



Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 European cohorts: Results from the ESCAPE and TRANSPHORM projects



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Abbreviations: BMI, body mass index; CTS, California Teachers Study; Cu, copper; CVD, cardiovascular disease; ESCAPE, European Study of Cohorts for Air Pollution Effects; Fe, iron; HRs, hazard ratios; K, potassium; LOOCV, leave-one-out cross validation; LUR, Land Use Regression models; Ni, nickel; PM, particulate matter; S, sulfur; SES, socio-economic status; Si, silicon; TRANSPHORM, Transport related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter; V, vanadium; XRF, X-ray fluorescence; Zn, zinc.

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ABSTRACT

Background: Associations between long-term exposure to ambient particulate matter (PM) and cardiovascular (CVD) mortality have been widely recognized. However, health effects of long-term exposure to constituents of PM on total CVD mortality have been explored in a single study only.

Aims: The aim of this study was to examine the association of PM composition with cardiovascular mortality.

Methods: We used data from 19 European ongoing cohorts within the framework of the ESCAPE (European Study of Cohorts for Air Pollution Effects) and TRANSPHORM (Transport related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter) projects. Residential annual average exposure to elemental constituents within particle matter smaller than 2.5 and 10 μm ($\text{PM}_{2.5}$ and PM_{10}) was estimated using Land Use Regression models. Eight elements representing major sources were selected a priori (copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc). Cohort-specific analyses were conducted using Cox proportional hazards models with a standardized protocol. Random-effects meta-analysis was used to calculate combined effect estimates.

Results: The total population consisted of 322,291 participants, with 9545 CVD deaths. We found no statistically significant associations between any of the elemental constituents in $\text{PM}_{2.5}$ or PM_{10} and CVD mortality in the pooled analysis. Most of the hazard ratios (HRs) were close to unity, e.g. for PM_{10} Fe the combined HR was 0.96 (0.84–1.09). Elevated combined HRs were found for $\text{PM}_{2.5}$ Si (1.17, 95% CI: 0.93–1.47), and S in $\text{PM}_{2.5}$ (1.08, 95% CI: 0.95–1.22) and PM_{10} (1.09, 95% CI: 0.90–1.32).

Conclusion: In a joint analysis of 19 European cohorts, we found no statistically significant association between long-term exposure to 8 elemental constituents of particles and total cardiovascular mortality.

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1. Introduction

Recent studies of health effects of particulate matter (PM) show accumulating evidence of adverse effects on cardiovascular (CVD) mortality (Brook et al., 2010; Hoek et al., 2013). However, effect estimates of long-term exposure to $\text{PM}_{2.5}$ and PM_{10} (particles < 2.5 μm and 10 μm in aerodynamic diameter) varied among different studies and geographical locations, showing elevated risks in some cities and areas in Europe and the United States (Cesaroni et al., 2013; Laden et al., 2006; Lepeule et al., 2012; Lipsett et al., 2011; Pope et al., 2002) but no or little association in others (Beelen et al., 2008; Puett et al., 2011).

Ambient $\text{PM}_{2.5}$ and PM_{10} represent a heterogeneous mixture of constituents from diverse sources e.g. fossil fuel combustion, biomass burning and human activity (Kelly and Fussell, 2012). However, little is known about which PM constituents are associated with higher risks. Several studies showed evidence of acute effects of PM components on CVD mortality, but results varied among studies (Cao et al., 2012; Ito et al., 2011; Valdes et al., 2012; Zhou et al., 2011). In the large national study of United States, only nickel (Ni) and vanadium (V) were associated with CVD mortality (Bell et al., 2009). The reasons for these differences are not clear but may include methodological differences, chance findings as well as true variations related to PM composition and/or population susceptibility. Long-term effects of specific elemental components on CVD mortality have only been examined by a single study in the U.S. which suggested that cardiopulmonary mortality was associated significantly with $\text{PM}_{2.5}$ (HR: 1.11, 95% CI: 1.03–1.21), sulfate (HR: 1.14, 95% CI: 1.01–1.29), nitrate (HR: 1.11, 95% CI: 1.03–1.19) and silicon (HR: 1.05, 95% CI: 1.00–1.10) (Ostro et al., 2010, 2011). Toxicological studies have identified several transition metals (copper, iron, vanadium, nickel,

and zinc) that are likely to promote inflammation and oxidative stress (Gerlofs-Nijland et al., 2007; Haplo et al., 2008, 2010).

A recent study within ESCAPE (European Study of Cohorts for Air Pollution Effects) reported overall no statistically significant associations between long-term exposure to PM mass ($\text{PM}_{2.5}$, PM_{10}) and cardiovascular mortality averaged over 19 ongoing cohorts in Europe (Beelen et al., accepted for publication). The magnitude of the association differed across cohorts and we hypothesized that some of the difference in effect estimates could be due to well-documented differences in particle composition in the study areas (De Hoogh et al., 2013). De Hoogh et al. (2013) documented that the correlation between particle mass and several elements was moderate to low, suggesting that the null effect for PM mass may hide effects for some components. Furthermore for some elements (e.g. V and Ni) the major source (shipping, residual oil combustion) was present only in a few of the study areas. Therefore, more specific examinations are needed taking individual particle components into account.

The aim of this paper was to investigate effects of long term exposure to PM constituents on CVD mortality within the ESCAPE (European Study of Cohorts for Air Pollution Effects) and TRANSPHORM (Transport related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter) projects. Standardized methods for exposure assessment, confounder and endpoint definition and statistical analysis were applied to 19 ongoing cohort studies.

2. Methods

The association between PM constituents and cardiovascular mortality was analyzed in each cohort separately using a common statistical

Table 1

Description of the included cohort studies: total study population (N total)^a, number of CVD deaths (N CVD)^a, mean age at baseline (SD), baseline period, total follow-up time (average). Order of studies is north to south.

Cohort	Study area description	N total	N CVD ^b	Age (years)	Baseline period	Follow-up time (person years)
FINRISK, Finland	Greater Helsinki Area and Turku City and its rural surroundings	10,224	225	47.9 (13.2)	1992; 1997; 2002; 2007	108,434 (10.6)
HUBRO, Norway	City of Oslo	18,234	332	48.3 (15.2)	2000–2001	175,076 (9.6)
SNAC-K, Sweden	City of Stockholm	2401	140	70.3 (8.1)	2001–2004	15,568 (6.5)
SALT/Twin gene, Sweden	Stockholm County	5473	206	58.0 (9.9)	1998–2002	47,767 (8.7)
60 y olds, Sweden	Stockholm County	3612	81	60.4 (0.1)	1997–1999	40,612 (11.2)
SDPP, Sweden	Stockholm County	7408	55	47.1 (5.0)	1992–1998	102,831 (13.9)
DCH, Denmark	City of Copenhagen and surrounding areas	35,458	678	56.7 (4.4)	1993–1997	469,571 (13.2)
EPIC-MORGEN, Netherlands	Cities of Amsterdam, Maastricht and Doetinchem and surrounding rural areas	16,446	185	43.9 (10.9)	1993–1997	217,722 (13.2)
EPIC-PROSPECT, Netherlands	City of Utrecht and surrounding rural areas	15,670	290	57.7 (6.0)	1993–1997	202,809 (12.9)
SALIA, Germany	Areas in the cities of Dortmund, Duisburg, Essen, Gelsenkirchen and Herne situated in the Ruhr area and adjacent towns Borken and Dülmen	4352	206	54.5 (0.6)	1985–1987; 1990–1994	81,093 (18.6)
EPIC-Oxford, UK	Urban and rural areas within 400 km around London–Oxford area	38,941	661	45.8 (13.7)	1993–2001	491,542 (12.6)
KORA, Germany	City of Augsburg and two adjacent rural counties	8399	270	49.5 (13.8)	1994–1995; 1999–2001	88,592 (10.5)
VHM&PP, Austria	State of Vorarlberg, excluding high mountain areas (>600 m) and areas within 300 m of state border	117,824	5858	41.9 (14.9)	1985–2005	2,039,328 (17.3)
SAPALDIA, Switzerland	City of Lugano	1250	14	42.0 (11.9)	1991	20,294 (16.2)
E3N, France	Cities of Paris, Grenoble, Lyon and Marseille and surrounding rural areas	10,915	89	53.0 (6.7)	1993–1996	147,021 (13.5)
EPIC-Turin, Italy	City of Turin	7261	46	50.4 (7.5)	1993–1998	97,549 (13.4)
SIDRIA-Turin, Italy	City of Turin	5054	29	44.2 (6.2)	1999	55,667 (11.0)
SIDRIA-Rome, Italy	City of Rome	9177	64	44.3 (6.0)	1999	102,856 (11.2)
EPIC-Athens, Greece	Greater Athens area	4192	116	49.4 (11.7)	1994–1999	46,852 (11.2)

^a Number of observations without missing value in any confounder variable of Model 3 (main model).

^b CVD = all cardiovascular mortality.

protocol for exposure assessment, outcome definition, confounder models and statistical analysis. Methods followed the ESCAPE analysis protocol described in previous papers (Beelen et al., *accepted for publication, in press*; Raaschou-Nielsen et al., 2013). Cohort-specific results were evaluated and pooled using meta-analysis at the coordinating institute (IRAS, Utrecht University). Pooling of the cohort data was not possible due to data transfer and privacy issues.

2.1. Study populations

Our analysis included 19 cohorts from 12 countries where PM measurements were available from north to south Europe: Finland (FINRISK), Norway (HUBRO), Sweden (SNAC-K, SALT, 60 y olds, SDPP), Denmark (DCH), The Netherlands (EPIC-MORGEN, EPIC-PROSPECT), Germany (SALIA, KORA), the United Kingdom (EPIC-Oxford), Austria (VHM&PP), Switzerland (SAPALDIA-Lugano), France (E3N), Italy (EPIC-Turin, SIDRIA-Turin, SIDRIA-Rome), and Greece (EPIC-Athens). Detailed information of the study design and the characteristics of each cohort are described in Appendix A. Key design characteristics are included in Table 1. All cohorts were samples from the general population. The study areas of most cohorts consisted of a large city and its surrounding area. Some of the cohorts included large regions of the country such as EPIC-MORGEN in The Netherlands and the VHM&PP cohort in Vorarlberg, Austria. Table 2 summarizes population characteristics of the cohorts. All included cohort studies were approved by the institutional medical Ethics Committees and conducted in accordance with the Declaration of Helsinki, or had authorization from the data protection authority. All subjects provided informed consent or authorization from the data protection authority.

2.2. Definition of cardiovascular mortality outcome

In all cohorts, follow-up was based upon linkage to mortality registries with one exception in Athens where follow-up was active. All CVD mortality was defined on the basis of the underlying cause of death recorded on death certificates as ICD-9: 400–440; ICD-10: I10–I70.

2.3. Exposure assessment

Within ESCAPE, we a priori selected 8 elements (copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V) and zinc (Zn)), reflecting major anthropogenic sources such as road traffic non tailpipe emissions including brake linings (Cu, Fe, Zn) and tire wear (Zn), industrial (smelter) emissions (Fe, Zn), crustal materials (Si, K), fossil fuel combustion (Ni, V, S) and biomass burning (K). These elements were included because they reflected the major local particle sources, had evidences for toxicity and had a high percentage (>75%) of well-detected samples. We restricted to eight key elements to limit false positive associations that could arise from analyzing all measured elements. Annual average elemental concentrations at the baseline residential addresses of study participants were estimated by Land Use Regression models (LUR) following a standardized procedure described previously (De Hoogh et al., 2013). Briefly, three two-week measurements of PM_{2.5} and PM₁₀ were conducted during different seasons between October 2008 and May 2011 at 20 sites (except in The Netherlands 40 sites) in each cohort study area (1 year per study area). Annual average concentrations of PM constituents were obtained by adjusting temporal variation measured at continuous background sampling sites in each study area in the entire period (Eeftens et al., 2012). Teflon filters were weighed before and after each measurement centrally at IRAS, Utrecht University and were then sent to Cooper Environmental Services (Portland, OR, USA) to detect elemental composition. All filters were analyzed for elemental compositions using X-ray fluorescence (XRF). Details of the measurements, analyses and results have been published elsewhere (De Hoogh et al., 2013). Area-specific LUR models were developed for each element to explain annual concentrations. Models explained modest to large fractions of variation of PM constituents (mean model R²: 0.43–0.79 across constituents) (see Tables B.2–B.17 in Appendix B). Only 16 out of 224 models of the 14 study areas could not be built as there were no variables that explained concentration variability (De Hoogh et al., 2013) (see Table B.1 in Appendix B). To avoid extreme values of PM constituents at cohort addresses, we truncated the values of the predictor variables to the upper or lower limit of those at the measurement sites.

Table 2

Population characteristics at baseline of the included cohort studies. Order of studies is north to south. Detailed description of each cohort can be found in Appendix C.

Cohort	% Women	% Never smokers	Cigarettes/day ^a	Years of smoking ^a	BMI ^a (kg/m ²)	Fruit intake ^b	Alcohol intake ^c	% Married/living with partner	% Low educational level	% (Self) employed
FINRISK, Finland	53.8%	45.4%	3.8 (7.8)	8.6 (12.2)	26.4 (4.6)	66.3%	0.9 (1.3)	70.1%	31.0%	69.2%
HUBRO, Norway	56.1%	46.0%	6.7 (8.4)	11.5 (14.4)	25.7 (4.1)	39.9%	50.6%	49.8%	17.7%	NA
SNAC-K, Sweden	60.0%	44.3%	7.1 (9.5)	9.8 (15.2)	26.0 (4.1)	NA	21.8%	54.2%	21.2%	28.6%
SALT/Twin gene, Sweden	55.7%	38.7%	8.5 (9.7)	16.7 (17.3)	28.6 (4.1)	NA	NA	68.0%	21.5%	NA
60 y olds, Sweden	52.5%	41.0%	8.0 (9.1)	15.2 (16.4)	26.8 (4.2)	64.2%	8.9 (9.7)	71.6%	27.5%	51.4%
SDPP, Sweden	61.7%	37.4%	8.5 (8.8)	12.3 (12.4)	25.6 (4.0)	92.4%	1.3 (1.9)	83.6%	25.5%	91.8%
DCH, Denmark	54.1%	36.3%	6.3 (10.4)	18.7 (17.1)	26.0 (4.1)	183.2 (151.2)	21.7 (22.8)	69.2%	29.6%	80.1%
EPIC-MORGEN, Netherlands	54.4%	35.0%	10.4 (11.1)	14.3 (13.7)	25.2 (4.0)	171.9 (129.2)	12.7 (18.0)	67.7%	11.9%	NA
EPIC-PROSPECT, Netherlands	100%	45.0%	5.7 (7.4)	15.2 (16.5)	25.5 (4.1)	231.6 (139.2)	9.0 (12.4)	76.9%	22.2%	NA
SALIA, Germany	100%	74.5%	2.6 (6.6)	4.4 (10.5)	NA	NA	NA	NA	28.8%	NA
EPIC-Oxford, UK	77.5%	63.3%	5.0 (8.3)	6.7 (11.2)	24.0 (3.9)	259.9 (204.5)	9.1 (11.7)	70.8%	36.5%	72.5%
KORA, Germany	50.8%	43.7%	9.2 (13.3)	12.0 (14.2)	27.2 (4.6)	59.5%	16.3 (22.3)	75.7%	12.6%	58.3%
VHM&PP, Austria	56.1%	69.9%	NA	NA	24.8 (4.3)	NA	NA	68.4%	NA	69.3%
SAPALDIA, Switzerland	55.7%	44.6%	11.1 (14.4)	11.1 (13.0)	23.8 (3.9)	NA	NA	58.1%	11.3%	80.8%
E3N, France	100%	49.3%	NA	NA	22.8 (3.2)	242.0 (164.7)	12.0 (15.1)	NA	5.0%	NA
EPIC-Turin, Italy	47.7%	42.6%	7.2 (8.2)	17.6 (16.3)	25.3 (3.8)	318.2 (182.2)	18.1 (20.3)	85.6%	43.6%	NA
SIDRIA-Turin, Italy	51.8%	37.5%	9.3 (10.2)	11.3 (10.6)	NA	NA	NA	95.4%	17.5%	72.2%
SIDRIA-Rome, Italy	52.8%	34.6%	10.1 (10.5)	11.7 (10.4)	NA	NA	NA	100%	44.9%	NA
EPIC-Athens, Greece	55.0%	39.5%	1.7 (15.0)	10.8 (13.1)	27.5 (4.5)	402.6 (258.2)	9.2 (14.5)	78.0%	23.6%	66.9%

NA is not available.

^a Mean (SD).^b Mean (SD) (g/day) or percentage with daily fruit consumption. For SDPP it is percentage daily/weekly fruit consumption.^c Mean (SD) (g/day) or percentage with daily alcohol consumption. For FINRISK it is number of glasses of alcoholic drink during last week. For SDPP it number of glasses of alcoholic drink per day. For HUBRO it is percentage with weekly alcohol consumption.

This procedure was previously applied for nitrogen oxides and PM₁₀, PM_{2.5} and PM_{2.5} absorbance (Beelen et al., accepted for publication, in press) and has been shown to result in more realistic exposure estimates for these pollutants (Wang et al., 2012).

2.4. Statistical analyses

2.4.1. Cohort specific analyses

Standard Cox proportional hazards models were calculated for the cohort specific analyses, with age as the underlying time scale using a common protocol (Beelen et al., accepted for publication, in press). Censoring occurred at the time of death for non-CVD causes, migration out of the country leading to loss of follow-up, loss to follow-up for other reasons, or at end of follow-up, whichever came first. Air pollution exposure was analyzed as a linear time-invariant variable. Potential individual-level confounders were available from questionnaire data at baseline. A priori we specified three confounder models with increasing level of adjustment. Confounder models were decided based upon previous cohort studies of air pollution and mortality and availability of data in a majority of the cohorts. Model 1 included age (time axis), gender, and calendar time (year(s) of enrollment) only. Model 2 adjusted for additional individual level variables: smoking status (never/former/present), smoking intensity, smoking duration (years), environmental tobacco smoke, fruit intake, vegetables intake, alcohol consumption (linear and squared term), body mass index (BMI) (linear and squared term) (kg/m²), educational level (low, medium, high), occupational class (white/blue collar classification), employment status, and marital status. Model 3 further adjusted for area-level socio-economic status (SES) variables (mostly mean income of neighborhood or municipality). Model 3 was selected as the main confounder model. Only subjects with complete information for Model 3 variables were included in the analyses (see Tables C.1–C.19 in Appendix C).

As constituents from similar sources may be correlated with each other, we additionally conducted two-pollutant models for all elements, adjusting for all the standard pollutants (NO₂, NO_x, PM_{2.5}, PM₁₀, PM_{2.5} absorbance and coarse particles) and other elements separately. We restricted our two-pollutant models to the cohorts with Pearson correlations between LUR based estimates of the two pollutants lower than 0.7 to avoid multicollinearity (Dominici et al., 2010).

In sensitivity analyses, we added to Model 3 prevalent hypertension and physical activity, and as further classical cardiovascular risk factors: prevalent diabetes and cholesterol level. Extended confounder models were used in sensitivity analyses because some of the air pollution effect might be mediated (hypertension) or affected (physical activity) by these factors. We further evaluated the impact of inclusion of modeled road traffic noise to Model 3 because noise and air pollution have been shown to be correlated and may both affect CVD mortality. Noise was used as continuous variable and as categorical variable (5 dB categories) (Beelen et al., 2009).

We did not perform individual effect modification analyses for the constituents as none of the evaluated factors (age, sex, fruit intake, smoking status) was an effect modifier in the analysis of PM_{2.5}, PM₁₀, PM_{2.5} absorbance and NO₂ and cardiovascular mortality in the same cohorts (Beelen et al., accepted for publication). As we did not observe significant associations with more specific cardiovascular diseases (stroke, ischemic heart disease) in our previous paper, we also refrained from analyzing the association of constituents and these causes.

2.4.2. Meta-analysis

Meta-analyses of cohort-specific estimates were conducted using the DerSimonian-Laird method with random effects (DerSimonian and Laird, 1986). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for fixed increments. The increments for each constituent were selected assessing particle constituents by rounding the average difference between the 10th and 90th percentiles of annual average concentrations in all study areas. Heterogeneity between cohorts was quantified by the I² statistic and tested by the X² test from Cochran's Q statistic (Higgins and Thompson, 2002).

We tested whether effect estimates differed by regions of ESCAPE (north: Sweden, Norway, Finland, Denmark; west and middle: the United Kingdom, The Netherlands, Germany, France, Austria, Switzerland; south: Italy and Greece) using stratified analysis and a regional indicator in the meta-regression.

In addition, we estimated combined effect estimates for cohorts with leave-one-out cross validation (LOOCV) R² lower and higher than 0.5 for each element. In a sensitivity analysis we excluded cohorts with a weight larger than 50% in the meta-analysis.

All cohort-specific analyses and meta-analyses were done in STATA, version 10–12 (StataCorp, College Station, TX, USA). We defined statistical significance as a p value < 0.05.

3. Results

3.1. Characteristics of the study population

The entire study population consisted of 322,291 participants contributing 4,551,184 person years at risk (average time of follow-up 14.1 years), with 9545 CVD deaths during follow-up (Table 1). Cohorts were recruited mostly in the 1990s. Cohorts differed in the number of participants, the mean baseline age, and availability of data on confounders (Table 2 and Tables C.1–C.19 in Appendix C). Age, gender, smoking status, and area-level SES were available for all cohorts. Smoking intensity and duration were available as continuous variables for all cohorts, except VHM&PP and E3N. VHM&PP had data on occupation and employment status, but not on education.

3.2. Air pollution exposure

Concentration distributions of estimated particle constituents varied substantially between and within study areas (Figs. 1 and 2). Cu, Fe and Zn (in $PM_{2.5}$ and PM_{10}) showed highest overall concentrations in southern Europe and high spatial contrasts in all study areas. Highest concentrations and contrasts of crustal elements (K and Si) were observed for cohorts in north and south Europe. Exposure contrasts of V and especially S were much larger between than within study areas. Cohort exposures more than four times the interquartile range above the 75th percentile occurred (Figs. 1 and 2), but the maximum value was never an isolated single high value. Correlations between estimated elemental concentrations and total mass concentrations in the same size fractions ($PM_{2.5}$ or PM_{10}) were modest on average ($0.5 < r < 0.7$) for traffic tracers (e.g. Cu, Fe and Zn) and for elements which made up a relatively large fraction of PM (e.g. K, S, Si) and were lower ($0.2 < r < 0.5$) for V and Ni (see Table D.1 in Appendix D). Correlation differed substantially across study areas for all the elements. In total, the eight elements contributed a median of 8.81% (min–max: 1.89%–12.71%) and 10.19% (min–max: 3.94%–18.34%) in the same size fraction of the total $PM_{2.5}$ and PM_{10} mass respectively within the 19 cohorts, with largest proportion for S (6.30% in $PM_{2.5}$, 3.72% in PM_{10}) and smallest proportion for V (0.02% in $PM_{2.5}$, 0.01% in PM_{10}). Less than 10% of the addresses in each cohort have been range-truncated for corresponding predictor variables.

3.3. Main results

We found no consistent associations between any of the elemental constituents of $PM_{2.5}$ or PM_{10} and CVD mortality in the main model (Model 3 in Table 3) based on combined analyses of 19 cohorts. Most of the combined HRs were close to unity for PM constituents, with exception of S in both $PM_{2.5}$ and PM_{10} and $PM_{2.5}$ Si. HR for $PM_{2.5}$ Si was 1.17 (95% CI: 0.93–1.47) per 100 ng/m^3 and for S in $PM_{2.5}$ and PM_{10} the HRs were 1.08 (95% CI: 0.95–1.22) and 1.09 (95% CI: 0.90–1.32) per 200 ng/m^3 respectively. The crude adjustment models (Model 1 with adjustment only for calendar year and gender in Table 3) showed highest HRs and widest confidence intervals. HRs were above 1, with the association for S in $PM_{2.5}$ being statistically significant. The HRs were reduced to unity with decreasing confidence interval after adjustment for especially individual level confounders (Model 2 in Table 3) and area-level socio-economic status variables (Model 3 in Table 3). Significant positive associations of some elements were observed in a few cohorts with CVD mortality individually such as the Dutch EPIC-PROSPECT cohort ($PM_{2.5}$ Si, Zn and PM_{10} S), and the German SALIA ($PM_{2.5}$ Si and PM_{10} Si, K, Zn) and KORA ($PM_{2.5}$ Fe, Si, Zn and PM_{10} Cu, Fe, Si, S) cohorts (Figs. 3 and 4).

Heterogeneity between the results of individual cohorts varied substantially across constituents (I^2 : 0%–58%) and was generally larger for the elemental constituents than for PM mass (Table 3). Most I^2 values indicated low (<25%) to moderate (<50%) heterogeneity (Higgins and Thompson, 2002). HRs using random effects (default method, Figs. 3 and 4) and fixed effects were similar.

3.4. Sensitivity analyses

Additional adjustments for hypertension and physical activity, diabetes and cholesterol, and noise did not change the main results of the combined HRs (Tables E.1–E.4 in Appendix E). Using two-pollutant models adjusting for NO_2 , NOx or PM metrics respectively, while restricting analyses to cohorts with correlations of the two pollutants lower than 0.7 did not change the HRs compared to the single pollutant models in the same cohorts (Figs. E.1–E.2 in Appendix E).

Restricting the meta-analyses to cohorts for which the exposure model had LOOCV R^2 's of at least 0.5 resulted in removal of many cohorts for estimates of K, Ni, S and V in $PM_{2.5}$. No significant difference was observed between cohorts with LOOCV R^2 higher and lower than 0.5. No association was found after this restriction (Table E.5 in Appendix E). Restricting analyses to cohorts with port and industrial predictor variables in the LUR models for trace markers of PM_{10} V and Ni (DCH, EPIC-MORGEN, SNAC-K, SALT, 60 y olds, SDPP, EPIC-Athens for both V and Ni and SALIA for V, SIDRIA/EPIC-Turin for Ni), we found slightly elevated but not significant associations with CVD mortality (V 1.04, 95% CI: 0.90–1.21 per 3 ng/m^3 ; Ni 1.07, 95% CI: 0.80–1.42 per 2 ng/m^3). Stratified analyses showed inconsistent differences of HRs among regions of Europe but generally no association was identified for any of the elemental constituents on CVD mortality (Table E.6 in Appendix E). The effect estimates remained insignificant when excluding the influential (weight > 50%) VHM&PP cohort for K and S in $PM_{2.5}$. HRs were 0.99 (95% CI: 0.86–1.14) and 1.19 (95% CI: 0.97–1.44) for K and S respectively without the VHM&PP cohort.

4. Discussion

This study found no statistically significant associations between a comprehensive set of elemental constituents of PM and overall cardiovascular mortality based on 19 European cohorts. Most of the combined hazard ratios were close to unity, with exception for $PM_{2.5}$ Si and S in $PM_{2.5}$ and PM_{10} .

The strengths of this study include: 1) the use of a large population of 19 study cohorts from 12 countries with a relatively long follow-up history and with detailed individual-level information; 2) the use of a comprehensive set of potential confounders including smoking status and intensity, area-level SES and other important variables, which are at least comparable to those used in previous studies e.g. the large U.S. ACS study (Pope et al., 2002); 3) the implementation of standardized Land Use Regression models for many of the measured PM elemental constituents for fine scale predictions (De Hoogh et al., 2013; Wang et al., 2013a, b); few previous European and American studies assessed PM constituents by modeling but assigned individual exposures from the nearest monitoring stations (Ostro et al., 2010).

Our study provides more insight to the findings of Beelen et al. (accepted for publication) who reported no significant associations between any of the pollutants NO_2 , NOx, $PM_{2.5}$, PM_{10} and $PM_{2.5}$ absorbance and CVD mortality within the ESCAPE project. The median correlations between elemental constituents and PM mass concentrations were low to modest at the cohort addresses, in agreement with the previously reported moderate correlation of modeled exposures at monitoring sites not used for modeling (De Hoogh et al., 2013). This suggests that mortality effects from elemental constituents could be different from the particle mass mortality effects.

However, we did not identify any significant associations between CVD mortality and PM elemental constituents across the 19 cohorts.

Most of the hazard ratios were close to unity for PM constituents. In the single published study evaluating long-term exposure to PM_{2.5} constituents, the California Teachers Study (CTS), significant HRs for cardio-pulmonary mortality were found for mass, sulfate, nitrate and Si, whereas HRs were elevated but non-significant for K, Fe and Zn (Ostro et al., 2011). Ni, V and Cu were not reported. In the CTS study, relatively high correlations between PM_{2.5} and constituents (0.67 [K] < r < 0.84 [Zn]) were found, so some of the reported associations may be a PM_{2.5} effect. Compared to the CTS study (Ostro et al., 2010, 2011), we moreover attributed within-area exposures of constituents to individual cohort members as substantial spatial variability has been identified within each study areas for most of the elements (De Hoogh et al., 2013). In addition, the CTS cohort has relatively larger exposure contrasts (between counties) to the elements (Fe, K, Si and Zn) and on average a slightly older population (53.4 years in the CTS compared to a cohort size-weighted average 50.5 years in our study) which may increase susceptibility to air pollution exposure compared to the cohorts in our study.

Although elemental effects on cardiovascular disease have been examined in a few short-term studies, results varied substantially across studies (Ito et al., 2011; Zhou et al., 2011). In countrywide studies, effects estimates were significantly increased only for V and Ni in the United States (Bell et al., 2009; Lippmann et al., 2006). Some large scale, short-term studies in the U.S. showed no association between CVD outcomes and Cu, Fe and Zn (Bell et al., 2009; Lippmann et al., 2006) in line with our study results whereas four other studies found associations with Cu, Fe or Zn in smaller regions (Ostro et al., 2007; Sarnat et al., 2008; Valdes et al., 2012; Zhou et al., 2011).

We found elevated HRs for PM_{2.5} Si and S in PM_{2.5} and PM₁₀ though not statistically significant. Chance may be an explanation for the elevated HRs, though the results are consistent with the CTS study on long-term exposures. For S the observation of elevated HRs in both the PM_{2.5} and PM₁₀ fraction is also suggestive for an association. For Si, it is inconsistent that only an elevated HR in the PM_{2.5} fraction was found, whereas Si is

much higher in the PM₁₀. Mineral and road dust are the primary sources of Si (Viana et al., 2008). The cardio-toxicity effects of PM_{2.5} Si have been presented in some studies (Ito et al., 2011; Valdes et al., 2012; Zhou et al., 2011) but not in others (Bell et al., 2009; Lippmann et al., 2006; Ostro et al., 2007; Sarnat et al., 2008). S is part of vehicle exhausts but is mostly determined by secondary aerosol formation. In this study, the spatial variation of S was mostly explained by various traffic, land use (green) and residential density variables (De Hoogh et al., 2013) and thus S represents a combination of urban sources including traffic emissions and possibly residential oil combustion.

The non-significant associations found in our study for the eight a priori selected elements could be due to a combination of exposure measurement error, exposure contrast, studied outcomes, the application of a current LUR to assess historic exposures or a true absence of an effect. First, it is unlikely that limited validity of the LUR models fully explains the lack of associations. The LUR models explained fairly large concentration contrasts of (especially the traffic-related) constituents in most of the study areas though poor predictions for several PM_{2.5} constituents (e.g. K, Ni, S and V) were found in several study areas. This is due to lack of GIS predictor variables for specific sources, for instance biomass burning for K or absence of the major source e.g. for Ni and V in several areas (De Hoogh et al., 2013). Moreover, our site selection was designed for estimating especially the health effects on traffic pollution which may restrict the power to detect other emission sources. We restricted the analyses to the cohorts with reliable concentration estimates and did not find significant associations with CVD mortality in these cohorts. In our study, V and Ni were mainly explained by a combination of industry, port, residential density and traffic variables, in agreement with previous European source apportionment studies which suggested fuel (and its derivatives e.g. shipping emission), residential oil combustion and industrial emissions (Viana et al., 2008). When we restricted analyses to the cohorts with port and industry variables for PM₁₀ V and Ni respectively, effect estimates were larger but far from statistically significant. Although these

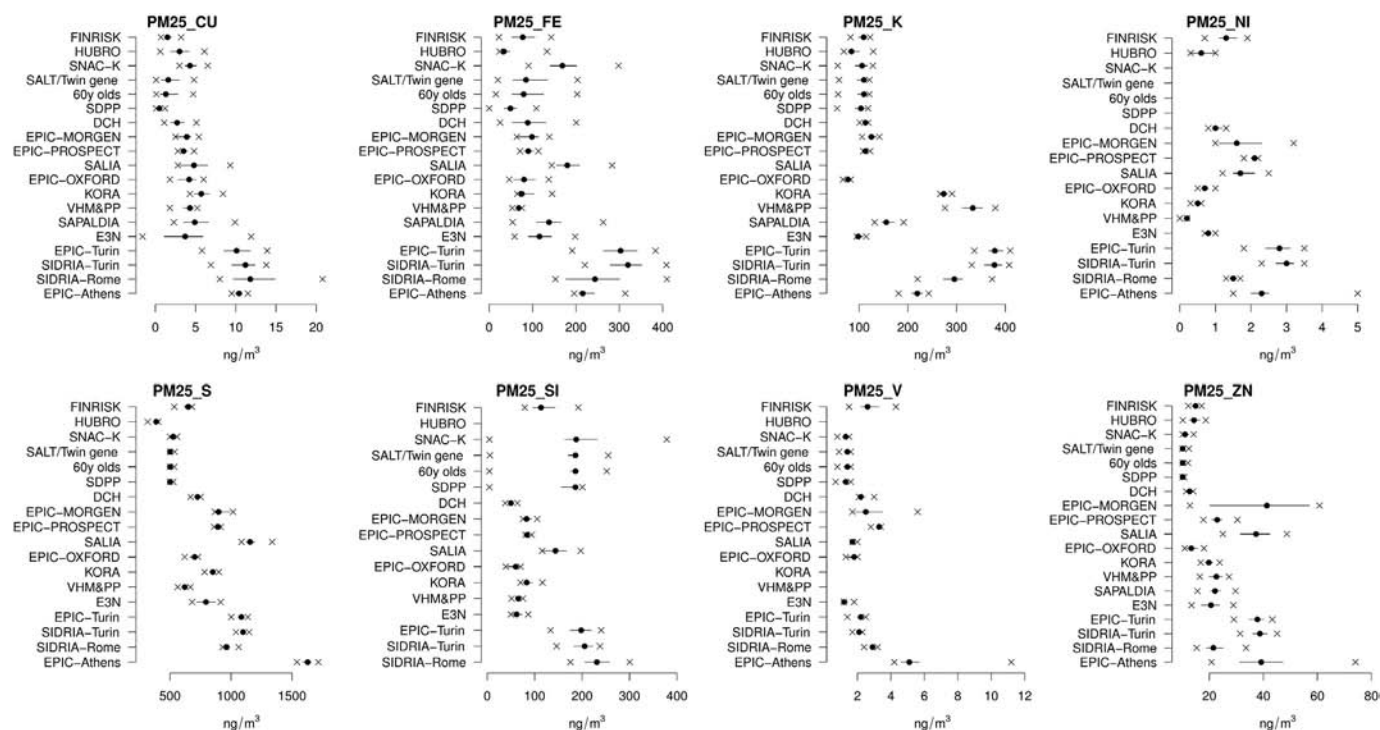


Fig. 1. Description of exposure to PM_{2.5} components concentration (ng/m³) at participant addresses in each cohort. The solid circle and bars shows the median and 25th and 75th percentiles of elemental constituents of PM_{2.5}; the x shows the 5th and 95th percentile values.

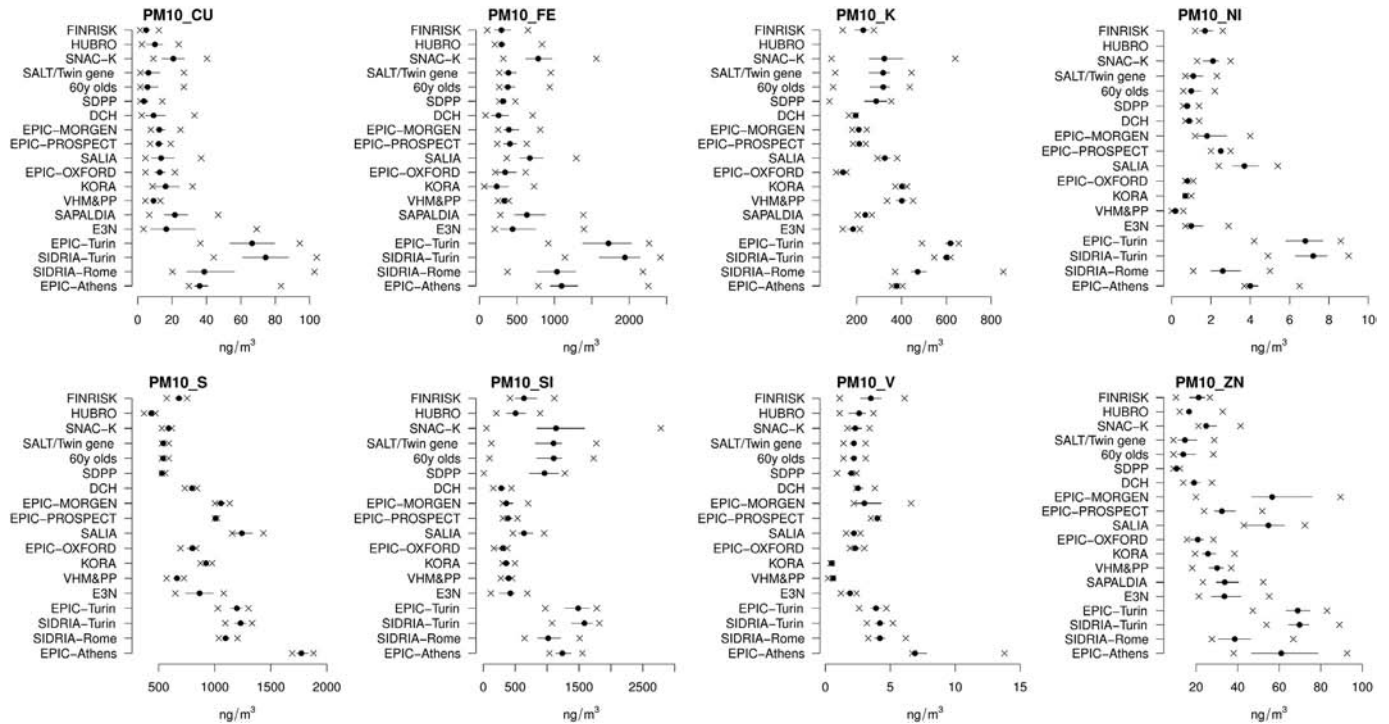


Fig. 2. Description of exposure to PM₁₀ components concentration (ng/m³) at participant addresses in each cohort. The solid circle and bars shows the median and 25th and 75th percentiles of elemental constituents of PM₁₀; the x shows the 5th and 95th percentile values.

analyses suggest that limited validity of LUR models does not fully explain the lack of associations, we cannot exclude the possibility that our effect estimates have been underestimated (Basagaña et al., 2013).

Second, limited contrast in exposure may have contributed to the non-significant findings for some elements. Limited contrast was found for particularly sulfur related to the relatively small size of our study areas, e.g. in comparison with CTS study which had 10-fold larger S contrast (Ostro et al., 2010). We did find large within cohort contrast for

especially Cu, Fe and Zn. The variation in Cu, Fe and Zn was explained by traffic related variables (e.g. traffic intensity and road length) in many cohort areas. Cu, Fe and Zn are recognized as trace markers of traffic from a combination of brake/tire-wear, vehicle exhausts and road dusts (Viana et al., 2008).

Third, the general explanations for a lack of association between CVD mortality and PM offered by Beelen et al. (accepted for publication) may apply. This included better medication and medical treatment and

Table 3

Association^a between CVD mortality and exposure to PM constituents: Results from random-effects meta-analyses (HRs and 95% CIs), p-value of Model 3 and I² (p-value) of test for heterogeneity of effect estimates between cohorts (using main confounder Models 1, 2 and 3).

Cohorts	Exposure	Model 1 ^b	Model 2 ^b	Model 3 ^b	Pm ^c	P _{het}	I ²
19	Cu	PM _{2.5}	1.03 (0.88–1.21)	0.96 (0.83–1.11)	0.90 (0.77–1.07)	0.26	42.77
19		PM ₁₀	1.00 (0.89–1.13)	0.95 (0.84–1.08)	0.93 (0.82–1.06)	0.29	48.83
19	Fe	PM _{2.5}	1.07 (0.94–1.23)	1.01 (0.89–1.15)	0.99 (0.87–1.11)	0.82	31.93
19		PM ₁₀	1.03 (0.91–1.16)	0.98 (0.86–1.12)	0.96 (0.84–1.09)	0.55	53.49
18	K	PM _{2.5}	0.98 (0.94–1.02)	0.98 (0.94–1.02)	0.98 (0.94–1.02)	0.37	0.00
18		PM ₁₀	1.02 (0.94–1.11)	1.01 (0.94–1.07)	1.00 (0.93–1.08)	0.92	15.03
14	Ni	PM _{2.5}	1.05 (0.86–1.28)	0.98 (0.78–1.24)	0.97 (0.78–1.21)	0.80	48.63
17		PM ₁₀	1.12 (0.93–1.36)	1.02 (0.87–1.19)	1.01 (0.88–1.16)	0.90	9.11
18	S	PM _{2.5}	1.27 (1.01–1.61)	1.09 (0.97–1.24)	1.08 (0.95–1.22)	0.25	0.00
18		PM ₁₀	1.21 (0.97–1.50)	1.11 (0.92–1.33)	1.09 (0.90–1.32)	0.40	36.46
16	Si	PM _{2.5}	1.28 (0.98–1.66)	1.21 (0.94–1.54)	1.17 (0.93–1.47)	0.21	52.04
18		PM ₁₀	1.09 (0.93–1.28)	1.03 (0.91–1.17)	1.01 (0.90–1.13)	0.85	33.87
15	V	PM _{2.5}	1.14 (0.86–1.52)	1.00 (0.79–1.27)	1.00 (0.80–1.24)	0.99	24.10
18		PM ₁₀	1.04 (0.83–1.30)	1.01 (0.86–1.18)	1.00 (0.85–1.17)	0.99	11.10
19	Zn	PM _{2.5}	1.08 (0.90–1.29)	1.06 (0.90–1.25)	1.04 (0.88–1.24)	0.63	58.59
19		PM ₁₀	1.06 (0.91–1.24)	1.03 (0.90–1.19)	1.00 (0.86–1.16)	0.99	57.47
19	Total	PM _{2.5} ^d	1.18 (1.00–1.38)	1.04 (0.93–1.17)	0.99 (0.91–1.08)	0.80	0.00
19		PM ₁₀ ^d	1.10 (0.95–1.26)	1.04 (0.92–1.16)	1.02 (0.91–1.14)	0.69	20.20

^a Effects are presented as hazard ratios for an increase of 5 ng/m³ for PM_{2.5} Cu, 20 ng/m³ for PM₁₀ Cu, 100 ng/m³ for PM_{2.5} Fe, 500 ng/m³ for PM₁₀ Fe, 50 ng/m³ for PM_{2.5} K, 100 ng/m³ for PM₁₀ K, 1 ng/m³ for PM_{2.5} Ni, 2 ng/m³ for PM₁₀ Ni, 200 ng/m³ for PM_{2.5} S, 200 ng/m³ for PM₁₀ S, 100 ng/m³ for PM_{2.5} Si, 500 ng/m³ for PM₁₀ Si, 2 ng/m³ for PM_{2.5} V, 3 ng/m³ for PM₁₀ V, 10 ng/m³ for PM_{2.5} Zn, and 20 ng/m³ for PM₁₀ Zn.

^b Model 1: adjusted for gender and calendar time; Model 2: as in Model 1 also adjusting for smoking status, smoking intensity, smoking duration, environmental tobacco smoke, fruit intake, vegetables intake, alcohol consumption, body mass index, education level, occupational class, employment status, marital status; and Model 3: as in Model 2 also adjusting for area-level socio-economic status.

^c Pm: p-value of HR from meta-analysis in Model 3.

^d Association between CVD mortality and PM_{2.5}, PM₁₀ mass concentrations reported by Beelen et al. (accepted for publication).

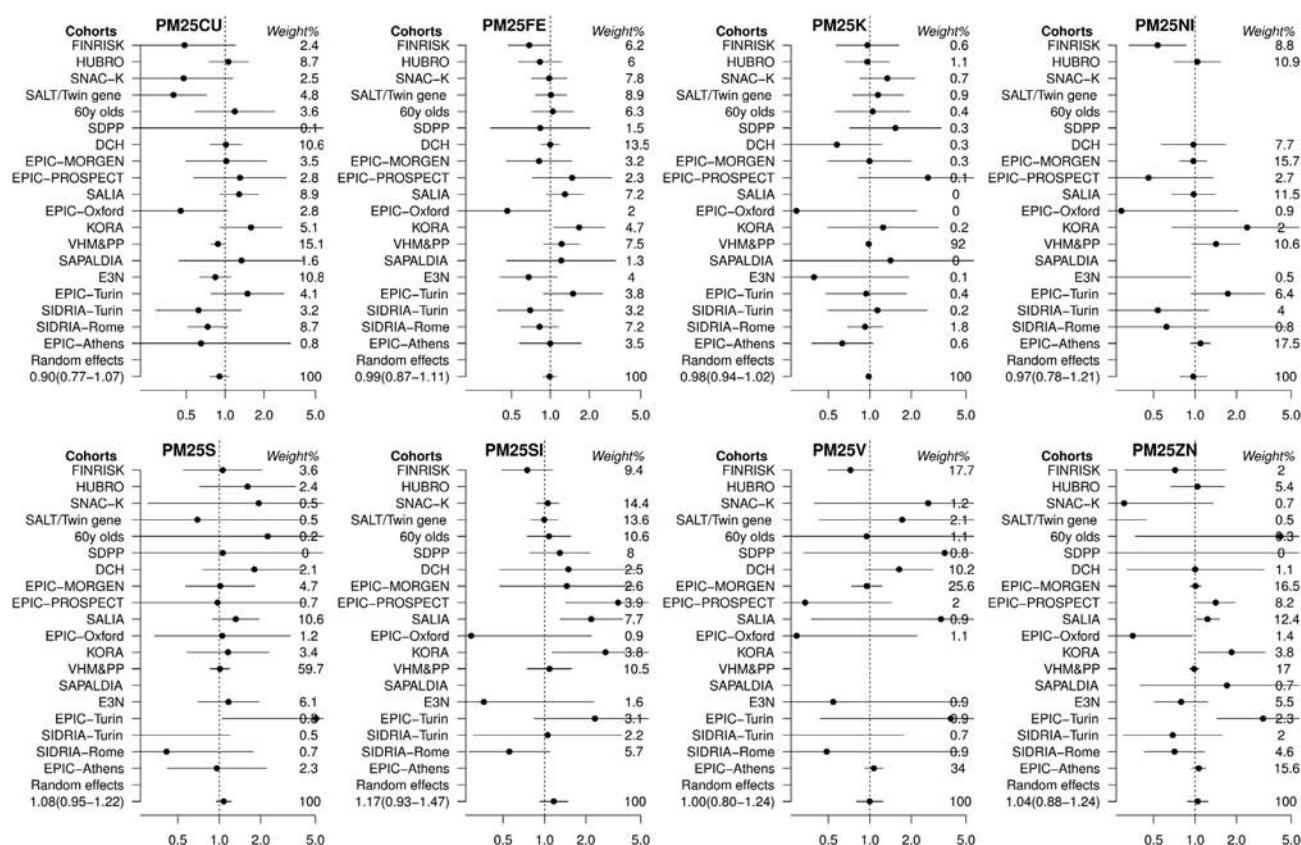


Fig. 3. Adjusted association between CVD mortality and exposure to PM_{2.5} constituents (Model 3): Results from cohort-specific analyses and from random effect-effects meta-analyses. HRs are presented for an increase of 5 ng/m³ for PM_{2.5} Cu, 20 ng/m³ for PM₁₀ Cu, 100 ng/m³ for PM_{2.5} Fe, 500 ng/m³ for PM₁₀ Fe, 50 ng/m³ for PM_{2.5} K, 100 ng/m³ for PM₁₀ K, 1 ng/m³ for PM_{2.5} Ni, 2 ng/m³ for PM₁₀ Ni, 200 ng/m³ for PM_{2.5} S, 200 ng/m³ for PM₁₀ S, 100 ng/m³ for PM_{2.5} Si, 500 ng/m³ for PM₁₀ Si, 2 ng/m³ for PM_{2.5} V, 3 ng/m³ for PM₁₀ V, 10 ng/m³ for PM_{2.5} Zn, and 20 ng/m³ for PM₁₀ Zn.

reduced smoking, resulting in a lower fatality rate of cardiovascular events (Nichols et al., 2013). We could not evaluate non-fatal events as our study was based on mortality registries. We only evaluated overall cardiovascular mortality and did not evaluate more specific cardiovascular causes such as ischemic heart disease or stroke. This choice was made to limit the chance of false positive findings and no significant associations between PM_{2.5} and these more specific disease categories were found. We selected overall CVD mortality because we could evaluate the largest number of cases and were concerned of differences in coding across countries especially when evaluating more specific causes.

Fourth, a main limitation in our study is that the LUR models used for exposure assessment were based on air pollution measurements in the period 2008–2011 while cohort studies included in ESCAPE started in the past (1985–2007 with most studies starting in the mid-90s). Four recent studies in The Netherlands (Eeftens et al., 2011), Great Britain (Gulliver et al., 2013), Rome (Cesaroni et al., 2012), and Vancouver (Wang et al., 2013a, 2013b) have shown that for periods up to 10 years spatial air pollution contrasts of NO₂ often remained the same. This indicates that the LUR models based on current NO₂ data are able to predict historical exposure well. This finding may be applicable to traffic-related constituents such as Cu, Fe and Zn whereas there is no quantitative evidence for the other constituents which derive from other sources (e.g. biomass burning, industrial emissions).

We did not consider seasonal exposures, as our main interest was in evaluating long-term exposure represented by annual averages and we had only one sample per season available to develop LUR models (De Hoogh et al., 2013). We did not evaluate organic components of PM. In our previous study (Beelen et al., accepted for publication) we did show that PM_{2.5} absorbance (a surrogate for elemental carbon) was also not associated with CVD mortality. We did not have fine scale ozone data available. Most of our study areas were relatively small and

ozone formation is slow, so we expected limited spatial variation of ozone except due to scavenging by NO (lower ozone near busy roads). As we therefore anticipated that ozone variation would simply be the opposite of NO and NO₂ variation, we did not additionally measure ozone.

Moreover, higher heterogeneity may in part also be explained by the larger heterogeneity in the LUR model performance seen for constituents. We did not consider moving in the current analysis, as we did not observe any difference between movers and non-movers in the main analysis (Beelen et al., accepted for publication).

In summary, we did not find statistically significant associations between any of the eight selected elemental constituents of PM₁₀ and PM_{2.5} and overall cardiovascular mortality in the 19 European cohort studies. Elevated risks though not statistically significant were found for CVD mortality and PM_{2.5} Si and S in PM_{2.5} and PM₁₀ respectively.

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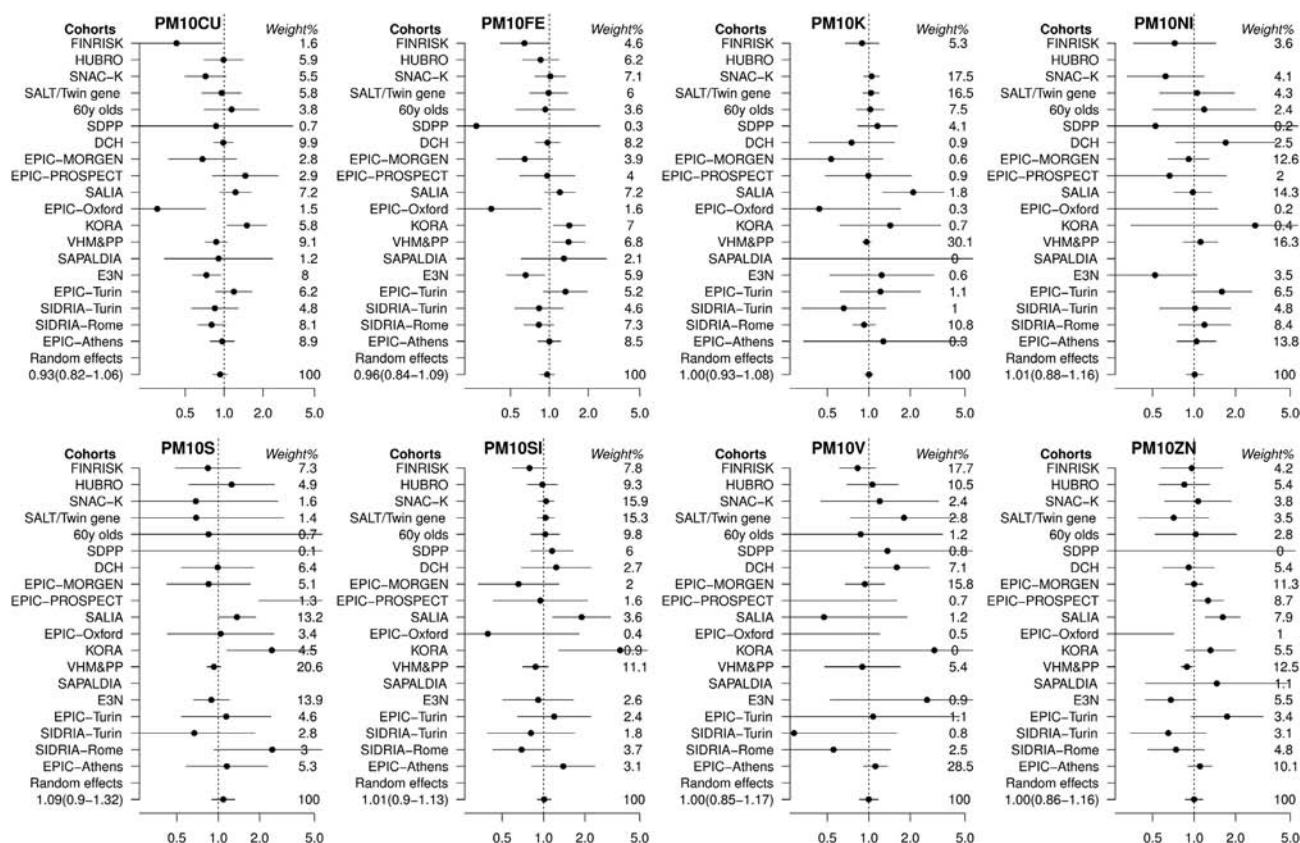


Fig. 4. Adjusted association between CVD mortality and exposure to PM₁₀ constituents (Model 3): Results from cohort-specific analyses and from random effect-effects meta-analyses. See Fig. 3 for increment unit of each element.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2014.01.026>.

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