A spatial joint analysis of metal constituents of ambient particulate matter and mortality in England

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The mortality cancer and population data used in this article were supplied by the Office for National Statistics (ONS), derived from the national mortality, cancer and birth registrations and the Census. SAHSU does not have permission to supply data to third parties, but the health and population data can be obtained from ONS on application. Air pollution estimates by ward for 2008–2011 for the study area, excluding London, for cardiovascular and respiratory mortality RR 1.51 (CI 95% 1.33, 1.72), and respiratory mortality RR 1.51 (CI 95% 1.33, 1.72), likely to represent the “highways” cluster. We did not find relevant associations for lung cancer incidence. Our analysis showed small but not fully consistent adverse associations between health outcomes and particulate metal exposures. The BPR approach identified subpopulations with unique exposure profiles and provided information about the geographical location of these to help interpret findings.

Keywords: Bayesian profile regression; Particulate matter elements; Multipollutant effect; Correlation; Clustering

What this study adds

- One of the largest studies to explore exposure to metal components of ambient air in relation to mortality and lung cancer incidence, with 13.6 million population.
- A large number of cases: 108,478 CVD deaths, 48,483 respiratory deaths, and 24,849 incident cases of lung cancer in the study period and providing good statistical power to examine small excess risks using Bayesian profile regression.
- Information on associations with health of particulate metals linked to nonexhaust road traffic emissions and possibly to other unknown sources.
- Identified areas outside of London (United Kingdom), rural areas, and areas with highways that show a higher risk for cardiovascular and respiratory mortality.
Introduction

Long-term exposure to fine particulate matter PM$_{10}$ and PM$_{2.5}$ is associated with increased mortality levels from cardiovascular disease, and lung cancer or respiratory mortality. It has been suggested that metal components of particulate matter may in part be responsible for toxic effects of air pollution on the cardiovascular and respiratory system and on cancer mortality, in particular, due to lung cancer.

Yang et al. conducted a systematic review, and a meta-analysis of short- and long-term exposure to fine particulate matter constitutes (PM$_{2.5}$) and adverse health outcomes, with cardiovascular and respiratory mortality. The review highlighted the positive association between nitrate, zinc, silicon, iron, nickel, potassium, and vanadium with adverse cardiovascular health, while nitrate, sulphate, and vanadium were relevant for respiratory outcomes.

In specific, metal components of particulate matter such as copper zinc and iron were found to be associated with increases in inflammatory markers in the blood, which might be expected to be associated with increased risks of cardiovascular and other diseases. In the Rome Longitudinal Study, particulate matter components from PM$_{2.5}$ absorbance (copper, zinc, and iron) were associated with an increase in the hazard ratio for cardiovascular and ischemic heart disease mortality. Moreover, exposure to particulate matter chemical mass (PM$_{1.0}$) like nickel and vanadium has been found to be associated with an increase in hospital admissions for cardiovascular and respiratory events. These studies have investigated exposure to components by evaluating one at the time or with some confounding adjustment for other exposures.

However, metal exposure components are well known to be highly correlated, spatially and temporally, and sophisticated statistical methods to account for the multipollutant multicollinearity aspects have been proposed. Previously, we analyzed the same data set with an univariate approach by fitting the Poisson regression to each elemental component separately, but high correlations precluded a multipollutant analysis. In this article, we conduct an ecological study at a small area level, using the Bayesian profile regression (BPR) to investigate the effect of metal components for PM$_{1.0}$ (iron and copper) and PM$_{2.5}$ (iron, copper, and zinc) in relation to cardiovascular and respiratory mortality and lung cancer incidence, in the London-Oxford (England) area.

The BPR method has been developed to account for multiple correlated covariates. For example, it has been used to examine the effect of multiple risk factors on lung cancer incidence. The BPR model partitions observation units into clusters according to covariate profiles defined by different levels of covariate values, in our case components of PM. Therefore, the focus is on the risks associated with the different exposures profile clusters. The method presents the advantage of allowing for a structured random effect, where different spatial regions are associated with different profiles of exposures. The analysis outcome can provide a useful starting point for targeted, region-specific intervention and hypothesis generation.

Methods

The study region covered a 10,782 km$^2$ area around London and Oxford (Figure 1) in 1533 wards, an English Census area classification (primary unit of the English electoral geography) with a mean surface area -7.0 km$^2$ and average 8892 inhabitants in the study period.

Exposure data

In the region of London and Oxford, the particulate matter was monitored during the years 2010–2011 as part of the European
Study of Cohorts and Air Pollution Effects (ESCAPE) project.\textsuperscript{1-19} Filters from the ESCAPE project were analyzed for elemental composition\textsuperscript{20} and developed land use regression (LUR) models for a number of the elemental components including metals as part of the TRANSPHORM project. In brief, 20 sites were monitored for three 2-week periods\textsuperscript{21} and PM$_{2.5}$ and PM$_{10}$ were separately collected using Harvard impactors. Their elemental composition was analyzed using energy dispersive x-ray fluorescence. The association of PM elemental components with land use covariates relative to traffic, population, industry, or nature was evaluated with LUR models (eTable 1; http://links.lww.com/EE/A100). Then, local estimates at the postcode level were predicted and aggregated at the super output area level (a building block of the UK Census geography with an average population 1,500) with a population-weighted mean.

In the analyses, we used copper (Cu), iron (Fe), and zinc (Zn) in the PM$_{10}$ fraction and copper and iron in the PM$_{2.5}$ fraction because the LUR models for this selection showed a good leave-one-out validation, explaining more than 77\% (R\textsuperscript{2}) of the observed variability, and more than 70\% for R\textsuperscript{2} and the LUR models for each elemental component (eTable 1; http://links.lww.com/EE/A100).

The correlations between the elements included in our studies range from 0.78 to 0.91 (eTable 2; http://links.lww.com/EE/A100), and the correlation of the elemental components and PM$_{2.5}$ and PM$_{10}$ ranged from 0.73 to 0.92 (eTable 3; http://links.lww.com/EE/A100) as a result of similar traffic and/or population-related variables in the LUR models. Other metals were estimated as part of the TRANSPHORM project, but we included only metals with good validation statistics for the study area.

### Confounder data

To adjust for possible confounders in this study, we included area-level ethnicity from Census 2011 and accounted for percent of White and Asian people per ward as covariates in the models. We also used the 2007 Index of Multiple Deprivation (IMD) as a relative measure of area-level deprivation (publicly available from the Department for Communities and Local Government data.gov.uk https://data.gov.uk/dataset/bdc1e1a5-aaf3-4f5a-9988-82a11e34e1b8/index-of-multiple-deprivation-imd-2007). This combines seven domains: “income,” “employment,” “education,” “barriers to housing and services,” “crime,” “health,” and “living environment.” The latter is divided into two subdomains: “indoor” measuring the quality of housing and “outdoor” linked to air quality and road traffic accidents. We excluded from the study the “health” and “outdoor living environment” domains,\textsuperscript{22} because we examined associations between health outcomes and air pollution measures. The remaining domains were linearly combined to generate a “modified IMD” relative score used in the analysis. High values of the modified IMD indicate higher deprivation. As a proxy for smoking, we used ward-level tobacco expenditure (pounds/week/inhabitant) data obtained from CACI (CACI tobacco expenditure data is © Copyright 1996–2014 CACI Limited).

### Health data

Mortality counts for cardiovascular (CDC10 100-I99) and respiratory (CDC10 J00-J99) disease and lung cancer incidence counts (C33 and C34 ICD10 codes) were extracted for 2008–2011 from Office National Statistics data held by the Small Area Health Statistics Unit (SAHSU). The counts were then adjusted by sex and 5-year age band.

### Statistical analysis

The effect of PM exposure to copper, iron, and zinc on health outcomes was analyzed and with BPR adjusted for the specified confounders. For more clarity, the regression parameters are expressed as relative risk (RR) and the posterior mean and 95\% credible bounds (CI) are given.

### Bayesian profile regression

The BPR approach identifies clusters of geographical areas, characterized by profiles defined by similar levels of elemental concentrations. This method assembles two submodels: a multi-dimensional Gaussian density for the definition of clusters based on exposures’ levels (profiles) and a Poisson distribution for disease rates that accounts for area confounders and area cluster membership.\textsuperscript{23}

The first submodel uses the Dirichlet process mixture model, on the vector of covariates $\text{PM}_i = (\text{PM}_{1i}, \ldots, \text{PM}_{6i})$, that is, the elemental exposures in our case. We denote $Z_i$ as the group, $Z$ to which area $i$ belongs. Each group $Z_i$ is characterized by its level of risk $\theta_{Z_i}$ and its profile of covariates, modeled by a multivariate Gaussian distribution with specific mean $\mu_{Z_i}$ and variance-covariance matrix $\Sigma_{Z_i}$. PM$_{1i}$, $\mu_{Z_i}$, $\Sigma_{Z_i}$, and $N(\mu_{Z_i}, \Sigma_{Z_i})$ which allow correlation between variables.

In our application, counts of deaths or incidence cases are modeled by a Poisson distribution. As in the Poisson regression model, the mean is expressed as the product of the relative risk

\begin{table}[h]
\centering
\caption{Descriptive statistics of health outcomes, modeled particulate metal concentrations, deprivation score, and ethnicity covariates for the 1533 wards in the study area in 2008–2011} 
\begin{tabular}{llllll}
\hline
Health outcomes & 10th centile & Mean & Median & 90th centile & LOOCV R$^2$ (for LUR) \\
\hline
Cardiovascular mortality & 117.50 & 215.97 & 203.20 & 327.87 & \\
Respiratory mortality & 42.65 & 96.34 & 87.85 & 160.41 & \\
Lung cancer incidence & 25.06 & 48.44 & 45.75 & 75.86 & \\
moderated metal concentrations using LUR & Metals in ng/m$^3$ & & & & \\
Cu PM$_{10}$ & 7.0 & 13.3 & 13.1 & 19.8 & 0.95 \\
Fe PM$_{10}$ & 223.2 & 378.9 & 357.0 & 596.7 & 0.95 \\
Zn PM$_{10}$ & 113.5 & 135.2 & 139.5 & 153.0 & 0.77 \\
Cu PM$_{2.5}$ & 2.6 & 4.3 & 4.6 & 5.7 & 0.79 \\
Fe PM$_{2.5}$ & 51.6 & 86.8 & 82.8 & 129.0 & 0.92 \\
Area-level confounders & & & & & \\
Deprivation (modified IMD) & 3.45 & 7.08 & 6.47 & 11.78 & \\
% of Asian & 2 & 13 & 9 & 33 & \\
% of White & 38 & 72 & 77 & 95 & \\
Tobacco expenditure (pounds/week/inhabitant) & 3.40 & 4.61 & 4.48 & 6.03 & \\
\hline
\end{tabular}
\end{table}
and the expected counts accounting for the age and sex structure of the population at risk. Given the group allocation, the log risk is modeled through a Poisson regression, which includes a random effect for the group \( (\theta Z_i) \) as well as confounders \( (\sum_{j=1}^{p_j} \alpha_j \text{Confound}_j) \), as follows:

\[
\log(\text{RR}_i) = \mu + \sum_{j=1}^{p_j} \alpha_j \text{Confound}_j + \theta Z_i + U_i.
\]

In addition, we include a spatially structured random effect \( U_i \) to account for local variations characterized by spatial dependences.\(^2^4\)

The two models are estimated jointly, as the allocation of the geographical areas to cluster is dependent on both the confounder and exposure in the first model and the health outcome information in equation (1).

The analysis creates a rich output at the cluster level: in terms of geographical locations, characterization of the metals in each clusters and cluster relative risk. From equation (1), we report as well the effect of the area level confounders, by analyzing separately the effects of exposure to elements within the \( \text{PM}_{10} \) and \( \text{PM}_{2.5} \) fractions on cardiovascular, respiratory mortality, and lung cancer incidence.

We included the predictive risk distribution to assess the influence of each exposure variable on health outcome risk, by computing the marginal distribution of the risk for increasing values of each elemental exposure. This corresponds to the risk distribution, given the exposure level of the study area. We computed the marginal effect of one variable, keeping in mind that other exposure levels may change. The inference was carried out with the R package PReMiuM\(^2^5\) and noninformative priors. For a detailed review of the BPR, see Coker et al.\(^1^8\)

### Results

**Descriptive statistics**

We recorded 108,478 cardiovascular and 48,483 respiratory deaths and 24,849 incident lung cancer cases in the study area.

![Clusters Location](image1)

![PM2.5 Copper](image2)

![PM2.5 Iron](image3)

Figure 2. Cardiovascular mortality for \( \text{PM}_{2.5} \), from top left the map of cluster location and the boxplot indicated the risk distribution associated within each cluster and the distribution of metals in the clusters.
for 2008–2011 (Table 1). Maps of the spatial distribution of the covariates and elemental concentrations show that highest values were in Greater London Area, with iron and zinc high in areas with motorways (eFigure 1; http://links.lww.com/EE/A100). The percentage population ethnicity for wards had a median of 77% white and 9% Asian ethnicity. Most of the areas with low percentage of White population were concentrated in Greater London, which also had higher percentage of Asian (eFigure 2; http://links.lww.com/EE/A100).

**Bayesian regression profile**

For BPR, the dependence between elemental exposures is considered and a single risk is associated with a profile of exposures. We identified six “typical” clusters for all the outcomes using profile regression, except for lung cancer incidence and respiratory mortality in PM$_{2.5}$, where there were five clusters. These are similarly characterized for all diseases or fractions of particulate matter considered (Figures 2 and 3 and eFigures 3–6; http://links.lww.com/EE/A100). A high concentration of particulate elements was seen represented in two or three clusters (depending on the outcome) over Greater London. Depending on the outcome, we found two clusters representing Greater London, both characterized by the presence of road networks and high concentrations of zinc in the PM$_{10}$ fraction and iron in the PM$_{2.5}$ fraction. One cluster covered rural areas, with the smallest concentrations of particulate elements. Overall, we notice a pattern where clusters with above average metals levels do not correspond to higher risk.

We observed that the risk associated with each cluster varied according to the considered outcome. For cardiovascular and respiratory mortality with the PM$_{10}$ fraction, higher risks

![Clustering Location](image)

**Figure 3.** Respiratory mortality PM$_{2.5}$ from top left the map of cluster location and the boxplot indicated the risk distribution associated within each cluster and the distribution of metals in the clusters.
compared with the study global mean were found in cluster represented by rural areas for cardiovascular (RR 1.07; CI 95% 1.02,1.12) and for respiratory mortality (RR 1.06; CI 95% 0.99,1.31) compared with the mean. In the latter, levels of copper and iron were lower than the study average concentrations, but the level of zinc was near the global average (eFigures 3 and 4; http://links.lww.com/EE/A100, clusters 5 and 4, respectively).

For the PM$_{10}$ fraction, the profile regression highlighted a cluster with high risk (RR 1.55; CI 95% 1.38, 1.71) for cardiovascuar mortality (cluster 5 in Figure 2). This cluster was composed of only 15 wards, but the particulate characterization of this cluster showed a average value of iron only.

For respiratory mortality, only one cluster of 22 wards (cluster 4 in Figure 3) showed a relevant risk (RR 1.51; CI 95% 1.33, 1.72), with both copper and iron values around the global mean. In both analyses, these two clusters presented high metals variations and mostly covering highways (motorways with dual carriage).

For lung cancer incidence, none of the clusters built from the various profiles of particulate elements had a mean incidence risk higher or lower than the global mean, that is, the clusters did not show any association with lung cancer risk. For both PM$_{10}$ and PM$_{2.5}$ metals, the higher metal values are noted in the clusters representing Greater London area (clusters 2 and 3 and cluster 1, respectively, in eFigure 5 and 6; http://links.lww.com/EE/A100). The spatial term explained about half of the observed risk differences were mainly due to covariates and unexplained spatial term as expressed in equation (1).

Elemental exposure explained part of the risk variability, about 10% for cardiovascular and respiratory mortality and only about 1.5% for lung cancer (eTable 4; http://links.lww.com/EE/A100). The observed risk differences were mainly due to covariates and unexplained spatial term as expressed in equation (1).

Elemental exposure explained part of the risk variability, about 10% for cardiovascular and respiratory mortality and only about 1.5% for lung cancer (eTable 4; http://links.lww.com/EE/A100). The spatial term explained about half of the risk variability, with a substantial part of the risk explained by the confounders, about 30% for cardiovascular and respiratory mortality and around 50% for lung cancer incidence.

As expected, the modified multiple deprivation index and tobacco sales had an adverse effect on the three diseases investigated (Table 2). Regarding ethnicity, only the proportion of white people living in an area had a protective effect on cardiovascular mortality. When we plotted the maps of the global risk, we noted clear zones of higher risk in an area located at the east of London, and which can be attributed to the high level of deprivation and tobacco expenditure.

Figure 4 depicts the evolution of the risk for increasing values of elemental PM$_{10}$ and PM$_{2.5}$ exposures, for cardiovascular, respiratory, and lung cancer. We did not detect excess risk for any of the diseases or the elements under study, but credible intervals are large, due to the clustering uncertainty. Indeed, even if a fixed partition is given in Figures 2 and 3 (eFigures 4 and 5; http://links.lww.com/EE/A100) for the sake of simplicity, other partitions of the wards would also be likely.

**Discussion**

This ecological study at a small area level examined associations between modeled particulate metal concentrations (copper, iron, and zinc) in relation to cardiovascular and respiratory mortality and lung cancer incidence in and around Greater London covering 13.6 million population with approximately 110,000 Cardiorespiratory deaths and 25,000 new lung cancer cases. Analyses were conducted using BPR, a method to allow for clustering of correlated elemental exposures. For cardiovascular and respiratory mortality, considering elements in the PM$_{10}$ fraction, the BPR approach suggested that a mixture associated with areas close to highway roads, could be linked to a higher mortality risk. All the metals included in our analysis have been linked to nonexhaust road traffic emissions, but we cannot exclude some contributions of these metals from industry and other local sources. In the United Kingdom, the national emissions inventory estimates that 47% of atmospheric Cu and 21% of Zn are primarily associated with brake and tyre wear (but does not provide information about contributions from resuspended road dust, which may be an important contributor to concentrations near roads).26

The high correlations between metal constituents of particulates mean that it is difficult to assign observed associations for zinc and copper exposures to these specific metals. The BPR approach offered an additional perspective by providing a

### Table 2

| Outcomes            | Model                          | Confounders | Mean   | CI 95%    |
|---------------------|--------------------------------|-------------|--------|-----------|
| **Cardiovascular mortality** | Clusters Metals in PM$_{10}$ | IMD         | 1.297  | (0.91, 1.05) |
|                     | Cluster Metals in PM$_{10}$   | % Asian     | 0.876  | (0.10, 0.95) |
|                     |                                | % White     | 0.806  | (0.01, 0.81) |
|                     |                                | Tobacco expenditure | 1.188  | (1.12, 1.25) |
| **Respiratory mortality** | Cluster Metals in PM$_{10}$ | IMD         | 1.188  | (1.12, 1.25) |
|                     | Cluster Metals in PM$_{2.5}$  | % Asian     | 0.683  | (0.0, 0.85) |
|                     |                                | % White     | 0.825  | (0.0, 0.89) |
|                     |                                | Tobacco expenditure | 1.357  | (1.26, 1.45) |
| **Lung cancer incidence** | Cluster Metals in PM$_{10}$ | IMD         | 1.426  | (1.26, 1.59) |
|                     | Cluster Metals in PM$_{2.5}$  | % Asian     | 0.817  | (0.74, 0.89) |

Mean, lower and upper bound of the 95% credible interval (CI) of the inter-decile relative risk.
unique framework to account for multicollinearity; in addition, spatial variability can be modeled within the same framework, by allowing the uncertainty from the clustering to be accounted in its profile of covariates once the Poisson regression is estimated. The uncertainty from the cluster assignment is carried through cluster profile risk into the Poisson regression.

The method presents some deterministic components in the selection of the best partition, because of the cluster “label switching” in the estimation phase that is solved by using a partitioning around medoids to define the final representative cluster configuration. Despite the limitation, the BPR is a sophisticated method, in line with the recommendations on statistical approach for multipollutant exposure provided by the Health Effects Institute.27

Our findings of associations of PM_{2.5} copper with increased risk of cardiovascular mortality (108,478 deaths) and PM_{10} zinc with respiratory mortality (48,483 deaths) were supported by BPR, which found mortality clustering with areas with high metal concentrations and high road networks, although results for metal constituents were not fully consistent within our study. We used associations between mortality 2008–2011 and particulate metals for 2010–2011, which are a representative of the preceding two years28 as the spatial gradients for annual average exposure can be considered reasonably stable over the relatively short time periods involved in this study. Therefore, the analysis should reflect short-/medium-term impacts of air pollution on the outcomes investigated (i.e., daily and up to a few years), as the same sources persist over time (e.g., road networks and the metals used in vehicles on road that contribute to metals found in particulates), but it may also include some impacts of longer-term exposure.

From these results, we are unable to ascribe effects to specific metals, and clustering of risk for cardiovascular and respiratory mortality was in areas with high concentrations of road networks, which is consistent with non-tailpipe emissions.12 We also note that elemental exposure explained 10% and 1.5% of the risk variability component for cardiorespiratory mortality and lung cancer incidence, respectively.

Only a small number of studies assessed long-term effects using similarly derived estimates from the TRANSPHORM project as used here but much fewer numbers of health events, found significant associations with inflammatory markers in blood but not health events. Hampel et al.11 found statistically significant associations between PM_{2.5} copper and PM_{10} iron with high-sensitivity C-reactive protein and PM_{2.5} zinc with fibrinogen in five European cohorts with available biomarkers.

Figure 4. Marginal evolution of the risk along the metal PM exposures, obtained from the profile regression. Solid lines: posterior mean, dotted lines 90% credible intervals.
Finally, as most other ambient air pollution studies, we use outdoor concentration of pollutants at residence, without taking into account indoor levels, travel exposure or places of work. The correlation between indoor and outdoor concentration is high for fine particulate (PM$_{2.5}$), suggesting that ignoring the indoor concentration is a small issue. However, in the London region, the difference of exposure at home and workplace may be different, because a part of the population living in suburban areas work in the city center, where exposures are higher.

Conclusions

We found associations suggestive of small increased risk of cardiovascular and respiratory mortality, but not lung cancer incidence in Greater London and surroundings in relation to metal concentrations of ambient particulate matter, likely derived from non-tailpipe road traffic emissions (brake and tyre-wear). We also observed clusters of increased risk in areas with high concentrations of road networks. Findings are consistent with a previous study finding associations of particulate metals with inflammatory markers, but further work is needed to better define exposures to non-tailpipe emissions.

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