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Associations between particulate matter composition and childhood blood pressure — The PIAMA study

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ABSTRACT

Background: Childhood blood pressure is an important predictor of hypertension and cardiovascular disease in adulthood. Evidence for an association between ambient particulate matter (PM) exposure and blood pressure is increasing, but little is known about the relevance of different PM constituents.

Objectives: We investigated the association between particulate matter composition and blood pressure at age 12 years.

Methods: Annual average concentrations of copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc in particles with diameters of less than 2.5 μm ($PM_{2.5}$) and 10 μm (PM_{10}) were estimated by land-use regression modeling for the home addresses of the participants of the prospective PIAMA birth cohort study. Associations between element concentrations and blood pressure measurements performed at age 12 years were investigated by linear regression with and without adjustment for confounders.

Results: After adjustment for potential confounders we found statistically significant positive associations of diastolic blood pressure with iron, silicon, and potassium in PM_{10} in children who lived at the same address since birth [mean difference (95% confidence interval) 0.67 (0.02;1.31) mm Hg, 0.85 (0.18;1.52) mm Hg, and 0.75 (0.09;1.41) mm Hg, respectively, per interquartile range increase in exposure]. Also, we found marginally significant ($p < 0.1$) positive associations between iron and silicon in $PM_{2.5}$ and diastolic blood pressure. Part of the observed effects was found to be attributable to NO_2, a marker of exhaust traffic emissions.

Conclusions: Exposure to particulate matter constituents, in particular iron may increase blood pressure in children. The possible association with iron may indicate the health relevance of non-exhaust emissions of traffic.

1. Introduction

Childhood blood pressure is an important predictor of hypertension and cardiovascular disease in later life (Liang and Mi, 2011; Morrison et al., 2012). There is growing interest in the long-term effects of air pollution on blood pressure in children, but findings so far are mixed. In a study from Lahore, Pakistan, systolic blood pressure and diastolic blood pressure were found to be increased in 10-year old schoolchildren, living and attending school in an area with high levels of air pollution as compared to their peers living and attending school in an area with low levels of air pollution (Sughis et al., 2012). In a study from the United Kingdom in 9–10-year-old children from 22 schools around London's Heathrow Airport no association was found between annual average nitrogen dioxide (NO_2) levels at school and blood pressure (Clark et al., 2012). Likewise, no association was found between annual average levels of air pollutants ($PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance and NO_2) and blood pressure at age 10 in two German birth cohort studies (Liu et al., 2014). We recently reported positive associations of annual average levels of $PM_{2.5}$ absorbance and NO_2 with diastolic, but not systolic blood pressure, at age 12 years in participants

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Abbreviations: BMI, body mass index; ESCAPE, European Study of Cohorts for Air Pollution Effects; GIS, geographic information system; LOOCV, leave-one-out-cross validation; LUR, land-use regression; NO_2, nitrogen dioxide; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PM, particulate matter; $PM_{2.5}$, particles with diameters of less than 2.5 μm; PM_{10}, particles with diameters of less than 10 μm; TRANSPHORM, Transport-related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter.

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of a Dutch birth cohort study who lived at same address since birth (Bilenko et al., 2015).

Particulate matter is emitted from a variety of sources including traffic, industry, biomass burning, long-range transport, spread and resuspension of abrasion of road surface material and wear of tires and brakes and therefore, its composition can vary considerably (Schwarze et al., 2006). There is growing evidence, that different constituents can affect health in different ways (Brook et al., 2010), which may explain part of the inconsistencies between the studies on air pollution and blood pressure that have been performed so far.

Metals and especially transition metals, have the ability to generate reactive oxygen species in biological tissues (Gonzalez-Flecha, 2004). However, evidence for the effects of specific particulate matter constituents on blood pressure is still limited for adults and lacking for children. Wu et al. found short-term exposure to several $PM_{2.5}$ constituents, including nickel, zinc, magnesium, strontium, lead and arsenic to be positively associated with systolic blood pressure and diastolic blood pressure in Chinese university students (Wu et al., 2013). Jacobs et al. observed significant associations of vanadium, nickel and iron with systolic blood pressure in elderly persons (Jacobs et al., 2012).

Within the framework of the collaborative ESCAPE (European Study of Cohorts for Air Pollution Effects) and TRANSPHORM (Transport-related Air Pollution and Health impacts — Integrated Methodologies for Assessing Particulate Matter) projects, we estimated individual exposures to a selection of eight elements in $PM_{2.5}$ and PM_{10} representing different sources such as brake linings and tires (copper, iron, and zinc), crustal materials (silicon, potassium), industrial/fossil fuel combustion (nickel, vanadium, sulfur), and biomass burning (potassium) for the participants of the prospective PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study (de Hoogh et al., 2013; Eeftens et al., 2012a; Beelen et al., 2013). The objective of the present study was to investigate the association between particulate matter composition and blood pressure in a population for which we reported associations between long-term exposure to air pollution and diastolic blood pressure previously (Bilenko et al., 2015). Since the relevance of exposure at different time points is not clear, we linked blood pressure to particulate matter composition at birth address and at the current address of the participants.

2. Methods

2.1. Study population

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is a prospective birth study. The methods of the PIAMA study have been described elsewhere (Wijga et al., 2014). In brief, pregnant women were recruited during their second trimester of pregnancy in 1996–1997 from a series of communities, varying from rural areas to large cities in northern, western and central parts of the Netherlands. A map of the PIAMA study areas is provided in Fig. S1. Postal questionnaires were sent to the parents during pregnancy, at the child's ages of 3 months and 1 year, and yearly thereafter up to the age of 8 years. At the child's age of 11 years, parents and children were asked to complete a questionnaire. A medical examination including measurements of blood pressure took place during a home visit at the age of about 12 years. The study population for the present analysis consisted of all children with measurements on blood pressure, estimates of air pollution exposure, and complete covariate data ($N = 1147$). The Institutional Review Boards of the participating institutes approved the study protocol, and written informed consent was obtained from the parents or legal guardians of all participants.

2.2. Measurement of blood pressure

Blood pressure was measured using automatic blood pressure meters (Omron M6, Omron Healthcare Europe BV, Hoofddorp, The Netherlands) according to the recommendations of the American Heart Association (Pickering et al., 2005). The cuff (15–22 cm (small) or 22–23 cm (normal) dependent on the mid-upper arm circumference) was placed on the non-dominant arm. Systolic blood pressure and diastolic blood pressure values were measured at least twice with 5 minute intervals according to a standard protocol while the child was seated. We used the mean of the measures in the present analysis.

2.3. Air pollution exposure assessment

Annual average air pollution concentrations for participants' home addresses at birth and at the time of blood pressure measurements were estimated by Land-Use Regression (LUR) models described elsewhere (de Hoogh et al., 2013; Eeftens et al., 2012a; Beelen et al., 2013). In brief, three 2-week air pollution monitoring campaigns were performed between February 2009 and February 2010 in the warm, cold and intermediate seasons. For each site, results from three measurements were averaged to estimate the annual average after adjustment using data from a continuous monitoring site (Eeftens et al., 2012b). Measurements of nitrogen dioxide were performed within that year at 80 sites. Simultaneous measurements of and $PM_{2.5}$ absorbance, $PM_{2.5}$ and PM_{10} were performed at half of the sites (Eeftens et al., 2012b; Cyrys et al., 2012). $PM_{2.5}$ and PM_{10} filters were analyzed for elemental composition using energy dispersive X-ray fluorescence spectrometry at Cooper Environmental Services (Portland, OR, USA) as described elsewhere (de Hoogh et al., 2013). Eight elements, copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S), silicon (Si), vanadium (V), and zinc (Zn), were a priori selected to represent major sources considering existing evidence for toxicity, and because they had a high percentage of detected samples (>75%) and good precision of measurements.

Predictor variables on nearby traffic intensity, population/household density and land use were derived from Geographic Information Systems (GIS) to explain special variation of particulate matter, NO_2 and element concentration. Regression models were developed to maximize the adjusted explained variance using a supervised forward stepwise approach. Model performance was evaluated with leave-one-out-cross validation (LOOCV). LUR models with leave-one-out cross validation R^2 are presented in the online supplement. The models explained substantial fractions of the variability in annual average concentrations for NO_2, $PM_{2.5}$, PM_{10}, $PM_{2.5}$, $PM_{2.5}$ absorbance, copper, iron, nickel, vanadium, and zinc ($R^2_{LOOCV} = 0.58–0.89$), but only limited fractions for PM_{coarse}, sulfur, potassium, and silicon ($R^2_{LOOCV} = 0.25–0.45$). The relatively poor performance of these models can be explained by the lack of specific GIS-variables for sources other than traffic (de Hoogh et al., 2013).

2.4. Confounding variables

The following variables were selected a priori based on a literature review and considered as potential confounders: gender; age at time of blood pressure measurements; height and Body Mass Index (BMI) defined as weight in kilograms divided by height squared in meters as measured at the time of blood pressure measurement (children were weighed and measured in their underwear by trained research staff as part of the medical examination); cuff size (small/normal); weight gain during the first year of life as reported in the 1-year questionnaire, physical activity defined as number of days per week with at least 1 h of sporting activity, and puberty development scale[24] as reported by child in the 11-year questionnaire; maternal education categorized as low, medium and high as reported in the 1-year questionnaire; maternal smoking during pregnancy, parental smoking in the child's home, breastfeeding, gestational age and birth weight (reported in the 3-month questionnaire), maternal hypertension during pregnancy (reported in the 14-year questionnaire), and pneumonia and/or otitis media in the first two years of life (reported in the 1- and 2-year questionnaires); ambient and room temperature. Daily data on ambient temperature were obtained from the National Network of the Royal Dutch Meteorological Institute and averaged for the 7 days preceding the blood pressure measurements. Room temperature was measured during the medical examination.

2.5. Statistical analysis

Associations of $PM_{2.5}$- and PM_{10}-derived elements with systolic blood pressure and diastolic blood pressure were analyzed by means of linear regression analyses with non-transformed exposures. The results are expressed as change in blood pressure per interquartile range increase in elemental concentrations. We performed crude and adjusted regression analyses taking into account the confounders listed above. We first adjusted for potential confounding variables that were not on the pathway between air pollution and blood pressure (sex, age, height, and BMI, cuff size, weight gain during the first year of life, breast feeding, maternal smoking during pregnancy, parental smoking in child's home, physical activity, puberty development scale, maternal education, ambient temperature, and room temperature). We subsequently adjusted for gestational age at birth, birth weight, maternal hypertension during pregnancy, and respiratory infections (pneumonia and/or otitis media during the first two years of life) which may be on the causal pathway between air pollution and childhood blood pressure. Time-varying confounders were selected from the questionnaire that coincided best with exposure. We performed analyses for the whole population and for the subset of children who lived at the same address since birth that is the subgroup for which we reported associations of air pollution exposure with blood pressure previously (Bilenko et al., 2015).

For elements, we also performed analyses with additional adjustment for PM mass to disentangle specific independent contribution of PM mass and elemental constituents to blood pressure; and analyses with additional adjustment for NO_2 to disentangle the effects of exhaust- and non-exhaust emissions.

3. Results

Characteristics of the 1147 children included in the current analysis are shown in Table 1. Substantial variability on blood pressure was found. Few parents smoked. Associations between systolic blood pressure and diastolic blood pressure and potential confounding variables are presented in Tables S2 and S3 of the online supplement. Parental education, and smoking in the child's home were significantly associated with diastolic blood pressure. Moreover, correlations of both systolic blood pressure and diastolic blood pressure with age, gestational age, room and ambient temperature were statistically significant. In addition, systolic blood pressure was significantly correlated with height, and weight gain during the 1st year of life.

Descriptive statistics of $PM_{2.5}$ and PM_{10} mass, concentrations, concentrations of the eight elements in $PM_{2.5}$ and PM_{10}, and NO_2 concentrations at the current home address are presented in Table 2. Distributions of air pollution concentrations at the birth address were similar (data not shown). The variability of the concentrations between children was found to be large except for sulfur and potassium in $PM_{2.5}$. Moderate to high correlations between $PM_{2.5}$ and PM_{10} mass concentrations and $PM_{2.5}$-and PM_{10}-derived element concentrations were found (Table S4). NO_2 was highly correlated with the particulate matter constituents. Correlations between exposures at the birth address and exposure at the current address for the same pollutant ranged from 0.57 for potassium in PM_{10} to 0.89 for nickel in $PM_{2.5}$ and vanadium in $PM_{2.5}$ and PM_{10}.

Tables 3 and S5 show the crude and adjusted associations of PM mass and element concentrations, and NO_2 at the current address and birth address, respectively, with systolic blood pressure and diastolic blood pressure. Estimates of the associations of diastolic blood pressure with air pollution were all positive for exposures at the current address and most of the exposures at the birth address. For systolic blood pressure, the picture was more mixed. After adjustment for potential confounders we found no statistically significant associations of the air pollutants studied with systolic blood pressure and diastolic blood pressure. Associations remained statistically non-significant after additional adjustment for covariates that may be on the pathway between air pollution and blood pressure (data not shown).

Table 1
Distribution of systolic blood pressure and diastolic blood pressure (BP) and potential confounders in the study population (N = 1147).

	Mean ± SD	Range
Systolic BP, mm Hg	114.8 ± 9.1	93–149
Diastolic BP, mm Hg	66.7 ± 6.4	43–90
Age, years [a]	12.7 ± 0.4	12.0–13.8
Height, cm [a]	160.1 ± 7.9	134.3–193.2
BMI, kg/m^2 [a]	18.7 ± 2.7	13.1–33.7
Puberty development scale [b]	1.5 ± 0.5	1.0–4.0
Birth weight, gram	3,555.0 ± 526.7	1370–5000
Gestational age at birth, weeks	39.9 ± 1.6	28.7–43.6
Weight gain during 1st year, gram	6,272.3 ± 994.1	2790–10,700
Room temperature, °C [a]	21.4 ± 2.2	15.0–28.7
Ambient temperature, °C [c]	9.6 ± 6.7	−7.7–24.8
	n	**%**
Female sex	573	50.0
Maternal education		
Low	185	16.1
Intermediate	473	41.2
High	489	42.6
Breastfeeding at age 3 months	644	56.1
Maternal smoking during pregnancy	148	12.9
Parental smoking in child's home		
Early life [d]	239	20.8
Current [b]	120	10.5
No. of days/week with ≥1 h physical activity [b]		
0–2	141	12.3
3 or more	1006	87.7
Maternal hypertension during pregnancy	111	9.7
Pneumonia and/or otitis media during first 2 years of life	386	33.7
Did not move during follow-up	471	41.1

[a] At BP measurement.
[b] From 11-year questionnaire.
[c] 7 days preceding blood pressure measurements.
[d] From 1-year questionnaire.

When we restricted the analysis to the participants who had lived at the same address since birth, we found diastolic blood pressure to be significantly positively associated with iron, silicon and potassium in PM_{10} [0.67 (0.02; 1.31) mm Hg, 0.75 (0.09; 1.41) mm Hg, and 0.85 (0.18; 1.52) mm Hg respectively] and marginally significantly

Table 2
Distribution of PM_{10} and $PM_{2.5}$ mass concentrations, element concentrations, and NO_2 concentrations at the current home address (N = 1147).

	Minimum	Median	Mean	Maximum	IQR
$PM_{2.5}$ [μg/m^3]	14.9	16.5	16.3	19.3	1.2
$PM_{2.5}$ Cu [ng/m^3]	1.1	3.1	2.9	7.1	1.4
$PM_{2.5}$ Fe [ng/m^3]	31.1	77.9	74.9	160.2	35.4
$PM_{2.5}$ K [ng/m^3]	103.4	111.7	112.0	137.3	7.3
$PM_{2.5}$ Ni [ng/m^3]	0.9	1.8	1.8	4.0	0.7
$PM_{2.5}$ S [ng/m^3]	747.0	875.9	853.6	979.8	107.4
$PM_{2.5}$ Si [ng/m^3]	58.8	80.3	78.2	183.9	21.9
$PM_{2.5}$ V [ng/m^3]	1.5	2.8	2.9	7.2	1.0
$PM_{2.5}$ Zn [ng/m^3]	10.7	22.2	21.6	57.6	9.3
PM_{10} [μg/m^3]	23.7	24.5	24.7	30.1	1.0
PM_{10} Cu [ng/m^3]	6.6	11.0	11.8	31.2	3.9
PM_{10} Fe [ng/m^3]	183.0	338.6	355.7	968.5	119.2
PM_{10} K [ng/m^3]	172.7	206.1	203.4	272.8	18.3
PM_{10} Ni [ng/m^3]	1.0	2.0	2.1	4.9	1.0
PM_{10} S [ng/m^3]	927.0	1000.8	996.9	1239.6	69.0
PM_{10} Si [ng/m^3]	284.6	341.6	355.5	805.7	74.5
PM_{10} V [ng/m^3]	1.9	3.5	3.5	8.5	1.2
PM_{10} Zn [ng/m^3]	12.6	30.2	30.6	77.6	14.2
NO_2 [μg/m^3]	9.6	21.8	21.5	40.0	7.6

IQR = interquartile range.

Table 3
Crude and adjusted associations [1] of systolic blood pressure and diastolic blood pressure with particle mass and particle element concentrations and NO_2 concentrations at the current address (N = 1147).

	Systolic blood pressure [mm Hg]				Diastolic blood pressure [mm Hg]			
	Crude		Adjusted [2]		Crude		Adjusted [2]	
Pollutant [IQR]	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
$PM_{2.5}$ [1.2 μg/m^3]	0.01	(−0.95; 0.97)	−0.12	(−1.02; 0.78)	0.66	(−0.01; 1.34)	0.59	(−0.09; 1.27)
$PM_{2.5}$, Cu [1.4 ng/m^3]	−0.01	(−0.77; 0.75)	−0.01	(−0.73; 0.70)	0.54	(−0.00; 1.07)	0.44	(−0.10; 0.98)
$PM_{2.5}$, Fe [35.4 ng/m^3]	−0.00	(−0.79; 0.78)	−0.03	(−0.77; 0.71)	0.48	(−0.08; 1.04)	0.38	(−0.18; 0.94)
$PM_{2.5}$, K [7.3 ng/m^3]	0.08	(−0.59; 0.76)	−0.21	(−0.83; 0.41)	0.18	(−0.30; 0.66)	0.16	(−0.31; 0.63)
$PM_{2.5}$, Ni [0.7 ng/m^3]	−0.03	(−0.55; 0.50)	0.11	(−0.39; 0.60)	0.25	(−0.12; 0.62)	0.17	(−0.21; 0.54)
$PM_{2.5}$, S [107.4 ng/m^3]	0.10	(−0.89; 1.09)	−0.06	(−1.00; 0.88)	0.74	(0.04; 1.44)	0.56	(−0.15; 1.27)
$PM_{2.5}$, Si [21.9 ng/m^3]	0.17	(−0.73; 1.08)	0.03	(−0.83; 0.89)	0.60	(−0.04; 1.24)	0.42	(−0.23; 1.07)
$PM_{2.5}$, V [1.0 ng/m^3]	−0.05	(−0.51; 0.41)	0.07	(−0.36; 0.50)	0.19	(−0.13; 0.52)	0.12	(−0.21; 0.44)
$PM_{2.5}$, Zn [9.3 ng/m^3]	0.15	(−0.56; 0.85)	−0.28	(−0.92; 0.36)	0.22	(−0.28; 0.72)	0.14	(−0.35; 0.62)
PM_{10} [1.0 μg/m^3]	−0.10	(−0.67; 0.47)	0.02	(−0.50; 0.55)	0.16	(−0.24; 0.56)	0.19	(−0.21; 0.59)
PM_{10}, Cu [3.9 ng/m^3]	−0.33	(−0.88; 0.22)	−0.15	(−0.66; 0.35)	0.12	(−0.27; 0.51)	0.12	(−0.26; 0.51)
PM_{10}, Fe [119.2 ng/m^3]	−0.26	(−0.86; 0.34)	−0.06	(−0.61; 0.49)	0.15	(−0.28; 0.58)	0.20	(−0.22; 0.61)
PM_{10}, K [18.3 ng/m^3]	−0.17	(−0.74; 0.39)	−0.06	(−0.58; 0.46)	0.21	(−0.19; 0.61)	0.26	(−0.13; 0.65)
PM_{10}, Ni [1.0 ng/m^3]	−0.06	(−0.69; 0.56)	0.13	(−0.46; 0.71)	0.26	(−0.18; 0.71)	0.20	(−0.25; 0.64)
PM_{10}, S [69.0 ng/m^3]	−0.06	(−0.73; 0.61)	−0.11	(−0.74; 0.53)	0.30	(−0.17; 0.78)	0.14	(−0.34; 0.62)
PM_{10}, Si [74.5 ng/m^3]	−0.17	(−0.76; 0.42)	−0.02	(−0.56; 0.52)	0.11	(−0.31; 0.53)	0.16	(−0.25; 0.57)
PM_{10}, V [1.2 ng/m^3]	−0.05	(−0.52; 0.42)	0.07	(−0.37; 0.51)	0.20	(−0.14; 0.54)	0.12	(−0.21; 0.46)
PM_{10}, Zn [14.2 ng/m^3]	0.01	(−0.66; 0.68)	−0.27	(−0.88; 0.35)	0.14	(−0.34; 0.61)	0.12	(−0.35; 0.59)
NO_2 [7.6 μg/m^3]	−0.13	(−0.83; 0.57)	−0.06	(−0.72; 0.59)	0.39	(−0.11; 0.89)	0.32	(−0.18; 0.82)

[1] Associations are expressed as change in blood pressure [mmHg] per interquartile range increase in metal concentrations (β) with 95% confidence intervals (CI).
[2] Adjusted for sex; age, height, and BMI; cuff size, weight gain during the first year of life, breast feeding, maternal smoking during pregnancy, parental smoking in child's home, physical activity, puberty development scale, maternal education, ambient temperature, and room temperature.

($p < 0.1$) positively associated with iron and silicon in $PM_{2.5}$ (Table 4), in addition to NO_2 and $PM_{2.5}$ absorbance as reported earlier (Bilenko et al., 2015). There was no association between $PM_{2.5}$- and PM_{10}-derived elements and systolic blood pressure. Scatterplots with simple regression lines for the associations of iron, silicon and potassium in PM_{10} with diastolic blood pressure in participants who had lived at the same address since birth are presented in Fig. S2.

Additional adjustment for particle mass did not substantially change the point estimates of the associations of diastolic blood pressure with iron, silicon and potassium in PM_{10}, and iron and silicon in $PM_{2.5}$ (Fig. 1). Additional adjustment for NO_2 reduced the point estimates of the associations of diastolic blood pressure with iron, potassium, and silicon in PM_{10} by 25–50% and associations with iron and silicon in $PM_{2.5}$ by more than 90% (Fig. 1). We found little indication of multicollinearity in two-pollutant models. Variance inflation factors were largest for models with NO_2 and copper and iron in $PM_{2.5}$, but not larger than 5.7.

Table 4
Adjusted associations [1] of systolic blood pressure and diastolic blood pressure with particle mass and particle element concentrations and NO_2 concentrations in children living at the same address since birth.

	Blood pressure [mm Hg]			
	Systolic		Diastolic	
Pollutant [IQR]	β	(95% CI)	β	(95% CI)
$PM_{2.5}$ [1.2 μg/m^3]	−0.41	(−1.77; 0.95)	0.62	(−0.44; 1.69)
$PM_{2.5}$, Cu [1.4 ng/m^3]	−0.14	(−1.18; 0.89)	0.61	(−0.21; 1.42)
$PM_{2.5}$, Fe [35.4 ng/m^3]	−0.08	(−1.13; 0.98)	0.80	(−0.03; 1.63)
$PM_{2.5}$, K [7.3 ng/m^3]	−0.18	(−1.30; 0.94)	0.34	(−0.54; 1.22)
$PM_{2.5}$, Ni [0.7 ng/m^3]	0.35	(−0.39; 1.08)	0.42	(−0.16; 0.99)
$PM_{2.5}$, S [107.4 ng/m^3]	0.02	(−1.39; 1.43)	0.81	(−0.30; 1.92)
$PM_{2.5}$, Si [21.9 ng/m^3]	−0.15	(−1.34; 1.03)	0.81	(−0.12; 1.74)
$PM_{2.5}$, V [1.0 ng/m^3]	0.33	(−0.31; 0.97)	0.34	(−0.16; 0.84)
$PM_{2.5}$, Zn [9.3 ng/m^3]	−0.60	(−1.81; 0.60)	−0.01	(−0.96; 0.94)
PM_{10} [1.0 μg/m^3]	−0.02	(−0.81; 0.77)	0.51	(−0.11; 1.13)
PM_{10}, Cu [3.9 ng/m^3]	−0.15	(−0.87; 0.57)	0.39	(−0.18; 0.96)
PM_{10}, Fe [119.2 ng/m^3]	−0.22	(−1.04; 0.61)	0.67	(0.02; 1.31)
PM_{10}, K [18.3 ng/m^3]	−0.09	(−0.95; 0.76)	0.85	(0.18; 1.52)
PM_{10}, Ni [1.0 ng/m^3]	0.44	(−0.43; 1.30)	0.56	(−0.12; 1.24)
PM_{10}, S [69.0 ng/m^3]	0.30	(−0.64; 1.24)	0.42	(−0.32; 1.16)
PM_{10}, Si [74.5 ng/m^3]	0.36	(−0.48; 1.21)	0.75	(0.09; 1.41)
PM_{10}, V [1.2 ng/m^3]	0.34	(−0.32; 1.00)	0.35	(−0.17; 0.87)
PM_{10}, Zn [14.2 ng/m^3]	−0.21	(−1.31; 0.89)	0.32	(−0.54; 1.18)
NO_2 [7.6 μg/m^3]	0.03	(−0.92; 0.98)	0.82	(0.08; 1.57)

[1] Associations are expressed as change in blood pressure [mm Hg] per interquartile range increase in metal concentrations (β) with 95% confidence intervals (CI). Adjusted for sex; age, height, and BMI; cuff size, weight gain during the first year of life, breast feeding, maternal smoking during pregnancy, parental smoking in child's home, physical activity, puberty development scale, maternal education, ambient temperature, and room temperature.

4. Discussion

In this study, we investigated the long-term effects of $PM_{2.5}$ and PM_{10} elemental composition on blood pressure in 12-year-old children. In children who lived at the same address since birth, we found suggestive evidence for positive associations of iron, silicon, and potassium in PM_{10} with diastolic blood pressure and no associations between element concentrations and systolic blood pressure.

To the best of our knowledge, there are no other studies on the associations between long-term exposure to elemental composition of ambient particulate matter and blood pressure in children or adults. However, our findings are consistent with recent short-term effect studies among adults, where $PM_{2.5}$-derived element concentrations during the days preceding the blood pressure measurements were found to be positively associated with blood pressure, but different studies pointed at different elements. Jacobs et al. (2012), for example, did find significant positive associations between systolic blood pressure and and 24-hour mean levels of vanadium and nickel in $PM_{2.5}$, in elderly persons. In contrast to the present study, they also found association between 24-hour mean levels of iron in $PM_{2.5}$ and systolic blood pressure. In another study among young adults (mean age 20 years), Wu et al. (2013) found that short-term exposure to several $PM_{2.5}$ metal constituents, including nickel and zinc had positive associations with both systolic blood pressure and diastolic blood pressure. In contrast, another study in adults (mean age 45 years) by Williams et al. (2012) reported negative associations between daily potassium levels and diastolic blood pressure. The direct comparison of the findings of the aforementioned studies with our findings, however, is limited due to the differences in study population (i.e. adults vs children) and exposure time-windows (days vs. annual averages).

We have no explanation for the lack of association between air pollutants and systolic blood pressure in the presence of an association with diastolic blood pressure in our study. However, findings are consistent

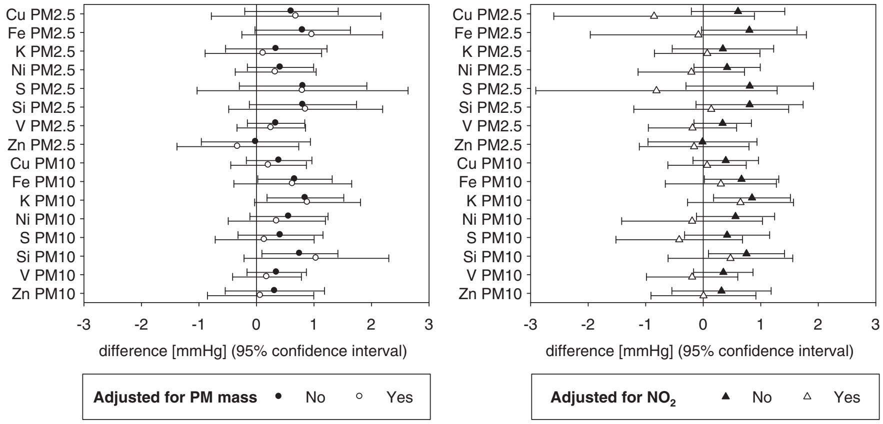

Fig. 1. Associations of diastolic blood pressure with particle element concentrations with additional adjustment for particulate matter mass and NO_2 concentrations in children living at the same address since birth.

with findings of two studies of the short-term air pollution effects on blood pressure of adults, where associations with air pollution were also found to be limited to diastolic blood pressure (Brook et al., 2009; Liu et al., 2009).

The biological mechanisms by which metal particle components affect blood pressure are not fully understood. Studies have linked various particle components to human physiological responses, such as nickel to changes in heart rate variability (Magari et al., 2002; Chuang et al., 2013), and vanadium to oxidative DNA damage (Sorensen et al., 2005). Iron as soluble metal can cause acute vasoconstriction in vitro and in vivo and contribute to the systemic effects of particles as they can more easily permeate the alveolar–capillary membrane than the whole particle itself (Urch et al., 2004). Transition metal ions perhaps released by injury to the vessel wall, may contribute to lipid peroxidation in atherosclerotic lesions (Stadler et al., 2004).

The clinical significance of a small increase in blood pressure is also not clear. However, small increases on the population level can result in considerable increases in the number of individuals with high blood pressure. Moreover, positive tracking of blood pressure has been shown, meaning that children with high blood pressure are more likely to have high blood pressure in adulthood (Chen and Wang, 2008). Tracking correlations were found to be constant for children 5 years and older and where somewhat stronger for systolic than for diastolic blood pressure (Chen and Wang, 2008). Moreover, small prolonged increases in blood pressure have been shown to have adverse effects on the cardiovascular system with large importance for later stages of life (Lewington et al., 2002).

The $PM_{2.5}$ and PM_{10} constituents that we studied have multiple sources. Traffic (copper, iron, zinc), crustal material (silicon and iron), and industrial/fuel oil combustion (vanadium and nickel) have been identified as sources of the elements investigated in our study by a recent review (Viana et al., 2008). Within the source types, copper and zinc were associated with tire and brake wear and iron was mostly associated with brake abrasion and road dust; silicon was associated with resuspended road dust, and vanadium and nickel were mainly derived from shipping emissions (Viana et al., 2008). Potassium has been suggested as a tracer for biomass burning, but it is also present in soil (Reche et al., 2011). The land-use regression models for potassium for the Netherlands, however, were dominated by traffic variables, reflecting resuspension of road dust (de Hoogh et al., 2013). The relatively poor performance of potassium models can be explained by the lack of specific GIS-variables for sources other than traffic. Also for sulfur and silicon, the relatively poor performance of the land-use regression models can be explained by the lack of specific GIS-variables for sources other than traffic (de Hoogh et al., 2013).

The observed associations of diastolic blood pressure with iron in $PM_{2.5}$ and PM_{10} are of particular interest, as due to substantial efforts to reduce exhaust emissions, the importance of non-exhaust emissions from traffic is increasing. A recent study in the Netherlands showed that contrasts of iron and copper between major roads and urban background were as large as the contrasts of soot, a marker of exhaust emissions (Boogaard et al., 2012). Point estimates of these associations remained largely unchanged after adjustment for particulate matter mass, suggesting independence of constituent effects from particulate matter mass, while two-pollutant models with NO_2 as a marker of exhaust emissions indicate that at least part of the observed associations with iron in PM_{10} is attributable to exhaust emissions. All confidence intervals become wider in two-pollutant models, in particular in two-pollutant models with NO_2 due to the high correlation between NO_2 and element concentrations.

The air pollution measurement campaign for the land-use regression was performed close to the 12-year medical examination that was conducted in 2008–2011. By applying the models to the children's birth addresses, however, we assume that the spatial patterns reflect the baseline period of the cohort i.e. 1996–1997. This assumption is supported by four studies that showed that spatial contrasts in measured and modeled annual average NO_2-levels were stable over periods of 7–12 years (Eeftens et al., 2011; Cesaroni et al., 2012; Wang et al., 2013). For the other pollutants studied, no such information is available. The assumption of a constant spatial pattern may be valid for traffic-related elements such as iron, copper, and zinc, but it is not clear whether it is also valid for elements related sources other than traffic.

A possible limitation of our exposure assessment may be that lack of information on time activity pattern, which could be related to air pollution exposure as well as to blood pressure which is less likely in children. Although we had information on most potential confounders, we lacked information about genetic factors and cardiovascular risk factors of the participants' parents. Although we performed multiple comparisons, we did not adjust for multiple testing as this reduces the probability of a false rejection of the null hypothesis that there is no association between exposure and outcome at the cost of increasing the frequency of incorrect statements about statistical non-significance of associations and missing possibly important findings. We rather interpreted results on the basis of consistency of effect estimates across elements and PM size fractions.

5. Conclusion

Exposure to particulate matter constituents, in particular iron may increase diastolic blood pressure in children. Part of the observed effects, however, was found to be attributable to NO_2, a marker of exhaust traffic emissions. The possible association with iron may indicate the health relevance of non-exhaust emissions of traffic (e.g. break, abrasion and road dust).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2015.07.010.

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