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

Regina Hampel[1], Annette Peters[1], Rob Beelen[2], Bert Brunekreef[2,3], Josef Cyrys[1,4], Ulf de Faire[5], Kees de Hoogh[6], Kateryna Fuks[7], Barbara Hoffmann[8], Anke Hüls[7], Medea Imboden[9,10], Aleksandra Jedynska[11], Ingeborg Kooter[11], Wolfgang Koenig[12], Nino Künzli[9,10], Karin Leander[5], Patrik Magnusson[13], Satu Männistö[14], Johanna Penell[5], Göran Pershagen[5], Harish Phuleria[9], Nicole Probst-Hensch[9,10], Noreen Pundt[15], Emmanuel Schaffner[9,10], Tamara Schikowski[7,9,10], Dorothea Sugiri[7], Pekka Tiittanen[16], Ming-Yi Tsai[9,10], Meng Wang[2], Kathrin Wolf[1], Timo Lanki[16], for the ESCAPE and TRANSPHORM study groups

[1] Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[2] Institute for Risk Assessment Sciences, Division Environmental Epidemiology, Utrecht University, Utrecht, The Netherlands

[3] Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[4] ESC-Environmental Science Center, University of Augsburg, Augsburg, Germany

[5] Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

[6] MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, London, UK

[7] IUF Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

[8] Medical School, the Heinrich Heine University of Düsseldorf, Düsseldorf, Germany

[9] Swiss Tropical and Public Health Institute, Basel, Switzerland

[10] University of Basel, Switzerland

[11] The Netherlands Organisation for Applied Scientific Research, Utrecht, The Netherlands

[12] Department of Internal Medicine II - Cardiology, University of Ulm Medical Center, Ulm, Germany

[13] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[14] Department of Chronic Disease Prevention, National Institute for Health and Welfare (THL), Helsinki, Finland

[15] Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, Essen, Germany

[16] Department of Environmental Health, National Institute for Health and Welfare (THL), Kuopio, Finland

Corresponding author:

Annette Peters

Institute of Epidemiology II

Helmholtz Zentrum München, German Research Center for Environmental Health

Ingolstädter Landstr. 1

85764 Neuherberg, Germany

Tel.: 0049 89/3187 4566

Fax.: 0049 89/3187 3380

Email: peters@helmholtz-muenchen.de

Contributions:

RH contributed to the design, statistical script, local data analyses and meta-analysis, and drafted the manuscript; AP contributed to the design, provided local cohort data and drafted the manuscript; TL contributed to the design and drafted the manuscript; RB contributed to the design and exposure assessment; BB contributed to the design; NK contributed to the design and provided local data; BH, GP, KL, MI, NPH, NP, PM, SM, TS, UDF, and WK provided local cohort data; AJ, DS, HP, IK , JC, KW, KDH, MW, and MT contributed to the exposure assessment; AH, ES, JP, KF, and PT performed the local data analyses. All authors contributed to critical reading of and comments to the manuscript, interpretation of data and approved the final draft.

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At a glance commentary:

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

What this paper adds to the field: This multi-center study is the first study investigating the association between inflammatory blood markers and long-term exposure to PM components. We observed increased hsCRP levels in association with exposure to transition metals (iron and copper) as well as higher fibrinogen levels associated with increased PM2.5 zinc concentrations. Our results might help to explain the findings of epidemiological studies which reported associations between air pollution and cardiovascular health end-points such as progression of respiratory or cardiovascular disease.

This article has an online data supplement, which is accessible from the issue's table of content online at “www.atsjournals.org”.

ABSTRACT

Rationale. Epidemiological studies have associated long-term exposure to ambient particulate matter with increased cardiovascular and respiratory mortality. 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 PM components 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 from five and 17,428 fibrinogen measurements from four cross-sectional cohort studies were available. Residential long-term concentrations of particulate matter<10µm (PM_{10}) and <2.5µm ($PM_{2.5}$) and selected components (copper, iron, potassium, nickel, sulfur, silicon, vanadium, zinc) were estimated with land-use regression models. Component effects were estimated with and without adjustment for PM mass using linear regression models for each cohort separately. Cohort-specific results were combined using random effects meta-analysis.

Measurements and Main Results. A 5ng/m³ increase in $PM_{2.5}$ copper and a 500ng/m³ increase in PM_{10} iron were associated with a 6.3%[0.7;12.3%] and 3.6%[0.3;7.1%] increase in hsCRP, respectively. The association between components and fibrinogen were slightly weaker. A 10ng/m³ increase in $PM_{2.5}$ zinc was associated with a 1.2%[0.1;2.4%] increase in fibrinogen. This association became non-significant when additionally adjusting for PM2.5.

Conclusions. Long-term exposure to transition metal concentrations 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.

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INTRODUCTION

There is evidence for an adverse association between long-term exposure to ambient particulate matter (PM) and cardiovascular as well as respiratory mortality[1-5]. 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[6-12] rather than long-term effects of PM components on cardiovascular health. In the long-term California Teacher Study, Ostro et al.[13] observed an increased risk for ischemic heart disease mortality in association with exposure to the $PM_{2.5}$ (PM<2.5µm in diameter) components iron, potassium, silicon, and zinc.

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[14]. 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 $PM_{2.5}$ and PM_{10} (PM<10µm in diameter) levels at residence are associated with an increased risk for natural mortality [15] and incident cardiac events[16], respectively. Systemic inflammation and subclinical atherosclerosis[17] [18] 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) and fibrinogen were investigated in five and four cohorts, respectively. Recent meta-analyses showed (Lanki et al., submitted) no or inconsistent associations on high-sensitivity CRP (hsCRP) and fibrinogen for PM_{10} and $PM_{2.5}$ among cohorts. One reason might be the different particle composition between these study regions[19]. The aim of this analysis was to assess the association between PM components 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[20].

METHODS

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: Cooperative Health Research in the Region of Augsburg, Germany (KORA), Heinz Nixdorf Recall Study, Germany (HNR), Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults, Switzerland (SAPALDIA), National FINRISK Study, Finland, and TwinGene, Sweden. For the analyses on fibrinogen, four cohorts were available: KORA, HNR, FINRISK, and the 60-year olds cohort study (SIXTY) from Sweden. Detailed information on the cohorts can be found in the Online Data Supplement.

Blood markers and covariates

The blood markers of interest were hsCRP and fibrinogen. Detailed information how the blood markers were determined in each cross-sectional cohort study 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 for a cohort a variable was not available or more than 10% of the values were missing the respective variable was replaced with the best available variable.

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[21]. 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)[19]. Analyses were performed by Cooper Environmental Services, Portland USA. Forty-eight elements were measured in both $PM_{2.5}$ and PM_{10} fraction. 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 components there was 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. The transition metals Cu and Fe reflect traffic and brake wear, 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[22] [23].

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[24]. Annual exposure concentrations for each individual's residence were predicted using the developed LUR models.

Statistical analyses

Linear regression models in SAS and STATA software 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, sex, education, body mass index (BMI), physical activity, smoking status, and alcohol intake. 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.

The association between PM components and hsCRP or fibrinogen is 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[25]. 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)[26]. 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 PM component. The fixed increments for each component were chosen based on the average of the cohort-specific ranges between the 10^{th} and 90^{th} percentile.

We performed several sensitivity analyses: i) As the single-pollutant models ignore correlations with PM we additionally included PM mass in the models following a two-step strategy introduced by Mostofsky et al.[27]: 1. step) Regression of a specific 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. ii) If a cohort showed a comparatively low R^2 for the LUR model of a specific component or iii) If the LUR model comprised only one predictor variable we excluded the respective cohort when pooling the effect estimates.

RESULTS

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.

Figure 1 and Table E1 show the distribution of the estimated PM components for each cohort as well as the corresponding model fit (R^2) of the LUR models. The LUR models for the 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 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 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[19] as well as in Table E3.

In general, higher concentrations of PM components were estimated for the HNR and SAPALDIA cohort, low to intermediate levels for KORA, and lower levels for FINRISK and the Swedish cohorts (Table E1). Moderate to strong correlations (r>0.6) between Cu and Fe were found for all cohorts, whereas the Spearman correlation coefficients for the other components were not consistent among the cohorts (Table E2). The strength of the correlation between PM mass and its components also differed from cohort to cohort.

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, Figure 2). There was no evidence for heterogeneity among the cohort-specific effect estimates. Figure 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 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 (Table E2). Figure 3 compares the pooled effect estimates of $PM_{2.5}$, PM_{10}, PM components and nitrogen oxides on hsCRP.

The pooled associations between PM components and fibrinogen were weaker and more heterogeneous among the cohorts (Table 2). Only an increase in $PM_{2.5}$ Zn led to significantly higher fibrinogen levels without heterogeneity among the cohorts and the strongest weight for HNR. Elevated concentrations of $PM_{2.5}$ Fe led to higher fibrinogen levels. However, this association was not significant. 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 (Figure E3). 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).

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 (Table E4, Figure E2). 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 component when adjusting for PM_{10}. Additionally including $PM_{2.5}$ led to a non-significant association between $PM_{2.5}$ Zn and fibrinogen and to an inverse borderline significant association with $PM_{2.5}$ K (Table E4, Figure E4).

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).

DISCUSSION

In this European multi-center study, we observed increased hsCRP values in association with elevated concentrations of PM_{10} Cu, $PM_{2.5}$ Cu, and $PM_{2.5}$ Fe at residence. The associations between the components and fibrinogen were somewhat more heterogeneous among the cohorts leading to non-significant pooled effect estimates. An increase in $PM_{2.5}$ Zn and Fe led to higher fibrinogen levels. However, only the former association reached significance.

It is assumed that exposure to PM may provoke a low-grade pulmonary inflammatory response leading to a release of inflammatory mediators and a subsequent systemic effects. On a long-term time-scale the progression of respiratory disease and atherosclerosis might be the consequence[28 29]. 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[20]. The production of ROS can lead to oxidative stress and possibly further to systemic inflammation[28]. Therefore, we hypothesized that blood markers of inflammation might be associated with long-term concentrations of PM components 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[18]. 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 cardiovascular or respiratory mortality were observed in different parts of the world[1 3 30-33], but there are only a few published studies on the

association between long-term air pollution exposure and blood markers of inflammation[34 35]. E.g. Hoffmann et al.[34] reported 23.9%[4.1;47.4%] higher hsCRP levels and 3.9%[0.3;7.7%] higher fibrinogen levels associated with a 3.91µg/m³ increase in long-term residential exposure to $PM_{2.5}$ in men and weaker associations in women. Forbes et al.[35] 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 1µg/m³ increase in PM_{10} in the survey from 1998 and no effects on hsCRP.

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[13 36]. Ostro et al.[13] observed an increased risk for ischemic heart disease 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..

To date, the effects of chemical components of PM on inflammatory blood markers were only assessed in a panel study[10] and in a semi-experimental investigation[37]. Wu et al.[10] observed a 3.9%[0.3, 7.6%] increase in fibrinogen in association with elevated 24h-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.[37] healthy adults were repeatedly exposed to ambient PM for five hours 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. 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.[37] we observed slightly stronger changes in hsCRP than in fibrinogen in association with higher Fe and Cu levels.

In our study, the strongest associations between PM components and hsCRP were detected for Cu and Fe. Within the ESCAPE project, concentrations of PM components at residence were not measured but estimated using LUR models. Hence, 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 (Table E3). For these 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 component levels and hsCRP are mainly related to sources from traffic and partly from industry. In support of that, we observed a moderate to strong correlation (r>0.6) between the components PM_{10} Fe, $PM_{2.5}$ Fe and $PM_{2.5}$ Cu and nitrogen oxides for all cohorts but HNR.

In our recent analysis (Lanki et al., submitted) conducted in the same participants as this study, we detected a 3.2%[0.3;6.1%] increase in hsCRP in association with a 20µg/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 PM components 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 independent of PM[38]. 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).

While pooled 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 Table E3). 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. Natural and industrial sources 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. Differences in the cohort-specific LUR models could only partly explain the heterogeneity. We can only speculate that differing methods between the cohorts to determine fibrinogen might also be reason for the observed heterogeneity. Overall, the excessive heterogeneity of these associations prohibits strong conclusions about the pooled associations between the PM components and fibrinogen.

This multi-center study is the first study investigating the association between inflammatory blood markers and estimated long-term exposure to PM components at residence. Strengths of this study are the high number of hsCRP and fibrinogen measurements available from five and four European cohorts, respectively. Further strengths are the common protocol for the air pollution measurement campaigns and LUR modeling[19 24], the common code book to define variables as similar as possible between the cohorts, and the identical analysis strategy making cohort-specific results comparable.

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 PM components showed little heterogeneity across cohorts which cannot be explained as findings by chance only.

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[39-41]. This has also been reported for LUR models for black

smoke in the UK[42]. Based on the findings of the mentioned studies we assume that 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.

In general, we cannot exclude individual exposure misclassification, but we expect the error to be non-differential potentially biasing the results towards the null.

In conclusion, we observed increased hsCRP levels 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 source of these elements. Although our detected associations were only small and might be considered subclinical, our results might help to explain the findings of epidemiological studies which reported associations between air pollution and cardiovascular health end-points such as progression of atherosclerosis, coronary events or stroke.

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

Figure 2. Cohort-specific and pooled associations between PM components and hsCRP.

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

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

Cohort (country)	Time of baseline visit	Age (years)*		BMI (kg/m²)*		Female*	Current smoking*	hsCRP (mg/l)			Fibrinogen (g/l)		
		Mean	SD	Mean	SD	%	%	N	Mean	SD	N	Mean	SD
KORA (Germany)	1994-1995, 1999-2001	50.2	13.6	27.2	4.6	50.1	23.9	7,137	2.7	4.9	7,151	2.8	0.7
HNR (Germany)	2000-2003	59.5	7.8	27.9	4.6	49.9	23.3	4,492	3.1	9.0	4,444	3.3	0.8
SAPALDIA (Switzerland)	2002	55.0	10.6	25.3	4.3	56.6	28.3	685	2.3	3.6	-	-	-
FINRISK (Finland)	1997, 2002, 2007	48.9	13.6	26.6	4.6	52.4	28.3	7,627	2.3	4.5	2,044	3.6	0.8
TwinGene (Sweden)	2004-2008	64.2	8.5	25.2	3.6	56.2	19.1	1,617	2.8	4.9	-	-	-
SIXTY (Sweden)	1997-1999	60.4	0.1	26.8	4.2	52.0	20.8	-	-	-	3,789	3.0	0.8

*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.

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

			hsCRP					fibrinogen			
Exposure	increment (ng/m³)	N cohorts	%-change (95%-CI)		I^2	p_{het}	N cohorts[e]	%-change (95%-CI)		I^2	p_{het}
PM_{10}	10	5	1.2	(-3.8;6.4)	0	0.899	4	0.1	(-1.4;1.7)	36	0.179
S	200	4[a]	0.3	(-6.5;7.7)	12	0.320	4	0.0	(-2.4;2.5)	44	0.317
K	100	5	3.4	(-5.3;13.0)	75	0.016	4	0.5	(-2.5;3.5)	87	0.006
Cu	20	5	2.7	(-1.2;6.7)	0	0.600	4	0.4	(-1.0;1.8)	56	0.148
Fe	500	5	3.6 *	(0.3;7.1)	0	0.863	4	0.2	(-1.3;1.6)	68	0.031
Ni	2	4[a]	2.0	(-5.9;10.5)	28	0.309	4	0.6	(-4.0;5.2)	84	0.068
V	3	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	5	-0.1	(-4.5;4.4)	0	0.507	4	0.8	(-0.4;1.9)	14	0.311
Si	500	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	5	2.4	(-7.5;13.4)	54	0.049	4	0.5	(-1.1;2.0)	0	0.662
S	200	4[a]	0.9	(-6.1;8.4)	10	0.339	4	0.0	(-3.0;2.9)	58	0.336
K	50	4[c]	-3.4	(-12.7;6.8)	52	0.127	3[c]	-1.1	(-2.6;0.5)	0	0.489
Cu	5	5	6.3 *	(0.7;12.3)	0	0.587	4	0.6	(-1.5;2.7)	61	0.099

Fe	100	5	3.4 †	(-0.3;7.2)	0	0.688	4	0.7	(-0.3;1.8)	37	0.178
Ni	1	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	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	5	2.1	(-2.8;7.2)	7	0.339	4	1.2 *	(0.1;2.4)	8	0.519
Si	100	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 <10µm, $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5µm, 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