

PM_{2.5} and Survival Among Older Adults Effect Modification by Particulate Composition

Marianthi-Anna Kioumourtoglou,^a Elena Austin,^c Petros Koutrakis,^a Francesca Dominici,^b
Joel Schwartz,^a and Antonella Zanobetti^a

Background: Fine particulate (PM_{2.5}) air pollution has been consistently linked to survival, but reported effect estimates are geographically heterogeneous. Exposure to different types of particle mixtures may explain some of this variation.

Methods: We used k-means cluster analyses to identify cities with similar pollution profiles, (ie, PM_{2.5} composition) across the United States. We examined the impact of PM_{2.5} on survival, and its variation across clusters of cities with similar PM_{2.5} composition, among Medicare enrollees in 81 US cities (2000–2010). We used time-varying annual PM_{2.5} averages, measured at ambient central monitoring sites, as the exposure of interest. We ran by-city Cox models, adjusting for individual data on previous cardiopulmonary-related hospitalizations and stratifying by follow-up time, age, gender, and race. This eliminates confounding by factors varying across cities and long-term trends, focusing on year-to-year variations of air pollution around its city-specific mean and trend. We then pooled the city-specific effects using a random effects meta-regression. In this second stage, we also assessed effect modification by cluster membership and estimated cluster-specific PM_{2.5} effects.

Results: We followed more than 19 million subjects and observed more than 6 million deaths. We found a harmful impact of annual PM_{2.5} concentrations on survival (hazard ratio = 1.11 [95%

confidence interval = 1.01, 1.23] per 10 µg/m³). This effect was modified by particulate composition, with higher effects observed in clusters containing high concentrations of nickel, vanadium, and sulfate. For instance, our highest effect estimate was observed in cities with harbors in the Northwest, characterized by high nickel, vanadium, and elemental carbon concentrations (1.9 [1.1, 3.3]). We observed null or negative associations in clusters with high oceanic and crustal particles.

Conclusions: To the best of our knowledge, this is the first study to examine the association between PM_{2.5} composition and survival. Our findings indicate that long-term exposure to fuel oil combustion and power plant emissions have the highest impact on survival.

(*Epidemiology* 2015;XXX: 00–00)

Long-term exposure to fine particulate matter (PM_{2.5}, ie, particles with aerodynamic diameter ≤ 2.5 µm) has been consistently associated with adverse health, including mortality.^{1,2} The effects of long-term PM_{2.5} exposure on mortality have been shown to differ in magnitude by location. Pelucchi et al³ found heterogeneous effects of long-term PM_{2.5} exposure on mortality across Europe, in a review meta-analysis of six studies, whereas Hoek et al⁴ in a large review of cohort studies on PM_{2.5} and mortality, also found both a notable pooled effect estimate and heterogeneity in effects across studies, likely due to differences in particle composition and population characteristics. Similarly, Zeger et al⁵ found heterogeneous effects across the United States, with the highest effects in the central United States, somewhat lower, effects in the eastern United States, and no effects in the West. Many factors have been identified that influence the heterogeneity in the effect estimates^{6–9}; differences in particulate composition, specifically, have been proposed as a key contributing factor to this heterogeneity.⁴

Nationwide studies have shown that particulate composition varies across the United States.¹⁰ To date, several studies have assessed the association between particulate components or sources and acute adverse effects. Franklin et al¹¹ found increased non-accidental mortality rates when PM_{2.5} mass contained a higher proportion of arsenic, sulfate, silicon, or nickel, in a study conducted in 25 US communities. These results are in agreement with a recent study¹² reporting modification of sulfate and silicon on the 2-day PM_{2.5} and all-cause

Submitted 29 May 2014; accepted 22 January 2015.

From the Departments of ^aEnvironmental Health, ^bBiostatistics, Harvard School of Public Health, Boston, MA; and ^cDepartment of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA.

This publication was developed under a STAR Research Assistance Agreement No. RD-834900 and was also made possible by USEPA STAR Fellowship Assistance Agreement no. FP-9172890-01, Grant RD 83479801, and R834894 awarded by the US Environmental Protection Agency. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the USEPA. Furthermore, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication. This publication was also made possible by training grant NIH T32 ES007069 and by NIEHS ES0002.

Disclosure: The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

This content is not peer-reviewed or copy-edited; it is the sole responsibility of the author.

Correspondence: Marianthi-Anna Kioumourtoglou, 401 Park Drive, Landmark Building, 3rd Floor East, PO Box 15697, Boston, MA 02215.
E-mail: marianthi.anna@mail.harvard.edu.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 1044-3983/15/XXX-0000

DOI: 10.1097/EDE.0000000000000269

mortality association. Krall et al¹³ directly linked short-term exposures to elemental and organic carbon, and silicon to mortality. Zanobetti et al¹⁴ found the association between PM_{2.5} and cardiovascular (CVD) admissions to be higher when the mass was high in bromine, chromium, nickel, and sodium. Bell et al¹⁵ reported associations between CVD emergency admissions and exposure to nickel, as well as vanadium and elemental carbon. Similarly, Peng et al¹⁶ and Tolbert et al¹⁷ found that increases in elemental carbon and organic carbon are associated with increase in risk of CVD emergency admissions.

It has not yet been determined, however, whether particle composition also modifies the association between long-term PM_{2.5} exposures and mortality, and whether it explains some of the observed effect heterogeneity across locations and studies. A recent European study, investigating the association between PM_{2.5} components and CVD survival, reported no important associations between any of the PM_{2.5} components and CVD mortality.¹⁸

Notably, studies of long-term effects of PM_{2.5} on survival rely on primarily cross-sectional exposure contrasts and, hence, are subject to potential confounding by factors that vary across cities. Moreover, such studies traditionally follow cohorts over time and examine the association of survival time with PM_{2.5} in a Cox proportional hazards model, where most of the exposure contrast is across cities. Causal modeling, in contrast, seeks to estimate the difference in the expected value of mortality in the population under the exposure they received versus what it would have been had they received an alternative exposure. Because that counterfactual cannot be observed, various methods—such as instrumental variables,¹⁹ marginal structural models,²⁰ and Mendelian randomization²¹—seek legitimate surrogates for the unobserved potential outcome. Mendelian randomization, for example, can be thought as a method for observational studies that is analogous to randomized trials, with the goal of making causal inferences about modifiable risk factors and adverse health, by focusing on variations in exposure thought to be uncorrelated with factors confounding the exposure-outcome association.²²

For this study, we focused on within-city year-to-year fluctuations in PM_{2.5} about its long-term trend, as representing exposure variations that are unlikely to be confounded. For example, a variable usually included as a confounder in PM_{2.5}-mortality studies is smoking. Smoking rates likely vary across cities, within cities across years, and within cities and years, across individuals. Our method seeks to decompose these three sources of variation. By conducting city-specific analyses, any potential confounding by factors varying across cities is eliminated. By removing long-term trends, any potential confounding by long-term trends in within-city smoking trends is also eliminated. Finally, as we estimate city-specific annual PM_{2.5} averages and, thus, assign the same exposure to all subjects within city and year, confounding by varying smoking rates across individuals is also not possible. Our

results, therefore, could only be confounded by variables that fluctuate with PM_{2.5} across their long-term trends. Given that these fluctuations in yearly PM_{2.5} concentrations occur mostly due to weather conditions, such as prevailing wind direction, any residual confounding is unlikely. With this method, hence, we approximate randomization of exposure with respect to confounders. We applied this approach to all-cause mortality data from Medicare enrollees from 81 cities, an open cohort of more than 19 million subjects. Although effect modification by other factors is likely,^{6–9} in this study we further examine whether particulate composition, specifically, modifies the PM_{2.5}-mortality relationship.

METHODS

Data Collection

Study Population

We obtained data from fee-for-service Medicare beneficiaries (≥65 years of age) from 81 cities across the United States for the years 2000–2010. Each Medicare record contains information on age, race, zip code, county, and state of residence. Furthermore, for subjects hospitalized during this period, we obtained records for the dates and diagnoses of each admission. Specifically, using codes from the *International Classification of Diseases*, 9th Revision (ICD-9; Center for Disease Control and Prevention 2008), we obtained admission records for congestive heart failure (CHF; code 428), myocardial infarction (MI; code 410), chronic obstructive pulmonary disease (COPD; codes 490–492, 494–496), and diabetes (code 250), as well as severity of each admission, expressed by the number of days spent in the coronary or intensive care units.

Medicare is an open cohort; subjects entered our cohort in 2000 or upon their enrollment after 2000. After enrollment, each subject was followed over time until the year of their death or December 2010 (end of our study period).

Although the Medicare data do not have information on individual-level behavioral risk factors (eg, smoking and body mass index), they do have rich individual-level information on cause-specific hospitalizations and age, sex, race, and zip code-level of residence. In addition, it has been shown that use of these data yield effect estimates that are similar to previously published studies that had included individual-level variables in their analyses.²³ Furthermore, our focus on year-to-year fluctuations in PM_{2.5} about its within-city trend makes it unlikely that potential individual-level confounders, such as individual socioeconomic status, smoking, and diet, fluctuate similarly and are correlated with our exposure.

Air Pollution Data

We obtained PM_{2.5} and particulate component data from the US Environmental Protection Agency's (EPA) Air Quality System database (<http://www.epa.gov/ttn/airs/airsaqs/detail-data/downloadaqsdata.htm>). In our analyses, we included sites

with at least 75% non-missing observations, both total and in each season, and calculated annual PM_{2.5} and PM_{2.5} component means. We chose 81 cities satisfying these criteria.

The PM chemical species included in the clustering were the ions nitrate, sodium ion, potassium ion, sulfate, ammonium, the elements sulfur, copper, iron, zinc, nickel, vanadium, titanium, magnesium, potassium, silicon, sodium, chlorine, calcium, bromine, strontium, lead and manganese, elemental carbon, and organic carbon. PM_{2.5} monitoring sites are population-oriented, measuring exposures where people live and work.²⁴ In our study, we used data from between one monitor per city up to 10 monitors in large Metropolitan Statistical Areas, such as New York, NY, and Los Angeles, CA. For speciated PM_{2.5} data, there was only one available monitor per city, with the exception of New York, NY (n = 3), St. Louis, MO (n = 2), Cleveland, OH (n = 2), Philadelphia, PA (n = 2), and Milwaukee, WI (n = 2). When more than one monitor was available in a city, we calculated annual city-specific averages.

Data Analysis

Spatial Clustering Based on PM_{2.5} Composition

To identify cities with similar long-term PM_{2.5} composition, we performed a cluster analysis, as described by Austin et al.²⁵ In brief, modified Z scores for each chemical species were calculated using the ratio of the species average between January 2003 and December 2008 at each site, divided by the corresponding PM_{2.5} concentration at that site. We then employed the k-means clustering algorithm to cluster together sites that have the most similar PM_{2.5} composition, using the Z scores. A detailed description of the clustering algorithm we employed is presented in the eAppendix (<http://links.lww.com/EDE/A889>).

Health Models

In contrast to prior studies, we fit separate survival analyses in each city, to avoid confounding by factors varying across cities. We employed Cox's proportional hazards models, with age (5-year categories), sex, race, and follow-up time as the stratification variables. Follow-up started on January 1st after entry into the cohort, and we used annual PM_{2.5} mass concentrations as time-varying exposures for all participants. We used the counting process extension of the proportional hazards model by Andersen and Gill,²⁶ thus creating multiple observations for each subject, with each observation representing a single person-year of mortality follow-up.

We adjusted linearly for year, thus estimating whether year-to-year PM_{2.5} variations around its long-term trends are associated with year-to-year survival variations in each city. Also, this eliminates confounding due to long-term trends. To increase the precision of the estimated effects, we adjusted for any previous admission for CHF, COPD, MI, or diabetes, as well as number of days spent in the intensive and coronary care units. These outcomes were selected based on their known association with mortality.²⁷ We also adjusted for zip

code-level median income, as a proxy for socioeconomic status, using zip code level data obtained from the 2000 US Census Bureau (Census 2000, <http://www.census.gov>). Finally, as a sensitivity analysis, we included annual city-specific smoking rates, obtained from the Behavioral Risk Factor Surveillance System (<http://www.cdc.gov/brfss/>), as a control to assess whether our method is indeed robust to confounding by smoking.

We combined the city-specific health effect estimates in a second stage, using a random effects meta-analysis.²⁸

Effect Modification by Particulate Composition

We also investigated whether the association between long-term PM_{2.5} exposure and mortality is modified by PM_{2.5} composition. To do so, we added dummy variables for each cluster in the second-stage meta-regression and thus obtained the estimated deviation from the overall effect of PM_{2.5} in each cluster, assessing whether the effect estimate in a specific cluster was significantly different from the pooled effect estimate.

All results are presented per 10 µg/m³ of PM_{2.5}. For our statistical analyses, we used the SAS software, version 9.3 (SAS Institute Inc., Cary, NC), and the R Statistical Software, version 2.14.1 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The distribution of number of subjects, deaths, and cause-specific hospitalizations in the 81 cities in our study are presented in the Table. Our cohort consisted of 19,274,534 subjects and we observed 6,383,358 deaths (33.1%) before the end of follow-up. On average, the participants were age 75.3 years (SD = 7.5); 57.6% were female and 87% white.

The average PM_{2.5} concentration was 12.8 µg/m³ (SD = 1.7). Overall, we observed positive associations between long-term exposure to PM_{2.5} and mortality, with a hazard ratio (HR) of 1.11 (95% confidence interval [CI] = 1.01, 1.23) per 10 µg/m³ increase in the annual PM_{2.5} concentrations. Including annual city-specific smoking rates in the model did not affect the estimated HRs.

Effect Modification by Particulate Composition

Spatial Clusters

We identified 21 unique clusters: four single-city clusters, six clusters with two cities, and 11 clusters with three or more cities. A map of all clusters is presented in eFigure 1 (<http://links.lww.com/EDE/A889>). The chemical characteristics of each cluster are presented in a heat map (eFigure 2; <http://links.lww.com/EDE/A889>), whereas detailed ratios of species over PM_{2.5} concentrations by cluster are presented in eFigure 3 (<http://links.lww.com/EDE/A889>).

In brief, clusters can be described in six general groups. The clusters in the first group (clusters 1–5 and 7) are located in the eastern United States, and they have high sulfate concentrations, consistent with power plant regional

TABLE. Distribution of Number of Subjects, Deaths, and Cause-specific Admissions, Presented as Percentiles Across the 81 Cities

	5%	25%	50%	75%	95%	Total
No. subjects	26,552	68,712	129,158	253,698	833,786	19,274,534
No. deaths	9,105	23,909	42,689	90,500	303,496	6,383,358
No. admissions						
Diabetes	2,739	7,472	13,098	22,069	59,575	1,801,223
CHF	931	2,772	4,644	8,488	26,401	686,430
MI	859	1,636	3,405	6,051	17,950	457,241
COPD	479	1,493	2,425	4,755	14,006	356,104

CHF indicates congestive heart failure; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease.

emissions. The clusters in the second group (clusters 6, 8, and 11) are located in the Midwest and are characterized on average by high sulfate, nitrate, and metal concentrations, such as manganese, zinc, iron, and lead, indicating more industrialized areas including smelters or metallurgical activity. The clusters in the third group (clusters 10, 13, and 16) include cities with large seaports and are characterized by high sodium, chlorine, and potassium concentrations, associated with oceanic particles, and high nickel and vanadium concentrations, consistent with heavy fuel oil combustion from ships. The clusters in the fourth group (clusters 12 and 14) are located inland in the western United States and have high crustal element concentrations, such as calcium, silicon, titanium, and iron. Clusters in the fifth group (clusters 9, 15, and 17) do not show a geographic cohesiveness, as they are located throughout the western and central United States. They are characterized by low sulfate and high concentrations of nitrate and K, associated with agricultural activities and biomass burning, and crustal elements. Finally, the sixth grouping contains the four single-city clusters (eAppendix; <http://links.lww.com/EDE/A889>).

PM_{2.5} Composition and Mortality

The effects of PM_{2.5} by cluster are presented in the Figure and in eTable 2 (<http://links.lww.com/EDE/A889>). We observed varying effect estimates across clusters, with most HRs higher than the null. Specifically, we found that the effect estimates were different than the pooled average in four clusters (namely clusters 2, 10, 13, and 16) and marginally different in clusters 8 and 11. The CIs in part reflect the number of cities within a cluster, with single-city clusters having the widest CIs.

The highest effect estimate was observed in cluster 16 (HR = 1.9 per 10 µg/m³ of PM_{2.5} [95% CI = 1.1, 3.3]). Cluster 16 contains Seattle, WA, and Portland, OR, and is characterized by high elemental carbon, nickel, and vanadium concentrations. High effect estimates were also observed in cluster 10 (1.7 [1.1, 2.7]), containing cities with harbors in the southern and southeastern United States and also characterized by high vanadium concentrations. In cluster 2, the observed HR was 1.5 (1.1, 1.9); cluster 2 includes several Southeastern cities and is characterized by very high sulfate concentrations. High

effects were also observed in cluster 11 (1.5 [0.94, 2.4]), a cluster containing Midwestern cities with high concentrations of metals consistent with industrial processes, such as lead, manganese, and zinc, as well as sulfate. We also observed a high effect estimate in Birmingham, AL (1.7 [0.76, 3.6]). Birmingham has the highest elemental carbon concentrations, as well as high concentrations of the metals manganese, zinc, lead, and iron, consistent with emissions from industrial facilities located in the area.

In cluster 13, we observed lower PM_{2.5} effects compared with the pooled effect across all cities (0.44 [0.25, 0.77]). Cluster 13 contains San Diego and Ventura, CA, and is characterized by high concentrations of oceanic particles, as indicated by the high sodium, chlorine, and potassium levels, as well as high nitrate concentrations. Lower effects were also observed in cluster 15 (0.65 [0.34, 1.3]) and cluster 14 (0.77 [0.43, 1.4]) that both have high concentrations of crustal species.

DISCUSSION

We conducted a nationwide, multi-year study to assess the effect of long-term PM_{2.5} exposures on mortality, using data from Medicare enrollees. We followed more than 19 million subjects between 2000 and 2010, with more than 6 million deaths, and observed harmful effects associated with a 10 µg/m³ increase in annual PM_{2.5}. We also examined whether the observed effects are modified by particle composition, as defined by clusters of PM_{2.5} species concentrations. Our analyses suggest that exposure to different PM_{2.5} mixtures results in varying effects on mortality.

Contrary to previous studies of air pollution and survival, we conducted our analyses by city, eliminating confounding that could arise by factors varying across cities. We investigated whether year-to-year PM_{2.5} fluctuations, about its long-term mean, are associated with year-to-year mortality fluctuations within-city. This design also eliminates potential confounding by long-term trends. Although this design could lead to loss of power, this is likely not an issue in this study, given the very large size of our cohort.

An exposure increase in 10 µg/m³ of annual PM_{2.5} average was associated with a HR of 1.11 (95% CI = 1.01, 1.23).

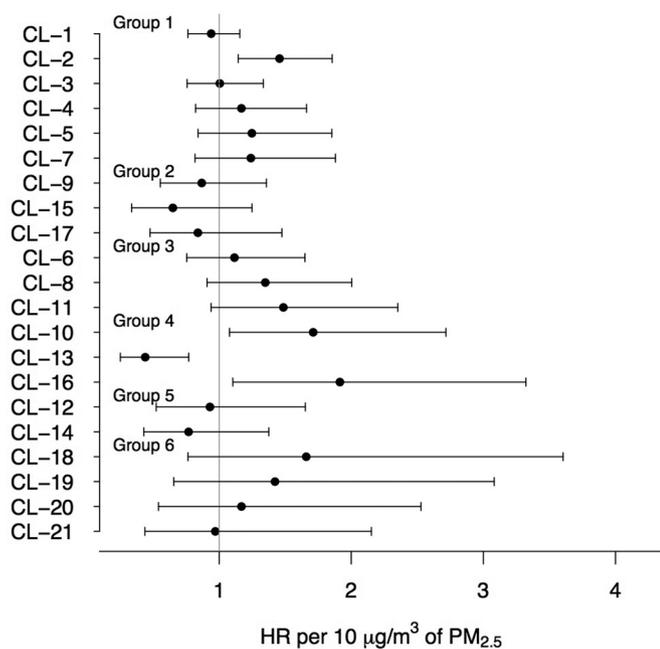


FIGURE. Within-cluster (CL) estimated HR per 10 $\mu\text{g}/\text{m}^3$ of PM_{2.5} (circles) and 95% CIs (lines). The results are ordered according to six groups of clusters.

This result is in very good agreement with previously published mortality effects.⁴ Specifically, a recent paper using data from the ESCAPE cohort reported HR = 1.13 (95% CI = 1.01, 1.25) per 10 $\mu\text{g}/\text{m}^3$ of PM_{2.5},²⁹ and the most recent reanalysis of the Harvard Six City Study reported a HR of 1.14 (95% CI = 1.07, 1.22).³⁰ Although we were not able to include potential confounders at the individual level in our analyses, we believe that any bias is likely to be small given the design's focus on pollution fluctuations unlikely to be associated with those confounders, the similarities of our findings with other studies, the very large number of subjects included, and the use of hospital admissions as proxies for health conditions. In a direct comparison of the Medicare cohort with the Harvard Six Cities study and the American Cancer Society study, conducted in the same cities as these two cohorts, Eftim et al²³ also showed that use of Medicare data for mortality analyses is appropriate.

Although several studies have assessed the effects of PM_{2.5} species,^{11,13} and sources,³¹ on acute mortality, no studies have investigated the relationship between particulate mixtures and survival. Only one study in Europe, also using ESCAPE data, assessed the effect of exposure to PM_{2.5} species on CVD survival.¹⁸ For that study, 19 cohort-specific Cox proportional hazard models were run and a combined effect estimate was calculated with a random effects meta-analysis. The authors assessed exposures to copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc and found no associations with any species, with the exception of suggestive evidence of an association with sulfate. The main difference between that study and ours is that they used time-invariant

PM_{2.5} species concentrations, predicted at the residences of the study participants using Land Use Regression Models.

We employed a clustering algorithm to identify cities with similar mixtures of air pollution and assessed the effect of these mixtures on survival. We observed the highest associations in clusters 10 and 16. These clusters included cities with harbors and were characterized by high nickel and vanadium concentrations, and low ratios of nickel and vanadium, indicating high emissions from ship heavy fuel oil (bunker fuel) combustion.³² High effects in cities with high concentrations of these two metals are consistent with prior literature of harmful impacts of fuel oil combustion on acute health.^{33–35} Toxicological studies also support the epidemiologic evidence.^{36–38}

We also observed strong effects in clusters with high secondary particle concentrations, such as clusters 2 and 10. In these clusters, we observed low elemental carbon to organic carbon ratios, indicating large secondary contributions, and high sulfate concentrations. Sulfate is associated with sulfur dioxide power plant emissions,^{39,40} and is formed in the atmosphere by photochemical reactions,⁴¹ leading to high spatial homogeneity.⁴² Studies of acute outcomes have also observed increased effects of sulfate-rich secondary PM_{2.5} concentrations and power plant emissions.^{35,43}

Finally, exposures to air pollution in industrialized areas, such as cluster 11 and Birmingham, AL, were also associated with survival in our analyses. Industrial emissions are usually characterized by high concentrations of transition metals, including iron, zinc, manganese, and copper, as well as lead. Transition metals are capable of redox recycling; exposure to airborne transition metals, therefore, can lead to oxidative stress, which underlies in part the toxicity of ambient particles.⁴⁴ It has also been shown, in a rat study, that transition metals are a key determinant of acute inflammatory responses.⁴⁵

We found no, or opposite, effects in clusters with high concentrations of crustal and oceanic particles. This is contrary to some studies of acute effects; Zanobetti et al,¹⁴ for instance, reported an association between sodium exposures and CVD admissions, and Krall et al¹³ observed an association between Si and mortality. This suggests that short-term exposures to such particles are related to acute effects, but the biological pathways for survival could be different.

The compositional pollution profile of each city likely plays a role in particle toxicity. For instance, we observed high effect estimates for clusters 10 and 16, but very low effect estimates in cluster 13, with all clusters belonging in the same group. We also observed high contributions of nickel and vanadium to PM_{2.5} concentrations in cluster 13, albeit not as high as in clusters 10 and 16, and very high oceanic contributions (eFigure 3; <http://links.lww.com/EDE/A889>). This suggests that exposure to different air pollution mixtures, and not solely sources, impacts survival. The possibility of effect modification by other factors, nevertheless, cannot be

excluded; investigation of multiple potential effect modifiers, however, was not within the scope of this study.

This study has some limitations. Information on individual characteristics, such as smoking and weight, is not available for Medicare enrollees. Given our choice of study design, however, any differences in such variables across cities, or within-city long-term trends, cannot confound our estimates. Also, Medicare does not provide the underlying cause of death; we were, thus, able to assess only all-cause mortality.

In addition, we analyzed only species provided by the EPA Speciation Trends Network that satisfied our inclusion criteria. The resulting air pollution mixtures, therefore, might not accurately describe the actual mixtures to which the subjects are exposed. This could result in measurement error, if a city is assigned to the wrong cluster. However, any such error is non-differential with respect to mortality and could only bias our results toward the null. Another source of measurement error, also non-differential in this setting, could arise from use of PM_{2.5} concentrations measured at central ambient monitors. This error has been shown to bias effect estimates toward the null, with more bias expected with larger contributions of local sources to the PM_{2.5} concentrations.⁴⁶

In conclusion, we observed harmful associations between PM_{2.5} and survival. More importantly, we showed that these associations vary depending on the different types of air pollution mixtures, with higher effects observed in cities with high concentrations of fuel oil combustion particles, indicating harbor-related emissions, and sulfate, a tracer for power plant emissions. Findings of our study can be used to inform policy for targeted source-specific regulations. To the best of our knowledge, this is the first study that provides strong evidence that chronic effects of PM_{2.5} on mortality are modified by simultaneous exposures to multiple PM_{2.5} components.

REFERENCES

- Dockery DW, Pope CA, Xu X, et al. An association between air pollution and mortality in six US cities. *N Engl J Med*. 1993;329:1753–1759.
- Krewski D, Jerrett M, Burnett RT, et al. Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality. Health Effects Institute, Boston, MA, December 2009. Research Report 140.
- Pelucchi C, Negri E, Gallus S, Boffetta P, Tramacere I, La Vecchia C. Long-term particulate matter exposure and mortality: a review of European epidemiological studies. *BMC Public Health*. 2009;9:453.
- Hoek G, Krishnan R, Beelen R, et al. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environmental Health*. 2013;12:43.
- Zeger SL, Dominici F, McDermott A, Samet JM. Mortality in the medicare population and chronic exposure to fine particulate air pollution in urban centers (2000–2005). *Environ Health Perspect*. 2008;116:1614–1619.
- Janssen NA, Schwartz J, Zanobetti A, Suh HH. Air conditioning and source-specific particles as modifiers of the effect of PM(10) on hospital admissions for heart and lung disease. *Environ Health Perspect*. 2002;110:43–49.
- Bell ML, Ebisu K, Peng RD, Dominici F. Adverse health effects of particulate air pollution: modification by air conditioning. *Epidemiology*. 2009;20:682–686.
- Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *Am J Epidemiol*. 2013;178:865–876.
- Cox LA Jr, Popken DA, Ricci PF. Warmer is healthier: effects on mortality rates of changes in average fine particulate matter (PM_{2.5}) concentrations and temperatures in 100 U.S. cities. *Regul Toxicol Pharmacol*. 2013;66:336–346.
- Bell ML, Dominici F, Ebisu K, Zeger SL, Samet JM. Spatial and temporal variation in PM_{2.5} chemical composition in the United States for health effects studies. *Environ Health Perspect*. 2007;115:989–995.
- Franklin M, Koutrakis P, Schwartz P. The role of particle composition on the association between PM_{2.5} and mortality. *Epidemiology*. 2008;19:680–689.
- Dai L, Zanobetti A, Koutrakis P, Schwartz JD. Associations of fine particulate matter species with mortality in the United States: a multicity time-series analysis. *Environ Health Perspect*. 2014;122:837–842.
- Krall JR, Anderson GB, Dominici F, Bell ML, Peng RD. Short-term exposure to particulate matter constituents and mortality in a national study of US urban communities. *Environ Health Perspect*. 2013;121:1148–1153.
- Zanobetti A, Franklin M, Koutrakis P, Schwartz J. Fine particulate air pollution and its components in association with cause-specific emergency admissions. *Environ Health*. 2009;8:58.
- Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution. *Am J Respir Crit Care Med*. 2009;179:1115–1120.
- Peng RD, Bell ML, Geyh AS, et al. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. *Environ Health Perspect*. 2009;117:957–963.
- Tolbert PE, Klein M, Peel JL, Sarnat SE, Sarnat JA. Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. *J Expo Sci Environ Epidemiol*. 2007;17:S29–S35.
- Wang M, Beelen R, Stafoggia M, et al. Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 European cohorts: results from the ESCAPE and TRANSPHORM projects. *Environ Int*. 2014;66:97–106.
- Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol*. 2000;29:722–729.
- Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560.
- Smith GD, Ebrahim S. “Mendelian randomization”: can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32:1–22.
- Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Smith GD. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27:1133–1163.
- Eftim SE, Samet JM, Janes H, McDermott A, Dominici F. Fine particulate matter and mortality: a comparison of the six cities and American Cancer Society cohorts with a medicare cohort. *Epidemiology*. 2008;19:209–216.
- Watson JG, Chow JC, DuBois D, Green M, Frank N, Pitchford M. Guidance For Network Design and Optimum Site Exposure For PM_{2.5} And PM₁₀ (EPA-454/R-99-022). US Environmental Protection Agency, 1999.
- Austin E, Coull BA, Zanobetti A, Koutrakis P. A framework to spatially cluster air pollution monitoring sites in US based on the PM_{2.5} composition. *Environ Int*. 2013;59:244–254.
- Andersen P, Gill R. Cox’s regression model counting process: a large sample study. *Annals Stat*. 1982;10:1100–1120.
- Heron M. Deaths: Leading causes for 2010. National vital statistics reports; vol 62, no 6. Hyattsville, MD: National Center for Health Statistics, 2013.
- Berkey CS, Hoaglin DC, Antczak-Bouckoms A, Mosteller F, Colditz GA. Meta-analysis of multiple outcomes by regression with random effects. *Stat Med*. 1998;17:2537–2550.
- Beelen R, Raaschou-Nielsen O, Stafoggia M, et al. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet*. 2014;383:785–795.
- Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect*. 2012;120:965.
- Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. *Environ Health Perspect*. 2000;108:941–947.

32. Peltier RE, Lippmann M. Residual oil combustion: 2. distributions of airborne nickel and vanadium within New York City. *J Expo Sci Environ Epidemiol*. 2010;20:342–350.
33. Bell ML. Assessment of the Health Impacts of Particulate Matter Characteristics. Health Effects Institute, Boston, MA, January 2012. Research Report 161.
34. Ostro B, Tobias A, Querol X, et al. The effects of particulate matter sources on daily mortality: a case-crossover study of Barcelona, Spain. *Environ Health Perspect*. 2011;119:1781–1787.
35. Kioumourtoglou M-A, Coull BA, Dominici F, Koutrakis P, Schwartz J, Suh H. The impact of source contribution uncertainty on the effects of source-specific PM_{2.5} on hospital admissions: a case study in Boston, MA. *J Expo Sci Environ Epidemiol*. 2014;24:365–371.
36. Kadiiska MB, Mason RP, Dreher KL, Costa DL, Ghio AJ. *In vivo* evidence of free radical formation in the rat lung after exposure to an emission source air pollution particle. *Chem Res Toxicol*. 1997;10:1104–1108.
37. Campen MJ, Nolan JP, Schladweiler MC, Kodavanti UP, Costa DL, Watkinson WP. Cardiac and thermoregulatory effects of instilled particulate matter-associated transition metals in healthy and cardiopulmonary-compromised rats. *J Toxicol Environ Health A*. 2002;65:1615–1631.
38. Lippmann M, Ito K, Hwang JS, Maciejczyk P, Chen LC. Cardiovascular effects of nickel in ambient air. *Environ Health Perspect*. 2006;114:1662–1669.
39. Hopke PK, Ito K, Mar T, et al. PM source apportionment and health effects: 1. Intercomparison of source apportionment results. *J Expo Sci Environ Epidemiol*. 2006;16:275–286.
40. Hsu SI, Ito K, Kendall M, Lippmann M. Factors affecting personal exposure to thoracic and fine particles and their components. *J Expo Sci Environ Epidemiol*. 2012;22:439–447.
41. Hazi Y, Heikkinen MSA, Cohen BS. Size distribution of acidic sulfate ions in fine ambient particulate matter and assessment of source region effect. *Atmos Environ*. 2003;37:5403–5413.
42. Wilson W, Mage D, Grant L. Estimating separately personal exposure to ambient and non-ambient particulate matter for epidemiology and risk assessment; why and how. *J Air Waste Manage Assoc*. 2000;50:1167–1183.
43. Ito K, Mathes R, Ross Z, Nádas A, Thurston G, Matte T. Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. *Environ Health Perspect*. 2011;119:467–473.
44. Kelly FJ. Oxidative stress: its role in air pollution and adverse health effects. *Occup Environ Med*. 2003;60:612–616.
45. Costa DL, Dreher KL. Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. *Environ Health Perspect*. 1997;105:1053–1060.
46. Kioumourtoglou MA, Spiegelman D, Szpiro AA, et al. Exposure measurement error in PM_{2.5} health effects studies: a pooled analysis of eight personal exposure validation studies. *Environ Health*. 2014;13:2.