (5.1 to 16.2)	12.1 (5.6 to 17.4)	12.4 (6.0 to 17.5)	10.6 (4.1 to 17.0)	10.8 (4.4 to 15.7)
EC	4.1 (2.1 to 15.2)	4.7 (1.6 to 14.4)	4.2 (2.3 to 13.0)	3.1 (1.3 to 14.4)	4.8 (2.3 to 18.0)
Na^+	0.9 (0.4 to 4.7)	1.1 (0.3 to 5.2)	1.0 (0.3 to 6.0)	0.7 (0.2 to 4.3)	0.8 (0.3 to 3.4)
Si	0.6 (0.3 to 3.1)	0.4 (0.1 to 1.5)	0.7 (0.3 to 1.5)	0.8 (0.2 to 5.9)	0.5 (0.3 to 1.7)
Western U.S. (*n* = 32)					
OCM	40.3 (16.7 to 78.6)	40.4 (3.0 to 82.8)	32.8 (11.2 to 71.8)	44.1 (25.7 to 77.2)	42.6 (18.8 to 78.1)
$SO_4^=$	12.3 (4.3 to 20.5)	8.2 (2.5 to 22.4)	14.6 (6.8 to 25.0)	16.6 (6.6 to 30.1)	11.5 (3.6 to 19.1)
NO_3^-	16.9 (3.6 to 38.6)	22.7 (3.8 to 39.2)	16.3 (3.8 to 43.4)	9.0 (2.5 to 41.5)	16.4 (3.2 to 37.5)
NH_4^+	7.7 (1.7 to 15)	8.3 (1.5 to 14.6)	7.8 (2.4 to 16.7)	6.5 (1.6 to 17.6)	7.3 (1.5 to 16.5)
EC	6.9 (3.3 to 11.9)	7.6 (3.2 to 15.2)	6.5 (3.3 to 11.3)	5.6 (2.7 to 10.4)	7.9 (3.5 to 14.1)
Na^+	1.3 (0.4 to 5.3)	1.1 (0.3 to 3.2)	1.8 (0.5 to 10.6)	1.8 (0.3 to 6.0)	1.1 (0.4 to 3.3)
Si	1.7 (0.5 to 4.8)	0.9 (0.2 to 3.4)	2.6 (0.7 to 6.9)	2.4 (0.4 to 6.2)	1.7 (0.4 to 3.7)

[a] The minimum and maximum values reflect the smallest and largest county-specific averages, respectively.

[b] *n* = number of counties.

The minimum and maximum values for any single county are also provided in Table 2, providing evidence of strong spatial variation in the contribution of each component to $PM_{2.5}$ total mass. No components other than those in Table 2 provided more than 1% of the $PM_{2.5}$ total mass averaged across the counties, yearly or by season. However, other components may contribute more to total mass in individual counties during particular seasons. The components that contributed 1% or more to $PM_{2.5}$ total mass for any single county for either a yearly or seasonal average were aluminum, calcium, chlorine, Fe, and potassium (K). These components on average contributed 0.18% to 0.62% of $PM_{2.5}$ total mass over the whole year, but in some counties contributed up to 5.4% for a given season (results not shown). Note that components or chemical forms, such as ferric oxide, that were not measured in the U.S. EPA database were not incorporated into this analysis.

Correlations between the components contributing 1% or more to total mass are provided in Table 3. These values reflect the correlations between county-level averages. The strongest correlations were between NH_4^+ and $SO_4^=$ and between NH_4^+ and NO_3^-. For the eastern United States, EC concentrations were more strongly associated with OCM in winter than in other seasons.

Figure 2 shows the correlations between levels of $PM_{2.5}$ chemical components and $PM_{2.5}$ total mass levels, on average across counties for the study period and by season for the continental United States and for the eastern and western portions of the country. The components that comprised the largest fraction of $PM_{2.5}$ total mass were also the components with the highest temporal correlations with $PM_{2.5}$ total mass. The components typically had the highest correlations with $PM_{2.5}$ total mass during the time periods when they reached their peak levels (e.g., summer for $SO_4^=$, winter for NO_3^-).

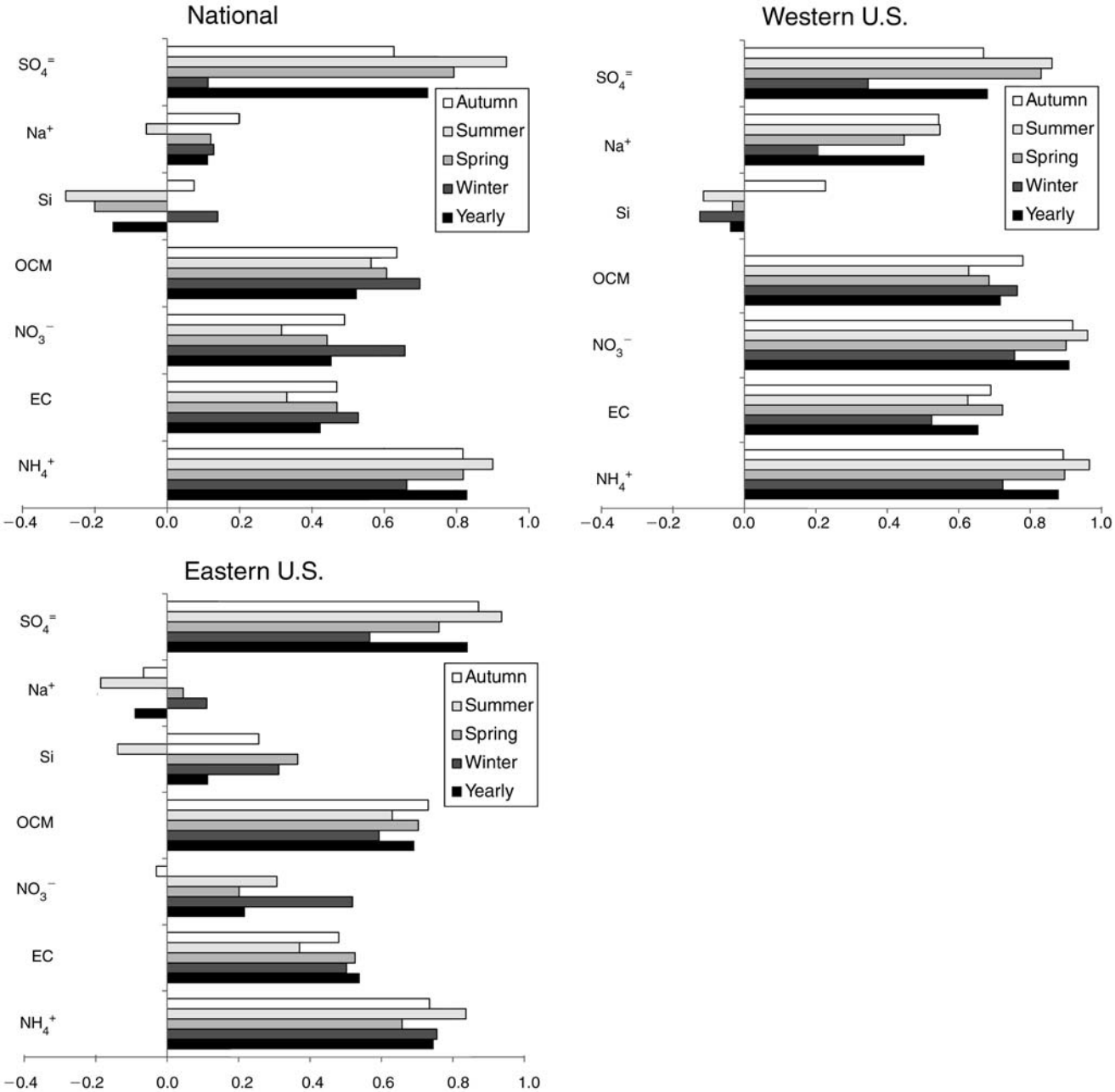

Figure 2. Correlations between county-level $PM_{2.5}$ components and $PM_{2.5}$ total mass, by region and season.

The results were similar for the sensitivity analysis using seasonally detrended data, which included the 180 counties with 1 year or more of data (results not shown). The highest correlations between component levels and $PM_{2.5}$ total mass were for NH_4^+ in both datasets (correlation = 0.83 for nondetrended data, 0.84 for detrended data) and $SO_4^=$ (correlation = 0.72 for nondetrended data, 0.78 for detrended data).

SEASONAL AND REGIONAL EFFECTS OF $PM_{2.5}$ ON CARDIOVASCULAR- AND RESPIRATORY-RELATED HOSPITAL ADMISSIONS

This segment of the project evaluated spatial and temporal patterns in the association between $PM_{2.5}$ total mass and cause-specific (cardiovascular, respiratory) hospital admissions (Bell et al. 2008). Figure 3 shows the results from the main model, which assumes a constant effect

Table 3. Correlations Between Selected $PM_{2.5}$ Components for Yearly and Seasonal Averages, for the U.S. and by Region

	United States (n^a = 187)						Eastern U.S. (n = 155)						Western U.S. (n = 32)					
	EC	NO_3^-	OCM	Si	Na^+	$SO_4^=$	EC	NO_3^-	OCM	Si	Na^+	$SO_4^=$	EC	NO_3^-	OCM	Si	Na^+	$SO_4^=$
Yearly																		
NH_4^+	0.18	0.64	0.08	−0.35	−0.01	0.72	0.28	0.70	0.17	−0.21	−0.28	0.65	0.46	0.98	0.32	−0.10	0.47	0.85
EC		0.27	0.59	0.33	0.27	0.02		0.09	0.54	0.18	0.23	0.31		0.46	0.64	0.35	0.29	0.41
NO_3^-			0.18	−0.02	0.17	−0.05			−0.21	−0.22	−0.26	−0.06			0.38	−0.10	0.47	0.76
OCM				0.26	0.24	0.00				0.27	0.09	0.47				−0.02	0.32	0.18
Si					0.14	−0.43					0.46	−0.03					−0.34	−0.14
Na^+						−0.07						−0.09						0.58
Winter																		
NH_4^+	−0.02	0.86	−0.03	−0.19	0.00	0.39	0.07	0.89	0.03	0.04	−0.06	0.33	0.11	0.99	0.11	−0.23	0.15	0.72
EC		0.08	0.73	0.57	0.18	−0.22		−0.16	0.69	0.28	0.28	0.42		0.16	0.66	0.58	0.03	−0.17
NO_3^-			0.10	0.00	0.01	−0.12			−0.23	−0.03	−0.08	−0.10			0.17	−0.20	0.19	0.63
OCM				0.35	0.12	−0.24				0.32	0.19	0.50				0.06	0.11	−0.18
Si					−0.04	−0.39					0.14	0.19					−0.35	−0.31
Na^+						0.08						0.13						0.11
Spring																		
NH_4^+	0.26	0.74	0.16	−0.41	−0.06	0.70	0.27	0.76	0.08	−0.11	−0.27	0.46	0.51	0.99	0.37	−0.19	0.37	0.89
EC		0.20	0.51	0.18	0.22	0.20		0.09	0.48	0.29	0.24	0.33		0.51	0.64	0.19	0.21	0.49
NO_3^-			−0.01	−0.18	0.01	0.05			−0.26	−0.18	−0.32	−0.20			0.41	−0.22	0.39	0.83
OCM				0.14	0.18	0.31				0.47	0.11	0.51				−0.05	0.30	0.31
Si					0.04	−0.42					0.34	0.20					−0.28	−0.18
Na^+						0.04						0.16						0.48
Summer																		
NH_4^+	0.31	0.53	0.40	−0.39	0.01	0.88	0.32	0.64	0.37	−0.33	−0.24	0.89	0.55	0.98	0.49	−0.21	0.58	0.91
EC		0.31	0.45	0.11	0.09	0.19		0.38	0.41	0.09	0.05	0.22		0.53	0.65	0.24	0.22	0.50
NO_3^-			0.28	−0.12	0.43	0.12			0.12	−0.28	−0.11	0.29			0.53	−0.21	0.57	0.82
OCM				−0.09	−0.03	0.37				−0.09	−0.14	0.45				0.02	0.14	0.33
Si					0.12	−0.38					0.48	−0.26					−0.45	−0.28
Na^+						−0.14						−0.20						0.69
Autumn																		
NH_4^+	0.25	0.62	0.20	−0.14	0.09	0.66	0.27	0.48	0.24	−0.05	−0.25	0.72	0.56	0.99	0.45	0.18	0.53	0.84
EC		0.36	0.57	0.41	0.24	0.01		0.07	0.47	0.24	0.14	0.27		0.56	0.65	0.42	0.35	0.47
NO_3^-			0.33	0.30	0.28	−0.15			−0.30	−0.05	−0.16	−0.21			0.49	0.20	0.51	0.75
OCM				0.38	0.29	0.02				0.36	0.10	0.52				0.08	0.42	0.28
Si					0.10	−0.43					0.19	0.04					−0.15	0.04
Na^+						−0.04						−0.09						0.67

[a] n = number of counties.

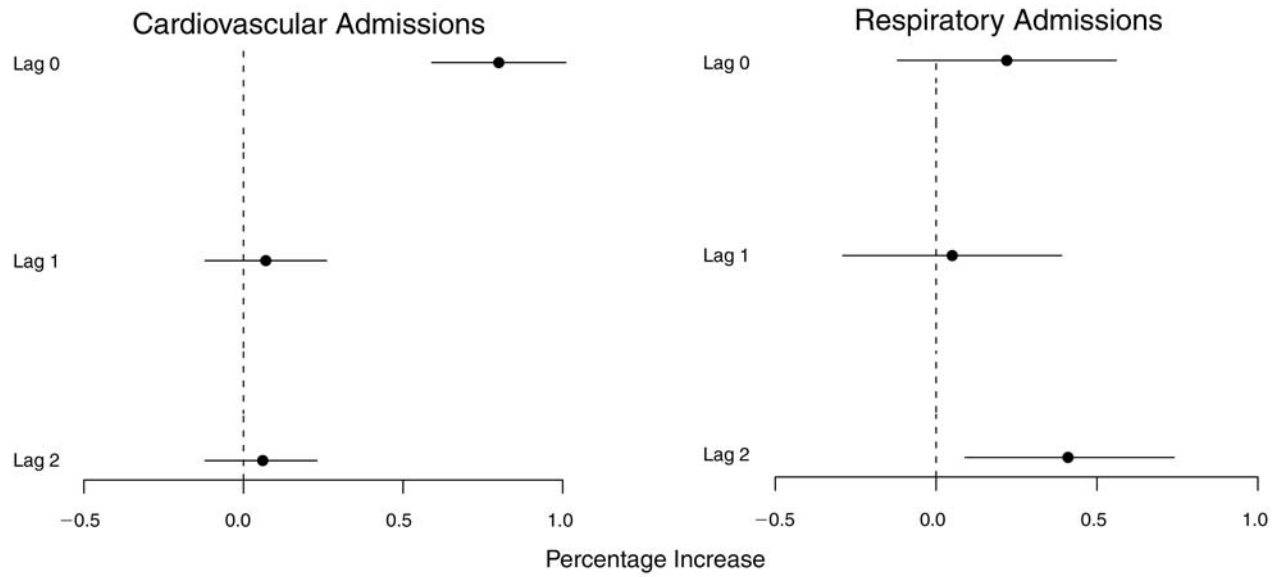

Figure 3. National estimates of the percentage increase in cardiovascular and respiratory hospital admissions per 10-μg/m^3 increase in $PM_{2.5}$, by lag using the main model.

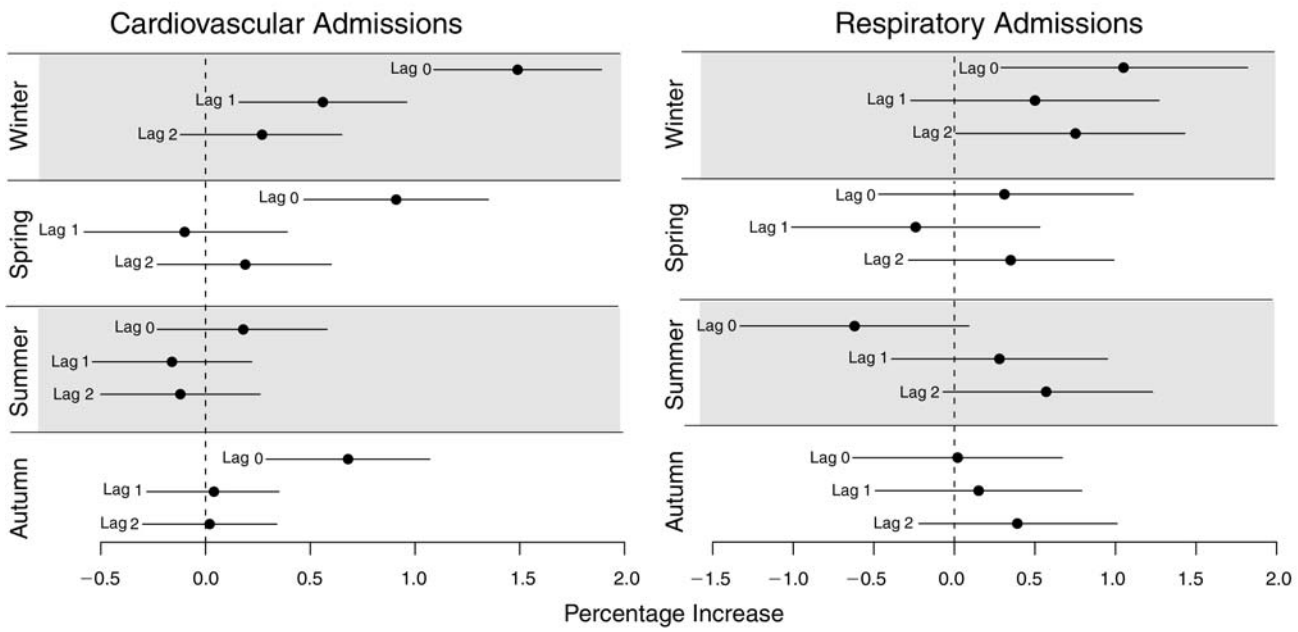

Figure 4. National estimates of the percentage increase in cardiovascular and respiratory hospital admissions per 10-μg/m^3 increase in $PM_{2.5}$, by lag and season using the seasonal model.

throughout the year, for cardiovascular and respiratory hospitalizations for lags 0, 1, and 2 days. The results are presented as the percentage increase in the risk of hospital admissions per 10-μg/m^3 increase in $PM_{2.5}$. Compared to other lag structures, the largest effects were observed at lag 0 for cardiovascular admissions, with a 0.80% (PI, 0.59–1.01) increase in admissions per 10-μg/m^3 increase in $PM_{2.5}$. For respiratory admissions, the strongest effect was at lag 2 days, with a 0.41% (PI, 0.09–0.74) increase in admissions per 10-μg/m^3 increase in $PM_{2.5}$.

Figure 4 shows the results for the seasonal model. The strongest effect on cardiovascular admissions was observed at lag 0 for all seasons. For respiratory admissions, the strongest effect occurred in winter at lag 0, although an

Table 4. Percentage Increase in Cardiovascular and Respiratory Hospital Admissions per 10 μg/m^3 Increase in Lag-0 $PM_{2.5}$ (95% PI), by Season and Region for the Main and Seasonal Models[a, b]

	Main Model Yearly	Seasonal Model			
		Winter	Spring	Summer	Autumn
Cardiovascular Admissions					
National (n[c] = 202)	**0.80 (0.59 to 1.01)**	**1.49 (1.09 to 1.89)**	**0.91 (0.47 to 1.35)**	0.18 (−0.23 to 0.58)	**0.68 (0.29 to 1.07)**
Northeast (n = 108)	**1.08 (0.79 to 1.37)**	**2.01 (1.39 to 2.63)**	**0.95 (0.32 to 1.58)**	**0.55 (0.08 to 1.02)**	**1.03 (0.48 to 1.58)**
Southeast (n = 58)	0.29 (−0.19 to 0.77)	1.06 (−0.07 to 2.21)	0.75 (−0.26 to 1.78)	−0.67 (−1.60 to 0.26)	0.17 (−0.72 to 1.07)
Northwest (n = 9)	0.74 (−1.74 to 3.29)	0.85 (−4.11 to 6.07)	−0.07 (−12.40 to 13.98)	−1.55 (−15.22 to 14.31)	−0.67 (−6.96 to 6.05)
Southwest (n = 25)	0.53 (0.00 to 1.05)	0.76 (−0.25 to 1.79)	1.78 (−0.87 to 4.51)	−1.20 (−4.90 to 2.65)	0.30 (−0.98 to 1.59)
Respiratory Admissions					
National (n = 202)	0.22 (−0.12 to 0.56)	**1.05 (0.29 to 1.82)**	0.31 (−0.29 to 0.99)	−0.62 (−1.33 to 0.09)	0.02 (−0.63 to 0.67)
Northeast (n = 108)	0.32 (−0.18 to 0.83)	**1.76 (0.60 to 2.93)**	0.34 (−0.88 to 0.97)	−0.80 (−1.65 to 0.07)	−0.01 (−0.87 to 0.85)
Southeast (n = 58)	0.20 (−0.57 to 0.97)	0.59 (−1.35 to 2.58)	−0.06 (−0.82 to 2.34)	−0.15 (−1.88 to 1.61)	−0.58 (−2.06 to 0.91)
Northwest (n = 9)	−0.29 (−3.59 to 3.11)	−0.07 (−6.74 to 7.08)	−8.52 (−14.26 to 22.03)	0.25 (−21.46 to 27.96)	−1.38 (−11.84 to 10.32)
Southwest (n = 25)	−0.02 (−0.78 to 0.74)	0.03 (−1.25 to 1.34)	1.87 (−2.18 to 4.39)	0.64 (−5.38 to 7.04)	1.77 (−0.73 to 4.33)

[a] Bell et al. 2008.

[b] **Bold** values are statistically significant.

[c] n = number of counties.

association was also observed at lag 2 in this season. A 10-μg/m^3 increase in lag-0 $PM_{2.5}$ was associated with a 1.49% (PI, 1.09–1.89) increase in cardiovascular hospital admissions and a 1.05% (PI, 0.29–1.82) increase in respiratory admissions in winter.

The results shown in Figures 3 and 4 are national averages across the 202 U.S. counties. We also stratified the results by region to investigate whether the results from the main and seasonal models were heterogeneous by location. Table 4 shows effect estimates for the main and seasonal models by region and season. The largest effects were observed in the winter in the Northeast for both cardiovascular and respiratory admissions, although effects for cardiovascular admissions were evident in all seasons for this region. Note that the number of counties included in the northeastern region far exceeded that in each of the other three regions.

The results of the Wald test indicate that $PM_{2.5}$ effect estimates for cardiovascular admissions (lag 0) are heterogeneous across seasons ($P < 0.01$). Seasonal effect estimates for respiratory admissions (lag 0) are also heterogeneous ($P < 0.01$). They also provide evidence for the heterogeneity of effect estimates across regions for cardiovascular admissions, but the effect estimates for respiratory admissions are not statistically different across regions.

The results from the harmonic model, which allows a smooth function of effect estimates through time of year, are provided in Figure 5 for cardiovascular disease and in Figure 6 for respiratory disease. The results from the seasonal model are superimposed onto results from the harmonic model in these figures. The findings from the harmonic model are similar to those from the seasonal model, which indicate that the results from the seasonal model are not an artifact of the cutoffs specified for seasonal definitions (e.g., winter as December to February).

ANALYSIS OF SPATIAL AND TEMPORAL HETEROGENEITY IN PM TOTAL MASS HEALTH EFFECT ESTIMATES AND SPATIAL AND TEMPORAL PATTERNS IN PM CHEMICAL COMPOSITION

This phase of the project related the spatial and temporal patterns observed in studies of health effects associated with PM total mass to the chemical composition of $PM_{2.5}$ (Bell et al. 2009b). $PM_{2.5}$ chemical components were selected for analysis based on their contribution to $PM_{2.5}$ total mass, their covariance with $PM_{2.5}$ total mass, or their observed associations with human health response in earlier studies. The components selected for analysis and the IQR of each component's percentage of $PM_{2.5}$ total mass are shown in Figure 7. Of these components, the largest contributors to $PM_{2.5}$ total mass were NO_3^-, $SO_4^=$, and OCM.

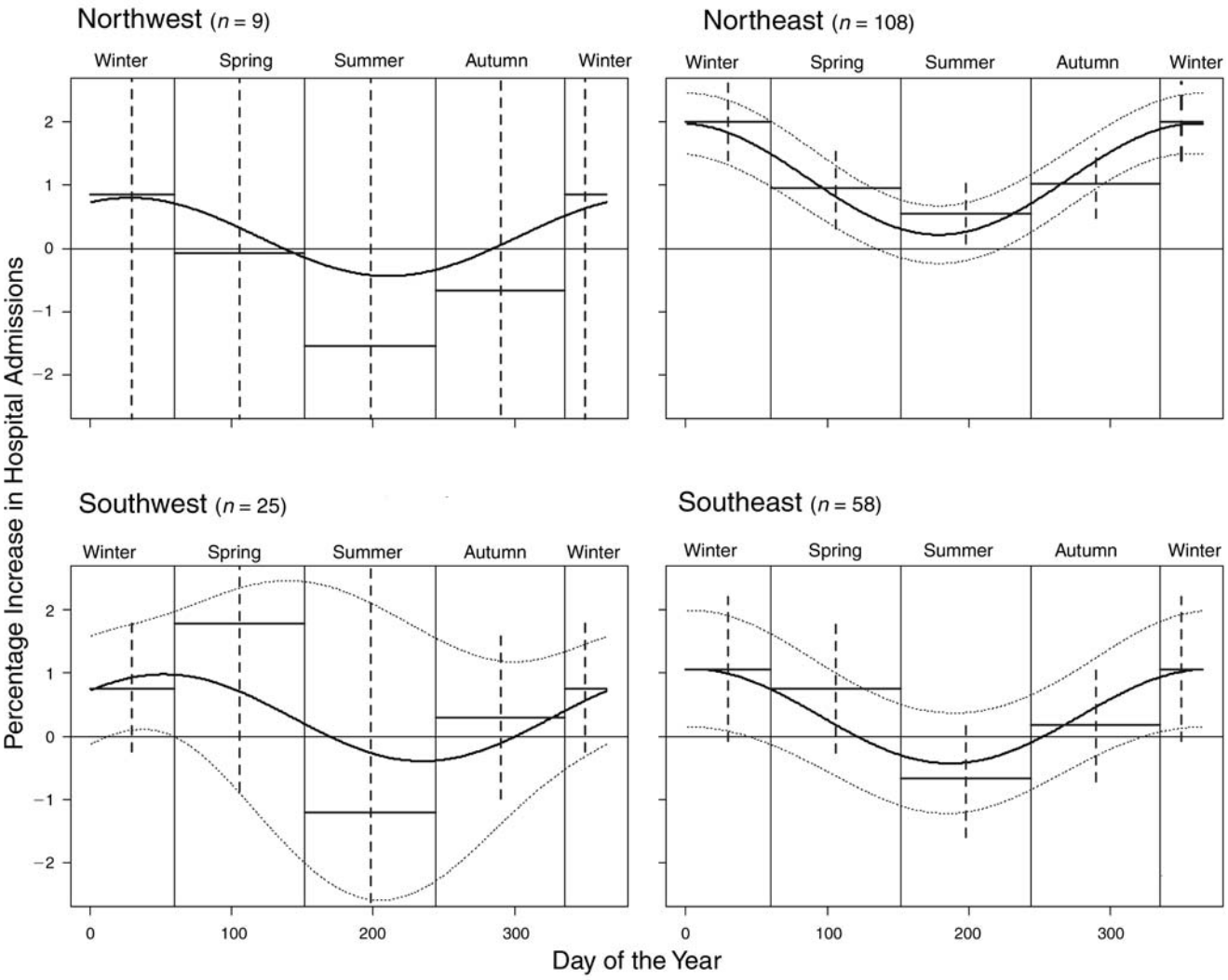

Figure 5. Percentage increase in total cardiovascular hospital admissions per 10-μg/m³ increase in lag-0 $PM_{2.5}$, by U.S. region, comparing results from the harmonic and seasonal interaction models. Vertical lines mark the divisions between seasons as defined by the seasonal interaction model. For the harmonic model (curved lines), solid lines represent the central estimate and dotted lines the 95% PI (for the Northwest region, the 95% PIs were too large to fit on this scale). For the seasonal interaction model (straight lines), horizontal solid lines represent the central estimate and vertical dashed lines the 95% PI. The number in parentheses (*n*) represents the number of U.S. counties included in each region. Note that the y-axis scale is identical across regions (Bell et al. 2008).

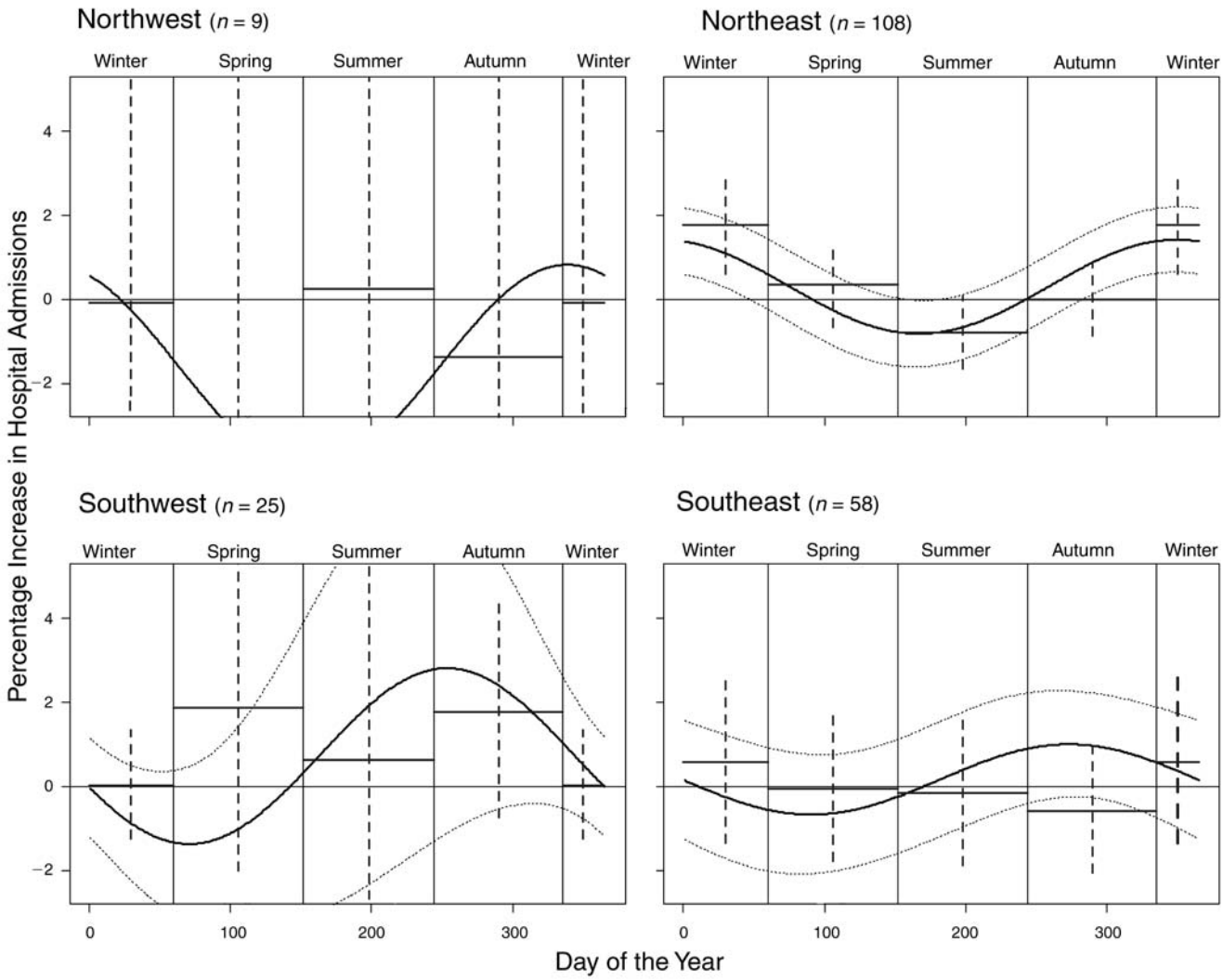

Figure 6. Percentage increase in total respiratory hospital admissions per 10-µg/m³ increase in lag-0 $PM_{2.5}$, by U.S. region, comparing results from the harmonic and seasonal interaction models. Vertical lines mark the divisions between seasons as defined by the seasonal interaction model. For the harmonic model (curved lines), solid lines represent the central estimate and dotted lines the 95% PI (for the Northwest region, the 95% PIs were too large to fit on this scale). For the seasonal interaction model (straight lines), horizontal solid lines represent the central estimate and vertical dashed lines the 95% PI. The number in parentheses (*n*) represents the number of U.S. counties included in each region. Note that the y-axis scale is identical across regions (Bell et al. 2008).

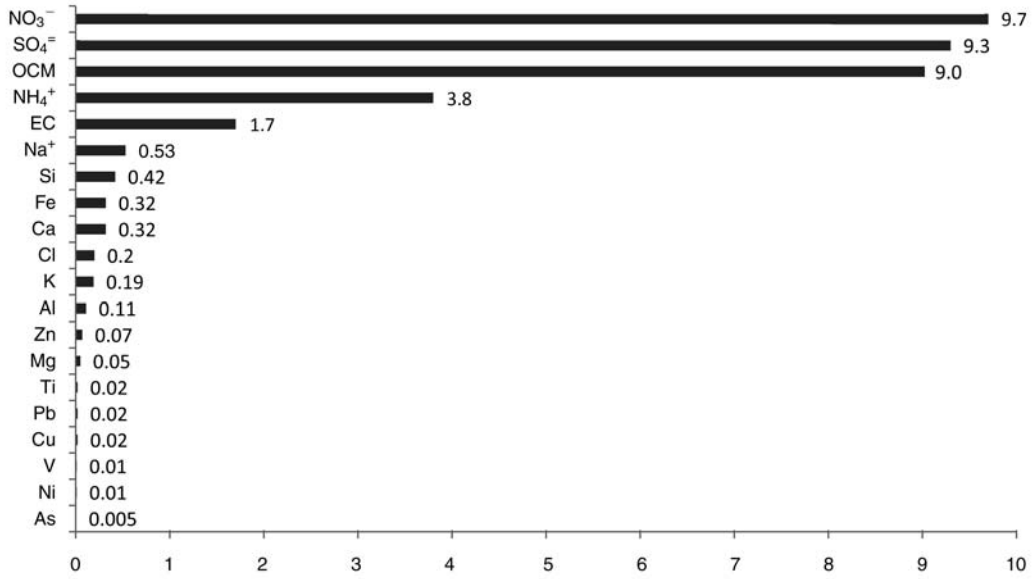

Figure 7. For each chemical component, the IQR of its average percentage of $PM_{2.5}$ total mass, for 106 U.S. counties from 2000 through 2005.

Table 5 provides the percentage increase in PM total mass health effect estimates ($PM_{2.5}$ effect estimates for cardiovascular or respiratory hospital admissions and PM_{10} effect estimates for mortality) per an IQR increase in the fraction of $PM_{2.5}$ total mass represented by each component. These results are based on a comparison of season- and community-specific values for health effect estimates and $PM_{2.5}$ component fractions. These findings provide evidence that the seasons and locations with higher $PM_{2.5}$ content of EC, Ni, or V have higher $PM_{2.5}$ total mass effect estimates for hospitalizations. Seasons and locations with a higher PM content of Ni also had higher PM_{10} effect estimates for mortality.

For the $PM_{2.5}$ effect estimates (for cardiovascular or respiratory hospitalizations) that were observed to be associated with the multiple components of the PM, multipollutant models were used to determine if observed associations were robust. Table 6 provides the percentage increase in $PM_{2.5}$ total mass effect estimates for hospitalization per an IQR increase in the fraction of $PM_{2.5}$ total mass that is EC, Ni, or V, with adjustments for one or more of the remaining copollutants. The fractions of $PM_{2.5}$ represented by these components were not highly correlated, on average, across the counties. The correlations were 0.48 for Ni and V, 0.33 for V and EC, and 0.30 for Ni and EC. Most of the observed associations in Table 5 lost statistical significance when adjusted by another pollutant. The association between the $PM_{2.5}$ V content and cardiovascular hospital admissions was robust to inclusion of EC as a covariate, but not to adjustment for Ni or to adjustment for both Ni and EC. The association between $PM_{2.5}$ Ni content and effect estimates for cardiovascular hospital admissions was robust to adjustment by EC or V, or both EC and V.

We conducted a sensitivity analysis to evaluate whether the observed associations were robust to exclusion of any single county or community. Overall estimates were calculated for each association, removing a single county or community, and repeated for each other county or community. The sensitivity to the removal of single communities or counties was tested for the following associations: the $PM_{2.5}$ EC content and $PM_{2.5}$ effect estimates for respiratory hospital admissions, the $PM_{2.5}$ V content and $PM_{2.5}$ effect estimates for respiratory hospital admissions, the $PM_{2.5}$ Ni content and $PM_{2.5}$ effect estimates for respiratory hospital admissions, the $PM_{2.5}$ EC content and $PM_{2.5}$ effect estimates for cardiovascular hospital admissions, the $PM_{2.5}$ V content and $PM_{2.5}$ effect estimates for cardiovascular hospital admissions, the $PM_{2.5}$ Ni content and $PM_{2.5}$ effect estimates for cardiovascular hospital admissions, and the $PM_{2.5}$ Ni content and PM_{10} effect estimates for nonaccidental mortality (Bell et al. 2009b).

The association between Ni in $PM_{2.5}$ and the relative rate for respiratory hospitalizations lost statistical significance

Table 5. Percentage Change in the Lag-0 PM Total Mass Health Effect Estimates per IQR Increase in the Component Fraction of $PM_{2.5}$ Total Mass (95% PI)[a,b,c,d]

	$PM_{2.5}$ and Cardiovascular Hospitalization n = 106	$PM_{2.5}$ and Respiratory Hospitalization n = 106	PM_{10} and Mortality n = 100
Al	−5.4 (−14.9 to 4.1)	856 (−122 to 293)	−6.6 (−15 to 1.5)
NH_4^+	−1.9 (−43 to 39)	−687 (−1500 to 129)	27 (−11 to 66)
As	−9.4 (−38 to 19)	−106 (−706 to 495)	−15 (−56 to 26)
Ca	−11 (−34 to 12)	408 (−45 to 861)	−11 (−26 to 3.0)
Cl	13 (−1.1 to 26)	200 (−75 to 475)	−8.2 (−26 to 10)
Cu	4.4 (−20 to 29)	243 (−277 to 762)	−4.3 (−30 to 21)
EC	**26 (4.4 to 47)**	**511 (81 to 941)**	−9.9 (−35 to 15)
Fe	−7.2 (−27 to 12)	−125 (−535 to 285)	1.1 (−13 to 15)
Pb	2.6 (−20 to 25)	−76 (−546 to 395)	−8.9 (−40 to 22)
Mg	−18 (−41 to 4.3)	87 (−375 to 548)	−7.2 (−25 to 11)
Ni	**19 (9.9 to 28)**	**223 (37 to 410)**	**145 (4.0 to 25)**
NO_3^-	16 (−11 to 42)	37 (−514 to 588)	−10 (−48 to 28)
OCM	−5.6 (−38 to 27)	350 (−289 to 989)	−17 (−50 to 16)
K	−13 (−35 to 8.0)	35 (−424 to 495)	−23 (−50 to 4.3)
Si	−11 (−26 to (4.5)	186 (−139 to 511)	−10 (−21 to 1.3)
Na^+	8.2 (−12 to 28)	355 (−55 to 766)	−13 (−39 to 13)
$SO_4^=$	−15 (−38 to 8.9)	−321 (−810 to 167)	31 (−2.7 to 64)
Ti	−22 (−44 to 0.3)	155 (−315 to 624)	−7.0 (−26 to 12)
V	**28 (11 to 44)**	**392 (46 to 738)**	29 (−0.5 to 58)
Zn	7.9 (−8.0 to 24)	−38 (−384 to 308)	6.4 (−14 to 27)

[a] The IQR increase in the fraction of $PM_{2.5}$ represented by each component is based on the IQR values displayed in Figure 7.

[b] Bell et al. 2009b.

[c] n = number of counties.

[d] **Bold** values are statistically significant.

with the exclusion of Queens County, New York, or New York County, New York. The association between V in $PM_{2.5}$ and the relative rate for respiratory hospitalizations lost statistical significance with the exclusion of Queens County, New York. Associations between cardiovascular hospital admissions and $PM_{2.5}$ content for EC, V, or Ni were robust to exclusion of any single county. The association between Ni in PM_{10} and the relative rate for mortality lost statistical significance with the exclusion of the New York, New York, community.

Using yearly effect estimates, we performed additional analysis to investigate the alternative hypothesis that community-level factors explain the between-community variation in health effects associated with PM total mass (Bell et al. 2009a,b). The results are provided in Table 7. The factors investigated include indicators of socioeconomic status (percentage of those 25 years and older with a high school degree or equivalent, median household income), racial composition (percentage of the population self-identifying as black or African-American), degree of urbanization (percentage of the population living in an urban setting, total population), and prevalence of AC (central AC, any AC including window units).

No associations were observed between the factors representing socioeconomic status, racial composition, or degree of urbanization and $PM_{2.5}$ effect estimates for cardiovascular or respiratory hospital admissions, or PM_{10} effect estimates for mortality (Bell et al. 2009b). The observed association between $PM_{2.5}$ Ni content and $PM_{2.5}$ effect estimates for cardiovascular hospitalizations was robust to adjustment by EC and V and any of these community-level census variables. Additional details are provided in Bell et al. (2009a).

Table 6. Percentage Increase in the Lag-0 $PM_{2.5}$ Total Mass Health Effect Estimates per IQR Increase in the Component Fraction of $PM_{2.5}$ Total Mass (95% PI) with and without Adjustment by Copollutants[a,b]

$PM_{2.5}$ Component / Copollutant Adjustment	$PM_{2.5}$ and Cardiovascular Hospitalization	$PM_{2.5}$ and Respiratory Hospitalization
EC		
None	**25.8 (4.4 to 47.2)**	**511 (80.7 to 941)**
Ni	14.0 (−7.6 to 35.5)	399 (−45.1 to 843)
V	14.9 (−7.8 to 37.6)	386 (−74.8 to 846)
Ni and V	11.9 (−10.4 to 43.2)	362 (−98.0 to 823)
Ni		
None	**19.0 (9.9 to 28.2)**	**223 (36.9 to 410)**
EC	**17.3 (7.7 to 26.9)**	176 (−18.7 to 370)
V	**15.5 (4.1 to 26.9)**	151 (−78.4 to 381)
EC and V	**14.9 (3.4 to 26.4)**	136 (−94.9 to 368)
V		
None	**27.5 (10.6 to 44.4)**	**392 (46.3 to 738)**
EC	**23.1 (4.9 to 41.4)**	279 (−93.2 to 651)
Ni	10.9 (−9.6 to 31.5)	230 (−193.7 to 653)
EC and Ni	8.1 (−13.3 to 29.5)	140 (−300 to 579)

[a] Bell et al. 2009b.

[b] **Bold** values are statistically significant.

Table 7. Association Between Community-Specific PM Total Mass Health Effect Estimates and Community-Level Characteristics[a,b]

		Percentage Increase in PM Health Effect Estimates per IQR Increase in County-Specific Variable (95% PI)		
	IQR	$PM_{2.5}$ and Cardiovascular Hospital Admissions	$PM_{2.5}$ and Respiratory Hospital Admissions	PM_{10} and Mortality
Socioeconomic Conditions				
Percentage of those ≥ 25 years with high school degree or equivalent	5.2%	−17.4 (−46.8 to 11.9)	−77.8 (−390 to 234)	−31.9 (−82.4 to 18.6)
Median household income (U.S. dollars)	$9,223	21.3 (−20.0 to 62.5)	45.9 (−411 to 503)	−12.3 (−62.3 to 37.7)
Race				
Percentage of population self-identifying as Black / African-American	17.3%	26.9 (−15.8 to 69.6)	−53.1 (−557 to 451)	48.7 (−15.8 to 113)
Degree of Urbanization				
Percentage of population living in urban setting	11.0%	34.4 (−29.0 to 97.8)	−41.9 (−774.7 to 691)	−20.1 (−102 to 61.7)
Total population	549,283 persons	−4.3 (−13.3 to 4.8)	−22.9 (−121 to 75.3)	5.1 (−14.4 to 24.5)

[a] The IQR applied was calculated based on the 106 counties used in the $PM_{2.5}$ hospitalization analysis.

[b] Bell et al. 2009b.

Higher effect estimates for hospitalizations — $PM_{2.5}$ effect estimates for cardiovascular admissions in particular — were observed for communities with a lower prevalence of AC (Bell et al. 2009a). Table 8 provides summary statistics on the prevalence of AC. Table 9 shows the percentage increase in PM total mass health effect estimates per an additional 20% increase in the population acquiring AC (i.e., a 20% increase in AC prevalence). The association between higher AC prevalence and lower risk estimates was generally higher in the summer. A 20% increase in the population using central AC lowered $PM_{2.5}$ risk estimates for cardiovascular hospital admissions, resulting in effect estimates of −42.5% (PI, –63.4 to –21.6) based on yearly estimates and −79.5% (PI, –143 to –15.7) based on summertime estimates.

Table 8. Summary Statistics on AC Prevalence[a]

	Average	Minimum to Maximum	IQR
AC Prevalence Data for Analysis of $PM_{2.5}$ and Hospital Admissions (168 Counties, 1999–2005)			
Central AC	0.56	0.06–0.95	0.50
Any AC	0.65	0.08–0.91	0.17
AC Prevalence Data for Analysis of PM_{10} and Mortality (84 Communities, 1987–2000)			
Central AC	0.53	0.05–0.89	0.43
Any AC	0.66	0.06–0.91	0.27

[a] From Bell et al. 2009a. Used with permission.

Table 9. Percentage Change in Community-Specific PM Effect Estimate for Mortality and Hospital Admissions per an Additional 20% of the Population Acquiring AC (95% PI)[a]

		Any AC Including Window Units		Central AC	
	Number of Counties	% Change in PM Effect Estimates	% Reduction in τ^2 [b]	% Change in PM Effect Estimates	% Reduction in τ^2
PM_{10} Risk Estimates for Mortality					
Yearly health effect estimates	84	−30.4 (−80.4 to 19.6)	−13	−39.0 (−81.4 to 3.3)	−5.4
Summer health effects, counties with PM_{10} peaking in summer	45	29.9 (−84.0 to 144)	−8.8	2.0 (−60.3 to 64.3)	−18
Winter health effects, counties with PM_{10} peaking in winter	6	−573 (−9100 to 7955)	−121	−1777 (−5755 to 2201)	−45
$PM_{2.5}$ Risk Estimates for Cardiovascular Hospital Admissions					
Yearly health effect estimates	168	−34.3 (−72.7 to 4.2)	−6.9	**−42.5 (−63.4 to −21.6)**[c]	17
Summer health effects, counties with $PM_{2.5}$ peaking in summer	103	−148 (−327 to 31.1)	3.6	**−79.5 (−143 to −15.7)**	12
Winter health effects, counties with $PM_{2.5}$ peaking in winter	42	−80.0 (−182 to 22.0)	4.5	−41.9 (−124 to 40.0)	−7
$PM_{2.5}$ Risk Estimates for Respiratory Hospital Admissions					
Yearly health effect estimates	168	44.5 (−87.4 to 176)	−3.8	27.6 (−46.7 to 102)	1.9
Summer health effects, counties with $PM_{2.5}$ peaking in summer	103	−74.8 (−417 to 267)	−1.0	−38.6 (−160 to 82.6)	−4.5
Winter health effects, counties with $PM_{2.5}$ peaking in winter	42	−32.5 (−245 to 180)	−6.0	43.8 (−125 to 213)	−5.4

[a] From Bell et al. 2009a. Used with permission.

[b] τ^2 represents the between-community variability of PM health effect estimates.

[c] **Bold** values are statistically significant.

CONCLUSIONS AND IMPLICATIONS

The ability of decision-makers to effectively protect public health from the impacts of PM is hindered by the lack of scientific evidence on which characteristics of PM affect its toxicity, including the differential toxicity of chemical components or sources. Several multicity studies have found between-community variation in PM health effect estimates, and some studies have indicated seasonal differences as well. If the chemical composition of PM affects its toxicity, the short-term effects related to PM might also vary by location and season, as the composition has seasonal and geographic variation; however, other factors could also contribute to temporal and seasonal variation in PM health effect estimates such as differences in copollutant levels or socioeconomic factors. If community characteristics that are not likely to exhibit strong seasonal patterns (e.g., baseline health status) alone explained the between-community variability of effect estimates for PM total mass, no seasonal patterns in health effects estimates would be observed.

This study involved the development of a database of the chemical components of $PM_{2.5}$, based on data from U.S. EPA monitoring networks, and an investigation of spatial and seasonal patterns in health effect estimates for $PM_{2.5}$ in a time-series analysis of the risk of cardiovascular and respiratory hospital admissions. The third phase of the project examined whether spatial and temporal variability in $PM_{2.5}$ chemical composition explains heterogeneity in health effect estimates based on either total $PM_{2.5}$ or PM_{10} mass. The findings of this study indicate that the chemical mixture of $PM_{2.5}$ varies spatially and seasonally and that such variation partially explains differences in the relative rates based on PM total mass. Of the 52 chemical components considered, only seven covaried with $PM_{2.5}$ total mass or contributed 1% or more to total mass: NH_4^+, NO_3^-, $SO_4^=$, OCM, EC, Na^+, and Si.

Short-term exposure to $PM_{2.5}$ was associated with higher risk of cardiovascular and respiratory hospital admissions, but these associations followed seasonal and regional patterns, indicating that the same level of PM may have differential toxicity depending on where and when it occurs. The strongest observed associations were for $PM_{2.5}$ and cardiovascular hospital admissions in winter. For cardiovascular or respiratory hospital admissions, the effect estimates for $PM_{2.5}$ total mass were higher in seasons and locations with a higher $PM_{2.5}$ content of Ni, V, or EC. Using a more limited dataset for PM_{10} and mortality, an association with $PM_{2.5}$ Ni content was observed. These findings may relate to the components themselves, or other components with which they covary because they have similar sources. This study cannot definitively determine the toxicity of $PM_{2.5}$ Ni or any other chemical component because multiple explanations exist for the findings. For example, Ni in $PM_{2.5}$ may be more harmful to human health than other chemical components, the levels of Ni may be acting as a surrogate for components or sets of components with similar sources, or Ni may exacerbate the effect of another pollutant or exposure on cardiovascular hospital admissions. The physiological mechanisms through which PM components affect health need further investigation. Earlier work has identified associations between Ni and heart-rate variability (Cavallari et al. 2008) and between V and oxidative DNA damage (Sørensen et al. 2005).

Scientific evidence on how individual chemical components or sources of PM affect human health is limited; however, several other studies have investigated this issue. A study of six California counties included analysis of the chemical components and sources of $PM_{2.5}$, including metals, crustal materials, carbon, and other combustion-related components (Ostro et al. 2007, 2008). Associations were observed between several components and the risk of mortality, and the associations differed by sex, race, and education level. Cardiovascular-related mortality was associated with combustion-related $PM_{2.5}$ ($SO_4^=$, EC) in a Phoenix, Arizona, study (Mar et al. 2000). Another study found an association between mortality and $SO_4^=$ and metals (Fe, Ni, Zn) in eight cities in Canada (Burnett et al. 2000), and a different study found an association between mortality and PM sources of combustion and traffic in six eastern U.S. cities (Laden et al. 2000). Mortality risk decreased in the southwestern region of the United States during a strike at copper smelters (Pope et al. 2007). The risk of cardiovascular hospital admissions was associated with $PM_{2.5}$ EC levels, whereas the risk of respiratory hospital admissions was associated with $PM_{2.5}$ OCM levels in a study of 119 U.S. counties from 2000 to 2006 (Peng et al. 2009). The levels of other $PM_{2.5}$ components studied by Peng et al. (2009) ($SO_4^=$, NO_3^-, Si, Na^+, and NH_4^+) were not associated with cardiovascular or respiratory admissions.

An earlier study compared 60 community-specific PM_{10} estimates for mortality from the NMMAPS (for 1987 through 2000) with levels of 16 $PM_{2.5}$ chemical components (aluminum, arsenic, chromium, copper, EC, Fe, lead, manganese, Ni, NO_3^-, OC, selenium, Si, $SO_4^=$, V, Zn) for 2000 through 2003 (Lippmann et al. 2006). The results indicated higher effect estimates in the communities with higher $PM_{2.5}$ Ni or V levels. A later study explored associations between PM_{10} risk estimates for mortality from the NMMAPS and levels of $PM_{2.5}$ components for 2000 through 2005 in 72 urban counties representing 69 U.S. communities. The results indicated that associations

between PM_{10} effect estimates for mortality and $PM_{2.5}$ Ni content were sensitive to the inclusion of the New York, New York, community (Dominici et al. 2007). The posterior probability for the parameter for the association between levels of $PM_{2.5}$ components and PM_{10} effect estimates for mortality was 0.99 for Ni and 1.0 for V; however, when the New York, New York, community was removed from the analysis, these values dropped to 0.76 for Ni and 0.89 for V. The authors note that the results do not preclude the hypothesis that $PM_{2.5}$ Ni or V is harmful to human health. Additional study of the characteristics of the New York, New York, particulate mixture, such as its relationship to the fuels used in the area, is warranted.

A study of 26 U.S. urban communities from 2000 through 2003 found that $PM_{2.5}$ effect estimates for cause-specific hospitalizations were modified by the chemical composition of the particles (Zanobetti et al. 2009). $PM_{2.5}$ effect estimates for cardiovascular hospital admissions were higher in communities with high contributions of bromine, chromium, Ni, and Na^+. For myocardial infarction, $PM_{2.5}$ total mass effect estimates were higher in communities with higher contributions of arsenic, chromium, manganese, OC, Ni, and Na^+. High contributions of arsenic, OC, and $SO_4^=$ to $PM_{2.5}$ were associated with higher $PM_{2.5}$ effect estimates for diabetes hospitalizations.

Using data on season- and community-specific health effects, this project found higher $PM_{2.5}$ effect estimates for cardiovascular and respiratory hospitalizations in locations and time periods with higher Ni, EC, or V content. An IQR range increase in the fraction of $PM_{2.5}$ that is represented by a given component was associated with an increase in lag-0 $PM_{2.5}$ effect estimates for cardiovascular hospital admissions: 26% (PI, 4.4–47) for EC, 19% (PI, 9.9–28) for Ni, and 28% (PI, 11–44) for V. For respiratory hospital admissions, effect estimates increased 511% (PI, 81–941) for EC, 223% (PI, 37–410) for Ni, and 392% (PI, 46–738) for V.

Between-community heterogeneity observed in PM health effect estimates may also be related to other factors that vary by location, such as population characteristics, the quality or availability of health care, baseline health status, or the presence of copollutants. County-level health effect estimates for PM total mass were not found to vary by county-level indicators of socioeconomic status, urbanicity, or racial composition; however, the county-level aggregation of data limited our ability to investigate such factors. In this study, counties with higher levels of central AC had lower $PM_{2.5}$ effect estimates for cardiovascular hospital admissions. Other research has also found an indication of lower air pollution effect estimates for higher AC levels (Janssen et al. 2002; Medina-Ramón et al. 2006; Franklin et al. 2007). Thus, while these findings indicate that the chemical composition of the particle mixture may relate to particle toxicity, other factors are also likely to be relevant.

This study highlights several research challenges for the investigation of the chemical composition of PM and health. As epidemiologic research moves from its historic focus on a single or small number of pollutants toward a whole-atmosphere approach to addressing complex mixtures, the number of exposure variables increases dramatically. In this study of the chemical composition of $PM_{2.5}$, we assessed over 50 components. Levels of these components (e.g., NH_4^+ and NO_3^-) can covary and thus have different potentials for exposure misclassification. In addition, several factors could contribute to differential exposure error by component: measurement error, detection limits in relation to ambient levels, and spatial heterogeneity of pollutant levels within a city (Flanagan et al. 2002; Pun et al. 2004; Schwab et al. 2006). The spatial misalignment issue, in which a single monitor or small number of monitors is used to assess community-level exposure, warrants further research because the spatial distribution of pollutant concentration levels may vary by component (Athanassiadis et al. 2003; Ito et al. 2004; Kim et al. 2005; Ivy et al. 2008). Further, although portions of this work involved aggregation of information by time (e.g., seasonal or long-term averages) and space (e.g., county-level averages), a separate analysis of temporal variation and spatial variation in $PM_{2.5}$ chemical components might provide additional insights into the relationship between particulate composition and toxicity. Additional research on factors other than chemical composition that affect $PM_{2.5}$ relative rates could include studies that involve individual-level information (e.g., socioeconomic status) and regional variation. Future work could also investigate alternative hypotheses for temporal variation in PM total mass health effect estimates and additional structures for our seasonal models. As the available data for the chemical components of $PM_{2.5}$ continue to grow, research will be better able to use the chemical components or sources of $PM_{2.5}$ directly to represent the exposure in epidemiologic models.

Current research efforts to improve exposure estimates include the use of modeled and measured personal exposure (e.g., Ebelt et al. 2005; Strand et al. 2007), land-use regression models (e.g., Clougherty et al. 2008), satellite imagery (e.g., Liu et al. 2007), and regional air quality modeling (e.g., Tian et al. 2009). Other approaches have been developed to investigate the sources of $PM_{2.5}$, such as factor analysis (e.g., Paatero et al. 2003; Lapina and Paterson 2004; Hopke et al. 2006) and air quality modeling and trajectory analysis (e.g., Park et al. 2007). Each approach has disadvantages and benefits. Most sources of PM produce multiple components, and most components arrive from multiple sources. For instance, EC is often used as a marker for traffic-related pollution, but also has other sources such as airborne soil and industry.

This work provides evidence that the chemical composition of particles affects toxicity, but shows that this alone does not explain the between-community variation in the health effects associated with PM total mass and that other factors, such as AC, also play a role. Understanding the relative toxicity of various sources and the characteristics of PM still warrants substantial future research. In particular, new scientific approaches are needed to disentangle the complex air pollution mixture, which includes varying types of particles and also the presence of copollutants (Dominici et al. 2010). Studies based on individual-level data for exposure and potential confounders or indicators of susceptibility (e.g., socioeconomic conditions) are also needed to advance the work described here, which is based on county- or community-level aggregated data. Results from toxicological studies can be used to help focus epidemiologic research on those characteristics of PM that are most likely contributing to underlying physiological mechanisms by which PM may exert its adverse effects.

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APPENDIX A. HEI Quality Assurance Statement

The conduct of this study was subjected to an independent audit by Dr. Richard Kwok (RTI International), an epidemiologist with experience in quality assurance for air quality monitoring studies. The audit included on-site reviews of study activities for conformance to the study protocol and standard operating procedures. The dates of the audit are listed below.

Written reports of the inspection were provided to the HEI Project Manager, who transmitted the findings to the Principal Investigator. The quality assurance audit found that the study was conducted by an experienced research team according to the study protocols. Interviews with study personnel revealed a consistently high concern for data quality. The report appears to be an accurate representation of the study.

Richard K. Kwok, Ph.D., Epidemiologist, Quality Assurance Oversight Auditor

QUALITY ASSURANCE AUDIT

July 27–29, 2009

The auditor conducted an on-site audit at Yale University to verify the integrity of the reported data. The audit reviewed the following aspects of the study: the final report; research and evaluation staffing; adequacy of equipment and facilities; internal quality assurance procedures; air quality exposure assessment methodology; and data processing procedures. Several data points for each parameter were traced through the entire data processing sequence to verify that the described procedures were being followed and to verify the integrity of the database. No errors were noted.

APPENDIX B. Abstracts of Other Publications Resulting from This Research

The following are abstracts of selected articles that either formed the basis for this work or report the findings of this research conducted by Michelle L. Bell and her colleagues under the Walter A. Rosenblith New Investigator Award.

SPATIAL AND TEMPORAL VARIATION IN $PM_{2.5}$ CHEMICAL COMPOSITION IN THE UNITED STATES FOR HEALTH EFFECTS STUDIES

(Michelle L. Bell, Francesca Dominici, Keita Ebisu, Scott L. Zeger, Jonathan M. Samet; reprinted from Bell et al. 2007)

Background

Although numerous studies have demonstrated links between particulate matter (PM) and adverse health effects, the chemical components of the PM mixture that cause injury are unknown.

Objectives

This work characterizes spatial and temporal variability of $PM_{2.5}$ (PM with aerodynamic diameter < 2.5 μm) components in the United States; our objective is to identify components for assessment in epidemiologic studies.

Methods

We constructed a database of 52 $PM_{2.5}$ component concentrations for 187 U.S. counties for 2000–2005. First, we describe the challenges inherent to analysis of a national $PM_{2.5}$ chemical composition database. Second, we identify components that contribute substantially to and/or covary with $PM_{2.5}$ total mass. Third, we characterize the seasonal and regional variability of targeted components.

Results

Strong seasonal and geographic variations in $PM_{2.5}$ chemical composition are identified. Only seven of the 52 components contributed ≥ 1% to total mass for yearly or seasonal averages: ammonium (NH_4^+), elemental carbon (EC), organic carbon matter (OCM), nitrate (NO_3^-), silicon, sodium (Na^+), and sulfate ($SO_4^=$). Strongest correlations with $PM_{2.5}$ total mass were with NH_4^+ (yearly), OCM (especially winter), NO_3^- (winter), and $SO_4^=$ (yearly, spring, autumn, and summer), with particularly strong correlations for NH_4^+ and $SO_4^=$ in summer. Components that co-varied with $PM_{2.5}$ total mass, based on daily detrended data, were NH_4^+, $SO_4^=$, OCM, NO_3^-, bromine, and EC.

Conclusions

The subset of identified $PM_{2.5}$ components should be investigated further to determine whether their daily variation is associated with daily variation of health indicators, and whether their seasonal and regional patterns can explain the seasonal and regional heterogeneity in PM_{10} (PM with aerodynamic diameter < 10 μm) and $PM_{2.5}$ health risks.

DOES THE EFFECT OF PM_{10} ON MORTALITY DEPEND ON PM NICKEL AND VANADIUM CONTENT? A REANALYSIS OF THE NMMAPS DATA

(Francesca Dominici, Roger D. Peng, Keita Ebisu, Scott L. Zeger, Jonathan M. Samet, and Michelle L. Bell; reprinted from Dominici et al. 2007)

Background

Lack of knowledge regarding particulate matter (PM) characteristics associated with toxicity is a crucial research gap. Short-term effects of PM can vary by location, possibly reflecting regional differences in mixtures. A report by Lippmann et al. [Lippmann et al., Environ Health Perspect 114:1662–1669 (2006)] analyzed mortality effect estimates from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) for 1987–1994. They found that average concentrations of nickel or vanadium in $PM_{2.5}$ (PM with aerodynamic diameter < 2.5 μm) positively modified the lag-1 day association between PM_{10} and all-cause mortality.

Objective

We reestimated the relationship between county-specific lag-1 PM_{10} effects on mortality and county-specific average concentrations of nickel or vanadium $PM_{2.5}$ using 1987 through 2000 effect estimates. We explored whether such modification is sensitive to outliers.

Methods

We estimated long-term average county-level nickel and vanadium $PM_{2.5}$ concentrations for 2000–2005 for 72 U.S. counties representing 69 communities. We fitted Bayesian hierarchical regression models to investigate whether county-specific short-term effects of PM_{10} on mortality are modified by long-term county-specific nickel or vanadium $PM_{2.5}$ concentrations. We conducted sensitivity analyses by excluding individual communities and considering log-transformed data.

Results

Our results were consistent with those of Lippmann et al. However, we found that when counties included in the NMMAPS New York community were excluded from the sensitivity analysis, the evidence of effect modification of nickel or vanadium on the short-term effects of PM_{10} on mortality was much weaker and no longer statistically significant.

Conclusions

Our analysis does not contradict the hypothesis that nickel or vanadium may increase the risk of PM to human health, but it highlights the sensitivity of findings to particularly influential observations.

FINE PARTICULATE AIR POLLUTION AND HOSPITAL ADMISSION FOR CARDIOVASCULAR AND RESPIRATORY DISEASES

(Francesca Dominici, Roger D. Peng, Michelle L. Bell, Luu Pham, Aidan McDermott, Scott L. Zeger, Jonathan M. Samet; reprinted from Dominici et al. 2006)

Context

Evidence on the health risks associated with short-term exposure to fine particles (particulate matter ≤ 2.5 μm in aerodynamic diameter [$PM_{2.5}$]) is limited. Results from the new national monitoring network for $PM_{2.5}$ make possible systematic research on health risks at national and regional scales.

Objectives

To estimate risks of cardiovascular and respiratory hospital admissions associated with short-term exposure to $PM_{2.5}$ for Medicare enrollees and to explore heterogeneity of the variation of risks across regions.

Design, Setting, and Participants

A national database comprising daily time-series data daily for 1999 through 2002 on hospital admission rates (constructed from the Medicare National Claims History Files) for cardiovascular and respiratory outcomes and injuries, ambient $PM_{2.5}$ levels, and temperature and dewpoint temperature for 204 U.S. urban counties (population > 200,000) with 11.5 million Medicare enrollees (aged > 65 years) living an average of 5.9 miles from a $PM_{2.5}$ monitor.

Main Outcome Measures

Daily counts of county-wide hospital admissions for primary diagnosis of cerebrovascular, peripheral, and ischemic heart diseases, heart rhythm, heart failure, chronic obstructive pulmonary disease, and respiratory infection, and injuries as a control outcome.

Results

There was a short-term increase in hospital admission rates associated with $PM_{2.5}$ for all of the health outcomes except injuries. The largest association was for heart failure, which had a 1.28% (95% confidence interval, 0.78%–1.78%) increase in risk per 10-μg/m^3 increase in same-day $PM_{2.5}$. Cardiovascular risks tended to be higher in counties located in the Eastern region of the United States, which included the Northeast, the Southeast, the Midwest, and the South.

Conclusion

Short-term exposure to $PM_{2.5}$ increases the risk for hospital admission for cardiovascular and respiratory diseases.

SEASONAL AND REGIONAL SHORT-TERM EFFECTS OF FINE PARTICLES ON HOSPITAL ADMISSIONS IN 202 U.S. COUNTIES, 1999-2005

(Michelle L. Bell, Keita Ebisu, Roger D. Peng, Jemma Walker, Jonathan M. Samet, Scott L. Zeger; reprinted from Bell et al. 2008)

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 U.S. 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 epidemiological studies on potential heterogeneity in the toxicity of constituents of the particulate matter mixture.

COARSE PARTICULATE MATTER AIR POLLUTION AND HOSPITAL ADMISSIONS FOR CARDIOVASCULAR AND RESPIRATORY DISEASES AMONG MEDICARE PATIENTS

(Roger D. Peng, Howard H. Chang, Michelle L. Bell, Aidan McDermott, Scott L. Zeger, Jonathan M. Samet, Francesca Dominici; reprinted from Peng et al. 2008)

Context

Health risks of fine particulate matter of 2.5 μm or less in aerodynamic diameter ($PM_{2.5}$) have been studied extensively over the last decade. Evidence concerning the health risks of the coarse fraction of greater than 2.5 μm and 10 μm or less in aerodynamic diameter ($PM_{10-2.5}$) is limited.

Objective

To estimate risk of hospital admissions for cardiovascular and respiratory diseases associated with $PM_{10-2.5}$ exposure, controlling for $PM_{2.5}$.

Design, Setting, and Participants

Using a database assembled for 108 U.S. counties with daily cardiovascular and respiratory disease admission rates, temperature and dew-point temperature, and $PM_{10-2.5}$ and $PM_{2.5}$ concentrations were calculated with monitoring data as an exposure surrogate from January 1, 1999, through December 31, 2005. Admission rates were constructed from the Medicare National Claims History Files, for a study population of approximately 12 million Medicare enrollees living on average 9 miles (14.4 km) from collocated pairs of PM_{10} and $PM_{2.5}$ monitors.

Main Outcome Measures

Daily counts of county-wide emergency hospital admissions for primary diagnoses of cardiovascular or respiratory disease.

Results

There were 3.7 million cardiovascular disease and 1.4 million respiratory disease admissions. A 10-μg/m^3 increase in $PM_{10-2.5}$ was associated with a 0.36% (95% posterior interval [PI], 0.05% to 0.68%) increase in cardiovascular disease admissions on the same day. However, when adjusted for $PM_{2.5}$, the association was no longer statistically significant (0.25%; 95% PI, –0.11% to 0.60%). A 10-μg/m^3 increase in $PM_{10-2.5}$ was associated with a nonstatistically significant unadjusted 0.33% (95% PI, –0.21% to 0.86%) increase in respiratory disease admissions and with a 0.26% (95% PI, –0.32% to 0.84%) increase in respiratory disease admissions when adjusted for

$PM_{2.5}$. The unadjusted associations of $PM_{2.5}$ with cardiovascular and respiratory disease admissions were 0.71% (95% PI, 0.45%-0.96%) for same-day exposure and 0.44% (95% PI, 0.06% to 0.82%) for exposure 2 days before hospital admission.

Conclusion

After adjustment for $PM_{2.5}$, there were no statistically significant associations between coarse particulates and hospital admissions for cardiovascular and respiratory diseases.

HOSPITAL ADMISSIONS AND CHEMICAL COMPOSITION OF FINE PARTICLE AIR POLLUTION

(Michelle L. Bell, Keita Ebisu, Roger D. Peng, Samet JM Francesca Dominici; reprinted from Bell et al. 2009b)

Rationale

There are unexplained geographical and seasonal differences in the short-term effects of fine particulate matter ($PM_{2.5}$) on human health. The hypothesis has been advanced to include the possibility that such differences might be due to variations in the $PM_{2.5}$ chemical composition, but evidence supporting this hypothesis is lacking.

Objectives

To examine whether variation in the relative risks (RR) of hospitalization associated with ambient exposure to $PM_{2.5}$ total mass reflects differences in $PM_{2.5}$ chemical composition.

Methods

We linked two national datasets by county and by season: (1) long-term average concentrations of $PM_{2.5}$ chemical components for 2000–2005 and (2) RRs of cardiovascular and respiratory hospitalizations for persons 65 years or older associated with a 10-$\mu g/m^3$ increase in $PM_{2.5}$ total mass on the same day for 106 U.S. counties for 1999 through 2005.

Measurements and Main Results

We found a positive and statistically significant association between county-specific estimates of the short-term effects of $PM_{2.5}$ on cardiovascular and respiratory hospitalizations and county-specific levels of vanadium, elemental carbon, or nickel $PM_{2.5}$ content.

Conclusions

Communities with higher $PM_{2.5}$ content of nickel, vanadium, and elemental carbon and/or their related sources were found to have higher risk of hospitalizations associated with short-term exposure to $PM_{2.5}$.

ADVERSE HEALTH EFFECTS OF PARTICULATE AIR POLLUTION: MODIFICATION BY AIR CONDITIONING

(Michelle L. Bell, Keita Ebisu, Roger D. Peng, Francesca Dominici; reprinted from Bell et al. 2009a)

Background

The short-term effects of particulate matter (PM) on mortality and morbidity differ by geographic location and season. Several hypotheses have been proposed for this variation, including different exposures with air conditioning (AC) versus open windows.

Methods

Bayesian hierarchical modeling was used to explore whether AC prevalence modified day-to-day associations between PM_{10} and mortality, and between $PM_{2.5}$ and cardiovascular or respiratory hospitalizations for those 65 years and older. We considered yearly, summer-only, and winter-only effect estimates (and two types of AC [central and window units]).

Results

Communities with higher AC prevalence had lower PM effects. Associations were observed for cardiovascular hospitalizations and central AC. Each additional 20% of households with central AC was associated with a 43% decrease in $PM_{2.5}$ effects on cardiovascular hospitalization. Central AC prevalence explained 17% of between-community variability in $PM_{2.5}$ effect estimates for cardiovascular hospitalizations.

Conclusions

Higher AC prevalence was associated with lower health effect estimates for PM.

EMERGENCY ADMISSIONS FOR CARDIOVASCULAR AND RESPIRATORY DISEASE AND THE CHEMICAL COMPOSITION OF FINE PARTICLE AIR POLLUTION

(Roger D. Peng, Michelle L. Bell, Alison S. Geyh, Aidan McDermott, Scott L. Zeger, Jonathan M. Samet; reprinted from Peng et al. 2009)

Background

Population-based studies have estimated health risks of short-term exposure to fine particles using mass of $PM_{2.5}$ as the indicator. Evidence regarding the toxicity of the chemical components of the $PM_{2.5}$ mixture is limited.

Objective

To investigate the association between hospital admission for cardiovascular and respiratory diseases and the chemical components of fine particles in the United States.

Methods

We used a national database comprising daily data for 2000–2006 on hospital admissions for cardiovascular and respiratory outcomes, ambient levels of major $PM_{2.5}$ chemical components (sulfate, nitrate, silicon, elemental carbon, organic carbon matter, sodium and ammonium ions), and weather. We estimated the associations between daily levels of $PM_{2.5}$ components and risk of hospital admissions in 119 U.S. urban communities for 12 million Medicare enrollees (aged 65 years or older) using Bayesian hierarchical statistical models.

Results

In multiple-pollutant models where associations are adjusted for the levels of other pollutants, an interquartile range (IQR) increase in elemental carbon was associated with a 0.80 (95% posterior interval [PI]: 0.34, 1.27) percent increase in risk of same-day cardiovascular admissions, and an IQR increase in organic carbon matter was associated with a 1.01 (95% PI: 0.04, 1.98) percent increase in risk of respiratory admissions on the same day. Other components were not associated with cardiovascular or respiratory hospital admissions in multiple-pollutant models.

Conclusions

Ambient levels of elemental carbon and organic carbon matter, which are generated primarily from vehicle emissions, diesel, and wood burning, were associated with the largest risks of emergency hospitalization across the major chemical constituents of fine particles.

APPENDIX AVAILABLE ON THE WEB

Appendix C contains supplemental material not included in the printed report. It is available on the HEI Web site (*http://pubs.healtheffects.org*).

Appendix C. United States Maps of Average Levels of $PM_{2.5}$ Components by County and Season

ABOUT THE AUTHOR

Michelle L. Bell received her Ph.D. in environmental engineering from the Johns Hopkins University in 2002. She is an associate professor of environmental health at the Yale School of Forestry and Environmental Studies, with joint appointments at the Yale School of Public Health, Environmental Health Sciences Division, and the Yale School of Engineering and Applied Science, Environmental Engineering Program. Her research spans epidemiology, biostatistics, and engineering, and her interests include the impact of air pollution and weather on health, the potential health consequences of climate change, exposure assessment, and related policy implications.

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ABBREVIATIONS AND OTHER TERMS

AC	air conditioning
APHEA	Air Pollution and Health: A European Approach
AQS	Air Quality System
ARIES	Aerosol Research and Inhalation Epidemiology Study
EC	elemental carbon
ICD-9	International Classification of Diseases, Ninth Revision
IQR	interquartile range
MDL	minimum detection limit (also method detection limit)
Na^+	sodium ion
NH_4^+	ammonium
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NPACT	National Particle Component Toxicity
NO_3^-	nitrate
NRC	National Research Council
OC	organic carbon
OCM	organic carbon matter
OCM2	alternate measure of OCM
PI	posterior interval
PM	particulate matter
$PM_{0.1}$	PM with an aerodynamic diameter $\leq$ 0.1 µm
$PM_{2.5}$	PM with an aerodynamic diameter $\leq$ 2.5 µm
PM_{10}	PM with an aerodynamic diameter $\leq$ 10 µm
$PM_{10-2.5}$	coarse fraction of PM between 2.5 µm and 10 µm or less in aerodynamic diameter
RR	relative risks
Si	silicon
$SO_4^=$	sulfate
TSP	total suspended particles
U.S. EPA	U.S. Environmental Protection Agency

ELEMENTS

Al	aluminum
Sb	antimony
As	arsenic
Ba	barium
Br	bromine
Cd	cadmium
Ca	calcium
Ce	cerium
Cs	cesium
Cl	chlorine
Cr	chromium
Co	cobalt
Cu	copper
Eu	europium
Ga	gallium
Au	gold
Hf	hafnium
In	indium
Ir	iridium
Fe	iron
La	lanthanum
Pb	lead
Mg	magnesium
Mn	manganese
Hg	mercury
Mo	molybdenum
Ni	nickel
Nb	niobium
P	phosphorus
K	potassium
Rb	rubidium
Sm	samarium
Sc	scandium
Se	selenium
Si	silicon
Ag	silver
Sr	strontium
Ta	tantalum
Tb	terbium
Sn	tin
Ti	titanium
W	tungsten
V	vanadium
Y	yttrium
Zn	zinc
Zr	zirconium

COMMENTARY
Health Review Committee

HEI

Research Report 161, *Assessment of the Health Impacts of Particulate Matter Characteristics,* M.L. Bell

INTRODUCTION

Over the past several decades, epidemiologic studies in diverse locations across the United States and the world have reported associations between daily increases in low levels of particulate matter (PM*) mass and daily increases in morbidity and mortality (Anderson et al. 1997; Katsouyanni et al. 1997; Samet et al. 2000a,b; Aga et al. 2003; HEI 2003; Pope and Dockery 2006; Katsouyanni et al. 2009). On the basis of these and other findings, many governmental agencies have set regulatory standards or guidelines for the concentrations of ambient particles that are of most concern because they can be inhaled deep into the human lung. In the United States, the U.S. Environmental Protection Agency (U.S. EPA) has established National Ambient Air Quality Standards for PM ≤ 10 µm in aerodynamic diameter (PM_{10}) and for PM ≤ 2.5 µm in aerodynamic diameter ($PM_{2.5}$, or fine particles). The standard for each size fraction is based on the concentration of PM mass in ambient air. Despite this regulatory focus on PM mass, scientists have hypothesized that the composition of ambient PM could also be important. Ambient PM has long been known to be a complex mixture of solid and liquid airborne particles whose size, chemical composition, and other physical and biological properties vary with location and time. This variability in PM characteristics could derive from a number of factors, including differences in local sources. Understanding the role that particular PM components might play in the health effects observed in humans therefore could be important in identifying which sources of PM could be most effectively targeted to improve air quality and health.

However, until recently, the necessary large-scale epidemiologic studies of associations between PM composition and health effects have not been possible. Data on particle composition had not been collected systematically across the country until 1999 when the U.S. EPA began monitoring $PM_{2.5}$ components in the newly created national Speciation Trends Network (now known as the Chemical Speciation Network).

Michelle Bell of Yale University submitted an application to HEI in 2004 under Request for Applications 04-2, the Walter A. Rosenblith New Investigator Award. This award was established to provide support for an outstanding new investigator at the assistant professor level to conduct work in the area of air pollution and health and is unrestricted with respect to the topic of research. In her application, "Assessment of the mortality effects of PM characteristics," Bell sought to take advantage of the data on the composition of $PM_{2.5}$. She proposed to evaluate the effects of short-term exposures to various components of the $PM_{2.5}$ mixture on short-term mortality, building on methods established by the National Morbidity, Mortality, and Air Pollution Study (NMMAPS; Samet et al. 2000a,b) and related research. The HEI Health Research Committee thought that the proposal addressed an important and timely topic and recommended it for funding.

This Commentary is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigator's Report into scientific and regulatory perspective.

SCIENTIFIC BACKGROUND

In 1997, the U.S. EPA issued new National Ambient Air Quality Standards for $PM_{2.5}$ on the basis of epidemiologic evidence that particles in this smaller size fraction were associated with adverse human health effects. Almost immediately, however, the U.S. Congress directed that the U.S. EPA undertake a major research program to answer key scientific questions, relevant to regulatory decisions, about the basis for the toxicity of PM. In 1998, the National Research Council (NRC) was asked to establish the Committee on Research Priorities for Airborne Particulate Matter whose role would be to (1) provide a conceptual plan, including identification of critical research needs, for

Dr. Bell's 3-year study, "Assessment of the Mortality Effects of Particulate Matter Characteristics," began in February 2005. Total expenditures were $281,550. The draft Investigator's Report from Bell was received for review in May 2009. A revised report, received in May 2010, was accepted for publication in June 2010. During the review process, the HEI Health Review Committee and the investigator had the opportunity to exchange comments and to clarify issues in both the Investigator's Report and the Review Committee's Commentary.

* A list of abbreviations and other terms appears at the end of the Investigator's Report.

integrated PM research and (2) evaluate progress toward achieving the plan over the next five years. One of the 10 critical research needs that the Committee identified was to "assess through toxicological and epidemiological studies the most important physical and chemical characteristics and constituents of PM that produce adverse health effects" (NRC 1998).

While the NRC Committee envisioned multifaceted research that would examine a broad range of PM characteristics and constituents, it recognized the challenges of taking them all into account. These challenges included the complexity of the hypotheses to be tested; the need for longer-term and more-comprehensive air quality monitoring data; the existence of high correlations between many of the characteristics and components of PM; and the need for statistical and other analytical methods up to the task of disentangling these issues.

Reviews conducted by HEI (2002) and by the NRC (2001, 2004) found that progress had been made in understanding the role that PM characteristics might play in explaining health effects but that it had been uneven among technical disciplines. Toxicologic evidence from animal and in vitro studies was predominant, with a strong focus on metals and a growing emphasis on the ultrafine fraction of PM. Some components (e.g., biological components and organic compounds) had received less research attention than others (NRC 2004).

Progress in epidemiologic research on particulate components had been slowed by the lack of monitoring data for components at a national scale. Numerous studies have been done on smaller local scales that suggest a role for certain types of particles. For example, Pope and colleagues (1992, 2007) studied variations in the health of Utah Valley residents associated with the yearlong closure of a local steel smelter that was a dominant source of PM_{10}. In 1998, the Electrical Power Research Institute, with multiple collaborators, initiated a project — the Aerosol Research and Inhalation Epidemiology Study (ARIES) — to investigate the relationships between components of $PM_{2.5}$ and PM_{10}, among other characteristics and daily mortality and hospitalizations in individual cities around the United States (Klemm and Mason 2000; Klemm et al. 2004) (e.g., Metzger et al. 2004, Peel et al. 2005). The project began in Atlanta, Georgia, and subsequent studies are now underway for Pittsburgh, Dallas, Birmingham, and St. Louis, to achieve broader geographical representation (ARIES 2010). However, these and other local studies cannot provide sufficient data to explore the variations in PM composition that have been observed regionally and seasonally across the United States.

Not until the U.S. EPA created the Speciation Trends Network in 2000 to monitor the chemical composition of $PM_{2.5}$ more widely did some of the necessary data begin to be collected. Over the next five years, the network was gradually expanded to include over 225 $PM_{2.5}$ speciation monitoring sites across the continental United States and Puerto Rico (Flanagan et al. 2006). Additional speciation data has subsequently become available from other networks, including the Interagency Monitoring to Protect Visual Environments (IMPROVE) network (Lippmann, 2009).

In its 2004 assessment of the research progress on PM components, the NRC concluded:

> The matrix of relationships between particle composition and possible health responses has been only partially explored. Researchers have focused on PM collected from specific emissions sources or on PM components of their particular interest, or they have focused on popular hypotheses or suggestive experimental evidence. A more systematic approach will be required to ensure that research encompasses a broader range of potentially important PM characteristics and yields data that can be used to establish the relative toxicity of different components (NRC 2004).

Bell's proposal to explore the accumulated data on $PM_{2.5}$ mass and its components offered such a systematic approach. Portions of her research build upon the NMMAPS analytical framework for time series of PM total mass. The NMMAPS study was a major epidemiologic study that used time-series methods to examine the relationship between short-term (e.g., daily) exposures to PM_{10} and daily rates of mortality and morbidity across 90 U.S. cities (Samet et al. 2000a,b). The study had originally been designed to address several earlier criticisms about the sensitivity of time-series results to various methodological choices (HEI 2003). Although the NMMAPS study largely clarified the impact of these methodological differences, particularly for studies of PM_{10}, substantive questions still persisted about the remaining differences observed in mortality and morbidity effect estimates across seasons and regions of the United States. Building on the methodologies developed under NMMAPS and related projects, Bell set out to address whether some of these differences in patterns of health effects might be explained by regional differences in PM components, seasonal weather patterns, and demographic factors. Her study was the first in a series of systematic studies funded by HEI to explore the roles of PM components and copollutants under the National Particle Component Toxicity (NPACT) program.

STUDY SUMMARY

STUDY OBJECTIVES

Bell's overall objective in her study was to "investigate the relationship between the chemical components of PM and human health, using national databases of pollution, weather, and health outcomes." Her specific aims were to

1. Investigate how the chemical composition of $PM_{2.5}$ varies spatially and temporally in the United States.
2. Determine whether the associations between short-term exposure to $PM_{2.5}$ and hospital admissions follow spatial and temporal patterns.
3. Evaluate whether observed spatial and temporal variation in the PM total mass effect estimates for morbidity (hospital admissions) and mortality can be partially explained by spatial and temporal heterogeneity in the chemical composition of $PM_{2.5}$.

Bell had originally planned to focus her study on the effect of $PM_{2.5}$ components on mortality effect estimates, building on mortality data from the NMMAPS database for the period of 1987 through 2002. That database accounts for approximately 40% of the U.S. population, but Bell planned to gather data for more recent years and additional locations. However, as investigators can no longer obtain mortality data for all states from a central repository, the National Center for Health Statistics, but must gain permission from individual states, extension of the mortality study was not feasible. Bell instead focused her study on the influence of $PM_{2.5}$ components on associations between $PM_{2.5}$ and hospital admissions. She included an ancillary study on the influence of $PM_{2.5}$ components on previously estimated associations between PM_{10} exposure and mortality from another study (Peng et al. 2005).

METHODS

Bell's study was conducted in stages consistent with her specific aims outlined above. Commentary Table 1 provides an overview by specific aim of the different datasets used and analyses conducted; it also identifies publications stemming from this research in which some supplementary analyses are presented.

Sources and Compilation of Data

$PM_{2.5}$ Total Mass and Components For 187 counties in the continental United States, Bell obtained data on $PM_{2.5}$ total mass and 52 $PM_{2.5}$ chemical components (see Figure 1 of the Investigator's Report) from the U.S. EPA Air Quality System (AQS) Data Mart, for 2000 through 2005 (U.S. EPA 2006).

Her estimates of $PM_{2.5}$ total mass exposure were based on county-level U.S. EPA monitoring conducted once every 3 days. $PM_{2.5}$ components were measured on average once every 6 days (the range was from 1 in 3.1 days to 1 in 11.9 days). In keeping with reporting in the AQS database, component concentrations were not corrected for minimum detection limits (MDL). The investigator eliminated from her database any data flagged as suspect by the U.S. EPA. Not all counties had data for $PM_{2.5}$ and for all components for the full period of the study.

Bell compared the standard U.S. EPA method for calculating organic carbon matter (OCM) with an alternative approach (OCM2), using monitor-specific OC field blanks to limit the introduction of spatial or temporal differences in OCM that were actually artifacts of the method used for correcting for field blanks and that could affect associations with health outcomes. This analysis was prompted by evidence that there had been substantial downward trends in OC field blank levels since 2002, trends that differed by type of sampler (Frank 2006).

Hospital Admissions Bell collected data on daily hospital admissions for cardiovascular- and respiratory-related illnesses for Medicare enrollees aged 65 years or older. The data, for the period 1999 through 2005, was from 202 counties representing largely urban areas. Cardiovascular- and respiratory-related admissions were categorized according to the International Classification of Diseases, Ninth Revision (ICD-9) codes and were selected to be consistent with previous studies by Bell and her colleagues (Dominici et al. 2006; Peng et al. 2008).

PM_{10} and Mortality Data Given the difficulties in accessing new mortality data with which to calculate estimates of the associations between recent $PM_{2.5}$ exposures and mortality to use in her study, Bell had to rely on PM_{10} mortality effect estimates previously developed by Roger Peng and colleagues (2005). These effect estimates were based on PM_{10} and mortality data available in the NMMAPS database for 100 U.S. cities for the period 1987 through 2000. Bell notes that in addition to a different PM size fraction and time frame covered, relative to $PM_{2.5}$, the estimates are based on "community"-level aggregation of data that can consist of a single county in some cases and, in others, by a set of adjacent counties.

Weather and Demographic Data Bell acquired county-level weather data for temperature and dew point temperature from the National Climatic Data Center. She obtained

Commentary Table 1. Overview of Bell Analyses

Specific Aim	Counties and Communities	Data: PM Size Fraction and Components (Time Period)	Data: Health Outcomes (Time Period)	Statistical Methods	Related Publications
1. Spatial and temporal variation in $PM_{2.5}$ chemical composition	187 continental U.S. counties Regional analysis: (number of counties) East: 155; West: 32	$PM_{2.5}$ 52 components (2000–2005)	None	National and regional averages of county- and season-specific daily $PM_{2.5}$ data Correlations between components, with and without seasonally detrended data	Bell et al. 2007
2. Seasonal and regional short-term effects of $PM_{2.5}$ on hospital admissions	202 continental U.S. counties with ≥ 200,000 population Regional analysis (number of counties) Northeast: 108; Southeast: 58; Northwest: 9; Southwest: 25	$PM_{2.5}$ (2000–2005)	Cardiovascular and respiratory admissions for Medicare enrollees ≥ 65 yr (1999–2005)	2-stage Bayesian hierarchical methods: • Main model • Seasonal model • Harmonic model Lag 0, 1, 2 days	Bell et al. 2008
3. Effect of $PM_{2.5}$ composition on $PM_{2.5}$ effect estimates for hospital admissions	106 continental U.S. counties Regional analysis: none	$PM_{2.5}$ components that covary with or are present at ≥ 1% of $PM_{2.5}$ mass ($SO_4^=$, NO_3^-, Si, EC, OCM, Na^+, and NH_4^+)[a] or that have been identified as toxic (Ni, V)[b] in other studies (2000–2005)	Cardiovascular and respiratory admissions for Medicare enrollees ≥ 65 yr (1999–2005)	2-stage Bayesian hierarchical methods: • Main model • Seasonal model $PM_{2.5}$ components included in second stage: • Single-pollutant models • Multiple-pollutant models (EC, Ni, V)	Bell et al. 2009b
				Additional analyses: Sensitivity of annual effect estimates to community-level variables (main model) Sensitivity of the effects of $PM_{2.5}$ EC, Ni, and V on $PM_{2.5}$ effect estimates for hospitalization to the exclusion of individual counties	Bell et al. 2009b (online supplement)
	168 U.S. counties	$PM_{2.5}$ only		Variation in annual, summer, and winter $PM_{2.5}$ effect estimates for hospital admission with prevalence of air conditioning	Bell et al. 2009a
Effect of $PM_{2.5}$ composition on PM_{10} effect estimates for nonaccidental mortality	100 U.S. communities	PM_{10} (1987–2000)	Nonaccidental mortality (1987–2000)	2-stage Bayesian hierarchical methods: • Main model (sensitivity analysis) • Seasonal model	Peng et al. 2005, for PM_{10} analyses only
	64 U.S. communities (for which both PM_{10} mortality and component data are available) Regional analysis: none	$PM_{2.5}$ components that covary with or are present at ≥ 1% of $PM_{2.5}$ ($SO_4^=$, NO_3^-, Si, EC, OCM, Na^+, and NH_4^+)[a] or that have been identified as toxic (Ni, V)[b] in other studies (1999–2005)		Single $PM_{2.5}$ components included in the second stage	(For this report only)
				Additional analyses: Sensitivity analysis of the relationship between annual PM_{10} effect estimates for mortality and $PM_{2.5}$ Ni content to the exclusion of individual communities	Bell et al. 2009b (online supplement)
	84 U.S. communities			Variation in annual, summer, and winter PM_{10} effect estimates for mortality with prevalence of air conditioning	Bell et al. 2009a

[a] Sulfate, nitrate, silicon, elemental carbon, organic carbon matter, sodium, and ammonium.

[b] Nickel and vanadium.

demographic data on measures of socioeconomic status, racial composition, and degree of urbanization from the 1990 and 2000 U.S. censuses. Values for air conditioning prevalence were based on U.S. Census data from the American Housing Survey (data were only available for a limited number of communities during select years).

Statistical Analyses

Spatial and Temporal Variation in the Chemical Composition of $PM_{2.5}$ (Specific Aim 1) Bell first calculated summary statistics describing the concentrations of all 52 $PM_{2.5}$ components on an annual and seasonal basis across all 187 counties. (Seasons were defined as summer [June through August], autumn [September through November], winter [December through February], and spring [March through May]). She then focused additional analyses on a subset of the components representing (1) ≥ 1% of $PM_{2.5}$ total mass for the annual average or for any one of the seasonal averages across all 187 counties and/or (2) ≥ 1% of $PM_{2.5}$ total mass in any county on an annual or seasonal basis. These components included ammonium (NH_4^+), elemental carbon (EC), OCM, nitrate (NO_3^-), silicon (Si), sodium ion (Na^+), and sulfate ($SO_4^=$). The underlying assumptions for this approach were that the contribution of $PM_{2.5}$ components to the health effects associated with exposures to PM total mass may be more likely to be those that covary with and/or make up a substantial portion of PM total mass, or that such components would be reasonable starting points for analysis. These seven components collectively made up more than 80% of annual average $PM_{2.5}$ total mass.

Bell explored broad spatial patterns in the distribution across the continental United States of the seven $PM_{2.5}$ components listed above. She calculated Pearson's correlations between concentrations of individual $PM_{2.5}$ components and between $PM_{2.5}$ total mass and component concentrations, both by year and by season. These correlations were estimated with and without seasonally detrended values.

Spatial and Temporal Patterns in Associations Between Short-Term $PM_{2.5}$ Exposure and Hospital Admissions (Specific Aim 2) To analyze variations in the associations between exposures to $PM_{2.5}$ total mass and hospital admissions across regions and seasons, Bell used a two-stage Bayesian hierarchical modeling approach that built on a progression of statistical methods first developed to analyze PM_{10} and mortality data (Samet et al. 2000a,b; Dominici et al. 2003; Peng et al. 2005) and later extended to the analysis of $PM_{2.5}$ and hospitalizations, by Dominici and colleagues (2006). In specific terms, these associations are reported as the county-specific percentage changes in the rates of mortality or hospitalizations per 10 μg/m^3 increase in PM but are more generally referred to as effect estimates.

First Stage Bell's analysis of the associations between short-term $PM_{2.5}$ concentrations and hospitalizations used three different statistical models, each representing different assumptions about the relationship between PM concentrations and hospitalization rates (Peng et al. 2005):

- Main model: The relationship is assumed to be constant throughout the year (Investigator's Report, equation 3).
- Seasonal model: The relationship is allowed to vary by season but is required to be constant within each season; the seasons are defined as four discrete 3-month periods (Investigator's Report, equation 4).
- Harmonic model: The relationship is allowed to vary continuously throughout the year (Investigator's Report, equation 5).

The main model follows an approach used in NMMAPS, in which a regression model is used to predict the natural log of the daily rate of hospitalizations (from cardiovascular or respiratory disease) in a particular county as a function of $PM_{2.5}$ concentrations on the same day (lag 0), on the previous day (lag 1), or two days before (lag 2) (Dominici et al. 2006). The use of distributed lag models, which estimate the cumulative effects of exposure over several days and which have been important for evaluation of exposures to PM total mass, was not possible given the intermittent nature of much of the $PM_{2.5}$ monitoring (i.e., occurring only every third day). The model also includes an indicator to account for the day of the week, smooth functions (natural cubic splines) of same day and previous days' temperatures and dew points to account for the possible role of weather, use of natural cubic splines of time to account for possible temporal trends, and use of interaction terms to evaluate possible differences in temporal trends in the lifetimes of individuals of different ages. The numbers of degrees of freedom (*df*) chosen for these controls (six for temperature, three for dew point, eight for time, and one for time in the interaction term) were informed by extensive sensitivity analyses of the association between PM_{10} and mortality in previous studies (Welty et al. 2005; Peng et al. 2006; Touloumi et al. 2006; Katsouyanni et al. 2009).

The seasonal model has essentially the same structure as the main model. It includes similar controls for weather and time, but uses indicator variables with the air pollution terms, to allow the effect estimates to be calculated

separately for the 3-month periods representing spring, summer, fall, and winter.

The harmonic model essentially allows the $PM_{2.5}$ and hospitalization association to vary smoothly and continuously throughout the year. All other variables in the model are the same as in the main model; however, the model was applied using the exposure day (lag) that produced the largest effect estimate in the first two models.

Second Stage In the second stage, Bell used a Bayesian hierarchical modeling approach to combine the county-specific health effect estimates into overall estimates for a given time period or region. Each overall effect estimate and statistical error is a weighted combination of the individual county-specific estimates, with greater weight given to county-specific estimates with less statistical error (i.e., with greater statistical certainty).

Using the main and seasonal models, Bell developed overall effect estimates for the continental United States (national) and for each of four regions (Northeast, Southeast, Southwest, and Northwest). She used the harmonic model to characterize temporal variations across the year in the four regions only.

Analysis of Spatial and Temporal Variation in $PM_{2.5}$ Total Mass Health Effect Estimates and Spatial and Temporal Heterogeneity in $PM_{2.5}$ Chemical Composition (Specific Aim 3) For this part of her study, Bell evaluated whether observed spatial and temporal variation in the PM total mass health effects could be at least partially explained by the regional and temporal variation in the chemical composition of $PM_{2.5}$. She focused on the role of the key $PM_{2.5}$ chemical components identified in the first part of her study (specific aim 1) but also considered 13 other components that also covaried with $PM_{2.5}$ or had been associated with adverse health outcomes in previous studies (aluminum, arsenic, calcium, chlorine, copper, iron, lead, magnesium, nickel [Ni], potassium, titanium, vanadium [V], and zinc). She examined their impact on (1) $PM_{2.5}$ associations with cardiovascular and respiratory hospitalizations estimated for this study using the seasonal model and (2) previously estimated PM_{10} associations with total nonaccidental mortality (Peng et al. 2005).

She first calculated the average county- (or community-) and season-specific fractions that each component contributed to total $PM_{2.5}$ mass for 106 counties (for use with the effect estimates for hospital admissions) and 64 communities (for use with effect estimates for mortality). These fractions were then included in the second-stage modeling to estimate the percentage change in the PM total mass health effect estimates per interquartile range (IQR) increase in each component's fraction of $PM_{2.5}$ total mass. In essence, this metric indicates the extent to which the presence of different levels of each chemical component among counties (or communities) or by seasons can explain the variations observed in the main effect of $PM_{2.5}$ or PM_{10} total mass on hospital admissions or on mortality, respectively.

Focusing on the individual components with the largest influences on $PM_{2.5}$ total mass effect estimates for hospital admissions (the EC, Ni, and V fractions of $PM_{2.5}$) and on the PM_{10} effect estimates for mortality (Ni), Bell conducted additional analyses to test the sensitivity of the effects of EC, Ni, and V to various factors:

- removal of individual counties or communities from the analysis
- adjustment for EC, Ni, and V individually or in combination by including them in multiple pollutant models
- adjustment for various community-level characteristics: socioeconomic status (percentage of those 25 years and older with a high school degree or equivalent, median household income), racial composition (percentage of the population self-identifying as black or African-American), and degree of urbanization (percentage of the population living in an urban area, total population)

Finally, using the main model, Bell examined the impact of the prevalence of air conditioning (either central air conditioning or any air conditioning including window units) on associations between $PM_{2.5}$ total mass and cardiovascular hospitalizations, $PM_{2.5}$ total mass and respiratory hospitalizations, and PM_{10} total mass and mortality.

KEY FINDINGS

SPATIAL AND TEMPORAL VARIATION IN THE CHEMICAL COMPOSITION OF $PM_{2.5}$ (SPECIFIC AIM 1)

Bell's exploratory analysis of all 52 $PM_{2.5}$ component concentrations for 187 continental U.S. counties suggested distinct seasonal and regional patterns in the concentrations of many components. Her seasonal and regional analyses focused on the seven components that represented 1% or more of $PM_{2.5}$ total mass on average across all counties. The analyses suggested some broad patterns:

- OCM was higher in the western than in the eastern regions and contributed the most nationwide to $PM_{2.5}$ mass in both summer and winter.

- NO_3^- was generally higher in the western than in the eastern regions, with some higher NO_3^- concentrations appearing in parts of the Northeast. NO_3^- was highest in the western region in the fall but was highest in the eastern region in the winter.
- EC spatial patterns were similar to those of NO_3^-.
- $SO_4^=$ was higher in the eastern than in the western United States and appeared to peak in summer.
- Na^+ levels were higher in the coastal regions.

Components comprising the largest fractions of $PM_{2.5}$ mass had the highest temporal correlations with $PM_{2.5}$ mass; these correlations were reported to be similar when seasonally detrended data were used in the analysis. The report indicates that NH_4^+ and $SO_4^=$ were most highly correlated with $PM_{2.5}$ mass, but Bell's related published work (Bell et al. 2007) identifies important correlations of $PM_{2.5}$ mass with OCM, NO_3^-, bromine, and EC as well. The components that were most strongly correlated with one another at the county level were NH_4^+ with $SO_4^=$, NH_4^+ with NO_3^-, and EC with OCM (particularly in winter). Although not discussed in detail here, Bell's results also point to regional and seasonal patterns in components that did not necessarily vary with $PM_{2.5}$ total mass.

SPATIAL AND TEMPORAL PATTERNS IN ASSOCIATIONS BETWEEN SHORT-TERM $PM_{2.5}$ EXPOSURES AND HOSPITAL ADMISSIONS (SPECIFIC AIM 2)

This section of the report compares the regional and seasonal variation in the relative rates of cardiovascular and respiratory hospital admissions associated with a 10-µg/m^3 change in $PM_{2.5}$ concentrations estimated using the three statistical models (main, seasonal, and harmonic) described earlier.

National Health Effects Estimates — Main and Seasonal Models

The results for the main model, which assumes a constant effect throughout the year, were provided only as annual estimates for the 202 counties combined and for lags 0, 1, and 2. The investigator reported that the largest statistically significant increase in cardiovascular admissions was associated with exposure on the same day; that is, a 0.80% (95% posterior interval [PI], 0.59–1.01) increase per 10-µg/m^3 increase in lag-0 $PM_{2.5}$. For respiratory admissions, the largest significant effect was a 0.41% (PI, 0.09–0.74) increase associated with a 10-µg/m^3 increase in $PM_{2.5}$ exposure occurring 2 days before (lag 2).

The seasonal model, which examines the effects of lag-0, lag-1, and lag-2 $PM_{2.5}$ exposures on hospital admissions in each of four discrete seasons, produced results showing marked seasonal differences. Statistically significant increases in cardiovascular admissions per 10-µg/m^3 increases in lag-0 $PM_{2.5}$ were observed in winter, spring, and fall, but were largest in winter: 1.49% (PI, 1.09–1.89). Associations of respiratory hospital admissions with $PM_{2.5}$ also varied by season but were largest in winter with statistically significant increases observed with lag-0 exposures (1.05% [PI, 0.29–1.82]) and with lag-2 exposures (0.72% [PI, 0.01–1.43]).

Regional Health Effects Estimates — All Three Models

When data from the 202 counties were stratified by region and analyzed using the three models, the results revealed regional differences in the relative rates of cardiovascular and respiratory hospitalizations associated with changes in $PM_{2.5}$ concentrations.

For the main model, the percentage increases in cardiovascular hospitalizations for a 10-µg/m^3 increase in lag-0 $PM_{2.5}$ concentration were greatest (1.08% [PI, 0.79–1.37]) across the 108 Northeast counties followed by the 25 counties in the Southwest (0.53% [PI, 0.00–0.76]). With the seasonal model, positive and statistically significant increases in cardiovascular admissions were observed only for the Northeast and were observed in all seasons.

When rates of hospitalizations for respiratory disease were examined, national yearly results from the main model showed a pattern of increases in hospitalizations, with 10-µg/m^3 increases in $PM_{2.5}$ exposures for lags 0, 1, and 2, but the increases were highest and statistically significant only for lag-2 exposures. For the seasonal model with lag-0 $PM_{2.5}$ exposures, the percentage increases in respiratory hospital admissions were largest in the winter nationally, a result that may have been largely influenced by results in the Northeast, which had the largest number of communities and where the effects were greatest. In other regions, seasonal effects of lag-0 $PM_{2.5}$ exposures were more variable and uncertain.

The harmonic model used to estimate the associations between $PM_{2.5}$ exposures and hospital admissions as a smooth function of time for each of the regions showed seasonal patterns that were generally consistent with those estimated with the discrete seasonal model. Results were reported only for changes in cardiovascular and respiratory hospital admissions associated with 10-µg/m^3 increases in lag 0-$PM_{2.5}$ concentrations. The investigator concluded from these findings that the seasonal effects estimated from the seasonal model were not simply artifacts of the choice of months used to define seasons.

ANALYSIS OF SPATIAL AND TEMPORAL PATTERNS IN PM TOTAL MASS HEALTH EFFECT ESTIMATES AND SPATIAL AND TEMPORAL PATTERNS IN $PM_{2.5}$ CHEMICAL COMPOSITION (SPECIFIC AIM 3)

In this section of the report, Bell reported that between-county (or between-community) and seasonal variations in $PM_{2.5}$ effect estimates for hospitalizations and PM_{10} effect estimates for mortality were partly explained by variation in particle composition. Because the seasonal model was used in these analyses, meaning that data were analyzed on a county level for each season, results were typically described in terms of both county and seasonal variation.

Hospitalization Results

With the exception of EC, county and seasonal variations in components that made up the largest mass fractions of $PM_{2.5}$ did not explain the variation in lag-0 $PM_{2.5}$ effect estimates for either cardiovascular or respiratory hospitalizations. Bell reported a statistically significant 26% increase in cardiovascular hospitalizations and a 511% increase in respiratory hospitalizations per IQR increase in EC fraction of $PM_{2.5}$.

For the remaining components studied, Bell reported that counties and seasons with higher $PM_{2.5}$ content of Ni and V had higher $PM_{2.5}$ total mass health effect estimates for both cardiovascular and respiratory hospitalizations.

Mortality Results

None of the major components, including EC, provided a statistically significant explanation of the variations in the associations between PM_{10} total mass and nonaccidental mortality. Positive relationships were observed between $PM_{2.5}$ Ni and V content and PM_{10} total mass effect estimates for nonaccidental mortality, but the association with $PM_{2.5}$ V content was not statistically significant.

Sensitivity of Component Effects to County or Community

The effects of the EC, Ni, and V content of $PM_{2.5}$ on $PM_{2.5}$ effect estimates for respiratory hospitalization and on the PM_{10} effect estimates for mortality were sensitive to the exclusion from the analysis of a few New York counties (New York and Queens) (see the online supplement for Bell et al. 2009a). That is, they decreased in magnitude and lost statistical significance when one or the other county was removed from the dataset. The effects of $PM_{2.5}$ EC, Ni, and V content on lag-0 $PM_{2.5}$-related cardiovascular hospitalizations, although slightly lower when these counties were removed, remained statistically significant.

Sensitivity of Component Effects to Adjustment for Other PM Components

The relationship between $PM_{2.5}$ Ni content and $PM_{2.5}$ total mass effect estimates for cardiovascular hospitalizations was not sensitive to adjustment for EC or V, individually or in combination (that is, it remained at a similar magnitude and was statistically significant). The relationship between $PM_{2.5}$ V content and $PM_{2.5}$-mass-related risk of hospitalization for cardiovascular disease was sensitive to adjustment for Ni but not for EC. The correlation between Ni and V was higher (0.48) than that between V and EC (0.33), which may account in part for this finding. The observed effects of EC, V, or Ni on $PM_{2.5}$-mass-related respiratory hospitalizations were all sensitive to adjustment for the other copollutants.

Sensitivity of PM Total Mass Effect Estimates to County- or Community-Level Variables

Bell found no evidence that the $PM_{2.5}$ mass effect estimates for hospitalization or the PM_{10} effect estimates for mortality were influenced by county-level indicators of socioeconomic status, degree of urban development, or racial composition. Air conditioning, in particular central air conditioning, was the one variable that was able to explain a significant percentage of the between-county variation in some $PM_{2.5}$-related health effects. Specifically, a 20% increase in the population using central air conditioning lowered $PM_{2.5}$ relative rates of cardiovascular hospitalizations by 42.5%, based on annual data, and 79.5%, based on a summer-only data. Its influence on PM_{10} effect estimates for mortality and $PM_{2.5}$ effect estimates for respiratory hospitalization were variable and uncertain.

HEI EVALUATION OF THE STUDY

Bell's study was one of the early time-series analyses to take advantage of emerging $PM_{2.5}$ speciation data to characterize spatial and temporal patterns in the variation of individual $PM_{2.5}$ components and to explore their role in modifying the health effects previously associated with exposures to $PM_{2.5}$ and to PM_{10} total mass.

Bell's project built on a progression of well-respected NMMAPS studies that have contributed to multicity time-series methods for exploring relationships between short-term (i.e., daily or every 3 to 6 days) PM total mass concentrations and daily mortality and hospitalization rates, first for PM_{10}, then for $PM_{2.5}$. What this study adds to its predecessors is its investigation of how the county and season average values of components of $PM_{2.5}$ modify the associations

between exposure to PM and hospitalizations or mortality. This "modification" approach is not the only one Bell might have taken to distinguish the health effects of PM components, but it is one of several reasonable types of analysis (see the Commentary sidebar "Investigating the Effects of PM Components on Health: Two Approaches").

As one of the largest studies done to date, ultimately covering 106 counties across the continental United States for which the necessary $PM_{2.5}$ component and health data were available, the Bell study provides one of the most comprehensive analyses available. In its independent review, the HEI Health Review Committee thought Bell's study was a relevant, well-conducted, and timely contribution to an important topic in the evaluation and regulation of ambient air pollution.

SPATIAL AND TEMPORAL VARIATION IN $PM_{2.5}$ COMPOSITION

Bell's straightforward approach to the evaluation of seasonal and temporal variation in $PM_{2.5}$ chemical composition was a reasonable one. Her basic descriptions of the spatial and temporal patterns of $PM_{2.5}$ and its components were consistent with findings from the published literature. More sophisticated analyses, such as cluster analysis or a formal multivariate one like principal components analysis, might have identified subtler patterns, but at the expense of transparency.

Our primary comments on this aspect of the study relate to the treatment of the $PM_{2.5}$ speciation data. Overall, Bell compiled the $PM_{2.5}$ speciation database for her study in a careful and systematic way. She appropriately explored the

Investigating the Effects of PM Components on Health: Two Approaches

Investigators seeking to explore the impacts on an outcome of several different hypothesized explanatory variables (in this study, the components of $PM_{2.5}$) usually collect data on each variable and evaluate them in a multiple regression analysis. Although problems of correlations between the explanatory variables can preclude including all variables in a single regression model and can complicate model choice, approaches to identifying and displaying results from models with the most useful subsets of explanatory variables have been extensively explored. For example, in time-series studies of the association of the gaseous pollutants nitrogen dioxide, carbon monoxide, and sulfur dioxide with hospital admissions, variables representing daily concentrations of these contaminants would be considered as three explanatory variables in a regression of daily admission counts, to be considered singly, in pairs, or all three together. In recent work related to this report, Roger Peng and colleagues, including Dr. Bell, (2009) have explored the effect of individual $PM_{2.5}$ components on hospitalizations using such a multiple-pollutant approach (see Commentary Table 2 and the related discussion).

Although some researchers have directly investigated associations of particle component concentrations with health effects in this way, this study, which includes many of the same collaborators as the Peng et al. study, took a different approach. The investigation proceeded more indirectly by exploring the extent to which variation over seasons and counties in the PM total mass effect estimates was explained by the variations in the fractions of the individual components of $PM_{2.5}$ mass over seasons and/or counties (see Statistical Analyses under Study Summary for details).

This approach has the advantage of using more data than a direct approach; that is, it can make more complete use of the intermittent chemical composition measurements (one in every 3 or 6 days) and thus can have greater statistical power. Its disadvantage is that it does make interpretation of the results indirect. For example, if one finds that counties and/or seasons with high PM total mass effect estimates for hospital admissions also tend to have PM with a high Ni fraction, one cannot tell whether days with high Ni were accompanied by days with high admissions. It is possible that seasons and/or counties with a high Ni fraction have their highest Ni days on low $PM_{2.5}$ days. This "ecological" limitation does not, however, necessarily outweigh the advantage that the indirect approach used in this study has of allowing for the use of more complete data. Collectively, the two types of approaches can contribute different types of scientific evidence on the health impacts of particles.

implications of reported temporal trends in OC field blanks (Frank 2006) by developing an alternative measure for OCM (i.e., OCM2) to use for comparison to the standard approach. It was reassuring to see that the two estimates of OCM were highly correlated, although the analysis does not entirely eliminate the possibility of differential artifacts in the OCM levels by season. Other authors have pointed out issues with artifacts in the OC sampling networks (e.g., Chow et al. 2010) that have led to changes in the way these values are now reported in the U.S. EPA AQS database (Neil Frank/U.S. EPA, personal communication, June 2, 2011). Another particular strength of Bell's treatment of the data was her evaluation of the sensitivity of between-component correlations to seasonal detrending of the data. Even though this demonstrated little such sensitivity, it was important to know that.

Missing from this presentation were more basic details about and evaluation of the implications of MDL for individual chemical species. The report indicates that the speciation "data were not corrected for minimum detection limit," an approach consistent with the U.S. EPA AQS database, which provides "reported sample values" regardless of their relationship to the MDL. However, as a result, we have little indication of whether detection rates vary across components, counties, or seasons in ways that might contribute to differential levels of exposure measurement error.

Bell correctly points out that her analyses focusing on components comprising a high proportion of total $PM_{2.5}$ are unlikely to be affected by this issue. However, her later health analyses give more emphasis to components that comprise smaller fractions of $PM_{2.5}$ (in particular, Ni and V), where the frequency and patterns of values below the actual detection limit could be more influential. For example, the reported mean concentration of Ni in this study is 1.85 ng/m^3, while the MDL reported by the Research Triangle Institute (RTI) for samples taken in 2010 was 1.9 ng/m^3 (RTI 2011). Similarly, the reported mean V concentration of 5.64 ng/m^3 is close to the 2010 MDL of 4.2 ng/m^3.

The investigator's decision to focus initially on those components that made up 1% or more of $PM_{2.5}$ mass or that covaried with $PM_{2.5}$ mass was a systematic and defensible approach. Exposure to $PM_{2.5}$ mass has long been associated with adverse health effects, and it was reasonable to hypothesize that components that make up a large fraction of the mass or that otherwise covary with it would be likely to explain those associations. However, the report provides no similar information on how the concentrations of the trace pollutants, particularly Ni and V, vary with total $PM_{2.5}$ or PM_{10} mass; a more thorough examination could have been informative. The decision to augment the few components selected by this approach with some that had been identified as toxic in previous studies made sense. However, the interpretation of the analysis would have been strengthened by inclusion of a more systematic rationale for components selected on the basis of toxicity.

Bell's selection of a small subset of the total components on which data were available did have the advantage of reducing the statistical problem of multiple comparisons. This problem refers to the likelihood that, when simultaneously testing inferences about multiple relationships (in this case the role of components of $PM_{2.5}$), some percentage of positive relationships may occur simply by chance.

ESTIMATION OF $PM_{2.5}$ ASSOCIATIONS WITH CARDIOVASCULAR AND RESPIRATORY DISEASES

Bell took a pragmatic and useful approach to her characterization of the relationship between exposures to $PM_{2.5}$ total mass and rates of hospital admissions for cardiovascular and respiratory diseases. She presented a comparison of results from simple and transparent analyses (the main and seasonal) and from the more sophisticated harmonic analysis, building on and extending work with her colleagues Roger Peng and others on PM_{10} and mortality (2005) and with Francesca Dominici and others on $PM_{2.5}$ and hospitalizations (2006).

We liked Bell's direct comparison of the results of the seasonal and harmonic models in the same figures (Investigator's Report, Figures 5 and 6). The figures support her conclusion that the results from the seasonal model were consistent with those of the harmonic model, indicating that they were not simply an artifact of the months chosen to define seasons. That said, the harmonic model has some theoretical advantages over the seasonal model approach; it uses fewer parameters (i.e., in statistical terms, it is more parsimonious) and uses a smooth representation of variation in health effects that is arguably more plausible than assumptions of sharp seasonal boundaries. However, we recognize that these advantages are bought at the expense of some loss of transparency due to the harmonic model's greater mathematical complexity. The decision to proceed with the seasonal model in the investigation of PM components was therefore reasonable.

Future work might consider ways of summarizing the fitted harmonic model in an interpretable way for quantitative inclusion in second-stage analysis, for comparison over counties. Possible approaches include examination of peak-to-trough differences (i.e., of amplitude) and the time of year at which maximum effects are observed.

UNDERSTANDING THE ROLE OF $PM_{2.5}$ COMPOSITION IN EXPLAINING HEALTH EFFECTS ASSOCIATED WITH PM TOTAL MASS

$PM_{2.5}$ Components and Hospital Admissions

Once the $PM_{2.5}$ effect estimates for hospitalizations had been estimated, the statistical methods for evaluating whether spatial and temporal patterns in PM health effect estimates were related to PM chemical composition could be quite simple. The Bayesian hierarchical approach used by Bell is an appropriate one and well explored for this context. The investigator's primary reliance on the seasonal model was also well justified, given the evidence for marked seasonal as well as regional variation in PM components and in the health effects associated with PM total mass. Bell undertook two important steps to investigate the robustness of her primary findings on the importance of the fractions of $PM_{2.5}$ represented by EC, Ni, and V. She evaluated their sensitivity to adjustment for one or more of the three components (that is, EC, Ni, and V), and she evaluated the sensitivity of the $PM_{2.5}$ Ni effects to socioeconomic status, race, and degree of urbanization.

However, the study's approach to evaluating the role of $PM_{2.5}$ components does have some limitations. One is that the concentrations of several of the key trace elements studied, Ni and V, are quite low, often near or below the MDL. Another is that the analyses provide measures of effect modification that are more difficult to communicate than more direct estimates of the influence of a specific variable on an outcome (see the sidebar). Effect modification characterizes the extent to which the outcome in an analysis depends on or varies with the level of some factor. In this study, the investigator reported results in terms of the percentage change in the $PM_{2.5}$ total mass health effect per IQR of the $PM_{2.5}$ component fraction. This presentation was as reasonable as any but less directly interpretable than results that describe directly the relationship between the rates of hospitalization and mass concentration of a particular PM component in ambient air.

For example, Peng, along with other colleagues including Bell (Peng et al. 2009), conducted an analysis in which the concentrations, rather than the mass fractions, of the seven components making up most of the $PM_{2.5}$ total mass were incorporated directly into Bayesian hierarchical multipollutant models, to directly predict the percentage increase in cardiovascular and respiratory admissions (Ni, V, or other trace elements were not included). Commentary Table 2 compares the approaches from this and the Peng and colleagues (2009) studies and shows that although they relied on similar data, they led to somewhat different results. In examining the seven components contributing 1% or more to $PM_{2.5}$ mass in single-pollutant models, the Bell study found that only the EC fraction modified the effect of $PM_{2.5}$ total mass on hospital admissions. Peng and colleagues (2009), on the other hand, found increased concentrations of NO_3^-, OCM, NH_4^+, as well as EC to be directly associated with increases in cardiovascular admissions, and OCM to be directly associated with respiratory admissions.

Other studies that have used an effect-modification approach, but, with metaregression techniques, have also identified different sets of $PM_{2.5}$ components as influential. For example, Zanobetti and colleagues (2009) evaluated the ability of $PM_{2.5}$ components to modify the effect of $PM_{2.5}$ mass on cause-specific emergency hospital admissions for 26 U.S. communities. They reported that bromine, chromium, and Na^+ modified $PM_{2.5}$ effect estimates for cardiovascular disease admissions; Ni, arsenic (As), chromium, manganese, OC, and Na^+ modified $PM_{2.5}$ effect estimates for myocardial infarction; and As, OC, and $SO_4^=$ modified the $PM_{2.5}$ effect estimates for diabetes. The reasons for the differences in findings among these studies are not clear but should be more fully explored in future work.

A second, and perhaps more important, limitation of Bell's specific application of the Bayesian hierarchical approach was the absence of any attempt to identify the extent to which associations between component fractions and the size of the $PM_{2.5}$ total mass effects were reflecting variation between seasons, variation between counties, or both. Consequently, for example, one cannot tell if the higher apparent effect of $PM_{2.5}$ on cardiovascular admissions when the fraction of Ni was high was due to greater effects in the seasons in which Ni was high, in the counties in which Ni was high, or both.

Bell took an important step in investigating this issue by testing the sensitivity of these results to the removal of individual counties (see the online supplement to Bell et al. 2009b). Her findings indicating the sensitivity of results to the removal of one or two New York counties were consistent with those of an earlier study by Dominici and colleagues (2007) on $PM_{2.5}$ component effects on nonaccidental mortality related to lag-1 PM_{10} exposures; this study also pointed to the importance of local contributions to the concentrations of PM components, Ni and V in particular. Another recent detailed investigation, by Peltier and Lippmann (2010), of spatial and seasonal patterns of Ni and V in the New York City area, further suggests that marked seasonal differences in these pollutants may also exist. In particular, the investigators found that the Ni fraction was highest in winter, which they inferred was associated with burning of residual fuel in parts of the city. V levels, on the other hand, did not vary seasonally in this study. Both spatial and seasonal associations are of interest, but because

Commentary Table 2. Comparison Results from the Bell Investigator's Report and Peng et al. 2009

Study	Components	Statistical Methods	Components with Statistically Significant Impacts: Cardiovascular Hospital Admissions	Components with Statistically Significant Impacts: Respiratory Hospital Admissions
Bell Investigator's Report (106 counties with ≥ 200,000 population)	Primary components: $SO_4^{=}$, NO_3^{-}, Si, EC, OCM, Na^+, and NH_4^+ Other: Al, As, Ca, Cl, Cu, Fe, Pb, K, Mg, Ni, Ti, V, Zn	Indirect method: Percentage increase in $PM_{2.5}$ effect estimate for hospital admissions per IQR increase in the component as a fraction of $PM_{2.5}$ mass Bayesian hierarchical methods with components included in the second stage as effect modifiers Single- and multiple-pollutant models	Single-pollutant models: EC, Ni, V Multiple-pollutant models: Ni, (robust to EC, V), V (robust to EC)	Single-pollutant models: EC, Ni, V Multiple-pollutant models: none
Peng, Bell, Geyh, McDermott, and Zeger 2009 (119 counties with ≥ 150,000 population)	Primary components: $SO_4^{=}$, NO_3^{-}, Si, EC, OCM, Na^+, and NH_4^+	Direct method: Percentage increase in hospital admissions per IQR increase in each component's mass concentration Bayesian hierarchical methods with components included in the first stage Single- and multiple-pollutant models	Single-pollutant models: NO_3^{-}, EC, OCM, and NH_4^+ Multiple-pollutant models: EC, OCM	Single-pollutant models: OCM Multiple-pollutant models: OCM

each may reflect different emissions sources and may be subject to different biases and confounding factors, knowing which provided the evidence would be helpful in interpreting the findings and could allow additional insight into the robustness of associations.

A third, though more secondary, concern was that the analysis did not include any attempt to allow for spatial structure or spatial clustering in coefficient patterns due to causes other than the chemical composition of $PM_{2.5}$. Bell's investigation of the sensitivity of her $PM_{2.5}$ Ni results to socioeconomic status, race, and degree of urbanization — which themselves may have some spatial structure — gets at this question indirectly, but differs from addressing spatial structure per se.

The point of accounting for spatial structure in the analysis would be to allow conclusions on the importance of chemical composition to be robust to the presence of spatial autocorrelation in coefficients and to better understand whether any associations identified reflect broad between-region patterns or more local within-region patterns. It would not need to be sophisticated; one simple approach would be to include regional indicators using the regions as defined for this study. An alternative approach would be to allow for such regional variation as a random effect in the model. Explicit spatial autocorrelation models do exist (for example, those developed in the recent extended analyses of mortality in the American Cancer Society cohort [Krewski et al. 2009]), but these are probably beyond what is needed.

$PM_{2.5}$ Components and Mortality

Given the recent impediments imposed on obtaining mortality data for research, Bell took a pragmatic approach to investigating the influence of PM components on mortality by using data on PM_{10} effect estimates for mortality. However, it was difficult to know whether the effects of components on $PM_{2.5}$- and PM_{10}-related health outcomes

in these studies — whether consistent or inconsistent — should be attributed to true underlying relationships or to artifacts of differences between particle-size fractions, time periods of the study, or counties or communities studied. For example, using metaregression methods, Franklin and colleagues (2008) evaluated the modification by $PM_{2.5}$ components of $PM_{2.5}$ effect estimates for nonaccidental mortality for 25 U.S. communities (not including New York City) for the same time period as in this report (2000–2005) and found a different set of components to be important. Franklin reported that $PM_{2.5}$ effect estimates for mortality were significantly higher in communities with higher fractions of Ni, as in this report, but also in those with higher fractions of Al, As, $SO_4^=$, and Si. Further investigation is necessary.

Other Methodologic Considerations for the Epidemiologic Analyses of $PM_{2.5}$ Components

Bell's reliance on the well-established and well-explored approaches used in NMMAPS was a good starting point for the portion of her analyses that used such models, and the provision of several sensitivity analyses, such as the use of both harmonic and seasonal interaction models, was a strength. However, the absence of an investigation of the sensitivity of her conclusions to the time spline and temperature control was an important limitation. Bell justified her model choices based on findings from previous studies indicating that the modeling approach is robust to differing assumptions for the smooth function of time and to various specifications for weather (Welty et al. 2005; Peng et al. 2006; Touloumi et al. 2006). However, the sensitivity analyses in these studies were for estimation of health effects associated with national or continental mean values of PM_{10}, not of $PM_{2.5}$ or its components. It was reassuring to discover, in later work related to this study, sensitivity analyses showing national yearly effects of $PM_{2.5}$ components on hospitalizations to be unaffected by a large range of degrees of freedom for the smooth function of time (2–14 *df*/year) as well as by assumptions about temperature and dew point (Peng et al. 2009). We do not know, and cannot presume from these other analyses, that the same insensitivity to model assumptions would exist for the analysis of variation in, and determinants of, county- and season-specific associations of $PM_{2.5}$ or its components with hospital admissions. In particular, we cannot be sure of the impact of the inclusion of temperature effects beyond a lag of 3 days; findings from other studies in the United States and elsewhere suggest that longer lags are required to capture cold's impact on mortality (Braga et al. 2001, Pattenden et al. 2003; Anderson and Bell 2009). Systematic analyses of sensitivities to model choices are critical for assessing the robustness of results and for their appropriate interpretation.

The study did include a valuable exploration of whether certain county- or community-level variables (socioeconomic conditions, race, degree of urbanization, and prevalence of air conditioning) could explain the variability in either hospitalizations or mortality associated with exposures to $PM_{2.5}$ total mass. The prevalence of central air conditioning was the one community-level variable found to explain some variation in associations of $PM_{2.5}$ total mass with rates of hospitalizations for cardiovascular disease. Bell's analysis of the percentage reduction in tau-squared (the τ^2 presented in Table 9 of the Investigator's Report), a measure of the between-community variation in the health effect estimates, provided some useful quantitative insight into just how much of that variation central air conditioning explained. Understanding the role of air conditioning in modifying $PM_{2.5}$ total mass effect estimates is of considerable interest in its own right. However, an extension of this analysis, to better understand how air conditioning affects the influence of $PM_{2.5}$ components on $PM_{2.5}$ effect estimates, would be useful further work.

Bell correctly points out that the major challenges facing epidemiologic studies of components are exposure measurement error and "spatial misalignment," the mismatch between particle-component measurements and health outcomes in study populations. The effects of such errors may not be easy to disentangle, since the errors may well have complex distributions; for example, they may be correlated with errors in the measurement of other components and of $PM_{2.5}$ mass itself. The absence of data on MDLs, particularly for trace metals, which themselves are often correlated, may further exacerbate this problem. The use of county–season averages of PM component fractions in this report can reasonably be expected to be less subject to errors than the use of daily concentrations. It therefore provides the analyses with some robustness to measurement error problems, but certainly not immunity to them.

DISCUSSION

In this study, Bell has shown persuasively that concentrations of $PM_{2.5}$ components vary across counties and regions of the United States as well as across seasons. Similarly, she has demonstrated that relationships between daily $PM_{2.5}$ concentrations and hospitalizations for cardiovascular and respiratory disease also vary over space and time. The question her report set out to answer is whether the variation in the $PM_{2.5}$ components could explain variation in the health effects associated with $PM_{2.5}$. That is, does differential particle composition account for the geographical and seasonal differences in $PM_{2.5}$ risk estimates observed, and thereby demonstrate differential particle toxicity?

The evidence for heterogeneity in toxicity rests not primarily on observing spatial and seasonal heterogeneity in

associations between PM and health effects, which may have many causes, but on the relationships observed between putative markers of toxicity (PM components) and the PM associations with health effects. If these associations are observed, alternative explanations for them must be adequately addressed.

In the case of $PM_{2.5}$ composition and its ability to explain the variations in PM health effects, we believe that a causal interpretation on the basis of the patterns found in this study is premature and we agree with Bell that further investigations are needed. Although the study did consider some alternative explanations for spatial variation (e.g., region, socioeconomic status), it did not establish whether the relationship between components and PM effects on hospitalizations or mortality were robust to inclusion of other possible explanations of variation. The study's finding that most of the alternative explanatory variables considered were not — with the exception of air conditioning and region — statistically significantly related to PM health associations provides only moderate reassurance. Nonsignificant predictors can still confound, and there always remains the possibility of unmeasured factors. No alternative explanations were considered for temporal variation. In view of these limitations and those discussed earlier, the evidence from Bell's study implicating EC, Ni, and V in the impacts on excess hospitalizations and Ni and V on mortality associated with PM_{10} should be considered only suggestive at this time.

The investigator's related suggestions — regarding specific sources for the components identified in this study — whether in this report (e.g., traffic) or in its related publications (e.g., power-generation, coal combustion, and residual oil as in Bell 2008) — should also be viewed cautiously. While an important motivation for identifying those components of PM that might contribute to adverse health outcomes is to be able to identify key sources, the methods used in this report were not sufficient to address this issue.

CONCLUSIONS

Bell's well-conducted study took a careful and logical approach to the exploration of $PM_{2.5}$ chemical speciation data and its implications for human health in the United States. Her work represents one of the first and largest efforts to take advantage of all the available $PM_{2.5}$ speciation data for 52 chemical species and to analyze them in conjunction with hospital admissions and nonaccidental mortality data from throughout the continental United States. In the spirit of the Rosenblith Award, her work bodes well for her development as an investigator.

Her results showed that the observed variations in relationships between $PM_{2.5}$ and health effects could partly be explained by variation in the chemical composition of $PM_{2.5}$. And although her study shared important methodologic similarities with other studies of PM composition that have relied on NMMAPS data and methods (e.g., Franklin et al. 2008; Peng et al. 2009; Zanobetti et al. 2009), the differences she found about the importance of individual components remain largely unexplained. That Bell's study has not been able to come to more than very tentative and partial conclusions about the toxicity of different PM components reflects the considerable complexity of the task rather than deficiencies of her approach, which indeed informs future studies in important ways. It seems clear that unraveling this puzzle is going to be a long haul.

Bell's work now sits within a broader, rapidly growing body of epidemiologic literature that reports on associations between PM components and a range of health outcomes. Studies differ along many more dimensions — study design, regional coverage, time period covered, study population characteristics, PM size fraction, PM number, components measured, copollutants measured, monitoring methods, health endpoints, and statistical methods applied. Some findings are similar; some are unique to particular studies. There has been little replication of analyses. While many studies look at a large number of associations with components, relatively little attention has been paid to the possible perils of multiple testing (Brunekreef 2010).

This current situation — while perhaps a natural reflection of the scientific method — makes both simple comparisons and systematic reviews challenging. It seems far from the more "systematic approach" to the "matrix of relationships between particle composition and possible health effects" called for by the NRC in 2004. Bell's study, however, represents an early step in the HEI's larger NPACT initiative. The systematic toxicology and epidemiologic studies in that multicenter effort are nearing completion and may help to bring more consistent, comparable approaches to these important investigations going forward.

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