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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 μm ($PM_{2.5}$) 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) (Tjønneland et al., 2007) in Denmark; the *Danish Nurse Cohort* (DNC) (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 (Schmermund et al., 2002); the *Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education 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 life-style 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.

546 HRs were negative after adjustment for NO_2 for components modeled with both algorithms
547 except for Ni and V. HRs for NO_2 were stable in all models except for increased HRs adjusting
548 for Cu.

549 For lung cancer mortality, positive HRs were observed for all components in single pollutant
550 models, though HRs for RF-modeled exposures were non-significant except for K, S and V
551 (Table S7). In two-pollutant models with adjustment for $PM_{2.5}$ mass or NO_2, HRs stayed stable
552 for SLR-modeled S, whereas HRs reduced substantially though remained elevated for RF-
553 modeled S. HRs for most other components reduced and became non-significant in two-
554 pollutant models. HRs for $PM_{2.5}$ mass and NO_2 remained stable in all models except for
555 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

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 $\mu g/m^3$ 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_2 widened somewhat more, due to the high correlations of Cu and Fe with NO_2 in our study. Therefore, the substantial attenuation in effect estimates for Cu and Fe should be interpreted with caution, because effects of NO_2 versus those from Cu or Fe cannot be separated well. The high correlations of Cu and Fe with NO_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 $PM_{2.5}$ as well as tracers of tailpipe (i.e., $PM_{2.5}$ absorbance) (Badaloni et al., 2017), but in the Badaloni study no adjustment for NO_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_2 or $PM_{2.5}$ 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_2, and the less substantial attenuation of effect estimates for Zn and natural mortality after adjustment for NO_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 $PM_{2.5}$ 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 $PM_{2.5}$ 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 NO_2. 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 NO_2, 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.

References

Adar SD, Filigrana PA, Clements N, et al. 2014. Ambient coarse particulate matter and human health: A systematic review and meta-analysis. Current environmental health reports 1:258-274.

Badaloni C, Cesaroni G, Cerza F, et al. 2017. Effects of long-term exposure to particulate matter and metal components on mortality in the rome longitudinal study. Environment international 109:146-154.

Basagana X, Aguilera I, Rivera M, et al. 2013. Measurement error in epidemiologic studies of air pollution based on land-use regression models. Am J Epidemiol 178:1342-1346.

Basagaña X, Rivera M, Aguilera I, et al. 2012. Effect of the number of measurement sites on land use regression models in estimating local air pollution. Atmospheric Environment 54:634-642.

Beelen R, Raaschou-Nielsen O, Stafoggia M, et al. 2014. Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 european cohorts within the multicentre escape project. The Lancet 383:785-795.

Beelen R, Hoek G, Raaschou-Nielsen O, et al. 2015. Natural-cause mortality and long-term exposure to particle components: An analysis of 19 european cohorts within the multi-center escape project. Environ Health Perspect 123:525-533.

Belis CA, Karagulian F, Larsen BR, et al. 2013. Critical review and meta-analysis of ambient particulate matter source apportionment using receptor models in europe. Atmospheric Environment 69:94-108.

Beulens JW, Monninkhof EM, Verschuren WM, et al. 2010. Cohort profile: The epic-nl study. International journal of epidemiology 39:1170-1178.

Brokamp C, Jandarov R, Rao MB, et al. 2017. Exposure assessment models for elemental components of particulate matter in an urban environment: A comparison of regression and random forest approaches. Atmos Environ (1994) 151:1-11.

Cesaroni G, Porta D, Badaloni C, et al. 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. Environmental Health 11:48.

Chen J, de Hoogh K, Gulliver J, et al. 2019. A comparison of linear regression, regularization, and machine learning algorithms to develop europe-wide spatial models of fine particles and nitrogen dioxide. Environment international 130:104934.

Chen J, de Hoogh K, Gulliver J, et al. Development of Europe-Wide Models for Particle Elemental Composition Using Supervised Linear Regression and Random Forest. Environ Sci Technol 2020. (in revision).

Clavel-Chapelon F, Group ENS. 2015. Cohort profile: The french e3n cohort study. International journal of epidemiology 44:801-809.

Cohen AJ, Brauer M, Burnett R, et al. 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the global burden of diseases study 2015. The Lancet 389:1907-1918.

de Hoogh K, Wang M, Adam M, et al. 2013. Development of land use regression models for particle composition in twenty study areas in europe. Environ Sci Technol 47:5778-5786.

De Hoogh K, Chen J, Gulliver J, et al. 2018. Spatial pm2. 5, no2, o3 and bc models for western europe–evaluation of spatiotemporal stability. Environment international 120:81-92.

EEA. 2015. Https://www.Eea.Europa.Eu/data-and-maps/indicators/eea-32-sulphur-dioxide-so2-emissions-1/assessment-3.

797 Eeftens M, Beelen R, Fischer P, et al. 2011. Stability of measured and modelled spatial
798 contrasts in no2 over time. Occupational and environmental medicine 68:765-770.
799 EPA US. 2019. Integrated science assessment (isa) for particulate matter (final report, 2019).
800 Eriksson AK, Ekbom A, Granath F, et al. 2008. Psychological distress and risk of pre-diabetes
801 and type 2 diabetes in a prospective study of swedish middle-aged men and women.
802 Diabetic Medicine 25:834-842.
803 Gulliver J, de Hoogh K, Hansell A, et al. 2013. Development and back-extrapolation of no2
804 land use regression models for historic exposure assessment in great britain. Environmental
805 science & technology 47:7804-7811.
806 Hoek G, Krishnan RM, Beelen R, et al. 2013. Long-term air pollution exposure and cardio-
807 respiratory mortality: A review. Environmental health 12:43.
808 Hoek G. 2017. Methods for assessing long-term exposures to outdoor air pollutants. Curr
809 Environ Health Rep 4:450-462.
810 Hundrup YA, Simonsen MK, Jørgensen T, et al. 2012. Cohort profile: The danish nurse
811 cohort. International journal of epidemiology 41:1241-1247.
812 Hvidtfeldt UA, Geels C, Sorensen M, et al. 2019. Long-term residential exposure to pm2.5
813 constituents and mortality in a danish cohort. Environ Int 133:105268.
814 Jerrett M, Turner MC, Beckerman BS, et al. 2017. Comparing the health effects of ambient
815 particulate matter estimated using ground-based versus remote sensing exposure
816 estimates. Environ Health Perspect 125:552-559.
817 Kerckhoffs J, Hoek G, Portengen Lt, et al. 2019. Performance of prediction algorithms for
818 modeling outdoor air pollution spatial surfaces. Environmental science & technology
819 53:1413-1421.
820 Lagergren M, Fratiglioni L, Hallberg IR, et al. 2004. A longitudinal study integrating
821 population, care and social services data. The swedish national study on aging and care
822 (snac). Aging clinical and experimental research 16:158-168.
823 Magnusson PK, Almqvist C, Rahman I, et al. 2013. The swedish twin registry: Establishment
824 of a biobank and other recent developments. Twin Research and Human Genetics 16:317-
825 329.
826 McGuinn LA, Ward-Caviness C, Neas LM, et al. 2017. Fine particulate matter and
827 cardiovascular disease: Comparison of assessment methods for long-term exposure. Environ
828 Res 159:16-23.
829 Ostro B, Lipsett M, Reynolds P, et al. 2011. Long-term exposure to constituents of fine
830 particulate air pollution and mortality: Results from the california teachers study. Environ
831 Health Perspect 118:363-369.
832 Ostro B, Hu J, Goldberg D, et al. 2015. Associations of mortality with long-term exposures to
833 fine and ultrafine particles, species and sources: Results from the california teachers study
834 cohort. Environ Health Perspect 123:549-556.
835 Raaschou-Nielsen O, Beelen R, Wang M, et al. 2016. Particulate matter air pollution
836 components and risk for lung cancer. Environment international 87:66-73.
837 Schmermund A, Möhlenkamp S, Stang A, et al. 2002. Assessment of clinically silent
838 atherosclerotic disease and established and novel risk factors for predicting myocardial
839 infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the
840 heinz nixdorf recall study. American heart journal 144:212-218.

Strak M, Weinmayr G, Rodopoulou S, et al. Long-term exposure to low-level air pollution and natural and cause-specific mortality – a pooled analysis of eight European cohorts within the ELAPSE project. (submitted)
Szpiro AA, Paciorek CJ, Sheppard L. 2011. Does more accurate exposure prediction necessarily improve health effect estimates? Epidemiology 22:680-685.
Thurston G, Ito K, Lall R, et al. 2013. Npact study 4: Mortality and long-term exposure to pm2. 5 and its components in the american cancer society's cancer prevention study ii cohort. National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components Health Effect Institute.
Thurston GD, Burnett RT, Turner MC, et al. 2016. Ischemic heart disease mortality and long-term exposure to source-related components of u.S. Fine particle air pollution. Environ Health Perspect 124:785-794.
Tjønneland A, Olsen A, Boll K, et al. 2007. Study design, exposure variables, and socioeconomic determinants of participation in diet, cancer and health: A population-based prospective cohort study of 57,053 men and women in denmark. Scandinavian journal of public health 35:432-441.
Tsai MY, Hoek G, Eeftens M, et al. 2015. Spatial variation of pm elemental composition between and within 20 european study areas--results of the escape project. Environ Int 84:181-192.
Ulmer H, Kelleher C, Fitz-Simon N, et al. 2007. Secular trends in cardiovascular risk factors: An age-period cohort analysis of 6 98 954 health examinations in 1 81 350 austrian men and women. Journal of internal medicine 261:566-576.
Vedal S, Campen M, McDonald J, et al. 2013. National particle component toxicity (npact) initiative report on cardiovascular effects. Research Report (Health Effects Institute):5-8.
Viana M, Kuhlbusch TAJ, Querol X, et al. 2008. Source apportionment of particulate matter in europe: A review of methods and results. Journal of Aerosol Science 39:827-849.
Wändell P-E, Wajngot A, De Faire U, et al. 2007. Increased prevalence of diabetes among immigrants from non-european countries in 60-year-old men and women in sweden. Diabetes & metabolism 33:30-36.
Wang M, Beelen R, Eeftens M, et al. 2012. Systematic evaluation of land use regression models for no2. Environmental science & technology 46:4481-4489.
Wang M, Beelen R, Stafoggia M, et al. 2014. Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 european cohorts: Results from the escape and transphorm projects. Environ Int 66:97-106.
Wang Y, Shi L, Lee M, et al. 2017. Long-term exposure to pm2.5 and mortality among older adults in the southeastern us. Epidemiology 28:207-214.
Wolf K, Stafoggia M, Cesaroni G, et al. 2015. Long-term exposure to particulate matter constituents and the incidence of coronary events in 11 european cohorts. Epidemiology 26:565-574.

Table 1. Population characteristics in the most adjusted model (model 3)

Sub-cohort	Population size[1]	N persons in main model 3 (%)	Average years of follow-up	Age at baseline (Mean ± SD)	Percent female	Percent current smokers	Years of smoking[2] (Mean ± SD)	No. of cigarettes/day[2] (Mean ± SD)	Percent overweight or obese (BMI≥25 kg/m^2)	Percent married or living with partner	Percent employed	Neighborhood 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	4,566	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

Figure 1

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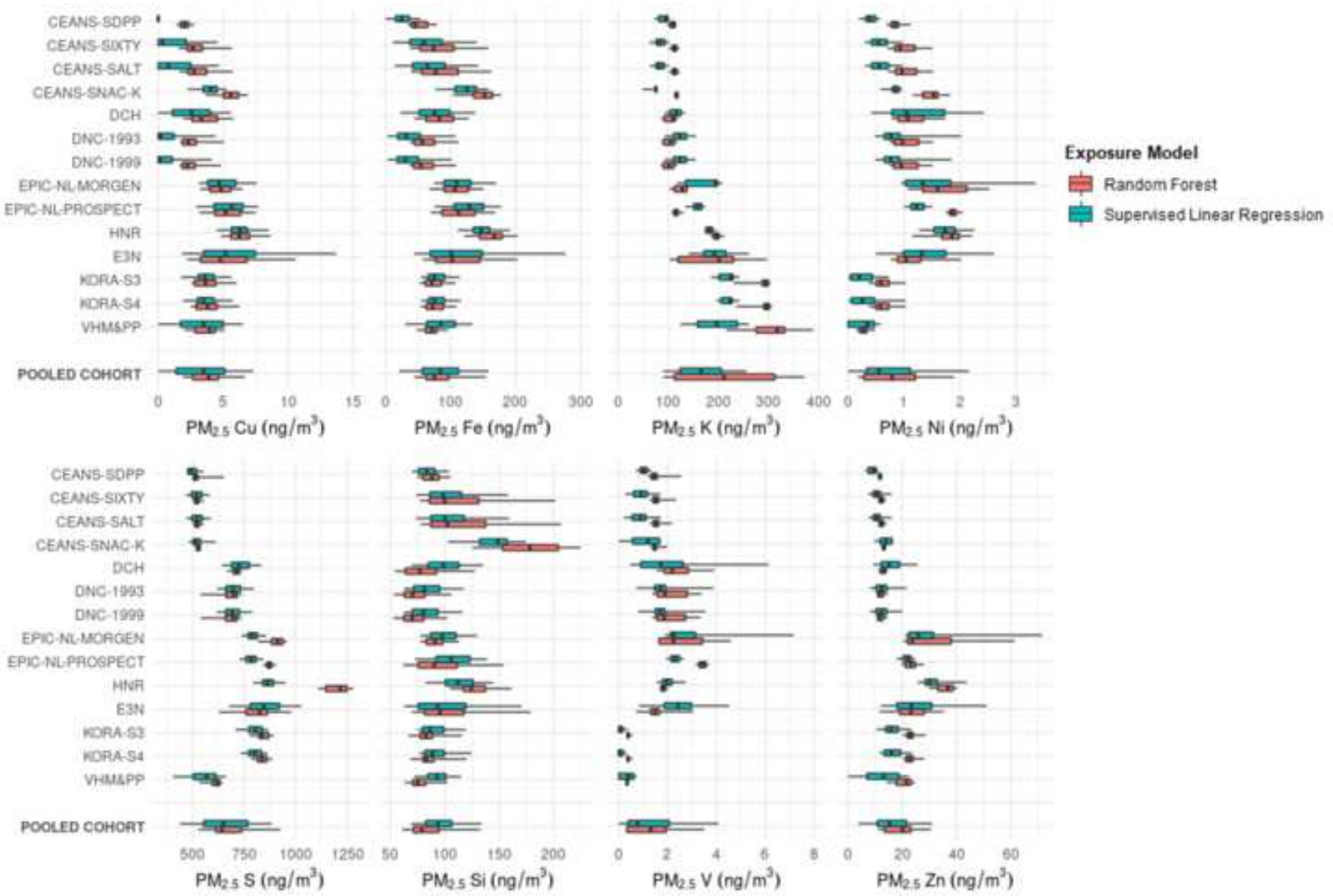

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