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Exposure to elemental composition of outdoor $PM_{2.5}$ at birth and cognitive and psychomotor function in childhood in four European birth cohorts

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ABSTRACT

Background: Little is known about developmental neurotoxicity of particulate matter composition. We aimed to investigate associations between exposure to elemental composition of outdoor $PM_{2.5}$ at birth and cognitive and psychomotor functions in childhood.

Methods: We analyzed data from 4 European population-based birth cohorts in the Netherlands, Germany, Italy and Spain, with recruitment in 2000–2006. Elemental composition of $PM_{2.5}$ measurements were performed in each region in 2008–2011 and land use regression models were used to predict concentrations at participants' residential addresses at birth. We selected 8 elements (copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc) and used principal component analysis to combine elements from the same sources. Cognitive (general, verbal, and non-verbal) and psychomotor (fine and gross) functions were assessed between 1 and 9 years of age. Adjusted cohort-specific effect estimates were combined using random-effects meta-analysis.

Results: 7246 children were included in this analysis. Single element analysis resulted in negative association between estimated airborne iron and fine motor function (−1.25 points [95% CI −2.45 to −0.06] per 100 ng/m^3 increase of iron). Association between the motorized traffic component, derived from principal component analysis, and fine motor function was not significant (−0.29 points [95% CI −0.64 to 0.06] per unit increase). None of the elements were associated with gross motor function or cognitive function, although the latter estimates were predominantly negative.

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Conclusion: Our results suggest that iron, a highly prevalent element in motorized traffic pollution, may be a neurotoxic compound. This raises concern given the ubiquity of motorized traffic air pollution.

1. Introduction

Air pollution is a serious threat to human health. The potential effects of air pollution on human brain are an active area of research (Block et al., 2012). Particulate matter (PM), highly prevalent in traffic related air pollution, could reach the brain and other organs by translocation to the systemic circulation following a deposition in the pulmonary region after inhalation (Block et al., 2012). The brain of a fetus could be reached via an indirect path as the placenta and the blood-brain barrier grant only a partial protection against entry of environmental toxicants to which the mother is exposed. As the brain is in the process of development and the detoxification mechanisms are relatively immature, the potential adverse effects of exposure to air pollution during pregnancy are of particular concern (Block et al., 2012; Grandjean and Landrigan, 2014).

Although the precise biological mechanisms are yet to be clarified, there is some evidence for a negative association between pre- and postnatal exposure to outdoor PM and children's cognition, psychomotor development, and behavioral problems (Guxens and Sunyer, 2012; Guxens et al., 2014, 2015; Suades-González et al., 2015). It has been hypothesized that traffic-related PM might be neurotoxic mainly through some of its components such as polycyclic aromatic hydrocarbons (PAHs), black carbon, and trace elements, potentially leading to increased oxidative stress and increased activation of brain microglia, the primary regulators of neuroinflammation (Block et al., 2012). Studies focusing on PAHs found negative association with children's cognition and behavioral problems (Edwards et al., 2010; Lovasi et al., 2014; Perera et al., 2006, 2009, 2013; Wang et al., 2010). Moreover, a recent study using magnetic resonance imaging found preliminary evidence for reduction in the white matter surface of the left hemisphere of the brain in childhood with increased prenatal concentrations of PAHs, associated with slower information processing speed (Peterson et al., 2015). Studies with focus on pre- and postnatal exposure to black carbon also found a negative association with cognitive and/or psychomotor development (Chiu et al., 2013; Suglia et al., 2008), although these findings were inconsistent.

To date, developmental neurotoxicity has been documented for only a small selection of existing trace elements (Grandjean and Landrigan, 2014). Studies addressing the association between pre- and/or postnatal exposure to trace elements in outdoor air and children's brain development are very limited in number. The few existing studies have linked higher levels of several airborne elements including arsenic, cadmium, chromium, lead, manganese, mercury, nickel, selenium, and vanadium, to elevated prevalence of autism spectrum disorder (Lam et al., 2016). Additionally, the only study to date that focused on airborne elements and cognition, found evidence for a negative association between childhood exposure at schools to airborne elements originating from motorized traffic sources and specific cognitive functions in school aged children (Basagaña et al., 2016). However, for many elements, sparse evidence of neurotoxicity is possibly a consequence of limited amount of research addressing the topic rather than absence of an association (Grandjean and Herz, 2015).

Therefore, the aim of this study was to analyze the association between exposure at birth to a set of elements measured in outdoor PM with aerodynamic diameter of $< 2.5\,\mu m$ ($PM_{2.5}$) and cognitive and psychomotor function in childhood using data from four European cohorts. The elemental components examined in this study were copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc, selected based on their reflection of major anthropogenic emission sources. This study builds on a previous epidemiological study that investigated the association between air pollution and neuropsychological development in 6 European cohorts (Guxens et al., 2014). In that study, the authors found a negative association between prenatal exposure to NO_2 and PM - latter borderline significant - and psychomotor function in childhood. The cohorts included in the current study are a subset of the cohorts studied previously due to the availability of elemental composition data. Also, in the current study we used additional neuropsychological domains and some of the tests included were carried out at older ages.

2. Methods

2.1. Population and study design

This study is part of the ESCAPE (European Study of Cohorts for Air Pollution Effects; www.escapeproject.eu) project. The aim of the project was to investigate the association between exposure to outdoor air pollution and health within prospective cohort studies. In the current study, we included 4 European population-based birth cohorts: GENERATION R (The Netherlands) (Kooijman et al., 2016), DUISBURG (Germany) (Wilhelm et al., 2008), GASPII (Italy) (Porta et al., 2007), and INMA-Sabadell (Spain) (Guxens et al., 2012), a selection based on the availability of elemental composition of $PM_{2.5}$ and neuropsychological data. Mother-child pairs were recruited between 2000 and 2006. A total of 7246 children aged between 1 and 9 years was included in this analysis and had data on exposures and at least one of the neuropsychological outcomes (Table 1). Local authorized Institutional Review Boards granted the ethical approval for the studies and all participants provided signed informed consent.

2.2. Exposure to elemental composition of outdoor $PM_{2.5}$ at birth

The exposure of each participant to the elemental composition of $PM_{2.5}$ at birth was estimated using standardized procedure based on land use regression (LUR) methodology (de Hoogh et al., 2013). A number of studies have shown that LUR models provide a cost-effective methodology to capture the spatial contrasts of air pollution (Hoek et al., 2008; Marshall et al., 2008). The locations of the measuring stations were based on the specific characteristics of each study area including a large diversity of potential sources of air pollution variability, and were selected in a manner to maximise the representativeness of the residential addresses of the cohort participants (Eeftens et al., 2012). We focused on fine particles rather than coarse, due to their higher potential to translocate to the systemic circulation because of the smaller size (Phalen et al., 2010). $PM_{2.5}$ concentrations in outdoor air were measured at 40 sites in the Netherlands/Belgium and Catalunya, and 20 sites in Ruhr area and Rome three times over a year (in summer, winter, and an intermediate season) during a two-week period each time to capture seasonal variations (Eeftens et al., 2012). The campaigns took place between 2008 and 2011. The filters were sent to Cooper Environmental Services (Portland, Oregon, USA) to analyze their elemental composition using X-Ray Fluorescence (XRF) (de Hoogh et al., 2013; Tsai et al., 2015). The results of the three measurements were then averaged, adjusting for temporal trends using data from a continuous reference site, resulting in one mean annual concentration for each element identified in the composition of $PM_{2.5}$.

Following previous ESCAPE studies on elemental components (de Hoogh et al., 2013; Pedersen et al., 2016; Wang et al., 2014) we selected 8 elements based on their reflection of major anthropogenic emission sources and on data availability determined by (i) the coefficient of variation acquired from duplicate samples, (ii) the percentage

Table 1
Description of the participating birth cohort studies.

Origin of the study (city/area)	Setting			Elemental components	Cognitive function					Psychomotor function				
	Cohort name	Birth	No. of participants	LUR models	Test	Domain	Age (years)	Evaluator	No.[a]	Test	Domain	Age (years)	Evaluator	No.[a]
		Period	At baseline	Available										
Dutch (Rotterdam)	Generation R	2001–2006	8737	Cu, Fe, K, Ni, S, Si, V, Zn	MCDI	verbal	1.5	Parents	4397	MIDI	FM, GrM	1	Parents	4704
					SON-R	non-verbal	6	Trained staff	4580					
German (Ruhr area)	Duisburg	2000–2004	232	Cu, Fe, Ni, S, Si, V, Zn	BSID II	General	1	Psychologist	186	N/A				
					BSID II	General	2	Psychologist	178					
					HAWIK-IV	General, verbal, non-verbal	9	Psychologist	95					
Italian (Rome)	GASPII	2003–2005	719	Cu, Fe, K, Ni, S, Si, V, Zn	DDST II	verbal	1.5	Parents	546	DDST II	FM, GrM	1.5	Pediatrician	546
					WISC-III	General, verbal, non-verbal	7	Psychologist	450	DDST II	FM, GrM	4	Parents	551
Spanish (Sabadell)	INMA-Sabadell	2004–2007	740	Cu, Fe, K, Ni, S, Si, V, Zn	BSID I	General	1.5	Psychologist	519	MSCA	FM, GrM	4	Psychologist	439
					MSCA	General, verbal, non-verbal	4	Psychologist	439					

BSID, Bayley Scales of Infant Development (I-first edition, II-second edition); DDST II, Denver Developmental Screening Test II; FM, Fine motor; GrM, Gross motor; HAWIK-IV, Hamburg Wechsler Intelligenztest für Kinder - IV; MCDI, McArthur Communicative Development Inventory; MIDI, Minnesota Infant Development Inventory; MSCA, McCarthy Scales of Children's Abilities; N/A, not available; SON-R, De Snijders-Oomen Niet-verbale Intelligentietest-Revisie; WISC, Wechsler Intelligence Scale for Children.

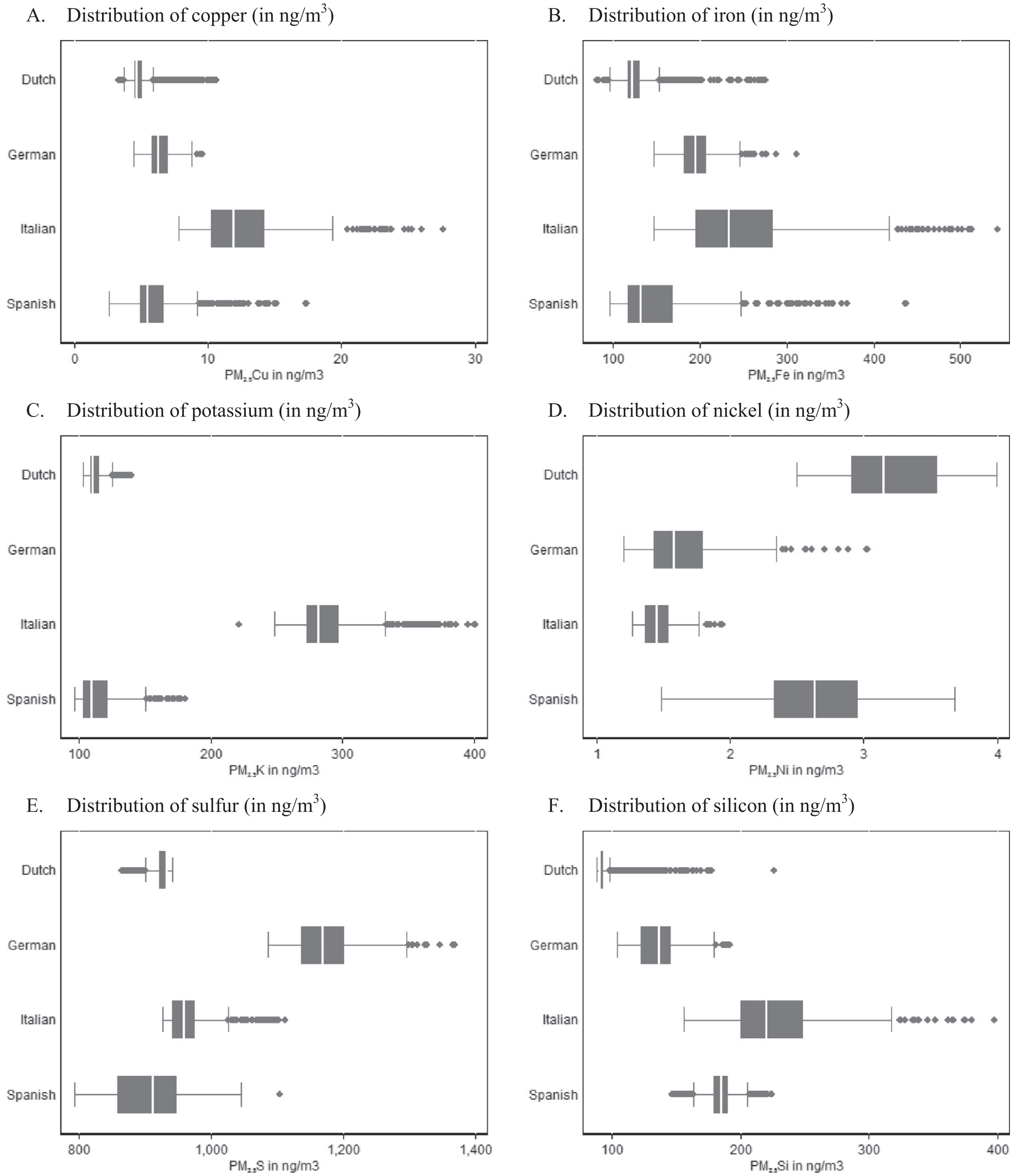
[a] Number of subjects with airborne elemental components of PM2.5 and cognitive/psychomotor function data available.

Table 2
Distribution of parental characteristics.

Study origin	Country	Name	No.	Maternal education level			Paternal education level			Maternal country of birth	Paternal country of birth	Maternal age at delivery (in years)
				Low	Medium	High	Low	Medium	High	Foreign	Foreign	
Dutch	The Netherlands	Generation R	5911	9.3	41.9	48.8	9.6	41.8	48.6	44.3	42.1	31.0 (5.0)
German	Germany	Duisburg	190	20.0	37.9	42.1	24.6	24.2	51.3	13.2	18.4	31.2 (4.7)
Italian	Italy	GASPII	614	13.6	50.7	35.8	1.7	66.5	31.7	3.8	2.4	33.4 (4.4)
Spanish	Spain	INMA-Sabadell	531	27.4	41.5	31.1	35.9	42.7	21.4	10.2	11.4	31.7 (4.2)

Study origin	Country	Name	No.	Maternal pre-pregnancy body mass index (in kg/m^2)	Maternal height (in cm)	Maternal alcohol during pregnancy	Maternal smoking during pregnancy	Parity	Marital status
						Yes	Yes	Nulliparous	Monoparental
Dutch	The Netherlands	Generation R	5911	22.6 (20.8 to 25.2)	168.0 (7.4)	42.5	14.3	57.1	11.2
German	Germany	Duisburg	190	22.9 (20.8 to 25.7)	167.6 (6.2)	11.5	22.6	56.8	2.7
Italian	Italy	GASPII	614	21.3 (19.8 to 23.7)	164.8 (5.8)	35.6	11.3	58.0	0.5
Spanish	Spain	INMA-Sabadell	531	22.7 (21.0 to 25.4)	162.4 (6.0)	21.1	29.4	57.3	1.1

Values are percentages for the categorical variables, mean (standard deviation) for the continuous normally distributed variables, and median (interquartile range) for the non-normally distributed variables.
No, number.



A. Distribution of copper (in ng/m^3)

B. Distribution of iron (in ng/m^3)

C. Distribution of potassium (in ng/m^3)

D. Distribution of nickel (in ng/m^3)

E. Distribution of sulfur (in ng/m^3)

F. Distribution of silicon (in ng/m^3)

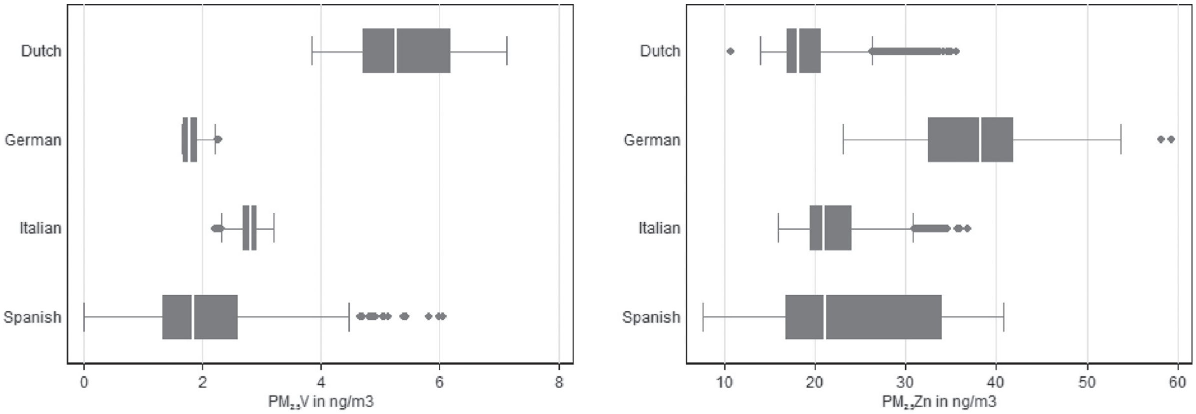
Fig. 1. Distribution of $PM_{2.5}$ elemental composition levels in ng/m3 (copper (A), iron (B), potassium (C), nickel (D), sulfur (E), silicon (F), vanadium (G) and zinc (H)), $PM_{2.5}$ mass in μg/m3 (I) and motorized traffic pollution scores (J) in the participating cohorts.

of samples in which the element was detected, and (iii) the availability of relevant geographical data needed as predictor variables in the LUR models. Copper, iron, and zinc reflect brake linings, tire wear, and industrial (smelter) emissions, silicon and potassium reflect crustal materials and biomass burning, and fossil fuel combustion is reflected by nickel, vanadium, and sulfur (Viana et al., 2008).

Following a previous study on birth outcomes (Pedersen et al., 2016), concentrations of the selected elements were assigned at each participants' home address at birth to obtain an estimation of the pregnancy exposure using mean annual area-specific LUR model estimates based on 2008–2011 data (Table 1). Fixed increments per elemental component were applied to facilitate comparability. The model predictors and a description of model performances are reported elsewhere (de Hoogh et al., 2013). Due to insufficient data quality, LUR models of potassium could not be developed for the German cohort (Table 1). Next, we pooled the exposure data of participants from the cohorts together and applied principal component analysis (PCA) to the estimated elemental concentrations at the residential addresses, in order to combine elements from the same sources into one score. Oblique promax rotations were allowed. Since the levels of potassium could not be estimated for the German cohort, that cohort was not included in the pooled PCA.

G. Distribution of vanadium (in ng/m^3)

H. Distribution of zinc (in ng/m^3)



I. Distribution of PM$_{2.5}$ mass (in μg/m^3)

J. Distribution of Motorized Traffic Pollution

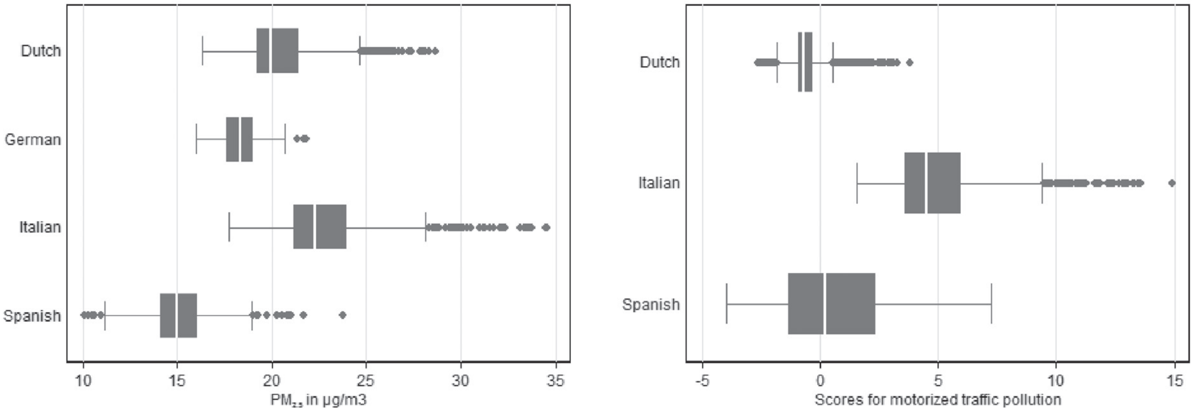


Fig. 1. (*continued*)

2.3. Cognitive and psychomotor function

Neuropsychological tests used to assess the cognitive and psychomotor function of children were administered by psychologists, pediatricians or trained research staff, or by questionnaires answered by the parents, and differed between the cohorts (Table 1). For each cohort, the tests and questionnaires that measured each neuropsychological function in a similar way and derived in comparable score distribution, were selected. Cognitive function scales measured general, verbal, and/or non-verbal cognitive functions and psychomotor function scales measured fine and gross motor functions (Table 1). To homogenize the scales, we converted all raw scores into standard deviation units using the z-score (z-score is calculated as the raw score minus the sample mean, divided by the standard deviation) and standardized them to a mean of 100 and a standard deviation of 15 (new score = 100 + (15 × z)) (Guxens et al., 2014). For each domain, higher scores corresponded to better neuropsychological function.

2.4. Potential confounding variables

Available potential confounding variables were defined a priori based on direct acyclic graph (DAG) (Supplementary material Fig. 1) and selected as similarly as possible across the cohorts. Maternal information included age at delivery (continuous in years), height (continuous in centimeters), pre-pregnancy body mass index (continuous in kg/m^2), smoking during pregnancy (yes or no), alcohol consumption during pregnancy (yes or no), marital status (monoparental household: yes or no), and parity (0, 1, ≥ 2). Parental information included educational level (low, medium, high) and country of birth (country of the cohort or foreign country). Maternal height and pre-pregnancy weight were obtained at the enrollment in the study, or self-reported in the first trimester of the pregnancy, at birth or two weeks after birth of the child. The other variables were collected through questionnaires either during pregnancy or at birth. For education level, standardization of cohort-specific categories was applied to create a common variable (Guxens et al., 2014). Child's age at the time of the cognitive and psychomotor function assessment, and the evaluator for the assessment, were also recorded.

2.5. Statistical analyses

We applied multiple imputation of missing values using chained equations to impute missing potential confounding variables among all participants with available data on exposure and at least one outcome variable (Supplementary material Table 1). We obtained 25 completed datasets that we analyzed using standard procedures for multiple imputation (Spratt et al., 2010; Sterne et al., 2009). Children with available exposure and outcome data (n = 7246) were more likely to have parents with higher socioeconomic status compared to those recruited initially in the cohorts but without available data on exposure and outcome (n = 3182) (Supplementary material Tables 2 and 3). We used inverse probability weighting (IPW) to correct for loss to follow-up, i.e. to account for selection bias that potentially arises when only population with available exposure and outcome data, and here thus with relatively higher socioeconomic status, is included as compared to a full initial cohort recruited at pregnancy (Weisskopf et al., 2015; Weuve et al., 2012). Briefly, we used information available for all participants at recruitment to predict the probability of participation in the study, and used the inverse of those probabilities as weights in the analyses so that results would be representative for the initial populations of the

Table 3

Fully adjusted combined associations between exposure to elemental components and the identified pollution component at birth, and general, verbal, and non-verbal cognitive function.

	General cognitive function			Verbal cognitive function			Non-verbal cognitive function		
	Coef. (95% CI)	Test for heterogeneity, P	I^2 (%)	Coef. (95% CI)	Test for heterogeneity, P	I^2 (%)	Coef. (95% CI)	Test for heterogeneity, P	I^2 (%)
$PM_{2.5}$ Cu	− 1.68 (− 5.08 to 1.72)	0.066	63.2	− 0.27 (− 1.58 to 1.04)	0.710	0.0	− 1.03 (− 2.35 to 0.30)	0.385	1.4
$PM_{2.5}$ Fe	− 1.26 (− 3.21 to 0.70)	0.201	37.7	− 0.28 (− 1.47 to 0.91)	0.836	0.0	− 1.09 (− 2.28 to 0.11)	0.684	0.0
$PM_{2.5}$ K	− 0.87 (− 2.79 to 1.06)	0.309	3.2	0.01 (− 1.62 to 1.63)	0.890	0.0	− 0.65 (− 2.74 to 1.43)	0.222	33.5
$PM_{2.5}$ Ni	− 1.99 (− 4.59 to 0.62)	0.784	0.0	− 0.22 (− 1.31 to 0.87)	0.611	0.0	− 0.17 (− 1.48 to 1.14)	0.357	7.2
$PM_{2.5}$ S	− 2.40 (− 5.85 to 1.05)	0.746	0.0	− 2.75 (− 5.92 to 0.43)	0.722	0.0	− 0.48 (− 3.71 to 2.76)	0.374	3.7
$PM_{2.5}$ Si	− 2.54 (− 5.53 to 0.45)	0.791	0.0	− 1.19 (− 3.36 to 0.98)	0.883	0.0	− 0.77 (− 2.95 to 1.41)	0.861	0.0
$PM_{2.5}$ V	− 4.56 (− 12.02 to 2.89)	0.210	35.9	− 0.24 (− 1.22 to 0.73)	0.419	0.0	− 1.04 (− 4.55 to 2.47)	0.020	69.6
$PM_{2.5}$ Zn	− 0.66 (− 1.87 to 0.55)	0.504	0.0	− 0.05 (− 0.92 to 0.81)	0.918	0.0	0.09 (− 0.74 to 0.92)	0.704	0.0
Motorized traffic[a]	− 0.26 (− 0.65 to 0.14)	0.426	0.0	− 0.16 (− 0.51 to 0.19)	0.670	0.0	− 0.20 (− 0.55 to 0.15)	0.677	0.0

Coef, coefficient; CI, confidence intervals; I2, percentage of the total variability due to between-areas heterogeneity; Cu, copper; Fe, iron; K, potassium; Ni, nickel; S, sulfur; Si, silicon; V, vanadium; Zn, zinc. Coefficient and 95% CI were estimated by random-effects meta-analysis by cohort. Models were adjusted for parental education levels, parental countries of origin, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal alcohol consumption during pregnancy, maternal smoking during pregnancy, marital status, parity and age of the child at neuropsychological testing per increments of 5 ng/m3 for Cu PM2.5; 100 ng/m3 for Fe PM2.5; 50 ng/m3 for K PM2.5; 1 ng/m3 for Ni PM2.5; 200 ng/m3 for S PM2.5; 100 ng/m3 for Si PM2.5; 2 ng/m3 for V PM2.5; 10 ng/m3 for Zn PM2.5; and 1 unit for motorized traffic component.

[a] Motorized traffic component was acquired using the principle component analysis (PCA). See Supplementary Table 6 for detailed configuration of the component.

cohorts. The variables used to create the weights are described in Supplementary material Table 4.

After visual inspection for linearity, we used linear regression models to analyze the relationships of each single element and PCA component with each neuropsychological function. Additionally, we performed the analyses with prenatal $PM_{2.5}$ and NO_2 levels and each neuropsychological function to make the comparison with the previous study (Guxens et al., 2014) straightforward. Concentrations of the pollutants were introduced as continuous variables and were not transformed. When the age of a child was not linearly related with cognitive or psychomotor function scale, we used the best transformation of age found using fractional polynomials (Royston et al., 1999). The models were adjusted for all potential confounding variables described in the previous sub-chapter.

We carried out a two-steps analysis. First, associations were analyzed separately for each cohort. Second, cohort-specific effect estimates were combined in a meta-analysis. Because the data originated from four different regions with divergent characteristics, we decided to use a conservative approach selecting a priori random effect meta-analysis method thereby also adding to the homogeneity and comparability of the analyses. We used Cochran *Q* test and I^2 statistic to indicate total variability in the estimates that is attributable to between-cohort heterogeneity (Higgins and Thompson, 2002). When the same outcome was measured at multiple ages in a cohort, the score at the oldest age was taken into account in the meta-analysis. Exception was made for the general cognitive function in the German cohort wherein the second oldest age was selected due to substantially larger sample size compared to the sample size of the oldest age (Table 1). Finally, to test the sensitivity of the results, we repeated the meta-analyses including younger ages among the cohorts where the outcomes were measured at different ages, as well as including the oldest age for the German cohort. All statistical hypothesis tests were two-tailed with significance level set at $p < 0.05$ and were carried out using STATA (version 14.0; StataCorporation, College Station, TX).

3. Results

Parental characteristics of the study population are shown in Table 2. The percentage of higher-educated mothers was highest in the Dutch cohort while the percentage of higher-educated fathers was highest in the German cohort. The highest percentage of both - lower educated mothers and lower educated fathers - was in the Spanish cohort. The highest percentage of mothers consuming alcohol during pregnancy was in the Dutch cohort whereas the highest percentage of mothers smoking during pregnancy was in the Spanish cohort. The proportion of parents that were born in a country different than that of the study and the percentage of single parent households was highest in the Dutch cohort.

Cohort specific concentration levels of each element are shown in Fig. 1. Correlations between the modelled concentrations of the pollutants varied considerably depending on the pollutant and the region (Supplementary material Table 5). The PCA resulted in identification of two principal components with a combined R^2 of 78% and a low correlation of < 0.20. Component 1 was loaded primarily with copper, iron and sulfur suggesting a reflectance of motorized traffic pollution. Component 2 was comprised predominantly of positive loadings of nickel and vanadium and negative loadings of silicon and potassium, making the conceptualization of component 2 highly ambiguous (Supplementary material Table 6). Therefore, this component was not analyzed further. The proportion of participants with a higher socio-economic status was larger in areas with higher levels of motorized traffic pollution expressed in tertiles (Supplementary material Table 7).

None of the elemental components nor the motorized traffic pollution source was associated with cognitive functions (general, verbal, and non-verbal) (Table 3 and Supplementary material Figs. 2–4). Effect estimates were predominantly negative, suggesting that higher

Table 4
Fully adjusted combined associations between exposure to elemental components and the identified pollution source at birth, and fine and gross motor function.

	Fine motor function			Gross motor function		
	Coef. (95% CI)	Test for heterogeneity, P	I^2 (%)	Coef. (95% CI)	Test for heterogeneity, P	I^2 (%)
$PM_{2.5}$ Cu	− 0.93 (− 2.24 to 0.37)	0.816	0.0	0.29 (− 2.15 to 2.72)	0.052	66.2
$PM_{2.5}$ Fe	− 1.25 (− 2.45 to − 0.06)	0.784	0.0	− 0.08 (− 1.93 to 1.77)	0.108	55.1
$PM_{2.5}$ K	− 1.10 (− 2.69 to 0.48)	0.390	0.0	1.03 (− 0.61 to 2.67)	0.353	4.0
$PM_{2.5}$ Ni	− 1.11 (− 5.91 to 3.69)	0.003	83.1	1.86 (− 0.76 to 4.49)	0.147	47.9
$PM_{2.5}$ S	− 1.01 (− 4.32 to 2.29)	0.598	0.0	1.76 (− 1.59 to 5.12)	0.776	0.0
$PM_{2.5}$ Si	− 1.52 (− 3.61 to 0.57)	0.970	0.0	− 1.64 (− 3.69 to 0.40)	0.455	0.0
$PM_{2.5}$ V	− 0.86 (− 4.93 to 3.22)	0.003	82.4	− 0.22 (− 4.18 to 3.74)	0.007	79.7
$PM_{2.5}$ Zn	− 0.36 (− 1.22 to 0.51)	0.655	0.0	0.59 (− 0.59 to 1.77)	0.217	34.5
Motorized traffic pollution[a]	− 0.29 (− 0.64 to 0.06)	0.879	0.0	0.10 (− 0.42 to 0.62)	0.120	52.8

Coef, coefficient; CI, confidence intervals; I2, percentage of the total variability due to between-areas heterogeneity; Cu, copper; Fe, iron; K, potassium; Ni, nickel; S, sulfur; Si, silicon; V, vanadium; Zn, zinc. Coefficient and 95% CI were estimated by random-effects meta-analysis by cohort. Models were adjusted for parental education levels, parental countries of origin, maternal age at delivery, maternal pre-pregnancy BMI, maternal height, maternal alcohol consumption during pregnancy, maternal smoking during pregnancy, marital status, parity and age of the child at neuropsychological testing per increments of 5 ng/m3 for Cu PM2.5; 100 ng/m3 for Fe PM2.5; 50 ng/m3 for K PM2.5; 1 ng/m3 for Ni PM2.5; 200 ng/m3 for S PM2.5; 100 ng/m3 for Si PM2.5; 2 ng/m3 for V PM2.5; 10 ng/m3 for Zn PM2.5 and 1 unit for motorized traffic component.

[a] Motorized traffic component was acquired using the principle component analysis (PCA). See Supplementary Table 6 for detailed configuration of the component.

pollution levels at birth were associated with a lower cognitive function, but significance was not reached in any of the associations (e.g. lower score by 1.68 points in general cognitive function [95% confidence interval (CI): − 5.08 to 1.72] for each 5 ng/m^3 increase in the prenatal levels of airborne copper). Increase in the levels of airborne iron, one of the main elements of motorized traffic component, was negatively associated with fine motor function (lower score by 1.25 points [95% CI − 2.45 to − 0.06] for each 100 ng/m^3 increase of iron), but the association between motorized traffic component and fine motor function was not significant (− 0.29 [95% CI − 0.64 to 0.06] for each one unit increase of the component) (Table 4 and Fig. 2). We did not find any associations between the elemental components or the motorized traffic pollution component and gross motor function (Table 4 and Supplementary material Fig. 5). Overall higher exposure to NO_2 and $PM_{2.5}$ was related to a decrease in general cognition and fine motor function, but also here no significance was reached in any of the associations (Supplementary material Table 8 and Figs. 6–10). Region-specific effect estimates were relatively homogeneous except for some results obtained in the analyses with nickel and vanadium where evidence for heterogeneity between the cohorts was observed (Table 3 and Table 4). Sensitivity analyses selecting younger ages, and the analyses wherein older ages in the German cohort were included, produced only minimal changes in the results (Supplementary material Table 9).

4. Discussion

To our knowledge, no previous study focused on the association between exposure to elemental composition of outdoor $PM_{2.5}$ at birth and cognitive and psychomotor function in childhood. This study is based on 4 European birth cohorts with data on 7246 children. Despite the lack of significant association between airborne $PM_{2.5}$ during pregnancy and cognitive and psychomotor development in childhood, we found an association with one of its elemental components. Higher estimated exposure at birth to airborne iron, a main element in motorized traffic pollution, was associated with lower fine motor function in children assessed between 1 and 4 years of age. Exposure to elemental composition of outdoor $PM_{2.5}$ at birth was not associated with gross motor function or cognitive functions, although the effect estimates of the latter were predominantly negative.

This study has considerable strengths: i) large sample size with western European geographical extent including two countries from the northern part of Europe and two from the southern part, with varying levels and sources of air pollution; ii) standardized air pollution assessment which was based on validated measurements; exposure assessment of a large number of elemental components measured in airborne $PM_{2.5}$ and modelled to the individual level of each participant; iii) prospective neuropsychological function assessment during childhood using validated neuropsychological tests and questionnaires; iv) use of advanced statistical methods including multiple imputation combined with inverse probability weighting to reduce possible attrition bias in the study; and v) adjustment for various socioeconomic and lifestyle variables that are known to be potentially associated with air pollution exposure during pregnancy and with neuropsychological performance of the offspring. However, we cannot completely discard residual confounding by sociodemographic and geographic factors since adjustment for parental education levels, parental country of birth, maternal age, or marital status might not fully account for factors that may influence cognitive and psychomotor development.

There are also several other limitations in our study. The neuropsychological tests and the type of evaluators assessing cognitive and psychomotor functions, and the ages at which children were assessed, are heterogeneous across the 4 cohorts. Nevertheless, we carefully selected those tests that represent similar neuropsychological domains, adding to their comparability. Another limitation of our study is related to the exposure assessment. Another limitation of our study is related to the exposure assessment. Herein, the major source of uncertainty lies in the inability to estimate air pollution levels at the exact period of interest (i.e. at birth). Sampling campaigns were carried out between 3.5 and 9 years after the children were born and historical element data from routine monitoring stations in the study areas was not available to back extrapolate the levels to the period of interest. Since the temporal component was missing, we assumed that the relative composition of $PM_{2.5}$, including the relative concentration of the elements, has remained constant between births of the participants and the measurements, as it has been done in a previous study on birth outcomes (Pedersen et al., 2016). This assumption is based on previous studies that demonstrated spatial stability over time for other traffic related air pollutants for periods stretching from 8 to 18 years (Gulliver et al., 2013; Cesaroni et al., 2012; Eeftens et al., 2011). Nevertheless, this assumption could result in non-differential exposure misclassification which could lead to an underestimation of the associations. Furthermore, we also cannot discard the possibility that some of our findings occur due to chance because of the multiple comparisons performed. Similar studies are necessary to confirm or refute our findings.

We observed a negative association between the exposure to airborne iron, the main component of motorized traffic pollution, and fine motor function. Our previous published study found a significant negative association between prenatal exposure to NO_2, a well-known marker for traffic related air pollution, and psychomotor function

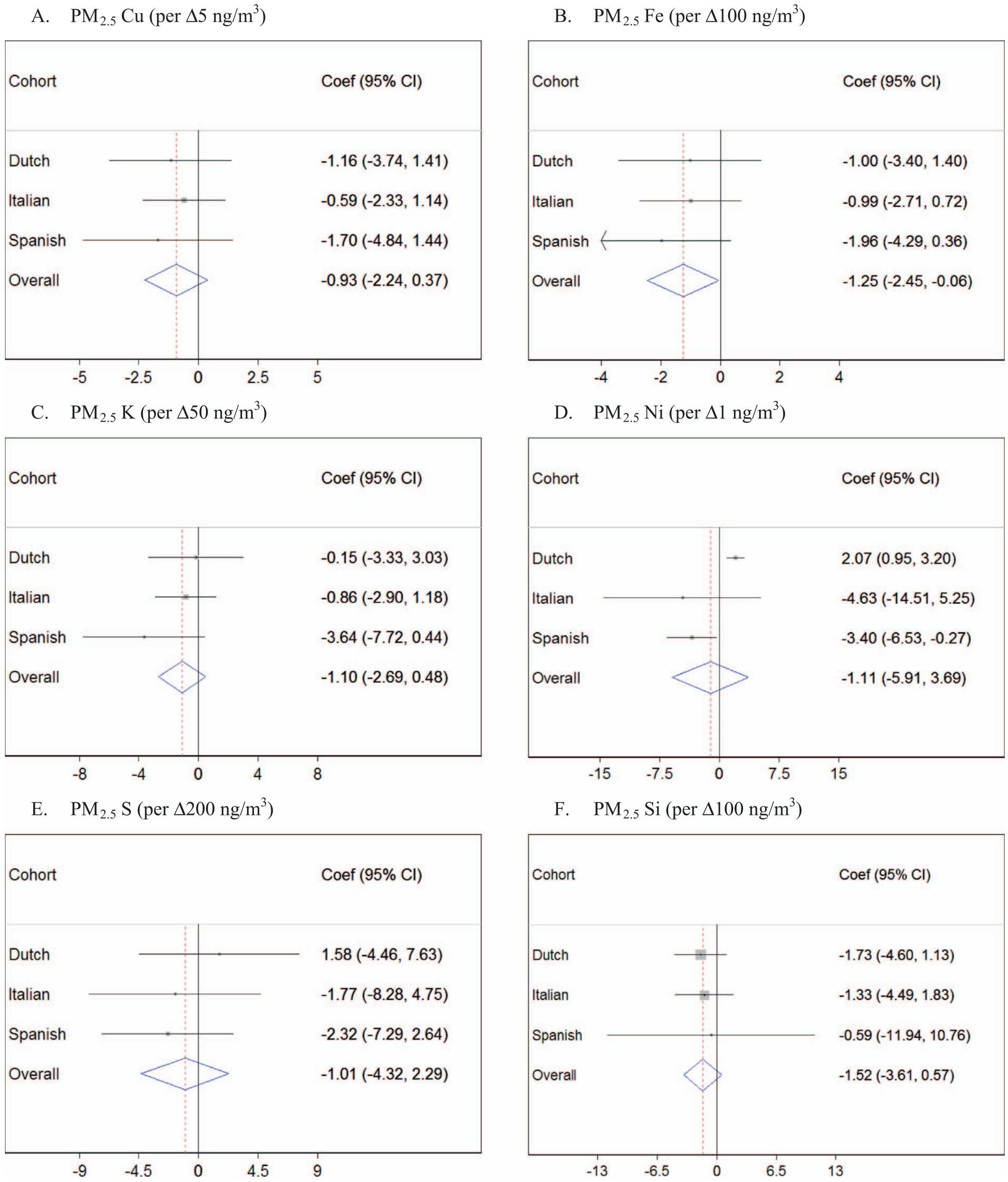
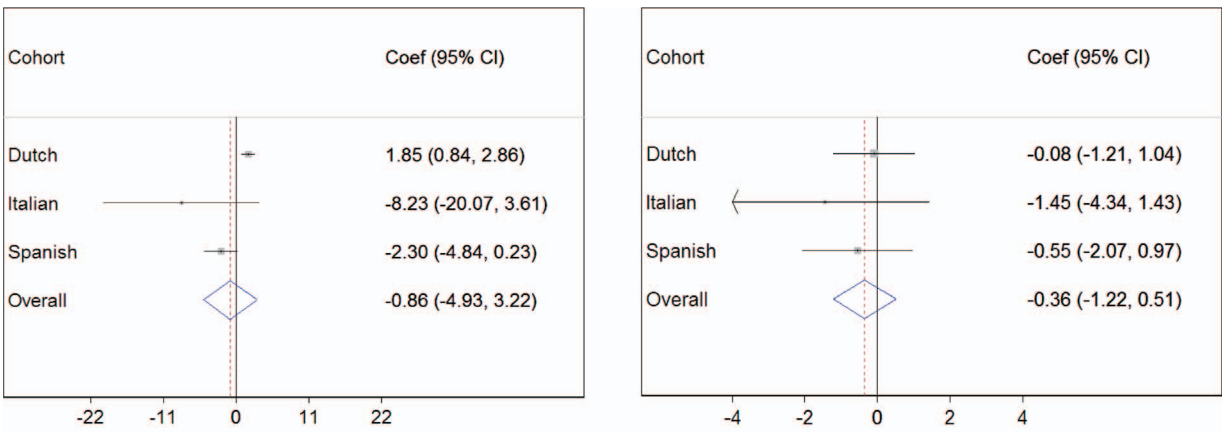


Fig. 2. Fully adjusted associations of exposure to PM$_{2.5}$ elemental composition at birth and motorized traffic pollution with fine motor function at average age of 1y in Dutch cohort, 4y in Italian cohort and 4y in Spanish cohort. Region-specific and summary risk estimates (coefficient and 95% confidence interval) for fine motor function expressed for an increase of (A) 5 ng/m3 in PM2.5 Cu levels, (B) 100 ng/m3 in PM2.5 Fe levels, (C) 50 ng/m3 in PM2.5 K levels, (D) 1 ng/m3 in PM2.5 Ni levels, (E) 200 ng/m3 in PM2.5 S levels, (F) 100 ng/m3 in PM2.5 Si levels, (G) 2 ng/m3 in PM2.5 V levels, (H) 10 ng/m3 in PM2.5 Zn levels, and (I) 1 unit in motorized traffic component levels at birth, adjusted for parental education levels, parental countries of origin, maternal age at delivery, maternal pre-pregnancy body mass index, maternal height, maternal alcohol consumption during pregnancy, maternal smoking during pregnancy, marital status, parity and age of the child at neuropsychological testing. Grey squares around region-specific coefficients represent the relative weight that the estimate contributes to the summary coefficient. Weights are from random-effects analyses.

Coef, coefficient; CI, confidence intervals; Cu, copper; Fe, iron; K, potassium; Ni, nickel; S, sulfur; Si, silicon; V, vanadium; Zn, zinc.

assessed in children between 1 and 6 years of age (Guxens et al., 2014). The association between prenatal exposure to PM$_{2.5}$ and psychomotor function was also negative, although these results were at the margin of significance. Repetition of these analyses in our current study resulted in small changes attributable to the changes in the study populations. Other epidemiological studies also found negative associations between traffic related air pollution or some of its components such as PAHs and NO$_2$ and lower psychomotor function in early childhood (Xu et al., 2016). This is the first study to assess a relationship between airborne iron and psychomotor function. It is plausible that airborne iron is a



G. $PM_{2.5}$ V (per Δ2 ng/m^3)

H. $PM_{2.5}$ Zn (per Δ10 ng/m^3)

I. Motorized Traffic Pollution (per Δ1 unit)

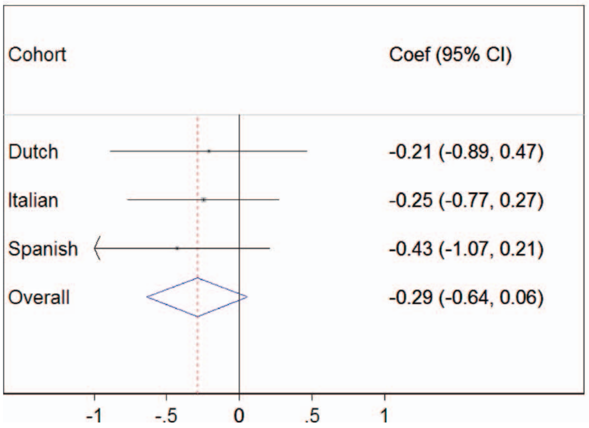


Fig. 2. (*continued*)

marker for traffic related air pollution and that the association that we found is in fact an association between traffic related air pollution and fine motor function. However, considering that iron is a documented, highly active oxidizer, and its excessive accumulation in the brain tissue can trigger neuroinflammation and oxidative stress which are linked to neurodegenerative diseases, neurodevelopmental disorders, and decreased cognitive function (Block et al., 2012; Daugherty and Raz, 2015), we also cannot discard the possibility that the association found in the current study can be attributed to the environmental exposure to airborne iron. Moreover, a recent study found the presence of magnetite ultra-fine particles of external origin in human brain samples. Magnetite ultra-fine particles are highly pervasive and abundant in air pollution and they arise from combustion as iron-rich particlulates which, upon release in the air, condense and/or oxidize (Maher et al., 2016). Nevertheless, more research is needed to confirm that airborne iron is one of the primary neurotoxic components of motorized traffic pollution instead of a marker for a different neurotoxicant or a group of neurotoxicants present in traffic related air pollution.

The associations between the elemental components, and the motorized traffic component, and cognitive function, were predominantly negative, but significance has not been reached in any case. Also in our previous published study we did not find an association between prenatal exposure to NO_2 or $PM_{2.5}$ and cognitive function (Guxens et al., 2014). Postnatal exposure at the average age of 8.5 years to source apportioned elemental components of outdoor PM at schools and child's working memory and attentional function at corresponding time point have been assessed in a recent study which found a negative relationship between exposure to source apportioned traffic pollution and the cognitive functions (Basagaña et al., 2016). That study assessed specific cognitive functions such as working memory and attentional function, instead of more global cognitive measurements like in the current study, which might be responsible for the differing results. Also, they assessed postnatal exposures in schools, as opposed to residential exposures at birth in our study. Pregnancy period is of a special interest due to the relatively immature detoxification mechanisms of fetuses and only partial protection of placenta and blood-brain barrier against entry of environmental toxicants, and therefore higher vulnerability of the developing brain. Still, brain maturation continues in childhood and adolescence and therefore a relationship with postnatal exposures is plausible as well. To our knowledge, that is the only other study to date that has assessed exposure to PM elements and/or source apportioned PM elements, and cognitive development. Previous epidemiologic studies assessing exposure to traffic related air pollutants during pregnancy and cognitive development in early childhood showed conflicting results (Guxens and Sunyer, 2012; Suades-González et al., 2015).

In summary, we found a negative association between estimated exposure to airborne iron at birth, an element highly prevalent in motorized traffic air pollution, and fine motor function in childhood with a score decrease of 1.25 points for every 100 ng/m^3 increase in predicted iron levels at birth. Although this seemingly small decrease of 1.25% from the population average might not be noticeable at an individual level, taking the population level into account, this decrease will shift the distribution of fine motor performance to the left and increase the number of people performing below average. Gross motor function and the cognitive functions were not significantly associated with any of the PM element exposures at birth, although the effect estimates of the latter were predominantly negative. Since this study is the first to focus on exposure to elemental composition of outdoor PM at birth and neuropsychological function in early childhood, the results require confirmation. Nevertheless, they are of potential concern due to the ubiquity of traffic related air pollution, which fortunately can be reduced through implementation of adequate policies worldwide.

Conflict of interest

None declared.

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Generation R, The Netherlands

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. The Generation R Study is supported by the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, The Netherlands Organization for Health Research and Development (ZonMw), The Netherlands Organization for Scientific Research (NWO), and The Ministry of Health, Welfare and Sport. TNO received funding from the Netherlands Ministry of Infrastructure and the Environment to support exposure assessment. VWVJ received grants from the Netherlands Organization for Health Research and Development (VIDI 016.136.361) and Consolidator Grant from the European Research Council (ERC-2014-CoG-64916). Furthermore, the study was made possible by financial support from the European Union's Horizon 2020 Research and Innovation Program (no.: 633595, DynaHealth) and also received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 733206 (LifeCycle).

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Appendix A. Supplementary data

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