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Long-term exposure to fine particle elemental components and natural and cause-specific mortality – a pooled analysis of eight European cohorts within the ELAPSE project

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Background  Inconsistent associations between long-term exposure to fine particulate matter (PM2.5) components and mortality/morbidity have been reported, partly related to challenges in exposure assessment. No studies have compared health effect estimates using exposure models developed with linear regression and the more flexible machine-learning algorithms.

Objectives  To investigate the associations between long-term exposure to PM2.5 elemental components and mortality in a large pooled European cohort, estimating exposure with Supervised Linear Regression (SLR) and Random Forest (RF) models.

Methods  We pooled data from eight European cohorts with 323,782 participants. Residential exposure to 2010 annual average concentration of eight PM2.5 components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) was estimated with Europe-wide SLR and RF models at 100x100m scale. We applied Cox proportional hazards models to investigate the associations between components and natural and cause-specific mortality. Additionally, two-pollutant analyses were conducted by adjusting each component for PM2.5 mass and nitrogen dioxide (NO2) separately.

Results  We observed 46,640 deaths with 6,317,235 person-years and average follow-
up of 19.5 years. All SLR-modeled components were statistically significantly associated with natural-cause mortality in single pollutant models with hazard ratios (HRs) from 1.05–1.27. Similar HRs were observed for RF-modeled copper, iron, potassium, sulfur, vanadium and zinc with wider confidence intervals (CIs). HRs for SLR-modeled nickel, sulfur, silicon, vanadium and zinc remained elevated and (borderline) significant after adjustment for both PM2.5 and NO2. HRs only remained (borderline) significant for RF-modeled potassium and vanadium in two-pollutant models. The HRs for vanadium were 1.03 (95% CI: 1.02, 1.05) and 1.06 (95% CI: 1.02, 1.10) for SLR- and RF-modeled exposures respectively per 2 ng/m3 adjusting for PM2.5 mass.

Conclusion Long-term exposure to vanadium in PM2.5 was most consistently associated with increased natural-cause mortality. Associations for the other components were weaker for exposure modeled with RF than SLR in two-pollutant models.

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Long-term exposure to fine particle elemental components and natural and cause-specific mortality – a pooled analysis of eight European cohorts within the ELAPSE project

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Declarations of Interest

None
Abstract

**Background** Inconsistent associations between long-term exposure to fine particulate matter (PM$_{2.5}$) components and mortality/morbidity have been reported, partly related to challenges in exposure assessment. No studies have compared health effect estimates using exposure models developed with linear regression and the more flexible machine-learning algorithms.

**Objectives** To investigate the associations between long-term exposure to PM$_{2.5}$ elemental components and mortality in a large pooled European cohort, estimating exposure with Supervised Linear Regression (SLR) and Random Forest (RF) models.

**Methods** We pooled data from eight European cohorts with 323,782 participants. Residential exposure to 2010 annual average concentration of eight PM$_{2.5}$ components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc) was estimated with Europe-wide SLR and RF models at 100x100m scale. We applied Cox proportional hazards models to investigate the associations between components and natural and cause-specific mortality. Additionally, two-pollutant analyses were conducted by adjusting each component for PM$_{2.5}$ mass and nitrogen dioxide (NO$_2$) separately.

**Results** We observed 46,640 deaths with 6,317,235 person-years and average follow-up of 19.5 years. All SLR-modeled components were statistically significantly associated with natural-cause mortality in single pollutant models with hazard ratios (HRs) from 1.05–1.27. Similar HRs were observed for RF-modeled copper, iron, potassium, sulfur, vanadium and zinc with wider confidence intervals (CIs). HRs for SLR-modeled nickel, sulfur, silicon, vanadium and zinc remained elevated and (borderline) significant after adjustment for both PM$_{2.5}$ and NO$_2$. HRs only remained (borderline) significant for RF-modeled potassium and vanadium in two-pollutant models. The HRs for vanadium were 1.03 (95% CI: 1.02, 1.05) and 1.06 (95% CI: 1.02, 1.10) for SLR- and RF-modeled exposures respectively per 2 ng/m$^3$ adjusting for PM$_{2.5}$ mass.

**Conclusion** Long-term exposure to vanadium in PM$_{2.5}$ was most consistently associated with increased natural-cause mortality. Associations for the other components were weaker for exposure modeled with RF than SLR in two-pollutant models.
1. Introduction

The most recently available Global Burden of Disease (GBD) study estimated that exposure to ambient particles with an aerodynamic diameter less than 2.5 \( \mu \text{m} \) (PM\(_{2.5}\)) was the fifth-ranking mortality risk factor, contributing to 4.2 million deaths per year (Cohen et al., 2017). PM\(_{2.5}\) is a mixture of a large number of components related to specific sources. Identifying which components of PM\(_{2.5}\) are main contributors to adverse health effects is important for targeted policy making. So far, only a limited number of studies have assessed associations of long-term exposure to PM\(_{2.5}\) components and mortality with inconclusive results. The California Teachers Study (Ostro et al., 2015) found an increased risk of Ischemic Heart Disease (IHD) mortality in associations with exposure to nitrate, elemental carbon (EC), copper and secondary organics in PM\(_{2.5}\). The American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II) suggested that long-term PM\(_{2.5}\) exposure from coal combustion and its key emission tracer elements (i.e., selenium and arsenic) were associated with increased IHD mortality risk, whereas exposure to silicon and potassium was not associated with mortality (Thurston et al., 2013; Thurston et al., 2016). In the Medicare population, the excess mortality risk associated with long-term PM\(_{2.5}\) exposure increased with relative concentration of EC, vanadium, copper, calcium and iron and decreased with nitrate, organic carbon and sulfate (Wang et al., 2017). The large European Study of Cohorts for Air Pollution Effects (ESCAPE) reported a robust relationship between natural-cause mortality and PM\(_{2.5}\) sulfur, and some evidence of associations with iron and copper in PM\(_{2.5}\) (Beelen et al., 2015). No statistically significant association with PM\(_{2.5}\) components was found for cardiovascular mortality in the ESCAPE study (Wang et al., 2014).

Long-term exposure assessment for particle components is more challenging than for PM\(_{2.5}\) mass because of limited routine monitoring (with the exception of nitrate, ammonium and sulphate) and less data on emission rates used as input to dispersion models. To date, the available epidemiological evidence used different exposure estimates, including direct monitoring (Ostro et al., 2011; Thurston et al., 2013; Thurston et al., 2016), chemical transport models at 4x4 km scale (Ostro et al., 2015) and fine spatial scale land use regression (LUR) models (Beelen et al., 2015; Wang et al., 2014). Different exposure assessment methods may lead to component-specific differences in exposure estimation error, potentially leading to bias. Studies have suggested that risk estimates of PM\(_{2.5}\) mass differed between exposure assessment methods (Jerrett et al., 2017; McGuinn et al., 2017). Studies comparing exposure assessment methods in their associations with health outcomes mainly focused on the comparison between direct monitoring, satellite products, dispersion/chemical transport models and LUR models. Recent developments in exposure assessment include combining different methods such as land use or chemical transport modeling and monitoring data using a variety of approaches including linear regression and machine learning algorithms (Hoek, 2017). Comparisons have been made between exposure predictions developed with different algorithms in terms of prediction accuracy (Brokamp et al., 2017; Chen et al., 2019; Kerckhoffs et al., 2019). However, a simulation study suggested that improving the prediction accuracy
of exposure models did not always improve the accuracy of health effect estimation (Szpiro et al., 2011). To our knowledge, no studies have compared exposure models developed with different algorithms regarding their relation with health outcomes.

The current study is part of the Effects of Low-level Air Pollution: a Study in Europe (ELAPSE). ELAPSE builds on the elemental composition, mortality and covariate data of the ESCAPE study (Beelen et al., 2014; Beelen et al., 2015; Wang et al., 2014). In ESCAPE each cohort was analyzed separately, whereas in ELAPSE respective ESCAPE cohorts were pooled to represent a contrast in low-level air pollution exposures. In addition, the ELAPSE project incorporated updated mortality follow-up data (from typically up to 2008 in ESCAPE to up to 2011–2017 in ELAPSE), which substantially increased the number of deaths and hence study power. The combined ability to do pooled analyses, plus accounting for new insights in the robustness of LUR models related to the number of monitoring sites (Basagaña et al., 2012; Wang et al., 2012), strengthened the exposure assessment in ELAPSE. Specifically, Europe-wide models covering combined study areas for PM$_{2.5}$ mass, nitrogen dioxide (NO$_2$), Black Carbon, ozone (De Hoogh et al., 2018) and the eight PM$_{2.5}$ elementals modeled in ESCAPE (Chen et al., in revision) were developed. The models furthermore allowed better coverage of those ESCAPE cohorts in large study areas of which typically only a fraction was covered by dedicated monitoring campaigns (e.g. only Paris in the national French E3N cohort) (de Hoogh et al., 2013; Tsai et al., 2015). The Europe-wide models for PM$_{2.5}$ composition were developed using two algorithms – the supervised linear regression (SLR) algorithm (De Hoogh et al., 2018) and the random forest (RF) algorithm, a machine-learning algorithm (Chen et al., in revision). The RF models outperformed the SLR models at the Europe-wide level, while the two models performed similarly explaining variability within individual study areas. Despite the similar within-area performance, the exposure predictions at random sites derived from SLR and RF models correlated only moderately at the national level.

We previously observed significantly positive associations between PM$_{2.5}$ and natural and cause-specific mortality using the same pooled cohort in the framework of ELAPSE (Strak et al., submitted). The first aim of this study was to evaluate whether specific components of PM$_{2.5}$ were associated with mortality. The second aim was to compare health effects estimated with two different exposure modeling approaches, namely SLR and RF algorithms.
2. Methods
2.1 Study populations

The ELAPSE pooled cohort contains eight cohorts across seven European countries able to participate in data pooling, areas with low-level air pollution exposure, and relatively recent recruitment date (Table 1 and Figure S1). The cohorts are the following: Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort in Sweden, which was constructed from four sub-cohorts: Stockholm Diabetes Prevention Program (SDPP) (Eriksson et al., 2008), the Stockholm Cohort of 60-year-olds (SIXTY) (Wändell et al., 2007), Stockholm Screening Across the Lifespan Twin study (SALT) (Magnusson et al., 2013) and Swedish National Study on Aging and Care in Kungsholmen (SNACK) (Lagergren et al., 2004); the Diet, Cancer and Health cohort (DCH) (Hundrup et al., 2012) in Denmark, consisting at baseline of two surveys conducted in 1993 and 1999; the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort in the Netherlands, including the Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (MORGEN) and Prospect (Beulens et al., 2010); the Heinz Nixdorf Recall study (HNR) in Germany (Schermund et al., 2002); the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l’Educatino Nationale (E3N) in France (Clavel-Chapelon and Group, 2015); the Cooperative Health Research in the Region of Augsburg (KORA) in Germany, consisting at baseline of two cross-sectional population-representative surveys conducted in 1994–1995 (S3) and 1999–2001 (S4); and the Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) in Austria (Ulmer et al., 2007). The study areas of most cohorts constituted a large city and its surrounding areas. Some cohorts covered large regions of the country such as the French E3N cohort and the Danish DNC cohort. All included cohort studies were approved by the medical ethics committees in their respective countries. Detailed information of each individual cohort is described in the supplemental material. For data pooling, we harmonized individual and area-level variables between cohorts according to a joint codebook.

2.2 Air pollution exposure assessment

Eight components were a priori selected in the ESCAPE study to represent major pollution sources: copper (Cu), iron (Fe) and zinc (Zn) representing non-tailpipe traffic emissions; sulfur (S) representing long-range transport of secondary inorganic aerosols; nickel (Ni) and vanadium (V) representing mixed oil burning/industry; silicon (Si) representing crustal material; and potassium (K) representing biomass burning (de Hoogh et al., 2013; Tsai et al., 2015). We assessed exposure to these eight elements in PM$_{2.5}$ at the participants’ baseline residential addresses using Europe-wide LUR models developed with two algorithms. The models have been described in detail elsewhere (Chen et al. in revision). Briefly, we estimated 2010 annual mean concentrations of PM$_{2.5}$ elemental composition based on the standardized ESCAPE monitoring data. We offered large-scale satellite-model and chemical transport model estimates of components as predictors to represent background concentrations and land use, traffic, population and industrial point source data to model local spatial variability.
We applied the supervised linear regression (SLR) (De Hoogh et al., 2018) and the random forest (RF) algorithm (Chen et al., 2019) to develop models for each component. The models explained a moderate to large fraction of the measured concentration variation at the European scale, ranging from 41% to 91% across components. The RF models consistently outperformed the SLR models in explaining overall variability, including both between and within study area variability. The models explained within-area variability less well, with similar performance for RF and SLR models. The SLR and RF model predictions correlated moderately at national level.

Exposure to 2010 annual mean concentration of PM$_{2.5}$ mass and NO$_2$ was assessed by Europe-wide LUR models developed previously (De Hoogh et al., 2018). The models were developed based on the European Environmental Agency (EEA) AirBase routine monitoring data with satellite-derived and chemical transport model air pollutants estimates, land use, traffic and population data as predictors. The PM$_{2.5}$ model explained 72% of measured spatial variation in the annual average concentration across Europe while the NO$_2$ model explained 59%.

We applied the exposure models to create 100x100 m grids of the predicted concentrations of the pollutants covering the entire study area, and transferred these to participating centers for exposure assignment. After assignment, anonymized data were returned to the Utrecht University for checking and pooling.

We performed truncations to deal with unrealistic SLR predictions of elemental composition concentrations: predictions at the high end (mostly related to close distance to industrial sources) were truncated to the maximum modeled value, calculated by fitting the SLR model with the maximum predictor values at ESCAPE monitoring sites for positive slopes (or the minimum predictor values for negative slopes). Negative predictions were set to zero (Chen et al., in revision). Truncation was performed in the main model population for SLR-modeled exposure: 11.3% for Cu, 0.5% for Fe, 11.6% for Ni, 14.3% for V and 2.6% for Zn. The truncation was mostly performed for predictions below zero. No truncation was needed for RF-modeled exposure (Table S1).

2.3 Mortality outcome definition

Identification of outcomes was based upon linkage to mortality registries. Natural mortality was defined based on the underlying cause of death recorded on death certificates as ICD-9 (International Classification of Diseases, 9th Revision) codes 001–779 and ICD-10 (10th Revision) codes A00–R99. We further defined mortality from cardiovascular disease (ICD-9: 400–440, ICD-10: I10–I70), respiratory disease (ICD-9: 460–519, ICD-10: J00–J99) and lung cancer (ICD-9: 162, ICD-10: C34).

2.4 Statistical analyses

To estimate hazard ratios (HRs) and 95% confidence interval (CIs) for associations of PM$_{2.5}$ component exposure with natural and cause-specific mortality, we applied Cox proportional hazards models following the general ELAPSE analytical framework (Strak et al., submitted). We used strata for sub-cohorts contributing to the pooled cohort to account for differences
in baseline hazard between the sub-cohorts unexplained by the available covariates. We used strata because the assumption of proportional hazards did not hold with respect to sub-cohort. Strata had a substantially better model performance compared to alternative specifications such as sub-cohort indicators. The decision to account for between cohort heterogeneity using strata implies that we mostly evaluate within-cohort exposure contrasts. Each PM$_{2.5}$ component was included as a linear function in the Cox models. Censoring occurred at the time of the event of interest, death from other causes, emigration, loss to follow-up for other reasons, or at the end of follow-up, whichever came first. We a priori specified three confounder models with increasing control for individual and area-level covariates: Model 1 included only age (as the time scale), sub-cohort (as strata), sex (as strata), and year of enrollment; Model 2 added individual-level covariates including marital status (married/ cohabiting, divorced/separated, single, widowed), smoking status (never, former, current), smoking duration (years of smoking) for current smokers, smoking intensity (cigarettes/day) for current smokers, squared smoking intensity, body mass index (BMI) categories (<18.5, 18.5–24.9, 25–29.9, and >30 kg/m$^2$), and employment status (employed/ self-employed vs. unemployed/ homemaker/ housewife/ retired); Model 3 further adjusted for neighborhood-level mean income in 2001. We considered model 3 as the main model.

In addition, two-pollutant models were conducted with our main model adjusting each component for PM$_{2.5}$ mass and NO$_2$ separately. We adjusted for PM$_{2.5}$ mass to investigate whether the association with individual components reflecting specific sources remained after adjustment for generic PM$_{2.5}$ mass for which we have strong evidence of associations (Beelen et al., 2014). We adjusted for NO$_2$ to disentangle the individual component effect from traffic exhaust emission for which NO$_2$ is used as a marker. Adjustment for NO$_2$ is especially important when assessing associations with the traffic non-exhaust components Cu, Fe and Zn. However, two-pollutant models can be difficult to interpret when the two pollutants reflect the same source or are strongly correlated. We did not model all possible combinations of pollutants in two-pollutant models because the correlations between some components were high and we preferred to limit the complexity of analyses. The PM$_{2.5}$ mass and NO$_2$ estimates used in the two-pollutant models were developed with the SLR algorithm (De Hoogh et al., 2018). We previously documented that, for PM$_{2.5}$ mass and NO$_2$ separately, SLR and RF models had similar performance, and that SLR- and RF-modeled exposure at external validation sites were highly correlated (PM$_{2.5}$ mass: Pearson r = 0.89; NO$_2$: r = 0.93) (Chen et al., 2019). Consequently, only the SLR-modeled PM$_{2.5}$ and NO$_2$ exposures were linked to the individual cohorts.

All analyses were performed in R version 3.4.0 using packages: survival, coxme, Matrix, foreach, glmnet, multcomp, survey, splines, Hmisc, mfp, VIM, ggplot2, frailtySurv, survsim, eha, stamod. Statistical significance was based on a p-value < 0.05.
3. Results

3.1 Characteristics of the study population

The total study population in the main model 3 (the most adjusted model) consisted of 323,782 subjects, contributing 6,317,235 person-years at risk. Fifteen percent of the total population was excluded from all analyses due to missing exposure (0.5%), individual-level covariates (12.7%) or neighborhood-level mean income (1.8%). A relatively large number of missing values occurred in E3N (missing smoking data) and KORA (missing neighborhood-level income). Table 1 shows baseline characteristics of participants in individual sub-cohorts. Sub-cohorts differed in the number of participants, the average years of follow-up, the mean baseline age, the percentage of female participants, the lifestyle factors and the neighborhood-level income, supporting the analysis accounting for difference in baseline hazards between sub-cohorts. During the follow-up, we observed 46,640 (14.4%) deaths from natural causes, 15,492 (4.8%) deaths from cardiovascular diseases, 2,846 (0.9%) deaths from non-malignant respiratory diseases and 3,776 (1.2%) deaths from lung cancer.

3.2 Exposure distribution and correlations

For Cu, Fe, K, S and Zn, concentrations were lower in the North European cohorts than in the other cohorts (Figure 1). The within-cohort contrast was substantial for Cu, Fe, Si and limited for K, Ni, S, V and Zn. Exposure distributions for the pooled cohort were similar for SLR- and RF-modeled estimates, though for most components the variability was smaller for RF. For individual cohorts, large differences between the two algorithms were found, e.g. S in HNR.

Correlations between exposure estimates derived from SLR and RF models were high for Cu and Fe (average within-cohort Spearman $r = 0.81$ for Cu, $r = 0.84$ for Fe) (Table 2). Correlations between SLR- and RF-modeled exposure were moderate for S, Si, Zn and low for K, Ni, V, with large variation between cohorts. We focus on within-cohort correlations as the epidemiological analysis exploits mostly within-cohort exposure contrast.

Correlations of composition with PM$_{2.5}$ mass were mostly low to moderate (average of cohort-specific Spearman $r$ ranging from 0.13 to 0.49) (Table S2). Correlations with NO$_2$ were mostly high for Cu and Fe (average of cohort-specific Spearman $r$ above 0.7) (Table S3). Correlations with PM$_{2.5}$ mass and/or NO$_2$ differed substantially in magnitude between cohorts, reflecting differences in study area size and presence of major sources. Average of cohort-specific correlations between Cu and Fe were high, while both Cu and Fe were moderately correlated with Zn (Figure S2). Correlation between Ni and V modeled with the same algorithm was moderate, while the correlation was low when Ni and V were modeled with different algorithms.

3.3 Associations of PM$_{2.5}$ composition with mortality
Natural mortality

Table 3 shows associations of PM$_{2.5}$ composition with natural mortality. In single pollutant models, all components were significantly associated with natural mortality except for RF-modeled Ni and Si. For Cu, Fe, K, S, V and Zn, the HR point estimates were similar for SLR- and RF-modeled exposures with generally wider confidence intervals (CIs) for RF. For Ni and Si, HRs were much higher for SLR-modeled than for RF-modeled exposures.

In two-pollutant models, HRs strongly attenuated for most components, while HRs remained stable for PM$_{2.5}$ mass and NO$_2$ (Table 3 and Table S4). For Cu and Fe, HR point estimates were similar for SLR- and RF-modeled exposures after adjustment for PM$_{2.5}$ mass, with wider CIs observed for RF. HRs decreased substantially and became non-significant after adjustment for NO$_2$ with HRs being above unity for SLR and below unity for RF. HRs for K remained positive and similar for SLR and RF after adjustment for NO$_2$, whereas after adjustment for PM$_{2.5}$ mass, the HRs reduced to unity for SLR but remained positive for RF. For Ni, S, Si and Zn, HRs remained positive and (borderline) significant for SLR in two-pollutant models, whereas HRs reduced to essentially unity for RF. The HRs for V were reduced but remained positive and (borderline) significant in two-pollutant models, with similar estimates observed for SLR and RF.

We observed the strongest associations of natural mortality with all PM$_{2.5}$ components in the minimally adjusted models (Model 1) (Figure S3). HRs attenuated substantially after adjusting for individual level covariates (Model 2), except for K which remained stable. HRs increased slightly or remained stable after further adjustment for area-level covariates (Model 3). This pattern was observed both for SLR- and RF-modeled exposures. For Cu, Fe, K, S, V and Zn, the HR point estimates were similar between SLR- and RF-modeled exposures for all three models, with generally wider CIs for RF. For Ni and Si, the effect estimates were larger for SLR- than for RF-modeled exposure in all models.

Cause-specific mortality

For cardiovascular mortality, we observed significantly positive HRs with all components in single pollutant models except for RF-modeled Ni and Si. In two-pollutant models, HRs for most components attenuated substantially while HRs for PM$_{2.5}$ and NO$_2$ remained stable and tended to be higher in models with RF-modeled component exposure (Table S5). With adjustment for NO$_2$, HRs for Cu and Fe remained elevated for SLR but became null or negative for RF. HR point estimates for SLR-modeled Ni, S, Si and Zn were positive in two-pollutant models adjusting for PM$_{2.5}$ mass or NO$_2$, while HRs were null or negative for RF. The HRs for V remained positive though non-significant after adjustment for PM$_{2.5}$ mass or NO$_2$, with similar estimates for SLR and RF.

For respiratory mortality, positive HRs of a similar magnitude were observed for SLR- and RF-modeled Cu, Fe and V in single pollutant models (Table S6). For S, Si and Zn, HRs were (borderline) significantly positive for SLR-modeled and close to unity for RF-modeled exposures. In two-pollutant models, HRs remained stable after adjustment for PM$_{2.5}$ mass.
HRs were negative after adjustment for NO$_2$ for components modeled with both algorithms except for Ni and V. HRs for NO$_2$ were stable in all models except for increased HRs adjusting for Cu.

For lung cancer mortality, positive HRs were observed for all components in single pollutant models, though HRs for RF-modeled exposures were non-significant except for K, S and V (Table S7). In two-pollutant models with adjustment for PM$_{2.5}$ mass or NO$_2$, HRs stayed stable for SLR-modeled S, whereas HRs reduced substantially though remained elevated for RF-modeled S. HRs for most other components reduced though became non-significant in two-pollutant models. HRs for PM$_{2.5}$ mass and NO$_2$ remained stable in all models except for reduced HRs for SLR-modeled S.
4. Discussion

We observed an elevated risk of mortality associated with long-term exposure to most PM$_{2.5}$ elemental components in single pollutant models. In two-pollutant models with adjustment for PM$_{2.5}$ mass or NO$_2$, effect estimates were attenuated for almost all component-outcome pairs. Effect estimates for SLR- and RF-modeled exposures agreed well in single pollutant models, except for Ni and Si, whereas effect estimates for RF were generally lower than for SLR in two-pollutant models.

Comparison with previous studies

Comparison with previous studies may be partly related to exposure levels and contrasts 20 years ago (most cohorts have baselines in the 1990s). Therefore our sulfur-related magnitude of health effect estimates may be overestimated.

Only a limited number of epidemiological studies have assessed associations between mortality and long-term exposure to PM$_{2.5}$ elemental components. Among the components studied, sulfate has received most attention. Sulfate is a secondary pollutant produced by atmospheric reactions of sulfur oxides (SO$_2$) emitted by combustion of sulfur-containing liquid and solid fuels. Because sulfate is primarily in the fine particle fraction, sulfate may travel for large distances, resulting in a relatively small within study area viability. Another important source is sea salt sulphate which is predominately in the coarse fraction but has a tail also in PM$_{2.5}$ that is long-range transported (Belis et al., 2013). The California Teachers Study (Ostro et al., 2011) reported an increased hazard ratio (HR) of 1.06 (95% CI: 0.97, 1.16) for natural cause mortality in association with a 2.2 μg/m$^3$ increase in PM$_{2.5}$ sulfate concentration, translating into a HR of 1.02 per 200 ng/m$^3$, assuming all S is present as sulfate (sulfate to S ratio of 3). Analyses of the American Cancer Society Cancer Prevention Study-II (ACS CPS-II) suggested that long-term PM$_{2.5}$ S exposure was associated with all-cause mortality (HR ranged from 1.01 to 1.03 per 528.8 ng/m$^3$ depending on the models) (Thurston et al., 2013). In ESCAPE, robust associations of PM$_{2.5}$ S exposure with natural mortality were found (Beelen et al., 2015). The effect estimate observed in ESCAPE was similar to the estimate in the current study (HR 1.14, 95% CI: 1.06, 1.23 per 200 ng/m$^3$ in ESCAPE; HR 1.14, 95% CI: 1.11, 1.17 and HR 1.13, 95% CI: 1.08, 1.18 per 200 ng/m$^3$ for SLR- and RF-modeled exposures, respectively, in ELAPSE). In the current study we obtained a much narrower confidence interval, probably due to the longer follow-up and the pooling of cohort data. The effect estimate of S in our study was much larger than the estimates from the U.S. cohorts. One major difference is that the U.S. cohorts investigated between-area contrasts only while both ELAPSE and ESCAPE focus on within-area contrasts. Because the transported sulfate has relatively uniform spatial variation at the city scale, the exposure contrast was much smaller in our study than in the U.S. studies, thus a small effect in our study could be inflated when adopting it to the same increment of exposure as in the U.S. studies. Another explanation might be that we measured elemental composition between 2008 and 2011, when emission of SO$_2$ has decreased compared to the baseline of all cohorts (EEA, 2015). Health effects in our study populations may be partly related to exposure levels and contrasts 20 years ago (most cohorts have baselines in the 1990s). Therefore our sulfur-related magnitude of health effect estimates may be overestimated.
In the current study, we also found robust associations between S and lung cancer mortality, which is observed in ACS CPS-II as well (Thurston et al., 2013). In ESCAPE, robust associations were observed for S and lung cancer incidence (Raaschou-Nielsen et al., 2016). We observed elevated associations of S with cardiovascular mortality, which is consistent with previous findings in ESCAPE (Wang et al., 2014; Wolf et al., 2015) and in one of the ELAPSE sub-cohorts (i.e. the DCH cohort). The latter study reported an elevated risk of cardiovascular mortality associated with long-term exposure to secondary inorganic aerosols (Hvidtfeldt et al., 2019).

The Women’s Health Initiative-Observational Study (WHI-OS) found no association of sulfur with cardiovascular deaths (HR 1.01, 95% CI: 0.92, 1.12 per 0.25 µg/m\(^3\)), but a statistically significant association with cardiovascular events (HR 1.09, 95% CI: 1.05, 1.14 per 0.25 µg/m\(^3\)) (Vedal et al., 2013). In the California Teachers Study, IHD mortality was associated with long-term exposure to sulfate (Ostro et al., 2011) and high-sulfur content fuel combustion (Ostro et al., 2015).

Both Ni and V are suggested to be tracers of mixed industrial/ fuel-oil combustion and derived mainly from shipping emissions in Europe (Viana et al., 2008). Our study found positive associations of natural mortality with long-term exposure to Ni (HR 1.08, 95% CI 1.06, 1.11 and HR 1.01, 95% CI 0.97, 1.05 per 1 ng/m\(^3\) for SLR- and RF-modeled exposures respectively) and V (HR 1.06, 95% CI 1.04, 1.08 and HR 1.09, 95% CI 1.05, 1.14 per 2 ng/m\(^3\) for SLR- and RF-modeled exposures respectively). The effect estimates are similar to the estimates in ESCAPE for natural mortality (HR for Ni 1.05, 95% CI 0.97, 1.13 per 1 ng/m\(^3\); HR for V 1.07, 95% CI 0.93, 1.23 per 2 ng/m\(^3\)) (Beelen et al., 2015), with much narrower CIs in ELAPSE. In ESCAPE, accuracy of exposure estimates for Ni and V was limited because of the absence of specific sources of Ni and V in several study areas combined with limited measurement precision especially in areas with low pollution levels (de Hoogh et al., 2013). The Europe-wide models made use of both within and between area measurement contrasts and resulted in models with good performance for Ni and V (Chen et al., in revision). Compared to ESCAPE, the ELAPSE models further added industrial source data as potential predictors which improved the model performance. The improved exposure assessment may have allowed us to better detect the potential component-mortality associations. Only a few studies have reported associations of mortality or morbidity with long-term exposure to Ni and V. In ESCAPE, association was found between PM\(_{10}\) Ni exposure and lung cancer incidence (Raaschou-Nielsen et al., 2016). In the Medicare population, stronger associations between long-term PM\(_{2.5}\) exposure and mortality were found for PM\(_{2.5}\) with higher V content (Wang et al., 2017). In the ACS CPS-II, associations between IHD mortality and Ni were reported (Thurston et al., 2013). The observed adverse effects of Ni and V on health could be due to the components per se or other components in emissions from oil combustion.

In the current study, the effect estimates for the traffic-related components Cu and Fe remained after adjustment for PM\(_{2.5}\) mass but were reduced substantially after adjustment for NO\(_2\). The modestly wider confidence intervals for models with PM\(_{2.5}\) mass compared to the single pollutant models suggest these models provide interpretable results. Confidence
intervals in two-pollutant models with NO\textsubscript{2} widened somewhat more, due to the high correlations of Cu and Fe with NO\textsubscript{2} in our study. Therefore, the substantial attenuation in effect estimates for Cu and Fe should be interpreted with caution, because effects of NO\textsubscript{2} versus those from Cu or Fe cannot be separated well. The high correlations of Cu and Fe with NO\textsubscript{2} in our study are consistent with correlations observed in the measurements (Tsai et al., 2015), suggesting the high correlations were not artificially introduced by the modeling methodology. Previous studies found mixed results regarding associations of mortality with Cu and Fe. Using LUR models developed in ESCAPE, the Rome longitudinal study found associations of mortality with Cu and Fe in PM\textsubscript{2.5} as well as tracers of tailpipe (i.e., PM\textsubscript{2.5} absorbance) (Badaloni et al., 2017), but in the Badaloni study no adjustment for NO\textsubscript{2} was made. Positive associations were observed in the California Teachers Study between Fe and IHD mortality, but not with natural-cause, cardiopulmonary or pulmonary mortality (Ostro et al., 2011). Although the Ostro study did not adjust for NO\textsubscript{2} or PM\textsubscript{2.5} mass, adjustment for organic carbon did substantially reduced HRs. Analyses of ACS CPS-II showed that traffic-related exposure was less strongly associated with excess mortality compared to coal combustion-related exposure (Thurston et al., 2013). However the ACS CPS-II study might have underestimated the effects of traffic-related air pollution because it investigated between-city variation, which represents only a small part of the expected overall variation in traffic-related air pollution.

Although Zn was a priori selected in ESCAPE to represent non-tailpipe traffic emissions, our Europe-wide models showed that a large fraction of the variation in the Zn measurements was explained by predictors representing industrial Zn emission (Chen et al., in revision), consistent with Zn being also a tracer for particles from industrial sources. This is consistent with source apportionment analyses in ACS CPS-II, where Zn was considered as a source identifier for metals industry (Thurston et al., 2016). The moderate correlations between Zn and NO\textsubscript{2}, and the less substantial attenuation of effect estimates for Zn and natural mortality after adjustment for NO\textsubscript{2} compared to Cu and Fe, also suggest that Zn was not only related to traffic emission. The Rome longitudinal study found positive associations between PM\textsubscript{2.5} Zn and mortality from natural causes, cardiovascular diseases and IHD, using LUR models developed in ESCAPE (Badaloni et al., 2017). The ACS CPS-II also found some evidence of positive associations between Zn and mortality (Thurston et al., 2013). In the California Teachers Study, positive associations between Zn and IHD mortality were reported, but not with natural-cause, cardiopulmonary or pulmonary mortality (Ostro et al., 2011).

K was selected to represent biomass burning emission in ESCAPE (Tsai et al., 2015). While our new model included a plausible background predictor for biomass combustion (satellite-model organic matter), the model may have limited ability to capture within-area variability of biomass combustion emission because of the lack of reliable fine-scale predictor variables (Chen et al., in revision). Our study found elevated HRs for K exposure associated with mortality from natural-cause, cardiovascular diseases and lung cancer. HRs decreased to close to unity after adjustment for PM\textsubscript{2.5} mass. K was reported to be associated with coronary
events in ESCAPE (Wolf et al., 2015). K in ESCAPE was rather related to traffic (for example from resuspension of road dust) than to biomass burning. The California Teachers Study found positive associations between IHD mortality and K (Ostro et al., 2011), whereas ACS CPS-II consistently observed null association between K and mortality (Thurston et al., 2013).

Si was selected to represent crustal material, which is abundant in coarse particles. There was little evidence for an association between long-term coarse PM exposure and mortality (Adar et al., 2014; Hoek et al., 2013). The 2019 Integrated Science Assessment (ISA) rated the association between PM_{coarse} exposure and natural-cause mortality as “suggestive” (EPA, 2019). Our study did not find consistent results for PM_{2.5} Si. The ACS CPS-II found that Si was consistently not associated with mortality across all models (Thurston et al., 2013). A negative and marginal association was observed for CVD events with Si in WHI-OS (Vedal et al., 2013). In contrast, analyses in the California Teachers Study showed positive associations of IHD mortality with Si (Ostro et al., 2011).

**Effect estimates using SLR- and RF-modeled exposures**

For most components, we observed generally consistent elevated mortality risks for SLR- and RF-modeled exposures in single pollutant models. However, less consistent associations for exposures by RF than SLR were found in two-pollutant models especially after adjusting for NO₂. We do not have a clear explanation for these differences. There is no clear pattern of differences related to the spatial distribution of the components. We found differences both for components with a strong local contribution such as Cu and components with a predominantly large-scale variation such as S. The less consistent association for RF-modeled exposure in two-pollutant models is not due to different correlation of components with PM_{2.5} mass or NO₂, which were similar for RF- and SLR-modeled exposures. The two sets of models had similar performance in explaining within-area variability in internal cross-validations (Chen et al., in revision), which is the exposure contrast primarily exploited in the current analysis. The comparison of performance of the two algorithms is limited as we do not have external validation measurements. We therefore had no prior to which models had lower biases. We observed that the predicted variability of exposure was less for RF, explaining the wider confidence intervals in the epidemiological analyses using RF-modeled exposures. It is possible that the power to detect weak associations in two-pollutant models was less for RF models. We note that RF models are more difficult to interpret in terms of how predictor variables act in the models, so a full analysis of the difference of specific predictors in the two algorithms is not possible.

**Strengths and limitations**

One important strength is the highly standardized dataset used in this study, which was pooled from eight European cohorts with detailed individual and area-level covariate information, including smoking and BMI, which involved harmonizing variables between cohorts. The pooling of data allowed for more statistical power in our current analyses compared to the previous ESCAPE analyses. Another strength is the improvement in exposure
assessment compared to ESCAPE. Analyses in ESCAPE may have had limited ability to detect component-specific mortality associations for Ni and V because of the lack of specific predictors in the exposure models for these components (de Hoogh et al., 2013). The Europe-wide PM$_{2.5}$ composition models were able to make use of specific predictors representing pollution sources such as industrial sources, which explained a large proportion of the variation in measurements of specific components such as Zn (Chen et al., in revision). The Europe-wide models were developed based on a large number of measurement sites combined from individual ESCAPE study areas. A previous study has suggested that underestimation of the effect estimates was less serious when a large number of measurement sites was used for LUR modeling (Basagana et al., 2013).

One main limitation of our study is that the exposure models were developed based on measurements in 2008–2011 while most included cohorts started in the mid-1990s. In the current study, we were not able to apply back-extrapolated exposure for PM$_{2.5}$ components because we had insufficient information on concentration of PM$_{2.5}$ components in Europe over time. Several studies in Europe have reported that the spatial contrast of NO$_2$ remained stable for periods up to 10 years (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2013), suggesting that spatial contrast for traffic-related components such as Cu and Fe may be stable over time. For Cu and Fe contrasts may actually be more stable, as non-tailpipe emissions have not been regulated, as opposed to tail-pipe emissions. We cannot rule out the possibility that spatial contrast for components from other sources may have been less stable. For example the magnitude of our sulfur-related health estimates might be overestimated because of decreased SO$_2$ emission over the years, which possibly resulted in a smaller contrast in sulfate exposure. The spatial pattern of major sources has likely not changed in a major way. Another limitation is that we did not consider residential mobility during follow-up in the current study. This may have resulted in measurement error, likely resulting in bias towards the null. Lastly, the exposure maps for RF-modeled K, Ni and V showed strong boundary effects which might affect the exposure estimates for some participants in the E3N cohort (Chen et al., in revision). However, we expected limited impact on the health effect estimation as only few people live at the borders and the correlations between SLR- and RF-modeled estimates did not stand out for these three elements, nor the E3N cohort.

5. Conclusions

Long-term exposures to especially vanadium in PM$_{2.5}$ was associated with increased mortality risk, with associations observed for both RF- and SLR-modeled exposures. For the other components, associations were generally weaker when exposure was assessed with RF compared to SLR in two-pollutant models.
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Table 1. Population characteristics in the most adjusted model (model 3)

| Sub-cohort  | Population size1 | N persons in main model 3 (%) | Average years of follow-up | Age at baseline (Mean ± SD) | Percen t female | Percent current smokers | Years of smoking2 (Mean ± SD) | No. of cigarettes/day2 (Mean ± SD) | Percent overweight or obese (BMI≥25 kg/m²) | Percent married or living with partner | Percent employed | Neighborhoo d income, *1000 euro (Mean ± SD) |
|-------------|------------------|-------------------------------|-----------------------------|-----------------------------|-----------------|------------------------|-------------------------------|--------------------------------------|----------------------------------------|-----------------|----------------|-----------------------------------|
| Pooled cohort | 381,036 | 323,782 (85.0) | 19.5 | 48.7 ± 13.4 | 66 | 24 | 25.4 ± 13.1 | 15.2 ± 8.9 | 43 | 72 | 70 | 20.1 ± 5.8 |
| CEANS-SDPP | 7,835 | 7,716 (98.5) | 15.9 | 47.1 ± 4.9 | 61 | 26 | 27.9 ± 8.6 | 13.5 ± 7.4 | 52 | 84 | 91 | 24.3 ± 4.2 |
| CEANS-SIXTY | 4,180 | 3,965 (94.9) | 15.5 | 60.0 ± 0.0 | 52 | 21 | 36.3 ± 9.9 | 13.4 ± 7.6 | 64 | 74 | 68 | 24.7 ± 6.9 |
| CEANS-SALT | 6,724 | 6,174 (91.8) | 10.4 | 57.8 ± 10.6 | 55 | 21 | 37.9 ± 9.3 | 12.7 ± 8.0 | 40 | 68 | 64 | 25.3 ± 6.6 |
| CEANS-SNACK | 3,248 | 2,830 (87.1) | 7.4 | 72.9 ± 10.4 | 62 | 14 | 43.3 ± 13.6 | 11.7 ± 8.2 | 53 | 46 | 23 | 28.7 ± 2.2 |
| DCH | 56,308 | 52,779 (93.7) | 18.2 | 56.7 ± 4.4 | 53 | 36 | 36.3 ± 7.7 | 16.5 ± 9.0 | 56 | 71 | 78 | 20.1 ± 3.4 |
| DNC-1993 | 19,664 | 17,017 (86.5) | 18.7 | 56.2 ± 8.4 | 100 | 37 | 31.6 ± 9.9 | 13.9 ± 8.2 | 28 | 68 | 70 | 19.2 ± 2.6 |
| DNC-1999 | 8,769 | 8,117 (92.6) | 14.4 | 47.9 ± 4.2 | 100 | 29 | 27.1 ± 7.1 | 13.3 ± 7.3 | 30 | 76 | 95 | 19.0 ± 2.4 |
| EPIC-NL Morgen | 20,711 | 18,292 (88.3) | 16.8 | 42.9 ± 11.3 | 55 | 35 | 24.8 ± 10.6 | 15.7 ± 8.6 | 49 | 65 | 69 | 12.2 ± 1.6 |
| EPIC-NL Prospect | 16,194 | 14,570 (90.0) | 16.4 | 57.7 ± 6.1 | 100 | 23 | 36.8 ± 7.6 | 13.7 ± 8.7 | 55 | 77 | 51 | 13.1 ± 1.4 |
| HNR | 4,809 | 4,733 (98.4) | 12.0 | 59.7 ± 7.8 | 50 | 24 | 34.5 ± 9.4 | 18.6 ± 12.0 | 74 | 75 | 40 | 25.2 ± 8.2 |
| E3N | 53,521 | 38,537 (72.0) | 16.8 | 53.0 ± 6.8 | 100 | 13 | 28.6 ± 7.6 | 11.3 ± 9.2 | 21 | 83 | 68 | 11.2 ± 3.0 |
| KORA-S3 | 4,966 | 2,572 (56.3) | 15.6 | 49.4 ± 13.9 | 51 | 20 | 25.2 ± 12.1 | 16.5 ± 9.5 | 67 | 80 | 55 | 36.7 ± 4.4 |
| KORA-S4 | 4,257 | 2,281 (53.6) | 12.9 | 49.3 ± 13.8 | 51 | 23 | 24.3 ± 11.6 | 15.7 ± 9.5 | 69 | 79 | 59 | 38.0 ± 7.3 |
| VHM&PP | 170,250 | 144,199 (84.7) | 23.1 | 42.1 ± 15.0 | 56 | 20 | 13.4 ± 8.3 | 15.6 ± 8.9 | 42 | 69 | 70 | 22.9 ± 1.7 |

1 Population size is the number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort.
2 For current smokers.
Table 2. Spearman correlation coefficients between component exposure at participant addresses estimated from Supervised Linear Regression and Random Forest models (N=323,782)

| Sub-cohort          | PM$_{2.5}$ Cu | PM$_{2.5}$ Fe | PM$_{2.5}$ K | PM$_{2.5}$ Ni | PM$_{2.5}$ S | PM$_{2.5}$ Si | PM$_{2.5}$ V | PM$_{2.5}$ Zn |
|---------------------|---------------|---------------|--------------|---------------|--------------|---------------|--------------|--------------|
| Average$^1$         | 0.81          | 0.84          | 0.22         | 0.33          | 0.59         | 0.56          | 0.27         | 0.60         |
| CEANS-SDPP         | 0.27          | 0.72          | 0.16         | 0.24          | 0.48         | -0.01         | 0.16         | 0.27         |
| CEANS-SIXTY        | 0.86          | 0.89          | -0.09        | 0.44          | 0.39         | 0.76          | -0.07        | 0.45         |
| CEANS-SALT         | 0.88          | 0.91          | -0.09        | 0.47          | 0.38         | 0.81          | -0.11        | 0.44         |
| CEANS-SNACK        | 0.86          | 0.90          | 0.49         | 0.47          | 0.79         | 0.70          | 0.39         | 0.53         |
| DCH                | 0.94          | 0.89          | -0.37        | 0.69          | 0.78         | 0.53          | 0.58         | 0.61         |
| DNC-1993           | 0.80          | 0.79          | 0.31         | 0.45          | 0.72         | 0.43          | 0.35         | 0.63         |
| DNC-1999           | 0.77          | 0.78          | 0.35         | 0.43          | 0.70         | 0.41          | 0.34         | 0.63         |
| EPIC-NL-Morgen     | 0.92          | 0.93          | 0.82         | 0.89          | 0.20         | 0.59          | 0.7           | 0.52         |
| EPIC-NL-Prospect   | 0.94          | 0.94          | 0.11         | 0.09          | 0.58         | 0.82          | -0.22        | 0.71         |
| HNR                | 0.81          | 0.70          | -0.33        | 0.53          | 0.56         | 0.72          | 0.53         | 0.79         |
| E3N                | 0.90          | 0.89          | 0.62         | 0.51          | 0.67         | 0.55          | 0.72         | 0.83         |
| KORA-S3            | 0.71          | 0.84          | 0.23         | -0.17         | 0.62         | 0.79          | -0.03        | 0.55         |
| KORA-S4            | 0.77          | 0.85          | -0.03        | 0.10          | 0.59         | 0.85          | 0.22         | 0.67         |
| VHM&PP             | 0.88          | 0.74          | 0.89         | -0.51         | 0.79         | -0.16         | 0.22         | 0.74         |
| **Pooled cohort**  | **0.91**      | **0.81**      | **0.79**     | **0.73**      | **0.91**     | **0.34**      | **0.78**     | **0.59**     |

$^1$Average of cohort-specific correlation coefficients. Cohort-specific correlations are shown because the analyses mostly exploit within-cohort exposure contrasts (i.e. stratified by sub-cohort id).
Table 3. Associations of PM$_{2.5}$ components with natural mortality in single pollutant and two-pollutant models

| Exposure | Exposure model | Single pollutant HR | Two-pollutant model adjusting for PM$_{2.5}$ | Two-pollutant model adjusting for NO$_2$ |
|----------|----------------|---------------------|---------------------------------------------|----------------------------------------|
| PM$_{2.5}$ Cu | SLR | 1.120 (1.094, 1.147) | 1.043 (1.011, 1.076) | 1.023 (0.983, 1.065) |
|           | RF  | 1.154 (1.111, 1.198) | 1.035 (0.989, 1.083) | 0.943 (0.887, 1.002) |
| PM$_{2.5}$ Fe | SLR | 1.139 (1.110, 1.169) | 1.065 (1.031, 1.100) | 1.024 (0.974, 1.076) |
|           | RF  | 1.132 (1.090, 1.176) | 1.055 (1.013, 1.099) | 0.921 (0.869, 0.976) |
| PM$_{2.5}$ K  | SLR | 1.049 (1.035, 1.064) | 0.998 (0.981, 1.015) | 1.027 (1.012, 1.041) |
|            | RF  | 1.056 (1.042, 1.070) | 1.021 (1.006, 1.037) | 1.031 (1.017, 1.046) |
| PM$_{2.5}$ Ni | SLR | 1.084 (1.063, 1.106) | 1.043 (1.020, 1.066) | 1.030 (1.006, 1.055) |
|            | RF  | 1.011 (0.971, 1.053) | 0.993 (0.953, 1.034) | 0.949 (0.909, 0.990) |
| PM$_{2.5}$ S  | SLR | 1.142 (1.113, 1.173) | 1.049 (1.009, 1.090) | 1.074 (1.039, 1.109) |
|            | RF  | 1.127 (1.079, 1.177) | 0.999 (0.951, 1.051) | 1.013 (0.964, 1.064) |
| PM$_{2.5}$ Si | SLR | 1.268 (1.205, 1.336) | 1.151 (1.087, 1.217) | 1.071 (0.995, 1.152) |
|            | RF  | 0.967 (0.921, 1.014) | 0.969 (0.924, 1.017) | 0.906 (0.863, 0.952) |
| PM$_{2.5}$ V  | SLR | 1.061 (1.044, 1.079) | 1.033 (1.015, 1.052) | 1.026 (1.007, 1.045) |
|            | RF  | 1.092 (1.050, 1.135) | 1.056 (1.015, 1.099) | 1.026 (0.985, 1.069) |
| PM$_{2.5}$ Zn | SLR | 1.051 (1.039, 1.064) | 1.015 (0.999, 1.031) | 1.021 (1.006, 1.036) |
|            | RF  | 1.062 (1.036, 1.089) | 0.992 (0.964, 1.021) | 1.002 (0.974, 1.030) |

N=323,782; HR (95% confidence interval) presented for the following increments: PM$_{2.5}$ Cu – 5 ng/m$^3$, PM$_{2.5}$ Fe – 100 ng/m$^3$, PM$_{2.5}$ K – 50 ng/m$^3$, PM$_{2.5}$ Ni – 1 ng/m$^3$, PM$_{2.5}$ S – 200 ng/m$^3$, PM$_{2.5}$ Si – 100 ng/m$^3$, PM$_{2.5}$ V – 2 ng/m$^3$, PM$_{2.5}$ Zn – 10 ng/m$^3$; main model adjusted for sub-cohort id, age, sex, year of enrollment, smoking (status, duration, intensity, intensity$^2$), BMI categories, marital status, employment status and 2001 neighborhood-level mean income

HR = Hazard Ratio, SLR = Supervised Linear Regression model, RF = Random Forest model
Figure 1. Distribution of component exposure at participant addresses estimated from Supervised Linear Regression and Random Forest models
The boundary of the box closest to zero indicates P25; furthest from zero – P75; bold vertical line inside the box – P50; whiskers indicate P5 and P95.
Sub-cohorts are shown from north to south
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Long-term exposure to fine particle elemental components and natural and cause-specific mortality – a pooled analysis of eight European cohorts within the ELAPSE project

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