**Long-term exposure to fine particle elemental components and mortality in Europe: results from six European administrative cohorts within the ELAPSE project**

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**Highlights**

* Assessed natural mortality following long-term exposure to eight particles components
* Data from six European administrative cohorts with almost 27 million participants
* Europe-wide hybrid land use regression models for concentrations estimation
* Positive associations of natural mortality with all components
* After PM2.5/NO2 adjustment only associations with potassium and silicon remained

**Abstract**

Evidence for the association between long-term exposure to ambient particulate matter components and mortality from natural causes is sparse and inconsistent. We evaluated this association in six large administrative cohorts in the framework of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project.

We analysed data from country-wide administrative cohorts in Norway, Denmark, the Netherlands, Belgium, Switzerland and in Rome (Italy). Annual 2010 mean concentrations of copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V) and zinc (Zn) in fine particulate matter (PM2.5) were estimated using 100x100m Europe-wide hybrid land use regression models assigned to the participants’ residential addresses. We applied cohort-specific Cox proportional hazard models controlling for area- and individual-level covariates to evaluate associations with natural mortality. Two pollutant models adjusting for PM2.5 total mass or nitrogen dioxide (NO2) were also applied. We pooled cohort-specific estimates using a random effects meta-analysis.

We included almost 27 million participants contributing more than 240 million person-years. All components except Zn were significantly associated with natural mortality [pooled Hazard Ratios (HRs) (95% CI): 1.037 (1.014, 1.060) per 5 ng/m3 Cu; 1.069 (1.031, 1.108) per 100 ng/m3 Fe; 1.039 (1.018, 1.062) per 50 ng/m3 K; 1.024 (1.006, 1.043) per 1ng/m3 Ni; 1.036 (1.016, 1.057) per 200 ng/m3 S; 1.152 (1.048, 1.266) per 100 ng/m3 Si; 1.020 (1.006, 1.034) per 2 ng/m3 V]. Only K and Si were robust to PM2.5 or NO2 adjustment [pooled HRs (95% CI) per 50 ng/m3 in K: 1.025 (1.008, 1.044), 1.020 (0.999, 1.042) and per 100 ng/m3 in Si: 1.121 (1.039, 1.209), 1.068 (1.022, 1.117) adjusted for PM2.5 and NO2 correspondingly].

Our results indicate positive associations of natural mortality with long-term exposure to PM2.5 K, considered as biomass burning indicator, and Si, mostly originating from crustal material.

**Keywords:** Air pollution, Particle components, Long-term exposure, Natural Mortality

**Declaration of interest:** None declared

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**1. Introduction**

The association between long-term exposure to fine particulate matter (PM2.5) and mortality from natural causes has been well established in many previous studies (Brunekreef et al., 2021; Chen & Hoek, 2020; WHO, 2013). Nevertheless, PM2.5 is a complex mixture of chemical components from various sources and evidence about their associations with mortality outcomes are rather inconsistent (Yang et al., 2019).

In the framework of the Effects of Low-level Air Pollution: A Study in Europe (ELAPSE) project two distinct kinds of cohorts were used: a pooled cohort using data from eight European cohort studies with individual covariates data that were pooled using a harmonized codebook and then analyzed as one dataset; and six administrative cohorts with limited individual level data and more small area level covariates that analyzed separately and the individual-cohort effect estimates were meta-analyzed. We recently published the results of the pooled cohort data analysis on the associations between long-term exposure to PM2.5 components and natural and cause specific mortality that indicated associations of natural mortality with specific PM2.5 components, which remained robust after adjustment for PM2.5 and NO2, especially with vanadium (V) (Chen et al., 2021). Beelen et al. (2015) reported robust effects of PM2.5 sulfur (S) on natural mortality within the multicenter European Study of Cohorts for Air Pollution Effects (ESCAPE) project, while indicative associations with iron (Fe) and copper (Cu) were also observed. ELAPSE pooled cohort analysis followed ESCAPE and included selected cohort studies with extensive follow up time. The California Teachers Study observed no associations of natural mortality with PM2.5 or its components (Ostro et al., 2011; 2015). Badaloni et al. (2017) found significant associations of long-term exposure to metals originating from non-tailpipe emissions (Cu, Fe and zinc (Zn)) on natural mortality in the Rome longitudinal study (RoLs). Coal combustion components (selenium (Se) and arsenic (As)) were associated with increased risk of death in the American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II) (Thurston et al., 2013). In the Medicare population, PM2.5 with a higher concentration of sulfate, nitrateor OC was associated with a lower mortality risk, while an increase in concentration of aluminum (Al), calcium (Ca), Cu, elemental carbon (EC), Fe, or vanadium (V) resulted in increased PM2.5 effects (Wang et al., 2017).

Currently, there are no established concentration limit values for particle components. Better understanding of the health effects related to the most harmful components could lead to focused prevention and more effective strategies and regulations for public health protection. The aim of the present study was to explore the associations of specific PM2.5 components representative of different sources with natural mortality in six large administrative cohorts across Europe within the ELAPSE project, comprising a database of nearly 27 million participants. Although administrative cohorts lack detailed information on individual lifestyle, they provide large statistical power to detect associations as the sample sizes are much larger than the pooled cohort analyzed in the same project (Brunekreef et al., 2021; Chen et al., 2021; Stafoggia et al., 2021). In previous reports involving administrative cohorts (Badaloni et al., 2017; Fischer et al., 2020), exposure assessment and analytical methods differed among cohorts, complicating comparison of the reported associations. In ELAPSE, we harmonized both exposure assessment (Chen et al., 2020) and statistical analytical protocols to enhance comparability between cohort-specific results.

**2. Methods**

**2.1 Study population & outcome**

We used data from five European countries (Belgium, Denmark, the Netherlands, Norway and Switzerland) and one European city (Rome, Italy) linking different administrative databases (censuses and/or population registries) with mortality registries. We defined the age at baseline for cohorts at 30+ years, except for Dutch cohort where participants aged 29+ years. Individuals were enrolled from 2000 to 2008 and followed-up until 2011 to 2016 depending on the cohort (Table 1). The underlying cause of death was recorded. In this paper, we focused on natural mortality (International Classification of Diseases (ICD-9: 001-779; ICD-10: A00-R99). Information on residential address, baseline socio-demographic characteristics and area-level socio-economic indicators were also collected. Although, availability of individual and area-level indicators differed per administrative cohort, information on age, sex, marital status, country of origin and area-level indicators of socio-economic status were available for most cohorts (Table 1). More information can be found in the Supplement, section 1.

**2.2 Exposure assessment**

We focused on eight PM2.5 elemental components as indicators of different sources of particle pollution: copper (Cu), iron (Fe) and zinc (Zn) as non-tailpipe traffic emissionsindicators; potassium (K) for biomass burning, nickel (Ni) and vanadium (V) for mixed oil burning/industry emissions, sulfur (S) for long-range transported secondary inorganic aerosols and silicon (Si) for crustal material (de Hoogh et al., 2013; Tsai et al., 2015).

We modeled PM2.5 elemental composition concentrations at the participants’ baseline residential addresses using Europe-wide hybrid land use regression (LUR) models, which integrated satellite observations, dispersion model estimates, land use, roadvariables, industrial point sources, and ESCAPE air pollution fixed monitoring data for 2010 (Chen et al., 2020). Because of a lack of routine monitoring of PM components other years could not be modelled. Hybrid models were developed for each component using the supervised linear regression (SLR) algorithm (de Hoogh et al., 2018). The models explained a moderate to large fraction of the measured variation at the European scale across components as evaluated by five-fold hold-out validation (HOV) and supported by extensive sensitivity analysis [HOV R2: 0.48 for Cu; 0.48 for Fe; 0.59 for K; 0.56 for Ni; 0.79 for S; 0.46 for Si; 0.63 for V; 0.41 for Zn] (Chen et al., 2020). PM2.5 and nitrogen dioxide (NO2) estimates were assessed by Europe-wide LUR models developed based on the European Environmental Agency (EEA) AirBase routine monitoring data during 2010, predictors of satellite observations, dispersion model estimates, land use and road variables (de Hoogh et al., 2018). The PM2.5 and NO2 models explained 72% and 59% of spatial variation in the measured concentrations, respectively. The resulting mapped surfaces (100x100 m) were overlaid with the geocoded residential address locations to assign exposures. Very high and negative predicted concentrations of elemental composition were considered unrealistic and were truncated: negative concentrations were set to zero, while those exceeding a maximum modeled value, specified in ESCAPE monitoring sites, were truncated to the maximum predicted concentration (Chen et al., 2020).

**2.3 Statistical analyses**

A two stage analytical approach was used. In the first stage, data were analysed separately for each cohort in the secure environment of local national servers due to strict national data protection regulations. In the second stage, the cohort-specific estimates were pooled using a random-effects meta-analysis.

In the first stage, Cox proportional hazard models with adjustment for individual- and area-level covariates were used to examine the association between each PM component and natural mortality. Each PM2.5 component was included as a linear function in single-exposure Cox models. Censoring occurred at the time of death from natural causes, loss to follow-up for other reasons, or at the end of follow-up, whichever came first. Hazard ratios (HRs) and respective 95% confidence intervals (CIs) were calculated for a fixed increment perPM2.5 component: Cu 5 ng/m3; Fe 100 ng/m3; K 50 ng/m3; Ni 1 ng/m3; S 200 ng/m3; Si 100 ng/m3; V 2 ng/m3; Zn 10 ng/m3 (Beelen et al., 2015; Chen et al., 2021; Hvidtfeldt et al., 2021b). The increments used to calculate HRs reflected a larger exposure contrast than the interquartile range (IQR) for almost all components and all administrative cohorts (Supplementary Table S1).

We pre-specified three models with increasing covariate control, following the modelling protocol of the ELAPSE study (Brunekreef et al., 2021; Chen et al., 2021; Hvidtfeldtet al., 2021a, Liu et al.,2021). Since administrative data were analyzed separately, we used maximal adjustment per cohort rather than a joint model with few common covariates. The first model (Model 1) included age (as time axis) and sex (as strata). The second model (Model 2) further adjusted for the available individual-level variables per administrative cohort (Table 1), hence it slightly differed per cohort. The third model (Model 3 - main model) extended Model 2 to include various area-level socio-economic status (SES) variables at both regional and small area level (Table 1). Given that associations between air pollution, lifestyle characteristics and health outcomes are affected by SES (Fairburnet al., 2019; Samoli et al., 2019), but also in order to compensate for the lack of detailed individual-level data, we included multiple variables at both the regional and small area spatial scale to reduce the potential confounding. The definition of the region and small area differed per cohort. We subtracted the regional level values from the small area variable before inclusion in the models. For the city-wide cohort of Rome, no regional covariates were considered. A robust variance estimator was applied in all models to account for clustered observations at small area level. Participants with missing information for the main model’s covariates were excluded from all analyses.

To assess the robustness of our results, Model 3 was further adjusted for PM2.5 total mass or NO2. PM2.5 is independently associated with natural mortality and may obscure associations with individual components. What is more, PM2.5 mass adjusts for the effects of the rest components except the one under study (Mostofsky et al., 2012). NO2 represents traffic exhaust emissions and may be considered as confounder especially when examining the associations with the traffic non-exhaust components i.e. Cu, Fe and Zn.

In the second stage, cohort-specific estimates were pooled by a univariate random-effects meta-analysis using the restricted maximum-likelihood estimator for the between-cohorts’ variance (Veroniki et al.,2016). Heterogeneity between cohort-specific estimates was assessed by the Cochran’s Q test and the I2 statistic (Higgins & Thompson, 2002).

All analyses were conducted in R software (version 3.4.0), using the libraries *survival*, *Matrix*, *MASS*, *foreach*, *multcomp*, *survey*, *Hmisc*, *ggplot2* and *rms* under common R scripts which were centrally developed and distributed among all cohorts’ analysts. Random effects meta-analysis was centrally performed using *metafor* library in R.

**3. Results**

Data of 26,421,806 participants were analysed, contributing with 244,780,728 person-years and 3,364,825 deaths from natural causes. The average natural mortality rate was 14 events per 1,000 person-years. The number of observations with full information on main model’s covariates varied from about 10.4 million in the Dutch cohort to more than 1.2 million in the Rome cohort (Table 1). The percent of subjects with missing data on exposure and confounders was small suggesting that selection bias retaled to missing values was rather unlikely. The mean age ranged from 53 to 55 years across cohorts, and almost half of the participants were women. All cohorts, but the Dutch, had individual-level data on education and occupational status and most of them had information about country of origin (not available for the Norwegian and Rome cohorts) and household income (not available for the Belgian and Swiss cohorts). Socio-economic variables at small and regional level varied in availability and definition across cohorts with only unemployment rate being available for all cohorts (Table 1).

The distribution of particles’ components varied across cohorts (Table 1 and Supplementary Table S1) reflecting the different sources of particulate pollution. The lowest mean concentrations for almost all components, with the exception of Ni and V (Swiss cohort), were observed in the Norwegian cohort, while the highest mean concentrations were observed in Rome cohort for all components but Zn (Belgian cohort). Nevertheless, the concentrations of most components showed less contrast in Rome than in the other national cohorts (based on the coefficient of variation). Cu, K, S and Zn levels varied the most within the Norwegian cohort, while Fe, Si, Ni and V exhibited large variability in the Danish, Belgian and Swiss cohort, respectively.

The correlation coefficients between the concentrations of various components varied among cohorts (Supplementary Figure S1). The Spearman correlation between Cu and Fe ranged from 0.6 (in Norway) to almost unity (in Rome) and between Cu and Zn from less than 0.1 (in Rome) to 0.8 (in Switzerland). Ni was moderately to highly correlated with V across cohorts with Spearman coefficients varying from 0.6 (in Danish and Dutch cohorts) to almost unity (in Rome). K was in general weakly correlated with the other components with the exception of Norwegian and Swiss cohorts, where the correlations were moderate to high.

Correlations of components with PM2.5 were mainly low to moderate for all cohorts (Supplementary Figure S1), although values were rather high for K, S and Zn in the Norwegian cohort (r ≥ 0.7). Correlations with NO2 were larger, in general, with the exception of K for which r < 0.2 for most of the cohorts. NO2 was highly correlated with Fe in the Danish and Swiss cohort and with Cu in the Rome and Swiss cohort (r ≥ 0.9).

The pooled hazard ratios for the association between PM2.5 components and natural mortality in the models with increasing confounder adjustment are presented in Table 2. We found positive associations of all components with natural mortality. In general, adjustment for the individual-level confounders (Model 2) resulted in modest or no decrease in the estimated HRs. Additional adjustment for area-level variables (Model 3) further decreased the HRs. In our main Model 3, we observed positive and statistically significant associations for all components, except from Zn [HR (95% CI): 1.011 (0.998, 1.023) per 10 ng/m3 increase]. The width of the confidence interval around the pooled effect estimate was also considerably smaller for Model 3 compared to Model 2 (e.g. Cu HR (95% CI): 1.060 (1.007, 1.117) and 1.037 (1.014, 1.060) per 5 ng/m3 increase for Models 2 and 3, respectively), probably related to lower heterogeneity of cohort-specific effect estimates.

The I2 values ranged from 84% for V to 99% for Zn (Figure 1). For all cohorts, except the Belgian, rather small positive associations were found in our main Model 3 (Table S2). The strongest associations for Ni and V were observed in the Norwegian cohort, while for the rest components the Danish cohort presented the highest HR estimates.

The effect estimates of all components decreased when adjusting for PM2.5. However, associations for Cu, Fe, K, S, Si and V remained positive and (borderline) significant (Figure 2). Adjustment for NO2 reduced all associations to unity, except from K and Si which were substantially reduced but remained (borderline) statistically significant [HRs (95% CIs): 1.020 (0.999, 1.042) per 50 ng/m3 increase for K; 1.068 (1.022, 1.117) per 100 ng/m3 for Si]. For Cu and Fe, the width of the confidence interval was substantially wider for the two-pollutant model with NO2 compared to the single-exposure model. Cohort-specific estimates for two pollutants models followed a similar pattern for almost all cohorts (Supplementary Table S3).

**4. Discussion**

We analyzed almost 27 million observations contributing with more than 240 million person-years to examine the association of natural mortality with long-term exposure to a-priori selected PM2.5 components, reflecting different particles’ sources, in six European countries. Our pooled estimates from single-exposure models indicated increased risk of mortality for all PM2.5 components except Zn. The effect estimates were decreased after adjustment for PM2.5 but remained positive for Cu, Fe, K, S, Si and V, while NO2-adjusted associations remained only for K and Si.

Cohort-specific results were heterogeneous with I2 values above 80% for all components, but this was largely driven by the narrow CIs of the included effect estimates. The magnitude of the cohort-specific estimates was rather consistent per analysis except for the Belgian cohort which displayed essentially nulleffect estimates for all components. Excluding this cohort from the meta-analysis, resulted in a decrease in I2 values ranging from 1% (for Si and Zn) to 17% (for S and V). Despite the harmonised exposure assessment and analytical protocol, the differences in covariate adjustment among centers depending on availability may have also contributed to the observed heterogeneity.

Cohort-specific HRs were decreased with increasing covariate adjustment especially when we included area level variables. This reduction was more evident in the Belgian cohort where the estimated effects in Model 3 were null for all components but K. In the Belgian cohort, results from Model 1 using either the population sample in Model 3 or the full study population (with about 1 million more subjects, Table 1) showed nearly identical HRs, suggesting selection bias was not substantial.

Our findings are consistent with the associations observed in single-exposure models in the pooled cohort analysis within the ELAPSE project when using the same exposure assessment method (Chen et al., 2021), although slightly lower in magnitude. The ELAPSE pooled cohort included data from eight cohorts mostly from large European cities and surrounding areas. Each cohort provided detailed information for individual-level covariates, including smoking and body mass index (BMI), and income at small area level. The rather consistent findings between the different types of cohorts analysed (pooled vs administrative) supports our results, despite the lack of individual covariate data (BMI, smoking, etc.) in the administrative cohorts. After adjustment for PM2.5, HRs were reduced substantially in the pooled cohort but modestly in the administrative cohorts; by contrast NO2 adjustment substantially reduced the estimates for both administrative and pooled cohorts (Chen et al., 2021).

We found evidence of associations between Cu and Fe with natural cause mortality in single-exposure models, the magnitude of which was modestly reduced following adjustment for PM2.5. This attenuation cannot be attributed to the correlation between these components and PM2.5 (Supplementary Figure S1) which was rather moderate. After adjustment for NO2, associations for Cu and Fe were nullified, but this finding needs to be interpreted with caution because of the high correlation for Cu and Fe with NO2. For Rome and Swiss cohorts there is some evidence that even after adjustment for NO2 or PM2.5, Cu and Fe were positively associated with natural-cause mortality (Supplementary Table S3), suggesting that non-tailpipe traffic pollution may affect mortality in addition to tailpipe emissions from motor vehicles. Our findings on Cu and Fe agree with those from the RoLs study in Rome that used the ESCAPE LUR exposure models (Badaloni et al. 2017). However, in the RoLs study Zn originating from non-tailpipe emissions was also related with increased risk of mortality in contrast to our results. This may be partly attributed to the fact that Zn in ELAPSE was mainly dominated by industrial sources rather than by non-tailpipe traffic emissions (Brunekreef et al., 2021; Chen et al., 2020).

We found consistent associations of natural mortality with K and Si even following PM2.5 or NO2 adjustment, indicating toxicity of biomass burning (for which K was considered an indicator) and crustal material sources (for which Si was considered an indicator) in PM2.5. The moderate to high correlations of K and Si with PM2.5 and especially NO2 did not seem to substantially change the estimated CIs suggesting a small impact of multi-collinearity in our data. Previous studies have associated K with cardiovascular outcomes such as coronary events (Wolf et al., 2015) and ischemic heart disease mortality (Ostro et al., 2011) but not with natural-cause mortality (Beelen et al., 2015; Thurston et al., 2013). Similarly, no association of natural mortality with Si has been previously reported (Beelen et al., 2015; Ostro et al., 2011; Thurston et al., 2013). ELAPSE, as an extended collaboration originating from ESCAPE, used a harmonized exposure model which incorporated various sources as potential predictors and predicted concentrations at a finer scale (100x100m) (Chen et al., 2020; Chen et al., 2021). Combined with the large statistical power gained by the use of large administrative cohorts,this may have enabled us to identify associations.

Ni and V were selected as indicators of mixed oil burning and industry emissions (de Hoogh et al., 2013; Tsai et al., 2015). Our findings suggest increased mortality risk for both in single-exposure models, but associations did not persist when adjusted for PM2.5 or NO2. On the other hand, Chen et al. (2021) reported robust associations of natural and cause specific mortality with V [HR (95% CI) for natural mortality adjusted for PM2.5: 1.033 (1.015, 1.052)]. In principle, our study has the statistical power to reveal associations compared to pooled cohort data analysis in Chen el. (2021). However, the cohorts involved in each study do not represented the same geographical areas where different sources and emissions may drive the results. Specifically, only Denmark and The Netherlands contributed data in both analyses. The combined V effect on natural mortality for Danish and Dutch administrative cohorts adjusted for PM2.5 was HR (95% CI): 1.004 (0.996, 1.012). The ESCAPE project reported positive but non-significant associations for both Ni and V with natural mortality (Beelen et al., 2015), while the American Cancer Society (ACS) Cancer Prevention Study-II reported mostly negative associations (CPS-II) (Thurston et al., 2013). Nevertheless, Wang et al. (2017) suggested higher mortality risks for PM2.5 mass with higher proportion of V concentration (80% vs 20%) in the Medicare population.

Although the single-exposure results indicated positive associations between natural mortality and S, an indicator of long range transported inorganic aerosol, estimates were not robust after adjustment for PM2.5 or NO2. In contrast, Beelen et al. (2015) reported consistent elevated mortality risks for PM2.5 S in single and two pollutant models using the ESCAPE project data. Thurston et al. (2013) also reported significant positive associations of S with increased risk of death in ACS-CPS-II study. As S mainly varies on a large spatial scale, it is rather unexpected that the large administrative cohorts indicated a less consistent association. One explanation might be that components concentrations were assessed between 2008 and 2011, when emissions of sulfur oxides has decreased (Chen et al., 2021; EEA, 2015) letting other components prevail.

Fischer et al. (2020) used a Dutch national database and local dispersion models based on 1x1 km maps to examine the effects of long-term exposure to particulate air pollution from different sources on natural mortality. They observed statistically significant associations withelemental carbon (EC), while the effects of secondary inorganic aerosol were less consistent. The associations of mortality with S, as long-range transported secondary inorganic aerosols indicator, were quite robust for the Dutch cohort included in our study. However, these results may not be directly comparable since according to Fischer et al. (2020) the spatial gradient of secondary inorganic aerosol in the Netherlands is small due to the slow formation of this pollutant after atmospheric chemical reactions. We did not assess the association of mortality with EC in the current study. Previous findings for the Dutch cohort within the ELAPSE project indicated robust associations of natural mortality with black carbon (BC), a comparable particulate element to EC (Brunekreef et al., 2021).

The main strength of our study is the enhanced statistical power with the combination of results from six large administrative cohorts, with almost 27 million participants as well as the harmonized exposure assessment and analyses undertaken within ELAPSE. One limitation of our study is the inevitably differential covariate adjustment both at individual and area-level across cohorts. Further, no data on lifestyle variables such as smoking or BMI were available at the individual level for all cohorts which may result in residual confounding. Nevertheless, the comparability of the direction and magnitude of the estimates between the pooled (with individual level covariates) and the administrative cohort analysis’ results, strengthens our confidence in the administrative cohorts’ analysis. What is more, within ELAPSE we have applied an estimation correction method proposed by Shin et al. (2014) to correct for unmeasured confounding due to lack of smoking and BMI data for the association between PM2.5 or NO2 and mortality and found robust effect estimates to the missing individual lifestyle covariates (Brunekreef et al., 2021). There is no reason to expect that this conclusion would differ in the investigation of PM component presented in our paper.

**5. Conclusions**

Our findings indicate an association of natural mortality with long-term exposure to PM2.5 K, an indicator of biomass burning, and Si which mainly derives from crustal material. Source apportionment methods and examination of source-specific mortality effects may further enlighten and compliment the results of the present analysis, although in principle it addresses a different research question related to the toxicity of the air mixture rather than its most toxic component (Dominici et al., 2010).

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**Table 1.** Main characteristics of the six administrative cohorts.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Belgian** | **Danish** | **Dutch** | **Norwegian** | **Rome** | **Swiss** |
| Cohort’s population | 6,440,472 | 3,323,612 | 10,439,068 | 2,310,480 | 1,263,712 | 4,293,521 |
| Participants with complete data | 5,446,267 | 3,027,734 | 10,376,406 | 2,119,512 | 1,263,712 | 4,188,175 |
| ***Health outcome*** | | | | | | |
| Person years at risk | 54,419,510 | 41,807,166 | 50,034,558 | 29,873,933 | 15,301,265 | 53,344,296 |
| Follow-up period | 2001 - 2011 | 2000 - 2015 | 2008 - 2012 | 2001 - 2016 | 2001 - 2015 | 2000 - 2014 |
| Number of natural deaths | 694,033 | 703,142 | 590,832 | 479,741 | 235,543 | 661,534 |
| Natural mortality rate per 1,000 py | 12.8 | 16.8 | 11.8 | 16.1 | 15.4 | 12.4 |
| ***PM2.5 components in* (ng/m3) *[mean (SD)]*** | | | | | | |
| Cu | 4.8 (2.7) | 1.1 (1.6) | 3.8 (1.7) | 0.5 (2.3) | 8.5 (2.1) | 5.2 (2.7) |
| Fe | 110.3 (48.3) | 43.0 (35.0) | 94.7 (33.0) | 36.3 (28.8) | 160.4 (43.7) | 108.4 (46.9) |
| K | 179.2 (16.3) | 122.6 (19.0) | 155.1 (23.2) | 53.2 (30.6) | 252.8 (9.8) | 224.2 (37.7) |
| Ni | 1.4 (0.6) | 0.9 (0.5) | 1.4 (0.7) | 0.7 (0.3) | 1.8 (0.4) | 0.4 (0.4) |
| S | 831.5 (74.2) | 702.2 (56.2) | 769.4 (63.1) | 386.2 (129.8) | 1110.2 (59.1) | 646.6 (85.0) |
| Si | 89.2 (25.5) | 85.8 (19.5) | 91.7 (17.7) | 79.5 (16.1) | 154.1 (25.9) | 96.3 (21.8) |
| V | 2.4 (1.0) | 2.0 (1.2) | 2.6 (1.3) | 1.5 (0.7) | 3.9 (0.7) | 0.6 (0.6) |
| Zn | 31.1 (26.7) | 13.2 (4.5) | 25.2 (18.2) | 7.4 (9.8) | 26.3 (4.1) | 20.8 (18.5) |
| ***Pollutants in* (μg/m3) *[mean (SD)]*** | | | | | | |
| PM2.5 | 18.6 (1.6) | 12.4 (1.5) | 16.3 (1.4) | 8.5 (2.5) | 16.7 (0.9) | 15.9 (2.4) |
| NO2 | 30.4 (7.3) | 20.3 (8.0) | 31.4 (7.1) | 15.8 (7.8) | 32.9 (6.1) | 23.7 (7.4) |
| ***Individual level covariates*** | | | | | | |
| Age(years) [mean (SD)] | 52.5 (15.1) | 53.0 (15.2) | 53.5 (15.0) | 53.9 (15.9) | 55.1 (15.4) | 52.7 (15.2) |
| Women (%) | 50.6 | 48.3 | 51.3 | 51.0 | 54.5 | 52.0 |
| Local origin (%) | 96.8 | 94.5 | 82.9 | NA | NA | 83.1 |
| Marital status |  |  |  |  |  |  |
| *Single* (%) | 12.3 | 10.6 | 18.8 | 17.6 | 15.3 | 14.0 |
| *Married/ living with partner* (%) | 68.4 | 69.4 | 63.3 | 59.5 | 66.3 | 69.3 |
| *Divorced/ separated* (%) | 9.9 | 12.5 | 10.0 | 12.4 | 7.0 | 8.7 |
| *Widowed* (%) | 9.4 | 7.5 | 7.9 | 10.5 | 11.4 | 8.1 |
| Education |  |  |  |  |  |  |
| *Low* (%) | 23.7 | 36.8 | NA | 30.7 | 24.9 | 24.5 |
| *Medium* (%) | 51.9 | 41.1 | NA | 45.9 | 58.8 | 52.7 |
| *High* (%) | 24.4 | 22.0 | NA | 23.4 | 16.2 | 22.7 |
| Occupational status |  |  |  |  |  |  |
| *Employed/ self-employed* (%) | 53.4 | 64.7 | NA | 66.0 | 45.8 | 61.4 |
| *Unemployed* (%) | 5.1 | 2.7 | NA | 1.2 | 5.0 | 2.2 |
| *Homemaker/ housewife* (%) | 8.5 | 32.6 | NA | 0.0 | 21.0 | 14.6 |
| *Retired* (%) | 33.0 | 0.0 | NA | 32.8 | 23.5 | 21.8 |
| Household income (levels) | NA | Deciles | Deciles | Quartiles | NA | NA |
| German as mother tongue (%) | NA | NA | NA | NA | NA | 65% |
| ***Area-level covariates at small area***a ***level [mean (SD)]*** | | | | | | |
| Mean Income (national currency) | 29,517.0 (5,528.5) | 164,736.8 (27,083.5) | 18,233.2 (2,499.7) | NA | 24,754.6 (8,077.7) | NA |
| Low household incomeb (%) | NA | NA | NA | 5.1 (2.4) | NA | NA |
| Low educationc (%) | 15.7 (4.9) | 32.7 (8.9) | NA | 24.5 (7.6) | 25.2 (6.6) | 28.4 (7.3) |
| High educationc (%) | NA | NA | NA | NA | 13.2 (8.6) | 19.8 (7.5) |
| Unemployment rate (%) | 8.2 (6.1) | 1.9 (0.7) | 27.1 (8.8) | 1.6 (0.4) | 14.9 (4.0) | 3.5 (1.5) |
| Non-western ethnicityd (%) | 5.4 (9.2) | NA | 10.1 (11.8) | NA | NA | NA |
| Socio-economic scoree | NA | NA | 0.02 (0.98) | NA | Quintilesf | 63.0 (7.3) |

a Different definition of small area per cohort; b National definition of low income; c National definition of low/ high education; d National definition for non-western ethnicity;

eCohort-specific definition. f A continuous score for each census block which categorized in quintiles within Rome; range from 1: very affluent to 5: very deprived.

SD: standard deviation; py: person years; NA: Not Available.

**Table 2.** Pooled hazard ratios (HR)and 95% confidence intervals (95% CI) from random effects meta-analysis of six administrative cohortsfor the association between PM2.5 components and natural mortality in single-exposure models with increasing levels of confounder adjustment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PM2.5**  **components** | **Increment** | **Model 1a** | **Model 2b** | **Model 3c** |
| Cu | 5 ng/m3 | 1.058  (1.002, 1.118) | 1.060  (1.007, 1.117) | 1.037  (1.014, 1.060) |
| Fe | 100 ng/m3 | 1.083  (1.025, 1.145) | 1.086  (1.031, 1.143) | 1.069  (1.031, 1.108) |
| K | 50 ng/m3 | 1.054  (1.005, 1.105) | 1.047  (1.013, 1.082) | 1.039  (1.018, 1.062) |
| Ni | 1 ng/m3 | 1.056  (1.022, 1.092) | 1.041  (1.014, 1.070) | 1.024  (1.006, 1.043) |
| S | 200 ng/m3 | 1.083  (1.018, 1.152) | 1.073  (1.020, 1.128) | 1.036  (1.016, 1.057) |
| Si | 100 ng/m3 | 1.225  (1.081, 1.388) | 1.196  (1.079, 1.326) | 1.152  (1.048, 1.266) |
| V | 2 ng/m3 | 1.048  (1.023, 1.074) | 1.032  (1.015, 1.049) | 1.020  (1.006, 1.034) |
| Zn | 10 ng/m3 | 1.025  (1.002, 1.049) | 1.020  (1.003, 1.038) | 1.011  (0.998, 1.023) |

a Model 1 included age (time axis), sex (as strata), and calendar year of enrolment; bModel 1 further adjusted for the available individual-level variables per administrative cohort; cModel 2 further adjusted for area-level socio-economic status (SES) variables at both the regional and neighborhood scale.

**Figure 1.** Cohort-specific and pooled hazard ratios (HRs) and 95% Confidence Intervals (95% CIs) per indicated increment from random effects meta-analysis of six administrative cohorts for the association between PM2.5 components and natural mortality.

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |

Cohort-specific results from Model 3 that included age (time axis), sex (as strata), calendar year of enrolment, individual-level variables and area-level socio-economic status (SES) variables at both the regional and neighborhood scale.

**Figure 2.** Pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) from random effects meta-analysis of six administrative cohorts for the association between PM2.5 components and natural mortality in two pollutants models adjusting for PM2.5 and NO2.



Results per: Cu 5 ng/m3; Fe 100 ng/m3; K 50 ng/m3; Ni 1 ng/m3; S 200 ng/m3; Si 100 ng/m3; V 2 ng/m3; Zn 10 ng/m3.