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Long-Term Exposure to Particle Components and Natural Cause Mortality: An analysis of 19 European Cohorts within the Multi-Center ESCAPE Project

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Abstract

Background

Studies have shown associations between mortality and long-term exposure to particulate matter air pollution. Few cohort studies have assessed the effects of the elemental composition of particulate matter on mortality.

Objectives

Our aim was to study the association between natural cause mortality and long-term exposure to elemental components of particulate matter.

Methods

Mortality and confounder data from 19 European cohort studies were used. Residential exposure to eight a priori selected components of particulate matter (PM) was characterized following a strictly standardized protocol. Annual average concentrations of Copper (Cu), Iron (Fe), Potassium (K), Nickel (Ni), Sulfur (S), Silicon (Si), Vanadium (V) and Zinc (Zn) within PM size fractions <2.5µm ($PM_{2.5}$) and <10µm (PM_{10}) were estimated using land-use regression models. Cohort-specific statistical analyses of the associations between mortality and air pollution were conducted using Cox proportional hazards models using a common protocol followed by meta-analysis.

Results

The total study population consisted of 291,816 participants, of which 25,466 died from a natural cause during follow-up (average time of follow-up 14.3 years). Elevated risks were shown for almost all elements with a statistically significant elevated hazard ratio for $PM_{2.5}$ S

185 (1.14 (95% CI: 1.06, 1.23) per 200 ng/m^3). In a two pollutant model, the association for S

186 was robust to adjustment for $PM_{2.5}$ mass whereas the association for $PM_{2.5}$ mass was reduced.

187 *Conclusions*

188 Long-term exposure to $PM_{2.5}$ S was associated with natural cause mortality. This association

189 was robust to adjustment by other pollutants including particle matter.

190

Introduction

Studies have shown associations between long-term exposure to particulate matter air pollution and mortality, with exposure characterized as the mass concentration of particles smaller than 10 µm (PM_{10}) or 2.5 µm ($PM_{2.5}$) (Brunekreef and Holgate 2002; Brook et al. 2010). Although these studies have identified associations between exposure to particulate matter mass and mortality, there is still uncertainty as to which particle components are the most harmful. In addition, particulate matter effect estimates for long-term studies on mortality differed between studies, and an explanation for this might be differences in the chemical composition of particulate matter (Hoek et al. 2013).

Particulate matter is a heterogeneous mixture varying spatially and temporally in chemical composition related to the sources from which it originates (Stanek et al. 2011; Kelly and Fussell 2012). Components for which associations with a range of health endpoints have been reported in epidemiological and / or toxicological studies include (transition) metals, elemental carbon, inorganic secondary aerosols (sulfate, nitrate), and organic components, but the evidence is not consistent (Stanek et al. 2011; Kelly and Fussell 2012).

Most studies that have assessed the mortality effects related to exposure to elemental components have been short-term exposure studies and results varied considerably between these studies (Stanek et al. 2011; Kelly and Fussell 2012). Few studies have investigated the mortality risks related to long-term exposure to particle components. Lack of spatially resolved elemental composition measurement data and a lack of models for elemental composition partly explains this (De Hoogh et al. 2013). The U.S. Six city and American Cancer Society cohort studies have suggested an association between long-term exposure to sulfate and mortality (Dockery et al. 1993; Pope et al. 1995; Krewski et al. 2000; Pope et al. 2002), but no other particle composition parameters have been evaluated in these studies. A cohort study among California Teachers found no statistically significant association between

long-term exposures to $PM_{2.5}$ and several of its constituents, including elemental carbon, organic carbon (OC), sulfates, nitrates, iron, potassium, silicon, and zinc and all-cause mortality, although statistically significant associations were found with especially ischemic heart disease mortality (Ostro et al. 2011).

In the framework of the multi-center 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, we added standardized exposure assessment for air pollution to mortality data from 19 ongoing cohort studies across Europe. Associations between particle mass ($PM_{2.5}$,PM_{10}, PM_{coarse} and $PM_{2.5}$ absorbance) and nitrogen oxides (NO_2 and NO_x) with natural cause mortality in the same cohorts have been reported previously (Beelen et al. 2014). We found a statistically significant elevated hazard ratio for $PM_{2.5}$ of 1.07 (95% CI: 1.02, 1.13) per 5 $\mu g/m^3$. In this paper we report associations of particle elemental composition and natural mortality in 19 European cohorts. The aim was to assess whether specific components are associated with natural cause mortality. A second aim was to assess whether the previously reported association with $PM_{2.5}$ mass was explained by specific elements. Associations of particle composition and cardiovascular mortality have been published separately (Wang et al. 2014).

Methods

As described earlier, the association between natural cause mortality and particle components was analyzed in each cohort separately following the analysis protocol of the ESCAPE study (Beelen et al. 2014). A common STATA script was used which was explained in a training workshop for all local analysts. Cohort-specific results were sent to the coordinating institute (IRAS, Utrecht University) for central evaluation. Cohort-specific effect estimates were combined by random-effects meta-analysis. Pooling of the cohort data was not possible due to data transfer and privacy issues.

Study populations

Nineteen cohorts from 12 countries across Europe were selected (Table 1 and see Supplemental Material, Description of each cohort and study area, Figure S1). The study areas of most cohorts consisted of a large city with surrounding smaller rural communities. Some cohorts included large regions of the country such as EPIC-MORGEN in the Netherlands, and the VHM&PP cohort in Austria. All included cohort studies were approved by the institutional medical ethics committees and undertaken in accordance with the Declaration of Helsinki. Each cohort study followed the rules for ethics and data protection set up in the country in which they were based.

Mortality outcome definition

In all cohorts, follow-up was based upon linkage to mortality registries. Natural cause mortality was defined on the basis of the underlying cause of death recorded on death

255 certificates as ICD-9 codes: 001-779 and ICD-10 codes: A00-R99.

256

257 Exposure assessment

258 Particle composition concentrations at the baseline residential addresses of study participants
259 were estimated by land use regression models following a standardized procedure described
260 elsewhere (De Hoogh et al. 2013; Eeftens et al. 2012a; Beelen et al. 2013). Measurements of
261 particles with aerodynamic diameter <2.5μm ($PM_{2.5}$) and <10μm (PM_{10}) were performed at
262 20 sites in each of the study areas. Within each study area, each of the 20 sites was measured
263 during three two-week measurements during summer, winter and an intermediate season
264 within one year. The total measurement period over all study areas was between October
265 2008 and May 2011. PM filters were weighed before and after each measurement centrally at
266 IRAS, Utrecht University and were then sent to Cooper Environmental Services (Portland,
267 OR, USA) to detect elements. All filters were analyzed for elemental composition using X-
268 Ray Fluorescence (XRF) (De Hoogh et al. 2013). The three measurements were then
269 averaged, adjusting for temporal trends using data from a background monitoring site with
270 continuous data (De Hoogh et al. 2013; Cyrys et al. 2012; Eeftens et al. 2012b).
271 In ESCAPE we a priori selected eight from the 48 measured elements for further
272 epidemiological evaluation. The set of elements was selected based upon evidence for health
273 effects (toxicity), representation of major anthropogenic sources, a high percentage of
274 detected samples (>75%), and good precision of measurements. We selected Cu, Fe, and Zn
275 mainly for (nontailpipe) traffic emissions; S for long-range transport; Ni and V for mixed oil
276 burning/industry; Si for crustal material; and K for biomass burning (Viana et al. 2008).
277 Elements may have multiple sources, so they do not necessarily represent single sources.
278 Predictor variables on nearby traffic intensity, population/household density and land use
279 were derived from Geographic Information Systems (GIS), and were evaluated to explain

spatial variation of annual average concentrations using land use regression modeling. If values of predictor variables for the cohort addresses were outside the range of values for the monitoring sites, values were truncated to the minimum and maximum values at the monitoring sites. Truncation was performed to prevent unrealistic predictions (e.g. related to too small distance to roads in GIS) and because we did not want to extrapolate the derived model beyond the range for which it was developed. Truncation has been shown to improve predictions at independent sites (Wang et al. 2012).

The results of the land use regression models were then used to estimate ambient particle composition concentration at the participants' baseline addresses. A detailed description of the fit and predictor variables of land use regression models is presented in Supplemental Material, LUR model results for all study areas, Tables S1-S9.

Statistical analyses

Cohort specific analyses

Cox proportional hazards models were used for the cohort specific analyses following the analysis protocol in the ESCAPE study (Beelen et al. 2014). Age was used as the time scale because of evidence of better adjustment for potential confounding by age (Thiébaut and Bénichou 2004). Censoring occurred at the time of death for non-natural causes, emigration, 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 confounders were available from questionnaires 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 only age (time axis), gender, and calendar time (year(s) of enrollment,

304 continuous for baseline periods of 5 years or less). Model 2 added individual level variables
305 (if available): smoking status (never/former/current), smoking intensity, smoking duration,
306 environmental tobacco smoke, fruit intake, vegetables intake, alcohol consumption (linear
307 and squared term), body mass index (BMI) (linear and squared term), educational level (low,
308 medium, high), occupational class (white/blue collar classification), employment status, and
309 marital status. Model 3 added area-level socio-economic status (SES) variables. Area-level
310 SES variables included mean income, percentage of people with a low income,
311 unemployment rate, educational level or deprivation index at mostly neighborhood or
312 municipality level. Supplemental Material, Study population characteristics at baseline for
313 each cohort, Tables S10-S28, gives detailed information about which variables were used in
314 each of the cohorts.
315 Model 3 was selected as the main confounder model. Only subjects with complete
316 information for Model 3 variables were included in the analyses.
317 Two-pollutant models were conducted for each element by including particle mass ($PM_{2.5}$,
318 PM_{10}, PM_{coarse}), $PM_{2.5}$ absorbance, NO_2, NO_x and the other elements to the model separately.
319 As two pollutants may reflect the same source, two-pollutant models representing the
320 independent effect of two pollutants may be difficult to interpret. We only included studies
321 for which the correlation between two pollutants was =< 0.7 in the evaluation.
322 In sensitivity analyses, we added to Model 3 prevalent hypertension and physical activity,
323 and as further classical cardiovascular risk factors: prevalent diabetes and cholesterol level.
324 Extended confounder models were used in sensitivity analyses because some potential effect
325 of air pollution might be mediated (e.g. hypertension) or affected (physical activity) by these
326 factors.
327 All cohort specific analyses were done in STATA versions 10-12 (StataCorp, College
328 Station, TX, USA).

329 *Meta-analysis*

330 Meta-analyses of cohort-specific effect estimates were conducted using the Dersimonian-
331 Laird method with random effects (DerSimonian and Laird 2009). Hazard ratios (HR) and
332 95% confidence intervals (CIs) were calculated for fixed increments which were chosen
333 based upon the mean difference between the 10^{th} and 90^{th} percentile of measured
334 concentrations across all study areas to keep increments broadly comparable between
335 pollutants. Heterogeneity between cohorts was quantified by the I^2 statistic and tested by the
336 X^2 test from Cochran's Q statistic (Higgins and Thompson 2002).
337 We tested whether effect estimates differed for cohorts for which the land use regression
338 model cross-validation explained variance was smaller or larger than 50%. In addition, we
339 tested whether effect estimates differed by region of Europe (North: Sweden, Norway,
340 Finland, Denmark; West and Middle: United Kingdom, the Netherlands, Germany, France,
341 Austria, and Switzerland; South: Italy and Greece). We did not perform effect modification
342 analyses for individual-level variables as this paper focuses on differences in effect estimates
343 related to elemental composition. Only sex was an effect modifier for the association between
344 $PM_{2.5}$ and natural mortality in the same cohorts (Beelen et al. 2014).
345 All tests were two-sided and p values of <0.05 were deemed statistically significant.
346 All meta-analyses were conducted in STATA, version 12.1 (StataCorp, College Station, TX,
347 USA).
348

Results

Characteristics of the study population

The total study population consisted of 291,816 participants contributing 4,168,461 person-years at risk (average time of follow-up 14.3 years), of which 25,466 died from a natural cause 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 confounders (Table 2, and see Supplemental Material, Study population characteristics at baseline for each cohort, Tables S10-S28). 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 the VHM&PP (Vorarlberg state) and E3N (Paris and surrounding rural areas) cohorts for which smoking status was available. VHM&PP had data on occupation and employment status, but not on education. On average for more than 90% of the subjects we had complete confounder information.

Air pollution exposure

Substantial variations of estimated annual mean concentrations at participant addresses were observed within and between the majority of cohorts and elements (Figure 1, Supplemental Material, Description of estimated annual mean PM_{10} elemental composition concentrations ($ng/\mu g^3$) at participant addresses in each cohort, Figure S2). The largest within-cohort contrasts were found for Cu, Fe, Si, and Zn, with the largest contrasts generally found in South European study areas. The main exception was Si where the largest within-area contrast was found for the North European study areas. The smallest within-cohort contrasts

were found for S. Higher concentrations of most elements were observed in Southern study areas. Estimated annual mean S in $PM_{2.5}$ concentrations, for example, show a steady increasing north– south gradient with averages from 635 ng/m^3 for FINRISK, Finland to 1626 ng/m^3 for EPIC-Athens, Greece. Correlations between elements and particle mass varied considerably between elements and cohorts; average correlation between elements and mass (in the same size fraction) was ~0.5 with a range from ~0.3 to ~0.7 (see Supplemental Material, Correlations between elemental constituents in $PM_{2.5}$ and PM_{10} at participant addresses in each cohort, Table S29), indicating that mortality effects from elements could be disentangled from PM mass effects in the majority of cohorts.

Good land use regression exposure models were developed for Cu, Fe, and Zn in both fractions (PM_{10} and $PM_{2.5}$) with average cross-validation explained variance (R^2) between 55% and 81% with a large variability between areas (see Supplemental Material, LUR model results for all study areas, Tables S1-S9). Traffic variables were the dominant predictors, reflecting nontailpipe emissions (De Hoogh et al. 2013). Models for the other elements performed moderately with generally average cross-validation R^2 between ~50% and ~60%. For $PM_{2.5}$ S the average cross-validation R^2 was 30% with a range from 2 to 67%, consistent with the relatively low spatial variation of sulfur concentrations.

Single pollutant results

Elevated HRs were found for almost all exposures with a statistically significant elevated combined HR for $PM_{2.5}$ S (1.14 (95% CI: 1.06, 1.23) per 200 ng/m^3 (Table 3, Figure 2 and see Supplemental Material, Forest plots (HRs and 95%-CIs) of association between natural cause mortality and exposure to particle composition, Figures S3-S18). Borderline statistically significant associations were found for $PM_{2.5}$ Si, PM_{10} Ni and PM_{10} K. For the non-tailpipe traffic pollutants Cu, Fe and Zn, as well as V, the evidence for an association

was smallest. HRs for confounder model 1 (only adjusted for calendar year and gender) were generally highest. After adjustment for individual level confounders HRs decreased (model 2). Sensitivity analyses showed that especially smoking variables were responsible for this decrease. Inclusion of area-level socio-economic status variables did only slightly change the HRs (model 3). Cohort specific HRs for $PM_{2.5}$ S were above 1 for all cohorts, except for SDPP and KORA (Figure 2). No heterogeneity between individual cohort effect estimates was found for $PM_{2.5}$ S. S is predominantly found in the $PM_{2.5}$ size fraction, and consistently the PM_{10} S HR is also elevated. Average correlation between $PM_{2.5}$ S and PM_{10} S over the different cohorts was 0.56 with a range of 0.18-1.00.

For the other elements there was more heterogeneity between individual cohort effect estimates although for most elements heterogeneity was low (25%) to moderate (50%) and not statistically significant (Table 3 and see Supplemental Material, Forest plots (HRs and 95%-CIs) of association between natural cause mortality and exposure to particle composition, Figures S3-S18).

Two-pollutant results

Results from the two-pollutant models suggested that the associations of elements were robust to adjustment for other elements and pollutants (see Supplemental Material, Two-pollutant model results, Figures S19-S20). We also investigated whether the previously observed $PM_{2.5}$ effects (Beelen et al. 2014) were robust after adjustment for $PM_{2.5}$ S. The median correlation between $PM_{2.5}$ and $PM_{2.5}$ S over the cohorts was 0.53 (range 0.26 – 0.86). Combined effect estimates for $PM_{2.5}$ S two-pollutant models adjusted for $PM_{2.5}$ did not differ from the single-pollutant models (Table 4). However, $PM_{2.5}$ effects adjusted for $PM_{2.5}$ S were reduced and became statistically non-significant. After adjustment for $PM_{2.5}$ S, associations with PM_{10} K and PM_{10} Ni were reduced (Table 4).

Sensitivity analyses

Additional adjustment for hypertension and physical activity, and diabetes and cholesterol did not change combined HRs compared to main model HRs (see Supplemental Material, Meta-analysis results of association between natural cause mortality and exposure to particle composition for the extended confounder models, Table S30).

Because the VHM&PP cohort had a weight of ~47% in the pooled $PM_{2.5}$ S analyses, we conducted a sensitivity analyses without this cohort. Confidence intervals became slightly wider, but $PM_{2.5}$ S HR remained similar after exclusion of the VHM&PP cohort: 1.12 (95% CI: 1.01, 1.24). Effect estimates for all elements were similar for the cohorts for which land use regression model cross-validation explained variance was smaller or larger than 50%; for $PM_{2.5}$ S 1.12 (95% CI: 1.01, 1.25) (N=14) and 1.16 (95% CI: 1.05, 1.28) (N=4), respectively. $PM_{2.5}$ S effect estimates were also not statistically different between the cohorts in different regions: 1.17 (95% CI: 0.94, 1.45) for North (N=7); 1.13 (95% CI: 1.04, 1.23) for West and Middle (N=7); and 1.27 (95% CI: 0.92, 1.75) for South (N=4). For the other elements also no differences were found between effect estimates based on validation R^2 or region.

Discussion

Long-term exposure to $PM_{2.5}$ S was associated with increased natural cause mortality risk, with no indication of heterogeneity between individual cohort effect estimates.
The association between $PM_{2.5}$ S and mortality was robust to adjustment for co-pollutants including $PM_{2.5}$ mass. The $PM_{2.5}$ mass effect estimate adjusted for $PM_{2.5}$ S was reduced and became statistically non-significant.

Comparison of S mortality associations with previous studies

Only few studies investigated mortality effects of long-term exposure to particle components. Sulfate has received the most attention in epidemiological studies. Elemental sulfur is assumed to be present as a marker for sulfate. Several cohort studies suggested an association between long-term exposure to sulfate and mortality. An association between sulfate and mortality was reported in the Six Cities study (Dockery et al. 1993). The adjusted HR comparing the most and least polluted city was 1.26, with a contrast in sulfate concentration of 8 $\mu g/m^3$, resulting in a HR of 1.03 per 1 $\mu g/m^3$. Within the initial ACS study the adjusted HR of all-cause mortality for the most polluted areas compared with the least polluted (19.9 $\mu g/m^3$ difference in sulfate) was 1.15 (95% CI: 1.09, 1.22) (Pope et al. 1995), resulting in a HR of 1.01 per 1 $\mu g/m^3$. Pope et al. (2002) investigated additional years of follow-up in the ACS Study and found a HR for sulfate for natural mortality of about 1.01 per 1 $\mu g/m^3$ (Pope et al. 2002). A recent analysis of the ACS cohort found that sulfate, elemental carbon and ozone all had positive and statistically significant associations with all-cause mortality, but sulfate had the most robust association (Smith et al. 2009). A HR for sulfate of 1.01 per 1 $\mu g/m^3$ was found. In the recent National Particle Component Toxicity (NPACT) initiative a similar risk for the association between sulfur exposure and all-cause mortality was found using ACS cohort data (Lippmann et al. 2013). Within the NPACT initiative also data from the Women's Health Initiative–Observational Study (WHI-OS) cohort were used to study the

association with cardiovascular mortality and (fatal and non-fatal) cardiovascular events (Vedal et al. 2013). Long-term exposure to air pollutant concentrations was estimated with a national exposure spatial model. No association was found with all cardiovascular deaths and sulfur significant (HR 1.01 (95%: 0.92, 1.12) per 0.25 $\mu g/m^3$), but associations of cardiovascular events with sulfur were statistically significant (HR 1.09 (95%: 1.05, 1.14) per 0.25 $\mu g/m^3$). A cohort study of ~45,000 active and former female public school professionals in the California Teachers Study investigated the association between mortality and long-term exposures to $PM_{2.5}$ and several of its constituents, including elemental carbon, organic carbon, sulfates, nitrates, iron, potassium, silicon, and zinc (Ostro et al. 2011). Participants whose residential addresses were within 8 or 30 km of a monitor collecting $PM_{2.5}$ constituent data were included in the analyses. No statistically significant associations between all-cause mortality and $PM_{2.5}$ mass and any of its measured constituents were observed. The HR for sulfate was 1.06 (95% CI: 0.97, 1.16) for an interquartile range contrast of 2.2 $\mu g/m^3$, corresponding to a HR of 1.03 per 1 $\mu g/m^3$. However, the HR for sulfate for ischemic heart disease mortality was 1.48 (95% CI: 1.20, 1.82) for an interquartile range contrast of 2.2 $\mu g/m^3$.

The $PM_{2.5}$ S effect estimate in our study for natural cause mortality(HR 1.14 per 0.2 $\mu g/m^3$ S) translates into a HR of 1.24 (95% CI: 1.10, 1.41) per 1 $\mu g/m^3$ sulfate, assuming all S is present as sulfate (sulfate to S ratio of 3). Our effect estimate is thus much larger than the estimate from the US cohort studies that investigated total mortality. A major difference between our study and these US studies is that our study was based upon contrasts within study areas, whereas the US studies focused on between-area contrasts. Sulfate is mostly formed in the atmosphere by oxidation of gaseous sulfur dioxide (SO_2) emissions (U.S. Environmental Protection Agency 2004). Sulfate is concentrated in fine particles which can be transported over long distances, resulting in a high regional background with typically

small spatial variation in metropolitan areas (U.S. Environmental Protection Agency 2004). Most of our study areas consist of a major city including surrounding smaller communities, with some cohorts covering a larger area (e.g. Vorarlberg region). Consistently, the exposure contrast in our study was much smaller than in the US studies, both for the S measurements (De Hoogh et al. 2013), and cohort exposures. Measured urban background $PM_{2.5}$ S concentrations were on average 9% higher than regional background concentrations. Concentrations at traffic sites were only 2% higher than at urban background sites. Predictor variables in the land use regression models for $PM_{2.5}$ S included especially traffic at various scales, population or address density, and urban green space (see Supplemental Material, LUR model results for all study areas, Tables S1-S9). Presumably because of the small measured within-study area contrasts, sulfur models were developed with mixed success, the average cross-validation R^2 was 30% for $PM_{2.5}$ S. Because land use regression models were developed for each study area separately, we could not exploit between-study area variations in $PM_{2.5}$ S which would have improved the model performance. In the ESCAPE study which focuses on within-area contrasts in pollution, these models reflect a combination of variations in primary sulfate emission and secondary sulfate formation (De Hoogh et al. 2013). Depending on meteorological conditions, SO_2 to sulfate conversion rates of 1-5% per hour have been observed (U.S. Environmental Protection Agency 2004), implying that some conversion already occurs at scales of 10 - 50 km (a typical wind speed is 10 km/hour). A study in Berlin, Germany documented measurable sulfate formation within 50km of the source (Lammel et al. 2005).

In the three US studies also $PM_{2.5}$ mass was associated with mortality. A problem to understand the role of sulfate in mortality risk is that sulfate concentrations were highly correlated with the concentration of $PM_{2.5}$ mass in the US studies and, thus, mortality associations with sulfate can be difficult to distinguish from $PM_{2.5}$ mass. The median

513 correlation between estimated $PM_{2.5}$ and $PM_{2.5}$ S over the 19 cohorts in our study was 0.53
514 (range 0.26 – 0.86), making it possible to disentangle the associations with $PM_{2.5}$ S and $PM_{2.5}$
515 mass. The lower correlation in our study is probably because of the finer resolution on which
516 concentrations were estimated. The median correlation of measured within-area contrast in
517 $PM_{2.5}$ and S was very similar (0.6), suggesting that the moderate model R^2 values for S did
518 not artificially induce the low correlation.
519 Another study which is interpreted as showing mortality effects of sulfur was an intervention
520 study in Hong Kong which studied the effects of limiting the sulfur content of fuel oils used
521 in both power plants and vehicles (Hedley et al. 2002). Initial findings were a decrease in
522 sulfur dioxide, associated with prompt and persistent reductions in mortality, suggesting that
523 increased mortality prior to the limitation may have been related to sulfate and/or sulfur
524 dioxide. Subsequent analysis, however, revealed that the reduction in sulfur dioxide was
525 highly correlated with reductions in both vanadium and nickel derived from residual oil
526 emissions (Hedley et al. 2006). In our study correlations between elements were smaller,
527 suggesting that the $PM_{2.5}$ S mortality effect could not be explained by exposure to other
528 elements such as V and Ni. This is also supported by the robust HRs for $PM_{2.5}$ S after
529 adjustment for co-pollutants.
530
531 *Interpretation of S associations*
532 The association reported with $PM_{2.5}$ S may be due to other correlated components.
533 Toxicological studies have provided little support for a causal effect of sulfate, despite fairly
534 consistent associations in epidemiological studies (Kelly and Fussell 2012). Sulfate may
535 indirectly affect health e.g. by solubilisation of metals increasing bio-availability and
536 catalysis of formation of secondary organic particle matter (Kelly and Fussell 2012). As
537 associations in our study were found for small-scale spatial variations in S, we speculate that

these point towards an influence of primary combustion from S containing fuels and might indicate a marker for within-city air pollution differences between city center and surrounding areas.

Associations for other elements

For none of the other elements in our study statistically significant associations were found, although HRs were elevated for almost all elements. There was more heterogeneity between individual cohort effect estimates for the other elements than for $PM_{2.5}$ S, although for most elements this was not statistically significant. For Cu, Fe, and Zn, mainly selected as marker for (non-tailpipe) traffic emissions, the evidence for an association was smallest. Source apportionment studies conducted elsewhere showed that Fe was mostly associated with road dust and brake abrasion, Zn and Cu were associated with tyre and brake abrasion (Viana et al. 2008). The land use regression models had the best fit for these elements because traffic predictors were available and traffic sites were overrepresented in the measurement campaign. The lack of an association is thus unlikely due to exposure measurement error. In our previous analysis in the same set of cohorts we found non-significant HRs, although elevated, for NO_2 (1.01 (95% CI: 0.99, 1.03) per 10 $\mu g/m^3$), NO_x (1.02 (95% CI: 1.00, 1.04) per 20 $\mu g/m^3$) and $PM_{2.5}$ aborbance (1.02 (95% CI: 0.97, 1.07) per 10^{-5} m^{-1}), pollutants affected by tailpipe emissions (Beelen et al. 2014).

In single pollutant models we found borderline statistically significant increased HRs for Si in $PM_{2.5}$ but not PM_{10}, despite the substantially higher concentrations in the coarse fraction. Source apportionment studies suggest that Si is primarily associated with crustal material in resuspended soil and road dust (Viana et al. 2008). Within our previous analyses we did not find an association between mortality and coarse particles (Beelen et al. 2014).

Both V and Ni were linked to crude oil and derived mainly from shipping emissions in source

apportionment studies, and K was linked to biomass burning (Viana et al. 2008). In single pollutant models we found borderline statistically significant increased HRs for Ni and K in PM_{10} which were reduced after adjustment for S. We had only general industry and port land use indicator predictor variables for our exposure models for Ni and V available. A specific predictor variable for wood smoke was not available (De Hoogh et al. 2013). The lack of more specific predictors in the V, Ni and K exposure models limits the ability to detect any element-specific mortality associations.

Strengths and limitations

Our study has several strengths: large sample size, broad European coverage, adjustment for a wide range of potential (individual) confounders, and multiple elements with a high percentage of detected samples (>75%) and good precision of measurements in all 19 cohorts. The advantage compared to previous long-term studies on elemental composition which compared between-city variation and ignored within-city variation is that our study could estimate spatial contrasts at much smaller spatial scales using the land use regression models that were developed in a standardized way in all 19 cohorts.

We used data from measurements in 2008-2011 for the development of our land use regression models but applied them to addresses at baseline (most in the mid-1990s). Emissions of sulfur in Europe have been reduced following a series of control measures during the last two decades (Fowler et al. 2007). However, recent studies in the Netherlands, Rome, UK and Vancouver showed that the spatial contrast of nitrogen dioxide air pollution is stable over a period of 10 years or longer (Eeftens et al. 2011; Cesaroni et al. 2012; Gulliver et al. 2013; Wang et al. 2013). In addition, spatial models for black smoke and sulfur dioxide in the UK provided reasonable predictions, even going back to the 1960s (Gulliver et al. 2011). We cannot rule out the possibility that for specific components spatial contrast was less stable.

588 We did not take moving of subjects to another address during follow-up into account in the
589 current analyses. In our previous analysis on particulate matter and nitrogen oxides and
590 natural cause mortality in the same cohorts, HRs for subjects who moved during follow-up
591 did not differ significantly from the HRs for the complete study population, although they
592 were slightly higher (Beelen et al. 2014).
593 We investigated 8 a priori selected elements in both the $PM_{2.5}$ and PM_{10} fraction, so there
594 might be issues related to multiple comparisons, and the correlation between different
595 elements and the extent to which they can act as surrogate for the elements causing the effect.
596 Although for almost all elements HRs were elevated, the association with $PM_{2.5}$ S clearly was
597 the strongest. In addition, the $PM_{2.5}$ S mortality associations remained robust, even after
598 adjustment for other elements as well as particle mass. In addition, cohort-specific $PM_{2.5}$ S
599 HRs were almost all above 1 (Figure 2) and there was no heterogeneity between cohort-
600 specific $PM_{2.5}$ S HRs (Table 3), indicating that there is consistency between cohort results.
601 We therefore do not think that our $PM_{2.5}$ S mortality association is a chance finding or can be
602 explained by any of the other measured elements.
603 The elements may have differences in the accuracy of the estimates of exposure which could
604 bias the resulting effect estimates and standard errors. When the measurements of two
605 elements are correlated, part of the association between mortality and the element with more
606 measurement error could be shifted to the estimate of association with the element with less
607 measurement error. Accuracy of exposure estimates may depend on both the precision of the
608 measurements as well as the performance of the exposure models. The eight selected
609 elements were detected in large majority (>75%) of the samples. Measurement precision was
610 best for S, Cu and Fe but poorer for Ni and V, especially in study areas with low
611 concentration levels (De Hoogh et al. 2013). The performance of the S land use regression
612 models was among the lowest based on the model R^2 value which makes it unlikely that the

associations seen with $PM_{2.5}$ S were inflated because of larger exposure estimation error in the other components.

Conclusion

In conclusion, long-term exposure to $PM_{2.5}$ S was associated with natural cause mortality. This association was robust to adjustment by other pollutants including particle mass.

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718 **Table 1: Description of the included cohort studies**

Cohort[a]	N total[b]	N NM[c]	Mean age (years) at baseline ± SD	Baseline period	Total follow-up time in person-years (mean follow-up)	Study area description
FINRISK, Finland	10,224	602	47.9 ± 13.2	1992; 1997; 2002; 2007	108,434 (10.6)	Greater Helsinki Area and Turku city and its rural surroundings
HUBRO, Norway	18,102	1182	48.3 ± 15.2	2000-2001	173,798 (9.6)	City of Oslo
SNAC-K, Sweden	2401	395	70.3 ± 8.1	2001-2004	15,568 (6.5)	City of Stockholm
SALT/Twin gene, Sweden	5473	581	58.0 ± 9.9	1998-2002	47,767 (8.7)	Stockholm County
60-y/IMPROVE, Sweden	3612	303	60.4 ± 0.1	1997-1999	40,612 (11.2)	Stockholm County
SDPP, Sweden	7408	248	47.1 ± 5.0	1992-1998	102,831 (13.9)	Stockholm County
DCH, Denmark	35,458	3770	56.7 ± 4.4	1993-1997	469,571 (13.2)	City of Copenhagen and surrounding areas
EPIC-MORGEN, Netherlands	16,446	795	43.9 ± 10.9	1993-1997	217,722 (13.2)	Cities of Amsterdam, Maastricht and Doetinchem and surrounding rural areas
EPIC-PROSPECT, Netherlands	15,670	1269	57.7 ± 6.0	1993-1997	202,809 (12.9)	City of Utrecht and surrounding rural areas
SALIA, Germany	4352	618	54.5 ± 0.6	1985-1987; 1990-1994	81,093 (18.6)	Areas in the cities of Dortmund, Duisburg, Essen,

						Gelsenkirchen and Herne situated in the Ruhr Area and adjacent towns Borken and Dülmen
EPIC-Oxford, UK	8598	443	46.0 ± 13.1	1993-2001	110,097 (12.8)	Urban and rural areas in a buffer of 10 km around London-Oxford area
KORA, Germany	8399	673	49.5 ± 13.8	1994-1995; 1999-2001	88,592 (10.5)	City of Augsburg and two adjacent rural counties
VHM&PP, Austria	117,824	13,081	41.9 ± 14.9	1985-2005	2,039,328 (17.3)	State of Vorarlberg, excluding high mountain areas (> 600m) and areas within 300m of state border
SAPALDIA, Switzerland	1250	65	42.0 ± 11.9	1991	20,294 (16.2)	City of Lugano
E3N, France	10,915	516	53.0 ± 6.8	1993-1996	147,021 (13.5)	City of Paris and surrounding rural areas
EPIC-Turin, Italy	7261	302	50.4 ± 7.5	1993-1998	97,549 (13.4)	City of Turin
SIDRIA-Turin, Italy	5054	129	44.2 ± 6.2	1999	55,667 (11.0)	City of Turin
SIDRIA-Rome, Italy	9177	239	44.3 ± 6.0	1999	102,856 (11.2)	City of Rome
EPIC-Athens, Greece	4192	255	49.4 ± 11.7	1994-1999	46,852 (11.2)	Greater Athens Area

719 [a] Order of cohorts is North to South gradient

720 [b] Total study population: Number of observations without missing value in any confounder variable of model 3 (main model)

721 [c] Number of death from natural-cause mortality

722 **Table 2: Population characteristics of the included cohort studies at baseline.**

Cohort[a]	% women	% never smokers	Cigarettes / day[b]	Years of smoking[b]	BMI (kg/m^2) [b]	Fruit intake[c]	Alcohol intake[d]	% married / living with partner	% low educational level	% employed / self-employed
FINRISK, Finland	54%	45%	3.8 ± 7.8	8.6 ± 12.2	26.4 ± 4.6	66%	0.9 ± 1.3	70%	31%	69%
HUBRO, Norway	56%	46%	6.8 ± 8.4	11.6 ± 14.4	25.7 ± 4.1	40%	51%	50%	18%	73%
SNAC-K, Sweden	60%	44%	7.1 ± 9.5	9.8 ± 15.2	26.0 ± 4.1	NA	22%	54%	21%	29%
SALT/Twin gene, Sweden	56%	39%	8.5 ± 9.7	16.7 ± 17.3	28.6 ± 4.1	NA	NA	68%	22%	NA
60-y/IMPROVE, Sweden	53%	41%	8.0 ± 9.1	15.2 ± 16.4	26.8 ± 4.2	64%	8.9 ± 9.7	72%	28%	51%
SDPP, Sweden	62%	37%	8.5 ± 8.8	12.3 ± 12.4	25.6 ± 4.0	92%	1.3 ± 1.9	84%	26%	92%
DCH, Denmark	54%	36%	6.3 ± 10.4	18.7 ± 17.1	26.0 ± 4.1	183.2 ± 151.2	21.7 ± 22.8	69%	30%	80%
EPIC-MORGEN, Netherlands	54%	35%	10.4 ± 11.1	14.3 ± 13.7	25.2 ± 4.0	171.9 ± 129.2	12.7 ± 18.0	68%	12%	NA
EPIC-PROSPECT, Netherlands	100%	45%	5.7 ± 7.4	15.2 ± 16.5	25.5 ± 4.1	231.6 ± 139.2	9.0 ± 12.4	77%	22%	NA
SALIA, Germany	100%	75%	2.6 ± 6.6	4.4 ± 10.5	NA	NA	NA	NA	29%	NA
EPIC-Oxford, UK	75%	60%	5.5 ± 8.8	7.3 ± 11.5	24.3 ± 4.3	253.6 ± 216.5	10.0 ± 12.3	67%	34%	77%
KORA, Germany	51%	44%	9.2 ± 13.3	12.0 ± 14.2	27.2 ± 4.6	60%	16.3 ± 22.3	76%	13%	58%

VHM&PP, Austria	56%	70%	NA	NA	24.8 ± 4.3	NA	NA	68%	NA	69%
SAPALDIA, Switzerland	56%	45%	11.1 ± 14.4	11.1 ± 13.0	23.8 ± 3.9	NA	NA	58%	11%	81%
E3N, France	100%	49%	NA	NA	22.8 ± 3.3	236.2 ± 162.5	12.4 ± 15.4	NA	5%	NA
EPIC-Turin, Italy	48%	43%	7.2 ± 8.2	17.6 ± 16.3	25.3 ± 3.8	318.2 ± 182.2	18.1 ± 20.3	86%	44%	NA
SIDRIA-Turin, Italy	52%	38%	9.3 ± 10.2	11.3 ± 10.6	NA	NA	NA	95%	18%	72%
SIDRIA-Rome, Italy	53%	35%	10.1 ± 10.5	11.7 ± 10.4	NA	NA	NA	100%	45%	NA
EPIC-Athens, Greece	55%	40%	1.7 ± 15.0	10.8 ± 13.1	27.5 ± 4.5	402.6 ± 258.2	9.2 ± 14.5	78%	24%	67%

[a] Order of cohorts is North to South gradient

[b] Mean ± SD

[c] Mean ± SD (g/day) or percentage with daily fruit consumption. For SDPP it is percentage daily/weekly fruit consumption.

[d] 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.

NA is not available or available with large number of missings (e.g. BMI in SALIA and smoking variables in E3N).

A detailed description of each cohort can be found in Supplemental Material, Study population characteristics at baseline for each cohort, Tables S10-S28.

Table 3: Association between natural cause mortality and exposure to elemental composition of PM: Results from random-effects meta-analyses (HRs and 95%-CIs) (using main confounder models 1, 2 and 3).[a]

Exposure	Number of cohorts	Model 1[b]	Model 2[b]	Model 3[b]	p-value model 3	I^2 (p-value)[c]
$PM_{2.5}$ Cu	19	1.08 (1.00, 1.17)	1.00 (0.94, 1.06)	0.98 (0.92, 1.04)	0.54	16.4 (0.25)
PM_{10} Cu	19	1.07 (1.00, 1.15)	1.02 (0.95, 1.08)	1.01 (0.95, 1.07)	0.83	43.5 (0.02)
$PM_{2.5}$ Fe	19	1.12 (1.05, 1.18)	1.04 (0.99, 1.10)	1.03 (0.98, 1.09)	0.20	10.1 (0.33)
PM_{10} Fe	19	1.08 (1.02, 1.15)	1.03 (0.97, 1.09)	1.02 (0.97, 1.08)	0.44	43.9 (0.02)
$PM_{2.5}$ Zn	19	1.07 (1.00, 1.15)	1.04 (1.00, 1.08)	1.03 (0.99, 1.08)	0.17	21.4 (0.19)
PM_{10} Zn	19	1.09 (1.01, 1.17)	1.04 (1.00, 1.09)	1.04 (0.99, 1.09)	0.18	31.5 (0.09)
$PM_{2.5}$ S	18[d]	1.29 (1.11, 1.50)	1.16 (1.08, 1.25)	1.14 (1.06, 1.23)	0.003	0 (0.94)
PM_{10} S	18[d]	1.23 (1.07, 1.42)	1.09 (1.00, 1.19)	1.09 (0.99, 1.19)	0.11	29.8 (0.11)
$PM_{2.5}$ Ni	14[e]	1.12 (1.02, 1.22)	1.05 (0.97, 1.15)	1.05 (0.97, 1.13)	0.27	20.3 (0.23)
PM_{10} Ni	17[f]	1.22 (1.05, 1.41)	1.09 (1.00, 1.19)	1.09 (1.00, 1.19)	0.08	30.3 (0.12)
$PM_{2.5}$ V	15[g]	1.22 (1.03, 1.44)	1.07 (0.95, 1.20)	1.07 (0.93, 1.23)	0.35	32.5 (0.11)
PM_{10} V	18[d]	1.07 (0.93, 1.24)	1.04 (0.96, 1.12)	1.03 (0.95, 1.12)	0.46	5.7 (0.39)
$PM_{2.5}$ Si	16[h]	1.18 (1.03, 1.34)	1.10 (0.99, 1.21)	1.09 (0.99, 1.09)	0.10	31.6 (0.11)
PM_{10} Si	18[d]	1.13 (1.00, 1.28)	1.04 (0.97, 1.11)	1.03 (0.97, 1.11)	0.37	47.6 (0.01)

$PM_{2.5}$ K	18[i]	1.06 (0.98, 1.14)	1.05 (0.99, 1.11)	1.07 (0.99, 1.15)	0.12	28.6 (0.13)
PM_{10} K	18[j]	1.05 (0.99, 1.12)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	0.08	0 (0.74)

[a] HRs are presented for the following increments: 5 ng/m³ $PM_{2.5}$ Cu, 20 ng/m³ PM_{10} Cu, 100 ng/m³ $PM_{2.5}$ Fe, 500 ng/m³ PM_{10} Fe, 10 ng/m³ $PM_{2.5}$ Zn, 20 ng/m³ PM_{10} Zn, 200 ng/m³ $PM_{2.5}$ S, 200 ng/m³ PM_{10} S, 1 ng/m³ $PM_{2.5}$ Ni, 2 ng/m³ PM_{10} Ni, 2 ng/m³ $PM_{2.5}$ V, 3 ng/m³ PM_{10} V, 100 ng/m³ $PM_{2.5}$ Si, 500 ng/m³ PM_{10} Si, 50 ng/m³ $PM_{2.5}$ K, and 100 ng/m³ PM_{10} K.

[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, educational level, occupational class, employment status, marital status; and Model 3: as in Model 2 also adjusting for area-level socio-economic status

[c] I^2 and Cochran's test for heterogeneity for model 3

[d] No modeled air pollution estimates available for SAPALDIA

[e] No modeled air pollution estimates available for SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP

[f] No modeled air pollution estimates available for HUBRO, SAPALDIA

[g] No modeled air pollution estimates available for HUBRO, KORA, VHM&PP, SAPALDIA

[h] No modeled air pollution estimates available for HUBRO, SAPALDIA, EPIC-Athens

[i] No modeled air pollution estimates available for SALIA

[j] No modeled air pollution estimates available for HUBRO

748 **Table 4: Results from random-effects meta-analyses from single pollutant and two-**

749 **pollutant models for association with natural cause mortality (using main model 3)**

750 **(HRs and 95%-CIs).[a]**

Exposure	Adjusted for	Single pollutant	Two-pollutant
$PM_{2.5}$ S [b]	$PM_{2.5}$	1.15 (1.06, 1.24)	1.13 (1.03, 1.24)
$PM_{2.5}$ S [c]	PM_{10} Ni	1.14 (1.04, 1.25)	1.14 (1.04, 1.25)
$PM_{2.5}$ S [d]	$PM_{2.5}$ Si	1.14 (1.05, 1.23)	1.13 (1.04, 1.22)
$PM_{2.5}$ S [e]	PM_{10} K	1.16 (1.06, 1.27)	1.15 (1.05, 1.26)
$PM_{2.5}$ [b]	$PM_{2.5}$ S	1.07 (1.02, 1.13)	1.02 (0.96, 1.09)
PM_{10} Ni [c]	$PM_{2.5}$ S	1.09 (0.98, 1.22)	1.06 (0.95, 1.18)
$PM_{2.5}$ Si [d]	$PM_{2.5}$ S	1.09 (0.98, 1.21)	1.08 (0.97, 1.20)
PM_{10} K [e]	$PM_{2.5}$ S	1.03 (0.99, 1.08)	1.02 (0.98, 1.06)

751 [a] Limited to studies for which correlation between 2 pollutants was < 0.7. HRs are presented for the following increments:

752 200 ng/m³ $PM_{2.5}$ S, 5 µg/m^3 for $PM_{2.5}$, 2 ng/m³ PM_{10} Ni, 100 ng/m³ $PM_{2.5}$ Si, 100 ng/m³ PM_{10} K.

753 [b] FINRISK and SAPALDIA not included.

754 [c] HUBRO, SALIA and SAPALDIA not included.

755 [d] HUBRO, SAPALDIA and EPIC-Athens not included.

756 [e] FINRISK, HURBO and SIDRIA-Rome not included.

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Figure legends

Figure 1: Description of estimated annual mean $PM_{2.5}$ elemental composition concentrations (ng/μg^3) at participant addresses in each cohort. The solid circle and bars shows the median and 25%, 75% percentile of elemental composition concentrations; the x shows the 5% and 95% percentile values.

Figure 2: Adjusted association between natural cause mortality and exposure to $PM_{2.5}$ S (using main model 3): Results from cohort-specific analyses and from random-effects meta-analyses.[a]

[a] HRs are presented per 200 ng/m³ $PM_{2.5}$ S