Long-term Exposure to Particulate Matter Constituents and the Incidence of Coronary Events in 11 European Cohorts

Kathrin Wolf,[a] *Massimo Stafoggia,*[b] *Giulia Cesaroni,*[b] *Zorana Jovanovic Andersen,*[c,d] *Rob Beelen,*[e] *Claudia Galassi,*[f] *Frauke Hennig,*[g] *Enrica Migliore,*[f] *Johanna Penell,*[h] *Fulvio Ricceri,*[i] *Mette Sørensen,*[j] *Anu W. Turunen,*[k] *Regina Hampel,*[a] *Barbara Hoffmann,*[g,l] *Hagen Kälsch,*[m] *Tiina Laatikainen,*[n,o] *Göran Pershagen,*[h] *Ole Raaschou-Nielsen,*[c] *Carlotta Sacerdote,*[f] *Paolo Vineis,*[p] *Chiara Badaloni,*[b] *Josef Cyrys,*[a,q] *Kees de Hoogh,*[r,s] *Kirsten T. Eriksen,*[c] *Aleksandra Jedynska,*[t] *Menno Keuken,*[t] *Ingeborg Kooter,*[t] *Timo Lanki,*[k] *Andrea Ranzi,*[u] *Dorothea Sugiri,*[g] *Ming-Yi Tsai,*[r,s] *Meng Wang,*[e] *Gerard Hoek,*[e] *Bert Brunekreef,*[e,v] *Annette Peters,*[a,w] *and Francesco Forastiere*[b]

Background: Long-term exposure to particulate matter (PM) has been associated with increased cardiovascular morbidity and mortality but little is known about the role of the chemical composition of PM. This study examined the association of residential long-term exposure to PM components with incident coronary events.

Methods: Eleven cohorts from Finland, Sweden, Denmark, Germany, and Italy participated in this analysis. 5,157 incident coronary events were identified within 100,166 persons followed on average for 11.5 years. Long-term residential concentrations of PM < 10 μm (PM_{10}), PM < 2.5 μm ($PM_{2.5}$), and a priori selected constituents (copper, iron, nickel, potassium, silicon, sulfur, vanadium, and zinc) were estimated with land-use regression models. We used Cox proportional hazard models adjusted for a common set of confounders to estimate cohort-specific component effects with and without

Submitted 2 July 2014; accepted 27 March 2015.

[a]Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany; [b]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [c]Danish Cancer Society Research Center, Copenhagen, Denmark; [d]Center for Epidemiology and Screening, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [e]Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands; [f]Unit of Cancer Epidemiology, AO Citta' della Salute e della Scienza–University of Turin and Center for Cancer Prevention, Turin, Italy; [g]IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; [h]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [i]Molecular and Genetic Epidemiology Unit, HuGeF-Human Genetics Foundation, Turin, Italy; [j]Diet, genes and environment, Danish Cancer Society Research Center, Copenhagen, Denmark; [k]Department of Environmental Health, National Institute for Health and Welfare, Kuopio, Finland; [l]Medical Faculty, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany; [m]West-German Heart Center, Department of Cardiology, University Hospital of Essen, Essen, Germany; [n]Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; [o]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland; [p]Imperial College London, St Mary's Campus, London, United Kingdom; [q]Environment Science Center, University of Augsburg, Augsburg, Germany; [r]Swiss Tropical and Public Health Institute, Basel, Switzerland; [s]University of Basel, Basel, Switzerland; [t]TNO, Netherlands Organization for Applied Scientific Research, Utrecht, The Netherlands; [u]Environmental Health Reference Centre, Regional Agency for Environmental Prevention of Emilia-Romagna, Modena, Italy; [v]Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands; and [w]German Research Center for Cardiovascular Disease (DZHK), Partner Site Munich, Germany.

Supported by the European Community's Seventh Framework Program (FP7/2007–2011): ESCAPE (Grant Agreement Number: 211250) and TRANSPHORM (ENV.2009.1.2.2.1, Grant Agreement Number: 243406). For the Finnish parts of the study, additional funding came from the Academy of Finland (Project Number 129317). Exposure assessment was performed by Tarja Yli-Tuomi, Pekka Taimisto, and Arto Pennanen from the Department of Environmental Health. Mortality, area-level SES, and building data were provided by Statistics Finland. The Swedish cohorts received funding from Stockholm County Council, Swedish Environmental Protection Agency, Swedish Research Council, Swedish Council of Working Life and Social Research, Swedish Diabetes Association, Swedish Heart-Lung Foundation, and Novo Nordisk Scandinavia. In particular, SALT was supported by grants from the Swedish Council for Working Life and Research and NIH (AG 09724). The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Since the year 2000, the collection of MI data has been co-financed by the German Federal Ministry of Health to provide population-based MI morbidity data for the official German Health Report (see www.gbe-bund.de). Steering partners of the MONICA/KORA Infarction Registry, Augsburg, include the KORA research platform, Helmholtz Zentrum München, and the Department of Internal Medicine I, Cardiology, Central Hospital of Augsburg. The SIDRIA cohort studies were cofunded by the Italian Ministry of Health. The Heinz Nixdorf Foundation, the German Ministry of Education and Science (BMBF), the German Aerospace Center (Deutsches Zentrumfür Luft- und Raumfahrt [DLR]), and the German Research Foundation (DFG HO 3314/2-1 and JO170/8-1), Bonn, Germany, provided generous support of this study.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com). This content is not peer-reviewed or copy-edited; it is the sole responsibility of the authors.

Correspondence: Kathrin Wolf, Institute of Epidemiology II, Helmholtz Zentrum München-German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany. E-mail: kathrin.wolf@helmholtz-muenchen.de.

ISSN: 1044-3983/15/2604-0565
DOI: 10.1097/EDE.0000000000000300

including PM mass, and random effects meta-analyses to pool cohort-specific results.

Results: A 100 ng/m³ increase in PM_{10} K and a 50 ng/m³ increase in $PM_{2.5}$ K were associated with a 6% (hazard ratio and 95% confidence interval: 1.06 [1.01, 1.12]) and 18% (1.18 [1.06, 1.32]) increase in coronary events. Estimates for PM_{10} Si and $PM_{2.5}$ Fe were also elevated. All other PM constituents indicated a positive association with coronary events. When additionally adjusting for PM mass, the estimates decreased except for K.

Conclusions: This multicenter study of 11 European cohorts pointed to an association between long-term exposure to PM constituents and coronary events, especially for indicators of road dust.

(*Epidemiology* 2015;26: 565–574)

The link between long-term exposure to ambient air pollution and especially particulate matter (PM) and adverse cardiovascular health effects is well established.[1–5] However, PM is a complex heterogeneous mixture of chemical constituents originating from a variety of sources and little is known regarding which specific components implicate toxic effects on human health.[6,7] Already in 1998, the US National Academy highlighted the importance of understanding the specific sources.[8] Several epidemiologic, toxicologic, and human exposure studies have been conducted since then, but evidence is still tenuous, partly due to the limited comparability of the findings.[6,9,10] Also, these analyses focused on short-term effects of PM constituents. So far, only a few studies investigated the influence of long-term PM component exposure on cardiovascular and respiratory morbidity and mortality or related outcomes.[11–15] Two studies from the US consistently observed an increased risk of ischemic heart disease mortality for $PM_{2.5}$ iron (Fe) and sulfur (S) or sulfate, but evidence was mixed for potassium (K), silicon (Si), zinc (Zn), nickel (Ni), and vanadium (V).[11,12] For both studies, concentrations were obtained from fixed monitoring stations, potentially leading to exposure misclassification. A further US study applied a national spatial prediction model to derive individual residential concentrations of elemental and organic carbon, S, and Si. The authors observed an association between S and incident cardiovascular events but not with cardiovascular mortality.[13]

In this study, individual PM component concentration was assessed based on a standardized framework within the European Study of Cohorts for Air Pollution Effects (ESCAPE, www.escapeproject.eu) and Transport Related Air pollution and Health impacts - Integrated Methodologies for Assessing Particulate Matter (TRANSPHORM, www.transphorm.eu) projects.[14,16] We previously observed a 13% increased risk for coronary events per 5 μg/m³ increase in $PM_{2.5}$ and 12% increased risk per 10 μg/m³ PM_{10} (hazard ratios [HRs] and 95% confidence intervals: 1.13 [0.98, 1.30] and 1.12 [1.01, 1.25], respectively).[17] However, no association was seen between PM or PM components and cardiovascular mortality.[14,18] We explained this lack of association with decreased fatality rates over the past years due to an improved treatment resulting in a lower power to detect an association. Furthermore, medication intake has likely biased the results because fatal events might have been preceded by nonfatal events. When looking at incident events, we included both fatal and nonfatal events and tried to reduce the medication bias at least in parts by excluding persons with prevalent events.

As current air quality guidelines are based on PM, a better understanding in the toxicity of its components is essential in evaluating the impact of PM on public health. Therefore, the objective of this analysis was to assess the association of residential long-term exposure to PM constituents on the incidence of coronary events in different European regions.

METHODS

ESCAPE combined existing cohort studies of mortality and chronic diseases in Europe to quantify the associations between long-term exposure to air pollutants and health outcomes. For this analysis, we could include 11 cohorts from Helsinki, Finland, Stockholm, Sweden, Copenhagen, Denmark, Augsburg and Ruhr areas (both Germany), and Rome and Turin (both Italy), for which information on coronary event incidence and long-term PM constituent concentration at the residence were available (eAppendix 1; http://links.lww.com/EDE/A911). Work in all cohorts was conducted in accordance with the Declaration of Helsinki, and with all local ethical requirements. All subjects provided informed consent or authorization from the data protection authority.

Exposure Assessment

Within ESCAPE, PM was measured based on a standardized methodology between 2008 and 2011.[19] In each study region, we performed three 14-day measurement periods at 20 monitoring sites over approximately 1 year. For each site, we averaged the measurements and adjusted for temporal trends with the help of continuous measurements taken at one background reference site which was operated the whole study period. Harvard impactors were used to collect samples of PM_{10} and $PM_{2.5}$ on Teflon filters which were then analyzed for elemental composition using X-ray fluorescence.[16] Out of 48 elements measured, we chose a priori eight constituents (S, K, Cu, Fe, Ni, V, Zn, Si) which indicated an association with human health,[6] which were detected in >75% of the samples and reflect various anthropogenic sources.[16,20] However, these elements are not necessarily source-specific and potential sources may differ among different regions.

Following a common protocol (http://www.escapeproject.eu/manuals/), land-use regression models were developed for each area and each exposure variable separately on the basis of the measured concentrations and potential predictor variables like traffic indicators, land use, household density, industry, and altitude (eAppendix 2, eTable 1; http://links.lww.com/EDE/A911), as presented previously.[16] Whereas K was present in both PM fractions, Cu, Fe, and Si were more

prominent in the coarse fraction of PM_{10} and S, Ni, V, and Zn were more prominent in $PM_{2.5}$. Because we aimed to investigate which specific components might be responsible for the toxicity of both PM fractions, we developed for each fraction separate models for all eight components. The performance of the land-use regression models was assessed with the average validation explained variance determined by leave-one-out cross-validation R^2. Models for S and Zn performed usually better in the south because the measured concentrations were higher combined with a higher spatial contrast in these areas (eAppendix 2, eTable 1; http://links.lww.com/EDE/A911). The model performance was mixed for K with low cross-validation R^2 (<0.30) for Helsinki (both fractions), Copenhagen (PM_{10}), and Turin ($PM_{2.5}$). For the Ruhr area, only a poor model could be built for PM_{10} K (cross-validation $R^2 = 0.14$) and none for $PM_{2.5}$ K. Reasons for failure might be a small within-area variability in combination with the lack of source-specific predictor variables. Cross-validation R^2 ranged from 0.47 (Helsinki) to 0.92 (Copenhagen) for Cu and Fe in both fractions with traffic as the main predictor. Although larger amounts of Ni and V were found in $PM_{2.5}$, concentration levels and within-area variability were generally higher for PM_{10}. Thus, models performed only poorly (<0.30) to moderately (0.30–0.50) for the $PM_{2.5}$ fraction but reasonably well (>0.50) for PM_{10} for most areas. No models could be built for $PM_{2.5}$ Ni for Stockholm and for $PM_{2.5}$ V for the Munich/Augsburg area, probably because of poor precision of the measurements with low concentrations. The PM_{10} V model for Munich/Augsburg area was very poor (cross-validation $R^2 = 0.04$) and included only one predictor variable which was only available at five out of the 20 monitoring stations resulting in very low concentrations with almost no variation. Therefore, we decided to exclude the Augsburg cohort from the PM_{10} V meta-analysis. Cross-validation R^2 for Si was moderate to good with traffic and population density as the main predictor variables. The regression models were then applied to the baseline residential addresses of the participants to predict individual long-term concentrations.

Outcome Definition

Assignment of outcome definitions was identical to our previous analysis.[17] Information on coronary events was derived by record-linkage of hospital discharge and mortality registries for nine cohorts. Cases were defined on the basis of the principal diagnosis on the hospital discharges including either International Classification of Disease (ICD) codes for "acute myocardial infarction" or "other acute and sub-acute forms of ischemic heart disease" (ICD-9 codes: 410, 411; ICD-10 codes: I21, I23, I20.0, I24). In addition, death certificates were checked for persons who died out-of-hospital from ischemic heart diseases (ICD-9: 410–414; ICD-10: I20–I25), and had no evidence of hospital admission for ischemic heart disease 28 days before death, and no evidence of hospitalization for any cause 2 days before death. For the Ruhr cohort, incident cases were adjudicated by an independent endpoint committee on the basis of medical records. For the Augsburg cohort, incident cases were selected on the basis of interview and inspection of medical records, and then clinically validated using the MONICA criteria. Because we were interested in incident events only, persons who suffered an acute coronary or cerebrovascular event previous to the enrollment were excluded from the analyses. The exact reference period depended on the data availability of the cohorts and ranged from 3 years for two Italian cohorts to lifelong for the Augsburg cohort.

Statistical Analyses

In the first step, Cox proportional hazards regression models with age as the underlying time variable were calculated locally in each cohort using a common statistical protocol and STATA script.[17] Potential covariates were harmonized on the basis of a common codebook. We defined confounders at baseline a priori based on our previous analysis.[17] The main model included year of enrollment, sex, marital status (single, married/living with partner, divorced/separated, widowed; for the Stockholm SDPP cohort only the binary variable "living with partner" was available; for the Rome cohort all participants were living in partnerships at baseline), education (primary school or less, up to secondary school or equivalent, university degree and more), occupation (employed, unemployed, homemaker/housewife, retired), smoking status (current, former, never), smoking duration (years), smoking intensity among current smokers (cigarettes per day), and an area-level socioeconomic indicator. The analyses were restricted to persons with no missing information in both the exposure variables and the covariates of the main model.

To investigate the effects of PM constituents on coronary events, we calculated single constituent and PM-adjusted constituent models. The latter are intended to account for the fact that the components as part of PM might reflect the total PM effect rather than the specific effect of the component, especially if component and total PM are highly correlated. Because simple two-pollutant models might induce multicollinearity, we first regressed total PM on each component separately and then included these residuals one by one together with total PM in the model. Then, the estimate of the residual component represents the independent component effect and the PM estimate specifies the effect of total PM mass.[21] According to Mostofsky and colleagues,[21] coefficients and standard errors for the constituent residual are identical to coefficients and standard errors for the component concentration if both are adjusted for PM. However, the interpretation of the PM estimate differs representing the impact of total PM in the residual model while representing the impact of all other components than the one included in a simple two-pollutant model.

In the second step, we performed random-effects meta-analyses with the DerSimonian and Laird[22] method to

pool cohort-specific effect estimates. To evaluate heterogeneity among cohorts, we used I^2 statistics and X^2 test from Cochran's Q statistic.[23] All results are expressed as HR and 95% confidence intervals for a fixed increment in each PM component. Increments were defined a priori as the rounded values of the average difference between the 10th and 90th percentile of the average concentrations at the measurement sites to enable broad comparisons among the HRs of different constituents.

As sensitivity analysis, we restricted the meta-analysis to cohorts with a good performance of the land-use regression model (cross-validation $R^2 > 0.5$). In addition, we performed meta-regression by cross-validation R^2, north to south gradient, and annual average PM. To investigate the role of traffic as a source for specific components, we stratified the cohorts by the inclusion of traffic variables in the cohort-specific land-use regression models (eAppendix 2, eTable 1; http://links.lww.com/EDE/A911). Moreover, we additionally adjusted for all available cardiovascular risk factors, in particular BMI, cholesterol level, physical activity (<1 hour/week, about 1 hour/week, >2 hours/week), alcohol consumption (never, 1–3 drinks/week, 3–6 drinks/week, >6 drinks/week), diabetes, and hypertension. In our previous analysis, PM estimates only changed marginally when including (1) diabetes and hypertension; (2) physical activity, alcohol consumption, and BMI (available in eight cohorts); and (3) all five variables and cholesterol level (available in four cohorts). Because these intermediates and risk factors were not gathered for all cohorts, we built this extended model as the best possible local confounder adjustment for each cohort. We thought this strategy a reasonable tradeoff between weakening the comparability among the cohorts and maintaining the overall picture without reducing the number of cohorts.

All cohort-specific analyses were conducted with STATA software (StataCorp, College Station, TX). For meta-analysis and meta-regression, we used R software (R Core Team (2013), URL http://www.R-project.org/).

RESULTS

A description of the cohorts and the main characteristics of the participants at baseline are presented in Table 1 and eAppendix 2, eTable 2 (http://links.lww.com/EDE/A911). Overall, we observed 5,157 incident coronary events among 100,166 persons followed for 1,154,386 person-years. The average follow-up was 11.5 years and the enrollment period encompassed 15 years (1992–2007). The mean age varied between 44 (Rome and SIDRIA-Turin cohorts) and 74 years (Stockholm cohort SNAC-K); the percentage of women ranged from 48% (EPIC-Turin) to 65% (Stockholm SNAC-K). The distribution of estimated PM component concentrations at residences for each cohort can be found in Figure 1 and eAppendix 2, eTable 3 (http://links.lww.com/EDE/A911). The highest concentrations and contrasts for most

TABLE 1. Individual Baseline Characteristics of the Study Populations of 11 European Cohorts (adapted from BMJ, 2014;348:f7412).

Variables	FINRISK	SNAC-K	SALT	60 Year Olds	SDPP	DCH	HNR	KORA	EPIC-Turin	SIDRIA-Turin	SIDRIA-Rome
	Turku & Helsinki, Finland	Stockholm, Sweden	Stockholm, Sweden	Stockholm, Sweden	Stockholm, Sweden	Copenhagen, Denmark	Ruhr Area, Germany	Augsburg, Germany	Turin, Italy	Turin, Italy	Turin, Italy
No. of subjects	9,995	2,684	6,084	3,686	7,723	35,693	4,433	8,301	7,230	5,137	9,200
Person-years at risk	105,060	16,256	51,756	39,978	106,995	464,055	34,941	84,595	91,490	56,366	102,894
No. of cases	212	200	204	165	181	3,293	135	282	157	123	205
Years of enrolment	1992, 1997, 2002, 2007	2001–2004	1998–2002	1997–1999	1992–1998	1993–1997	2000–2003	1994–1995, 1999–2001	1993–1998	1999	1999
Annual average PM concentration at residence address, 5th, 50th, 95th percentile											
PM_{10} (μg/m³)	10, 14, 20	6, 16, 29	7, 15, 21	7, 15, 21	6, 14, 17	14, 17, 20	25, 28, 32	16, 21, 24	39, 47, 52	41, 49, 54	31, 35, 47
$PM_{2.5}$ (μg/m³)	6, 8, 9	6, 8, 10	5, 8, 9	5, 7, 9	5, 7, 9	10, 11, 13	27, 30, 33	17, 18, 20	13, 14, 15	29, 31, 35	17, 19, 23

Order of studies is based on gradient.
SNAC-K indicates Swedish National Study on Aging and Care in Kungsholmen; SALT, Screening Across the Lifespan Twin study; SDPP, Stockholm Diabetes Prevention Program study; DCH, Danish Diet, Cancer and Health cohort study; HNR, Heinz Nixdorf Recall Study; KORA, Cooperative Health Research in the Augsburg Region; EPIC, European Prospective Investigation into Cancer and Nutrition; SIDRIA, International Study on Asthma and Allergies in Childhood; PM_{10}, particulate matter with an aerodynamic diameter <10 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm.

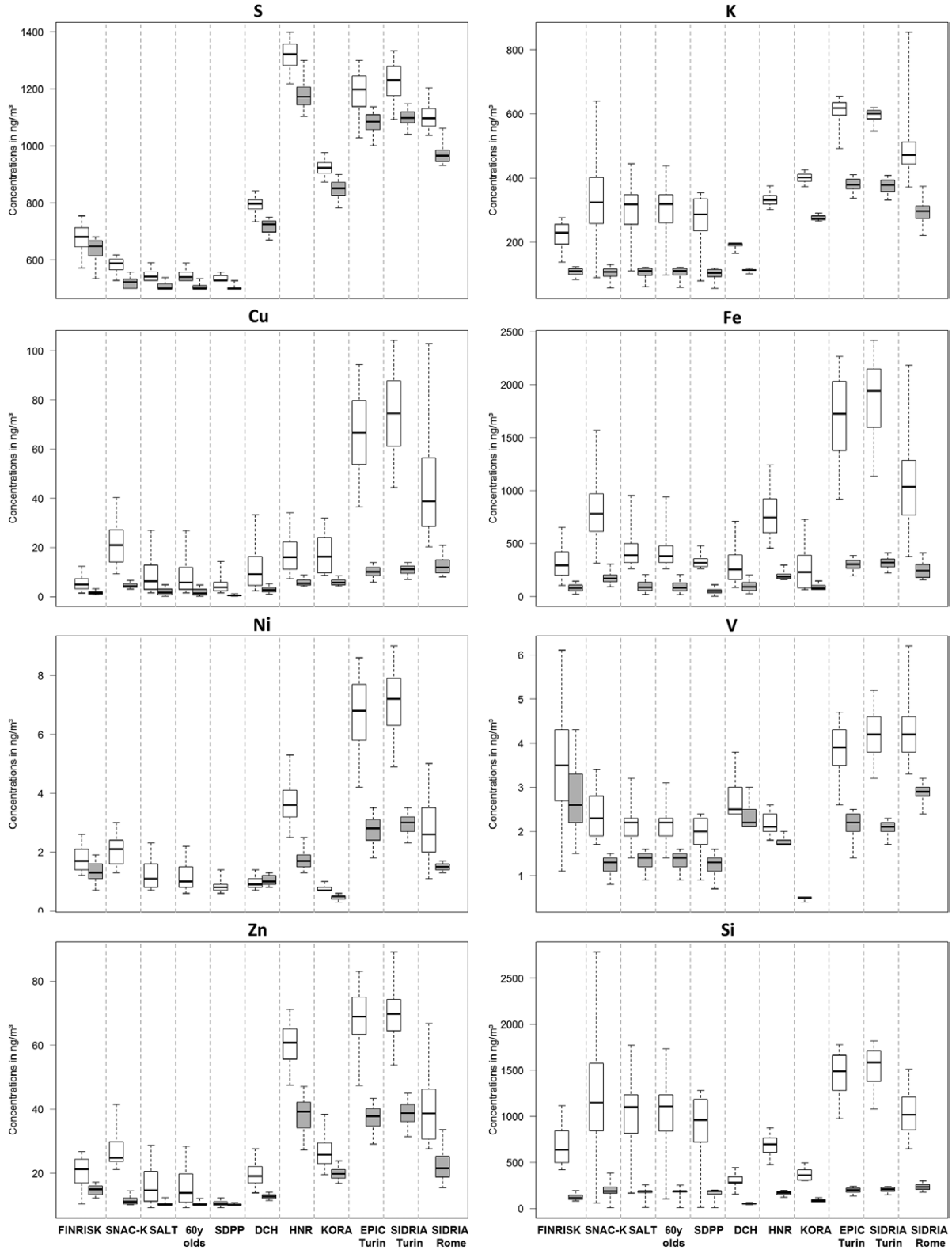

FIGURE 1. Distribution of PM_{10} (*white*) and $PM_{2.5}$ (*grey shaded*) components sulfur (S), potassium (K), copper (Cu), iron (Fe), nickel (Ni), vanadium (V), zinc (Zn), silicon (Si). Boxplots represent 5th, 25th, 50th, 75th, and 95th percentiles. Order of studies is based on a north to south gradient. FINRISK indicates Turku & Helsinki, Finland; SNAC-K, Stockholm, Sweden; SALT, Stockholm, Sweden; 60 year olds, Stockholm, Sweden; SDPP, Stockholm, Sweden; DCH, Copenhagen, Denmark; HNR, Ruhr Area, Germany; KORA, Augsburg, Germany; EPIC-Turin, Turin, Italy; SIDRIA-Turin, Turin, Italy; SIDRIA-Rome, Turin, Italy.

elements were observed for the Italian cohorts. Pearson correlation coefficients between components and total PM were mostly low to moderate (eAppendix 2, eTable 4; http://links.lww.com/EDE/A911).

Table 2 shows the pooled results of constituent and PM-adjusted constituent models of the association between incidence of coronary events and PM components. Substantial heterogeneity between the cohort-specific effect estimates was present for $PM_{2.5}$ Si in single constituent models and $PM_{2.5}$ Zn in PM-adjusted models. Except for K (both PM fractions), the estimates were attenuated in the PM-adjusted models. We observed elevated risks for incident coronary events for increases in both PM fractions of K, PM_{10} Si and $PM_{2.5}$ Fe. Single constituent models also indicated an increased risk for PM_{10} Ni. For all other constituents, positive suggestive associations were found. The effect estimates of total PM remained stable by design (eAppendix 2, eTable 5; http://links.lww.com/EDE/A911). Forest plots of single constituent models of PM_{10} K and Si and $PM_{2.5}$ K and Fe illustrate the cohort-specific weights and effect estimates (Figure 2). While Rome was the most influential cohort for K in both fractions, PM_{10} Si was dominated by the Swedish cohorts and $PM_{2.5}$ Fe by the large Danish cohort. An exclusion of the Danish cohort reduced the $PM_{2.5}$ Fe estimate substantially (1.04 [0.95, 1.15]). Forest plots of the other components can be found in eAppendix 2, eFigures 1 and 2 (http://links.lww.com/EDE/A911).

When pooling only cohorts with a good performance of the land-use regression model, the effect estimates remained stable or slightly increased (compare bottom lines of Figure 2 and eAppendix 2, eFigures 1 and 2; http://links.lww.com/EDE/A911). However, meta-regression by cross-validation R^2, north to south gradient or annual average PM did not reveal a substantial influence of these factors on cohort-specific component estimates (eAppendix 2, eTable 6; http://links.lww.com/EDE/A911). In local analyses, we observed an increased risk for coronary events for the EPIC Turin cohort (eAppendix 2, eFigure 2; http://links.lww.com/EDE/A911), where estimated $PM_{2.5}$ annual average concentrations were above the EU air quality standard of 25μg/m³ for all cohort participants (data not shown). Results of stratified meta-analyses by traffic as land-use regression predictor variable are presented in Figure 3. For PM_{10} K, we observed similar effect sizes compared with the overall effect for the subset of cohorts with traffic. Traffic was also the determining source for $PM_{2.5}$ K and PM_{10} Ni. The additional adjustment for all available cardiovascular risk factors resulted in similar effect estimates for all PM components (eAppendix 2, eTable 7; http://links.lww.com/EDE/A911).

TABLE 2. Association Between Incidence of Coronary Events and Elemental Composition of PM[a] in 11 European Cohorts: Results from Random-effects Meta-analyses and I^2 (P Value) of Test for Heterogeneity of Effect Estimates Between Cohorts

			Single Constituent Model		PM-Adjusted Constituent Model[b]	
Exposure	Increment	No. of Cohorts	Hazard Ratio (95% CI)	I^2 (P)	Hazard Ratio (95% CI)	I^2 (P)
PM_{10} (μg/m³)	10	11	1.12 (1.01, 1.25)	0 (0.81)		
S (ng/m³)	200	11	1.13 (0.96, 1.34)	0 (0.55)	1.00 (0.77, 1.29)	23 (0.23)
K (ng/m³)	100	11	1.06 (1.01, 1.12)	0 (0.98)	1.10 (1.00, 1.21)	0 (0.66)
Cu (ng/m³)	20	11	1.03 (0.96, 1.10)	14 (0.31)	0.99 (0.90, 1.10)	27 (0.19)
Fe (ng/m³)	500	11	1.07 (0.98, 1.17)	34 (0.12)	1.03 (0.89, 1.19)	36 (0.11)
Ni (ng/m³)	2	11	1.13 (1.00, 1.28)	0 (0.49)	1.09 (0.94, 1.28)	0 (0.48)
V (ng/m³)	3	10[c]	1.10 (0.94, 1.30)	0 (0.90)	1.06 (0.86, 1.30)	0 (0.73)
Zn (ng/m³)	20	11	1.08 (0.97, 1.20)	0 (0.89)	1.03 (0.89, 1.18)	0 (0.46)
Si (ng/m³)	500	11	1.08 (1.01, 1.15)	0 (0.66)	1.08 (0.87, 1.33)	21 (0.24)
$PM_{2.5}$ (μg/m³)	5	11	1.13 (0.98, 1.30)	0 (0.60)		
S (ng/m³)	200	11	1.11 (0.87, 1.41)	9 (0.36)	1.11 (0.72, 1.70)	44 (0.06)
K (ng/m³)	50	10[d]	1.18 (1.06, 1.32)	0 (0.61)	1.21 (1.07, 1.37)	0 (0.67)
Cu (ng/m³)	5	11	1.05 (0.94, 1.17)	9 (0.36)	1.03 (0.93, 1.15)	1 (0.43)
Fe (ng/m³)	100	11	1.07 (1.01, 1.13)	0 (0.49)	1.05 (0.95, 1.16)	21 (0.24)
Ni (ng/m³)	1	7[e]	1.10 (0.89, 1.37)	35 (0.16)	1.07 (0.82, 1.39)	42 (0.11)
V (ng/m³)	2	10[c]	1.21 (0.84, 1.75)	40 (0.09)	1.13 (0.79, 1.60)	30 (0.17)
Zn (ng/m³)	10	11	1.14 (0.96, 1.36)	17 (0.29)	1.11 (0.81, 1.53)	56 (0.01)
Si (ng/m³)	100	11	1.12 (0.97, 1.3)	45 (0.05)	1.08 (0.94, 1.25)	31 (0.15)

[a]Models were adjusted for age (time variable), year of enrolment, sex, marital status, education, occupation, smoking status, smoking duration, smoking intensity and socioeconomic area-level indicators.

[b]Components were included as residuals from a model regressing total PM on the component; land-use regression model not available for [c]KORA, [d]HNR, [e]SALT/SDPP/SNAC-K/60 year olds.

PM_{10} indicates 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, P value of heterogeneity.

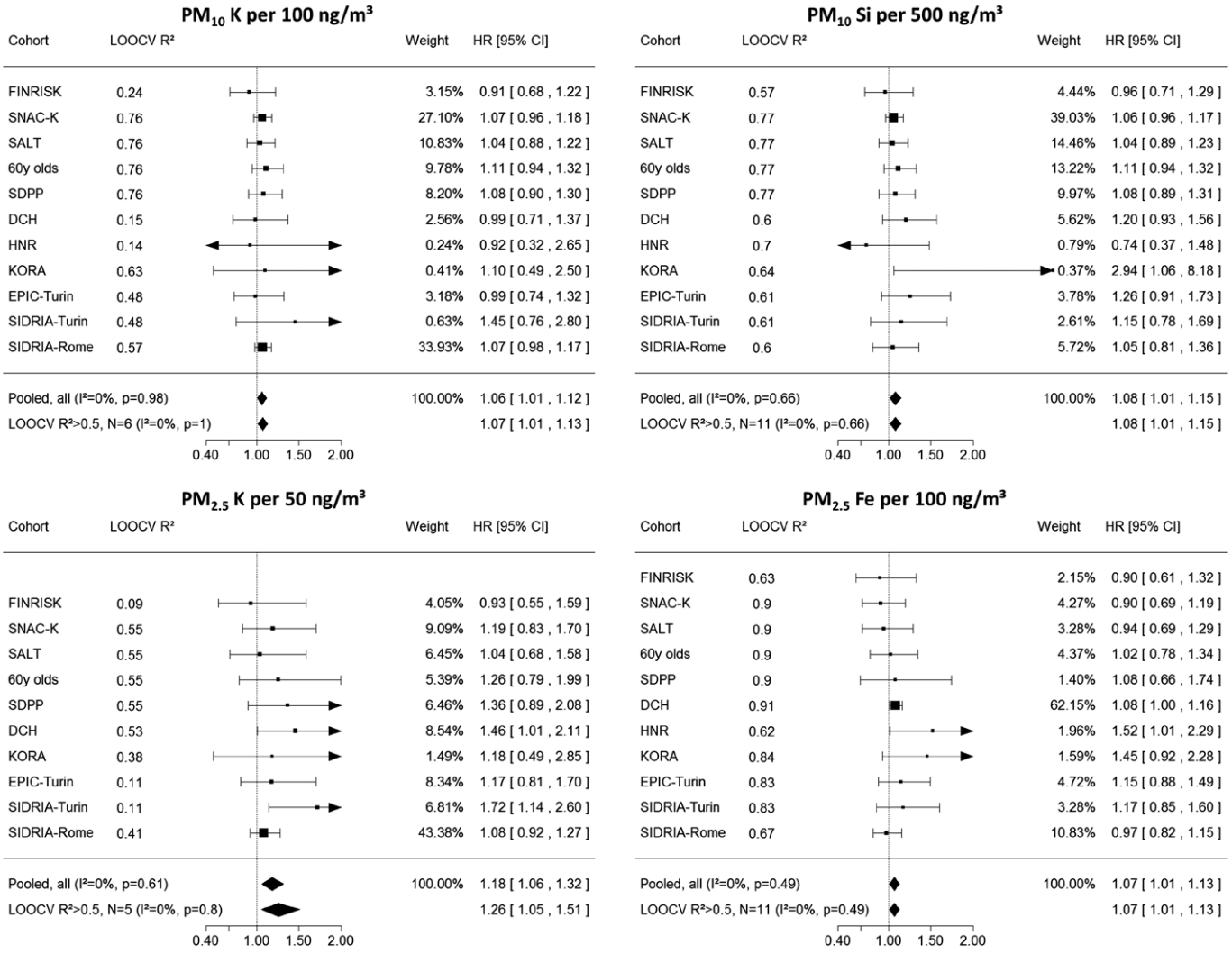

FIGURE 2. Cohort-specific and pooled effects on incidence of coronary events (hazard ratios and 95% confidence interval) per fixed increase of selected PM components. Order of studies is based on north to south gradient. PM_{10}: particulate matter with an aerodynamic diameter <10 μm, $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5 μm, K: potassium, Fe: iron, Ni: nickel, DL: DerSimonian & Laird, I^2: I^2 statistic, *P*: *P* value of test for heterogeneity, LOOCV R^2: cross-validation explained variance of land-use regression models. All models were adjusted for age (time variable), year of enrolment, sex, marital status, education, occupation, smoking status, smoking duration, smoking intensity, and socioeconomic area-level indicator.

DISCUSSION

In this European multi-center study, we observed an elevated risk for incident coronary events in association with long-term exposure to PM constituents, especially of K, Si, and Fe. The results were robust to model specification and confounder adjustment. Our previous analyses on the association of PM and coronary events in the same cohorts indicated risk increases for $PM_{10,}$ $PM_{2.5}$, PM_{coarse} (2.5–10 μm in aerodynamic diameter) and soot ($PM_{2.5}$ absorbance) but no association was seen for nitrogen oxides. Our results suggested an influence of PM components originating from resuspension of road dust.

A cohort study among California Teachers observed an increased risk of ischemic heart disease mortality for a number of PM components, such as $PM_{2.5}$ Fe, K, Si, Zn, and sulfate[11] while a recent analysis of the American Cancer Society (ACS) cohort within the National Particle Component Toxicity (NPACT) initiative reported an association for Fe and S but not for K, Si, Zn, Ni, and V for the same outcome.[12] Although neither study is directly comparable with our analysis, the reported HR of the Teachers study of 1.27 [1.07, 1.49] per 70 ng/m³ increase in $PM_{2.5}$ K is similar in size to our pooled findings (HR of 1.26 [1.09, 1.47]) for the same increment.[11] However, the NPACT ACS study as well as our parallel analysis on cardiovascular mortality could not detect an association.[12,14] K is often considered as a marker of biomass combustion but has other sources as well, such as soil and sea salt. Our study design was optimized to estimate small-scale

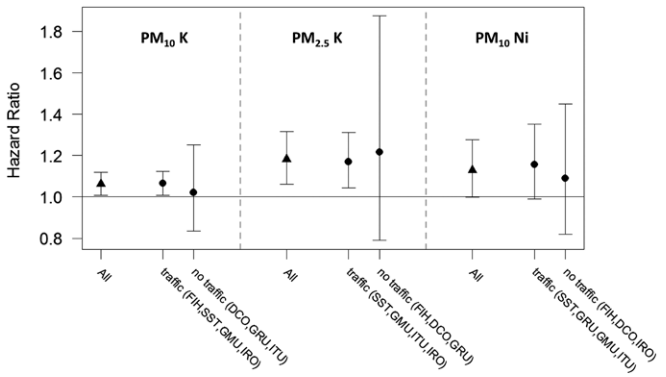

FIGURE 3. Hazard ratios and 95% confidence intervals of incidence of coronary events per fixed increment in PM component. Results from random-effects meta-analyses of 11 European cohorts (*triangles*) and subsets of cohorts based on sources of land-use regression predictor variables (*circles*). PM_{10}: particulate matter with an aerodynamic diameter <10 μm; $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5 μm; K: potassium; Ni: nickel; FIH: region Finland, Helsinki/Kuopio, cohort FINRISK; SST: region Sweden, Stockholm, cohorts SALT, SDPP, SNAC-K, 60 Year Olds; DCO: region Denmark, Copenhagen, cohort DCH; GRU: region Germany, Ruhr area, cohort HNR; GMU: region Germany, Munich/Augsburg, cohort KORA; IRO: region Italy, Rome, cohort SIDRIA Rome; ITU: region Italy, Turin, cohorts EPIC Turin and SIDRIA Turin.

variations in traffic-related air pollutants, thus traffic sites and traffic-related predictors were overrepresented in the exposure assessment. Biomass combustion could not be considered as a predictor because this information was not available in Geographic Information Systems data for most regions. Levoglucosan, a more specific marker of wood burning, was determined for four ESCAPE areas (Augsburg/Munich, Germany; the Netherlands/Belgium; Oslo, Norway and Catalunya, Spain) and showed only a low to moderate correlation with K (Spearman correlation ranged from −0.15 to 0.57).[24] Moreover, stratification by predictor variables illustrated that especially our PM_{10} K findings were mainly attributable to cohorts with traffic predictors in the land-use regression models for K. For most of these cohorts, land-use regression models also performed better, and the sensitivity analysis restricted to cohorts with a good performance showed similar effect estimates for both fractions. We therefore interpret our K findings rather as related to traffic (for example from resuspension of road dust) than to biomass burning.

In line with this interpretation, both Si and Fe which have been suggested as more specific tracers for road dust indicated an association with coronary events. For an increase of 30 ng/m³ $PM_{2.5}$ Si, our estimate with a HR of 1.03 [0.99, 1.08] was however lower compared with the HR of 1.11 [1.02, 1.20] reported by Ostro and colleagues[11] for ischemic heart disease mortality. A further NPACT study analyzing data of the Women's Health Initiative study applied a national spatial prediction model to derive individual residential concentrations of elemental and organic carbon, S, and Si.[13] However, both NPACT studies did not observe an association between $PM_{2.5}$ Si and incident coronary heart disease events or ischemic heart disease mortality.[12,13] In particular, the PM_{10} fraction of Si was highly correlated with total PM in some areas, which led to wide confidence intervals in PM-adjusted models. Main predictors were traffic and population or residential area. Si has also been suggested as an indicator for soil dust. However, a distinction between road dust and soil is often not possible due to overlapping source profiles.[20]

Fe might also reflect nontailpipe emissions from brake abrasion and land-use regression models for Fe performed well with traffic and population as prevailing predictor variables. Our estimate of 1.07 (1.01, 1.13) was similar to the NPACT ACS study of 1.05 (1.00, 1.10) but much lower than the one from the Teachers study with 1.29 (1.09, 1.52; all estimates calculated per 100 ng/m³ $PM_{2.5}$ Fe).[11,12] When removing the Danish cohort from the meta-analysis, our effect estimate was attenuated.

We could not see a clear risk increase in association with Zn or Cu, more specific markers of brake and tire wear. However for Zn, meta-regression analysis indicated slightly higher effect estimates with higher annual average $PM_{2.5}$ concentrations. Especially in Turin, where $PM_{2.5}$ annual average concentrations exceeded the EU air quality limit value, we observed an increased risk for coronary events.

Elevated Ni concentrations, a tracer for oil combustion, indicated an increased risk for the PM_{10} fraction. Stratification by predictor variables showed that this finding was also mainly driven by cohorts with traffic predictors. Land-use regression models for $PM_{2.5}$ Ni were mostly poor due to the lack of source-specific predictors and the lack of main sources (ports) in most areas. V is considered to derive from similar sources as Ni but effect estimates were not as clear. When pooling only cohorts with cross-validation $R^2 > 0.5$, the estimate indicated an association for V in the PM_{10} fraction. However for $PM_{2.5}$ V, no cohort fulfilled this criterion. Whereas PM_{10} S estimates were elevated in single constituent models the adjustment for total PM reduced the estimate to unity. Contrary to the NPACT studies, S did not seem to be associated with coronary events in this study. However, we have to take into account that specific predictor variables for this marker of secondary particles were lacking.

In summary, our component-specific results can only partly explain our previously observed association between coronary events and PM. The elevated estimates of K, Si, and Fe concentrations indicated an impact of road dust. Markers of further nonexhaust traffic emissions like brake and tire wear (Cu, Zn) showed no association though exposure estimation actually showed a higher precision. Source-specific predictors for secondary particles and oil and biomass combustion were missing, which weakened not only the precision of the exposure models and hence the potential to detect an association in the epidemiologic analysis.

Mechanisms

Several biologic mechanisms have been suggested for how PM and its components may impact cardiovascular health.[2,6] Long-term PM exposure may induce oxidative stress and inflammatory processes, both in the lung but also systemically, which in turn are assumed to provoke and accelerate the progression of atherosclerosis. In parts, transition metals like Fe, Ni, and V and their potential to generate reactive oxygen species may contribute considerably to the oxidative stress burden as implicated by in vitro and in vivo experiments.[6,25] Furthermore, an animal study in rats showed that exposure to transition metal-rich PM leads to cardiac dysfunction by multiple mechanisms like decreased T-wave amplitude and area, reduced heart rate or increased nonconducted P-wave arrhythmias,[26] all of which could provide a link for our findings of an increased risk of cardiac events, as these events can be triggered by autonomic dysfunction, repolarization abnormalities, and arrhythmias.

Strengths and Limitations

To date this is the first multi-center study investigating the effects of individual long-term exposure to PM constituents at residence on incidence of coronary events. Major strengths of this study are the common and centrally validated exposure assessment, including uniform and standardized measurement and modeling procedures to assign outdoor pollutant concentrations to the residential addresses of the participants.[16,19,27] Further strengths are the harmonization of the pre-existing cohort data and cohort-specific analyses using a common code book and analysis codes.

A major limitation is that specific predictor variables for sources such as biomass combustion were not available in the geographic data bases that we had access to. The most detailed predictor data were available for motorized road traffic. Furthermore, the measurement campaigns were designed to capture general variation among regional, urban background, and traffic sites. Fewer sites were generally included to capture differences in other sources, such as industry or ports. Therefore, the land-use regression models for PM components from traffic sources performed better than from other sources, such as industry or biomass combustion. Similar to earlier studies on elemental composition, our results can be interpreted as the effect of the component or the source(s) of the element. As many models did not contain specific source predictor variables but more general predictors (e.g., population), we cannot disentangle effects of related elements, e.g., Si and Fe. We did not measure organic components, such as organic carbon, or specific organic compounds, such as PAHs. $PM_{2.5}$ absorbance, which is highly correlated with elemental carbon, pointed to an association with coronary events in our previous analysis (1.10 [0.98, 1.24] per 10^{-5}/m increase).[17] Moreover, because elements may stand for different sources in different regions, a meta-analysis might not always be meaningful. Furthermore, exposure assessment was conducted in 2008 to 2011, while cohorts were enrolled from 1992 to 2007. However, our previous study comprising the same cohorts found similar effects for PM when using back-extrapolated concentrations taking long-term and seasonal time trends into account.[17] In addition, several studies on nitrogen dioxide reported stability of land-use regression modeled spatial contrasts over time,[28–31] which might be applicable to traffic-related components as well.

CONCLUSION

Our results indicated an association between long-term exposure to several air pollution constituents and incidence of coronary events in European cohorts, in specific K, Si, and Fe pointing to an impact of resuspension of road dust. Although the cohort participants differed in their characteristics and the study regions in their PM composition, the results were mostly homogeneous.

ACKNOWLEDGMENTS

We thank Daniela Raffaele and Marco Gilardetti for exposure data collection in Turin. We thank Giovanna Berti, Ennio Cadum, Francesco Lollobrigida (Environmental Protection Agency of Piedmont) for their collaboration to the exposure assessment in Turin. For Rome, we would like to thank Simone Bucci, Patrizio Pasquinelli and Eleonora Zirro which contributed to the exposure assessment.

REFERENCES

1. Rückerl R, Schneider A, Breitner S, Cyrys J, Peters A. Health effects of particulate air pollution: a review of epidemiological evidence. *Inhal Toxicol*. 2011;23:555–592.
2. Brook RD, Rajagopalan S, Pope CA III, et al. Particulate matter air pollution and cardiovascular disease. An update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.
3. Gold DR, Mittleman MA. New insights into pollution and the cardiovascular system: 2010 to 2012. *Circulation*. 2013;127:1903–1913.
4. Sun Q, Hong X, Wold LE. Cardiovascular effects of ambient particulate air pollution exposure. *Circulation*. 2010;121:2755–2765.
5. Hoek G, Krishnan RM, Beelen R, et al. Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ Health*. 2013;12:43.
6. Kelly F, Fussell J. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. *Atmos Environ*. 2012;60:504–526.
7. Schwarze PE, Ovrevik J, Låg M, et al. Particulate matter properties and health effects: consistency of epidemiological and toxicological studies. *Hum Exp Toxicol*. 2006;25:559–579.
8. Committee on Research Priorities for Airborne Particulate Matter; Board on Environmental Studies and Toxicology; Commission on Life Sciences; Commission on Geosciences, Environment, and Resources; National Research Council; *Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio*. Washington, DC: National Academy Press; 1998.
9. Wichers Stanek L, Sacks JD, Dutton SJ, Dubois JJB. Attributing health effects to apportioned components and sources of particulate matter: an evaluation of collective results. *Atmos Environ*. 2011;45:5655–5663.
10. Levy JI, Diez D, Dou Y, Barr CD, Dominici F. A meta-analysis and multisite time-series analysis of the differential toxicity of major fine particulate matter constituents. *Am J Epidemiol*. 2012;175:1091–1099.
11. Ostro B, Reynolds P, Goldberg D, et al. Erratum: Assessing long-term exposure in the California teachers study *Environ Health Perspect*. 2011;119:A242–A243.
12. Lippmann M, Chen LC, Gordon T, Ito K, Thurston GD. National particle component toxicity (NPACT) initiative: integrated epidemiologic and toxicologic studies of the health effects of particulate matter components. *Res Rep Health Eff Inst*. 2013:5–13.

13. Vedal S, Campen MJ, McDonald JD, et al. National particle component toxicity (NPACT) initiative report on cardiovascular effects. *Res Rep Health Eff Inst*. 2013;178:5–8.
14. Wang M, Beelen R, Stafoggia M, et al. Long-term exposure to elemental constituents of particulate matter and cardiovascular mortality in 19 European cohorts: results from the ESCAPE and TRANSPHORM projects. *Environ Int*. 2014;66:97–106.
15. Eeftens M, Hoek G, Gruzieva O, et al. Elemental composition of particulate matter and the association with lung function. *Epidemiology*. 2014;25:648–657.
16. de Hoogh K, Wang M, Adam M, et al. Development of land use regression models for particle composition in twenty study areas in Europe. *Environ Sci Technol*. 2013;47:5778–5786.
17. Cesaroni G, Forastiere F, Stafoggia M, et al. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ*. 2014;348:f7412.
18. Beelen R, Stafoggia M, Raaschou-Nielsen O, et al. Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. *Epidemiology*. 2014;25:368–378.
19. Eeftens M, Tsai MY, Ampe C, et al. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2: results of the ESCAPE project. *Atmos Environ*. 2012;62:303–317.
20. Viana M, Kuhlbusch TAJ, Querol X, et al. Source apportionment of particulate matter in Europe: a review of methods and results. *J Aerosol Sci*. 2008;39:827–849.
21. Mostofsky E, Schwartz J, Coull BA, et al. Modeling the association between particle constituents of air pollution and health outcomes. *Am J Epidemiol*. 2012;176:317–326.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
24. Jedynska A, Hoek G, Wang M, et al. Spatial variations of levoglucosan in four European study areas. *Sci Total Environ*. 2015;505:1072–1081.
25. Araujo JA, Nel AE. Particulate matter and atherosclerosis: role of particle size, composition and oxidative stress. *Part Fibre Toxicol*. 2009;6:24.
26. Farraj AK, Hazari MS, Haykal-Coates N, et al. ST depression, arrhythmia, vagal dominance, and reduced cardiac micro-RNA in particulate-exposed rats. *Am J Respir Cell Mol Biol*. 2011;44:185–196.
27. Eeftens M, Beelen R, de Hoogh K, et al. Development of land use regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol*. 2012;46:11195–11205.
28. Gulliver J, de Hoogh K, Hansell A, Vienneau D. Development and back-extrapolation of NO_2 land use regression models for historic exposure assessment in Great Britain. *Environ Sci Technol*. 2013;47:7804–7811.
29. Wang R, Henderson SB, Sbihi H, Allen RW, Brauer M. Temporal stability of land use regression models for traffic-related air pollution. *Atmos Environ*. 2013;64:312–319.
30. Cesaroni G, Porta D, Badaloni C, et al. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health*. 2012;11:48.
31. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO(2) over time. *Occup Environ Med*. 2011;68:765–770.