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*Published in:*
Environment international

*DOI:*
10.1016/j.envint.2021.106792
10.1016/j.envint.2021.106792



*Publication date:*
2021

Environment International 157 (2021) 106792

Contents lists available at ScienceDirect

Environment International

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

# Ultrafine particles, particle components and lung function at age 16 years: The PIAMA birth cohort study

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ARTICLE INFO

Handling Editor: Zorana Jovanovic Andersen

*Keywords:*
Ultrafine particles
Particulate matter
Elemental composition
Lung function
Adolescence

ABSTRACT

*Background:* Particulate matter (PM) air pollution exposure has been linked to lung function in adolescents, but little is known about the relevance of specific PM components and ultrafine particles (UFP).
*Objectives:* To investigate the associations of long-term exposure to PM elemental composition and UFP with lung function at age 16 years.
*Methods:* For 706 participants of a prospective Dutch birth cohort, we assessed associations of forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC) at age 16 with average exposure to eight elemental components (copper, iron, potassium, nickel, sulfur, silicon, vanadium and zinc) in $PM_{2.5}$ and $PM_{10}$, as well as UFP during the preceding years (age 13–16 years) estimated by land-use regression models. After assessing associations for each pollutant individually using linear regression models with adjustment for potential confounders, independence of associations with different pollutants was assessed in two-pollutant models with PM mass and $NO_2$, for which associations with lung function have been reported previously.
*Results:* We observed that for most PM elemental components higher exposure was associated with lower $FEV_1$, especially $PM_{10}$ sulfur [e.g. adjusted difference −2.23% (95% confidence interval (CI) −3.70 to −0.74%) per interquartile range (IQR) increase in $PM_{10}$ sulfur]. The association with $PM_{10}$ sulfur remained after adjusting for $PM_{10}$ mass. Negative associations of exposure to UFP with both $FEV_1$ and FVC were observed [-1.06% (95% CI: −2.08 to −0.03%) and −0.65% (95% CI: −1.53 to 0.23%), respectively per IQR increase in UFP], but did not persist in two-pollutant models with $NO_2$ or $PM_{2.5}$.
*Conclusions:* Long-term exposure to sulfur in $PM_{10}$ may result in lower $FEV_1$ at age 16. There is no evidence for an independent effect of UFP exposure.

## 1. Introduction

Reduced lung function in childhood and adolescence is associated with long-term cardio-respiratory morbidity and mortality later in life (Lange et al., 2015; Sin et al., 2005). There is a growing number of studies showing that long-term air pollution exposure adversely affects lung function in adolescence, although evidence is still inconsistent (Guo et al., 2019; He et al., 2019; Milanzi et al., 2018; Schultz et al., 2017). While most previous studies focused on mass concentrations of particulate matter smaller than 2.5 μm ($PM_{2.5}$) or smaller than 10 μm ($PM_{10}$) as well as traffic-related pollutants such as nitrogen dioxide ($NO_2$) and soot, it remains unclear whether these pollutants are primarily contributing to the observed negative associations as air pollution is a heterogeneous mixture.

Previous epidemiological studies suggested that the detrimental effects of PM may be related to its elemental composition (Kelly and Fussell 2012). PM emitted from different sources is characterized by different elemental composition, e.g. road traffic non-tailpipe emissions including brake lines are characterized by copper (Cu), iron (Fe), and zinc (Zn); tire wear by Zn; industrial emissions by Fe and Zn; crustal

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https://doi.org/10.1016/j.envint.2021.106792
Received 16 February 2021; Received in revised form 12 July 2021; Accepted 21 July 2021
Available online 10 August 2021

materials by silicon (Si) and potassium (K)); fossil fuel combustion by nickel (Ni), vanadium (V), and sulfur (S); and biomass burning by K (Viana et al., 2008). Thus, knowing more specifically which elements are responsible for the toxicity of PM could help preventing adverse health effects more effectively (Schwarze et al., 2006). Evidence is currently limited regarding associations between specific elements and lung function. Lung function was negatively associated with long term exposure to S and Ni in $PM_{10}$ in a pooled analysis of 5 European birth cohorts (BAMSE (Sweden), GINIplus and LISAplus (Germany), MAAS (United Kingdom) and PIAMA (the Netherlands)) at age 8 (Eeftens et al., 2014) and with Cu, Fe in $PM_{2.5}$ at age 12 years in the PIAMA cohort (Gehring et al., 2015b), but whether these associations persist into adolescence is not clear.

Ultrafine particles (UFP; particles with diameters less than 100 nm) can penetrate more deeply into airways and alveoli than larger particles and therefore may be more hazardous (HEI, 2013). Due to their small size, UFP contribute little to $PM_{2.5}$ mass concentration and are thus not well-reflected by $PM_{2.5}$ measurements. Previous epidemiological studies of the associations between UFP and respiratory health mostly focused on short-term exposure (i.e. hours to weeks) (Ohlwein et al., 2019). Studies on the associations between long-term exposure to UFP and lung function are lacking due to difficulties in exposure assessment.

We previously assessed associations of exposure to $NO_2$, $PM_{2.5}$, $PM_{10}$, $PM_{coarse}$, and "soot" during three periods (pre-school, primary school and secondary school) that match appropriate settings for prevention in the Netherlands with lung function at age 16 in the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort (Milanzi et al., 2018) and found that higher exposure to all pollutants during all periods was associated with a significantly lower forced expiratory volume in 1 s ($FEV_1$) at age 16. In the current study, we extended the previous study to a broader range of air pollutants (UFP, PM elemental composition) and assessed to what extent exposure to UFP and PM elemental compositions contributed to the observed associations of PM and $NO_2$ with lung function.

## 2. Material and methods

### 2.1. Study design and population

This study used data from the Dutch population-based PIAMA birth cohort study. The design of the PIAMA study has been described in detail elsewhere (Wijga et al., 2014). In brief, pregnant women were recruited in 1996–1997 from communities in the North, West, and Central regions of the Netherlands. Information on demographic factors, lifestyle, household and health characteristics has been collected during pregnancy, at the participants' ages of 3 months and 1 year and then annually till age 8 via questionnaires completed by the parents. At ages 11, 14 and 16, both the parents and the participants themselves completed questionnaires. The present study included participants with air pollution exposure data and lung function measurements at age 16 ($n = 706$). Ethical approval was obtained from the ethical review boards of participating institutes and written informed consent was obtained from participants as well as their parents/legal guardians.

### 2.2. Lung function assessment

Lung function including $FEV_1$ and forced vital capacity (FVC) was measured by spirometry at age 16 as part of medical examinations in two centers with Jaeger Masterscreen pneumotachographs (CareFusion, Yoba Linda, CA, USA) and EasyOne spirometers (ndd Medical Technologies Inc, Zurich, Switzerland), respectively. We corrected for systematic differences between spirometers using equations as described elsewhere and in the supplement (Milanzi et al., 2019). All measurements were conducted by experienced technicians following the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Miller et al., 2005). All flow volume curves have been reviewed by highly experienced lung function analysts in the two research centers. In the current analysis, we included lung function measurements that fulfilled the ATS/ERS criteria (Miller et al., 2005) and measurements that did not meet these criteria (difference between the largest and next largest values for $FEV_1$ and FVC $\leqslant$150 mL), but were obtained from technically acceptable flow volume curves with the two largest $FEV_1$ and FVC values within 200 mL as in our previous analysis (Milanzi et al., 2018).

### 2.3. Air pollution exposure assessment

Annual average concentrations of nitrogen dioxide ($NO_2$), particulate matter <2.5 μm ($PM_{2.5}$) and <10 μm ($PM_{10}$), and $PM_{2.5}$ and $PM_{10}$ elemental composition at the participants' residential addresses were estimated by land-use regression (LUR) models described elsewhere (Beelen et al., 2013; de Hoogh et al., 2013; Eeftens et al., 2012). In brief, three two-week air pollution monitoring campaigns were performed at 80 sites for $NO_2$ and 40 sites for $PM_{2.5}$ and $PM_{10}$ in the warm, cold, and intermediate seasons in 2008–2010. All $PM_{2.5}$ and $PM_{10}$ filters were analyzed for elemental composition using x-ray fluorescence (de Hoogh et al., 2013). For each site, results from the three measurements were averaged to estimate the annual average. Eight elements (Cu, Fe, K, Ni, S, Si, V and Zn) were selected *a priori* in the European Study of Cohorts for Air Pollution Effects (ESCAPE) to reflect different anthropogenic sources: road traffic non-tailpipe emissions including brake lines (Cu, Fe, Zn) and tire wear (Zn); industrial emissions (Fe, Zn); crustal materials (Si, K); fossil fuel combustion (Ni, V, S); and biomass burning (K) (de Hoogh et al., 2013).

Annual average concentrations of UFP were estimated based on a recently developed Dutch-national spatial model which combines regional background measurements with measurements from a mobile platform (Kerckhoffs et al., 2021). In brief, regional background UFP data were derived from 20 regional background sites across the Netherlands that have been measured each three times for a period of 14 days. Annual average regional background concentrations were estimated using a kriging method (van de Beek et al., 2021). For mobile monitoring, an electric car (REVA, Mahindra Reva Electric Vehicles Pvt. Ltd., Bangalore, India) was used to measure UFP concentrations at 14,392 road segments over a 14-month period (June 2016-November 2017). Measurements of UFP started after 9:15 AM and stopped before 4:00 PM to avoid rush hour traffic and to increase comparability between road segments (Kerckhoffs et al., 2016; van Nunen et al., 2017). All measurements were performed using a condensation particle counter (TSI, CPC 3007) installed in the back of an electric car. Routes were sampled between 1 and 3 times (average 2.2 times) and concentrations of UFP from repeated sampling were averaged per road segment. Road segments were on average 110 m long (SD: 68 m) and accumulated on average 43 s of UFP data (IQR: 9–44 s) over the study period.

Land use predictors such as traffic intensity and population/household density were derived from Geographic Information Systems (GIS) to explain the spatial variation in $NO_2$, PM mass, PM elemental composition, and UFP concentrations and selected using a supervised stepwise linear regression. For UFP, we used estimates from the deconvolution method that was applied to segregate the average UFP concentrations into a local and a background signal and is thought to be more physically realistic.

The performance of the LUR models for PM mass, $NO_2$ and elemental compositions was assessed using leave-one-out cross-validation $R^2$ and found to be good for $NO_2$, $PM_{10}$, $PM_{2.5}$, Cu, Fe, Ni, V and Zn ($R^2$ = 0.58–0.89), but poorer for K, S and Si ($R^2$ = 0.25–0.45). The performance of the UFP model was evaluated by an external validation with 3x24 h measurements at 42 sites in two major cities (Amsterdam and Utrecht), which resulted in an $R^2$ value of 0.60 (Table S1).

For the current analysis, we defined exposure as the average exposure at the participant's home address during the secondary school period until the measurement of lung function at age 16 as in previous

analyses (Milanzi et al., 2018), that is exposure at age 13–16 years spanning the period of 2009–2013 and that coincides best with the air pollution measurement campaigns for the LUR models. Earlier time windows were not included in this analysis as evidence for the long-term validity of the PM elemental composition models is currently lacking. Average exposures for the time window of interest were calculated from the annual average estimates provided by the (purely spatial) LUR models without adjustment for temporal trends, taking into account changes in residential address and using occupancy as weights.

### 2.4. Covariates

We adjusted for the same potential confounders as in our previous analyses of the association between air pollution and lung function within the same population (Milanzi et al., 2018), namely age, sex, weight, height, parental education (maximum educational level attained by the mother or father, low/medium/high), maternal and paternal atopy, breastfeeding, Dutch nationality (both parents born in the Netherlands), maternal smoking during pregnancy, indoor tobacco smoke exposure, furry pets in the home, molds in the home and gas cooking, obtained from parent-completed questionnaires, and active smoking (defined as smoking at least once per week, yes/no), and respiratory infections in the last 3 weeks before lung function measurement obtained from participant-completed questionnaires. We did not include variables that might be on the causal pathway between exposure and outcome to avoid over-adjustment. Time-varying covariates such as indoor tobacco smoke, furry pets, molds, and gas cooking were defined based on the questionnaires that coincided best with the time window of air pollution exposure. In addition, we adjusted for average $NO_2$ and $PM_{10}$ concentrations during the seven days preceding lung function measurements to account for potential short-term effects using daily average concentrations measured at the background monitoring site of the Dutch National Air Quality Monitoring Network that was closest to a participant's home.

### 2.5. Statistical analyses

Categorical variables were presented as numbers (proportions) and continuous variables were presented as mean ± standard deviation. Pearson correlation coefficients were calculated between different air pollutants. Associations between air pollutants and lung function were assessed using linear regression models assuming a linear exposure-response relationship. Lung function was natural log-transformed in all models due to the strongly nonlinear relationships between lung function, age, height and weight (Dockery et al., 1983; Raizenne et al., 1996). Associations with lung function were assessed with separate single pollutant models adjusting initially for sex, natural log-transformed age height and weight at the time of lung function measurements, and then in addition for all other potential confounders. Association estimates are presented as the percent change in absolute values of each lung function parameter for an interquartile range (IQR) increase in air pollution exposure and calculated from estimated regression coefficients β as $(e^{\beta \times IQR} - 1) \times 100$. Analyses were performed based on the participants with complete information on potential confounders (N = 706 for initially adjusted and N = 667 for fully adjusted analyses).

Two-pollutant models with elemental composition and UFP and additional adjustment for PM mass and $NO_2$, respectively, were used to disentangle the independent effects of specific air pollutants. We performed stratified analyses by parental education level (High/Low or medium) to test the role of parental education as a modifier of the relationship between air pollution and lung function (Munoz-Pizza et al., 2020). Significance of interactions was tested by adding exposure-modifier interaction terms to the model. Stratified analyses by moving (defined as any change in address since birth) were also conducted. Sensitivity analyses were conducted excluding active smokers (n = 50) and excluding asthmatics (n = 58) at age 16. All analyses were performed using R software 3.6.1 with significance levels of 0.05.

## 3. Results

### 3.1. Population characteristics

General characteristics and distributions of the lung function indicators for the study population are presented in Table 1. Among the 706 participants included in the analyses, mean age was 16.4 ± 0.2 years, and 334 (47.3%) were male. The mean body mass index (BMI) was 20.8 ± 2.7 kg/m$^2$. Compared to the PIAMA cohort baseline population, the current study population had a higher percentage of participants with highly educated parents, a higher percentage of participants who received breastfeeding for more than 12 weeks, and lower percentages of participants with exposure to maternal smoking during pregnancy and secondhand smoking during the postnatal life (Table S2).

### 3.2. Air pollution exposure

The distributions of the estimated average air pollution concentrations are presented in Table 2. Correlations between air pollutants are presented in Fig. S1. UFP had moderate correlations with $NO_2$, $PM_{10}$, and Fe (r = 0.68–0.79) and low correlations with Ni, S and V (r = 0.35–0.45). Elements representing similar sources generally had high correlations (e.g. r = 0.83–0.96 for Cu and Fe representing non-tailpipe traffic emission, r = 0.98–0.99 for Ni and V representing fossil fuel combustion).

### 3.3. Air pollution and lung function

Associations of long-term exposure to air pollutants with $FEV_1$ at age 16 are shown in Table 3. Minimally adjusted and fully adjusted association estimates were consistent with regard to the direction of the association, with associations generally tending to be somewhat stronger for fully adjusted models. However, differences between minimally and fully adjusted models were small suggesting that the included covariates

**Table 1**
Basic characteristics for the study population (N = 706).

| Characteristic[#] | |
|---|---|
| Boys, n/N (%) | 334/706 (47.3) |
| Age [years], mean ± std/N | 16.4 ± 0.2/706 |
| Weight [kg], mean ± std/N | 64.3 ± 10.2/706 |
| Height [cm], mean ± std/N | 176.0 ± 8.7/706 |
| BMI [kg/m$^2$], mean ± std/N | 20.8 ± 2.7/706 |
| Parental atopy | |
| Atopic mother, n/N (%) | 227/706 (32.2) |
| Atopic father, n/N (%) | 237/705 (33.6) |
| Presence of pets at age 16, n/N (%) | 440/678 (64.9) |
| Presence of molds at age 16, n/N (%) | 104/694 (15.0) |
| Breastfeeding more than 12 weeks, n/N (%) | 424/706 (60.1) |
| Gas cooking at age 16, n/N (%) | 554/678 (81.7) |
| Maternal smoking during pregnancy, n/N (%) | 91/700 (12.9) |
| Indoor tobacco smoke exposure at age 16, n/N (%) | 44/706 (6.2) |
| Parental education, n/N (%) | |
| Low | 52/706 (7.4) |
| Intermediate | 209/706 (29.6) |
| High | 445/706 (63.0) |
| Dutch nationality, n/N (%) | 672/692 (95.2) |
| Asthma at age 16, n/N (%) | 58/677 (8.6) |
| Active smoker at age 16, n/N (%) | 50/706 (7.1) |
| Respiratory infections at age 16[¶], n/N (%) | 296/706 (41.9) |
| Lung function | |
| $FEV_1$ [L], mean ± std/N | 3.95 ± 0.72/706 |
| FVC [L], mean ± std/N | 4.71 ± 0.86/706 |

[#] The value of N is smaller than indicated for some variables due to missing data.

[¶] Respiratory infections in the 3 weeks before lung function measurement.

**Table 2**
Distribution of average air pollution exposure levels for the secondary school period (age 13–16 years).

| Air pollutant | Min | Median | Mean ± Std | 75th percentile | Maximum | IQR |
|---|---|---|---|---|---|---|
| UFP, particles·cm$^{-3}$ | 8,614 | 10,146 | 10,359 ± 1,238.1 | 11,014 | 16,294 | 1,602 |
| $PM_{10}$ Cu, ng·m$^{-3}$ | 6.6 | 10.6 | 11.0 ± 2.9 | 12.4 | 31.2 | 3.2 |
| $PM_{10}$ Fe, ng·m$^{-3}$ | 183.0 | 320.5 | 333.2 ± 85.5 | 383.6 | 701.8 | 109.0 |
| $PM_{10}$ K, ng·m$^{-3}$ | 172.7 | 204.7 | 200.8 ± 16.2 | 210.8 | 260.7 | 19.7 |
| $PM_{10}$ Ni, ng·m$^{-3}$ | 1.0 | 1.8 | 1.7 ± 0.5 | 2.2 | 3.3 | 1.0 |
| $PM_{10}$ S, ng·m$^{-3}$ | 927.0 | 998.2 | 976.7 ± 35.7 | 1,002.7 | 1,087.5 | 65.1 |
| $PM_{10}$ Si, ng·m$^{-3}$ | 284.6 | 332.6 | 340.2 ± 48.8 | 365.6 | 605.8 | 64.6 |
| $PM_{10}$ V, ng·m$^{-3}$ | 1.9 | 3.1 | 2.9 ± 0.7 | 3.5 | 5.3 | 1.5 |
| $PM_{10}$ Zn, ng·m$^{-3}$ | 12.6 | 301.0 | 30.9 ± 11.1 | 35.8 | 77.0 | 12.8 |
| $PM_{2.5}$ Cu, ng·m$^{-3}$ | 1.1 | 2.6 | 2.6 ± 0.8 | 3.2 | 5.3 | 1.4 |
| $PM_{2.5}$ Fe, ng·m$^{-3}$ | 31.2 | 65.7 | 66.8 ± 20.1 | 82.2 | 160.2 | 31.9 |
| $PM_{2.5}$ K, ng·m$^{-3}$ | 103.4 | 112.1 | 112.1 ± 5.6 | 114.8 | 135.6 | 6.7 |
| $PM_{2.5}$ Ni, ng·m$^{-3}$ | 0.9 | 1.6 | 1.5 ± 0.4 | 1.8 | 2.8 | 0.9 |
| $PM_{2.5}$ S, ng·m$^{-3}$ | 747.0 | 853.6 | 834.1 ± 55.5 | 883.9 | 979.8 | 107.9 |
| $PM_{2.5}$Si, ng·m$^{-3}$ | 58.8 | 79.0 | 74.1 ± 11.8 | 81.0 | 183.9 | 18.6 |
| $PM_{2.5}$ V, ng·m$^{-3}$ | 1.5 | 2.6 | 2.4 ± 0.6 | 2.9 | 4.4 | 1.3 |
| $PM_{2.5}$ Zn, ng·m$^{-3}$ | 10.7 | 22.8 | 22.1 ± 7.0 | 25.6 | 57.6 | 8.8 |
| $NO_2$, μg·m$^{-3}$ | 10.3 | 20.9 | 20.6 ± 5.3 | 24.4 | 44.4 | 8.0 |
| $PM_{10}$, μg·m$^{-3}$ | 23.7 | 24.4 | 24.5 ± 0.7 | 24.8 | 27.7 | 0.8 |
| $PM_{2.5}$, μg·m$^{-3}$ | 14.9 | 16.5 | 16.2 ± 0.7 | 16.7 | 18.7 | 1.2 |

Std: Standard deviation; IQR: interquartile range; UFP: Ultrafine particles; $NO_2$: nitrogen dioxide.

**Table 3**
Minimally and fully adjusted mean differences (%) in $FEV_1$ and FVC at age 16 associated with average air pollutant concentrations during the secondary school period (age 13–16 years).

| Air pollutant | | $FEV_1$ | | FVC | |
|---|---|---|---|---|---|
| | Increment[a] | Minimally adjusted(N = 706)[b] | Fully adjusted(N = 667)[c] | Minimally adjusted(N = 706)[b] | Fully adjusted(N = 667)[c] |
| UFP | 1,602 | −0.97 (−1.98, 0.04) | −1.06 (−2.08, −0.03) | −0.48 (−1.34, 0.40) | −0.65 (−1.53, 0.23) |
| $PM_{10}$ Cu | 3.2 | −0.40 (−1.27, 0.48) | −0.38 (−1.26, 0.50) | 0.04 (−0.71, 0.80) | −0.02 (−0.77, 0.75) |
| $PM_{2.5}$ Cu | 1.4 | −1.84 (−3.12, −0.55) | −2.10 (−3.40, −0.79) | −0.41 (−1.53, 0.72) | −0.65 (−1.79, 0.50) |
| $PM_{10}$ Fe | 109.0 | −0.76 (−1.76, 0.25) | −0.78 (−1.80, 0.24) | −0.11 (−0.98, 0.77) | −0.26 (−1.14, 0.62) |
| $PM_{2.5}$ Fe | 31.9 | −1.67 (−2.90, −0.42) | −1.98 (−3.24, −0.70) | −0.30 (−1.38, 0.79) | −0.60 (−1.71, 0.52) |
| $PM_{10}$ K | 19.7 | −0.66 (−1.61, 0.30) | −0.70 (−1.66, 0.26) | −0.26 (−1.08, 0.57) | −0.39 (−1.21, 0.45) |
| $PM_{2.5}$ K | 6.7 | −0.92 (−1.86, 0.03) | −0.95 (−1.91, 0.01) | 0.26 (−0.56, 1.09) | 0.18 (−0.65, 1.02) |
| $PM_{10}$ S | 65.1 | −1.99(−3.44, −0.53) | −2.23(−3.70, −0.74) | 0.18 (−1.09, 1.47) | 0.00 (−1.30, 1.32) |
| $PM_{2.5}$ S | 107.9 | −2.28 (−3.81, −0.73) | −2.58 (−4.13, −1.00) | −0.18 (−1.53, 1.19) | −0.44 (−1.82, 0.95) |
| $PM_{10}$ Si | 64.6 | −0.81 (−1.85, 0.24) | −0.91 (−1.97, 0.15) | −0.24 (−1.14, 0.66) | −0.47 (−1.38, 0.45) |
| $PM_{2.5}$Si | 18.6 | −1.66 (−2.89, −0.42) | −1.84 (−3.09, −0.58) | 0.03 (−1.05, 1.12) | −0.12 (−1.22, 0.99) |
| $PM_{10}$ Ni | 1.0 | −1.68 (−3.17, −0.17) | −1.91 (−3.41, −0.38) | −0.20 (−1.5, 1.13) | −0.46 (−1.78, 0.88) |
| $PM_{2.5}$ Ni | 0.9 | −1.68 (−3.28, −0.06) | −1.93 (−3.54, −0.29) | −0.15 (−1.55, 1.27) | −0.38 (−1.79, 1.06) |
| $PM_{10}$ V | 1.5 | −1.64 (−3.23, −0.03) | −1.88 (−3.49, −0.25) | −0.12 (−1.52, 1.29) | −0.35 (−1.75, 1.08) |
| $PM_{2.5}$ V | 1.3 | −1.64 (−3.23, −0.03) | −1.88 (−3.49, −0.25) | −0.12 (−1.52, 1.29) | −0.35 (−1.75, 1.08) |
| $PM_{10}$ Zn | 12.8 | −0.97 (−1.88, −0.05) | −1.00 (−1.92, −0.06) | 0.18 (−0.62, 0.98) | 0.09 (−0.71, 0.91) |
| $PM_{2.5}$ Zn | 8.8 | −0.93 (−1.92, 0.06) | −0.98 (−1.98, 0.03) | 0.30 (−0.56, 1.16) | 0.23 (−0.64, 1.11) |

[b]Adjusted for sex, age, log-transformed of weight and height.
[a] Units of increment concentrations were particles·cm$^{-3}$ for UFP and ng·m$^{-3}$ for PM elemental compositions.
[c] Adjusted for sex, age and log-transformations of weight and height, parental education, maternal atopy, paternal atopy, breastfeeding, respiratory infections in the previous 3 weeks, Dutch nationality, maternal smoking in pregnancy, indoor tobacco smoke exposure in the home at age 16, furry pets at age 16, mold in the home at age 16, gas cooking at age 16, and average $PM_{10}$ and $NO_2$ concentrations for the 7 days preceding the lung function measurement.

were no strong confounders of the associations of interest. We observed that higher UFP exposure tended to be associated with lower $FEV_1$, (e.g., mean percentage difference for an IQR increase in UFP exposure −1.06% (95% CI: −2.08, −0.03)). Generally, levels of all elements in PM were negatively associated with $FEV_1$. Association estimates were larger for Cu, Fe, K and Si in $PM_{2.5}$ compared to $PM_{10}$. Trends towards negative associations of UFP exposure with FVC were also observed (e.g. mean percentage difference −0.65% (95% CI: −1.53, 0.23) per IQR increase in UFP; Table 3). The associations between PM elemental composition and FVC were all close to zero and not statistically significant.

In two-pollutant models, the association of UFP with $FEV_1$ attenuated towards the null when additionally adjusted for $NO_2$ or $PM_{2.5}$ while the negative associations of $NO_2$ and $PM_{2.5}$ with $FEV_1$ persisted (Fig. 1, see Fig. S2 for the two-pollutant models for FVC). The negative associations of most elements (e.g. $PM_{2.5}$ K, $PM_{2.5}$ Zn, $PM_{10}$ Cu, $PM_{10}$ Si) with $FEV_1$ disappeared after adjustment for PM mass or $NO_2$ (Figs. S3 and S4) while the associations with PM mass or $NO_2$ remained. Only the association between $PM_{10}$ S and $FEV_1$ remained (mean percentage difference was −1.90% (95% CI: −3.45, −0.32) and −1.95% (95% CI: −4.29, 0.44) after additional adjustment for PM10 and $NO_2$, respectively.

The associations of air pollution with $FEV_1$ and FVC remained largely unchanged in sensitivity analyses excluding active smokers (n = 50) or asthmatics (n = 58) at age 16 (Figs. S5 and S6). The association estimates for participants with high and low/medium parental education were largely similar and interactions were not statistically significant (Fig. S7). Associations between air pollution exposure and lung function tended to be stronger for participants who did not change their address since birth compared to those who changed address at least once, but the differences in associations between movers and non-movers were not statistically significant (Fig. S8).

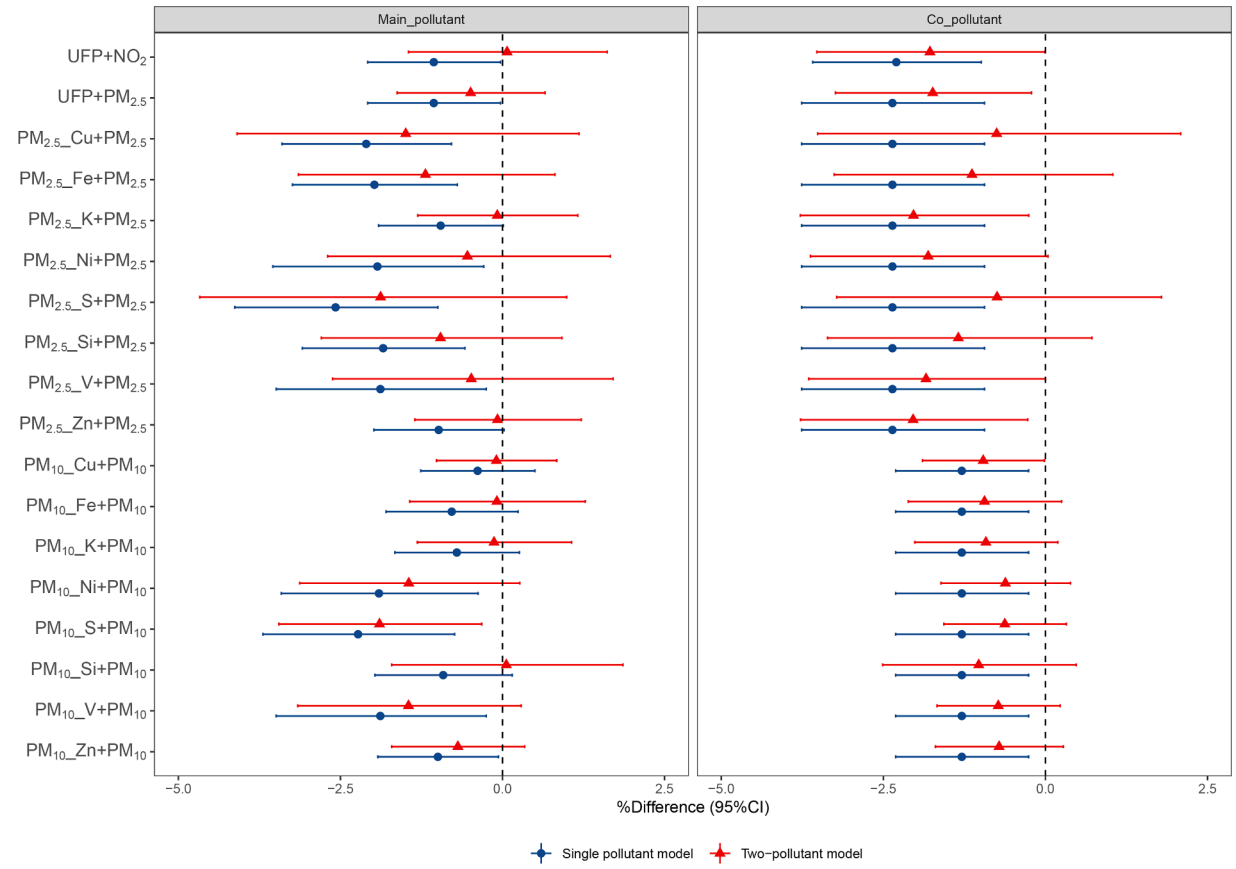


**Fig. 1.** Adjusted associations of average concentrations of ultrafine particles and elemental composition during the secondary school period (age 13–16 years) with $FEV_1$ at age 16 years from two-pollutant models.* *Main pollutant stands for UFP or PM elemental composition while co-pollutant stands for $NO_2$ or PM mass in the two-pollutant models. Concentrations during the secondary school time window were used for all air pollutants. The estimates were adjusted for sex, age and log-transformations of weight and height, parental education, maternal atopy, paternal atopy, breastfeeding, respiratory infections in the previous 3 weeks, Dutch nationality, maternal smoking in pregnancy, indoor tobacco smoke exposure in the home at age 16, furry pets at age 16, mold in the home at age 16, gas cooking at age 16, and average $PM_{10}$ and $NO_2$ concentrations for the 7 days preceding the lung function measurement.

## 4. Discussion

In the PIAMA cohort, we observed that higher exposure to various PM elemental constituents at age 13–16 years was associated with slightly lower $FEV_1$ but not FVC at age 16. The negative association with $PM_{10}$ S attenuated, but remained significant after adjustment for PM mass and $NO_2$, suggesting a potentially independent effect. The associations of UFP exposure with $FEV_1$ and FVC were generally null when adjusting for $PM_{2.5}$ or $NO_2$.

Epidemiological evidence on the associations between specific PM elemental constituents and respiratory morbidity is currently largely limited to acute effects (hours to weeks of exposure) (Cakmak et al., 2014; Lippmann et al., 2013; Lippmann et al., 2000; Ng et al., 2019; Roemer et al., 2000; Wu et al., 2021). Evidence on long-term effects remains scarce. We previously reported significant associations of S and Ni in $PM_{10}$ with lung function at age 6–8 years independent of $PM_{10}$ mass concentrations in five European birth cohorts including PIAMA (Eeftens et al., 2014). Also, at age 8–12 years in the PIAMA cohort, negative associations of S and Ni with lung function were observed (−0.6% (95% CI: −1.4 to 0.2%) for $PM_{10}$ sulfur, −0.6% (−1.5 to 0.2%) for $PM_{10}$ Ni per IQR increase), but these diminished after adjustment for $PM_{10}$ (Gehring et al., 2015a). Based on the same standardized exposure assessment, we again found higher levels of S in $PM_{10}$ to be associated with slightly lower $FEV_1$ at age 16, indicating that the association is not limited to childhood.

Suggestive associations of long-term UFP exposure with both $FEV_1$ and FVC were observed in the current study. These associations were essentially similar in sensitivity analyses excluding active smokers and asthmatics. However, these associations attenuated towards the null in two-pollutant models with $NO_2$ and $PM_{2.5}$ while the associations with $NO_2$ and $PM_{2.5}$ persisted. Differences in model performance may explain findings from two-pollutant models with $NO_2$ and $PM_{2.5}$. However, it is not possible to say whether the performance of the $NO_2$ and $PM_{2.5}$ models was better than the performance of the UFP model as model performance has been assessed in different ways, namely by leave-one-out cross-validation ($NO_2$ and $PM_{2.5}$) and external validation (UFP). The $R^2$ resulting from these validations are not directly comparable, but the leave-one out cross-validation $R^2$ has been shown to be larger than $R^2$ from external (Wang et al., 2012). To date, only one cross-sectional study among 655 children in Australia studied associations between long-term exposure to UFP and lung function and found no association (Clifford et al., 2018). There are three studies reporting positive associations between long-term exposure to UFP and asthma development, two of them after adjustment for $NO_2$ (Lavigne et al., 2019; LeMasters et al., 2015; Wright et al., 2021), suggesting an independent adverse effect of UFP on respiratory health. However, asthma is not the same as lung function.

PM containing sulfur is emitted from the burning of residual oil (e.g. shipping, oil refineries) and industrial processes (Viana et al., 2008), which is consistent with the fact that port areas appear in the LUR models for these two elements (Table S1). Traffic is the other important predictor in the LUR model for sulfur. The independent associations with sulfur suggest, if confirmed in other studies, a role for air pollution from sources other than traffic in lung function.

The prospective study design and availability of the participants' residential histories from birth are strengths of our study. Ultrafine particles are a mixture of particles formed by regional scale nucleation events and local primary emitted particles (HEI, 2013). A strength of the UFP model is the combination of mobile monitoring with targeted regional modelling taking into account that UFP concentrations do not only vary within cities due to contributions of local sources (e.g. nearby traffic), but we also observed substantial regional differences (van de Beek et al., 2021) that were about as large as the differences between traffic and urban background sites within a city (Kerckhoffs et al., 2021).

However, this study also has several limitations. First, we acknowledge the limitation that our air pollution exposure models are purely spatial and do not account for temporal trends. Others developed spatial-temporal UFP models (Simon et al., 2020; Simon et al., 2018), but these models were limited to two cities and are less feasible for a larger study area such as an entire country. We used spatial LUR models based on an air pollution measurement campaigns performed in 2008–2010 for all pollutants except UFP, for which we relied on data from a measurement campaign performed in 2016–2017, to assess air pollution exposure during 2009–2013 (exposures at age 13–16) under the assumption of constant spatial contrasts in air pollution levels. This assumption is supported by previous studies that reported that the spatial contrasts in measured and modeled annual average $NO_2$ levels were stable over periods of 7–12 years (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2013; Gulliver et al., 2011; Wang et al., 2013). A previous study (Montagne et al., 2015) reported an $R^2$ value of 0.36 when using UFP models to predict UFP measurements collected 10 years previously. The findings for $NO_2$ and UFP may also apply to other traffic-related constituents such as Cu and Fe, but it is not clear whether it is also valid for elements related to sources other than traffic.

Avoiding rush hour traffic might be another potential limitation, as it may have resulted in lower spatial contrast. However, we consider the comparability of measurements between sites to be more important than the loss of contrast. Moreover, we have previously demonstrated high correlations ($R^2 > 0.95$) between UFP concentrations measured at different times of the day including rush hours, daytime non-rush hours and 24-hour averages, and reported small differences between the 24-hour average concentrations and the average of the period used for mobile monitoring (Downward et al., 2018).

Another limitation is that the study population has more participants from highly educated parents compared to the baseline PIAMA population. However, as no significantly different associations were observed between participants with high and low parental education in our stratified analyses (Fig. S7) this selection likely does not limit the generalizability of our findings to the full PIAMA cohort and further to the general population. We lack statistical power with regard to analyses in subgroups that may be more vulnerable to the air pollution exposure. Larger cohorts and/or analyses within multiple cohorts are needed for this.

In our analyses, we relied on residential exposure to air pollution, not taking into account exposure at other locations such as schools. However, children and adolescents spend most of their time at home and correlations between exposures at home and school address during the secondary school period were high for most elements including sulfur with a few exceptions (e.g. copper, iron and potassium in $PM_{10}$, Table S3). Therefore, measurement error from only including residential exposure is likely small.

In conclusion, our study suggests that long-term exposure to Sulfur in $PM_{10}$ may result in lower $FEV_1$ at age 16. There is no evidence for an independent effect of UFP exposure.

## Author contribution

UG designed the study. ZY performed the formal analysis and wrote the initial manuscript under the supervision of UG. UG, GH, GHK, JK, JMV, RV and UG contributed to the methodology, and UG, GHK, RV, and UG secured funding. All authors (i) provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, (ii) reviewed a the mansuscript, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GHK reports grants from the Lung Foundation of the Netherlands, for the current work. He reports grants from Ubbo Emmius Foundation, grants from TETRI Foundation, grants from GSK, grants from European Union, Marie Sklodowska-Curie program, grants from Vertex, grants from TEVA the Netherlands. He reports personal fees from advisory board meetings from GSK, and PURE IMS, outside the submitted work (money to institution). The rest of the authors declare that they have no relevant conflict of interests.

*Acknowledgements*

The authors would like to thank PIAMA participants and parents who contributed to the study and Marjan Tewis for data management.

*Financial Support*

The modeling of UFP concentrations was supported by an ASPASIA grant from the Dutch Research Council (NWO) to Dr. Ulrike Gehring (project number 015.010.044), the Environmental Defense Fund, EXPOSOME-NL (NWO grant number 024.004.017) and EXPANSE (EU-H2020 Grant number 874627). The PIAMA study was supported by The Netherlands Organization for Health Research and Development; The Netherlands Organization for Scientific Research; Lung Foundation Netherlands (formerly The Netherlands Asthma Fund); The Netherlands Ministry of Spatial Planning, Housing, and the Environment; The Netherlands Ministry of Health, Welfare, and Sport; and the National Institute of Public Health and the Environment (RIVM). Zhebin Yu is supported by the Chinese Scholarship Council.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106792.

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