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Abstract

Background: Particulate matter (PM) air pollution is a human lung carcinogen; however, the components responsible have not been identified. We assessed the associations between PM components and lung cancer incidence.

Methods: We used data from 14 cohort studies in eight European countries. We geocoded baseline addresses and assessed air pollution with land-use regression models for eight elements (Cu, Fe, K, Ni, S, Si, V and Zn) in size fractions of $PM_{2.5}$ and PM_{10}. We used Cox regression models with adjustment for potential confounders for cohort-specific analyses and random effect models for meta-analysis.

Results: The 245 782 cohort members contributed 3 229 220 person–years at risk. During follow-up (mean, 13.1 years), 1878 incident cases of lung cancer were diagnosed. In the meta-analyses, elevated hazard ratios (HRs) for lung cancer were associated with all elements except V; none was statistically significant. In analyses restricted to participants who did not change residence during follow-up, statistically significant associations were found for $PM_{2.5}$ Cu (HR, 1.25; 95% CI, 1.01–1.53 per 5 ng/m^3), PM_{10} Zn (1.28; 1.02–1.59 per 20 ng/m^3), PM_{10} S (1.58; 1.03–2.44 per 200 ng/m^3), PM_{10} Ni (1.59; 1.12–2.26 per 2 ng/m^3) and PM_{10} K (1.17; 1.02–1.33 per 100 ng/m^3). In two-pollutant models, associations between PM_{10} and $PM_{2.5}$ and lung cancer were largely explained by $PM_{2.5}$ S.

Conclusions: This study indicates that the association between PM in air pollution and lung cancer can be attributed to various PM components and sources. PM containing S and Ni might be particularly important.

Key words: air pollution; particulate matter; sulphur; nickel; cohort study; lung cancer

1. Introduction

We recently reported from the European Study of Cohorts for Air Pollution Effects (ESCAPE) that particulate matter (PM) in air pollution with a diameter < 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$) is associated with a risk for the development of lung cancer (Raaschou-Nielsen and others 2013). This result, among others, formed the basis for classification of outdoor air pollution and PM in outdoor air as carcinogenic to humans in a recent Monograph of the International Agency for Research on Cancer (Loomis and others 2013). Most knowledge about associations between air pollution and risk for lung cancer is based on measures of exposure to PM as a whole (Hamra and others 2014), sulphur oxide-related pollution (Dockery and others 1993; Pope III and others 2002), oxides of nitrogen (Nafstad and others 2003; Raaschou-Nielsen and others 2011) or cruder indicators such as proximity to traffic (Beelen and others 2008; Hystad and others 2013). PM is a complex mixture of particles from different sources with different composition. Little is known about the associations between specific components of PM and risk for cancer, although this could be of major importance in choosing the most efficient strategies for reducing the exposure of populations to carcinogenic air pollution.

As the concentrations of specific components of PM in air are often correlated, it is difficult to single out the specific components responsible for observed associations with health effects. A specific issue in air pollution epidemiology is to assess whether associations for specific components are stronger than associations for particle mass (Mostofsky and others 2012). Particle mass is used in air quality regulations. Associations with lung cancer have been indicated in studies of exposure to the PM components elemental Carbon (Garshick and others 2012; Steenland and others 1998) and polycyclic aromatic hydrocarbons (Yuan and others 2014), but, to our knowledge, no work on associations between exposure to other elements of PM and risk for lung cancer in general populations has been published. PM elements in air can serve as indicators of air pollution from different sources, but their compounds may also be carcinogenic for the lung *per se*, as seen for nickel (International Agency for Research on Cancer Monograph Working Group 2012).

Within the European study of Transport-related Air Pollution and Health Impacts—Integrated Methodologies for Assessing Particulate Matter (TRANSPHORM; www.transphorm.eu/), we analysed data from the 14 cohort of the ESCAPE (www.escapeproject.eu/) study on lung cancer where PM air pollution was measured to determine associations between elementary components of PM air pollution at the residence and risk for lung cancer. A secondary aim was to investigate whether any particular elementary component could explain the previously observed association between PM air pollution and lung cancer.

2. Methods

2.1 Study design and participants

We conducted a prospective study of data collected within the ESCAPE and TRANSPHORM projects. The 14 cohorts were in Sweden (European Prospective Investigation into Cancer and Nutrition[EPIC]-Umeå, Swedish National Study on Aging and Care in Kungsholmen [SNAC-K], Stockholm Screening Across the Lifespan Twin Study and TwinGene [SALT], Stockholm 60 years old and IMPROVE study [60-y/IMPROVE], Stockholm Diabetes Prevention Program [SDPP]), Norway (Oslo Health Study [HUBRO]), Denmark (Diet, Cancer and Health Study [DCH]), the Netherlands (EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands [MORGEN], EPIC-PROSPECT), the UK (EPIC-Oxford), Austria (Vorarlberg Health Monitoring and Prevention Programme [VHM&PP]), Italy (EPIC-Turin, Italian Studies of Respiratory Disorders in Childhood and Environment [SIDRIA]-Turin and Rome, and Greece (EPIC-Athens); Figure 1). Most of the study areas were large cities and the surrounding suburban or rural communities, as specified in Table 1 and in the online appendix (pp. 2–15). Information on lifestyle etc. among cohort participants was obtained by questionnaires or interviews at enrolment (see online appendix, Table S1). The use of cohort data was approved by the local ethical and data protection authorities. All participants signed informed consent forms at inception of the studies.

2.2 Procedures and lung cancer definition

Exposure was assessed in each area separately by standardised procedures. The association between long-term exposure to air pollution and incidence of lung cancer was analysed in each cohort separately at the local centre by common standardised protocols for outcome definition, confounder models and statistical analysis. Cohort-specific effect estimates were subsequently combined in a meta-analysis centrally. A pooled analysis of all cohort data was not possible because of data-transfer and privacy issues. We included cancers located in the bronchus and the lung (ICD10/ICDO3: C34.0–C34.9) and only primary cancers (i.e. not metastases); lymphomas in the lung (ICDO3 morphology codes 9590/3–9729/3) were not included. The cohort members were followed up for cancer incidence in national or local cancer registries, except in the SIDRIA cohorts in Italy and Athens. In the SIDRIA cohorts, hospital discharge and mortality register data were used. In Athens, cases were identified by active follow-up using questionnaires and telephone interviews with participants or next-of-kin, followed by verification of the cancer case through pathology records, medical records, discharge diagnosis or death certificates (online appendix, Table S1).

2.3 Exposure assessment

Air pollution concentrations at the baseline residential addresses of study participants were estimated by Land Use Regression (LUR) models following a standardized procedure that has been described elsewhere (de Hoogh and others 2013; Eeftens and others 2012a). In brief, air pollution monitoring campaigns were performed between October 2008 and May 2011 in all study areas. Three two-week measurements of particles with aerodynamic diameter <2.5μm ($PM_{2.5}$) and <10μm (PM_{10}) were performed at 20 sites in each cohort area. The three measurements were then averaged, adjusting for temporal trends using data from a background monitoring site with continuous data (Eeftens and others 2012a; Eeftens and others 2012b). PM 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 analyse elemental composition using X-Ray Fluorescence (XRF)(de Hoogh and others 2013). We collected information about potential predictor variables relating to nearby traffic intensity, population/household density and land use from Geographic Information Systems (GIS), and evaluated these to explain spatial variation of annual average concentrations using regression modelling. LUR model results for all study areas are shown in the online appendix (Tables S2-S9). The LUR models were evaluated using Leave-One-Out-Cross-Validation, which successively leaves one site out of the data and refits the model with the remaining N-1 sites. The LUR models were used to estimate ambient air pollution concentration at the participants' baseline addresses. 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 and others 2012)

We selected eight of the 48 measured elements for epidemiological evaluation (de Hoogh and others 2013; Tsai) on the basis of evidence for their health effects (toxicity), their representivity of major anthropogenic sources, a high percentage of detected samples (> 75%) and precise measurements. We selected Cu, Fe and Zn as indicators mainly of non-tailpipe traffic emissions such as brake and tyre wear; S mainly for long-range transport; Ni and V for mixed oil-burning and industry; Si for crustal material and K for biomass burning (de Hoogh and others 2013; Eeftens and others 2014; Viana and others 2008; Wang and others 2014). Each element can have multiple sources. Land use regression models for Cu, Fe, and Zn in both fractions (PM_{10} and $PM_{2.5}$) had average cross-validation explained variance (R2) between 52% and 84% with a large variability between areas (online appendix, Tables S2-S9). Traffic variables contributed to most of these models, reflecting nontailpipe emissions. Models for the other elements performed moderately with average cross-validation R2 generally between ~50% and ~60%. For $PM_{2.5}$ S the average cross-validation R2 was 32% with a range from 2 to 67%, consistent with the relatively low spatial variation of sulphur concentrations within the cohort areas.

2.4 Statistical analyses

Proportional hazards Cox regression models were fitted for each cohort, with age as the underlying time scale. Participants were followed up for lung cancer from enrolment until censoring. Participants with a cancer (except non-melanoma skin cancer) before enrolment were excluded. Others were censored at the time of death, a diagnosis of any other cancer (except non-melanoma skin cancer), emigration, disappearance, loss to follow-up for other reasons or end of follow-up, whichever came first. We censored participants with another cancer because cancer treatment and change of life style might change the subsequent risk for development of another cancer. The proportional hazards assumption was tested in our previous study with the identical set of potential confounders and no violation was observed (Raaschou-Nielsen and others 2013). Exposure to air pollution was analysed as a linear variable in three a-priori specified-confounder models identical to those applied previously (Raaschou-Nielsen and others 2013). Model 1 included gender, calendar time (year of enrolment, linear) and age (time axis). Model 2 included additional adjustment for smoking status (never, former, current), smoking intensity, $(\text{smoking intensity})^2$, smoking duration, time since quitting smoking, environmental tobacco smoke, occupation, fruit intake, marital status, educational level and employment status (all in reference to baseline). We entered a squared term of smoking intensity because we expected a non-linear association with lung cancer. Model 3 (the main model) included further adjustment for area-level socio-economic status, which might be correlated with both air pollution levels and lung cancer incidence rates and, thus, having the potential of being a confounder (Pope III and others 2002). The definition of area-level socio-economic status differed by cohort (online appendix, p. 2-15). In eight of the cohorts, income was used. In four cohorts, national or regional indices were used that incorporated multiple dimensions of SES. In one cohort education and another unemployment rate was used. In seven cohorts data was included at the municipality level, in the remaining five cohorts a smaller spatial scale was used (neighbourhood or census tract).

Information on at least age, gender, calendar time, smoking status, smoking intensity and smoking duration was available for all cohorts. Further information on the available variables for each cohort is given in the online appendix (pp. 2–15 and Table S10). We repeated the overall analyses after restriction to participants who had lived at the baseline address throughout the follow-up period, thus minimizing misclassification of long-term exposure relevant to the development of lung cancer in this sub-population.

First we fit models with one pollutant at a time and then we fit two-pollutant models for each element, including concentrations of particle mass ($PM_{2.5}$, PM_{10}, PM_{coarse}), $PM_{2.5}$ absorbance, NO_2 and NO_x, which were previously estimated at the cohort members' addresses (Raaschou-Nielsen and others 2013). The main purpose of the two pollutant analyses was to investigate whether the effect of the complex mixture can be represented better by individual components reflecting specific sources than with generic particle mass. We included cohort-specific results from two-pollutant models only if the Pearson correlation between the two pollutants was $\leq$ 0.7.

In the meta-analysis, we used random-effects models to pool the results for cohorts (DerSimonian and Laird 1986). I^2 statistics (Higgins and Thompson 2002) and p values for the χ^2 test from Cochran's Q were calculated to determine heterogeneity among cohort-specific effect estimates. Effect modification in relation to performance of the land-use regression models was tested with the χ^2 test of heterogeneity between meta-analysis estimates in two strata of cohorts, one stratum including cohorts with leave-one-out cross-validation R^2 below 0.50 and another stratum above.

We used a common STATA (www.stata.com) script for all analyses. All tests were two-sided, and p values < 0.05 were deemed statistically significant.

3. Results

The 14 cohorts in eight European countries consisted of 245 782 people, who contributed 3 229 220 person–years at risk; 1878 incident lung cancer cases were diagnosed during follow-up (average follow-up, 13.1 years) (Table 1). The details of each cohort, including the characteristics of participants, the available variables and their distribution, are given in the online appendix (pp. 2–15). Participants were recruited into most of the cohort studies in the 1990s. The number of participants and the number of lung cancer cases varied substantially among cohorts; the Austrian and Danish cohorts contributed more than half the lung cancer cases (Table 1).

Substantial variations in estimated annual mean concentrations of PM elements at participant addresses were found both within and between cohorts. Higher concentrations of all elements except Si were observed in southern study areas. For S, the variation within cohorts was smaller than that between cohorts. The patterns seen for $PM_{2.5}$ (Figure 2) and PM_{10} (online appendix, Figure S1) elements were similar. The correlation between PM constituents and their corresponding PM_{10} and $PM_{2.5}$ mass concentration differed widely across cohorts and PM constituent with typical median correlation coefficients between 0.4 and 0.6 (online appendix, Table S11).

In the overall analyses, exposure to all elements except V was associated with higher risks for lung cancer. None of these associations were statistically significant in model 3, the main model. Hazard ratios (HRs) were generally lower in models 2 and 3 than in the cruder model 1, consistent with our findings for $PM_{2.5}$ and PM_{10}; this difference in HRs between the models was due to adjustment for smoking (Raaschou-Nielsen and others 2013). The results for 14 of the element-particle size combinations showed no or low heterogeneity among the cohorts, whereas heterogeneity was observed in the risk estimates for $PM_{2.5}$ S (I^2=0.47; p=0.03) and $PM_{2.5}$ Ni (I^2=0.30; p=0.17) (Table 2).

In general, the results of the two-pollutant models showed little effect of mutual adjustment for elements, although the risk estimate for PM Cu was affected by adjustment for PM Fe and *vice versa* (online appendix Figures S2–3). The previously observed increased HR for lung cancer in association with PM_{10} and $PM_{2.5}$ was robust to adjustment for elements in two-pollutant models, although the association with PM_{10} was attenuated by adjustment for $PM_{2.5}$ S and the association with $PM_{2.5}$ was attenuated by adjustment for $PM_{2.5}$ S, $PM_{2.5}$ K and PM_{10} K. The HR associated with $PM_{2.5}$ S was robust to adjustment for PM_{10} and $PM_{2.5}$ (Table 3; online appendix, Figures S2–4).

Analyses restricted to participants who did not change residence during follow-up, implying less misclassification of long-term exposure, showed higher HRs than observed in the full population (Table 4). The higher HRs associated with exposure to $PM_{2.5}$ Cu, PM_{10} Zn and PM_{10} K among participants who did not change residence were not due to selection of cohorts for whom this information was available, whereas selection might have played a minor role in the higher risk estimates associated with PM_{10} S, $PM_{2.5}$ S and PM_{10} Ni (Table 4). We observed statistically significant associations in non-movers between risk for lung cancer and exposure to $PM_{2.5}$ Cu (HR, 1.25; 95% CI, 1.01–1.53 per 5 ng/m^3), PM_{10} Zn (1.28; 1.02–1.59 per 20 ng/m^3), PM_{10} S (1.58; 1.03–2.44 per 200 ng/m^3), PM_{10} Ni (1.59; 1.12–2.26 per 2 ng/m^3) and PM_{10} K (1.17; 1.02–1.33 per 100 ng/m^3). None of these estimates from the meta-analysis showed signs of heterogeneity between cohort-specific HRs (Table 4). $PM_{2.5}$ S was associated with a high HR, which, was not, however, statistically significant; this result was based on heterogeneous cohort-specific results (I^2=0.57; p=0.01). Forest plots for exposure of participants who did not change residence to all 16 PM components are shown in the online appendix (Figures S5–20); the different contributions of the cohorts to the meta-analysis estimates reflect differences in number of lung cancer cases and the contrast of exposure.

There was no statistically significant difference in meta-analysis HRs for any PM element between cohorts with land-use regression models showing leave-one-out cross-validation R2 values below and above 0.50, respectively (all p were > 0.20) (results not shown).

4. Discussion

This study shows non-significantly elevated HRs for lung cancer associated with concentrations of Cu, Fe, Zn, S, Ni, Si and K in airborne PM at the residence. Analyses restricted to participants who did not change residence during follow-up showed elevated HRs for all PM elements, which were larger than for the full population. Associations were statistically significant for $PM_{2.5}$ Cu, PM_{10} Zn, PM_{10} S, PM_{10} Ni and PM_{10} K. Adjustment for other pollutants in two-pollutant models had little effect on risk estimates, with the exception of $PM_{2.5}$ S: adjustment for $PM_{2.5}$ S reduced the HR for $PM_{2.5}$ and PM_{10}, whereas the HR for $PM_{2.5}$ S was robust to adjustment for PM mass.

4.1 Previous studies

Our previous study based on ESCAPE data showed associations between risk for lung cancer and PM in air pollution (Raaschou-Nielsen and others 2013). PM concentrations were estimated from land-use regression models that included variables for the densities of population, household, traffic and streets in the cohort areas and variables for ports and industry in some areas, indicating that PM from multiple sources may be related to the lung cancer risk. In line with this, the present study showed associations between lung cancer and multiple PM components from different sources, including fossil fuel combustion, e.g. in shipping, residential heating, industry and road traffic and non-tailpipe traffic emissions (Viana and others 2008).

In the two-pollutant models, $PM_{2.5}$ S was more robustly associated with risk for lung cancer than $PM_{2.5}$ or PM_{10} (Table 3). In both the Harvard Six Cities Study (Dockery and others 1993) and the American Cancer Society Study on Particulate Air Pollution and Mortality (ACS study) (Pope III and others 1995), associations were found between sulphate air pollution and lung cancer mortality, in addition to the associations reported for $PM_{2.5}$ (Krewski and others 2000). A strong correlation between $PM_{2.5}$ and sulphate air pollution, however, made it difficult to disentangle their effects in previous studies. The correlation between $PM_{2.5}$ and sulphate was 0.98 in the Harvard Six Cities Study (Krewski and others 2000) and 0.73 in the ACS study (Pope III and others 1995); in the present study, the correlation was more moderate with a range between 0.26 and 0.67 (mean: 0.47) (online appendix, Table S11).

Previous studies of occupational exposure to nickel compounds have convincingly established associations with cancers of the lung, nasal cavity and paranasal sinuses (International Agency for Research on Cancer Monograph Working Group 2012); we also found an association with PM_{10} Ni. Although inhalation of Ni from ambient air is considered to be a minor route of exposure for the general population, it is present in combusted fossil fuel, which is the major contributor of atmospheric Ni (International Agency for Research on Cancer Monograph Working Group 2012). The association observed in the present study could be due to Ni compounds *per se* or their presence in pollution from fossil fuel combustion.

4.2 Sulphur in PM

In this study, PM S was associated with risk for lung cancer, although the relation was statistically significant only for PM_{10} S among people who did not change residence during follow-up. The result for $PM_{2.5}$ S was based on heterogeneous cohort-specific results (with seven HRs above 1 and three HRs below 1) and therefore less robust than the estimates for other elements. Further, the established association between the overall, mass-based PM measures and risk for lung cancer (Loomis and others 2013) could to a great extent be explained by $PM_{2.5}$ S in the two-pollutant models, whereas the HR associated with $PM_{2.5}$ S was virtually unaffected by adjustment for PM mass. Acknowledging the caveats of two-pollutant models to investigate effects of complex mixtures (Mostofsky and others 2012), these findings indicate a more robust association with $PM_{2.5}$ S than with the two PM mass measures (PM_{10} and $PM_{2.5}$). The correlation between S and PM mass was generally moderate (median correlation coefficient = 0.48 for $PM_{2.5}$ and 0.32 for PM_{10}) and PM is affected by many more sources than long-range transport of sulphur containing particles.

Arguments for a particular role of $PM_{2.5}$ S in PM-associated lung carcinogenicity include the relatively high HR associated with $PM_{2.5}$ S (Tables 2 and 4) and the finding that $PM_{2.5}$ S explained some of the associations between $PM_{2.5}$ and PM_{10} and risk for lung cancer in two-pollutant models. The association between $PM_{2.5}$ S and risk for lung cancer was, however, sensitive to adjustment, never reached statistical significance and showed statistically significant heterogeneity between cohort-specific HRs in the meta-analysis. Further, sulphate particles, which make up a large proportion of PM S in ambient air, are not known to be carcinogenic. S in PM probably represents a mixture of pollutants that is also rich in other (secondary) combustion-related components, such as secondary organics or polycyclic aromatic hydrocarbons. More studies are needed to determine the role of S and associated components in the carcinogenicity of PM in air pollution.

4.3 Strengths and limitations

The study benefited from a large number of participants in the 14 cohort studies, widely different levels of air pollution and virtually complete follow-up. The strengths of our study also include the use of standardised protocols for exposure assessment and data analysis. We assessed multiple PM elements, with a high percentage of detectable samples and highly precise measurements in all 14 cohorts. Further, we took advantage of exposure assessment at address level, such that within-city contrasts in PM element concentrations were used in the risk analyses. We adjusted the analyses for a number of potential confounders. In particular, all cohort-specific analyses were adjusted for the important smoking variables smoking status, smoking intensity and smoking duration. Other potential confounding factors affected the risk estimates associated with PM only marginally (Raaschou-Nielsen and others 2013), although the possibility of residual confounding or confounding from risk factors not accounted for, such as radon, cannot be excluded.

The study also benefited from knowledge about residential mobility during follow-up. Exposure was assessed at the address at the time of enrolment, and some participants changed residence after enrolment. We conducted an additional analysis including only participants who did not change residence during follow-up in order to obtain a more precise assessment of long-term exposure. The stronger associations between PM elements and risk for lung cancer in this sub-population add credibility to our findings. Information about addresses and exposure from several decades before enrolment would have been ideal due to the long incubation period for lung cancer. Such information would also have facilitated analyses of latency periods, which our data did not permit.

Our study has some limitations. We used measurements made in 2008–2011 to develop land use regression models but applied them to addresses of participants at baseline, which was mainly 10–15 years earlier. Recent research in Canada, Italy and the Netherlands shows, however, that spatial contrasts of NO_2 are stable over 10-year periods (Cesaroni and others 2012; Eeftens and others 2011; Wang and others 2013), and spatial models for black smoke in the United Kingdom provided reasonable predictions, even going back to the 1960s (Gulliver and others 2011). We cannot rule out the possibility that the spatial contrast was less stable for specific elements. The information about potential confounders was collected at baseline and would therefore not reflect changes in life style after baseline. The mean age of the participating cohort members ranged from 43 to 73 years and we believe that life style in these age groups is more stable than earlier in life.

We used land-use regression models to estimate exposure to PM elements, which involves some degree of misclassification. Any misclassification would, however, be non-differential and would consequently not be expected to create artificial associations. In the two-pollutant models, different degrees of misclassification of PM elements would affect the results. Thus, when two PM elements are correlated, some of the association between lung cancer and the element with greater misclassification could be shifted to the risk estimate for the element with less misclassification. Measurement precision was best for S, Cu and Fe but poorer for Ni and V (de Hoogh and others 2013), but the performance of the land use regression model for S was among the lowest when evaluated by the model R^2. Therefore, a lower degree of misclassification hardly explains why $PM_{2.5}$ S rather than other elements accounted for the associations between PM_{10} and $PM_{2.5}$ and risk for lung cancer. Two pollutant models can be difficult to interpret especially if the same sources contribute to several PM components and create high correlations. Further, only two of the many PM constituents were included in each model. The results of these models, thus, should not be interpreted as the independent effect of the specific element but rather as a representation of the effect of a complex mixture. Still, they can contribute to a better understanding of the PM mixture and its association with risk for lung cancer.

Analysis of eight elements in two different PM fractions involved 16 main analyses and 16 analyses of participants who did not change residence during follow-up; we therefore cannot exclude the possibility that some of the significant associations were due to multiple testing.

4.4 Conclusion

In conclusion, associations with risk for lung cancer were found with several PM elements from different sources; the strongest associations were seen for participants who did not change their address during follow-up. Considering strengths and limitations, this study indicates that the association between PM in air pollution and lung cancer can be attributed to various PM components and sources; S- and Ni-containing PM might be particularly important, but this must be confirmed in future studies.

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Supplementary data

Supplementary data are available online.

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Table 1. Characteristics of 14 cohorts, lung cancer cases, mean particulate matter concentrations and smoking prevalence among participants at baseline

Cohort[a]	Study area	N participants	N lung cancer cases[b]	Mean age at baseline; years (SD)	Baseline period	Mean follow-up time (years)	Person-years at risk	$PM_{2.5}$ (µg/m^3); mean (SD))	PM_{10} (µg/m^3); mean (SD))	Present/ex-/never smokers (%)
HUBRO	City of Oslo, Norway	17,640	75	47.8 (15.0)	2000-2001	8.5	150,424	8.9 (1.3)	13.5 (3.1)	26/27/47
SNAC-K	City of Stockholm, Sweden	2384	18	73.1 (10.7)	2001-2004	5.8	13,840	8.0 (1.3)	16.4 (6.0)	14/37/49
SALT/Twin gene	Stockholm County, Sweden	4731	29	57.9 (10.2)	1998-2002	8.3	39,263	7.3 (1.3)	14.9 (3.9)	24/36/40
60-y/IMPROVE	Stockholm County, Sweden	3813	38	60.4 (0.1)	1997-1999	11.2	42,553	7.3 (1.3)	15.0 (3.8)	21/38/41
SDPP	Stockholm County, Sweden	7116	35	47.1 (5.0)	1992-1998	13.5	96,257	6.6 (1.2)	13.6 (3.2)	26/36/38
DCH	City of Copenhagen and surrounding areas, Denmark	37,447	638	56.8 (4.4)	1993-1997	12.4	463,525	11.3 (0.9)	17.1 (1.9)	37/28/35
EPIC-MORGEN	Cities of Amsterdam, Maastricht and Doetinchem and surrounding rural areas,	15,993	92	43.7 (10.7)	1993-1997	12.1	193,042	16.9 (0.6)	25.6 (1.7)	36/29/35

	Netherlands									
EPIC-PROSPECT	City of Utrecht and surrounding rural areas, Netherlands	14,630	112	57.6 (6.0)	1993-1997	11.5	168,599	16.8 (0.5)	25.3 (1.2)	22/33/45
EPIC-Oxford	Urban and rural areas in a zone of 10 km around London-Oxford area, United Kingdom	8132	24	45.5 (13.0)	1993-2001	11.1	97,556	10.2 (1.0)	16.9 (1.9)	12/27/61
VHM&PP	State of Vorarlberg, excluding high mountain areas (> 600 m) and areas within 300 m of State border, Austria	108,018	678	42.8 (14.9)	1985-2005	15.6	1,679,225	13.6 (1.2)	20.7 (2.4)	13/7/80
EPIC-Turin	City of Turin, Italy	7216	48	50.4 (7.6)	1993-1998	12.1	87,147	30.1 (2.0)	46.6 (4.6)	25/32/43
SIDRIA-Turin	City of Turin, Italy	4816	19	44.0 (6.2)	1999	10.5	50,590	31.0 (1.7)	48.1 (4.1)	42/21/38
SIDRIA-Rome	City of Rome, Italy	9105	53	44.3 (6.0)	1999	11.2	102,027	19.4 (1.8)	36.5 (5.0)	42/23/35
EPIC-Athens	Greater Athens Area, Greece	4096	18	49.0 (11.7)	1994-1999	11.0	45,173	20.4 (2.7)	45.2 (13.7)	41/20/39

Table 2. Pooled hazard ratios for lung cancer in association with exposure to elemental components of PM* for all participants and measures of heterogeneity between underlying cohort-specific results. Pooled hazard ratios and heterogeneity derive from random-effects meta-analyses with confounder models 1, 2 and 3†.

Exposure	No. of cohorts	No. of lung cancer cases	Model 1†	Model 2†	Model 3†	Measures of heterogeneity‡	
			HR (95% CI)			I^2 (%)	p§
$PM_{2.5}$ Cu	14	1,878	1.21 (1.04-1.41)	1.11 (0.95-1.30)	1.13 (0.96-1.32)	0	0.61
PM_{10} Cu	14	1,878	1.14 (1.03-1.26)	1.07 (0.96-1.18)	1.07 (0.97-1.19)	0	0.62
$PM_{2.5}$ Fe	14	1,878	1.19 (1.06-1.33)	1.06 (0.92-1.22)	1.08 (0.92-1.27)	16	0.28
PM_{10} Fe	14	1,878	1.14 (1.01-1.28)	1.05 (0.93-1.18)	1.05 (0.93-1.19)	0	0.78
$PM_{2.5}$ Zn	14	1,878	1.00 (0.91-1.11)	0.99 (0.90-1.10)	1.02 (0.92-1.12)	0	0.74
PM_{10} Zn	14	1,878	1.11 (0.98-1.24)	1.05 (0.93-1.18)	1.08 (0.96-1.22)	0	0.59
$PM_{2.5}$ S	14	1,878	1.76 (1.29-2.39)	1.31 (0.76-2.25)	1.34 (0.74-2.42)	47	0.03
PM_{10} S	14	1,878	1.18 (0.94-1.49)	1.03 (0.81-1.30)	1.03 (0.81-1.31)	0	0.70
$PM_{2.5}$ Ni	10¶	1,758	1.15 (0.81-1.62)	1.04 (0.74-1.47)	1.02 (0.74-1.41)	30	0.17
PM_{10} Ni	13**	1,803	1.39 (1.04-1.88)	1.17 (0.94-1.45)	1.15 (0.93-1.42)	0	0.70
$PM_{2.5}$ V	12††	1,125	1.24 (0.80-1.91)	0.97 (0.75-1.26)	0.92 (0.71-1.21)	0	0.74
PM_{10} V	14	1,878	1.07 (0.69-1.65)	0.94 (0.67-1.33)	0.93 (0.68-1.26)	10	0.34
$PM_{2.5}$ Si	12‡‡	1,785	1.11 (0.90-1.38)	1.10 (0.89-1.37)	1.12 (0.90-1.40)	0	0.72
PM_{10} Si	14	1,878	1.12 (0.87-1.46)	1.03 (0.90-1.18)	1.04 (0.90-1.21)	3	0.42
$PM_{2.5}$ K	14	1,878	1.06 (0.91-1.23)	1.02 (0.92-1.13)	1.03 (0.93-1.14)	0	0.64
PM_{10} K	13**	1,803	1.05 (0.94-1.17)	1.05 (0.95-1.16)	1.06 (0.96-1.17)	0	0.67

* HRs 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.

† Model 1: age (time scale in Cox model), sex, calendar time; model 2: Model 1 + smoking status, smoking intensity, $(\text{smoking intensity})^2$, smoking duration, time since quitting smoking, environmental tobacco smoke, occupation, fruit intake, marital status, educational level, employment status; model 3: Model 2 + area-level socio-economic status. We included only participants for whom data were not missing for any of the variables included in model 3, thus using an identical data set for analyses with all three models

‡ Relating to model 3

§ Cochran test for heterogeneity

q No modelled air pollution estimates available for SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP

**No modelled air pollution estimates available for HUBRO

†† No modelled air pollution estimates available for HUBRO, VHM&PP

‡‡ No modelled air pollution estimates available for HUBRO, EPIC-Athens

Table 3. Hazard ratios for lung cancer associated with exposure to $PM_{2.5}$ (per 5 µg/m^3), PM_{10} (per 10 µg/m^3) and $PM_{2.5}$ S (per 200 ng/m^3) both in one pollutant and in mutually adjusted two-pollutant models. The results derive from random-effects meta-analyses of cohort-specific results using confounder model 3*.

Pollutant	Second pollutant adjusted for	No. of cohorts	HR (95% CI)
$PM_{2.5}$	None	14	1.20 (0.97-1.49)
$PM_{2.5}$	$PM_{2.5}$ S	14	1.02 (0.80-1.31)
PM_{10}	None	14	1.23 (1.04-1.46)
PM_{10}	$PM_{2.5}$ S	14	1.11 (0.91-1.35)
$PM_{2.5}$ S	None	14	1.34 (0.74-2.42)
$PM_{2.5}$ S	$PM_{2.5}$	14	1.30 (0.71-2.38)
$PM_{2.5}$ S	PM_{10}	14	1.28 (0.67-2.43)

*Model 3: age (time scale in Cox model), sex, calendar time, smoking status, smoking intensity, (smoking intensity)^2, smoking duration, time since quitting smoking, environmental tobacco smoke, occupation, fruit intake, marital status, educational level, employment status, area-level socio-economic status

Table 4. Hazard ratios for lung cancer in association with exposure to elemental components of PM* for participants who did not change residence during follow-up and measures of heterogeneity between the underlying cohort-specific results. The results derive from random-effects meta-analyses with confounder model 3†

	Participants who did not change residence					All participants (same cohorts)
				Measure of heterogeneity		
Exposure	No. of cohorts	No. of lung cancer cases	HR (95% CI)	I^2 (%)	P‡	HR (95% CI)
$PM_{2.5}$ Cu	10§	893	1.25 (1.01-1.53)	0	0.67	1.14 (0.97-1.35)
PM_{10} Cu	10§	893	1.14 (0.96-1.35)	16	0.30	1.08 (0.96-1.20)
$PM_{2.5}$ Fe	10§	893	1.08 (0.93-1.25)	0	0.63	1.08 (0.90-1.29)
PM_{10} Fe	10§	893	1.10 (0.94-1.28)	0	0.81	1.05 (0.92-1.20)
$PM_{2.5}$ Zn	10§	893	1.11 (0.88-1.39)	0	0.57	0.99 (0.83-1.17)
PM_{10} Zn	10§	893	1.28 (1.02-1.59)	0	0.74	1.09 (0.92-1.30)
$PM_{2.5}$ S	10§	893	2.05 (0.73-5.75)	57	0.01	1.47 (0.65-3.30)
PM_{10} S	10§	893	1.58 (1.03-2.44)	6	0.39	1.10 (0.85-1.44)
$PM_{2.5}$ Ni	6¶	804	1.13 (0.77-1.65)	0	0.68	1.01 (0.73-1.41)
PM_{10} Ni	9**	839	1.59 (1.12-2.26)	0	0.44	1.29 (0.96-1.72)
$PM_{2.5}$ V	8††	621	1.07 (0.71-1.61)	0	0.96	1.02 (0.70-1.49)
PM_{10} V	10§	893	1.12 (0.77-1.64)	0	0.47	1.01 (0.70-1.45)
$PM_{2.5}$ Si	8‡‡	821	1.26 (0.85-1.86)	33	0.17	1.11 (0.88-1.41)
PM_{10} Si	10§	893	1.13 (0.95-1.36)	0	0.54	1.02 (0.88-1.18)
$PM_{2.5}$ K	10§	893	1.18 (0.99-1.40)	0	0.46	1.02 (0.92-1.14)
PM_{10} K	9**	839	1.17 (1.02-1.33)	0	0.68	1.07 (0.96-1.18)

* HRs 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.

† Model 3: age (time scale in Cox model), sex, calendar time, smoking status, smoking intensity, (smoking intensity)^2, smoking duration, time since quitting smoking, environmental tobacco smoke, occupation, fruit intake, marital status, educational level, employment status, area-level socio-economic status.

‡ Cochrans test for heterogeneity

§ HUBRO, SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP, DCH, VHM&PP, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens

q HUBRO, DCH, VHM&PP, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens

** SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP, DCH, VHM&PP, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens

†† SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP, DCH, SIDRIA-Turin, SIDRIA-Rome, EPIC-Athens

‡‡ SNAC-K, SALT/Twin gene, 60-yr/IMPROVE, SDPP, DCH, VHM&PP, SIDRIA-Turin, SIDRIA-Rome

Figure 1

Figure 1. Cohort locations. Four cohorts were located in Stockholm, two in the Netherlands and two in Turin.

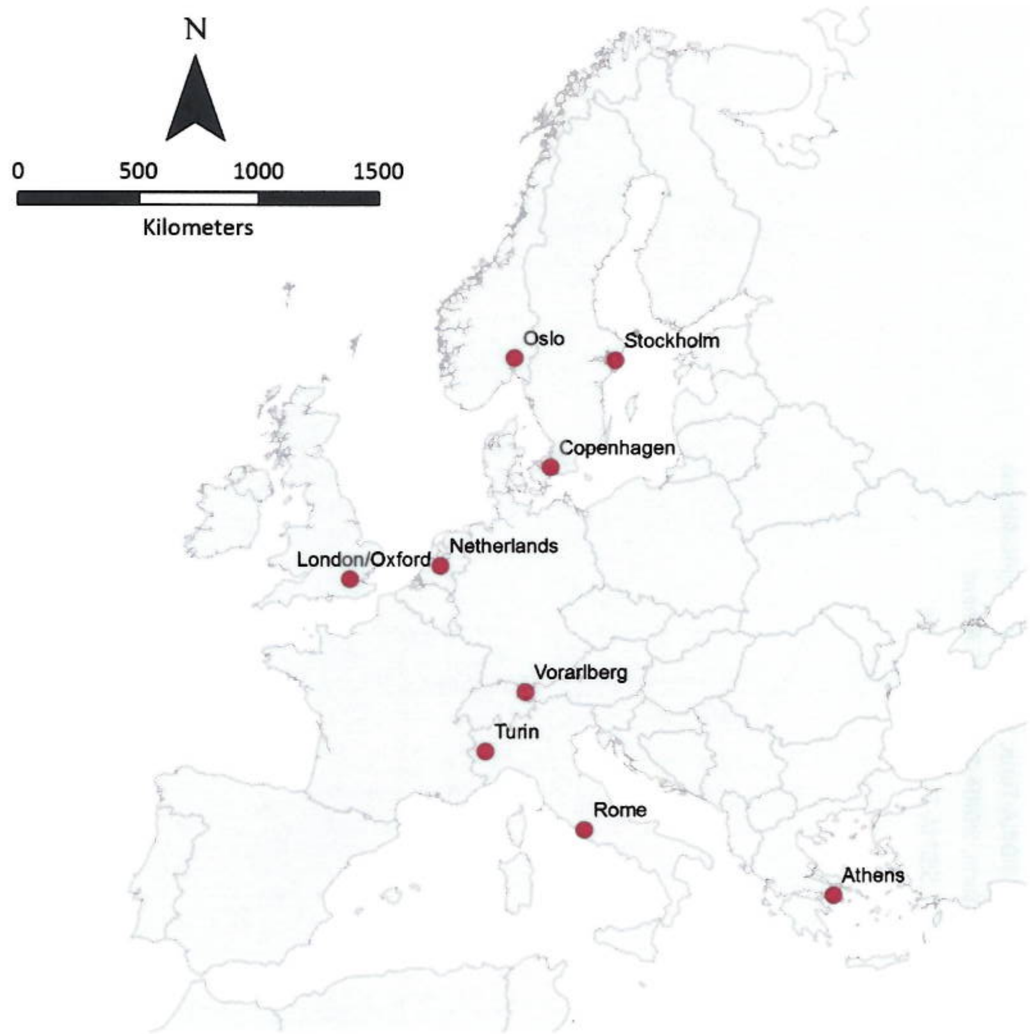
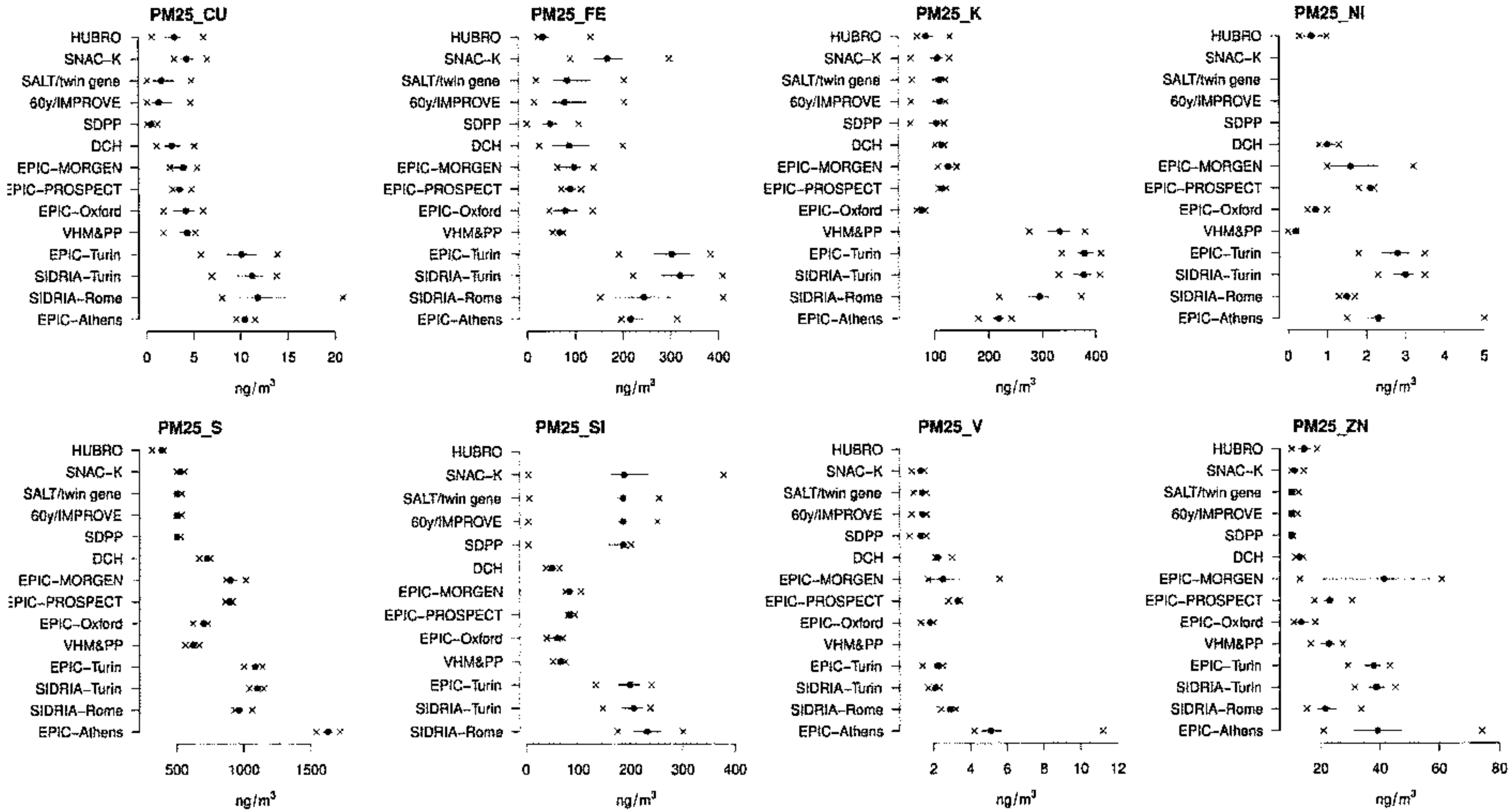


Figure 2

Figure 2: Estimated annual mean concentrations (ng/m^3) of $PM_{2.5}$ elemental components at participants' addresses in each cohort. The solid circles and bars show the median and 25% and 75% percentile concentrations; the x shows the 5% and 95% percentile values.



Supplementary Information
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