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**Associations of PM_{2.5} Constituents and Sources with Hospital Admissions:
Analysis of Four Counties in Connecticut and Massachusetts (USA) for
Persons ≥ 65 Years of Age**

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Abstract

Background: Epidemiological studies have demonstrated associations between short-term exposure to PM_{2.5} (particulate matter $\leq 2.5\mu\text{m}$) and hospital admissions. The chemical composition of particles varies across locations and time periods. Identifying the most harmful constituents and sources is an important health and regulatory concern.

Objectives: To examine pollutant sources and risk of hospital admissions.

Methods: For four counties in Connecticut and Massachusetts, we obtained PM_{2.5} filter samples and analyzed them for PM_{2.5} elements. Source apportionment was used to estimate daily PM_{2.5} contributions from sources (traffic, road dust, oil combustion, sea salt, and a regional source representing coal combustion and other sources). Associations between daily PM_{2.5} constituents and sources and risk of cardiovascular and respiratory hospitalizations for the Medicare population (over 333,000 persons ≥ 65 years) were estimated with time-series analyses (Aug. 2000-Feb. 2004).

Results: PM_{2.5} total mass and PM_{2.5} road dust contribution were associated with cardiovascular hospitalizations, as were PM_{2.5} constituents of calcium, black carbon, vanadium, and zinc. For respiratory hospitalizations, associations were observed with PM_{2.5} road dust and sea salt, and aluminum, calcium, chlorine, black carbon, nickel, silicon, titanium, and vanadium. Effect estimates were generally robust to adjustment by co-pollutants of other constituents. An interquartile range increase in same day PM_{2.5} road dust ($1.71 \mu\text{g}/\text{m}^3$) was associated with a 2.11% (95% CI: 1.09, 3.15%) and 3.47% (95% CI: 2.03, 4.94%) increase in cardiovascular and respiratory admissions, respectively.

Conclusions: Results suggest some particle sources and constituents are more harmful than others. Results suggest that in this region, the most harmful particles include black carbon, calcium, and road dust PM_{2.5}.

Introduction

Associations between airborne particles and health are well established (Pope and Dockery 2006), including evidence of higher risk for smaller particles with aerodynamic diameter $\leq 2.5\mu\text{m}$ (PM_{2.5}). Several countries regulate PM_{2.5} (e.g., U.S., United Kingdom, Taiwan), and the World Health Organization (WHO) established health-based guidelines. Increasing scientific evidence suggests that particles differ in toxicity. This hypothesis is consistent with known heterogeneity in particles' chemical composition (Bell et al. 2007). For example, sulfate constitutes a higher fraction of PM_{2.5} in the eastern U.S. than the western U.S. Composition of PM_{2.5} in Seoul, Korea is more similar to PM_{2.5} in the western U.S. than PM_{2.5} in the eastern U.S. (Son et al. 2012). Variations in composition may affect health risks and explain why effect estimates for PM_{2.5}, measured by total mass, differ by location.

The Health Effects Institute (HEI), a National Academies of Sciences committee, and WHO identified study of health effects of the particle mixture as a critical research need (HEI 2002; National Research Council 2004; WHO 2007). Evidence on which particles are most harmful would inform effective policies by allowing stricter control of the most harmful agents and could aid understanding of biological pathways, which may differ by constituents or health outcomes. Multiple biologically plausible mechanisms have been demonstrated or hypothesized (e.g., systematic inflammation, vascular function) (Brook et al. 2010), although physiological responses to different PM_{2.5} constituents and sources are not fully understood.

Many epidemiological studies estimate air pollution exposure with existing ambient monitoring data from regulatory agencies. This approach is cost effective and can cover large populations and time periods. Limited availability of PM_{2.5} constituent data, compared to data for PM_{2.5},

limits research on particulate composition and health. National U.S. monitoring networks for $PM_{2.5}$ constituents began in 1999, with many monitors beginning operation in 2000. The U.S. Environmental Protection Agency (EPA) has monitored $PM_{2.5}$ since 1997, with many monitors starting in 1999. The $PM_{2.5}$ monitoring network is more extensive, with 1387 active monitors in the continental U.S., whereas the $PM_{2.5}$ Chemical Speciation Network has 192 monitors (U.S. EPA 2012). Additional monitors with chemical speciation are available for rural sites through the IMPROVE network. While data from EPA's constituent network are useful, data are unavailable for all time periods and locations of interest.

Several methods have been introduced to estimate pollution for times and locations without monitors, such as regional air quality modeling, but methods to estimate complex $PM_{2.5}$ chemical composition remain limited. Understanding health impacts is hindered by lack of daily measurements of constituents in national monitoring networks. To date, we are aware of only one study that has applied source apportionment methods to examine associations between $PM_{2.5}$ sources and hospitalizations (Lall et al. 2011). We applied an alternative approach, compared to previous studies, to obtain additional $PM_{2.5}$ constituent measurements. We then used these data to estimate exposure from $PM_{2.5}$ sources and associated risk estimates, which are particularly relevant for policy makers as $PM_{2.5}$ is currently regulated based only on mass concentration, without regard to composition.

We used data from X-ray fluorescence elemental analysis of $PM_{2.5}$ filters collected at five EPA monitoring sites in four counties in Connecticut and Massachusetts. Therefore, we generated a new data set of $PM_{2.5}$ chemical constituents by analyzing $PM_{2.5}$ total mass filters for elemental composition. This new data set had almost 10 times more data (days of observation) than the EPA's Chemical Special Network for the four counties. Constituent data were used in source

apportionment analysis to identify particle sources. We then estimated relative risks of cardiovascular and respiratory hospitalizations associated with short-term exposure to PM_{2.5} constituents and sources.

Methods

Exposure for PM_{2.5}, constituents, and sources

To estimate exposures we: 1) obtained filters used by regulatory agencies to measure PM_{2.5} total mass, 2) analyzed those filters for PM_{2.5} elements, and 3) used these data as inputs to source apportionment analysis. This approach generates estimates for a given day (24-hour) of PM_{2.5} mass, constituents, and sources for each location.

We acquired PM_{2.5} Teflon filter samples from Connecticut and Massachusetts Departments of Environmental Protection for August 2000-February 2004. We considered five primary monitoring locations in four counties (see Supplemental Material, Figure S1): (1) New Haven, CT in New Haven County; (2) Hartford, CT in Hartford County; (3) Bridgeport, CT in Fairfield County; (4) Danbury, CT in Fairfield County; and (5) Springfield, MA in Hampden County. Sampling occurred daily, with some missing periods for Hartford, New Haven, and Springfield, and every third day for Bridgeport and Danbury. Because the sample days for Bridgeport and Danbury are unbiased, measurements of every third day should not affect central risk estimates, although it reduces sample size. Days with missing data were omitted from analysis.

The daily (midnight to midnight) PM_{2.5} filter samples were analyzed for levels of PM_{2.5} elements, using optical reflectance for black carbon (BC) (Cyrus et al. 2003; Gent et al. 2009) and X-ray fluorescence for several elements (Watson et al. 1999). Optical reflectance was

performed at Harvard University and X-ray fluorescence at the Desert Research Institute in Reno, NV. These $PM_{2.5}$ and constituent data were used in earlier research for other health outcomes; more information is provided elsewhere (Bell et al. 2010; Gent et al. 2009; Lee et al. 2011).

Elemental analysis of $PM_{2.5}$ filters produced a more extensive data set than would be available using EPA's constituent data. For example, in EPA's Air Explorer (U.S. EPA 2011) $PM_{2.5}$ constituent data from this study area and time period include 3 monitors, one each in Fairfield, New Haven, and Hampden Counties, with measurements beginning April 2002, June 2003, and December 2000, respectively. No EPA monitors assessed constituents in Hampden County. $PM_{2.5}$ constituent data generated from $PM_{2.5}$ filters had 9.9 times more data than EPA's constituent monitoring network considering all four counties, and 6.4 times more data considering the 3 counties with measurements in both data sets. However, EPA's network provides information on some constituents (e.g., nitrate, ammonium), which were unavailable for our study.

Daily contributions of $PM_{2.5}$ sources were estimated for each monitoring location using positive matrix factorization (PMF) (Bell et al. 2010; Norris et al. 2008; Paatero and Tapper 1994). This method identifies major $PM_{2.5}$ sources and quantifies their daily contribution to $PM_{2.5}$ mass and constituents. The approach estimates daily $PM_{2.5}$ levels from each source for each site. PMF identified five sources: motor vehicles, road dust/crustal materials, oil combustion, sea salt, and regional sources, which relate to emissions from power plants and other urban areas. We applied PMF results in previous work, which provides more details on methods (Bell et al. 2010).

For each county, we estimated daily levels of PM_{2.5} sources, BC, and selected constituents. We choose to analyze constituents identified as potentially harmful in previous epidemiological studies (Dominici et al. 2007; Franklin et al. 2008; Lippmann et al. 2006; Ostro et al. 2007, 2008) : aluminum (Al), BC, bromine (Br), calcium (Ca), chlorine (Cl), nickel (Ni), potassium (K), sulfur (S), silicon (Si), titanium (Ti), vanadium (V), and zinc (Zn). These elements were among those used in PMF analysis.

For Fairfield County, exposures were estimated with population-weighted averaging of values for the two monitoring locations in that county (Bridgeport and Danbury). Each of 209 census tracts in Fairfield County was assigned the exposure of the nearest monitor, and those exposures were averaged, weighted by the tracts' 2000 US Census population. Seventy-four percent of the county's population resided closest to the Bridgeport monitor. For other counties, we used values from the single monitor within the county. PM_{2.5} filter samples were not collected daily, so not all days had source exposure estimates at all monitoring sites.

Weather data

Hourly temperature and dew point temperature data for each county were obtained from the National Climatic Data Center. These values were converted to daily levels (midnight to midnight), as daily weather values are extensively used in previous relevant research (Samet et al. 2000a, 2000b). For each county, weather variables were estimated using data from a monitor or monitors in each county or a nearby county. For counties with multiple monitors, values from those monitors were averaged to generate county-level averages.

Health data

We used the Medicare beneficiary denominator file from the Centers for Medicare and Medicaid Services (CMS) to identify the at-risk population of Medicare beneficiaries ≥ 65 years of age, residing in the four counties, and enrolled in the Medicare fee-for-service plan August 2000-February 2004. We calculated the monthly number of beneficiaries in each county to account for new enrollment and disenrollment, and extended monthly data to daily data by accounting for deaths, hospital admissions, and discharges occurring one day prior to an index date. We linked this time-series data with CMS Medicare inpatient claims data to identify patients discharged from acute-care hospitals. We included only emergency hospitalizations and used date of admission to calculate daily numbers of admissions. Cause of admission was determined by principal discharge diagnosis code according to *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. Analysis was conducted separately for respiratory disease (chronic obstructive pulmonary disease [ICD-9-CM 490-492] and respiratory tract infection [464-466, 480-487]) and cardiovascular disease (heart failure [428], heart rhythm disturbances [426-427], cerebrovascular events [430-438], ischemic heart disease [410-414, 429], and peripheral vascular disease [440-448]). On average across the study and summed across counties, there were $> 333,900$ beneficiaries at risk in our population.

Data analysis

We performed time-series analysis to estimate associations between $PM_{2.5}$ sources or constituents and cardiovascular or respiratory hospitalizations by applying a log-linear Poisson regression model:

$$\ln(E[Y_t^c]) = \ln(N_t^c) + \beta x_{t-l}^c + \alpha DOW^t + ns(T_t^c, df_T) + ns(D_t^c, df_D) + ns(Ta_t^c, df_{Ta}) + ns(Da_t^c, df_{Da}) + ns(t, df_t) + I(r)$$

where:

Y_t^c = hospitalizations in county c on day t

N_t^c = at risk population in county c on day t

β = coefficient relating pollution to hospitalization rate

x_{t-l}^c = pollution level in county c on day t at lag of l days

DOW_t = day of week on day t

α^c = coefficient relating day of week to hospitalizations in county c

$ns(T_t^c, df_T)$ = natural cubic spline of temperature in county c on day t with df_T (degrees of freedom (d.f.) for temperature) = 6

$ns(D_t^c, df_D)$ = spline of dew point temperature in county c day t with df_D (d.f. = 3)

$ns(Ta_t^c, df_{Ta})$ = spline of average of 3 previous days' temperature in county c day t with df_{Ta} (d.f. = 6)

$ns(Da_t^c, df_{Da})$ = spline of average of 3 previous days' dew point temperature in county c day t with df_{Da} (d.f. = 3)

$ns(t, df_t)$ = spline of time (t) with $df_t = 8/\text{yr}$ (i.e., $8 \times 3.5 \text{ yrs} = 28$)

$I(r)$ = indicator of region (coastal for Fairfield or New Haven Counties, inland for Hartford or Hampden Counties)

We considered single day lags of exposure on the same day as hospitalization (L0), previous day (L1), and two days previous (L2). For constituents demonstrating statistically significant associations in single pollutant models, sensitivity analysis was performed adjusting one-at-a-time for other constituents when the correlation between the second pollutant and the first was < 0.60 (to avoid collinearity). Results from all analyses represent estimated effects across all 4 counties. Statistical significance was considered $p\text{-value} < 0.05$.

Results

Table 1 summarizes hospitalizations across all counties (Supplemental Material, Table S1 provides county-level summaries). On average, 73.2 cardiovascular and 26.1 respiratory hospitalizations occurred per day, with the most admissions in New Haven County and the least in Hampden County. The data set contained 95,831 cardiovascular and 34,169 respiratory admissions. Analysis of PM_{2.5} filters for constituents generated 3,273 observation days, whereas the EPA monitoring network for constituents had 329 observation days for our study period and timeframe. Our data set included constituent data for Hartford County, which had no constituent monitor during the study period.

Table 2 summarizes estimated PM_{2.5} sources and constituent levels. Daily PM_{2.5} averaged 14.0 µg/m³ and was highest in New Haven County (average 17.0 µg/m³). The regional source, which relates to coal combustion and other factors, on average contributed the largest fraction (40.8%) of PM_{2.5} compared to other sources. Contributions of motor vehicles to PM_{2.5} were similar across counties (26.0-29.7% for any county). Hartford County had a higher percentage of PM_{2.5} from oil combustion (18.2%) than other counties. Correlations between PM_{2.5} sources were low (range -0.08-0.24) (Supplemental Material, Table S2). Correlations ≥ 0.60 were observed for several pairs of PM_{2.5} constituents, with the highest for Al and Si (0.96).

Figure 1 shows effect estimates for PM_{2.5}, sources, and constituents for cardiovascular or respiratory hospitalizations according to exposure lag. Central estimates for PM_{2.5} indicate positive associations for both outcomes and all lags, but only the lag 0 association with cardiovascular admissions was statistically significant (1.88%; 95% CI: 0.47, 3.31% for an IQR increase of 10.7 µg/m³). For PM_{2.5} sources, road dust was significantly associated with

respiratory hospitalizations (all lags), with the strongest association estimated for an IQR increase ($1.71 \mu\text{g}/\text{m}^3$) at lag 1 (4.51% increase; 95% CI: 3.30, 6.01%). Significant associations also were estimated for road dust and cardiovascular admissions (2.11%; 95% CI: 1.09, 3.15% at lag 0), and for sea salt and respiratory admissions (0.27%; 95% CI: 0.08, 0.47% for a $0.13 \mu\text{g}/\text{m}^3$ increase at lag 0).

Cardiovascular hospitalizations were significantly associated with BC (all lags), Ca (lag 0, 1.65%; 95% CI: 0.50, 2.82%), V (lags 0 and 1), and Zn (lag 0, 0.95%; 95% CI: 0.05, 1.86%) based on single pollutant models (Figure 1 and Table 3). For BC and V, associations were strongest for lag 0 (4.83%; 95% CI: 3.08, 6.62% for BC, and 1.16%; 95% CI: 0.43, 1.89% for V).

Respiratory admissions were significantly associated with Al, Ca, Cl, BC, Ni, Si, Ti, and V for all lags (Figure 1 and Table 3). Central effect estimates were highest for lag 1 for most constituents (Al, Ca, Si, Ti, and V), but were largest on the same day (lag 0) for Cl and Ni, and lag 2 had the strongest association for BC.

We performed sensitivity analyses of co-pollutant adjustment for associations with cardiovascular admissions (Table 3 and Figure 2), and respiratory admissions [Table 3, Figure 3, and Supplemental Material, Figure S2 (associations between chlorine and respiratory hospitalization shown on a narrower y-axis scale)]. In all cases, central effect estimates were in the same direction (i.e., positive associations), and most associations remained statistically significant, with some exceptions (e.g., V adjusted by BC). In particular, the association between same day Zn and cardiovascular hospitalizations lost statistical significance for most co-pollutant adjustments (central estimate range: 0.44-0.99%).

Discussion

Same day $PM_{2.5}$ was significantly associated with cardiovascular, but not respiratory admissions. Central estimates for $PM_{2.5}$ at lag 1 or 2 for cardiovascular admissions, and all lags for respiratory admissions, were positive but not significant. Previous studies explored $PM_{2.5}$ and hospitalizations for the Medicare population (Bell et al. 2008; Dominici et al. 2006). An earlier study for 202 U.S. counties estimated a 0.86% (95% posterior interval (PI): 0.63, 1.08%) increase in Medicare cardiovascular hospitalizations per IQR increase (for the IQR used in the present study) in same day $PM_{2.5}$, and a 0.44% (95% PI: 0.09, 0.79%) increase in respiratory hospitalizations for lag 2 $PM_{2.5}$ (Bell et al. 2008). In our 4-county study, we estimated a stronger association with cardiovascular admissions (1.88%; 95% CI: 0.47, 3.31% at lag 0) and a higher central estimate for respiratory admissions (0.59%; 95% CI: -1.35, 2.57% at lag 2). However, for counties in the Northeast U.S. (i.e., the region in which the present study was conducted), the previous study reported associations with $PM_{2.5}$ that were similar to our estimates (1.16% increase in cardiovascular admissions; 95% PI: 0.85, 1.47% and a non-significant 0.30% increase in respiratory admissions; 95% PI: -0.18, 0.78%). Therefore, although the previous study involved a larger study area and somewhat different methods, $PM_{2.5}$ findings were broadly consistent between the two studies.

Recent studies examined $PM_{2.5}$ constituents or sources and hospitalizations or other health outcomes (Bell et al. 2010; Ebisu and Bell 2012; Ostro et al. 2007; Valdes et al. 2012; Zhou et al. 2011). Whereas we estimated positive associations of BC with cardiovascular and respiratory admissions at all lags, a study of 119 U.S. counties reported an association between EC and cardiovascular Medicare admissions only at lag 0, and no association with respiratory admissions (Peng et al. 2009). Similarly, we estimated associations between Si and respiratory admissions at

all lags that were not identified in the national study. A study of cardiovascular admissions among residents of New York, NY ≥ 40 years of age estimated associations with 11 PM constituents, including 6 examined in the present study, and reported statistically significant associations for EC and Zn, but not Ni or Si (Ito et al. 2011), consistent with our study. However, cardiovascular admissions were significantly associated with Br in the New York study, in contrast with our study, and we identified significant associations with V that were not observed in the New York study. In a previous study of children (≤ 5 or ≤ 19 years of age) in 6 California counties, EC and Si, but not Zn or K, were associated with respiratory hospitalizations (Ostro et al. 2009). We also estimated associations of respiratory admissions with BC and Si, but not Zn or K, in our Medicare population (≥ 65 years of age). A recent study reported a significant association between EC and cardiovascular hospitalizations, and a non-significant positive association with respiratory hospitalizations, based on constituent data from a single monitoring station in Denver (Kim et al. 2012).

We estimated significant positive associations between cardiovascular admissions and $PM_{2.5}$ road dust (lag 0 and lag 1), and between respiratory admissions and road dust (all lags) and sea salt (lag 0 and lag 2). In contrast, a previous source apportionment study of $PM_{2.5}$ sources and hospitalizations in New York, New York (Lall et al. 2011) reported that soil $PM_{2.5}$, which is related to our road dust category, was not associated with respiratory or cardiovascular admissions, except for a significant negative association with cardiovascular admissions at lag 2. In addition, they reported a positive association between traffic $PM_{2.5}$ and cardiovascular admissions, in contrast with null findings for motor vehicle sources and cardiovascular admissions in our study. However, as in our study, Lall et al. did not identify associations

between traffic sources $PM_{2.5}$ and respiratory admissions, or associations of residual oil or S with respiratory or cardiovascular admissions.

Zanobetti et al. (2009) examined whether associations between $PM_{2.5}$ mass and hospitalization rates for 26 U.S. communities were modified by the chemical composition of the particles, instead of estimating associations between hospitalization and $PM_{2.5}$ constituents or sources directly. The authors reported that higher contributions of Ni and Br strengthened associations between $PM_{2.5}$ mass and cardiovascular hospitalization rates. Our findings were partly consistent, with a significant association between Ni and respiratory admissions, but no association of Br with respiratory or cardiovascular admissions. Our results indicated higher risk of respiratory admissions with higher levels of Ni and no associations for Br.

Our results on chemical constituents add to the body of evidence indicating that some $PM_{2.5}$ constituents and sources are more harmful than others. However, the specific constituents and sources that are associated with adverse health outcomes differ by study. This could relate to differences in populations or study designs, with some studies investigating the health risk of a specific constituent and others investigating how a constituent's contribution to $PM_{2.5}$ affects $PM_{2.5}$ relative risk estimates or other research questions. The apparent lack of consistency among findings may also relate to heterogeneity of the particle mixture. For example, a given constituent may reflect a different relative contribution of sources in one community than another (e.g., emissions from industry vs. traffic). The chemical composition of $PM_{2.5}$ from a specific source may differ across cities (e.g., traffic source affected by distribution of vehicle and fuel types and traffic patterns).

While all of the PM_{2.5} constituents that we studied have multiple sources, several were dominated by specific sources, and were therefore used as source indicators. In the study area, motor vehicles are a main contributor to Zn and BC, road dust to Si and Al, oil combustion to V and Ni, sea salt to Cl, and regional sources to S (Bell et al. 2010). However, in some instances we observed associations with sources, but not with their marker constituents. This could relate to uncertainties in source apportionment approaches or measures of constituents, the range of sources for each constituent, and variation in measurement quality. For example, while Al is produced from re-suspended soil, other sources include steel processing, cooking, and prescribed burning (Kim et al. 2005; Lee et al. 2005; Ozkaynak et al. 1996; Wang et al. 2005). V is produced from oil combustion, but also manufacture of electronic products and coke plant emissions (Wang et al. 2005; Weitkamp et al. 2005). Analysis with PMF may detect associations for sources, while marker constituents do not, or vice versa (Ito et al. 2004).

Additional research is needed to further investigate health consequences of PM_{2.5} constituents and sources, including how features of the concentration-response relationship may differ by particle type (e.g., lag structure, seasonal patterns). Other studies have reported seasonal patterns in PM_{2.5} associations with hospitalizations (Bell et al. 2008; Ito et al. 2011), but the limited timeframe of our data set, and the larger proportion of data collected during the winter than in the summer, prohibited extensive analysis by season. Results may not be generalizable to other locations or time periods. Even in a given location, the chemical composition of PM_{2.5} may change over time due to changes in sources.

Special consideration should be given to exposure methods, as spatial heterogeneity differs by constituent or source (Peng and Bell 2010). Use of a smaller spatial unit (e.g., zip code) could lessen exposure misclassification. An additional challenge is that key data for particle sources

and constituents may be unavailable. For example, our data set did not include organic composition or ammonium sulfate, and the sources identified using our factorization approach might have differed if additional data had been available. Minimum detection limits hinder our ability to estimate exposure for all constituents and to incorporate them in source apportionment methods. As constituent monitoring networks continue, data will expand with more days of observations available; however, such data are still substantially less than that of many other pollutants, and not all counties have such monitors.

Particle sources are of key interest to policy makers, but source concentrations cannot be directly measured and must be estimated using methods such as source apportionment, land-use regression, or air quality modeling. Our approach utilized $PM_{2.5}$ filters to provide an expansive data set of constituents for use in source apportionment. This method could be expanded to generate data beyond that of existing monitoring networks, but requires substantial resources.

Researchers have applied a variety of approaches to estimate how $PM_{2.5}$ constituents or sources affect health outcomes. One of the most commonly applied methods is use of constituent levels (or sources) for exposure, as applied here and elsewhere (e.g., Ebisu and Bell 2012; Gent et al. 2009; La et al. 2011). Other methods use the constituent's contribution (e.g., fraction) to $PM_{2.5}$ to estimate associations or as an effect modifier of $PM_{2.5}$ risk estimates (e.g., Franklin et al. 2008), residuals from a model of constituent on $PM_{2.5}$ (e.g., Cavallari et al. 2008), or interaction terms such as between $PM_{2.5}$ and monthly averages of the constituent's fraction of $PM_{2.5}$ (e.g., Valdés et al. 2012).

Mostofsky et al. (2012) summarized several such modeling approaches, noting that each method has distinct benefits and limitations, and answers different scientific questions. Our approach

(constituent levels) has the advantage of results that are readily interpretable, which can aid use of findings in other scientific disciplines and decision-making. However, potential limitations include confounding by co-varying constituents and $PM_{2.5}$ in situations where $PM_{2.5}$ is associated with the health outcome. Including a variable for $PM_{2.5}$ in the model with the constituent addresses confounding by $PM_{2.5}$, but does not address potential confounding by co-varying constituents, and could over-adjust if the constituent and $PM_{2.5}$ are correlated, which is likely for constituents representing a large proportion of $PM_{2.5}$ total mass. Methods based on residuals of models of constituents on $PM_{2.5}$ address confounding by $PM_{2.5}$, but produce results that are difficult to interpret and do not estimate relative risk based on the absolute magnitude of a change in constituent level.

The results of various approaches should be interpreted in the context of the scientific question they address and the method's limitations. Mostofsky et al. (2012) applied six approaches to analysis of constituents and risk of ischemic stroke onset, finding fairly similar results across methods with the same constituents identified as those with the largest risk estimates. The authors note that although effect estimates are not directly comparable across methods, the relative ranking of constituents' estimates was similar across methods. We applied one of the methods discussed in Mostofsky et al. (2012) to adjust key constituent results by $PM_{2.5}$. Findings were similar to main results, with identical rankings of central estimates for key results in Table 3 (results not shown).

Our results contribute to growing evidence that some particle types are more harmful than others. This suggests that policies aimed at restricting some sources more than others may be more effective for protecting health than regulating particle mass. As research on air pollution and health moves towards a multi-pollutant approach (Dominici et al. 2010; Li et al. 2011), policy

makers will have better information to develop multi-pollutant regulations to protect public health. $PM_{2.5}$ levels that meet current regulations may still be harmful if there exists no threshold below which $PM_{2.5}$ is not associated with health (Anenberg et al. 2010; Brauer et al. 2002), but also if the composition of $PM_{2.5}$ below regulatory standards has higher than normal contributions from harmful constituents.

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Table 1. Summary of hospital admissions data.

	Mean \pm SD (admissions/day)	Median (admissions/day)	IQR (admissions/day)	Total admissions across study period
Cardiovascular	73.2 \pm 14.0	73	20	95,831
Respiratory	26.1 \pm 9.3	24	10	34,169

Table 2. Summary of exposure estimates for PM_{2.5} sources and chemical constituents, across all counties.

	Mean ± SD	Median	IQR	Percent of PM_{2.5} total mass
PM_{2.5} (µg/m³)	14.0 ± 9.37	11.7	10.7	n/a
Al	0.041 ± 0.048	0.0285	0.0353	0.29%
BC	1.08 ± 1.000	0.7788	1.32	7.71%
Br	0.0018 ± 0.002	0.0014	0.0023	0.01%
Ca	0.033 ± 0.027	0.0257	0.0275	0.24%
Cl	0.016 ± 0.076	0.0031	0.0079	0.12%
Ni	0.0033 ± 0.004	0.0020	0.0033	0.02%
K	0.049 ± 0.035	0.0403	0.0333	0.35%
S	1.27 ± 1.045	0.9710	0.975	9.07%
Si	0.072 ± 0.092	0.0479	0.0625	0.52%
Ti	0.0051 ± 0.005	0.0040	0.0043	0.04%
V	0.0052 ± 0.008	0.0029	0.0052	0.04%
Zn	0.018 ± 0.018	0.0126	0.0150	0.13%
Source				
Motor vehicle	3.91 ± 4.31	2.53	3.79	28.0%
Oil combustion	1.82 ± 2.50	1.07	2.09	13.1%
Road dust	1.67 ± 1.93	1.05	1.71	12.0%
Regional source	5.69 ± 6.41	3.62	5.34	40.8%
Sea salt	0.244 ± 0.92	0.05	0.13	1.75%
Weather				
Temperature (°C)	49.4 ± 18.2	49.7	30.46	n/a
Dew point temperature (°C)	40.2 ± 19.1	40.6	30.80	n/a

Table 3. Summary of results for co-pollutant adjustment for PM_{2.5} chemical constituents and associations with cardiovascular or respiratory hospital admissions, for constituents with significant associations in single pollutant models.

Pollutant	Hospitalization cause	Lag	Single pollutant effect (% increase in risk per IQR increase in pollutant)	Co-pollutant adjustment ^a		Range of central effect estimates (%)
				Robust to adjustment by:	Not robust to adjustment by:	
Ca	Cardiovascular	0	1.65 (0.50,2.82)	Br, Cl, K, Ni, S, Zn	V	1.18 to 2.01
BC	Cardiovascular	0	4.83 (3.08,6.62)	Al, Br, Cl, K, Ni, Si, S, Ti, V	n/a	4.48 to 6.00
V	Cardiovascular	0	1.16 (0.43,1.89)	Al, Br, Ca, Cl, K, Si, S, Ti, Zn	BC	0.39 to 1.17
Zn	Cardiovascular	0	0.95 (0.05,1.86)	Cl	Al, Br, Ca, Ni, Si, S, Ti, V	0.44 to 0.99
Al	Respiratory	1	2.74 (1.62,3.88)	Br, Cl, BC, Ni, K, S, V, Zn	n/a	1.99 to 4.34
Ca	Respiratory	1	4.31 (2.61,6.03)	Br, Cl, Ni, K, S, V, Zn	n/a	3.13 to 6.82
Cl	Respiratory	0	0.24 (0.09,0.39)	Al, Br, Ca, BC, Ni, K, S, Si, Ti, V, Zn	n/a	0.19 to 0.24
BC	Respiratory	2	7.20 (4.64,9.82)	Al, Br, Cl, Ni, K, S, Si, Ti, V	n/a	5.71 to 9.54
Ni	Respiratory	0	2.92 (1.66,4.19)	Al, Br, Ca, Cl, K, S, Si, Ti, Zn	BC	1.34 to 3.21
Si	Respiratory	1	2.41 (1.41,3.42)	Br, Cl, BC, Ni, K, S, V, Zn	n/a	1.70 to 3.75
Ti	Respiratory	1	3.47 (2.30,4.65)	Br, Cl, BC, Ni, K, S, V, Zn	n/a	2.77 to 4.19
V	Respiratory	1	2.75 (1.76,3.75)	Al, Br, Ca, Cl, BC, K, S, Si, Ti, Zn	n/a	1.92 to 2.98

^aIn this table, associations are considered robust to co-pollutant adjustment if they remain statistically significant; associations are not considered robust to co-pollutant adjustment if they lose statistical significance.

Figure Legends

Figure 1. Percent change in risk of cardiovascular or respiratory hospital admissions per IQR increase in exposure to PM_{2.5} sources, PM_{2.5} total mass, or PM_{2.5} chemical constituents. The point represents the central estimate; the horizontal line represents the 95% confidence interval. IQR values correspond to those in Table 1.

Figure 2. Percent change in risk of cardiovascular hospital admissions per IQR increase in exposure to PM_{2.5} constituent, with adjustment by other PM_{2.5} constituents calcium, black carbon, vanadium and zinc. The point represents the central estimate; the horizontal line represents the 95% confidence interval. IQR values correspond to those in Table 1.

Figure 3. Percent change in risk of respiratory hospital admissions per IQR increase in exposure to selected PM_{2.5} constituents with adjustment by other PM_{2.5} constituents. The point represents the central estimate; the horizontal line represents the 95% confidence interval. IQR values correspond to those in Table 1.

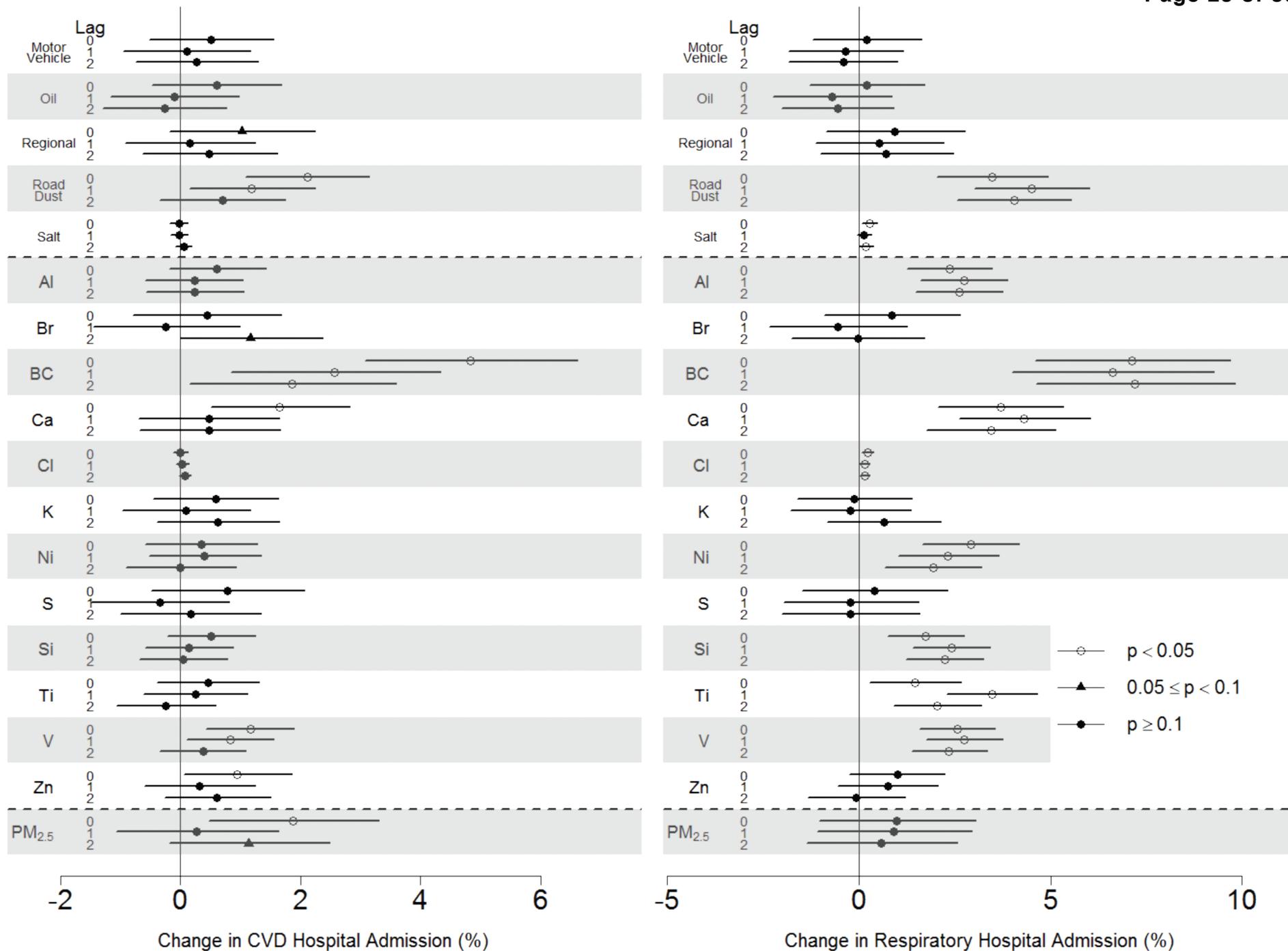


Figure 1.

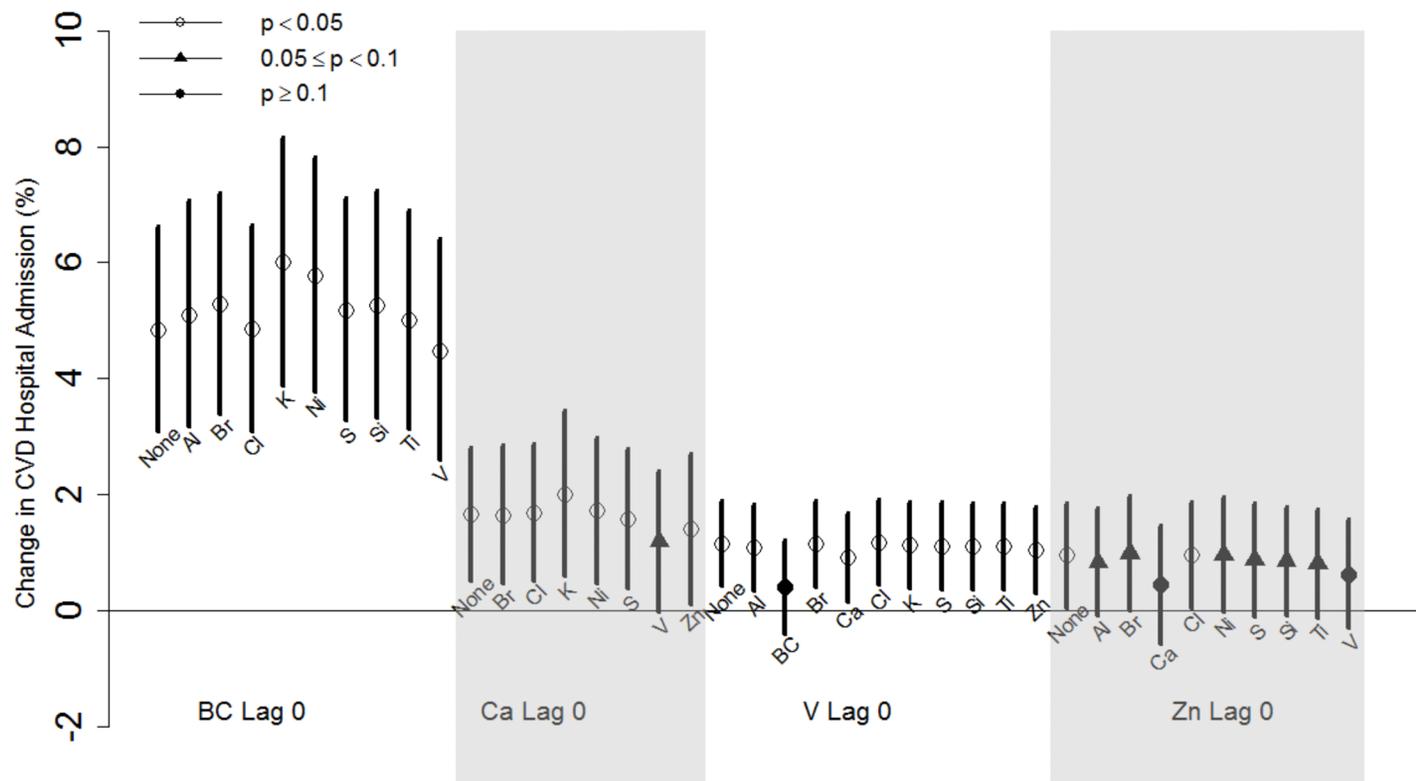


Figure 2.

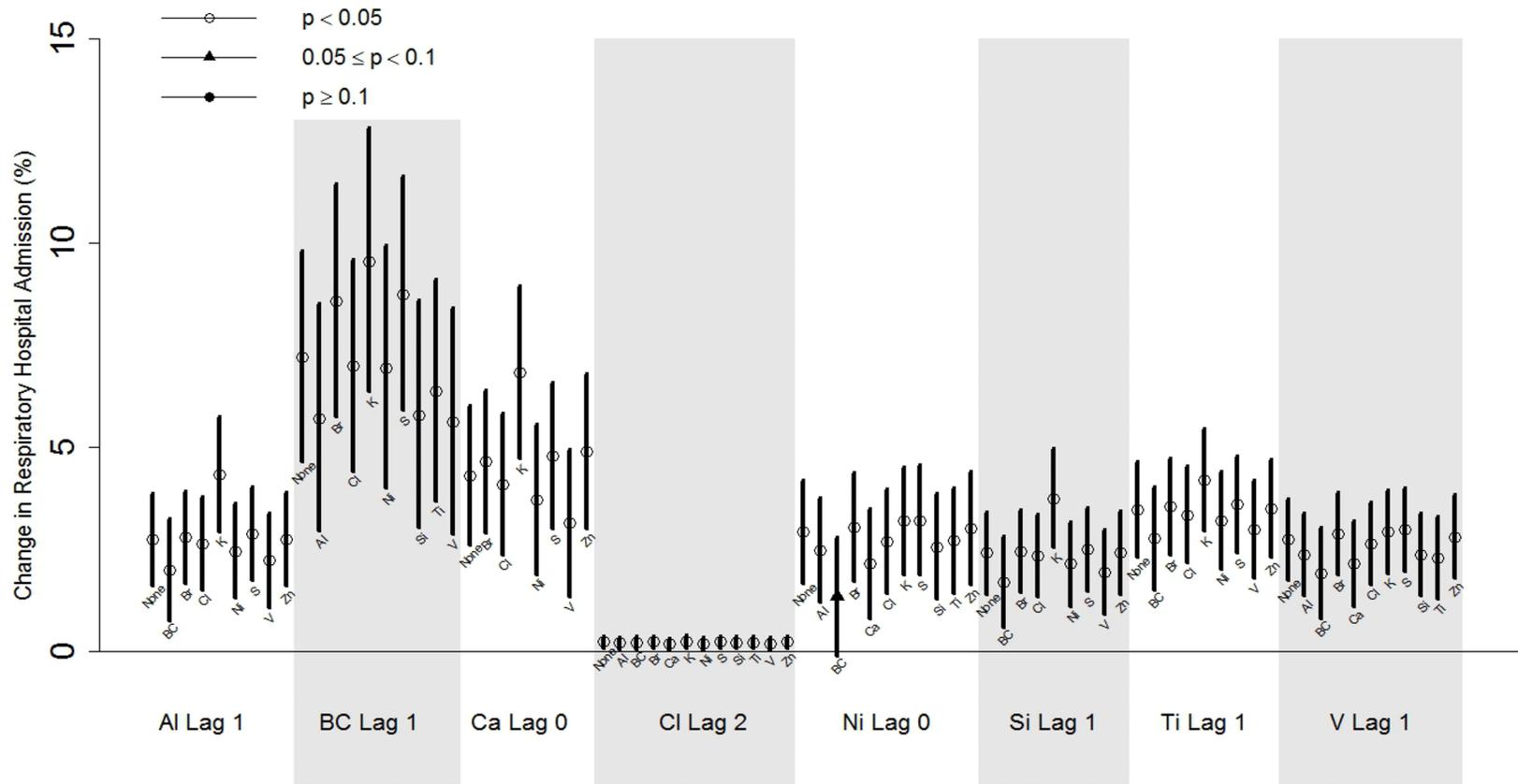


Figure 3.