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$PM_{2.5}$ and survival among older adults: Effect modification by particulate composition

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Abstract

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, (i.e. $PM_{2.5}$ composition) across the US. 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 (HR = 1.11 [95% confidence interval = 1.01–1.23] per 10 $\mu g/m^3$). 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.

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Conclusions—To 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.

Long-term exposure to fine particulate matter ($PM_{2.5}$, i.e. 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 al.[3], found heterogeneous effects of long-term $PM_{2.5}$ exposure on mortality across Europe, in a review meta-analysis of 6 studies, while Hoek et al.[4], 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 al.[5] found heterogeneous effects across the US, with the highest effects in the central US, somewhat lower, effects in the eastern US 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 US.[10] To date, several studies have assessed the association between particulate components or sources and acute adverse effects. Franklin et al.[11] 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 study[12] reporting modification of sulfate and silicon on the 2-day $PM_{2.5}$ and all-cause mortality association. Krall et al.[13] directly linked short-term exposures to elemental and organic carbon, and silicon to mortality. Zanobetti et al.[14] 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 al.[15] reported associations between CVD emergency admissions and exposure to nickel, as well as vanadium and elemental carbon. Similarly, Peng et al.[16] and Tolbert et al.[17] 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. Since that counterfactual cannot be observed, various methods – such as instrumental variables,[19]

marginal structural models,[20] and mendelian randomization[21] – 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, since 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 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 (e.g. 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 (SES), 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 (AQS) database (http://www.epa.gov/ttn/airs/airsaqs/detaildata/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] Briefly, 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.

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-yr categories), sex, race and follow-up time as the stratification variables. Follow-up started on 1 January following 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 SES, 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 $\mu g/m^3$ of $PM_{2.5}$. For our statistical analyses we used the SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA), 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 aged 75.3 years (SD = 7.5); 57.6% were female and 87% white.

The average $PM_{2.5}$ concentration was 12.8 $\mu g/m^3$ (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 $\mu g/m^3$ 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: 4 single-city clusters, 6 clusters with 2 cities and 11 clusters with 3 or more cities. A map of all clusters is presented in eFigure 1. The chemical characteristics each cluster are presented in a heat map (eFigure 2), while detailed ratios of species over $PM_{2.5}$ concentrations by cluster are presented in eFigure 3.

Briefly, clusters can be described in six general groups. The clusters in the first group (clusters 1–5 and 7) are located in the eastern US, and they have high sulfate concentrations, consistent with power plant regional 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 metallurgic 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 US 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 US. 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 (see eAppdendix).

$PM_{2.5}$ composition and mortality—The effects of $PM_{2.5}$ by cluster are presented in Figure 1 and in eTable 2. We observed varying effect estimates across clusters, with most hazard ratios higher than the null. Specifically, we found that the effect estimates were different than the pooled average in 4 clusters (namely clusters 2, 10, 13 and 16) and marginally different in clusters 8 and 11. The confidence intervals 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/m^3 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 US 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 $\mu g/m^3$ 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, is 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 $\mu g/m^3$ of annual $PM_{2.5}$ average was associated with a HR of 1.11 (95%CI = 1.01–1.23). 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 $\mu g/m^3$ 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 al.[23] 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 cardiovascular 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 cluster 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., for instance, reported an association between sodium exposures and CVD admissions,[14] and Krall et al.[13] 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). 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.

Additionally, 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 towards 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 towards 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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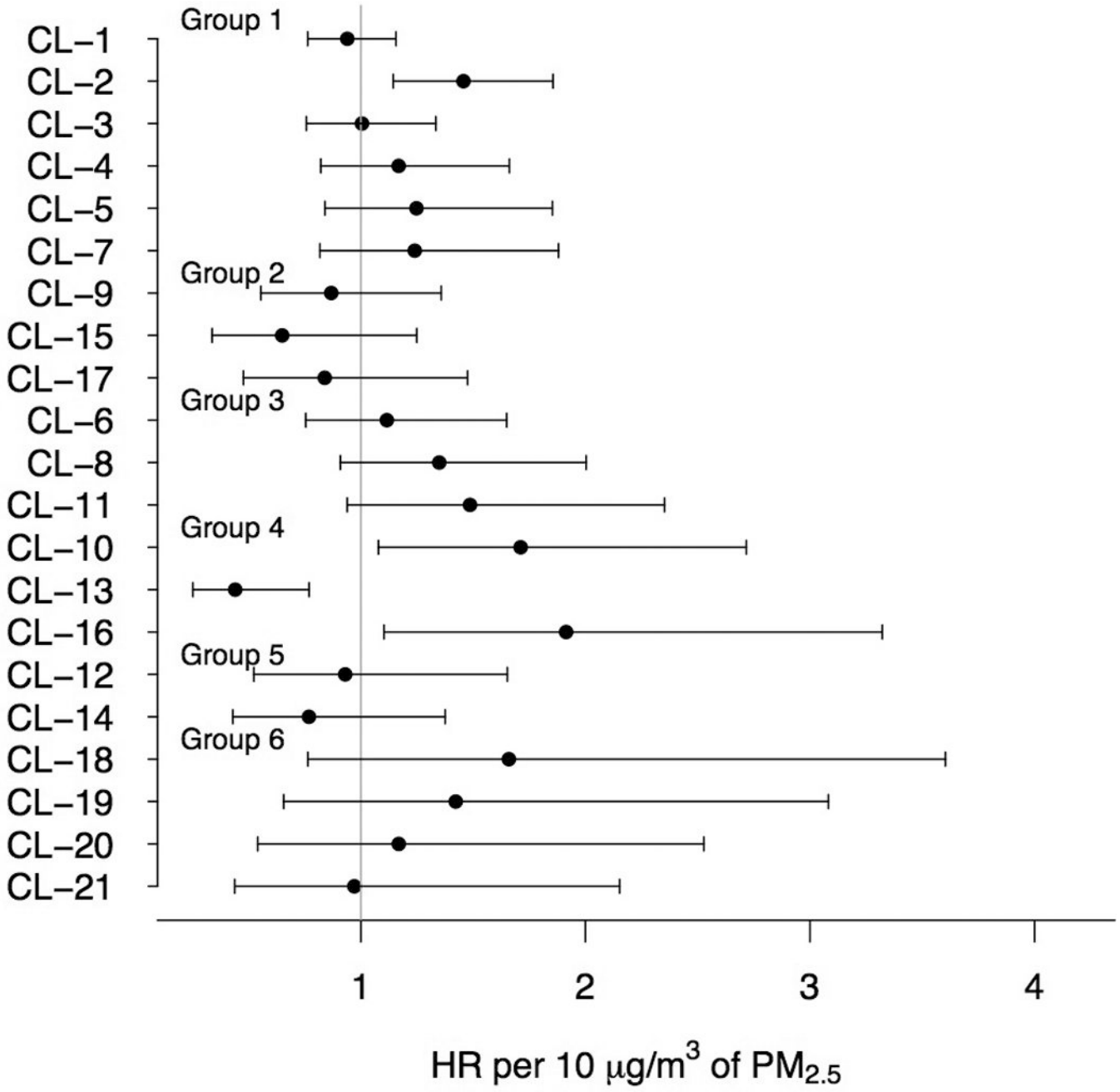

Figure 1.

Within-cluster (CL) estimated HR per 10 μg/m^3 of $PM_{2.5}$ (circles) and 95% CIs (lines). The results are ordered according to the 6 groups of clusters.

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