Particulate Matter Composition and Respiratory Health

The PIAMA Birth Cohort Study

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Background: Ambient particulate matter (PM) exposure is associated with children's respiratory health. Little is known about the importance of different PM constituents. We investigated the effects of PM constituents on asthma, allergy, and lung function until the age of 11–12 years.
Methods: For 3,702 participants of a prospective birth cohort study, questionnaire-reported asthma and hay fever and measurements of allergic sensitization and lung function were linked with annual average concentrations of copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc in particles with diameters of less than 2.5 and 10 μm ($PM_{2.5}$ and PM_{10}) at birth addresses and current addresses from land-use regression models. Exposure–health relations were analyzed by multiple (repeated measures) logistic and linear regressions.
Results: Asthma incidence and prevalence of asthma symptoms and rhinitis were positively associated with zinc in PM_{10} at the birth address (odds ratio [95% confidence interval] per interquartile range increase in exposure 1.13 [1.02, 1.25], 1.08 [1.00, 1.17], and 1.16 [1.04, 1.30], respectively). Moreover, asthma symptoms were positively associated with copper in PM_{10} at the current address (1.06 [1.00, 1.12]). Allergic sensitization was positively associated with copper and iron in PM_{10} at the birth address (relative risk [95% confidence interval] 1.07 [1.01, 1.14] and 1.10 [1.03, 1.18]) and current address. Forced expiratory volume in 1 second was negatively associated with copper and iron in $PM_{2.5}$ (change [95% confidence interval] -2.1% [-1.1, -0.1%] and -1.0% [-2.0, -0.0%]) and $FEF_{75–50}$ with copper in PM_{10} at the current address (-2.3% [-4.3, -0.3%]).
Conclusion: PM constituents, in particular iron, copper, and zinc, reflecting poorly regulated non-tailpipe road traffic emissions, may increase the risk of asthma and allergy in schoolchildren.

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There is a vast body of evidence for the chronic adverse effects of ambient air pollution exposure on the respiratory health of children. Recent reviews conclude that there is consistent evidence for a positive association between traffic-related air pollution and asthma prevalence and incidence in children.[1–3] Findings were more heterogeneous for asthma incidence than for asthma prevalence.[2] Furthermore, there is evidence for adverse effects of outdoor air pollution on lung function of children.[4] The association between air pollution exposure and allergic sensitization is less clear.[2]

To date, many studies on the health effects of ambient air pollution used nitrogen dioxide (NO_2), mass concentrations of particulate matter (PM) with aerodynamic diameters of less than 10 μm (PM_{10}) and less than 2.5 μm ($PM_{2.5}$), and elemental carbon/filter reflectance as surrogates for the complex air pollution mixture. However, PM composition can vary considerably as PM is emitted from a large variety of sources including traffic, industry, biomass burning, and long-range transport.[5] With the substantial reduction of tailpipe emissions from motorized traffic, non-tailpipe emissions from resuspension of road dust formed by abrasion of road surface material and wear of tires and brakes may become more important.[5] There is increasing evidence that different constituents of PM affect health in different ways.[5]

We previously reported positive associations between traffic-related air pollution (NO_2, $PM_{2.5}$, and $PM_{2.5}$ absorbance) and the incidence and prevalence of asthma during the first 8 years of life from our prospective Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study.[6] Furthermore, as part of the European collaborative European Study of Cohorts for Air Pollution Effects (ESCAPE) study, we recently reported negative associations between air pollution (NO_2, NO_x, $PM_{2.5}$, and $PM_{2.5}$ absorbance) and lung function at age 6–8 years from five European birth cohort studies, including PIAMA.[7] Since then, another follow-up of our cohort, including a questionnaire survey and a medical examination of a subset of the population, was completed when the participants were 11–12 years old. Furthermore, within the framework of collaborative Transport related Air Pollution and Health impacts-Integrated Methodologies for Assessing Particulate Matter project, land-use regression models have been developed for a selection of eight elements in $PM_{2.5}$ and PM_{10} representing different sources such as non-exhaust emissions of traffic from brake linings and tires (copper, iron, and zinc), industrial (smelter) emissions (iron and zinc), crustal materials (soil; silicon, and potassium), fossil fuel combustion (nickel, vanadium, and sulfur) and biomass burning (potassium).[8–10] We therefore investigated the effects of different PM characteristics and PM constituents on asthma, hay fever, allergic sensitization, and lung function of the participants of the PIAMA birth cohort study until the age of 11–12 years. Because we currently know very little about the relevance of the timing of the exposure in addition to the exposure level, we explored associations with early life exposures and with exposures later in life.

MATERIALS AND METHODS

Study Population

The PIAMA study is a prospective birth cohort study.[11] Women were recruited in 1996–1997 during their second trimester of pregnancy from a series of communities in the North, West, and Centre of the Netherlands. Non-allergic pregnant women were invited to participate in a "natural history" study arm; allergic women, identified through a screening questionnaire were primarily allocated to an intervention arm (involving the use of mite-impermeable mattress and pillow-covers) with a random subset allocated to the natural history arm. The study population for this study consisted of participants in the intervention and natural history studies with data on at least one of the health outcomes studied and with data on air pollution exposure and potential confounders available to be included in at least one of the adjusted analyses (N = 3,702). 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.

Health Outcomes

Information on the children's respiratory health was collected by questionnaire annually until age 8 years and between 11 and 12 years. From these questionnaires, the same health outcomes as in previous analyses,[6] namely incident doctor-diagnosed asthma, asthma symptoms in the past 12 months, hay fever ever, and rhinitis in the past 12 months (see Supplemental Digital Content at http://links.lww.com/EDE/A883 for exact definitions) were studied.

At age 12 years, a blood sample was taken from all children who gave consent. Specific immunoglobulin E levels for house dust mite (*Dermatophagoides pteronyssinus*), cat, cocksfoot (*Dactylis glomerata*), and birch pollen were measured in blood samples by a radioallergosorbent test-like method used at the Sanquin Laboratories (Amsterdam, The Netherlands). Sensitization was defined as a positive reaction (specific IgE level ≥ 0.70 IU/ml) to at least one of the allergens tested.

Spirometry was performed when the children were approximately 8 and 12 years old following the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS).[12] A detailed description of the tests can be found in the Supplemental Digital Content, http://links.lww.com/EDE/A883. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured at both ages; mid-expiratory flows (FEF_{25-75}) were assessed at age 12 only. A total of 555 children had lung function measurements at both ages (8 and 12 years). Height and weight were measured as described in the Supplemental Digital Content, http://links.lww.com/EDE/A883.

Long-term Air Pollution Exposure Assessment

Air pollution concentrations at the participants' birth addresses and current home addresses at the time the questionnaires were completed for questionnaire-based health outcomes and at the time of the medical examination were estimated by land-use regression.[8–10] In brief, air pollution monitoring campaigns were performed between October 2008 and February 2010 in the study area. Three 2-week measurements of nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were performed at 80 sites within 1 year. In addition, simultaneous measurements of $PM_{2.5}$, PM_{10}, PM_{coarse} (2.5–10 µm), and soot (determined as the reflectance of $PM_{2.5}$ filters) were performed at half of the sites.[13,14] All $PM_{2.5}$ and PM_{10} filters were analyzed for elemental composition using x-ray fluorescence.[10]

For each site, results from three measurements were averaged to estimate the annual average.[14] Predictor variables on nearby traffic intensity, population/household density and land use were derived from Geographic Information Systems (GIS) to explain spatial variation of PM, NO_2 and concentrations of copper, iron, potassium, nickel, sulfur, silicon, vanadium, and zinc. Elements were selected to represent major sources of air pollution. A brief description of the models and their performance is provided in eTable 1 (http://

links.lww.com/EDE/A883); detailed descriptions have been published elsewhere.[8–10] The models explained substantial fractions of the variability in annual average concentrations for NO_2, $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance, copper, iron, nickel, vanadium, and zinc (leave-one-out cross-validation R^2, $R2_{LOOCV}$ = 0.58–0.89, eTable 1; http://links.lww.com/EDE/A883), but only limited fractions for PM_{coarse}, potassium, sulfur, 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 and low spatial variation (sulfur).[10]

Covariates

Information on covariates such as sex, maternal education (low: primary school, lower vocational, or lower secondary education; medium: intermediate vocational education or intermediate/higher secondary education; high: higher vocational education and university), parental allergies, older siblings (yes/no), breastfeeding for at least 3 months (yes/no), maternal smoking during pregnancy (yes/no), smoking at the child's home (yes/no), use of gas for cooking (yes/no), mold/dampness (yes/no), furry pets in the child's home (yes/no), and day-care center attendance (yes/no) was available from questionnaires. Information on the percentage of low-income households in the neighborhood was available from Statistics Netherlands. Average ambient levels of PM_{10} and NO_2 for the 7 days preceding the lung function tests were retrieved from the National Air Quality Monitoring Network (see the Supplemental Digital Content, http://links.lww.com/EDE/A883).

Statistical Analysis

Associations between air pollution and asthma incidence until age 11 years were analyzed by means of discrete-time hazard models,[15] associations with repeated yearly questionnaire reports of asthma symptoms, hay fever, and rhinitis until age 11 years by generalized estimation equations with a logit-link using a six-dependent correlation matrix.[16] Analyses were performed with exposures at the birth address (constant) and exposures at the address at the time of the follow-up (time-varying), representing exposure during the past 12 months. Associations of air pollution levels at the birth and current address with allergic sensitization were analyzed by means of log-binomial regression because of the high prevalence. All analyses were performed with and without adjustment for the potential confounding variables mentioned above except short-term air pollution exposures. Linear regression analyses with natural log (ln) transformed lung function parameters (FEV_1, FVC, FEF_{25-75}) as dependent variables were used to analyze associations between air pollution and continuous lung function parameters.[17] Associations were calculated for exposures at the birth address and exposures at the address at the time of spirometry, with adjustment for sex and natural log-transformed age, height, and weight only (crude model), and with adjustment for the potential confounding variables mentioned above and respiratory infections during the past 3 weeks (adjusted model). In addition, we performed linear regression analyses of the association between annual changes in lung function from age 8 to 12 years and average air pollution exposure during that period. Time-varying covariates were defined for the first year of life in analyses with birth address exposures and for the year of the follow-up otherwise to coincide with exposure.

Because the intervention with mite-impermeable mattress covers did not reduce the risk of asthma and allergic sensitization,[18] no adjustment was made for study arm (ie, intervention or natural history study). Confounding by birth weight, which may be on the causal pathway between air pollution and the health outcomes studied, was explored as part of a sensitivity analysis. Air pollution levels were entered as continuous variables without transformation in all models. Associations are presented for an interquartile range increase in exposure to facilitate comparison of effect estimates between exposures. For lung function, potential effect modification by moving (defined as any change of address since birth) was explored in stratified analyses to investigate the relevance of chronic exposures (non-movers) versus more recent exposures (movers). In addition, potential effect modification by sex was explored in stratified analyses. Analyses were performed with the Statistical Analysis System (SAS 9.4, Cary, NC) for Windows. Effects are presented as relative risks for allergic sensitization, as odds ratio for all other binary outcomes, as percent change in lung function parameter and as mean change in annual lung function growth with 95% confidence intervals for a given increase in exposure.

RESULTS

Population Characteristics

General characteristics and distributions of the health outcomes are presented in Table 1 and frequency distributions of questionnaire-based health outcomes are presented in Figure 1. Participants who were included in this analysis more often had highly educated parents and more often lived in non-smoking homes than non-participants (eTable 2; http://links.lww.com/EDE/A883). For all other characteristics, differences between participants and non-participants were small.

Air Pollution Exposure

Distributions of annual average concentrations of NO_2, $PM_{2.5}$ absorbance, $PM_{2.5}$, PM_{10}, and PM_{coarse} mass as well as elemental composition of $PM_{2.5}$ and PM_{10} at the participants' birth addresses are presented in Table 2. Spatial variability was larger for NO_2 and $PM_{2.5}$ absorbance (maximum–minimum concentration ratios of 4–7, data not shown) than for $PM_{2.5}$ and PM_{10}, and largest for copper and iron in $PM_{2.5}$ (maximum–minimum ratios of 8–10). Some elements were mainly contained in the coarse fraction (>2.5µm) of PM_{10} (copper, iron, and silicon), whereas others (sulfur, nickel, vanadium, and zinc) were mainly contained in $PM_{2.5}$. Correlations between air pollutants at the birth address are presented in eTable 3

TABLE 1. Distribution of Population Characteristics and Health Outcomes (Total N = 3,702)

Characteristic		
Female gender, No. (%)	1,793	(48)
Maternal education, No. (%)		
Low	848	(23)
Intermediate	1,555	(40)
High	1,299	(35)
Allergic mother, No. (%)	1,123	(30)
Allergic father, No. (%)	1,137	(31)
At least 12 weeks of breastfeeding, No. (%)	1,817	(49)
Mother smoking during pregnancy[a], No. (%)	629	(17)
Smoking at home[b,c], No. (%)		
First year of life	897	(24)
Age 11 years	294	(11)
Use of gas for cooking, No. (%)		
First year of life	3,038	(83)
Age 11 years	1,965	(76)
Visible signs of mold or dampness in child's home[c], No. (%)		
First year of life	1,019	(28)
Age 11 years	836	(33)
Furry pets in home, No. (%)		
First year of life	1,726	(47)
Age 11 years	1,541	(60)
Day-care center attendance 1st year of life, No. (%)	903	(24)
Moved between birth and 11-year questionnaire, No. (%)	1,575	(61)
Moved between birth and medical examination, No. (%)	892	(61)
Health outcomes, medical follow-up at age 12 years		
Allergic sensitization[d], No. (%)	503	(39)
Lung function		
FEV_1, L; mean (SD), N	2.71 (0.43)	1,249
FVC, L; mean (SD), N	3.22 (0.51)	1,249
FEF_{25-75}%, L/s; mean (SD), N[e]	2.93 (0.72)	607
Age, years; mean (SD), N	12.7 (0.5)	1,249
Height, cm; mean (SD), N	160.0 (7.7)	1,249
Weight, kg; mean (SD), N	48.3 (9.4)	1,249
Change in FEV_1 from 8 to 12 years [ml/yr]; mean (SD), N	193.9 (66.8)	511
Change in FVC from 8 to 12 years [ml/yr]; mean (SD), N	258.9 (81.9)	511
Respiratory infection[f], No. (%)	433	(34)

[a]At least during the first 4 weeks.
[b]At least once a week.
[c]During the past 12 months.
[d]House dust mite, cat, birch pollen, *Dactylis glomerata*; cut off 0.7 kU/L.
[e]Only children with three acceptable maneuvers with all FEV_1 and all FVC within 150 ml of maximum FEV_1 and FVC, respectively.
[f]During 3 weeks before lung function measurement.

(http://links.lww.com/EDE/A883). Correlation patterns were complex. Some elements (eg, potassium in $PM_{2.5}$) had a low correlation with most of the other air pollutants suggesting different sources. Distributions of concentrations, and correlations between air pollutants, for the 11-year addresses were similar to those for the birth addresses (data not shown). Correlations between levels of the same pollutant at the birth and 11-year address were moderate to high, ranging from 0.56 (potassium in PM_{10}) to 0.91 (sulfur in $PM_{2.5}$, eTable 4; http://links.lww.com/EDE/A883). Correlations of long-term exposures with short-term exposures were all low for short-term PM_{10} and varied between -0.09 and 0.60 for short-term NO_2 (eTable 5; http://links.lww.com/EDE/A883).

Air Pollution and Health

Differences between crude (eTable 6; http://links.lww.com/EDE/A883) and adjusted (Table 3) associations of annual average air pollution levels at the birth address with asthma, hay fever, and allergic sensitization were mostly small. NO_2, zinc in PM_{10}, sulfur in $PM_{2.5}$, and potassium in $PM_{2.5}$ and PM_{10} at the birth address were positively associated with asthma incidence during the first 11 years of life, after adjustment for potential confounders. NO_2, zinc, silicon, and potassium in PM_{10} and potassium in $PM_{2.5}$ at the birth address were positively associated with asthma symptoms. NO_2 at the birth address was positively associated with hay fever. NO_2, zinc and potassium in $PM_{2.5}$ and in PM_{10}, and sulfur in $PM_{2.5}$ were positively associated with rhinitis. PM_{10} and copper and iron in PM_{10} were positively associated with allergic sensitization. We found few associations of annual average air pollution levels at the current address with asthma, hay fever, and allergic sensitization; they were largely limited to copper and potassium in PM_{10} (eTable 7; http://links.lww.com/EDE/A883). Effect sizes were similar for NO_2, particle mass, and element concentrations. Effect sizes for exposures at the birth address (ranging from 1.07 for asthma symptoms and silicon in PM_{10} to 1.29 for rhinitis and sulfur in $PM_{2.5}$) generally were somewhat larger than effects for exposures at the current address (all estimated risks between 1.06 and 1.11), after adjustment for confounders.

Estimated effects of air pollution exposures on lung function were generally largest for FEF_{25-75} and lowest for FVC. After adjustment for potential confounders, FEV_1 was associated with NO_2, $PM_{2.5}$ absorbance, copper and iron in $PM_{2.5}$, and FEF_{75-50} was associated with PM_{coarse} and copper in PM_{10} at the current address (Table 4, crude associations are presented in eTable 10; http://links.lww.com/EDE/A883). Few associations were found between lung function and exposure at the birth address (eTable 11; http://links.lww.com/EDE/A883). Estimated reductions in lung function were around 1%–2% for all pollutants. No association was found between lung function growth from 8 to 12 years of age and air pollution exposure during the follow-up (eTable 10; http://links.lww.com/EDE/A883).

Sensitivity Analyses

Associations with symptoms and with lung function remained unchanged after additional adjustment for birth weight (data not shown). Associations with lung function

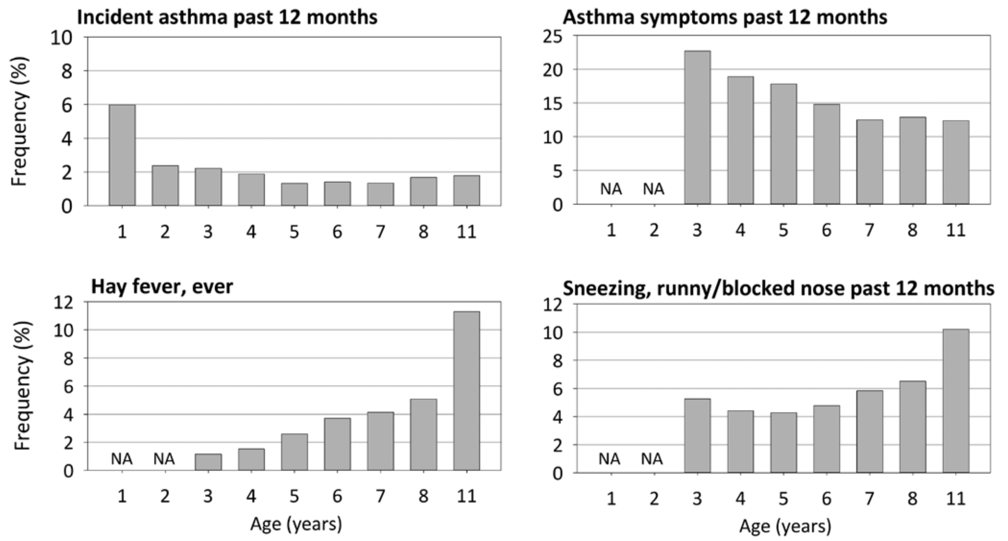

FIGURE. Percentage of children with incident asthma, hay fever, and related symptoms at ages 1 to 11 years. NA indicates not available.

remained largely unchanged when we restricted our analysis to measurements that fulfilled the ATS/ERS criteria or excluded children (n = 73) who took asthma medication during the 48 hours before the lung function measurement (data not shown).

Because of the high correlations between exposure levels for some elements (in particular copper, iron, sulfur, and silicon) and PM mass, the associations found for these elements may actually be partly attributable to PM mass. We explored to what extent the observed associations with elemental composition of $PM_{2.5}$ and PM_{10} were independent of PM mass by additionally adjusting models with elemental composition for $PM_{2.5}$ and PM_{10} mass, respectively. Our findings indicate that observed associations with elemental composition are largely independent of PM mass (eFigures 1 and 2; http://links.lww.com/EDE/A883).

For FEF_{25-75}, and to a lesser extent for FEV_1, but not for FVC, the negative associations with air pollution exposures tended to be stronger in children who lived at the same address since birth (eFigure 3; http://links.lww.com/EDE/A883). Confidence intervals for movers and non-movers, however, largely overlap. The adverse effects of air pollution exposures on asthma (symptoms), rhinitis, and FVC tended to be stronger in girls than in boys (eFigures 4 and 5; http://links.lww.com/EDE/A883). Confidence intervals of effect estimates for boys and girls largely overlapped.

DISCUSSION

We investigated the effects of NO_2 and different PM characteristics and PM constituents on asthma, hay fever, allergic sensitization, and lung function until the age of 11–12 years. We found adverse effects of air pollution on asthma, rhinitis, allergic sensitization, and lung function most consistently for exposure to NO_2, copper, iron, zinc, and potassium. We found fewer associations for these outcomes with $PM_{2.5}$ absorbance and particle mass.

The epidemiologic evidence on the effects of specific PM constituents on respiratory and allergic disease is currently limited and the comparison with the findings of this study is hampered by differences in health outcomes, constituents, study design, and age of the participants. In a birth-cohort study from New York City, a positive association was found between PM metal content, in particular nickel, and wheeze during the first 2 years of life.[19] Very recently, as part of the European collaborative ESCAPE study, negative associations were reported between nickel and sulfur in PM_{10} and lung function at age 6–8 years from five European birth cohort studies, including PIAMA.[20] In a time-series study in the Greater Baltimore area (US), higher levels of zinc in $PM_{2.5}$ were associated with asthma exacerbations in children ages 0–17 years.[21] A European multicenter panel study found acute adverse effects of iron and silicon in PM_{10} on peak expiratory flow (PEF) and prevalence of phlegm in children ages 6–12 years.[22]

Indirect evidence comes from a study in Eastern Germany. In a cross-sectional analysis, higher lifetime prevalence of asthma or wheezy bronchitis, bronchitis, wheeze, shortness of breath and cough without cold, and increased rates of allergic sensitization were found in children ages 5–14 years living in two counties impacted by industrial pollution (chemical and power plants in Bitterfeld, mining and smelting of non-ferrous metals including lead and copper in Hettstedt) than in children living in a neighboring county without industrial pollution.[23] In a subsequent longitudinal analysis, a decline in air pollution levels was associated with a decrease in bronchitis and sinusitis and improved lung function (FVC and to a lesser extent FEV_1) in these children.[24,25] Only particle mass, but not particle metal composition, was measured in the East German

TABLE 2. Distribution of Air Pollution Concentration Levels at the Birth Address (N = 3,682)

Pollutant	Mean	SD	Min	P10	P25	P50	P75	P90	Max
NO_2 (μg/m^3)	23.1	6.6	9.2	14.0	18.5	23.1	26.9	31.8	59.6
$PM_{2.5}$ abs (10^{-5} m^{-1})	1.2	0.2	0.8	0.9	1.1	1.2	1.3	1.5	3.0
PM_{10} (μg/m^3)	24.9	1.2	23.7	23.9	24.1	24.6	25.3	26.4	33.2
$PM_{2.5}$ (μg/m^3)	16.4	0.7	15.3	15.4	15.6	16.5	16.8	17.1	21.1
PM_{coarse} (μg/m^3)	8.4	0.8	7.6	7.7	7.8	8.1	8.6	9.6	14.0
Cu $PM_{2.5}$ (ng/m^3)	3.1	1.1	1.1	1.5	2.2	3.2	3.7	4.5	10.6
Cu PM_{10} (ng/m^3)	12.8	4.8	6.6	7.6	9.8	11.6	14.6	19.3	52.3
Fe $PM_{2.5}$ (ng/m^3)	79.6	27.2	31.1	41.6	59.7	80.8	94.4	115.8	255.2
Fe PM_{10} (ng/m^3)	385.5	127.3	183.0	250.3	300.1	362.9	442.2	546.0	1,207.2
K $PM_{2.5}$ (ng/m^3)	112.1	5.7	103.4	105.8	107.8	111.6	114.7	118.9	141.1
K PM_{10} (ng/m^3)	207.9	17.3	172.7	186.0	199.5	208.5	215.3	225.1	307.6
Ni $PM_{2.5}$ (ng/m^3)	1.9	0.8	0.9	0.9	1.3	1.8	2.5	3.1	4.0
Ni PM_{10} (ng/m^3)	2.2	1.0	1.0	1.0	1.5	2.1	2.8	3.8	4.9
S $PM_{2.5}$ (ng/m^3)	858.5	58.5	747.0	771.4	787.3	880.6	901.8	925.3	989.5
S PM_{10} (ng/m^3)	1,004.7	64.9	927.0	932.8	943.4	1,001.6	1,018.4	1,092.6	1,261.9
Si $PM_{2.5}$ (ng/m^3)	79.5	14.6	58.8	60.3	65.1	80.6	89.0	91.9	226.4
Si PM_{10} (ng/m^3)	376.6	83.4	284.6	296.9	313.8	356.7	405.1	486.5	828.2
V $PM_{2.5}$ (ng/m^3)	3.1	1.3	1.5	1.5	2.1	2.9	3.9	5.2	7.2
V PM_{10} (ng/m^3)	3.7	1.6	1.9	1.9	2.6	3.5	4.6	6.1	8.5
Zn $PM_{2.5}$ (ng/m^3)	21.0	6.2	10.7	13.1	16.1	21.4	24.7	29.0	57.5
Zn PM_{10} (ng/m^3)	30.9	10.9	12.6	18.3	22.7	30.0	36.0	44.7	84.8

Cu indicates copper; Fe, iron; K, potassium; Ni, nickel; S, sulfur; Si, silicon; V, vanadium; Zn, zinc.

study. However, later experimental work with dust collected in the same areas indicated that higher concentrations of transition metals, in particular copper and zinc, may have been partly responsible for the observed associations with PM.[26]

In vivo and in vitro studies with PM collected in the Utah Valley area (US) before and after closure of a steel mill provide further evidence for a contribution of metals (iron, copper, nickel, and zinc among others) to the increase in hospital admissions for respiratory illnesses including pneumonia, pleurisy, bronchitis, and asthma in children and adults associated with PM exposure.[27–29] Experimental studies in mice also suggest that transition metals in PM, including zinc, copper, and cadmium may be involved in allergic responses.[30] Transition metals, such as iron and copper, are believed to contribute to particle-induced formation of reactive oxygen species through the Fenton reaction, whereas zinc may trigger effects more directly by interacting with cellular proteins.[5]

We investigated the effects of eight different elements in PM on asthma, hay fever, allergic sensitization, and lung function of children. A review of European studies dealing with source apportionment of PM identified the following sources for these eight elements: traffic (copper, iron, and zinc), crustal material (silicon and iron), and industrial/fuel oil combustion (vanadium and nickel).[31] 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.[31] The observed associations of asthma symptoms, rhinitis, allergic sensitization, and lung function with copper, iron, and zinc therefore suggest that traffic affects health not only through exhaust emissions but also through non-exhaust emissions.

Potassium has been suggested as a tracer for biomass burning, like residential wood burning, but potassium is also present in soil.[32] The land-use regression models for potassium for the Netherlands, however, were dominated by traffic variables, reflecting resuspension of road dust.[10] Therefore, associations of health outcomes with potassium in this study most likely represent effects of traffic-related air pollution. Also, the associations of health outcomes with PM_{coarse}, potassium, sulfur, and silicon we observed should be interpreted with caution as the performance of the land-use regression models for these pollutants was relatively poor and consequently observed effect estimates are most likely underestimates of the true effects.

Non-exhaust emissions from traffic arising from abrasion of brake, tire, and road surface material, as well as from resuspension of PM by passing traffic, in contrast to exhaust emissions are currently not regulated by the European Union, despite their considerable contribution to traffic-related ambient PM_{10}.[33] As substantial efforts to reduce exhaust emissions have been successful, non-exhaust emissions from traffic are gaining importance.[34]

TABLE 3. Adjusted[a] Associations of Asthma, Hay Fever, and Allergic Sensitization with Exposure at the Birth Address

	Incident Asthma[b]	Asthma Symptoms[b]	Hay Fever[b]	Rhinitis[b]	Allergic Sensitization
Exposure (Increment)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	RR (95% CI)
NO_2 (8.4 μg/m³)	1.13 (1.01, 1.25)	1.09 (1.01, 1.18)	1.15 (1.00, 1.32)	1.15 (1.02, 1.30)	1.08 (0.99, 1.17)
$PM_{2.5}$ abs. ($0.29\cdot10^{-5}$ m^{-1})	1.07 (0.97, 1.18)	1.05 (0.98, 1.13)	1.06 (0.94, 1.20)	1.07 (0.96, 1.18)	1.07 (0.99, 1.15)
$PM_{2.5}$ (1.2 μg/m³)	1.12 (0.97, 1.29)	1.06 (0.96, 1.18)	1.15 (0.96, 1.37)	1.12 (0.97, 1.30)	1.10 (0.98, 1.23)
PM_{10} (1.2 μg/m³)	1.06 (0.97, 1.15)	1.04 (0.98, 1.11)	1.02 (0.91, 1.14)	1.03 (0.93, 1.13)	1.06 (1.00, 1.13)
PM_{coarse} (0.8 μg/m³)	1.06 (0.98, 1.14)	1.04 (0.98, 1.10)	1.08 (0.98, 1.19)	1.05 (0.96, 1.14)	1.04 (0.99, 1.10)
Cu $PM_{2.5}$ (1.5 ng/m³)	1.06 (0.94, 1.19)	1.04 (0.95, 1.13)	1.06 (0.91, 1.23)	1.08 (0.95, 1.22)	1.07 (0.98, 1.16)
Cu PM_{10} (4.8 ng/m³)	1.03 (0.95, 1.12)	1.03 (0.97, 1.09)	1.09 (0.99, 1.21)	1.03 (0.94, 1.13)	1.07 (1.01, 1.14)
Fe $PM_{2.5}$ (34.8 ng/m³)	1.05 (0.94, 1.17)	1.03 (0.95, 1.12)	1.06 (0.92, 1.23)	1.07 (0.95, 1.21)	1.06 (0.98, 1.16)
Fe PM_{10} (142.1 ng/m³)	1.05 (0.96, 1.15)	1.06 (0.99, 1.13)	1.07 (0.95, 1.20)	1.03 (0.93, 1.14)	1.10 (1.03, 1.18)
K $PM_{2.5}$ (6.9 ng/m³)	1.13 (1.03, 1.25)	1.08 (1.00, 1.17)	1.14 (0.99, 1.30)	1.15 (1.03, 1.29)	1.01 (0.93, 1.11)
K PM_{10} (15.8 ng/m³)	1.13 (1.05, 1.21)	1.10 (1.04, 1.16)	1.06 (0.97, 1.17)	1.09 (1.00, 1.18)	1.05 (1.00, 1.12)
Ni $PM_{2.5}$ (1.2 ng/m³)	1.08 (0.95, 1.23)	1.06 (0.96, 1.17)	1.04 (0.87, 1.25)	1.09 (0.94, 1.26)	1.02 (0.96, 1.09)
Ni PM_{10} (1.3 ng/m³)	1.09 (0.97, 1.22)	1.06 (0.97, 1.16)	1.06 (0.90, 1.24)	1.08 (0.95, 1.22)	1.04 (0.96, 1.12)
S $PM_{2.5}$ (114.5 ng/m³)	1.21 (1.01, 1.44)	1.13 (0.99, 1.29)	1.21 (0.94, 1.56)	1.29 (1.05, 1.59)	1.05 (0.91, 1.21)
S PM_{10} (74.9 ng/m³)	1.06 (0.96, 1.17)	1.03 (0.96, 1.11)	1.05 (0.92, 1.21)	1.09 (0.98, 1.21)	1.02 (0.94, 1.11)
Si $PM_{2.5}$ (23.9 ng/m³)	1.04 (0.91, 1.20)	1.00 (0.90, 1.11)	1.10 (0.91, 1.33)	1.07 (0.92, 1.24)	1.06 (0.95, 1.18)
Si PM_{10} (92.0 ng/m³)	1.08 (0.99, 1.18)	1.07 (1.00, 1.15)	1.07 (0.95, 1.21)	1.09 (0.98, 1.21)	1.06 (1.00, 1.13)
V $PM_{2.5}$ (1.7 ng/m³)	1.07 (0.96, 1.19)	1.05 (0.97, 1.14)	1.03 (0.88, 1.20)	1.07 (0.95, 1.21)	1.02 (0.96, 1.07)
V PM_{10} (2.0 ng/m³)	1.07 (0.96, 1.19)	1.05 (0.96, 1.14)	1.03 (0.88, 1.20)	1.07 (0.95, 1.21)	1.02 (0.96, 1.07)
Zn $PM_{2.5}$ (8.6 ng/m³)	1.11 (0.99, 1.25)	1.05 (0.96, 1.15)	1.13 (0.97, 1.32)	1.15 (1.01, 1.31)	0.97 (0.88, 1.07)
Zn PM_{10} (13.4 ng/m³)	1.13 (1.02, 1.25)	1.08 (1.00, 1.17)	1.14 (1.00, 1.30)	1.16 (1.04, 1.30)	1.01 (0.93, 1.10)

Associations are presented as odds ratios (OR) and relative risks (RR) with 95% confidence intervals.

[a]Adjusted for sex, maternal education, parental allergies, breastfeeding, maternal smoking during pregnancy, smoking in the child's home, use of gas for cooking, mold/dampness in the child's home, pets at home, daycare attendance during 1st year of life, and neighborhood percent low income households.

[b]Main effects from discrete-time hazard models for incident asthma and generalized estimation equations otherwise.

Cu indicates copper; Fe, iron; K, potassium; Ni, nickel; S, sulfur; Si, silicon; V, vanadium; Zn, zinc.

Iron and copper in proximity to busy roads have been associated with brake wear,[35] and zinc may derive from tire wear.[34] In our study, iron and copper, but not zinc, were mainly contained in the coarse fraction of PM_{10}. Exposure contrasts for three elements in PM_{10} were similar to those of other traffic-related pollutants such as NO_2 and $PM_{2.5}$ absorbance. Asthma symptoms and allergic sensitization were associated with higher iron and copper in PM_{10} and lower FEF_{25-75} was associated with higher copper in PM_{10}. Moreover, asthma incidence, symptoms of asthma, and rhinitis were positively associated with zinc in PM_{10}.

Effects of markers of non-exhaust emissions were of similar magnitude as effects of exhaust emission markers (NO_2) in this study. If confirmed by other studies, this means that the impact of non-exhaust emissions from traffic on lung function, asthma, and allergy of children may be as large as the impact of exhaust emissions from traffic.

We investigated associations with exposure in early life and more recent exposure. Asthma and hay fever and related symptoms were mainly associated with early life exposure, whereas allergic sensitization was associated with both early life and current exposure, and lung function with current exposure rather than early life exposure. The relevance of exposures in early life as well as later childhood for the development of asthma and allergies has been suggested by earlier analyses in the same cohort.[6] However, correlations between levels of the same pollutant at the birth and current address were moderate to high despite the fact that more than 60% of the population had moved at least once during the follow-up. The greater relevance of current exposures for lung function is consistent with earlier findings from this and other cohorts for FEV1, FVC, and PEF[7] and is supported by the findings from studies that suggested reversibility of the air pollution effects on FVC, FEF_{25-75}, and PEF.[36] The stronger association with mid-expiratory flows than with FEV_1 and the lack of an association with FVC in this study suggest that air pollution exposure exerts its effects especially on the small airways rather than the larger airways.

The stronger associations with lung function in non-movers compared with movers suggest that those with the most constant exposure are at greatest risk. However, these findings disagree with findings for lung function at age 6–8 years from this and other cohorts, where associations were slightly stronger in movers.[7]

The prospective design, the availability of the participants' residential histories and the detailed air pollution

TABLE 4. Adjusted[a] Associations Between Lung Function and Exposure at the Current Address

	FEV_1	FVC	FEF_{25-75}
Exposure (Increment)	**% Difference (95% CI)**	**% Difference (95% CI)**	**% Difference (95% CI)**
NO_2 (8.2 μg/m³)	-1.5 (-2.5, -0.5)	-1.1 (-2.0, -0.1)	-2.5 (-5.6, 0.7)
$PM_{2.5}$ abs. ($0.28 \cdot 10^{-5}$ m^{-1})	-0.9 (-1.8, -0.0)	-0.7 (-1.5, 0.1)	-2.0 (-4.6, 0.7)
$PM_{2.5}$ (1.2 μg/m³)	-1.0 (-2.2, 0.2)	-0.7 (-1.8, 0.4)	-2.4 (-6.1, 1.5)
PM_{10} (1.1 μg/m³)	-0.5 (-1.2, 0.2)	-0.2 (-0.9, 0.4)	-1.4 (-3.4, 0.6)
PM_{coarse} (0.7 μg/m³)	-0.5 (-1.1, 0.0)	-0.3 (-0.8, 0.3)	-1.9 (-3.6, -0.2)
Cu $PM_{2.5}$ (1.6 ng/m³)	-1.1 (-2.1, -0.1)	-0.9 (-1.9, 0.1)	-2.1 (-5.3, 1.1)
Cu PM_{10} (4.3 ng/m³)	-0.3 (-1.0, 0.3)	-0.1 (-0.8, 0.5)	-2.3 (-4.3, -0.3)
Fe $PM_{2.5}$ (36.7 ng/m³)	-1.0 (-2.0, -0.0)	-0.8 (-1.8, 0.1)	-1.8 (-4.8, 1.3)
Fe PM_{10} (135.1 ng/m³)	-0.3 (-1.0, 0.4)	-0.1 (-0.7, 0.6)	-1.9 (-4.0, 0.3)
K $PM_{2.5}$ (7.1 ng/m³)	0.0 (-0.8, 0.9)	0.2 (-0.6, 1.0)	-0.4 (-3.0, 2.2)
K PM_{10} (16.9 ng/m³)	-0.6 (-1.2, 0.1)	-0.4 (-1.1, 0.2)	-0.1 (-2.3, 2.1)
Ni $PM_{2.5}$ (1.2 ng/m³)	-0.5 (-1.2, 0.2)	-0.5 (-1.2, 0.1)	-1.6 (-3.7, 0.6)
Ni PM_{10} (1.3 ng/m³)	-0.6 (-1.5, 0.2)	-0.6 (-1.4, 0.2)	-2.2 (-4.8, 0.4)
S $PM_{2.5}$ (112.1 ng/m³)	-1.1 (-2.4, 0.2)	-1.0 (-2.3, 0.2)	-1.9 (-6.0, 2.3)
S PM_{10} (72.9 ng/m³)	-0.6 (-1.4, 0.2)	-0.5 (-1.3, 0.2)	-2.1 (-4.6, 0.6)
Si $PM_{2.5}$ (23.6 ng/m³)	-0.7 (-1.7, 0.4)	-0.7 (-1.7, 0.4)	-1.6 (-4.9, 1.7)
Si PM_{10} (80.7 ng/m³)	-0.4 (-1.1, 0.3)	-0.2 (-0.9, 0.5)	-1.2 (-3.4, 1.0)
V $PM_{2.5}$ (1.8 ng/m³)	-0.4 (-1.0, 0.2)	-0.4 (-1.0, 0.1)	-1.5 (-3.4, 0.4)
V PM_{10} (2.0 ng/m³)	-0.4 (-1.0, 0.2)	-0.4 (-1.0, 0.1)	-1.5 (-3.4, 0.4)
Zn $PM_{2.5}$ (8.9 ng/m³)	0.1 (-0.8, 0.9)	0.1 (-0.7, 1.0)	-0.1 (-2.8, 2.6)
Zn PM_{10} (13.6 ng/m³)	-0.1 (-0.9, 0.7)	0.0 (-0.7, 0.8)	-0.6 (-3.1, 2.0)

Associations are presented as percentage difference with 95% confidence intervals.

[a]Adjusted for sex, ln age, ln height, ln weight, respiratory infections during the past 3 weeks, maternal education, parental allergies, breastfeeding, maternal smoking during pregnancy, smoking in the child's home, use of gas for cooking, mold/dampness in the child's home, pets at home, daycare attendance during 1st year of life, neighborhood percent low income households, and short-term exposure, air pollution (associations with NO_2 were adjusted for NO_2, all other associations were adjusted for PM_{10}).

Cu indicates copper; Fe, iron; K, potassium; Ni, nickel; S, sulfur; Si, silicon; V, vanadium; Zn, zinc.

exposure assessment, in particular the availability of individual estimates of residential exposure to PM constituents, are important strengths of our study. Children of highly educated and to a lesser extent children of atopic mothers were overrepresented in the study population and probably as a consequence of this, participants were slightly more often breastfed and less often exposed to environmental tobacco smoke and pets. As the effect estimates remained largely unchanged after adjustment for potential confounders including parental education and parental atopy, this most likely did not result in any bias of the observed associations. Another limitation of this study is that exposure models were based on air pollution measurements performed in 2008–2010 and that this does not capture temporal variability. The measurements were conducted close to the 11- to 12-year follow-up conducted in 2008–2009 (questionnaire) and 2008–2011 (medical examination). Applying the models to the children's historical addresses, however, we implicitly assume that the spatial patterns did reflect the baseline period of the cohort, ie, 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.[37–40] Further support for the validity of the estimated air pollution levels for the historical addresses comes from the National Air Quality Monitoring Network: annual average NO_2 and PM_{10} levels were relatively stable between 2000 and 2007, which covers most of the study period.[41] For the other pollutants, no such information is available. The findings for NO_2 may be applicable to traffic-related constituents such as copper, iron, and zinc. It is, however, not clear to what extent this applies to the other constituents that derive from sources other than traffic. As metals largely relate to non-exhaust emissions of traffic, which are less regulated than exhaust emissions (affecting NO_2), changes in concentrations over time are likely less for metals than for NO_2. Concentrations of copper, iron, and zinc may even have increased slightly with increasing traffic intensity. Furthermore, we consider it highly unlikely that measurement error for the baseline addresses is differential and would lead to false-positive associations with asthma and allergy. Rather, we would expect the use of the exposure models for historical addresses to introduce random noise and bias exposure—response relations toward the null. Although we performed fairly large numbers of comparisons, we did not adjust for multiple testing as it 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.[42] Moreover, multiple testing in situations like the present with several levels of multiplicity, more than one (related) endpoint and several (related) exposures, is complex and no adequate adjustments exist.[43] Instead of adjusting for multiple comparisons, we interpreted results on the basis of consistency of effect estimates across elements and PM size fractions.

In conclusion, our study provides evidence for an adverse effect of PM constituents, in particular copper, iron, potassium, silicon, and zinc, on asthma, rhinitis, allergic sensitization, and lung function of schoolchildren. Associations with copper, iron, and zinc may indicate the health relevance of non-exhaust emissions of traffic. This finding is important because the importance of non-exhaust emissions from traffic is increasing because of the substantial efforts to reduce exhaust emissions.

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