International Journal of Hygiene and Environmental Health 217 (2014) 819–829

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Associations between particulate matter elements and early-life pneumonia in seven birth cohorts: Results from the ESCAPE and TRANSPHORM projects

Elaine Fuertes[a,b], Elaina MacIntyre[a], Raymond Agius[c], Rob Beelen[d], Bert Brunekreef[d,e], Simone Bucci[f], Giulia Cesaroni[f], Marta Cirach[g,h], Josef Cyrys[i,j], Francesco Forastiere[f], Ulrike Gehring[d], Olena Gruzieva[k], Barbara Hoffmann[l,m], Aleksandra Jedynska[n], Menno Keuken[n], Claudia Klümper[m], Ingeborg Kooter[n], Michal Korek[k], Ursula Krämer[m], Anna Mölter[c], Mark Nieuwenhuijsen[g,h], Göran Pershagen[k], Daniela Porta[f], Dirkje S. Postma[o], Angela Simpson[p], Henriette A. Smit[e], Dorothea Sugiri[m], Jordi Sunyer[g,h,q,r], Meng Wang[d], Joachim Heinrich[a,*]

[a] Institute of Epidemiology I, Helmholtz Zentrum München, German Research Centre for Environmental Health, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany
[b] School of Population and Public Health, University of British Columbia, 2206 East Mall, V6T 1Z3 Vancouver, Canada
[c] Centre for Epidemiology, Institute of Population Health, Manchester Academic Health Science Centre, The University of Manchester, Oxford Road, M13 9PL Manchester, United Kingdom
[d] Institute for Risk Assessment Sciences, Utrecht University, Yalelaan 2, NL-3584 CM Utrecht, The Netherlands
[e] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, STR 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands
[f] Department of Epidemiology, Lazio Regional Health Service ASL RME, Via di Santa Costanza 53, 00198 Rome, Italy
[g] Centre of Research in Environmental Epidemiology, Doctor Aiguader, 88 E-08003 Barcelona, Spain
[h] CIBER Epidemiología y Salud Pública (CIBERESP), Melchor Fernández Almagro 3, Madrid, Spain
[i] Institute of Epidemiology II, Helmholtz Zentrum München, German Research Centre for Environmental Health, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany
[j] Environmental Science Center, University of Augsburg, Maximilianstraße 3, 86150 Augsburg, Germany
[k] Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, SE-171 77 Stockholm, Sweden
[l] Medical Faculty, Heinrich-Heine University of Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany
[m] IUF-Leibniz Research Institute for Environmental Medicine, Auf'm Hennekamp 50, 40225 Düsseldorf, Germany
[n] TNO, Netherlands Organization for Applied Scientific Research, Delft, The Netherlands
[o] University of Groningen, University Medical Center Groningen, The Department of Pulmonology, Groningen Research Institute for Asthma and COPD, Hanzeplein 1, NL-9700 RB Groningen, The Netherlands
[p] Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, 131 Princess Street, M1 7DN Manchester, United Kingdom
[q] IMIM (Hospital del Mar Research Institute), Doctor Aiguader 88, 08003 Barcelona, Spain
[r] Department of Experimental and Health Sciences, Pompeu Fabra University, Doctor Aiguader 88, 08003 Barcelona, Spain

ARTICLE INFO

Article history:
Received 10 March 2014
Received in revised form 14 May 2014
Accepted 21 May 2014

Keywords:
Birth cohort
Childhood pneumonia
Elemental composition
Meta-analysis
Particulate matter
Zinc

ABSTRACT

Evidence for a role of long-term particulate matter exposure on acute respiratory infections is growing. However, which components of particulate matter may be causative remains largely unknown. We assessed associations between eight particulate matter elements and early-life pneumonia in seven birth cohort studies (N_{total} = 15,980): BAMSE (Sweden), GASPII (Italy), GINIplus and LISAplus (Germany), INMA (Spain), MAAS (United Kingdom) and PIAMA (The Netherlands). Annual average exposure to copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc, each respectively derived from particles with aerodynamic diameters $\leq 10\,\mu m$ (PM_{10}) and $2.5\,\mu m$ ($PM_{2.5}$), were estimated using standardized land use regression models and assigned to birth addresses. Cohort-specific associations between these exposures and parental reports of physician-diagnosed pneumonia between birth and two years were assessed using logistic regression models adjusted for host and environmental covariates and total PM_{10} or $PM_{2.5}$ mass. Combined estimates were calculated using random-effects meta-analysis. There was substantial within and between-cohort variability in element concentrations. In the adjusted meta-analysis, pneumonia

* Corresponding author. Tel.: +49 89 3187 4150; fax: +49 89 3187 4499.
E-mail address: heinrich@helmholtz-muenchen.de (J. Heinrich).

http://dx.doi.org/10.1016/j.ijheh.2014.05.004

was weakly associated with zinc derived from PM_{10} (OR: 1.47 (95% CI: 0.99, 2.18) per 20 ng/m^3 increase). No other associations with the other elements were consistently observed. The independent effect of particulate matter mass remained after adjustment for element concentrations. In conclusion, associations between particulate matter mass exposure and pneumonia were not explained by the elements we investigated. Zinc from PM_{10} was the only element which appeared independently associated with a higher risk of early-life pneumonia. As zinc is primarily attributable to non-tailpipe traffic emissions, these results may suggest a potential adverse effect of non-tailpipe emissions on health.

Introduction

Pneumonia is the leading cause of death of children under five years (Liu et al., 2012) and its public health impact (hospitalization, emergency care, antibiotic use, economic costs) is substantial in most countries (Woodhead, 2009). In addition to bacterial and viral pathogens, which are necessary for the development of pneumonia, host and environmental factors are believed to influence susceptibility (Rudan et al., 2008). Evidence for a role of particulate matter on acute respiratory infections is growing, although few studies have focused on pneumonia (Mehta et al., 2013; Romieu et al., 2002). Notably, a recent analysis of more than 16,000 children from ten birth cohorts, conducted as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE; www.escapeproject.eu), reported associations between several long-term traffic-related air pollutants and early-life pneumonia (MacIntyre et al., 2013).

Which specific characteristics of air pollutants are causative or particularly detrimental to health is unknown (Kelly and Fussell, 2012; Stanek et al., 2011). Particulate matter components vary temporally and spatially in several respects, especially across areas with different climatological and geographical patterns, such as those in Europe (Querol et al., 2004). Traffic emissions are known to influence the concentration and composition of particulate matter and particles originating from anthropogenic sources (e.g. fuel combustion) differ both in size and composition from those attributable to crust and road abrasion (Pakkanen et al., 2001; Slezakova et al., 2007). Metals are suspected of being particularly toxic components of particulate matter (Schauer et al., 2006). For example, the risk of lifetime pneumonia was more than three times higher in schoolchildren born in an area in Eastern Germany with metal-rich particulate matter compared to a control area (Kohlhammer et al., 2007).

The Transport Related Air Pollution and Health Impacts-Integrated Methodologies for Assessing Particulate Matter project (TRANSPHORM; www.transphorm.eu), in conjunction with the ESCAPE initiative, brings together several international collaborations with the aim of improving the knowledge of transport related airborne particulate matter and its impact on health. The current study is part of this effort, and utilizes data from seven birth cohorts. Specifically, we aimed to identify associations between pneumonia during early-life and exposure to eight different particulate matter elements, that are independent of previously observed associations with particulate matter mass (MacIntyre et al., 2013). Although the adverse effects of particulate matter element exposure have been examined in the context of other health outcomes (Strak et al., 2012; Wang et al., 2014), this study is the first to examine the relationship between annual average particulate matter element concentrations at the home address and the development of pneumonia during early childhood.

Methods

Data sources

Data from seven population based birth cohorts, for which particulate matter element concentration estimates derived according to ESCAPE and TRANSPHORM protocols were available, are included in this study. BAMSE (children, allergy, milieu, Stockholm, epidemiological survey) is a population-based birth cohort of children born during 1994–1996 in Stockholm Country, Sweden (Wickman et al., 2002). GASPII (gene and environment: prospective study on infancy in Italy) is a birth cohort of children born during 2003–2004 in Rome, Italy (Porta and Fantini, 2006; Porta et al., 2007). INMA ("INfancia y Medio Ambiente; environment and childhood") is a network of Spanish birth cohorts. Only children recruited from the city of Sabadell, Spain, during 2005–2008 are included in this analysis as particulate matter measurements were available for this study area (Guxens et al., 2012a,b). MAAS (Manchester Asthma and Allergy Study) is a population-based birth cohort (with a small nested allergen control intervention) of children born during 1995–1997 in the Greater Manchester conurbation in the United Kingdom (Custovic et al., 2002). PIAMA (Prevention and Incidence of Asthma and Mite Allergy) is a population-based birth cohort (with a small mattress cover intervention) of children born during 1996–1997 in cities and small towns across the Netherlands (Brunekreef et al., 2002). GINIplus (German Infant Nutrition Intervention study – plus influence of pollution and genetics) is a population-based birth cohort (with a nutrition intervention) of children born during 1995–1998 in Wesel and Munich, Germany (Filipiak et al., 2007). LISAplus (influence of Life-style related factors on the Immune System and the development of Allergies in childhood – plus the influence of traffic emissions and genetics) (LISAplus) is a population-based prospective birth cohort of children born during 1997–1999 in Wesel, Munich, Leipzig and Bad Honnef, Germany (Heinrich et al., 2002). Only the LISAplus centres covering the city of Munich and the Ruhr area (Wesel) in Germany participated in the ESCAPE project and are thus included in the current study (the centres covering the cities of Leipzig and Bad Honnef are excluded). For the GINIplus and LISAplus cohorts, which have nearly identical study designs and outcome definitions, data were pooled and results are presented by geographical area (GINI/LISA North (Ruhr area/Wesel) and GINI/LISA South (Munich)). Each cohort received ethical approval from their local authorized Institutional Review Boards.

Assessment of pneumonia

A parental report (yes/no) of a doctor diagnosis of pneumonia between birth and two years of age was the primary outcome of interest. Questionnaire-based information was collected at 12 and 24 months for BAMSE, GINIplus and PIAMA, at 6, 12, 18 and 24 months for LISAplus, at 6 and 15 months for GASPII and at 14 months for INMA. For MAAS, information was only available at 36 months, and the question posed did not require a doctor diagnosis. The exact questions used by each cohort are provided in the Supplemental Material (Table S1).

Assessment of particulate matter element exposure

Eight elements (copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V) and zinc (Zn)), derived from

particles with aerodynamic diameters less than 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$), were included in this analysis, all of which had more than >75% of samples above the limit of detection. Although elements have multiple sources, Cu, Fe and Zn were selected as markers for non-tailpipe traffic emissions, S for long-range transport, Ni and V for mixed oil burning/industry, Si for crustal material and K for biomass burning (Viana et al., 2008).

Annual average exposures to each element were estimated for each participant's home address at birth using centrally developed and standardized site-specific land use regression models as previously described (De Hoogh et al., 2013; see Supplemental Material, Table S2, for brief information on model performance). Briefly, between October 2008 and February 2010, using a harmonized protocol, particulate matter measurements were taken at 20 locations in Stockholm Country, Rome, the Ruhr area, Munich/Augsburg and Greater Manchester and at 40 locations in the Catalonia area and the Netherlands/Belgium for fourteen consecutive days in the cold, intermediate and warm seasons, as part of the ESCAPE project (www.escapeproject.eu/manuals) (Eeftens et al., 2012a,b). Harvard impactors collected $PM_{2.5}$ and PM_{10} samples on separate Teflon filters, which were subsequently analyzed for elemental composition using X-ray fluorescence. Site-specific annual averages were calculated using the average of the three measurement periods and were adjusted for temporal variation using data from a centrally located background reference site which operated continuously throughout the measurement year. Details of the measurements, analyses and results have been previously published (De Hoogh et al., 2013).

Area-specific land-use regression models were developed for all elements in both particulate matter size fractions to explain annual concentrations. Data on traffic intensity, population/household density and land use, derived from Geographic Information Systems in circular buffers ranging from 25 to 5000 m, were used as predictor variables in the development of these models. A detailed description of these input data can be found in Eeftens et al. (2012a). Predictors were derived for the cohort addresses. If any predictor at an address had a lower or higher value than observed at any of the particulate matter measurement sites, its value was truncated to the minimum or maximum observed value at the measurement site, respectively, as has been recommended for land use regression models of NO_2 (Wang et al., 2012). No model could be developed for K from $PM_{2.5}$ for GINI/LISA North or MAAS, Ni from $PM_{2.5}$ for BAMSE and V from $PM_{2.5}$ for GINI/LISA South as no predictors were significant. Exposures to each of the eight elements for both particulate matter size fractions were estimated to the birth addresses of all participants.

Analytic strategy

Cohort-specific associations between pneumonia and the elements, entered as non-transformed continuous variables, were assessed using logistic regression. Although this study builds upon a homogenous exposure assessment method and analysis protocol, random-effects meta-analysis models (as opposed to pooled models or fixed-effects meta-analysis) were used to calculate combined estimates to account for any remaining potential within- and between-cohort heterogeneity (DerSimonian and Laird, 1986). The I^2 statistic was used to examine statistical heterogeneity among cohort-specific effect estimates and can be interpreted as the percentage of the variability in effect sizes attributable to the between-study variability rather than sampling error (Huedo-Medina et al., 2006). All analyses for MAAS were done locally in SPSS 20 (IBM Corp, 2011). All other analyses were conducted centrally using the statistical program R, version 2.13.1 (R Core Team, 2012).

A priori, we chose to calculate three types of models. Crude models contained only the effect of each element and adjustments for sex and municipality (the latter is a four level categorical variable only used for the BAMSE cohort). Minimally adjusted models included adjustments for relevant covariates (older siblings (any/none), breastfeeding (up to six months for BAMSE, PIAMA, GINIplus, LISAplus and MAAS, and yes at both three and six months for GASPII and INMA), birth season (winter: January–March; spring: April–June; summer: July–September; fall: October–December), atopy of either parent (yes/no), daycare attendance reported at any time during follow-up (yes/no), maternal smoking during pregnancy (yes/no), exposure to secondhand smoke in the home at any time during follow-up (yes/no), parental socioeconomic status (highest education attained by either parent for BAMSE, GINIplus, LISAplus, PIAMA and INMA – low, medium and high; highest occupational level of either parent for GASPI – low, medium and high; and household income for MAAS – low, medium, high and very high), use of natural gas for cooking (yes/no), mold/dampness in the home (yes/no) and intervention (yes/no, only for GINIplus, PIAMA and MAAS)). Due to issues with model singularities, the GASPII models were not adjusted for smoking during pregnancy, use of natural gas for cooking and parental socioeconomic status, and the INMA models were not adjusted for sex, parental socioeconomic status, birth season and secondhand smoke in the home (data not available for this latter covariate). Covariates were defined as similarly as possible across cohorts using questionnaire-derived information and are based on those from the previously published meta-analysis of these cohorts (MacIntyre et al., 2013). The third set of models (main models) were further adjusted for the potential confounding effect of PM_{10} mass or $PM_{2.5}$ mass, depending on the source of the element, as particulate matter mass may be related to both element concentrations and health outcomes. Results from these main models, which are two-pollutant adjusted models, are the primary findings reported in this paper.

All results are presented as odds ratios (95% confidence intervals). For elements derived from PM_{10} particles, elevated risks of disease are analyzed per 2 ng/m^3 Ni, 3 ng/m^3 V, 20 ng/m^3 Cu and Zn, 100 ng/m^3 K, 200 ng/m^3 S and 500 ng/m^3 Fe and Si. For elements derived from $PM_{2.5}$ particles, elevated risks of disease are analyzed per 1 ng/m^3 Ni, 2 ng/m^3 V, 5 ng/m^3 Cu, 10 ng/m^3 Zn, 50 ng/m^3 K, 100 ng/m^3 Fe and Si and 200 ng/m^3 S. These increments were chosen by rounding down the mean 10th and 90th percentile range of element concentrations from all ESCAPE study areas.

The potential impact of colinearity was examined by excluding models in which elements and particulate matter mass were highly correlated (Pearson's correlation > 0.80). We also investigated whether the results remained stable after excluding cohorts for which the element land use regression models had leave-one out cross validation R^2's lower than 0.50 (see Supplemental Material, Table S2, and De Hoogh et al., 2013). For cohorts with information at both the first and second birthday (BAMSE, GINIplus, LISAplus and PIAMA), associations stratified by year of diagnosis were considered as a stronger effect of particulate matter mass on pneumonia during the first year of life has been observed (MacIntyre et al., 2013).

Results

Study population

After excluding children with no information on particulate matter elemental exposure ($N = 1421$) and subsequently, no information on pneumonia ($N = 991$), data on 15,980 children were available for analysis. The size of the cohorts varied from 490 children in INMA to 3971 children in BAMSE. The cumulative incidence of pneumonia was 5.6% in the total population and was higher for cohorts that collected data at both the first and second year

Table 1
Characteristics of the study population.

	BAMSE (SE) N_{total} = 3971 *n* (%)	GASPII (IT) N_{total} = 689 *n* (%)	GINI/LISA North (DE) N_{total} = 2651 *n* (%)	GINI/LISA South (DE) N_{total} = 3491 *n* (%)	INMA (ES) N_{total} = 490 *n* (%)	MAAS (UK) N_{total} = 861 *n* (%)	PIAMA (NL) N_{total} = 3827 *n* (%)
Pneumonia (0–2 years)	315 (7.9)	15 (2.2)	155 (5.8)	206 (5.9)	8 (1.6)	19 (2.2)[a]	155 (4.1)
Between 0–1 year	142 (3.6)	–	82 (3.2)	86 (2.5)	–	–	89 (2.4)
Between 1–2 years	213 (5.6)	–	89 (3.6)	138 (4.2)	–	–	88 (2.4)
Male sex	2012 (50.7)	346 (50.2)	1362 (51.4)	1829 (52.4)	260 (53.2)	472 (54.8)	1979 (51.7)
Older siblings	1907 (48.0)	273 (39.6)	1420 (53.7)	1442 (41.4)	203 (41.6)	410 (51.3)	1937 (50.8)
Breastfeeding until 6 months	1872 (47.8)	365 (53.0)	1039 (40.2)	2113 (61.8)	331 (80.1)	251 (29.2)	939 (24.9)
Parental atopy	1156 (29.5)	188 (27.3)	1585 (59.8)	2605 (74.7)	254 (51.9)	699 (81.2)	1952 (51.0)
Maternal smoking during pregnancy	509 (12.8)	84 (12.3)	442 (17.0)	458 (13.3)	142 (29.3)	88 (11.4)	654 (17.3)
Secondhand smoke at home	541 (13.6)	211 (30.6)	1206 (45.6)	966 (27.7)	–	270 (32.2)	1315 (34.4)
Daycare	2769 (72.2)	182 (26.4)	68 (2.6)	498 (14.3)	148 (30.3)	571 (68.1)	1143 (29.9)
Cooking with gas stove	461 (11.6)	683 (99.1)	125 (4.8)	306 (8.9)	300 (61.9)	604 (77.7)	3186 (83.8)
Indoor mold/dampness	1001 (25.3)	111 (16.1)	551 (21.2)	1105 (31.9)	76 (15.7)	137 (17.6)	1915 (50.1)
Observational study	–	–	1493(63.5)[b]	1235(55.8)[c]	–	765 (88.9)	3106 (81.6)
Interventional	–	–	858 (36.5)	980 (44.2)	–	105 (12.2)	329 (8.6)[d]
study	–	–	–	–	–	–	373 (9.8)[e]
Birth season							
Winter	695 (17.5)	127 (18.4)	796 (30.0)	1041 (29.8)	119 (24.3)	168 (19.5)	714 (18.7)
Fall	950 (23.9)	238 (34.5)	739 (27.9)	934 (26.8)	96 (19.6)	210 (24.4)	919 (24.0)
Summer	1154 (29.1)	193 (28.0)	603 (22.7)	808 (23.1)	118 (24.1)	237 (27.5)	1189 (31.1)
Spring	1172 (29.5)	131 (19.0)	513 (19.4)	708 (20.3)	156 (31.9)	246 (28.6)	1005 (26.3)
Socio-economic status[f]							
Low	101 (2.5)	62 (9.1)	369 (14.0)	195 (5.6)	56 (11.4)	131 (16.1)	495 (13.1)
Med	1753 (44.2)	298 (43.7)	1069 (40.5)	621 (17.8)	87 (17.8)	324 (39.9)	1390 (36.8)
High	2111 (53.2)	322 (47.2)	1202 (45.5)	2663 (76.5)	347 (70.8)	225 (27.7)	1895 (50.1)
Very high[g]						133 (16.4)	
Moved during follow-up period	1478 (37.2)	70 (10.2)	555 (20.9)	1041 (29.8)	49 (10.0)	–	640 (16.7)

n = number of cases; % = percentage of cases; SE = Sweden; IT = Italy; DE = Germany; ES = Spain; UK = United Kingdom; NL = The Netherlands.
[a] During first three years.
[b] Intervention was limited to GINIplus cohort (*N* = 2351).
[c] Intervention was limited to GINIplus cohort (*N* = 2215).
[d] Intervention with mite impermeable mattress cover.
[e] Intervention with placebo mattress cover.
[f] Defined as the highest education attained by either parent (BAMSE, GINI, LISA, PIAMA, INMA); the highest occupational level attained by either parent (GASPII); or household income (MAAS): 1st – <10 K Pounds; 2nd – 10–20 K Pounds; 3rd – 20–30 K Pounds; 4th – >30 K pounds.
[g] MAAS only.

birthdays (BAMSE, GINIplus, LISAplus and PIAMA) compared to those that collected data at only one time point (INMA and MAAS) or only up to the age of 1.5 years (GASPII). Information on the outcome and covariate distributions across cohorts is provided in Table 1.

Distribution and correlations of elements

Element concentration distributions by cohort are depicted in Fig. 1 and summary statistics are provided in the Supplemental Material (Table S3). Mean annual average element concentrations were greater in the PM_{10} fraction than the $PM_{2.5}$ fraction in all cases except for S and V in the INMA cohort. In general, the range of element concentrations differed greatly across cohorts. There was large within- cohort exposure contrasts for elements acting as markers of non-tailpipe traffic emissions (Cu, Fe and Zn), especially for those derived from PM_{10}. The exposure concentrations for these elements also overlapped well across cohorts. The same was observed for Ni, although the within-cohort spread of exposure concentrations was limited for GINI/LISA South and MAAS as all exposure concentrations tended to be low. There was limited overlap in exposure concentrations across cohorts for K, S, Si and V. However, within-cohort exposure contrasts were large in BAMSE and GASPII for Si (and to a lesser extent K) from PM_{10} and in PIAMA for V (both size fractions).

Pearson correlations between elements and particulate matter mass differed substantially across cohorts, and were lower for MAAS and GINI/LISA South (Table 2). On average, these correlations were highest for Fe (range across cohorts: 0.02–0.92), Si (0.03–1.00) and K (−0.01 to 1.00) derived from PM_{10}. Cohort-specific correlations between elements are presented in the Supplemental Material (Tables S4–S10) and were more frequently greater than 0.80 in GASPII and PIAMA and less frequently greater than 0.80 in GINI/LISA North and GINI/LISA South. The large variability in concentrations and correlations between cohorts may be in part explained by the heterogeneous nature of the cohorts (mostly urban centres (GASPII, GINI/LISA South and INMA), urban and rural areas (BAMSE and GINI/LISA North) and covering almost the entire country (PIAMA)) and the different particulate matter element sources across the geographical areas covered by the cohorts.

Associations between elements and pneumonia

Table 3 summarizes the meta-analytic results for the tested associations between the elements and early-life pneumonia. In crude models, pneumonia was positively associated with Zn derived from both PM_{10} and $PM_{2.5}$, Si from PM_{10} and Fe from $PM_{2.5}$. Associations were similar when restricted to children with available covariate data (not shown). Upon adjustment for relevant host and environmental covariates (minimum models), these associations remained stable and Ni and S from PM_{10} also appeared to be associated with pneumonia. However, further adjustment for the potential confounding effect of PM_{10} mass or $PM_{2.5}$ mass led to a

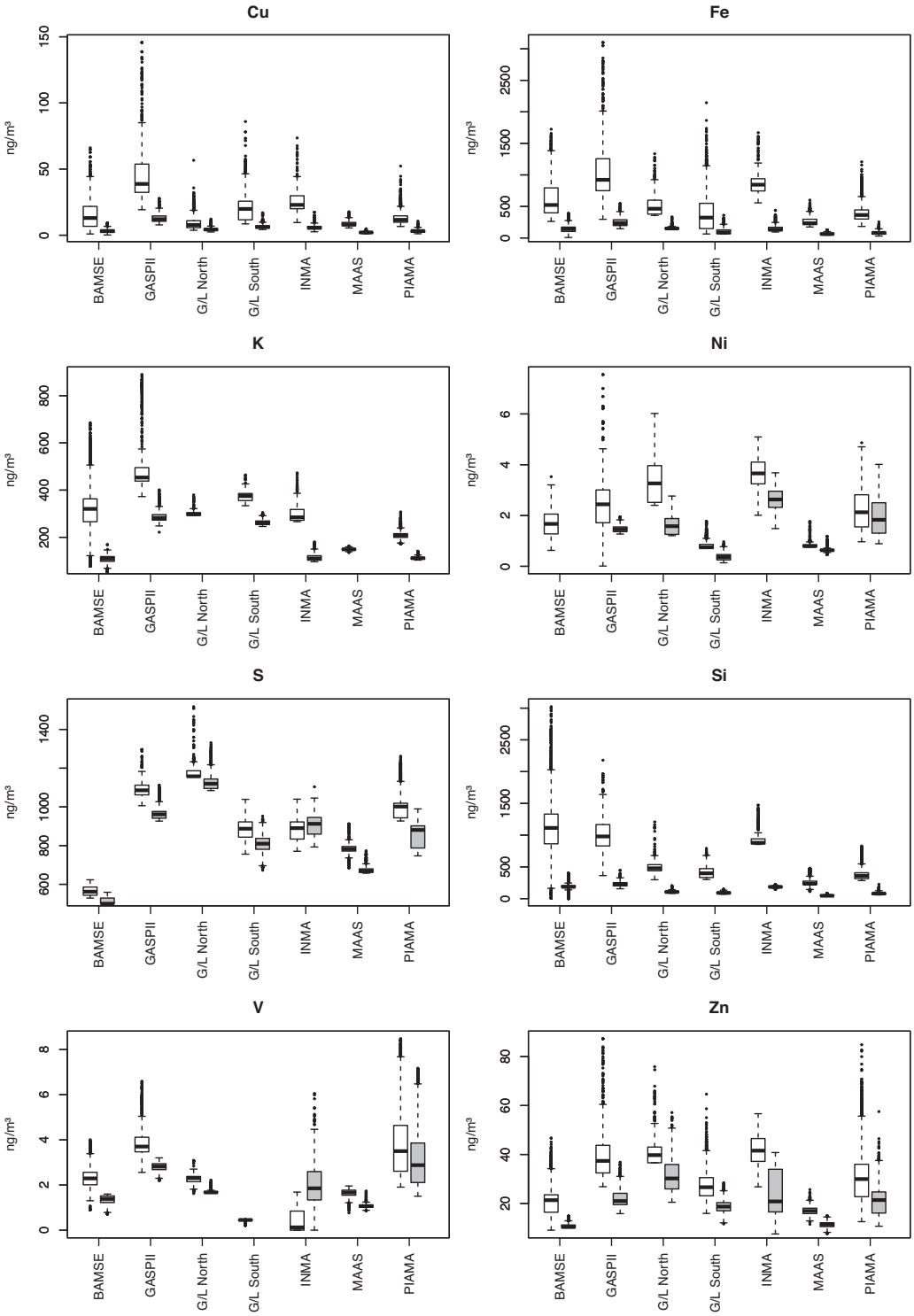

Fig. 1. Distribution of annual average PM_{10} (white) and PM2.5 (gray) derived element concentrations per cohort. G/L North = GINI/LISA North; G/L South = GINI/LISA South. Detailed information on the development of the land use regression models used to estimate these exposures is available in De Hoogh et al. (2013) and summarized in the Supplemental Material (Table S2). For the elements derived from $PM_{2.5}$, no data on K was available for GINI/LISA North ($N = 2651$) and MAAS ($N = 861$), on Ni for BAMSE ($N = 3971$) and on V for GINI/LISA South ($N = 3491$).

universal decrease in all risk estimates and only Zn derived from PM_{10} remained weakly associated with pneumonia (1.47 (0.99, 2.18) per 20 ng/m^3 increase). Cu and Fe, the other elements acting as markers of non-tailpipe traffic emissions, were not found to be consistently associated with pneumonia. In the main models, there was heterogeneity across cohorts for the association between early-life pneumonia and S derived from PM_{10} and $PM_{2.5}$ and Fe and Si derived from $PM_{2.5}$. The largest I^2 statistics were found for elements derived from $PM_{2.5}$ mass.

The cohort-specific and combined results for the main models are presented in Figs. 2 and 3 for PM_{10} and $PM_{2.5}$ derived elements, respectively. Cohort-specific associations revealed that Zn derived from PM_{10} was only associated with pneumonia in the PIAMA cohort (cohort weight 32% in the meta-analysis), although effect

Table 2
Pearson correlations between annual average elemental concentrations and particulate matter mass per cohort.

		BAMSE	GASPII	GINI/LISA North	GINI/LISA South	INMA	MAAS	PIAMA
PM_{10}	Cu	0.31	0.86	0.74	0.20	0.63	0.44	0.61
	Fe	0.76	0.89	0.92	0.02	0.72	0.55	0.84
	K	1.00[a]	0.68	0.60	−0.01	0.88	0.34	0.74
	Ni	0.11	0.30	0.86	0.01	0.54	0.11	0.61
	S	0.48	0.30	0.73	0.19	0.47	0.15	0.53
	Si	1.00[b]	0.54	0.45	0.03	0.89	0.54	0.90
	V	0.74	0.73	0.54	0.02	0.43	0.17	0.52
	Zn	0.67	0.87	0.35	0.18	0.20	0.30	0.47
$PM_{2.5}$	Cu	0.71	0.84	0.69	−0.01	0.79	0.08	0.84
	Fe	0.66	0.86	0.53	0.01	0.59	0.19	0.75
	K	0.42	0.66	NA	0.00	0.51	NA	0.56
	Ni	NA	0.18	0.62	0.02	0.44	0.07	0.57
	S	0.56	0.71	0.72	0.03	0.52	−0.08	0.79
	Si	0.52	0.60	0.17	0.28	0.83	0.17	0.73
	V	0.38	0.37	0.41	NA	0.36	0.13	0.54
	Zn	0.53	0.76	0.69	0.20	0.54	0.15	0.50

Grey squares: Pearson's correlation > 0.80; NA = not available.
[a] Pearson correlation = 0.9995784.
[b] Pearson correlation = 0.9995369.

estimates were elevated for almost all cohorts. The meta-analytic effect estimate for this association was slightly attenuated after excluding the PIAMA cohort (1.47 (0.99, 2.18) and 1.35 (0.81, 2.25) per 20 ng/m^3 with and without PIAMA, respectively). The small number of cases in some of the cohorts, namely INMA, GASPII and MAAS, led to large cohort-specific confidence intervals for certain elements.

The adverse independent effect of PM_{10} mass on pneumonia, previously reported by MacIntyre et al. (2013), did not substantially change after adjustment for element concentrations although the confidence intervals were wider in nearly all cases (Fig. 4). The results for $PM_{2.5}$ mass were similar, although effect estimates were more varied and confidence intervals larger.

Sensitivity analyses

Excluding cohorts for which element concentrations and particulate matter mass were highly correlated (15 models from 108 were excluded) or cohorts for which the element land use regression models had leave-one out cross validation R^2's lower than 0.50 (34 models from 108 were excluded) did not measurably alter the observations made using the entire available dataset (Supplemental Material, Table S11). When analyses were stratified by year of pneumonia diagnosis, Zn derived from PM_{10} was associated with pneumonia diagnosed during the first (1.53 (1.10, 2.11) per 20 ng/m^3) and second (1.43 (1.01, 2.02) per 20 ng/m^3) year of life. No associations were observed with the other elements.

Table 3
Associations between annual average particulate matter element concentrations and pneumonia in a random effects meta-analysis of seven European birth cohorts.

Element	Crude models (N = 15,962)[a]			Minimum models (N = 14,961)[b]			Main models (N = 14,961)[b]		
	OR (95%CI)	I^2	P_{het}	OR (95%CI)	I^2	P_{het}	OR (95%CI)	I^2	P_{het}
PM_{10}									
Cu	1.07 (0.83, 1.37)	41	0.115	1.08 (0.83, 1.40)	40	0.123	0.89 (0.65, 1.23)	37	0.146
Fe	1.22 (0.96, 1.54)	44	0.101	1.26 (0.97, 1.63)	48	0.071	1.05 (0.77, 1.44)	24	0.248
K	1.32 (0.89, 1.95)	56	0.034	1.24 (0.86, 1.80)	47	0.079	0.96 (0.48, 1.93)	31	0.194
Ni	1.22 (0.99, 1.49)	0	0.962	1.31 (1.06, 1.63)*	0	0.974	1.09 (0.83, 1.43)	0	0.666
S	1.76 (0.92, 3.36)	73	0.001	2.21 (1.10, 4.44)*	72	0.002	1.86 (0.88, 3.94)	67	0.006
Si	1.74 (1.02, 2.95)*	68	0.005	1.74 (1.01, 3.00)*	65	0.009	1.45 (0.77, 2.74)	18	0.292
V	1.48 (0.78, 2.81)	37	0.148	1.63 (0.77, 3.44)	43	0.102	1.08 (0.76, 1.53)	0	0.455
Zn	1.50 (1.14, 1.97)*	36	0.154	1.53 (1.15, 2.02)*	32	0.185	1.47 (0.99, 2.18)	43	0.102
$PM_{2.5}$									
Cu	1.42 (0.91, 2.22)	64	0.010	1.49 (0.90, 2.46)	65	0.008	0.87 (0.55, 1.38)	25	0.234
Fe	1.40 (1.05, 1.87)*	52	0.052	1.50 (1.06, 2.12)*	61	0.018	1.28 (0.85, 1.94)	52	0.050
K[c]	2.03 (0.91, 4.52)	80	<0.001	2.03 (0.93, 4.43)	76	0.003	1.44 (0.90, 2.32)	26	0.248
Ni[d]	1.11 (0.93, 1.32)	0	0.660	1.15 (0.96, 1.39)	0	0.584	0.84 (0.67, 1.05)	0	0.953
S	1.85 (0.76, 4.50)	75	<0.001	2.07 (0.78, 5.52)	76	<0.001	1.19 (0.36, 3.94)	76	<0.001
Si	1.88 (0.84, 4.22)	76	<0.001	1.98 (0.85, 4.65)	76	<0.001	1.45 (0.63, 3.31)	64	0.010
V[e]	2.13 (0.82, 5.54)	52	0.066	2.45 (0.72, 8.30)	58	0.036	1.36 (0.44, 4.17)	45	0.103
Zn	1.37 (1.02, 1.85)*	50	0.061	1.47 (1.11, 1.94)*	39	0.130	1.24 (0.91, 1.68)	31	0.195

Crude models: adjusted for sex and municipality (BAMSE only); minimum models: further adjustments for older siblings, breastfeeding, birth season, parental atopy, daycare attendance, maternal smoking during pregnancy, exposure to secondhand smoke in the home, parental socioeconomic status, use of natural gas for cooking, mold/dampness exposure in the home and intervention; main models: further adjustments for $PM_{2.5}$ mass (for $PM_{2.5}$-derived elements) or PM_{10} mass (for PM_{10}-derived elements).
I^2 = percentage of the variability in effect sizes attributable to the between-study variability rather than sampling error; P_{het} = p-value of heterogeneity of effect estimates across cohorts.
[a] The number of children in the crude models differs from the base study population (N = 15,980) because 18 children are missing information on "municipality" in BAMSE.
[b] The total number of children included in the adjusted models is slightly different than that reported in MacIntyre et al. (2013) because of small differences in confounder definitions.
[c] No data on this element was available for GINI/LISA North (N = 2651) or MAAS (N = 861).
[d] No data on this element was available for BAMSE (N = 3971).
[e] No data on this element was available for GINI/LISA South (N = 3491).
* p-value < 0.05.

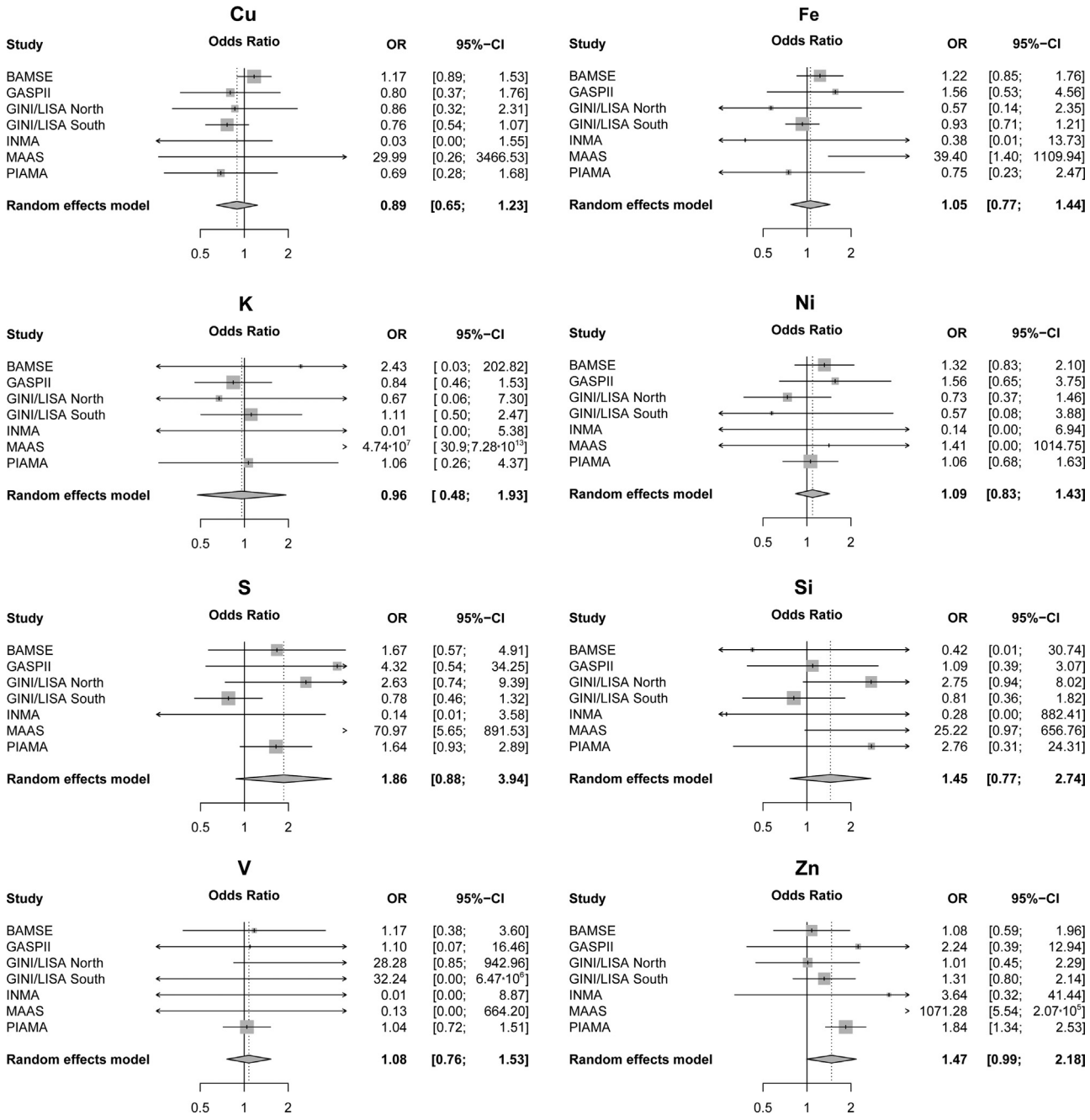

Fig. 2. Associations between annual average particulate matter element concentrations from PM_{10} and pneumonia. Only associations from the main models are presented, which are adjusted for sex, municipality (BAMSE only), older siblings, breastfeeding, birth season, parental atopy, daycare attendance, maternal smoking during pregnancy, exposure to secondhand smoke in the home, parental socioeconomic status, use of natural gas for cooking, mold/dampness exposure in the home, intervention and PM_{10} mass.

Discussion

The previously observed associations between annual average particulate matter mass exposure and pneumonia reported by MacIntyre et al. (2013) were not explained by the elements investigated in this study. Effect estimates for the majority of elements were inconsistent across cohorts, which resulted in heterogeneous combined risk estimates. Large differences in exposure contrasts between cohorts likely further contributed to this heterogeneity (Fig. 1 and Supplement Material, Table S3). Zinc derived from PM_{10}, which is a marker for non-tailpipe traffic emissions, was the only element weakly associated with a higher risk of early-life pneumonia.

How Zn could act on biological pathways to potentially influence the risk of pneumonia is unclear. Adverse associations between ambient air zinc and paediatric asthma morbidity have been observed, and pulmonary inflammation is hypothesized as a possible biological mechanism (Hirshon et al., 2008). Results from experimental studies also indicate that Zn is a particularly toxic component of particulate matter, and when inhaled can lead to lung injury and inflammation (Adamson et al., 2000; Prieditis and Adamson, 2002). A recent review of the literature supports an adverse role of environmental exposure to Zn on the lung via multiple oxidative effects (Wu et al., 2013).

Although Zn appeared best associated with early-life pneumonia in this study, it is likely that other characteristics of particulate

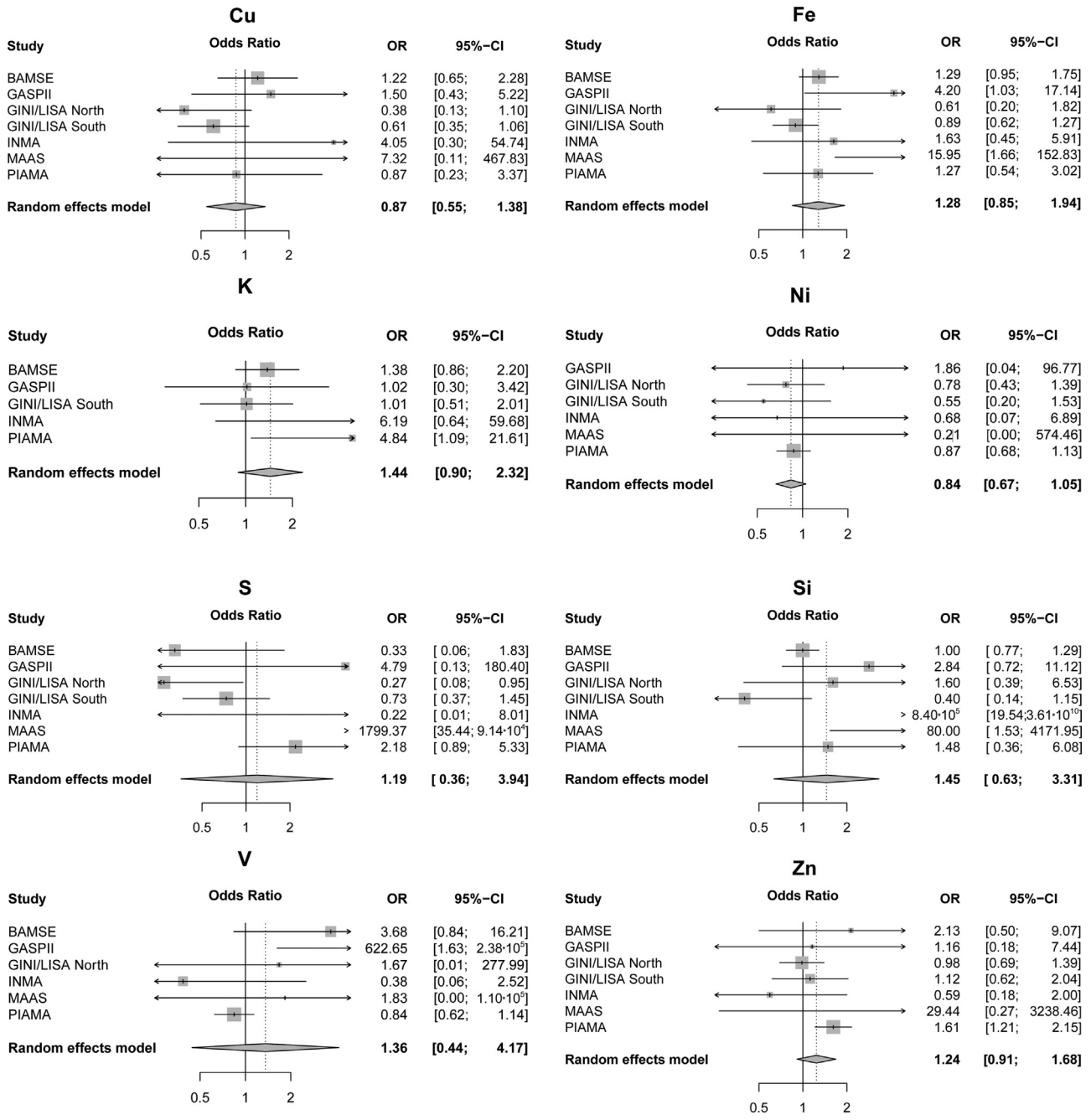

Fig. 3. Associations between annual average particulate matter element concentrations from $PM_{2.5}$ and pneumonia. Only associations from the main models are presented, which are adjusted for sex, municipality (BAMSE only), older siblings, breastfeeding, birth season, parental atopy, daycare attendance, maternal smoking during pregnancy, exposure to secondhand smoke in the home, parental socioeconomic status, use of natural gas for cooking, mold/dampness exposure in the home, intervention and $PM_{2.5}$ mass.

matter are relevant, such as size and solubility, as well as additive, synergistic and even antagonistic interactions with other airborne pollutants (Kelly and Fussell, 2012). It may thus be more important to focus on the sources of specific compounds than on the compounds themselves. In the ESCAPE areas included in this analysis, the spatial variation in Zn was primarily explained by traffic predictor variables (De Hoogh et al., 2013), and thus any potential association with this element must be interpreted as an indication of a role of specific pollutants produced by traffic sources (either tailpipe related or non-tailpipe related). As previously summarized (see Thorpe and Harrison (2008) and references therein), tire wear is a major contributor of Zn in the urban environment and high concentrations of Zn have been found in brake linings and to a lesser extent in the re-suspension of road dust and tailpipe emissions. In studies from Europe, Zn has been primarily associated with non-tailpipe traffic emissions (Viana et al., 2008). In the current study, which covered seven areas in Europe, Zn was specifically intended to act as a marker for non-tailpipe traffic emissions, as were Cu and Fe, for which results were inconsistent. This latter result may suggest that although Zn, Cu and Fe were intended to act as markers for non-tailpipe traffic emissions, they also likely have other (differing) contributing sources.

Although analyses were defined a priori, it is possible that the weak association between pneumonia and Zn from PM_{10} is a chance finding given the number of associations tested. However, this association was robust to several sensitivity analyses. Furthermore,

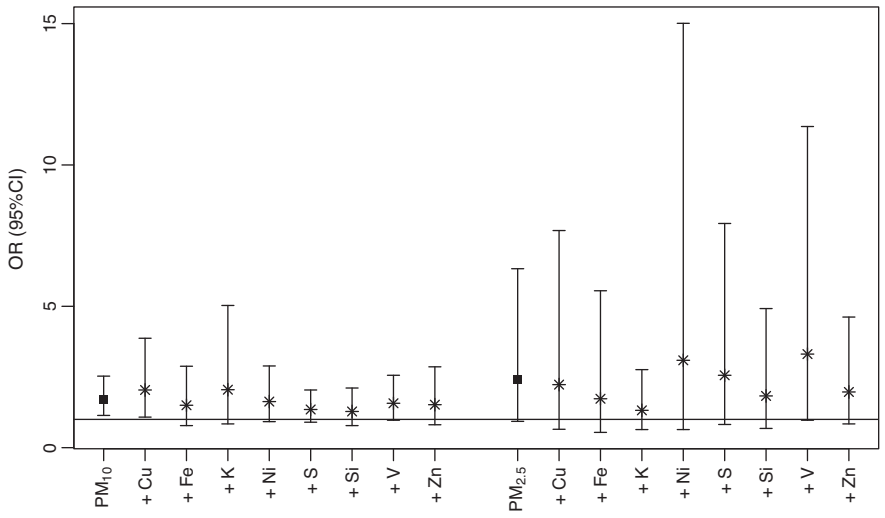

Fig. 4. Associations between pneumonia and annual average particulate matter mass concentrations (black squares; per 10 μg/m^3 PM_{10} and 5 μg/m^3 $PM_{2.5}$), and after correction for annual average element concentrations (stars). Models are adjusted for sex, municipality (BAMSE only), older siblings, breastfeeding, birth season, parental atopy, daycare attendance, maternal smoking during pregnancy, exposure to secondhand smoke in the home, parental socioeconomic status, use of natural gas for cooking, mold/dampness exposure in the home and intervention. For the elements derived from $PM_{2.5}$, no data on K was available for GINI/LISA North (N = 2651) and MAAS (N = 861), on Ni for BAMSE (N = 3971) and on V for GINI/LISA South (N = 3491).

excluding cohorts in which Zn and PM_{10} mass were highly correlated did not affect the result, thereby suggesting that this result is not biased by collinearity with particulate matter mass. However, our model adjustments for particulate matter mass may have prevented us from detecting the adverse effects of other elements or air pollutants highly correlated with this factor. Furthermore, including particulate matter mass directly into the models may be an over-adjustment, which could partly explain the attenuation of the risk estimates observed between the minimum and main models (Mostofsky et al., 2012).

A major strength of this study is the assignment of unique element concentrations to each participant's birth address using a standardized land use regression modelling approach (De Hoogh et al., 2013). Any between-cohort heterogeneity observed should thus be mostly attributable to differences in the mixture and sources of elements in the geographical areas covered by the cohorts. However, given that the land use regression models utilized here are the first to be developed for particulate matter elements, information on the validity of these models is more limited than for land use regression models developed for air pollutants (such as NO_2), which have been shown to be temporally stable (Eeftens et al., 2011; Wang et al., 2013). Indeed, data from measurements performed in 2008–2010 were used to build the element exposure models which were applied to the children's birth addresses (birth dates range from 1994 to 2008) under the implicit assumption that the spatial variability of the element concentrations (and thus of their sources) would not have changed over this time period. Unlike in previous ESCAPE studies, we were unable to back-extrapolate predicted concentrations to account for long-term changes in element concentration levels (as was done in MacIntyre et al., 2013) as historical elemental composition data were not available from routine networks for any of the cohorts. This lack of temporal overlap is a limitation of this study. It should also be noted that the position of the air pollution monitors used to inform the land use regression models were chosen to over represent traffic sites, and thus sources of other elements (e.g. wood burning, metal industry and agriculture) may not have been optimally captured. This may have contributed to the low explained variance of some land use regression models and consequently hindered our ability to detect true within-cohort exposure contrasts. In this study, the land use regression models for the markers for non-tailpipe traffic emissions (Cu, Fe and Zn) tended to have higher explained variance. Finally, the influence of any potential measurement error of the elemental concentrations on the results is unknown.

The probability of outcome misclassification is not known for our study. However, the wording used in the parental questionnaires was similar across cohorts and required a parental report of a doctor diagnosis for all cohorts except MAAS (for which a doctor diagnosis was not specified). Maternal recall of acute health care events during early childhood is believed to be good (D'Souza-Vazirani et al., 2005). Nevertheless, the follow-up schedule of the cohorts was not identical and pneumonia rates were highest for cohorts with yearly follow-ups. We were also unable to adjust the models for epidemics, vaccination status or frequency of infections as these data were not available for all cohorts. We chose to focus on the early years of life as postnatal development of the respiratory and immune system makes this a period of particular susceptibility to traffic-pollution (Bateson and Schwartz, 2007; Heinrich and Slama, 2007). Unlike the previous study which found evidence suggesting that associations between air pollutants and early-life pneumonia may be strongest during the first year of life (MacIntyre et al., 2013), we observed no consistent differences by year of diagnosis. Finally, exposure misclassification attributable to moving or to differences in individual behaviours (e.g. daycare attendance) is always a concern when exposure estimates are modelled at the home address. Effect estimates for Zn derived from PM_{10} were similar between those who had moved between birth and anytime during the following period and non-movers (data not shown).

Conclusions

Previously observed associations between annual average particulate matter mass concentrations and pneumonia were not explained by the elements we investigated. Zn from PM_{10} was the only element independently, albeit weakly, associated with a higher risk of early-life pneumonia. As Zn is primarily attributable to non-tailpipe traffic emissions, these results may suggest a potential adverse effect of non-tailpipe emissions on respiratory health.

Funding

This research received funding from the European Community's Seventh Framework Program (FP7/2007-2011): ESCAPE (grant agreement number: 211250) and TRANSPHORM (ENV.2009.1.2.2.1). The Swedish Research Council FORMAS, the Stockholm County Council, the Swedish Foundation for Health Care Sciences and Allergy Research, and the Swedish Environmental Protection Agency supported BAMSE. The Italian Ministry of Health (ex art.12 D.Lgs 502/92, 2001) supported GASPII. The GINIplus study was supported for the first three years by grants of the Federal Ministry for Education, Science, Research and Technology (grant no. 01 EE 9401-4). The LISAplus study was supported by grants 01 EG 9732 and 01 EG 9705/2 from the Federal Ministry for Education, Science, Research and Technology, by the Federal Ministry for Environment (IUF, FKZ 20462296) and by the Helmholtz Zentrum München, Munich Center of Health. The Netherlands Organization for Health Research and Development, The Netherlands Organization for Scientific Research, The Netherlands Asthma Fund, The Netherlands Ministry of Spatial Planning, Housing, and the Environment and The Netherlands Ministry of Health, Welfare and Sport supported PIAMA. An Asthma UK Grant 04/014, the Moulton Charitable Trust, the James Trust and Microsoft Research supported MAAS. Grants from the Spanish Ministry of Health-Instituto de Salud Carlos III (Red INMA G03/176, CB06/02/0041, FISPI041436, FIS-PI081151, FIS-PI042018, FIS-PI09/02311, FIS-PI06/0867, FIS-PS09/00090, FIS-FEDER 03/1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314, and 09/02647), Generalitat de Catalunya-CIRIT 1999SGR 00241, Conselleria de Sanitat Generalitat Valenciana, Universidad de Oviedo, Obra social Cajastur, Department of Health of the Basque Government (2005111093 and 2009111069), Provincial Government of Gipuzkoa (DFG06/004 and DFG08/001) and Fundación Roger Torné supported INMA. The aforementioned funding sources had no involvement in the design of the study, collection, analysis and interpretation of data, writing of the report and decision to submit the article for publication.

Conflicts of interests

All authors have no conflicts of interests.

Acknowledgements

We thank everyone involved in exposure monitoring and modelling, particularly Matthias Birk, Thomas Kusch, Kees Meliefste and Marjan Tewis. Some of the results of this study have been previously published in the form of an abstract (Fuertes et al., 2013).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijheh.2014.05.004.

References

Adamson, I.Y., Prieditis, H., Hedgecock, C., Vincent, R., 2000. Zinc is the toxic factor in the lung response to an atmospheric particulate sample. Toxicol. Appl. Pharmacol. 166 (2), 111–119.

Bateson, T.F., Schwartz, J., 2007. Children's response to air pollutants. J. Toxicol. Environ. Health A 71 (3), 238–243.

Brunekreef, B., Smit, J., de Jongste, J., Neijens, H., Gerritsen, J., Postma, D., et al., 2002. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: design and first results. Pediatr. Allergy Immunol. 13 (15), 55–60.

Custovic, A., Simpson, B.M., Murray, C.S., Lowe, L., Woodcock, A., on behalf of the NAC Manchester Asthma and Allergy Study Group, 2002. The national asthma campaign Manchester Asthma and Allergy Study. Pediatr. Allergy Immunol. 13, 32–37.

De Hoogh, K., Wang, M., Adam, M., Badaloni, C., Beelen, R., Birk, M., et al., 2013. Development of land use regression models for particle composition in twenty study areas in Europe. Environ. Sci. Technol. 47 (11), 5778–5786.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.

D'SouzaVazirani, D., Minkovitz, C.S., Strobino, D.M., 2005. Validity of maternal report of acute health care use for children younger than 3 years. Arch. Pediatr. Adolesc. Med. 159 (2), 167–172.

Eeftens, M., Beelen, R., de Hoogh, K., Bellander, T., Cesaroni, G., Cirach, M., et al., 2012a. 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. 46 (20), 11195–11205.

Eeftens, M., Beelen, R., Fischer, P., Brunekreef, B., Meliefste, K., Hoek, G., 2011. Stability of measured and modelled spatial contrasts in NO_2 over time. Occup. Environ. Med. 68, 765–770.

Eeftens, M., Tsai, M.-Y., Ampe, C., Anwander, C., Beelen, R., Bellander, T., et al., 2012b. Spatial variation of $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance and PM coarse concentrations between and within 20 European study areas and the relationship with NO_2 – results of the ESCAPE project. Atmos. Environ. 62, 303–317.

Filipiak, B., Zutavern, A., Koletzko, S., von Berg, A., Brockow, I., Grübl, A., et al., 2007. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. J. Pediatr. 151 (4), 352–358.

Fuertes, E., MacIntyre, E., Gehring, U., Gruzieva, O., Klumper, C., Molter, A., et al., Associations Between Particulate Matter Constituents And Early-Life Pneumonia In Seven Birth Cohorts: Results from the TRANSPHORM project, 2013. Abstracts of the International Society of Environmental Epidemiology (ISEE), the International Society of Exposure Science (ISES), and the International Society of Indoor Air Quality and Climate (ISIAQ), Basel, Switzerland. Environ. Health Perspect..

Guxens, M., Aguilera, I., Ballester, F., Estarlich, M., Fernández-Somoano, A., Lertxundi, A., et al., 2012a. Prenatal exposure to residential air pollution and infant mental development: modulation by antioxidants and detoxification factors. Environ. Health Perspect. 120 (1), 144–149.

Guxens, M., Ballester, F., Espada, M., Fernández, M.F., Grimalt, J.O., Ibarluzea, J., et al., 2012b. Cohort profile: the INMA – INfancia y Medio Ambiente – (Environment and Childhood) project. Int. J. Epidemiol. 41 (4), 930–940.

Heinrich, J., Bolte, G., Hölscher, B., Douwes, J., Lehmann, I., Fahlbusch, B., et al., 2002. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. Eur. Respir. J. 20 (3), 617–623.

Heinrich, J., Slama, R., 2007. Fine particles, a major threat to children. Int. J. Hyg. Environ. Health 210, 617–622.

Hirshon, J.M., Shardell, M., Alles, S., Powell, J.L., Squibb, K., Ondov, J., et al., 2008. Elevated ambient air zinc increases pediatric asthma morbidity. Environ. Health Perspect. 116, 826–831.

Huedo-Medina, T.B., Sánchez-Meca, J., Marín-Martínez, F., Botella, J., 2006. Assessing heterogeneity in metaanalysis: Q statistic or I2 index? Psychol. Methods 11 (2), 193206.

IBM Corp., 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, USA, www.spss.com

Kelly, F.J., Fussell, J.C., 2012. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. Atmos. Environ. 60, 504–526.

Kohlhammer, Y., Rzehak, P., Behr, J., Wichmann, H-E., Heinrich, J., 2007. High prevalence of pneumonia in children of a smelter town. Int. J. Occup. Environ. Health 13, 167–174.

Liu, L., Johnson, H.L., Cousens, S., Perin, J., Scott, S., Lawn, J.E., et al., 2012. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 379 (9832), 2151–2161.

MacIntyre, E.A., Gehring, U., Molter, A., Fuertes, E., Klumper, C., Kramer, U., et al., 2013. Air pollution and respiratory infections during early childhood: an analysis of ten European birth cohorts within the ESCAPE project. Environ. Health Perspect. 122 (1), 107.

Mehta, S., Shin, H., Burnett, R., North, T., Cohen, A.J., 2013. Ambient particulate air pollution and acute lower respiratory infections: a systematic review and implications for estimating the global burden of disease. Air Qual. Atmos. Health 6 (1), 69–83.

Mostofsky, E., Schwartz, J., Coull, B.A., Koutrakis, P., Wellenius, G.A., Suh, H.H., et al., 2012. Modeling the association between particle constituents of air pollution and health outcomes. Am. J. Epidemiol. 176 (4), 317–326.

Pakkanen, T.A., Loukkola, K., Korhonen, C.H., Aurela, M., Mäkelä, T., Hillamo, R.E., et al., 2001. Sources and chemical composition of atmospheric fine and coarse particles in the Helsinki area. Atmos. Environ. 35 (32), 5381–5391.

Porta, D., Fantini, M.P., 2006. Prospective cohort studies of newborns in Italy to evaluate the role of environmental and genetic characteristics on common childhood disorders. Ital. J. Pediatr. 32 (6), 350–357.

Porta, D., Forastiere, F., Lallo, D.D., Perucci, C.A., 2007. Enrolment and follow-up of a birth cohort in Rome. Epidemiol. Prev. 31 (6), 303–308.

Prieditis, H., Adamson, I.Y., 2002. Comparative pulmonary toxicity of various soluble metals found in urban particulate dusts. Exp. Lung Res. 28 (7), 563–576.

Querol, X., Alastuey, A., Ruiz, C.R., Artiñano, B., Hansson, H.C., Harrison, R.M., et al., 2004. Speciation and origin of PM10 and PM2.5 in selected European cities. Atmos. Environ. 38 (38), 6547–6555.

R Core Team, 2012. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, ISBN 3-900051-07-0 www.R-project.org

Romieu, I., Samet, J.M., Smith, K.R., Bruce, N., 2002. Outdoor air pollution and acute respiratory infections among children in developing countries. Occup. Environ. Med. 44, 640–649.

Rudan, I., Boschi-Pinto, C., Biloglav, Z., Mulholland, K., Campbell, H., 2008. Epidemiology and etiology of childhood pneumonia. Bull. World Health Organ. 86 (5), 408–416B.

Schauer, J.J., Lough, G.C., Shafer, M.M., Christensen, W.F., Arndt, M.F., DeMinter, J.T., et al., 2006. Characterization of metals emitted from motor vehicles. Health Effects Inst. 133, 1–76, discussion 77–88.

Slezakova, K., Pereira, M.C., Reis, M.A., Alvim-Ferraz, M.C., 2007. Influence of traffic emissions on the composition of atmospheric particles of different sizes – Part 1: Concentrations and elemental characterization. J. Atmos. Chem. 58 (1), 55–68.

Stanek, L.W., Sacks, J.D., Dutton, S.J., Dubois, J.J.B., 2011. Attributing health effects to apportioned components and sources of particulate matter: an evaluation of collective results. Atmos. Environ. 45, 5655–5663.

Strak, M., Janssen, N.A., Godri, K.J., Gosens, I., Mudway, I.S., Cassee, F.R., et al., 2012. Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential – the RAPTES Project. Environ. Health Perspect. 120 (8), 1183–1189.

Thorpe, A., Harrison, R.M., 2008. Sources and properties of non-exhaust particulate matter from road traffic: a review. Sci. Total Environ. 400 (1–3), 270–282.

Viana, M., Kuhlbusch, T.A.J., Querol, X., Alastuey, A., Harrison, R.M., Hopke, P.K., et al., 2008. Source apportionment of particulate matter in Europe: a review of methods and results. Aerosol Sci. 39, 827–849.

Wang, M., Beelen, R., Eeftens, M., Meliefste, K., Hoek, G., Brunekreef, B., 2012. Systematic evaluation of land use regression models for NO_2. Environ. Sci. Technol. 46 (8), 4481–4489.

Wang, M., Beelen, R., Stafoggia, M., Raaschou-Nielsen, O., Andersen, Z.J., Hoffmann, B., et al., 2014. 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. 66, 97–106.

Wang, R., Henderson, S.B., Sbihi, H., Allen, R.W., Brauer, M., 2013. Temporal stability of land use regression models for traffic-related air pollution. Atmos. Environ. 64, 312–319.

Wickman, M., Pershagen, G., Nordvall, S.L., 2002. The BAMSE Project: presentation of a prospective longitudinal birth cohort study. Pediatr. Allergy Immunol. 13 (Suppl. 15), 11–13.

Woodhead, M., 2009. The European vision of community-acquired pneumonia. Semin. Respir. Crit. Care Med. 30 (02), 136–145.

Wu, W., Bromberg, P.A., Samet, J.M., 2013. Zinc ions as effects of environmental oxidative lung injury. Free Radical Biol. Med. 65, 57–69.