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Long-term effects of elemental composition of particulate matter on inflammatory blood markers in European cohorts

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ABSTRACT

Background: Epidemiological studies have associated long-term exposure to ambient particulate matter with increased mortality from cardiovascular and respiratory disorders. Systemic inflammation is a plausible biological mechanism behind this association. However, it is unclear how the chemical composition of PM affects inflammatory responses.

Objectives: To investigate the association between long-term exposure to elemental components of PM and the inflammatory blood markers high-sensitivity C-reactive protein (hsCRP) and fibrinogen as part of the European ESCAPE and TRANSPHORM multi-center projects.

Methods: In total, 21,558 hsCRP measurements and 17,428 fibrinogen measurements from cross-sections of five and four cohort studies were available, respectively. Residential long-term concentrations of particulate matter <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$) in diameter and selected elemental components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, zinc) were estimated based on land-use regression models. Associations between components and inflammatory markers were estimated using linear regression models for each cohort separately. Cohort-specific results were combined using random effects meta-analysis. As a sensitivity analysis the models were additionally adjusted for PM mass.

Results: A 5 ng/m^3 increase in $PM_{2.5}$ copper and a 500 ng/m^3 increase in PM_{10} iron were associated with a 6.3%

Abbreviations: BMI, body mass index; CRP, C-reactive protein; Cu, copper; ESCAPE, European Study of Cohorts for Air Pollution Effects project; Fe, iron; HNR, Heinz Nixdorf Recall Study; hs, high-sensitivity; IHD, ischemic heart disease; K, potassium; KORA, Cooperative Health Research in the Region of Augsburg; LUR, Land use regression; Ni, nickel; PM, particulate matter; S, sulfur; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; Si, silicon; SIXTY, 60-year old cohort study; TRANSPHORM, transport related air pollution and health impacts — integrated methodologies for assessing particulate matter; V, vanadium; XRF, x-ray fluorescence; Zn, zinc.

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[0.7; 12.3%] and 3.6% [0.3; 7.1%] increase in hsCRP, respectively. These associations between components and fibrinogen were slightly weaker. A 10 ng/m^3 increase in $PM_{2.5}$ zinc was associated with a 1.2% [0.1; 2.4%] increase in fibrinogen; confidence intervals widened when additionally adjusting for $PM_{2.5}$.
Conclusions: Long-term exposure to transition metals within ambient particulate matter, originating from traffic and industry, may be related to chronic systemic inflammation providing a link to long-term health effects of particulate matter.

1. Introduction

There is evidence for an adverse association between long-term exposure to ambient particulate matter (PM) and mortality from cardiovascular as well as respiratory disease (Pope, 2007; Rückerl et al., 2011; Lepeule et al., 2012; Cesaroni et al., 2013; Hoek et al., 2013; Beelen et al., 2014b). PM represents a complex mixture of many components originating from different sources. However, there is a limited number of studies exploring the association between PM components and health. Furthermore, previous epidemiological studies have mainly investigated short-term effects (Ostro et al., 2007; Bell et al., 2009; Zanobetti et al., 2009; Wichers Stanek et al., 2011; Wu et al., 2011, 2012, 2013) rather than long-term effects of PM components on cardiovascular health. Two studies from the US consistently observed an increased risk of ischemic heart disease (IHD) mortality for $PM_{2.5}$ iron and sulfur/sulfate, but evidence was inconsistent for potassium, silicon, zinc, nickel and vanadium (Ostro et al., 2010; Lippmann et al., 2013).

The few studies on long-term health effects of size specific PM mass or its chemical components have mainly been conducted in North America and to a lesser extent in Europe (Pelucchi et al., 2009; Lippmann et al., 2013; Vedal et al., 2013). Therefore, the ESCAPE (**E**uropean **S**tudy of **C**ohorts for **A**ir **P**ollution **E**ffects) project has been initiated in order to assess the association between long-term exposure to outdoor air pollution at residence and health in a wide range of European cohorts (http://www.escapeproject.eu/).

Within this project it has been shown that higher $PM_{2.5}$ (PM < 2.5 μm in diameter) and PM_{10} (PM < 10 μm in diameter) levels at residence are associated with an increased mortality risk (Beelen et al., 2014a) and incident cardiac events (Cesaroni et al., 2014), respectively. Systemic inflammation and subclinical atherosclerosis (Libby et al., 2002; Hansson, 2005) may precede these events. Hence, within the ESCAPE project the associations between long-term air pollution concentrations and the acute-phase proteins C-reactive protein (CRP), measured by a high-sensitivity (hs) assay, and fibrinogen were investigated in five and four cohorts, respectively. Recent meta-analyses showed no or inconsistent associations on high-sensitivity CRP (hsCRP) and fibrinogen for PM_{10} and $PM_{2.5}$ among cohorts (Lanki et al., in press). One reason might be the different particle compositions between these study regions (de Hoogh et al., 2013). The aim of this analysis was to assess the association between elemental components of PM and hsCRP and fibrinogen as part of the ESCAPE and TRANSPHORM (Transport related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter, http://www.transphorm.eu/) projects. The focus of the analyses was on the transition metals, which have been suggested to be harmful in short-term toxicological and epidemiological studies (Kelly and Fussell, 2012).

2. Materials and methods

2.1. Study populations

In the ESCAPE project, long-term air pollution concentrations were modeled for existing cohort data in different parts of Europe. HsCRP was available for five cohorts in Northern and Central Europe: The Cooperative Health Research in the Region of Augsburg, Germany (KORA), the Heinz Nixdorf Recall Study, Germany (HNR), the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults, Switzerland (SAPALDIA), the National FINRISK Study, Finland, and TwinGene, Sweden. For analyses on fibrinogen, four cohorts were available: KORA, HNR, FINRISK, and the 60-year old cohort study (SIXTY) from Sweden. Detailed information on the cohorts can be found in the Online Data Supplement.

2.2. Blood markers and covariates

The blood markers of interest were hsCRP and fibrinogen. Detailed information on their determination in each cohort can be found in the Online Data Supplement. The definition of the covariates (e.g. participant and lifestyle characteristics) was harmonized in a common codebook. If a variable was not available for a cohort the respective variable was replaced with the best available variable.

2.3. Exposure data

In each study region PM was measured in three 2-week periods in different seasons (winter, summer, intermediate season) at 20 monitoring sites between 2008 and 2011 (Eeftens et al., 2012b). The sites represented the anticipated spatial variation of air pollution at the home addresses of study subjects. All PM_{10} and $PM_{2.5}$ samples were analyzed for elemental composition using Energy Dispersive X-ray fluorescence (XRF) (de Hoogh et al., 2013). Analyses were performed by Cooper Environmental Services, Portland USA. Forty-eight elements were measured in both $PM_{2.5}$ and PM_{10} fractions. A priori, eight elements were selected for further analyses: copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V), and zinc (Zn). For these elemental components there was prior evidence for health effects, they represent major anthropogenic sources, and were detected in >75% of the samples. The nonmetal S is an indicator for secondary particles from long-range transport. The alkali metal K is considered as an inorganic tracer of biomass combustion, but is also a component of e.g. soil. The transition metals Cu and Fe reflect non-tailpipe emissions of traffic, Ni and V are tracers for oil combustion, and Zn is a putative marker for brake and tire wear but can also be emitted from industrial sources. The metalloid Si is an indicator for road dust and soil (Cyrys et al., 2003; Gu et al., 2013).

Land use regression (LUR) models were developed for each cohort and each exposure variable following a common manual (http://www.escapeproject.eu/manuals/). A large number of potential predictors of air pollution concentrations derived from geographical information systems (e.g. traffic intensity, population density, forms of land-use) were tested in the models aiming to maximize explained variability (Eeftens et al., 2012a). Annual exposure concentrations for each individual's residence were predicted using the developed LUR models. These estimated annual component concentrations were used for further statistical analyses.

2.4. Statistical analyses

Linear regression models in SAS and STATA softwares were used for the cohort-specific analyses following a common analysis strategy. In order to assure normally distributed residuals hsCRP values were log-transformed. All models were adjusted for a priori selected covariates based on literature on the determinants of hsCRP and fibrinogen concentrations. Our model included age (continuous variable), sex,

education (primary school or less, up to secondary school or equivalent, university degree), body mass index (BMI, continuous variable), physical activity (≤3 times/month, once a week, 2–3 times/week, >3 times/week), smoking status (current smoker, ex-smoker, never smoker), and alcohol intake (no alcohol intake, 1–3 drinks per week, 3–6 drinks per week, >6 drinks per week). In addition, the model included an indicator variable for baseline visit for FINRISK and KORA, which had more than one recruitment period, as well as an area indicator for FINRISK, which consisted of two clearly separate study areas. In our main paper (Lanki et al., in press), we run a further model additionally including alcohol intake (excluding wine), wine intake, household income, fish, fruit, and meat intake, cardiovascular disease, diabetes, arthritis, ulcerative colitis, and passive smoking. As the exposure effects of this extended model did not differ essentially from the main model, we did not run the extended model in this analysis.

The associations between predicted annual concentrations of elemental components of PM and hsCRP or fibrinogen were estimated by including each component separately in the model.

In the meta-analyses, cohort-specific exposure effects were treated as random effects and pooled using Empirical Bayes method (Raudenbush, 2009). Heterogeneity between the cohort-specific estimates was evaluated with Cochrane's Q-test and I^2 index (percentage of variation across cohorts that is due to heterogeneity rather than chance) (Higgins and Thompson, 2002). We regarded a p-value of the Q-test <0.1 and an I^2 >50% as an indication for heterogeneity. Effect estimates are presented as percent change from the outcome mean per fixed increase in the elemental PM component. The fixed increments for each component were chosen based on the average of the cohort-specific ranges between the 10th and 90th percentiles.

2.5. Sensitivity analyses

As the single-pollutant models ignore correlations with PM we additionally included PM mass in the models. To avoid multicollinearity, we followed a two-step strategy introduced by Mostofsky et al. (2012): 1. step) Regression of a specific elemental component on PM mass resulting in residuals which are uncorrelated with PM and represent component variation independent of PM. 2. step) Inclusion of these residuals and PM mass in the model simultaneously.

Furthermore, if a cohort showed a comparatively low R^2 for the LUR model of a specific elemental component or if the LUR model comprised only one predictor variable we excluded the respective cohort when pooling the effect estimates.

3. Results

3.1. Characteristics of the study population

A brief description of the participants of each cohort is shown in Table 1. The mean age varied between 48.9 (FINRISK) and 64.2 years (TwinGene). SAPALDIA and FINRISK showed the largest percentage of current smokers and the lowest mean hsCRP levels. FINRISK participants had on average the highest fibrinogen values.

3.2. Air pollution exposure

Fig. 1 and Supplemental Table 1 show the distribution of the estimated elemental components of PM for each cohort as well as the corresponding model fit (R^2) of the LUR models. The LUR models for the elemental components led in general to a moderate to high model fit (R^2 values >0.5). All cohorts showed high R^2 for Cu and Fe of both PM fractions (average R^2 for each elemental component: ≥0.75). A good model fit (R^2>0.60) was also observed for Si and Zn of PM_{10} and $PM_{2.5}$ for all cohorts but FINRISK (R^2 for $PM_{2.5}$ Zn: 0.20 and PM_{10} Zn: 0.21) and the Stockholm cohorts (R^2 for $PM_{2.5}$ Zn: 0.35). LUR models of some elemental components could not be developed because no predictor variable showed a significant influence. In detail, S, Ni, V, and Si of PM_{10} and $PM_{2.5}$ were not available for SAPALDIA. For KORA concentrations of V of PM_{10} and $PM_{2.5}$ could not be estimated with any confidence. Furthermore, $PM_{2.5}$ K and $PM_{2.5}$ Ni were not available for HNR and TwinGene/SIXTY, respectively. A more detailed description of the LUR models can be found elsewhere (de Hoogh et al., 2013) as well as in Supplemental Table 3.

In general, higher concentrations of elemental components of PM were estimated for the HNR and SAPALDIA cohorts, low to intermediate levels for KORA, and lower levels for FINRISK and the Swedish cohorts (Supplemental Table 1). Moderate to strong correlations (|r|>0.6) between Cu and Fe were found for all cohorts, whereas the Spearman correlation coefficients for the other elemental components were not consistent among the cohorts (Supplemental Table 2). The strength of the correlation between PM mass and its elemental components also differed from cohort to cohort. Strong correlations (|r|>0.8) between $PM_{2.5}$ and elemental components were only observed for SAPALDIA (Fe and K) and FINRISK (K, S, and Zn). PM_{10} was strongly correlated with Fe, K, and Zn for SAPALDIA, with Fe for HNR, with S for FINRISK, and with K and Si for the Swedish cohorts.

3.3. Main results

Our meta-analysis showed increased hsCRP values in association with elevated concentrations of PM_{10} Fe, $PM_{2.5}$ Cu, and $PM_{2.5}$ Fe (Table 2, Fig. 2). There was no evidence for heterogeneity among the cohort-specific effect estimates.

Fig. 2 depicts the forest plots of Cu and Fe of both PM fractions. KORA and HNR showed the strongest weights for the associations of PM_{10} Cu, Fe and $PM_{2.5}$ Cu with hsCRP, while for $PM_{2.5}$ Fe FINRISK presented the strongest weight.

The elemental components PM_{10} Fe, $PM_{2.5}$ Fe and $PM_{2.5}$ Cu showed a moderate to strong correlation (r>0.6) with nitrogen oxides (NO_2 and NO_x) for all cohorts but HNR (Supplemental Table 2). Fig. 3 compares the pooled effect estimates of $PM_{2.5}$, PM_{10}, elemental components of PM and nitrogen oxides on hsCRP.

The pooled associations between elemental components of PM and fibrinogen were weaker and more heterogeneous among the cohorts (Table 2). Only an increase in $PM_{2.5}$ Zn was significantly associated with higher fibrinogen levels without heterogeneity among the cohorts (strongest weight for HNR). Heterogeneity among the cohort-specific component effects on fibrinogen was detected for $PM_{2.5}$ Cu and Si as well as for PM_{10} Fe, Ni, and Si because of (strong) component effects for KORA and no or protective effects for the other cohorts (Supplemental Fig. 3). We found a highly significant positive association of PM_{10} K in HNR (5.0% [1.5;8.5%]) but an adverse effect in KORA (−2.5% [−5.2;0.2%]) and SIXTY (−0.5% [−1.3;0.3%]) participants. However, the R^2 of the PM_{10} K LUR model for HNR was low (0.22) in comparison to KORA (0.69) and SIXTY (0.80).

3.4. Sensitivity analyses

When including component residuals and PM mass in our models the association between PM_{10} Fe and hsCRP strengthened, whereas the confidence intervals for $PM_{2.5}$ Fe and Cu effect slightly widened (Supplemental Table 4, Supplemental Fig. 2). While an increase in PM_{10} Si was not significantly associated with hsCRP in the single-pollutant model, we observed a significant association with this elemental component when adjusting for PM_{10}. Additionally including $PM_{2.5}$ led to similar effect estimate of $PM_{2.5}$ Zn but with broader confidence intervals (p-value >0.05) and to an inverse borderline significant association between $PM_{2.5}$ K and fibrinogen (Supplemental Table 4, Supplemental Fig. 4).

Excluding cohorts with a comparatively low LUR model fit or with LUR models comprising only one predictor variable from the meta-analyses did not change our results essentially (not shown).

Table 1
Description of the participant characteristics and blood markers for each cohort.

Cohort (country)	Time of baseline visit	Age (years)[a]		BMI (kg/m^2)[a]		Female[a]	Current smoking[a]	hsCRP (mg/l)					Fibrinogen (g/l)				
		Mean	SD	Mean	SD	%	%	N	Mean	SD	Median	IQR	N	Mean	SD	Median	IQR
KORA (Germany)	1994–1995, 1999–2001	50.2	13.6	27.2	4.6	50.1	23.9	7137	2.7	4.9	1.3	2.4	7151	2.8	0.7	2.7	0.8
HNR (Germany)	2000–2003	59.5	7.8	27.9	4.6	49.9	23.3	4492	3.1	9.0	1.5	2.5	4444	3.3	0.8	3.3	1.0
SAPALDIA (Switzerland)	2002	55	10.6	25.3	4.3	56.6	28.3	685	2.3	3.6	1.0	1.8	–	–	–	–	–
FINRISK (Finland)	1997, 2002, 2007	48.9	13.6	26.6	4.6	52.4	28.3	7627	2.3	4.5	1.1	1.9	2044	3.6	0.8	3.5	1.0
TwinGene (Sweden)	2004–2008	64.2	8.5	25.2	3.6	56.2	19.1	1617	2.8	4.9	1.4	2.6	–	–	–	–	–
SIXTY (Sweden)	1997–1999	60.4	0.1	26.8	4.2	52	20.8	–	–	–	–	–	3789	3.0	0.8	2.9	1.0

[a] For all cohorts but SIXTY numbers are based on participants with hsCRP measurements. The description did not differ essentially for participants with fibrinogen measurements. BMI: body mass index, hsCRP: high-sensitivity C-reactive protein, SD: standard deviation, IQR: interquartile range.

4. Discussion

4.1. Summary

In this European multi-center study, we observed increased hsCRP concentrations in association with elevated concentrations of PM_{10} Fe, $PM_{2.5}$ Cu, and $PM_{2.5}$ Fe at residence. The associations between the elemental components and fibrinogen were somewhat more heterogeneous among the cohorts leading to non-significant pooled effect estimates. Only an increase in $PM_{2.5}$ Zn was significantly associated with elevated fibrinogen levels.

4.2. Particulate matter and blood markers

It is assumed that exposure to PM may provoke a low-grade pulmonary inflammatory response leading to a release of inflammatory mediators and subsequent systemic effects. On a longer time-scale the progression of respiratory disease and atherosclerosis might be the consequence (Pope and Dockery, 2006; Brook et al., 2010). PM represents a complex mixture of many chemical components originating from e.g. fossil fuel combustion, industry, and natural sources. Chemical compounds and elements with the potential to produce reactive oxygen species (ROS), such as transition metals (in this study Fe, Cu, Ni, V, and Zn), are assumed to be especially harmful (Kelly and Fussell, 2012). The production of ROS can lead to oxidative stress and possibly further to systemic inflammation (Brook et al., 2010). Therefore, we hypothesized that blood markers of inflammation might be associated with long-term concentrations of elemental components of PM and that these associations might be stronger than those of $PM_{2.5}$ or PM_{10} which may also include relatively harmless components.

CRP, a sensitive marker of the acute-phase response, is the most established inflammatory marker for the evaluation and prediction of cardiovascular disease (Libby et al., 2002). While CRP is associated with the development of atherosclerosis, fibrinogen is a precursor of fibrin which is responsible for thrombus formation. High levels of fibrinogen are a marker of acute inflammation, while moderately elevated levels can indicate systemic activation of the clotting cascade.

Associations between long-term exposure to PM and mortality from cardiovascular or respiratory disorders were observed in different parts of the world (Zhang et al., 2011; Dong et al., 2012; Hales et al., 2012; Lepeule et al., 2012; Carey et al., 2013; Cesaroni et al., 2013), but there are only a few published studies on the association between long-term air pollution exposure and blood markers of inflammation (Forbes et al., 2009; Hoffmann et al., 2009; Hajat et al., 2015). Hoffmann et al. (2009) reported 23.9% [4.1;47.4%] higher hsCRP levels and 3.9% [0.3;7.7%] higher fibrinogen levels associated with a 3.91 $\mu g/m^3$ increase in long-term residential exposure to $PM_{2.5}$ in men and weaker associations in women. Forbes et al. (2009) investigated long-term air pollution effects on fibrinogen in three cross-sectional studies of the English population conducted in 1994, 1998, and 2003. The authors observed a −0.39% [−0.73: 0.05%] decrease in fibrinogen per 1 $\mu g/m^3$ increase in PM_{10} in the survey from 1998 and no effects on hsCRP. In participants of the Multi-Ethnic Study of Atherosclerosis, increases in long-term $PM_{2.5}$ concentrations were associated with interleukin-6, which stimulates the synthesis of CRP, while no air pollution effects were detected on CRP and fibrinogen (Hajat et al., 2015).

4.3. Elemental components of PM and health

So far, the association between long-term exposure to transition metals within PM and predictors or risk factors of adverse events has not been investigated and also studies on the association between long-term exposure to multiple PM components and mortality are rare (Lipfert et al., 2006; Ostro et al., 2010; Lippmann et al., 2013; Wang et al., 2014). Ostro et al. (2010) observed an increased risk for IHD mortality in association with $PM_{2.5}$ components related to fossil fuel (Fe, Zn) and biomass combustion (K) as well as to crustal origin (Si) in female teachers from California, U.S. Furthermore, a higher risk for IHD mortality was reported in association with increased levels of $PM_{2.5}$ Fe, Ni, and Zn in the US American NPACT Study (Lippmann et al., 2013). However, no significant associations between PM components and cardiovascular mortality were observed in a meta-analysis in 19 European cohorts which was also part of the ESCAPE and TRANSPHORM projects (Wang et al., 2014).

To date, the effects of chemical components of PM on inflammatory blood markers were only assessed in a panel study (Wu et al., 2012) and in a semi-experimental investigation (Strak et al., 2013). Wu et al. (2012) observed a 3.9% [0.3, 7.6%] increase in fibrinogen in association with elevated 24 h-averages in $PM_{2.5}$ Fe. This association strengthened (5.9% [0.2;12.0%]) when including $PM_{2.5}$ in the model. No effects of Cu, Ni, V, and Zn on fibrinogen were detected. Furthermore, short-term changes in PM components were not associated with changes in hsCRP. In a study by Strak et al. (2013) healthy adults were repeatedly exposed to ambient PM for 5 h at five different locations with different source characteristics. The authors observed a 1.5% [0.0;3.1%] increase in hsCRP at the next morning after exposure in association with elevated $PM_{2.5}$ V levels. Fe, Cu, and Ni of $PM_{2.5}$ had positive but only borderline significant effects on hsCRP. No significant associations of transition metals were observed for fibrinogen. A recent study, investigated short-term effects of $PM_{2.5}$ sources, resulting from source apportionment, on inflammatory blood markers (Siponen et al., 2015). The authors detected increased CRP concentrations in association with elevated levels of $PM_{2.5}$ sources related to long-range transport and biomass combustion but no effects on fibrinogen. Because of the different study designs and exposure definition it is difficult to compare our results with findings of these studies. However, in accordance to Strak et al. (2013) we observed slightly stronger changes in hsCRP than in fibrinogen in association with higher Fe and Cu levels.

4.4. Elemental components of PM and hsCRP

In our study, the strongest associations between elemental components of PM and hsCRP were detected for Cu and Fe. Within the ESCAPE project, concentrations of elemental components of PM at

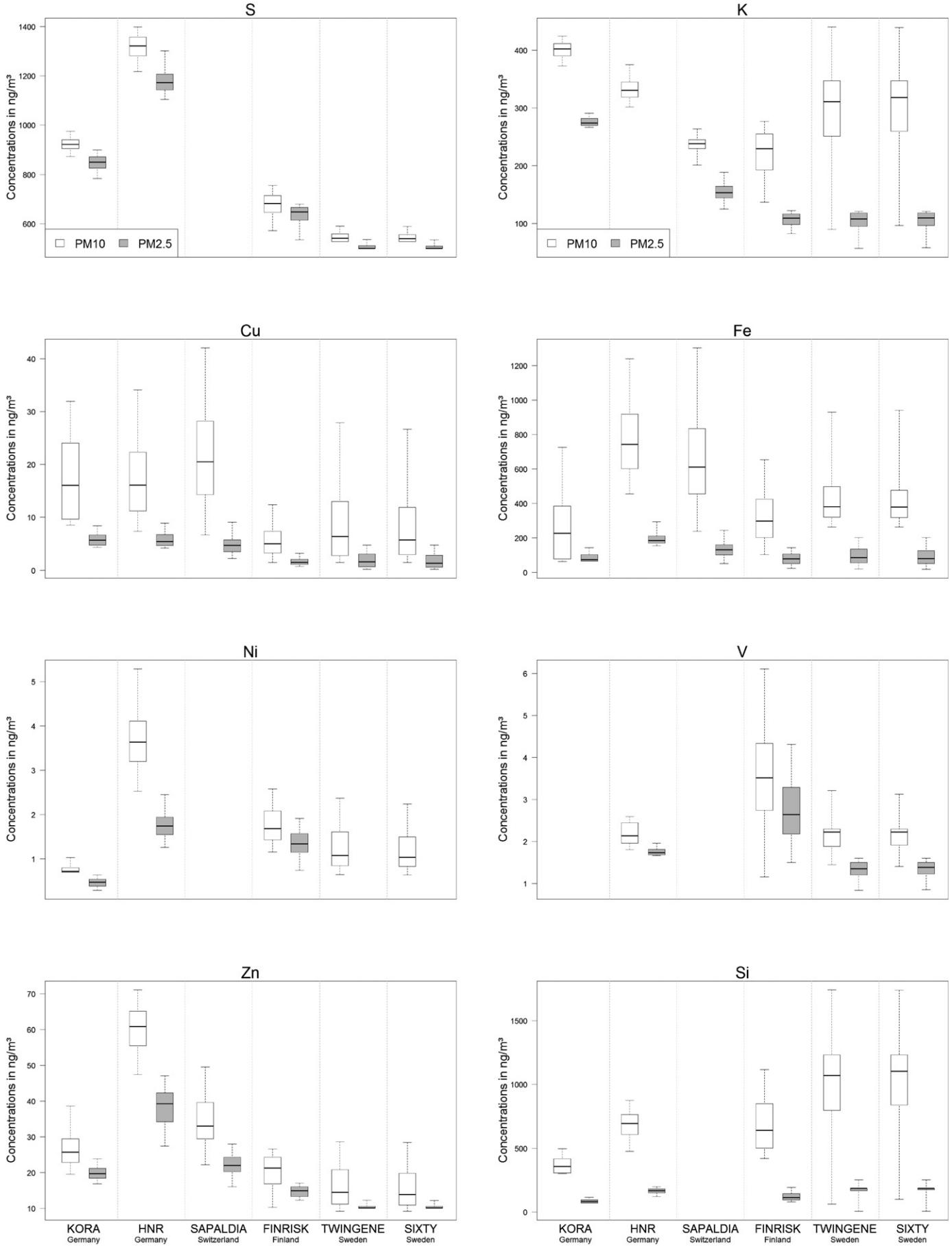
S
K
Cu
Fe
Ni
V
Zn
Si
Concentrations in ng/m³
PM10
PM2.5
KORA Germany
HNR Germany
SAPALDIA Switzerland
FINRISK Finland
TWINGENE Sweden
SIXTY Sweden

Table 2
Pooled associations between $PM_{2.5}$, PM_{10} and its elemental components with hsCRP and fibrinogen per fixed increment.

Exposure	Increment	hsCRP					Fibrinogen				
		N cohorts	%-change	(95%-CI)	I^2	p_{het}	N cohorts[e]	%-change	(95%-CI)	I^2	p_{het}
PM_{10}	10 μg/m³	5	1.2	(−3.8; 6.4)	0	0.899	4	0.1	(−1.4; 1.7)	36	0.179
S	200 ng/m³	4[a]	0.3	(−6.5; 7.7)	12	0.320	4	0.0	(−2.4; 2.5)	44	0.317
K	100 ng/m³	5	3.4	(−5.3; 13.0)	75	0.016	4	0.5	(−2.5; 3.5)	87	0.006
Cu	20 ng/m³	5	2.7	(−1.2; 6.7)	0	0.600	4	0.4	(−1.0; 1.8)	56	0.148
Fe	500 ng/m³	5	3.6**	(0.3; 7.1)	0	0.863	4	0.2	(−1.3; 1.6)	68	0.031
Ni	2 ng/m³	4[a]	2.0	(−5.9; 10.5)	28	0.309	4	0.6	(−4.0; 5.2)	84	0.068
V	3 ng/m³	3[a,b]	0.8	(−10.1; 13.1)	21	0.314	3[b]	−0.3	(−2.4; 1.7)	0	0.815
Zn	20 ng/m³	5	−0.1	(−4.5; 4.4)	0	0.507	4	0.8	(−0.4; 1.9)	14	0.311
Si	500 ng/m³	4[a]	2.3	(−3.4; 8.3)	53	0.180	4	0.4	(−2.3; 3.1)	85	0.010
$PM_{2.5}$	5 ng/m³	5	2.4	(−7.5; 13.4)	54	0.049	4	0.5	(−1.1; 2.0)	0	0.662
S	200 ng/m³	4[a]	0.9	(−6.1; 8.4)	10	0.339	4	0.0	(−3.0; 2.9)	58	0.336
K	50 ng/m³	4[c]	−3.4	(−12.7; 6.8)	52	0.127	3[c]	−1.1	(−2.6; 0.5)	0	0.489
Cu	5 ng/m³	5	6.3**	(0.7; 12.3)	0	0.587	4	0.6	(−1.5; 2.7)	61	0.099
Fe	100 ng/m³	5	3.4*	(−0.3; 7.2)	0	0.688	4	0.7	(−0.3; 1.8)	37	0.178
Ni	1 ng/m³	3[a,d]	2.4	(−10.9; 17.7)	77	0.101	3[d]	−0.3	(−2.6; 2.1)	40	0.231
V	2 ng/m³	3[a,b]	2.9	(−3.1; 9.3)	0	0.683	3[b]	−1.8	(−4.4; 0.9)	0	0.623
Zn	10 ng/m³	5	2.1	(−2.8; 7.2)	7	0.339	4	1.2**	(0.1; 2.4)	8	0.519
Si	100 ng/m³	4[b]	2.5	(−2.2; 7.4)	6	0.452	4	0.5	(−2.0; 3.0)	76	0.005

hsCRP: high-sensitivity C-reactive protein, PM_{10}: particulate matter with an aerodynamic diameter <10 μm, $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5 μm, S: sulfur, K: potassium, Cu: copper, Fe: iron, Ni: nickel, V: vanadium, Zn: zinc, Si: silicon, p_{het}: p-value of heterogeneity.

[a] Not available for SAPALDIA.
[b] Not available for KORA.
[c] Not available for HNR.
[d] Not available for TwinGene/SIXTY.
[e] No fibrinogen for SAPALDIA.
** p-value of pooled effect estimate <0.05.
* p-value of pooled effect estimate <0.1.

residence were not measured but estimated using LUR models. The estimated component concentrations might reflect different sources in different study areas. The LUR models of PM_{10} Fe, $PM_{2.5}$ Fe, and $PM_{2.5}$ Cu contained traffic indicators such as traffic load or road length in all study areas (Supplemental Table 3). For these elemental components, indicators for industry were only included for some cohorts (HNR: PM_{10} Fe, $PM_{2.5}$ Fe, $PM_{2.5}$ Cu; SIXTY/TwinGene: $PM_{2.5}$ Cu, $PM_{2.5}$ Fe; KORA: $PM_{2.5}$ Cu). In general, we assume that our observed associations between increased elemental component levels and hsCRP are mainly related to sources from traffic and to a lesser extent from industry. In support of the relevance of traffic, we observed a moderate to strong correlation ($r > 0.6$) between the elemental components PM_{10} Fe, $PM_{2.5}$ Fe and $PM_{2.5}$ Cu and nitrogen oxides for all cohorts but HNR. We can only speculate why Cu of the size fraction $PM_{2.5}$ showed a stronger association with hsCRP than Cu of PM_{10}. Differences in solubility or inhalability between the two size fractions of a component leading to differential toxicity might be the reason. Alternatively, different sources of Cu might not be equally toxic or equally well taken into account by the LUR models; unlike PM_{10} Cu, $PM_{2.5}$ Cu was linked not only to traffic but also to industry in some cohort areas. For both Cu and Fe concentrations in PM_{10} were rather higher than in $PM_{2.5}$ (de Hoogh et al., 2013). This points to sources like brake wear for these metals in the coarse fraction of PM. Whereas this in itself does not explain differences in associations with biomarkers, it does point to these elements representing different sources and pollution mixtures in $PM_{2.5}$ and PM_{10}, respectively.

In our recent analysis (Lanki et al., in press) conducted in the same participants as this study, we detected a 3.2% [0.3; 6.1%] increase in hsCRP in association with a 20 μg/m³ increase in NO_x but no associations between $PM_{2.5}$ or PM_{10} and blood markers of inflammation. Our present finding suggests that not all elemental components of PM are equally harmful but that potentially long-term exposure to transition metals might be associated with inflammatory responses. In general, traffic-related PM components and nitrogen oxides originate from similar sources, but their chemical properties and spatial distribution differ. It has been reported that NO_2 is associated with adverse health effects also independently from PM (WHO, 2013). Both NO_2 and PM (especially the transition metals) are assumed to trigger oxidative stress but whether the gaseous and particulate pollutants exhibit the same biological pathway is unknown. It is yet possible that NO_2 has no direct effect on systemic inflammation but acts as an indicator for traffic-related components such as Cu or Fe (or vice versa). Since transition metals and nitrogen oxides showed a (strong) correlation for almost all cohorts we could not perform two-pollutant models in order to test whether or not these pollutants have independent effects on inflammatory blood markers.

4.5. Elemental components of PM and fibrinogen

While pooled elemental component associations with hsCRP were homogeneous we observed rather heterogeneous associations with fibrinogen among the cohorts. Only increases in $PM_{2.5}$ Zn were significantly associated with higher fibrinogen levels. However, LUR models for $PM_{2.5}$ Zn differed between the cohorts making it difficult to identify a potentially influential source (see Supplemental Table 3). In detail, for FINRISK only an indicator for urban green was included in the LUR model, while the models of all other cohorts comprised traffic indicators. Industrial sources and a variable for surface area of semi-natural and forested areas were also part of the LUR models of HNR and KORA. Moreover, KORA showed significant $PM_{2.5}$ Cu and Si as well as PM_{10} Fe, Ni, and Si associations with fibrinogen while no or protective associations were detected for the other cohorts. A highly significant positive effect of PM_{10} K was found in HNR but an adverse association in KORA participants. The LUR model of PM_{10} K contains only an industry-related source for HNR while the LUR models for the other cohorts included traffic indicators. As the limited number of the cohorts prevented more in-depth analyses, we can only speculate whether

Fig. 1. Distribution of elemental PM components sulfur (S), potassium (K), copper (Cu), iron (Fe), nickel (Ni), vanadium (V), zinc (Zn), and silicon (Si). Boxplots represent the 5th, 25th, 50th, 75th and 95th percentiles.

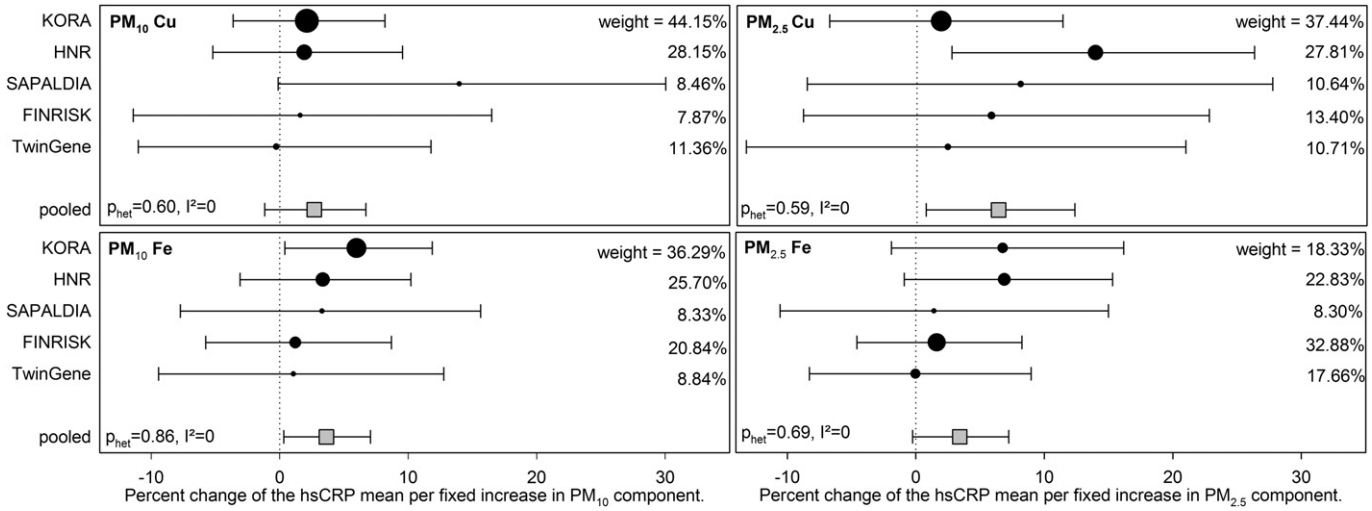

Fig. 2. Cohort-specific and pooled associations between elemental components of PM and hsCRP.

varying source emission across Europe, differences between cohorts in influential sources or in the extent of exposure misclassification depending on LUR model performance were a reason for the heterogeneity in effect estimates. Overall, the excessive heterogeneity of these associations prohibits strong conclusions about the pooled associations between the elemental components of PM and fibrinogen.

4.6. Strengths and limitations

This multi-center study is the first study investigating the association between inflammatory blood markers and estimated long-term exposure to elemental components of PM at residence. Strengths of this study are the large number of hsCRP and fibrinogen measurements available from five and four European cohorts, respectively. Also, we used a common protocol for the air pollution measurement campaigns and LUR modeling (Eeftens et al., 2012a; de Hoogh et al., 2013), a common code book to define potential confounders as similar as possible between the cohorts, and an identical analysis strategy.

In total, for each cohort a considerable number of statistical tests have been performed. However, the observed increases in hsCRP related to elevated levels of elemental components of PM showed little heterogeneity across cohorts which cannot be explained as findings by chance only.

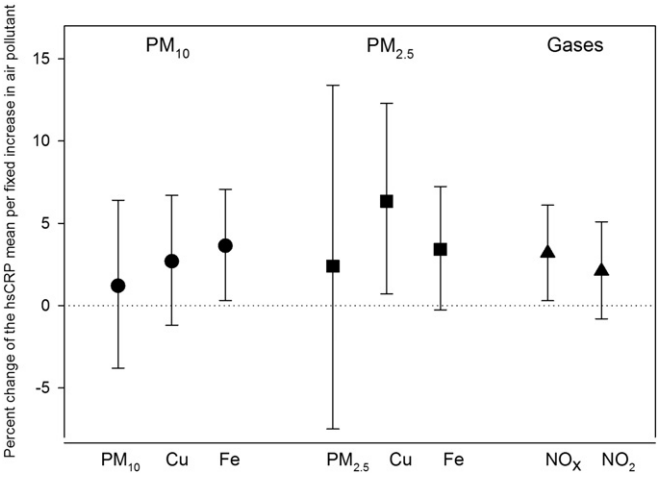

Fig. 3. Pooled associations between PM_{10}, $PM_{2.5}$, elemental components of PM and nitrogen oxides with hsCRP.

The long-term exposure concentrations estimated at residence are based on exposure measurements conducted between 2008 and 2011. Blood sampling was performed up to 16 years earlier; therefore, exposure misclassification cannot be excluded. However, it has been shown that LUR models give stable NO_2 exposure estimates with good agreement between measured spatial exposure contrasts for different time points (Eeftens et al., 2011; Cesaroni et al., 2012; Wang et al., 2013). This has also been reported for LUR models for black smoke in the UK (Gulliver et al., 2011). Based on the findings of the mentioned studies we assume that unlike the absolute component levels the spatial contrasts within the ESCAPE study areas have not changed essentially during the last few decades.

Our LUR models were optimized to estimate traffic-related air pollutants, thus traffic sites and traffic-related predictors were overrepresented in the exposure assessment. Biomass and residential wood combustion (a source for K) could not be considered as predictors since this information was not available for most regions. Estimated component concentrations might reflect different sources between the cohorts because of different predictor variables included in the LUR models. Especially for K the estimated component might not stand for the pathogenic component itself but for a different source. The long-term exposures estimated for the residential addresses are likely to misclassify true individual long-term exposures. We expect the error to be a combination of classical and Berkson error, potentially biasing the results towards the null.

It would be interesting to analyze both short- and long-term effects of elemental components of PM on hsCRP and fibrinogen in order to clarify the relationship between air pollution and systemic inflammation. However, daily concentrations of elemental components were not available for the cohorts of this study but might be considered for future analyses.

5. Conclusion

In conclusion, we observed increased hsCRP concentrations in association with long-term exposure to transition metals (Fe, Cu) as well as higher fibrinogen levels associated with increased $PM_{2.5}$ Zn concentrations. Non-tailpipe emissions of vehicular traffic are significant sources of these elements.

The interpretation of our findings remains difficult because the elemental components are correlated, might represent one or more sources, and are estimated rather than directly measured. However, although our detected associations were only small and might be considered subclinical, our results shed light on the potential role of elemental components of PM in contributing to PM health effects. In particular,

long-term exposure to transition metals within ambient PM, originating from traffic and industry, may be related to chronic systemic inflammation providing a link to long-term health effects of PM.

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Appendix A. Supplementary data

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