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Title: Elemental composition of particulate matter and the association with lung function in 5 European birth cohorts – results of the ESCAPE & TRANSPHORM projects

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ABSTRACT

Background

Negative effects of long-term exposure to particulate matter (PM) on lung function have been shown repeatedly. Spatial differences in the composition and toxicity of PM may explain differences in observed effect sizes between studies.

Methods

We conducted a multi-centre study in 5 European birth cohorts: BAMSE (Sweden), GINIplus and LISAplus (Germany), MAAS (UK) and PIAMA (The Netherlands), for which lung function measurements were available for ages 6-8 years. Individual annual average residential exposure to copper, iron, potassium, nickel, sulphur, silicon, vanadium and zinc within PM <2.5µm and <10µm was estimated using land-use regression models. Associations between air pollution and lung function were analysed by linear regression within cohorts, adjusting for potential confounders, and then combined by random effects meta-analysis.

Results

We observed small reductions in forced expiratory volume in the first second, forced vital capacity and peak expiratory flow related to exposure to most elemental pollutants, some of which (sulphur, nickel), showed more substantial negative associations. E.g. PM_{10} nickel and PM_{10} sulphur were associated with decreases in forced expiratory volume in the first second of 1.6% (95% confidence interval 0.4,2.7%) and 2.3% (-0.1,4.6%) per increase in exposure of 2 ng/m³ and 200 ng/m³, respectively. Associations remained after adjusting for PM mass. However, associations with these elements were not evident in all cohorts and heterogeneity was larger than for PM mass.

Conclusions

While we detected small associations between lung function and annual average levels of some of the evaluated elements, particularly nickel and sulphur, lower lung function was more consistently associated with? increased PM mass.

1 Introduction

Particulate matter (PM) has been widely regarded as serious problem for public health.[1-3] Environmental guidelines and standards refer to the mass concentration of particles smaller than 10 μm (PM_{10}) or smaller than 2.5 μm ($PM_{2.5}$).[4-6] However, PM is emitted from a wide variety of sources (e.g. combustion, wear of brakes, tires and clutch, industrial emissions, and crustal materials) [7,8], and there is increasing epidemiological evidence that its constituents affect health in different ways.[8] Knowing more specifically which elements or sources are responsible for the toxicity of PM, may be instrumental in preventing adverse health effects more effectively.[8,9]

Lung function is an objective marker for respiratory health and a predictor of cardiorespiratory morbidity and mortality.[10] Negative long-term effects of PM on lung function have been shown repeatedly.[2,11] A recently published study also found significant effects of both nitrogen oxides and $PM_{2.5}$ on forced expiratory volume in the first second and peak expiratory flow in the same cohorts used in the present paper, and found higher levels of heterogeneity for PM (especially PM_{10}) than for nitrogen oxides.[12] Associations between PM and forced expiratory volume in the first second differ between studies [11,13], which may be partly due to spatial differences in PM composition and -hence- toxicity of particulate air pollutants. Recent reviews identified little conclusive evidence on the ability of specific PM constituents to affect especially long-term respiratory health.[1,2,14,15] Some studies have looked at short-term effects of PM composition on lung function [16,17], but to our knowledge, the health effects of long-term exposure to specific metal constituents on lung function have not been studied so far. There is a need for studies which disentangle the differential effects on lung function which might result from various PM constituents.[18] This paper aims to

investigate the associations between 8 elemental constituents of fine PM (Copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulphur (S), silicon (Si), vanadium (V) and zinc (Zn)) and lung function in five European birth cohorts, using standardized assessment methods. Furthermore, we examine if previously observed negative effects of $PM_{2.5}$/PM_{10} on lung function, can be attributed to any of these 8 elemental constituents.

The current study is part of the ESCAPE (European Study of Cohorts for Air Pollution Effects; www.escapeproject.eu) and TRANSPHORM (Transport related Air Pollution and Health impacts- Integrated Methodologies for Assessing Particulate Matter; www.transphorm.eu) projects.

2 Methods

2.1 Study population

Our analysis included five European birth cohorts: the Barn Allergi Milio Stockholm Epidemiologi (BAMSE) study from Sweden, the German Infant Nutritional Intervention study – plus influence of pollution and genetics (GINIplus) and the Lifestyle-related factors on the Immune System and development of Allergies in childhood – plus the influence of traffic emissions and genetics (LISAplus), both from Germany, the Manchester Asthma and Allergy Study (MAAS) from the UK and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study from the Netherlands. All cohorts were initiated in the mid- to late 1990s to study the onset and development of asthma and allergies during childhood in relation to various environmental factors. More information about study designs and study populations is provided in SDC 1. Data from sub-cohorts GINIplus North (Wesel) and GINIplus South (Munich) were analysed separately to prevent between-area differences in estimated exposure affecting the results. Data from GINIplus and LISAplus North (both Wesel, Ruhr Area) were

analysed jointly since the same procedures were followed. From these cohorts, we selected all participants with successful lung function measurements at ages 6-8 years, exposure estimates at the 6/8-year address, and complete information on all main confounders. We included 1808 children from Stockholm County, 600 from Munich, 851 from Wesel, 500 from Manchester and 900 from The Netherlands (SDC 1).

2.2 Exposure assessment

We selected 8 elements (Cu, Fe, K, Ni, S, Si, V and Zn), reflecting a variety of anthropogenic sources such as brake linings (Cu, Fe, Zn) and tyre wear (Zn), industrial (smelter) emissions (Fe, Zn), crustal materials (Si, K), fossil fuel combustion (Ni, V, S) and biomass burning (K), considering existing evidence for toxicity[14,15,19,20] and ensuring a high percentage (>75%) of detected samples. Elemental concentrations were estimated for each individual address using land-use regression models developed for each of the 5 study areas.[21] Briefly, between October 2008 and February 2010, three 14-day particulate matter measurements were taken at 20 locations in Stockholm County, Manchester, Ruhr Area and Munich/Augsburg study areas, and 40 sites in the Netherlands/Belgium in the cold, intermediate and warm seasons. We used Harvard impactors to collect samples of $PM_{2.5}$ and PM_{10} on Teflon filters and analysed all filters for elemental composition using X-Ray Fluorescence, as described elsewhere.[21] For each site, results from the 3 measurements were averaged to estimate the annual average, by adjusting for temporal variation using a centrally located background reference site, which was operated for a whole year in each study area.[22] Predictor variables on various metrics of nearby traffic intensity, population/household density and land use (e.g. industry, ports, urban green) were derived from Geographic Information Systems (GIS) in circular buffers ranging from 25 to 5000 m, and were evaluated to explain spatial variation of elemental concentrations.[23] Area-specific Land Use Regression models were made separately for each

element within each PM size fraction, as presented previously.[21] A brief overview of model performance can be found in SDC 2. With the exception of Zn, elements were predominantly found in either $PM_{2.5}$ (K, Ni, S, V) or PM_{10} (Cu, Fe, Si).[21] This made it less useful to subtract $PM_{2.5}$ from PM_{10} for elemental composition than for mass. We assumed that the composition of PM_{10} was primarily representative for the coarse component. If no significant predictors could be included in a land use regression model, we did not estimate cohort exposures as all would be the same. Therefore, there were no exposures estimated for the $PM_{2.5}$ Ni in Stockholm, $PM_{2.5}$ V in Munich, and $PM_{2.5}$ K in Wesel and Manchester. The relevant geographic predictors were derived for the cohort addresses. Whenever a predictor had a lower or higher value for one of the cohort addresses than for any of the measurement sites, its value was truncated to (respectively) the minimum or maximum which occurred for the measurement sites. Exposures to each element were estimated for the birth and 6/8-year addresses. The second was the main exposure, because we observed stronger associations with lung function than for the birth address in our previous analyses.[12]

2.3 Health outcomes

At age 6 years (in the Munich and Wesel cohorts) or age 8 years (in the Stockholm County, Manchester and Dutch cohorts), all children performed spirometry tests and a Peak Expiratory Flow test (except for the Manchester cohort), adhering to the guidelines recommended by the European Respiratory Society and the American Thoracic Society.[24] More detailed descriptions of the lung function measurements can be found in SDC 1. As our primary outcome, we assessed forced expiratory volume in the first second, which was available for all cohorts, has high reproducibility and reflects airway obstruction.[25] As 6-year old children can generally perform reliable spirometry, but have shorter expiratory times. forced expiratory volume in the first second cannot always be reliably determined. We therefore used forced

196 expiratory volume in the first 0.5 seconds instead, for the German cohorts which were
197 measured at age 6. In addition, we studied forced vital capacity and peak expiratory flow,
198 which (respectively) were available for all except the German and Manchester cohorts.

199 2.4 Statistical analyses

200 We used linear regression to analyze associations between exposure estimates and lung
201 function (log-transformed forced expiratory volume in the first second, forced vital capacity
202 and peak expiratory flow). Elemental concentrations were entered as continuous variables
203 without transformation. Effect estimates were calculated for fixed increments, chosen by
204 rounding the mean P10-P90 range for all ESCAPE study areas. We further checked for
205 collinearity of predictor variables using a correlation matrix and variance inflation factor.
206
207 Data analyses were performed at IRAS, Utrecht University, the Netherlands, for the Dutch
208 and German cohorts using SAS (SAS 9.2, Cary, NC, USA). Analyses for the Stockholm
209 County and Manchester cohorts were done locally, using STATA (Version 11, StataCorp LP,
210 College Station, TX, USA) and SPSS v20 (SPSS Inc.,), respectively. Cohort-specific
211 estimates were combined using random effect meta-analyses to account for heterogeneity
212 between the cohorts.[26] We used the I^2 statistic to quantify heterogeneity.[27] . Meta-analyses
213 were performed in STATA (Version 12, StataCorp LP, College Station, TX, USA) using the
214 "metan" command.

215 2.5 Confounding variables

216 A common set of potential confounders were defined *a priori* for all cohorts, following our
217 previous analysis.[12] In a crude model, we only adjusted for gender and log-transformed age
218 weight, and height. In addition, we adjusted for individual categorical confounders which

were not on the causal pathway, but were significant ($p<0.05$) risk factors for the outcome in at least one cohort: recent respiratory infections, non-native ethnicity (binary, as few children were of non-native ethnicity), parental socio-economic status, atopic mother, atopic father, breastfeeding, maternal smoking during pregnancy, environmental tobacco smoke, dampness or mould in the home, furry pets in the home and study area (only for the Stockholm County cohort). We did not adjust for short-term exposures as daily concentration data on PM constituents were not available for the study areas, and no indication of confounding of long-term associations by short-term exposures was found previously.[12] All confounder information was available from questionnaires for all cohorts. Covariates were defined as similarly as possible given the available information.

2.6 Two-pollutant models

Because of the correlations between many elemental constituents and PM mass (particularly Cu, Fe, S, Si), associations found for these elements may be biased and instead reflect a relationship with PM mass. We used two-pollutant models with elemental concentrations adjusting for $PM_{2.5}$ or PM_{10} mass to assess the independent effects of specific constituents. We also present associations with $PM_{2.5}$ and PM_{10} mass, adjusted for each of their constituents. For the main outcome, forced expiratory volume in the first second, we also present two-pollutant models for all other combinations of the pollutants and constituents.

2.7 Sensitivity analyses

Some elemental constituents were highly correlated with PM mass, which resulted in collinearity in some PM mass-adjusted models. In order to check if this affected the effect estimates, we removed all models for which the Variance Inflation Factor of the elemental constituent was higher than 3, from the meta-analysis.

We investigated if effect estimates changed, if in the meta-analysis we excluded those cohorts and elements for which the land use regression models had relatively low cross-validation R^2's[21], by excluding 26 (out of 80) exposure models with Leave-One Out Cross Validation R^2's lower than 0.50.

In our previous analysis,[12] lung function was associated with exposure at the 6/8-year address, and not with exposure at the birth address. To verify the contribution of exposure at different time points, we conducted an analysis, including both estimated exposures from the birth address and the 6/8-year address as co-pollutants, for those children who moved since birth. In addition, we performed separate analyses for children who moved and who did not move since birth, and for asthmatic and non-asthmatic children.

3 Results

3.1 Characteristics of the study population

Distributions of lung function indicators and population characteristics for each cohort can be found in Table 1. The Stockholm County cohort had a relatively low percentage of children with atopic parents. The Manchester cohort had a higher percentage of asthmatic children compared to the other cohorts (Table 1).

3.2 Distribution and correlation of air pollution exposures

The within-cohort variability of estimated pollutant concentrations differed widely between cohorts (Figure 1). There was large within-cohort variation for elements from non-tailpipe emissions (Cu, Fe, Zn), especially in PM_{10}. Exposure levels for these elements were relatively comparable for all cohorts. Similar levels were also observed for Ni, although the within-

265 cohort variation was limited for the Munich and Manchester cohorts, because exposure levels
266 were low. There was little similarity across cohorts for K, S, Si and V exposures. However,
267 exposure contrasts for PM_{10} Si (and to some extent PM_{10} K) were large in the Stockholm
268 County cohort, and for $PM_{2.5}$ and PM_{10} V in the Dutch cohort.
269
270 Correlations between elements and PM mass were much higher in Stockholm County, Wesel,
271 the Netherlands, than in Munich and Manchester (Table 2). Correlations between the
272 measured concentrations were different for some elements, especially for the Munich cohort
273 (SDC 3, Figure A). A potential explanation might be that the study area covered by this
274 cohort is highly heterogeneous, and thus may not be as adequately covered by the monitoring
275 area as for the other cohorts. Further correlations between elements are presented in SDC 3,
276 Tables A-E. Correlations between the estimated elemental exposures were slightly higher for
277 traffic-related elements (e.g. Cu, Fe) and for elements whose mass makes up a relatively large
278 fraction of PM mass (e.g. K, S, Si).

279 3.3 Associations between air pollution and lung function

280 Associations between elemental concentrations and forced expiratory volume in the first
281 second varied between cohorts (Figure 2, Table 3). Heterogeneity was often larger for the
282 elemental constituents than for PM mass and statistically significant for $PM_{2.5}$ Cu and $PM_{2.5}$
283 Fe (Table 3). A 2 ng/m³ increase in PM_{10} Ni was significantly associated with a 1.6% (95%
284 confidence interval 0.4-2.7%) lower forced expiratory volume in the first second and a 200
285 ng/m³ increase in PM_{10} S was associated with a 2.3% (-0.1-4.6%) reduction for the same
286 outcome, consistent across four of the five cohorts. There were no large differences between
287 the crude and confounder-adjusted models (SDC 4, Table A). Generally, confidence intervals
288 for the elemental constituents were inflated and most negative associations disappeared when

289 we additionally adjusted for PM mass (Table 3). However, associations for PM_{10} Ni (-1.3% (-
290 -3.1,0.5%)) and PM_{10} S (-2.1% (-4.8,0.7%)) weakened only slightly, and also did not change
291 much after adjustment for the other elemental co-pollutants or for NO_2 or $PM_{2.5}$ absorbance
292 (SDC 5). The association between forced expiratory volume in the first second and PM_{10} mass
293 was reduced to null when adjusted for PM_{10} Ni or PM_{10} S, but not when we adjusted for the
294 other elements (Figure 3). Negative associations of forced expiratory volume in the first
295 second with $PM_{2.5}$ mass generally remained, after adjustment for various elemental
296 constituents (Figure 3).
297
298 Forced vital capacity and peak expiratory flow were also negatively associated with Ni and S
299 (SDC 4, Tables B and C and Figures A and B). In addition, negative associations were found
300 with $PM_{2.5}$ K, $PM_{2.5}$ V and PM_{10} Zn for forced vital capacity and with $PM_{2.5}$ Cu, PM_{10} K,
301 PM_{10} Si and $PM_{2.5}$ and PM_{10} V for peak expiratory flow in the confounder-adjusted models.
302 Heterogeneity in associations was lower for peak expiratory flow than for the other two lung
303 function parameters. Associations with Ni and S persisted after additional adjustment for PM
304 mass, while most other associations attenuated (SDC 4, Tables B and C). The negative
305 associations between forced vital capacity and $PM_{2.5}$ and PM_{10} mass were attenuated after
306 adjustment for $PM_{2.5}$ Cu and Fe, PM_{10} Ni and V and both size fractions of S (Figure 3).
307 Associations between peak expiratory flow and $PM_{2.5}$ and PM_{10} mass disappeared after
308 adjusting for $PM_{2.5}$ Ni and PM10 K, respectively, but not after adjustment for the other
309 elemental pollutants (Figure 3).

310 3.4 Sensitivity analyses

311 Estimated concentrations of PM mass were highly correlated (R>0.80) with $PM_{2.5}$ Cu (Dutch
312 cohort), PM_{10} Fe (Wesel and Dutch cohorts), PM_{10} K (Stockholm County cohort), PM_{10} Ni

313 (Wesel cohorts), $PM_{2.5}$ S (Dutch cohort) and PM_{10} Si (Stockholm County and Dutch cohorts)
314 (Table 2). This led to Variance Inflation Factors above 3 for all health outcomes in PM mass-
315 adjusted models. Combined effect estimates with and without these specific cohorts and
316 exposures are shown in SDC 6. The negative association between PM_{10} Ni and forced
317 expiratory volume in the first second and peak expiratory flow became slightly stronger after
318 exclusion of the Wesel cohort. For forced expiratory volume in the first second, the combined
319 estimate became -2.1% (-3.7,-0.7) compared to -1.3% (-3.1,0.5). Otherwise, results remained
320 unchanged when we left out models with variance inflation factors above 3.
321
322 When we restricted the meta-analyses to those cohorts for which the exposure models had
323 Leave-One Out Cross Validation R^2's of at least 0.50 (see SDC 2), the association of PM_{10} Ni
324 remained strong, but associations with PM_{10} S disappeared (SDC 7). $PM_{2.5}$ V land use
325 regression models had low Leave-One Out Cross Validation R^2's for all cohorts except the
326 Dutch cohort. Hence, our sensitivity analysis for $PM_{2.5}$ V was entirely based on the estimate
327 for the Dutch cohort (SDC 7).
328
329 Few associations were seen between exposure at the birth address and lung function (SDC 8,
330 Table A). A consistent negative association with $PM_{2.5}$ Zn at the birth address was found for
331 all outcomes. However, among the children who moved since birth (47% of total), exposure at
332 the 6/8-year address was more negatively associated with lung function than exposures at the
333 birth address for many exposure-outcome combinations. However, confidence intervals
334 largely overlap (SDC 8, Figure A). Stratified analyses did not reveal systematically different
335 associations for children who did and did not move since birth (SDC 8, Table B).
336

In the sensitivity analysis stratified by asthma status, we found that for the majority of exposures, associations with forced expiratory volume in the first second were more negative in asthmatic children (SDC 9). However, confidence intervals for asthmatic and non-asthmatic children largely overlap.

4 Discussion

We observed small reductions of forced expiratory volume in the first second, forced vital capacity and peak expiratory flow in children, associated with increased exposure to especially Ni and S. The negative associations with Ni and S remained unchanged after adjustment for PM mass, , suggesting that these elements may be associated with lung function independently. However, the earlier reported associations [12] between $PM_{2.5}$ mass and lung function were not consistently explained by any of the eight elements. Associations with elements were more heterogeneous across cohorts than PM mass associations.

4.1 Comparison with previous studies

Negative effects of long-term exposure to particulate matter mass on lung function have been shown repeatedly [2,11], in our recent analysis [12] and previously in the cohorts used in the present study.[28-30] To date, no study has looked at lung function in relation to long-term exposure to PM constituents. Studies on PM from specific sources such as desert dust [31], woodsmoke [32] and traffic [11] have found associations with forced expiratory volume in the first second and forced vital capacity. We found the most consistent associations with the elements Ni and S. Previous toxicological studies found adverse effects of residual oil fly ash components (particularly Ni and V) on human bronchial epithelium cells.[33] Epidemiological studies also report short-term effects of Ni, sulphate (which includes the element S) and V for various health outcomes.[14,15,19,20] Particulate matter containing Ni, sulphate and V is emitted

360 from the burning of residual oil (e.g. from shipping) and some industrial processes.[34] Port
361 areas appear in several land use regression models for elements,[21] including both fractions of
362 Ni, S and V in the Dutch cohort, and PM_{10} S, PM_{10} Si and $PM_{2.5}$ Zn in the Wesel cohorts.

363 4.2 Heterogeneity

364 Heterogeneity as assessed by the I^2 statistic was low to moderate for the different elements,
365 though generally higher than for particle mass. It is likely that the large differences in
366 elemental exposure contrasts between cohorts contributed to the heterogeneity found in the
367 effect estimates. These between-cohort contrasts were smaller for NO_2, $PM_{2.5}$, $PM_{2.5}$
368 absorbance and PM_{10}.[12] A presentation of relative instead of absolute changes in lung function
369 helped limit the heterogeneity between cohorts. However, in this and our previous study, [12] we
370 cannot rule out that the moderate heterogeneity may be due to differences in age at lung
371 function measurements, characteristics of the cohorts, and lung function parameters (forced
372 expiratory volume in the first versus first half second).

373 4.3 PM mass and elemental constituents associations

374 The previously observed associations between lung function and $PM_{2.5}$ mass were not
375 explained by any of the eight elements. A first explanation could be that measurement and
376 exposure estimation errors were smaller for $PM_{2.5}$ mass than for the elements, resulting in less
377 attenuation. Spatial contrasts for several elemental constituents are strikingly larger than those
378 for PM mass, both within and between study areas. The ability of land use regression models
379 to explain these contrasts differed between areas, and between elements (SDC 2).[21] The
380 explained variance of models for K, Ni, S, Si and V was generally lower than for PM mass.
381 For the non-tailpipe components Cu, Fe and Zn, models were equally predictive as for PM
382 mass. While land use regression models for Cu, Fe, Si and Zn had higher explained variance,

and thus exposure estimation was presumably more accurate, these elements did not have the most profound associations with lung function. Moreover, when we omitted models with low cross-validation R^2's, in a sensitivity analysis, this did not change the results (SDC 7). Secondly, it is possible that other (elemental or organic) components of PM are related to decreased lung function, e.g. PAHs or quinones.[14,15] Thirdly, some constituents were highly correlated with PM mass, and hence it was challenging to isolate the effects of individual constituents from this complex mixture. A sensitivity analysis showed that combined effect estimates for individual elements and PM mass remained largely unchanged after adjustment for other co-pollutants.

4.3 Strengths and limitations

The five cohorts included in this analysis were comparable in study design, and recruitment period (1994-1999). Children of highly educated and/or allergic parents were somewhat overrepresented in the analysis population (SDC 1).[12] As the effect estimates in the present study remained largely unchanged after adjustment for potential confounders including parental education and parental allergy, this likely did not result in serious bias. Similar methods were employed for health effect assessment, while exposure assessment methods were completely harmonized across all study areas, and each centre used the same statistical methods. The time of day and period of the year when the lung function measurements were taken was not standardized within or between cohorts. However, there were no systematic differences regarding time and season between areas with high and low levels of air pollution within the different cohorts. Lung function was measured once per participant, so that the analysis was cross-sectional. While it is possible that we found associations due to multiple testing, we tried to limit the number of models by *a priori* defining the same exposures and confounders for all cohorts.

4.4 Effects of long-term exposure at the birth versus 6/8-year address

As before,[12] we found stronger associations with the 6/8-year address exposure than with the birth address exposure, which could be due to better exposure estimation at the more recent address, as recent measurements formed the basis for land use regression modelling. It is also possible that lung function is primarily affected by recent exposure, and that any growth deficits resulting from exposure earlier in life may be compensated by moving to a less polluted area.[35] For Ni and S, no clear difference was found (SDC 8, figure A). While it has been suggested that growth deficits need not be permanent if the child moves to a less polluted environment [35,36], studies have shown that children with reduced lung function at an early age still have substantial deficits later in life.[37]

5 Conclusions

This study marks a starting point in unravelling the adverse effects on lung function, resulting from differences in the composition of particulate matter. We detected small associations between lung function and annual average levels of some evaluated elements, particularly nickel and sulphur. The associations remained similar after adjustment for PM mass, suggesting a possible independent effect of these constituents. Lower lung function was more consistently associated with increased PM mass.

6 List of Supplemental Digital Content (SDC)

SDC 1: Description of study design, population and lung function measurements

SDC 2: Table showing the Leave-one out cross-validated R^2 (R^2_{LOOCV}) and root mean squared error (RMSE) of the land use regression models used for exposure estimation

SDC 3: Figure showing Pearson correlations (R) between elements and PM mass for cohort estimates and measured concentrations, and tables showing Pearson correlations (R) between all elemental pollution estimates within each cohort

SDC 4: Crude associations of elemental exposure with all outcomes and confounder-adjusted and confounder and PM mass-adjusted associations with forced vital capacity and peak expiratory flow.

SDC 5: Extended two-pollutant analyses for forced expiratory volume in the first second

SDC 6: Table showing sensitivity analysis addressing collinearity of exposures in 2-pollutant models

SDC 7: Table showing sensitivity analysis on exposure estimation by models with low explained variance

SDC 8: Sensitivity analyses related to exposure at the birth address

SDC 9: Table showing stratified associations of elemental composition with forced expiratory volume in the first second for asthmatic and non-asthmatic children

7 References

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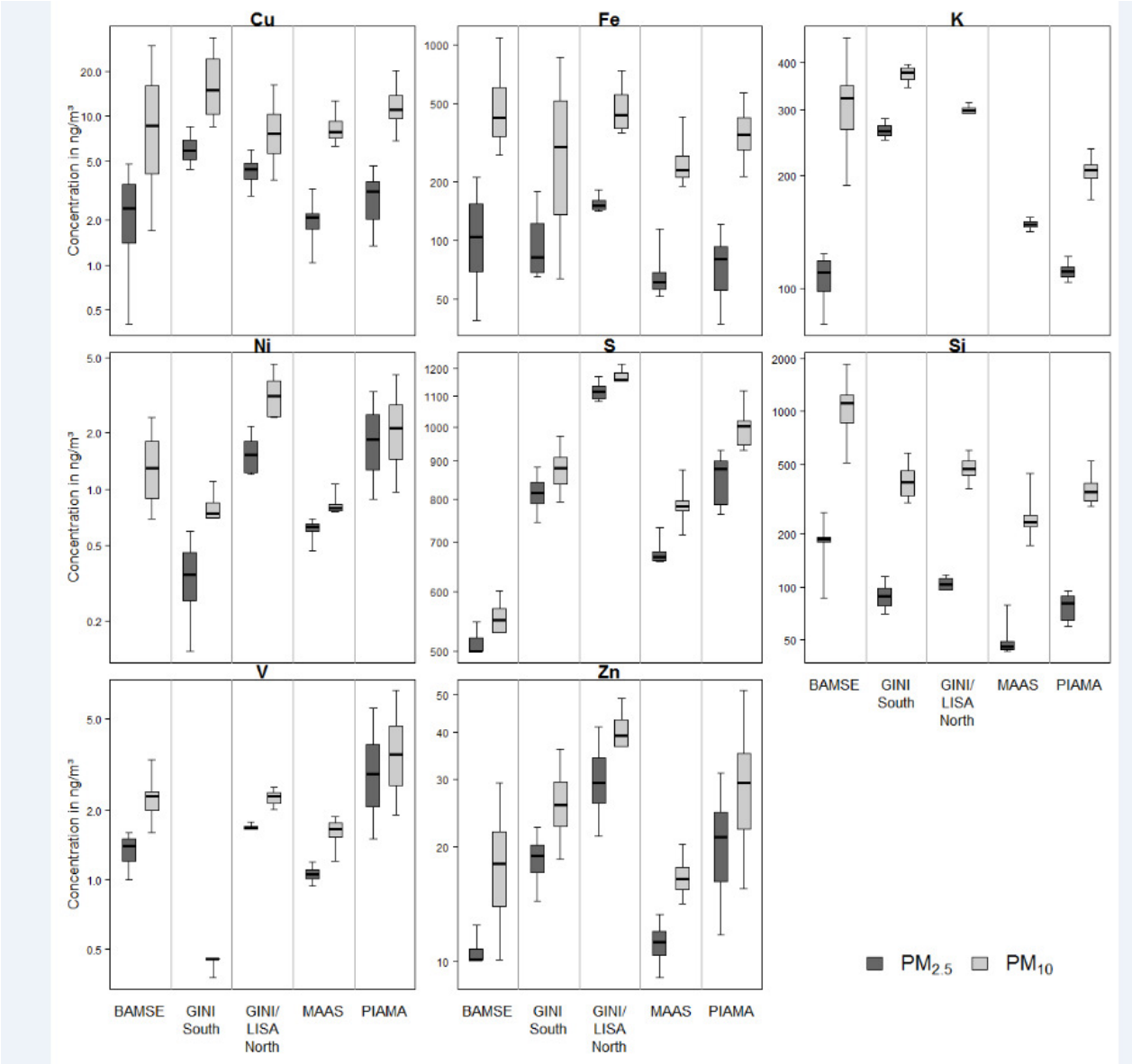
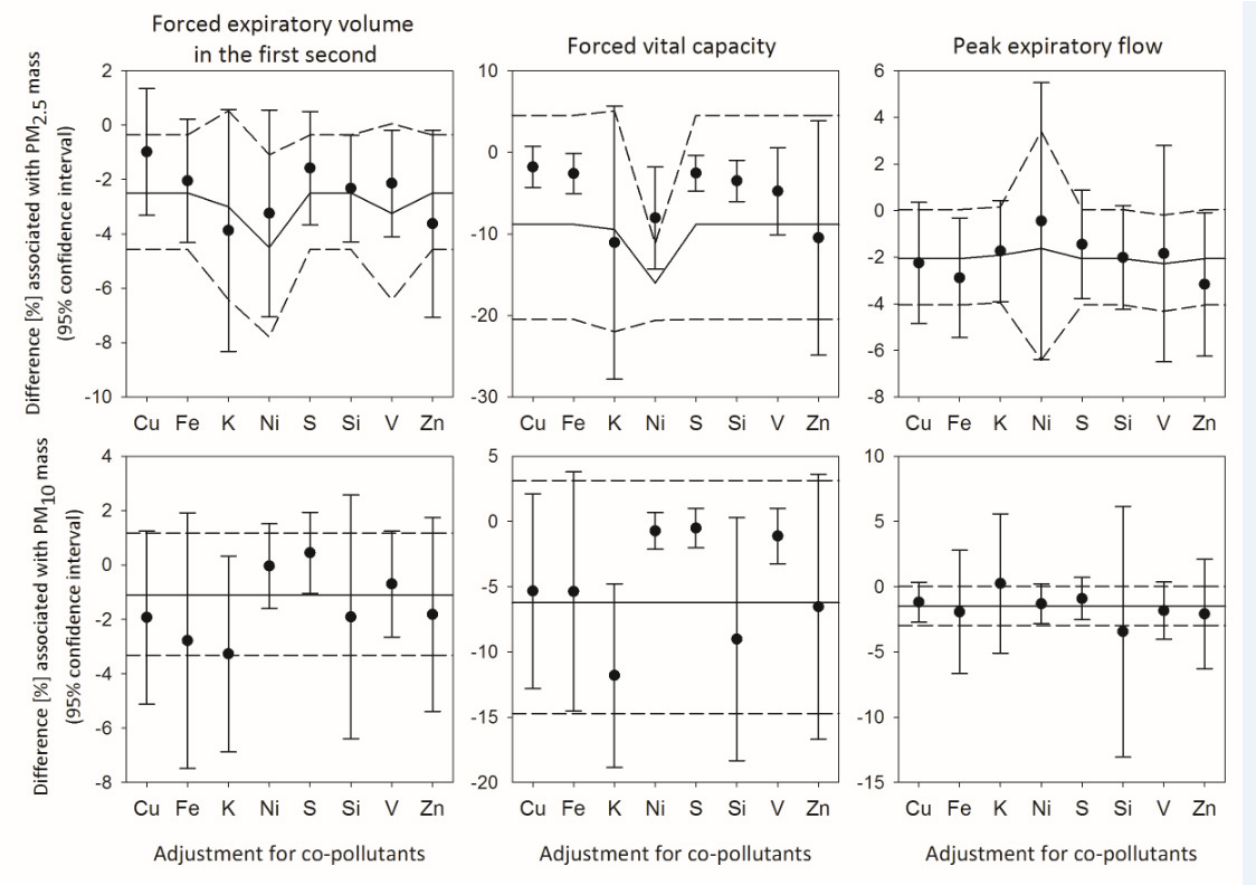
Figure 1: Distribution (mean, median, interquartile range, 5th and 95th percentile) of estimated annual average concentrations for copper (Cu), iron (Fe), potassium (K), nickel (Ni), Sulphur (S), silicon (Si), vanadium (V) and zinc (Zn), for $PM_{2.5}$ and PM_{10}.



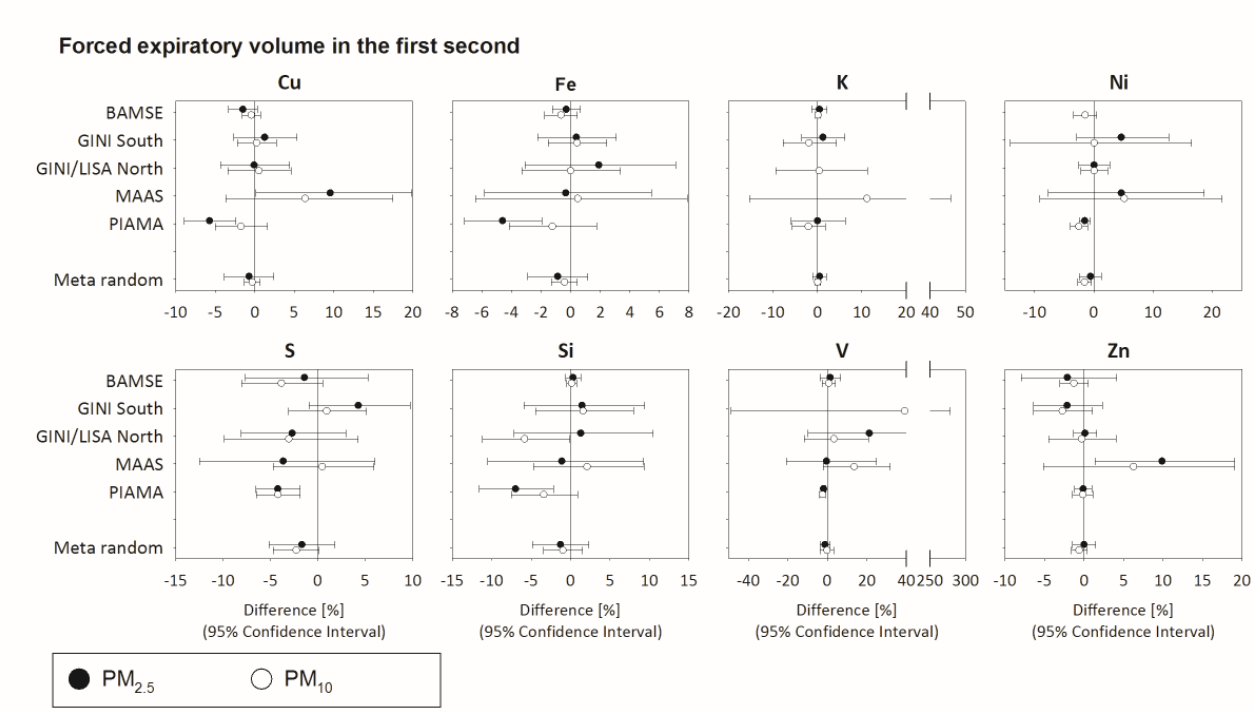
No usable land use regression models were available for $PM_{2.5}$ K for GINI/LISA North and MAAS, for $PM_{2.5}$ Ni for BAMSE and for $PM_{2.5}$ V for GINI South, see also section 3.3 “Exposure to air pollutants”.

Figure 2: Confounder-adjusted [a] cohort-specific [b] and combined associations [c] between estimated air pollution levels and forced expiratory volume in the first second



[a] Adjusted for age, sex, height and weight, recent respiratory infections, non-native ethnicity/nationality, parental education, allergic mother, allergic father, breastfeeding, maternal smoking during pregnancy, smoking at home, mould/dampness at home, furry pets at home. [b] BAMSE = Stockholm County, Sweden, GINI South = Munich, Germany, GINI/LISA North = Wesel, Germany, MAAS = Manchester, UK, PIAMA = The Netherlands. [c] Associations are presented for an increase of in 5 ng/m³ Cu $PM_{2.5}$, 20 ng/m³ Cu PM_{10}, 100 ng/m³ Fe $PM_{2.5}$, 500 ng/m³ Fe PM_{10}, 50 ng/m³ K $PM_{2.5}$, 100 ng/m³ K PM_{10}, 1 ng/m³ Ni $PM_{2.5}$, 2 ng/m³ Ni PM_{10}, 200 ng/m³ S $PM_{2.5}$, 200 ng/m³ S PM_{10}, 100 ng/m³ Si $PM_{2.5}$, 500 ng/m³ Si PM_{10}, 2 ng/m³ V $PM_{2.5}$, 3 ng/m³ V PM_{10}, 10 ng/m³ Zn $PM_{2.5}$, 20 ng/m³ Zn PM_{10}.

555 Figure 3: Association between particulate matter mass and forced expiratory volume in the
556 first second, forced vital capacity and peak expiratory flow, after adjustment for elemental
557 composition.



558

559

560 Solid and dotted lines show the effect estimate and 95% confidence intervals of the single-pollutant association between
561 $PM_{2.5}$ (above) and PM_{10} (bottom) and forced expiratory volume in the first second (left), forced vital capacity (middle) and
562 peak expiratory flow (right), as reported by Gehring et al, 2013.[12] No exposures estimates were available for $PM_{2.5}$ Ni in the
563 Stockholm County cohort, $PM_{2.5}$ V in the Munich cohort and $PM_{2.5}$ K in the Wesel and Manchester cohorts (see section 2.2),
564 which means the two-pollutant models adjusted for these elements are based on fewer studies. Therefore, for these elements,
565 single-pollutant $PM_{2.5}$ associations were recalculated to include only those cohorts which also had valid element exposures.
566 Dots with error bars show the remaining association with $PM_{2.5}$ and PM_{10} mass, after adjusting for each of the elements
567 mentioned below.

568

569 Table 1: Description of the health and confounder characteristics of the study population

570 included in the main analyses.

	BAMSE, Stockholm County, Sweden (N=1,808)		GINI South, Munich, Germany (N=600)		GINI/LISA North, Wesel, Germany (N=851)		MAAS, Manchester, UK (N=500)		PIAMA, The Netherlands (N=900)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Forced expiratory volume in the first (half) second	1.78	0.27	1.09	0.16	1.10	0.16	1.59	0.24	1.80	0.25
Forced vital capacity	2.07 [a]	0.33	N/A	N/A	N/A	N/A	1.83	0.28	2.01	0.30
Peak expiratory flow	4.85[b]	0.68	3.10 [c]	0.53	3.03 [d]	0.52	N/A	N/A	3.79	0.64
Age (years)	8.3	0.49	6.1	0.12	6.2	0.23	8.0	0.1	8.1	0.29
Height (cm)	132	6.0	119	4.6	121	5.2	128.3	5.5	132	5.6
Weight (kg)	30.3	5.4	21.8	2.9	23	3.6	28.4	5.8	29	4.8
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Female sex	885	49.0	308	51.3	424	49.8	242	48.4	459	51.0
Recent respiratory infections [e]	176	9.7	206	34.3	334	39.3	0	0	223	24.8
Other ethnicity [f]	358	19.8	0	0	0	0	26	5.2	36	4.0
Parental socio-economic status [g]										
Low	125	6.9	30	5.0	74	8.7	73	14.6	89	9.9
Intermediate	891	49.3	117	19.5	333	39.1	204	40.8	314	34.9
High	792	43.8	453	75.5	444	52.1	142	28.4	497	55.2
							81	16.2		
Allergic mother	315	17.4	338	56.3	312	36.7	303	60.6	582	64.7
Allergic father	331	18.3	306	51.0	255	30.0	317	63.4	293	32.6
Breastfeeding	1730	95.7	421	70.2	491	57.7	250	50.0	484	53.8
Mother smoking during pregnancy [h]	217	12	76	12.7	112	13.2	53	10.6	132	14.7
Current smoking at home	310	17.2	120	20.0	305	35.8	183	36.6	140	15.6
Current signs of dampness /moulds in the home [i]	167	9.2	146	24.3	152	17.9	65	13.0	260	28.9
Current any pets in the home	460	25.4	147	24.5	225	26.4	214	42.8	436	48.4
Study region [j]			N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Stockholm	572	31.6								
Järfälla	527	29.2								
Solna	449	24.8								
Sundbyberg	260	14.4								
Moved between birth and LF measurements	1137	63.9	322	53.7	288	33.8	237	47.4	455	50.6
Asthma [k]	202	11.2	23	3.8	36	4.3	76	15.3	95	10.6
Allergic sensitization [l]	600	35.6	216	39.5	219	29.3	133	42.5	343	46.1

571

572 [a] n=1833; [b] n=2281; [c] n=502; [d] n=685; [e] BAMSE: Respiratory infection at the time of lung function measurement; GINI

573 South and GINI/LISA North: lower or upper respiratory infection during past 4 weeks; MAAS: only asymptomatic children

574 were measured; PIAMA: cold or respiratory infection during past 3 weeks; [f] BAMSE: Scandinavian; GINI South and

575 GINI/LISA North: German; MAAS: Caucasian; PIAMA: Dutch; [g] Based on mother's education in BAMSE; based on

576 maximum of mother's and father's education in GINI South, GINI/LISA North and PIAMA; based on father's income

577 categories (<10,000; 10,000-20,000; 20,000-30,000; >30,000) in MAAS; [h] At least during the first 4 weeks; [i] During the past

578 12 months; [j] Only relevant for BAMSE; [k] number of subjects included: N=1807 for BAMSE, N=846 for GINI/LISA North
579 and N=896 for PIAMA; [l] N=1688 for BAMSE, N=547 for GINI South, N=747 for GINI/LISA North, N=313 for MAAS and
580 N=744 for PIAMA
581

582 Table 2: Pearson correlations (R) between elemental composition and PM mass for each

583 cohort.

		BAMSE (Stockholm County, Sweden)	GINI South (Munich, Germany)	GINI/LISA North (Wesel, Germany)	MAAS (Manchester, UK)	PIAMA (The Netherlands)
Cu	$PM_{2.5}$	0.71	-0.01	0.61	0.04	0.82
	PM_{10}	0.26	0.15	0.68	0.39	0.47
Fe	$PM_{2.5}$	0.69	0.07	0.47	0.19	0.76
	PM_{10}	0.66	0.02	0.90	0.51	0.85
K	$PM_{2.5}$	0.33	0.01	NA	NA	0.50
	PM_{10}	1.00	-0.01	0.55	0.43	0.75
Ni	$PM_{2.5}$	NA	0.10	0.52	0.04	0.62
	PM_{10}	0.13	0.05	0.86	0.09	0.58
S	$PM_{2.5}$	0.53	0.16	0.62	-0.08	0.85
	PM_{10}	0.43	0.14	0.65	0.21	0.46
Si	$PM_{2.5}$	0.44	0.34	0.02	0.18	0.73
	PM_{10}	1.00	0.03	0.38	0.53	0.91
V	$PM_{2.5}$	0.29	NA	0.33	0.15	0.58
	PM_{10}	0.76	0.02	0.46	0.23	0.48
Zn	$PM_{2.5}$	0.52	0.21	0.64	0.10	0.46
	PM_{10}	0.55	0.20	0.27	0.40	0.44

584 NA = no land use regression model possible, see also section 2.2

585

586

Table 3: Confounder-adjusted and PM mass-adjusted model associations between estimated air pollution levels and forced expiratory volume in the first second: results from random-effects meta-analyses expressed as percent change with 95% confidence intervals, I^2 and p-value of heterogeneity of effect estimates between cohorts.

# Cohorts	Exposure		Exposure increment [a]	Confounder adjusted model (N=4,659) [b]				PM mass-adjusted model (N=4,659) [c]			
				% diff.	(95% CI)	I^2	p_{het}	% diff.	(95% CI)	I^2	p_{het}
5	$PM_{2.5}$ mass [d]		5 µg/m³	-2.5	-4.6 , 0.4	9	0.3578				
5	PM_{10} mass [d]		10 µg/m³	-1.1	-3.3 , 1.2	19	0.2923				
5	Cu	$PM_{2.5}$	5 ng/m³	-0.7	-3.8 , 2.5	71	0.0076	0.1	-3.2 , 3.5	59	0.0428
5		PM_{10}	20 ng/m³	-0.3	-1.3 , 0.7	0	0.5982	0.0	-1.3 , 1.3	12	0.3355
5	Fe	$PM_{2.5}$	100 ng/m³	-0.9	-2.9 , 1.2	62	0.0337	-0.1	-1.9 , 1.6	37	0.1774
5		PM_{10}	500 ng/m³	-0.4	-1.3 , 0.5	0	0.8573	0.2	-1.6 , 2.0	35	0.1901
3 [e]	K	$PM_{2.5}$	50 ng/m³	0.5	-1.0 , 2.1	0	0.9448	1.2	-0.4 , 2.8	0	0.4740
5		PM_{10}	100 ng/m³	0.1	-0.5 , 0.7	0	0.7052	0.1	-3.6 , 4.0	0	0.6554
4 [f]	Ni	$PM_{2.5}$	1 ng/m³	-0.6	-2.4 , 1.3	33	0.2173	0.2	-2.1 , 2.7	40	0.1735
5		PM_{10}	2 ng/m³	-1.6	-2.7 , -0.4	8	0.3597	-1.3	-3.1 , 0.5	28	0.2319
5	S	$PM_{2.5}$	200 ng/m³	-1.7	-5.0 , 1.8	54	0.0672	-0.8	-4.9 , 3.4	52	0.0790
5		PM_{10}	200 ng/m³	-2.3	-4.6 , 0.1	38	0.1682	-2.1	-4.8 , 0.7	47	0.1112
5	Si	$PM_{2.5}$	100 ng/m³	-1.3	-4.7 , 2.3	53	0.0733	0.6	-0.5 , 1.7	0	0.5951
5		PM_{10}	500 ng/m³	-1.0	-3.4 , 1.5	44	0.1267	-1.1	-5.7 , 3.8	43	0.1320
4 [g]	V	$PM_{2.5}$	2 ng/m³	-1.1	-3.5 , 1.3	14	0.3236	0.5	-4.0 , 5.2	44	0.1499
5		PM_{10}	3 ng/m³	-0.1	-3.6 , 3.4	48	0.1037	0.9	-3.9 , 6.0	49	0.0968
5	Zn	$PM_{2.5}$	10 ng/m³	0.0	-1.5 , 1.5	40	0.1546	0.8	-0.7 , 2.5	33	0.2046
5		PM_{10}	20 ng/m³	-0.6	-1.6 , 0.4	0	0.4663	-0.6	-2.5 , 1.3	46	0.1132

[a] Effects are presented for exposure increments, which were derived by rounding down the mean P10-P90 range in all ESCAPE study areas; [b] Adjusted for age, sex, height, weight, recent respiratory infections, non-native ethnicity, parental socio-economic status, allergic mother, allergic father, breastfeeding, mother smoking during pregnancy, smoking at home, mould/dampness at home and furry pets in the home; [c] Confounder-adjusted model additionally adjusted for PM mass; [d] As reported in Gehring et al (2013); [e] No exposure available for the Wesel and Manchester cohorts; [f] No exposure available for the Stockholm County cohort; [g] No exposure available for the Munich cohort.