



# Exposure to ambient ultrafine particles and allergic sensitization in children up to 16 years

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## ABSTRACT

**Background:** Few epidemiological studies so far have investigated the role of long-term exposure to ultrafine particles (UFP) in inhalant and food allergy development.

**Objectives:** The purpose of this study was to assess the association between UFP exposure and allergic sensitization to inhalant and food allergens in children up to 16 years old in the Netherlands.

**Methods:** 2295 participants of a prospective birth cohort with IgE measurements to common inhalant and food allergens at ages 4, 8, 12 and/or 16 were included in the study. Annual average UFP concentrations were estimated for the home addresses at birth and at the time of the IgE measurements using land-use regression models. Generalized estimating equations were used for the assessment of overall and age-specific associations between UFP exposure and allergic sensitization. Additionally, single- and two-pollutant models with NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> were assessed.

**Results:** We found no significant associations between UFP exposure and allergic sensitization to inhalant and food allergens (OR (95% CI) ranging from 1.02 (0.95–1.10) to 1.05 (0.98–1.12), per IQR increment). NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> showed significant associations with sensitization to food allergens (OR (95% CI) ranging from 1.09 (1.00–1.20) to 1.23 (1.06–1.43) per IQR increment). NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> were not associated with sensitization to inhalant allergens. For NO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>2.5</sub> absorbance, the associations with sensitization to food allergens persisted in two-pollutant models with UFP.

**Conclusion:** This study found no association between annual average exposure to UFP and allergic sensitization in children up to 16 years of age. NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> were associated with sensitization to food allergens.

## 1. Introduction

Traffic-related air pollution (TRAP), mainly nitrogen dioxide (NO<sub>2</sub>) and soot, and particulate matter <2.5 µm (PM<sub>2.5</sub>), have been associated with sensitization to food and inhalant allergens in children, although evidence remains inconsistent (Bowatte et al., 2015; Codispoti et al., 2015; Gehring et al., 2015; Jung et al., 2015). A recent multi-cohort analysis of the associations of particulate matter <10 µm (PM<sub>10</sub>),

PM<sub>2.5</sub> and NO<sub>2</sub> exposure with immunoglobulin E (IgE) sensitization in children until 16 years did not find evidence for an association with overall allergic sensitization. However, the study suggested that these pollutants may increase the risk of sensitization to specific inhalant allergen extracts and molecules (Melén et al., 2021).

Ultrafine particles (UFP) are an important component of TRAP, but little is known about the health effects of long-term exposure to UFP because of the difficulty of long-term exposure assessment (Ohlwein

**Abbreviations:** UFP, ultrafine particles; TRAP, traffic-related air pollution; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, particulate matter <2.5 µm; PM<sub>10</sub>, particulate matter <10 µm; IgE, immunoglobulin E; LUR, land-use regression; SLR, stepwise linear regression; LASSO, least absolute shrinkage and selection operator; RF, random forest; IQR, inter-quartile range; OR, odds ratio.

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et al., 2019). Due to their small size, UFP have the potential to penetrate deeper into the lungs and enter into the bloodstream, possibly leading to different health effects than other air pollution components (da Costa e Oliveira et al., 2019). UFP have not been investigated regarding allergic sensitization in children in an epidemiological study. Animal studies indicate a potential effect of UFP exposure on allergic inflammation as they may act as proallergic adjuvants (Li et al., 2016). An experimental study also suggests long-term effects on allergic inflammation in adult asthma patients 28 days after exposure to UFP (Schaumann et al., 2014). Epidemiological studies have found associations between long-term UFP exposure and higher levels of respiratory inflammatory biomarkers in children, especially in children with pre-existing respiratory diseases (da Costa e Oliveira et al., 2019). Additionally, systemic inflammatory effects in children have been found (Clifford et al., 2018). This indicates that UFP can have pro-inflammatory effects in children, potentially contributing to the development of allergic sensitization.

Assessment of long-term exposure to UFP remains a challenge and different methods have been applied, including empirical land-use regression (LUR) modelling, to capture spatial variation. Empirical models may differ in the approach or algorithm used in model development. Kerckhoffs et al. developed a nation-wide UFP LUR model for the Netherlands using six different approaches for LUR modelling (Kerckhoffs et al., 2021). The deconvoluted supervised stepwise linear regression (SLR) model was designated as the preferred model based on atmospheric principles (physical reality of spatial distribution of UFP), though the predictive performance was similar to that of other models (Kerckhoffs et al., 2021). However, more accurate exposure estimates do not necessarily lead to more accurate health effect estimates, as suggested in a simulation study (Szpiro et al., 2011). We therefore build on the investigation by Kerckhoffs et al. (2021) by comparing the associations with IgE sensitization for the UFP exposure estimates produced by the different approaches.

The aim of this study was to analyze the association between annual average UFP exposure and IgE sensitization in children aged 4–16 years in the PIAMA birth cohort in the Netherlands. This expands previous research done in this cohort on air pollution exposure and allergic sensitization at ages 4, 8 and 12 years (Brauer et al., 2007; Gehring et al., 2010, 2015), particularly by adding UFP exposure. We further investigated whether associations differed among different methods used in UFP exposure model development.

## 2. Materials and methods

### 2.1. Study population

The PIAMA birth cohort was set up in 1996–1997 and has been described elsewhere (Wijga et al., 2014). In short, the cohort was set up to investigate the effects of mite-allergen avoidance, lifestyle and environmental factors on asthma and allergy development. The baseline population consisted of 3963 children, whose parents completed questionnaires during pregnancy, when the child was 3 months old, and then annually from 1 to 8 years. Both children and parents completed questionnaires at ages 11, 14 and 16/17 years. Clinical examinations, including IgE measurements, were performed in subgroups of children at ages 1, 4, 8, 12 and 16. All participants with at least one IgE measurement at age 4, 8, 12 or 16 and air pollution exposure estimates at the birth address and/or the address at the time of the medical examination were included ( $n = 2295$ ). The Institutional Review Boards of the participating institutes approved the study protocol, and written informed consent was obtained from the parents or legal guardians of all participants.

### 2.2. Air pollution exposure assessment

Annual average UFP exposure estimates were obtained for the participants' birth address and residential address at the time of the 4, 8, 12

and 16 year medical examinations using the UFP nationwide model, developed by Kerckhoffs et al. (2021). This model was based on measurements of UFP collected with mobile monitoring on 14,392 road segments and long-term regional background measurements (3 times 14 days at 20 sites) across the Netherlands in 2016–2017. External long-term measurements (3 times 24 h at 42 sites in Amsterdam and Utrecht) were used for evaluating model performance. Three different approaches were used to model spatial variation of UFP measured by mobile monitoring: SLR, LASSO and random forest (RF). Additionally, for each approach, deconvoluted models were developed, which separate local and background concentration signals. All six models were used to assess annual average UFP exposure and resulting estimates of exposure-health relationships were compared.

Annual average exposure to  $\text{NO}_2$ ,  $\text{PM}_{2.5}$ ,  $\text{PM}_{2.5}$  absorbance and  $\text{PM}_{10}$  was estimated using previously developed LUR models (Beelen et al., 2013; Eeftens et al., 2012). These components were measured in three two-week monitoring campaigns in 2008–2010. LUR model development was done using SLR.

Exposure was defined as the predicted annual average pollutant concentration at the birth address and the annual average pollutant concentration at the address at the time of IgE measurement, to assess both early life exposure and current exposure to UFP. Additionally, the exposure misclassification due to residential mobility is eliminated by assigning the exposure to the new address if a participant moved in between IgE measurements. The predictions from the LUR models (based on measurements performed in 2016–2017) were used without back-transformation to the time of birth and/or IgE measurement that occurred before model development, as we did not have sufficient information about historic time trends of UFP. Predictions from the LUR models for  $\text{NO}_2$ ,  $\text{PM}_{2.5}$ ,  $\text{PM}_{2.5}$  absorbance and  $\text{PM}_{10}$  (based on measurements performed in 2008–2010) were also not back-extrapolated.

### 2.3. Measurement of allergic sensitization

Blood samples were taken at ages 4, 8, 12 and 16 year to measure IgE concentrations against common allergens. IgE was determined by a radioallergosorbent test-like method according to the standard operating procedure used at the Sanquin Laboratories (Amsterdam, The Netherlands). Two sets of allergens were investigated:

- Inhalant allergens: *Dermatophagoides pteronyssinus* (house dust mite), cat, *Dactylis glomerata* (grass) and birch at ages 4, 8, 12 and 16.
- Food allergens: milk and egg at ages 4, 8 and 12.

These sets of allergens were investigated separately, and sensitization to inhalant and food allergens was defined as IgE levels of at least 0.35 kUA/L to any of the inhalant allergens or any of the food allergens, respectively.

### 2.4. Covariate assessment

Covariates were selected a priori based on literature and previous analyses in this cohort (Brauer et al., 2007; Gehring et al., 2010, 2015; Melén et al., 2021). Included covariates were: sex (male/female), parental atopy ( $0/\geq 1$  atopic parent), Dutch nationality (yes/no), parental education ( $0/\geq 1$  parent with higher vocational or university education), breastfeeding at 12 weeks (yes/no), older siblings (yes/no), maternal smoking during pregnancy (yes/no), daycare attendance (yes/no), smoking in the participant's home (yes/no), mold/damp spots in the living room and/or participant's bedroom (yes/no), gas cooking (yes/no), furry pets (yes/no). Information on covariates was obtained from questionnaires and for the time-varying covariates (i.e. smoking, mold, gas cooking and furry pets in the participant's home), the questionnaire closest to the time of medical examination was used, as questionnaires were not always filled out at the same time as the medical examination. The time gap between questionnaire and IgE measurement

was never more than one year.

## 2.5. Statistical analysis

Generalized estimating equations with a compound symmetry correlation structure were used to assess the association between UFP exposure and IgE sensitization, accounting for correlations between repeated observations within the same individuals (Gehring et al., 2010; Melén et al., 2021). Interaction terms between age and exposure were included in the model to assess age-specific associations with exposure. Age was added as a categorical variable (4, 8, 12, 16). To facilitate comparisons of associations with exposure estimates from the different algorithms that generate different exposure contrasts, association estimates were expressed per inter-quartile range increase of air pollution exposure. Separate analyses were performed with estimated exposure at the birth address and exposure at the residential address at the time of the medical examination. All analyses were performed with and without adjustment for the potential confounders listed above.

Single pollutant models for UFP, NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> were explored first. Two-pollutant models with UFP and one of the other pollutants (NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub>) were then performed to assess independence of associations with UFP from associations with the other pollutants.

All analyses were performed using Statistical Analysis System (SAS 9.4, Cary, NC, USA) for Windows.

## 3. Results

### 3.1. Population characteristics

Distributions of the prevalence of sensitization are presented in Table 1. At all ages, sensitization to house dust mite was the most prevalent inhalant allergen. At age 16, nearly 50% of the children were sensitized to at least one of the four inhalant allergens. Of the food allergens, sensitization to milk was the most prevalent and the highest prevalence of sensitization to any food allergen was at age 4. Characteristics of the study population and the entire PIAMA cohort are provided in Table A.1. The study population included 45–50% girls (variation across years), mostly highly educated parents (54–63%), predominantly Dutch nationality (90–92%). In only 5–19% of the homes smoking occurred in the year of the medical exam. Mold in the home was reported for 5–10% of the children. There were only modest differences between the full PIAMA cohort and the population invited for specific examinations. At age 4 there was a higher percentage of atopic parents as a result of overrepresentation of atopic mothers in the study design (Table A.1).

### 3.2. Air pollution exposure

Annual average estimated exposure levels of UFP, NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> at the birth address are given in Table 2. UFP exposure at the birth and the current address as estimated by the other model development algorithms as well as age-specific estimated UFP

exposure levels at the address at the time of the specific medical examination can be found in Table A.2. The variability of UFP (IQR/median) was similar to PM<sub>2.5</sub> absorbance, smaller than for NO<sub>2</sub> and larger than for PM<sub>2.5</sub> and PM<sub>10</sub>. Median UFP exposure at the birth address ranged from 9270 to 12,661 particles/cm<sup>3</sup> between the different exposure models. The deconvoluted SLR model had the largest IQR from the six methods (Table A.2).

Pearson correlations between the estimated UFP levels from the different models were generally high (Figure A.1). The deconvoluted LASSO model predictions had the lowest correlations with predictions from other models, ranging from 0.66 to 0.78. Correlations between the other models ranged from 0.83 to 0.99. Correlations between UFP and the co-pollutants NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> are shown in Figure A.2. UFP was moderately correlated with PM<sub>2.5</sub> and highly correlated with NO<sub>2</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub>. Of all UFP models, the estimated UFP levels from the LASSO deconvoluted model had the lowest correlations with the co-pollutants.

Correlations between UFP exposure at the birth address and the current address were high at age 4 (0.73–0.83 for the six exposure models) and decreased with age. At age 16, these correlations ranged from 0.37 to 0.56 (Table A.3).

### 3.3. Air pollution and allergic sensitization

Table 3 shows the adjusted overall estimates of associations of UFP exposure (estimated with the deconvoluted SLR model) and the co-pollutants with sensitization to inhalant and food allergens from single pollutant analyses. Crude associations and associations for the other UFP exposure models are provided in Table A.4. Positive associations between UFP exposure and allergic sensitization to inhalant allergens after adjustment for potential confounders were found. The ORs (95% CI) were 1.03 (0.96–1.10) for the birth address and 1.02 (0.95–1.10) for the current address. The adjusted ORs for the associations with sensitization to food allergens were slightly higher (OR (95% CI) 1.04 (0.97–1.12) for the birth address and 1.05 (0.98–1.12) for the current address). Differences in ORs between UFP exposure models were small, with ORs for the preferred exposure model (deconvoluted SLR) being modestly larger than for the RF and LASSO models. None of the associations between UFP exposure and sensitization to inhalant or food allergens were statistically significant.

Overall adjusted associations of co-pollutants NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> with sensitization to any inhalant allergen were generally positive but not statistically significant with ORs (95% CI) ranging from 0.98 (0.90–1.07) to 1.08 (0.93–1.25) (Table 3). All co-pollutants at both the birth and current address, except PM<sub>10</sub> at the current address, were significantly positively associated with sensitization to food allergens after adjustment for confounders (ORs (95% CI) ranging from 1.09 (1.00–1.20) to 1.23 (1.06–1.43)).

Fig. 1 shows the age-specific associations of UFP exposure with sensitization to inhalant and food allergens for the deconvoluted SLR model after adjustment for confounders. All other UFP models showed similar patterns of associations: for sensitization to inhalant allergens, the ORs fluctuated around 1.0. Associations were positive for sensitization to food allergens for all ages but, as for sensitization to inhalant allergens, ORs were close to unity and non-significant.

Age-specific analyses with NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> exposure showed that the significant associations with sensitization to food allergens were largely limited to ages 4 and 8 (Table A.6). Odds ratios for the association of exposure at the current address with food allergen sensitization at ages 4, 8 and 12 years were 1.12 (0.92–1.36), 1.22 (1.03–1.43) and 1.12 (0.95–1.32) for NO<sub>2</sub> and 1.34 (1.03–1.74), 1.28 (1.03–1.60) and 1.06 (0.85–1.31) for PM<sub>2.5</sub>.

Associations of UFP exposure (estimated from the deconvoluted SLR model) with sensitization to inhalant and food allergens generally decreased to unity after the addition of co-pollutants in the models (Table 4). The estimates of the associations between the co-pollutants

**Table 1**

Prevalence of allergic sensitization. Results are presented as prevalence percentage of participants with available data (% (N)).

Sensitization	4 years	8 years	12 years	16 years
<b>Any inhalant allergen</b>	19.7% (736)	31.8% (1706)	42.5% (1302)	47.4% (753)
House-dust mite	14.2% (744)	22.5% (1708)	32.1% (1302)	37.6% (753)
Cat	6.6% (741)	8.3% (1708)	13.5% (1302)	13.9% (753)
Dactylis glomerata (grass)	6.6% (731)	15.9% (1704)	25.9% (1300)	28.3% (753)
Birch	2.1% (729)	7.8% (1707)	14.2% (1300)	16.9% (753)
<b>Any food allergen</b>	28.1% (716)	16.7% (1705)	20.5% (1295)	Not measured
Milk	26.2% (722)	15.3% (1707)	19.2% (1295)	Not measured
Egg	7.7% (714)	4.2% (1703)	4.9% (1295)	Not measured

**Table 2**

Annual average estimated air pollution exposure levels at the birth address (N = 2278).

Pollutant	Mean (SD)	Minimum	25th percentile	Median	75th percentile	Maximum	IQR
UFP <sup>a</sup> (particles/cm <sup>3</sup> )	11630 (2905)	8598	9885	10848	12152	31230	2267
NO <sub>2</sub> (µg/m <sup>3</sup> )	24.10 (7.13)	9.23	19.18	24.02	28.07	63.43	8.90
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	16.42 (0.73)	15.27	15.64	16.53	16.79	21.12	1.16
PM <sub>2.5</sub> abs (10 <sup>-5</sup> m <sup>-1</sup> )	1.26 (0.27)	0.85	1.07	1.25	1.38	3.11	0.31
PM <sub>10</sub> (µg/m <sup>3</sup> )	24.94 (1.18)	23.73	24.12	24.64	25.28	33.19	1.16

<sup>a</sup> As estimated with the deconvoluted supervised linear regression model.**Table 3**Adjusted<sup>a</sup> overall associations between annual average air pollution exposure and allergic sensitization at age 4–16 years to inhalant or food allergens.

Exposure	Inhalant allergens		Food allergens	
	Birth address OR (95% CI)	Current address OR (95% CI)	Birth address OR (95% CI)	Current address OR (95% CI)
UFP <sup>b</sup>	1.03 (0.96–1.10)	1.02 (0.95–1.10)	1.04 (0.97–1.12)	1.05 (0.98–1.12)
NO <sub>2</sub>	1.08 (0.97–1.21)	1.07 (0.96–1.20)	<b>1.13 (1.00–1.28)</b>	<b>1.16 (1.02–1.31)</b>
PM <sub>2.5</sub>	1.04 (0.91–1.19)	1.08 (0.93–1.25)	<b>1.23 (1.06–1.43)</b>	<b>1.21 (1.02–1.43)</b>
PM <sub>2.5</sub> abs	1.01 (0.92–1.12)	1.00 (0.90–1.12)	<b>1.13 (1.01–1.26)</b>	<b>1.12 (1.00–1.26)</b>
PM <sub>10</sub>	1.01 (0.92–1.10)	0.98 (0.90–1.07)	<b>1.09 (1.00–1.20)</b>	1.06 (0.97–1.17)

Odds ratios are presented for an IQR (Table 2 and A.2) increase in pollutant exposure.

<sup>a</sup> Adjusted for sex, parental atopy, Dutch nationality, parental education, breastfeeding at 12 weeks, older siblings, maternal smoking during pregnancy, daycare attendance, smoking in the participant's home, mold/damp spots in the living room and/or participant's bedroom, gas cooking, furry pets.<sup>b</sup> As estimated with the deconvoluted SLR model.

and sensitization to inhalant allergens decreased compared to the single pollutant models. However, the association estimates for sensitization to food allergens remained similar to the association estimates from the single pollutant models or increased. Associations with NO<sub>2</sub> at the current address, and PM<sub>2.5</sub> absorbance and PM<sub>2.5</sub> at the birth address, remained significant, although the 95% confidence intervals became wider.

As a sensitivity analysis, the overall analysis for the association between UFP exposure (estimated with the deconvoluted SLR model) and inhalant and food allergens was performed with a reference group free from sensitization, meaning that in the analysis with inhalant allergens all subjects with sensitization to food allergens were excluded and vice versa. The results from these analyses showed very little difference from the main analyses (Table A.4).

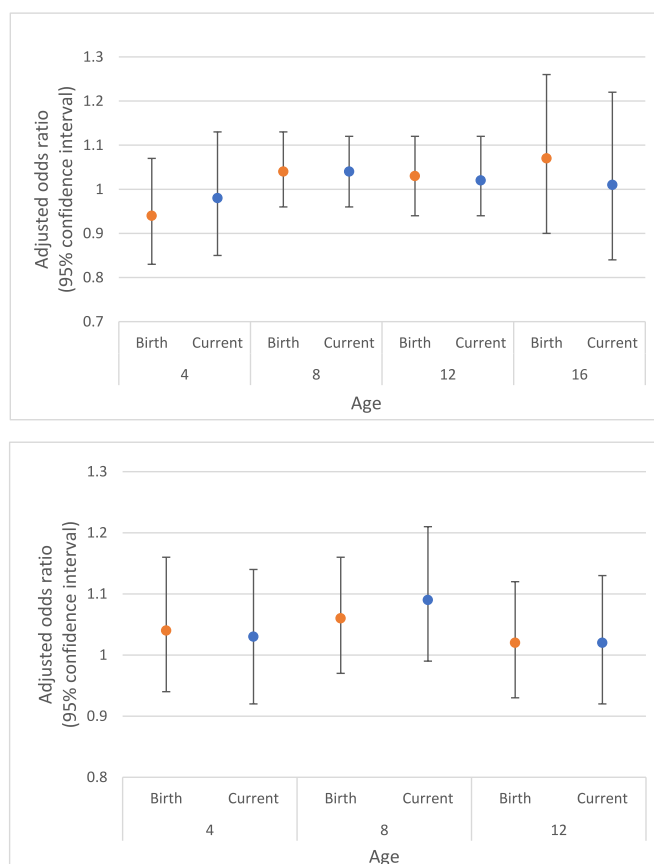
#### 4. Discussion

We found no significant association between annual average UFP exposure and allergic sensitization to inhalant or food allergens in a birth cohort of children followed up at ages 4, 8, 12 and 16 years. Exposure to NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub> was significantly associated with sensitization to food allergens but not inhalant allergens, which remained for all pollutants except PM<sub>10</sub> in two-pollutant models with UFP.

##### 4.1. Air pollution and allergic sensitization

Our study extends previous analyses of the association between annual average air pollution exposure and allergic sensitization performed in the PIAMA cohort by assessing associations with UFP (Brauer et al., 2007; Gehring et al., 2010, 2015; Melén et al., 2021). Recently, a multi-cohort analysis, which also included data from the PIAMA cohort, found no associations of NO<sub>2</sub>, NO<sub>x</sub>, PM<sub>2.5</sub>, PM<sub>2.5</sub> absorbance and PM<sub>coarse</sub> with sensitization to inhalant and/or food allergens up to age 16 in the pooled analyses, apart from an association with sensitization to birch pollen extract. This analysis with sensitization to birch pollen extract was only done in part of the cohorts. In the PIAMA cohort-specific analysis, positive associations with sensitization to food allergens were found (Melén et al., 2021).

To our knowledge, this is the first epidemiological study assessing



**Fig. 1.** Adjusted<sup>a</sup> age-specific associations of UFP exposure (estimated from the deconvoluted SLR model) at birth and current address with sensitization to inhalant (upper panel) and food allergens (lower panel).

Odds ratios are presented for an IQR (Table 2) increase in UFP exposure.

<sup>a</sup>Adjusted for sex, parental atopy, Dutch nationality, parental education, breastfeeding at 12 weeks, older siblings, maternal smoking during pregnancy, daycare attendance, smoking in the participant's home, mold/damp spots in the living room and/or participant's bedroom, gas cooking, furry pets.



**Table 4**Adjusted<sup>a</sup> associations of UFP (deconvoluted SLR model) and co-pollutant exposure with sensitization to inhalant or food allergens in two-pollutant models.

Exposure		Inhalant allergens		Food allergens	
		Birth address OR (95% CI)	Current address OR (95% CI)	Birth address OR (95% CI)	Current address OR (95% CI)
UFP + NO <sub>2</sub>	UFP	0.97 (0.86–1.09)	0.97 (0.88–1.08)	0.94 (0.82–1.07)	0.95 (0.85–1.07)
	NO <sub>2</sub>	1.13 (0.93–1.37)	1.11 (0.94–1.31)	1.23 (0.99–1.52)	<b>1.24 (1.01–1.51)</b>
UFP + PM <sub>2.5</sub>	UFP	1.02 (0.94–1.12)	1.00 (0.93–1.09)	0.97 (0.88–1.06)	1.00 (0.92–1.09)
	PM <sub>2.5</sub>	1.01 (0.85–1.20)	1.07 (0.90–1.27)	<b>1.28 (1.05–1.54)</b>	1.20 (0.98–1.47)
UFP + PM <sub>2.5</sub> abs	UFP	1.06 (0.94–1.19)	1.04 (0.94–1.15)	0.93 (0.82–1.06)	0.98 (0.87–1.09)
	PM <sub>2.5</sub> abs	0.95 (0.80–1.13)	0.96 (0.82–1.11)	<b>1.22 (1.01–1.48)</b>	1.16 (0.97–1.38)
UFP + PM <sub>10</sub>	UFP	1.07 (0.95–1.21)	1.06 (0.96–1.17)	0.94 (0.83–1.08)	1.02 (0.92–1.13)
	PM <sub>10</sub>	0.94 (0.80–1.09)	0.93 (0.82–1.05)	1.16 (0.99–1.36)	1.05 (0.91–1.20)

Odds ratios are presented for an IQR (Table 2 and A.2) increase in pollutant exposure.

<sup>a</sup> Adjusted for sex, parental atopy, Dutch nationality, parental education, breastfeeding at 12 weeks, older siblings, maternal smoking during pregnancy, daycare attendance, smoking in the participant's home, mold/damp spots in the living room and/or participant's bedroom, gas cooking, furry pets.

the association between annual average UFP exposure and allergic sensitization. At present, the evidence for associations between UFP exposure and asthma and allergies is scarce and inconsistent. Prenatal exposure to UFP has been found to be associated with childhood asthma development (Lavigne et al., 2019; Wright et al., 2021), but not with lung function in children (Clifford et al., 2018; Yu et al., 2021). An experimental pilot study on UFP exposure and allergic inflammation in adult asthma patients found an increased inflammatory response to allergens 28 days after exposure to UFP (Schaumann et al., 2014). However, the design and population used in this study limit comparability with our results.

Our findings of positive associations between NO<sub>2</sub>, PM<sub>2.5</sub>, and PM<sub>2.5</sub> absorbance with sensitization to food allergens at age 4 and 8 are consistent with findings from previous analyses within the PIAMA and other cohorts (Brauer et al., 2007; Gruzieva et al., 2012; Melén et al., 2021). However, evidence remains inconsistent and clinical relevance remains unclear. Exact mechanisms of the relationship between air pollution exposure and sensitization to food allergens are not fully elucidated (Peters et al., 2022). Exposure of the gastrointestinal tract to air pollutants happens in different ways including direct dietary ingestion of particles, clearance of inhaled particles from the lungs to the gastrointestinal tract by mucociliary transport, and induced systemic inflammation by gaseous pollutants (Feng et al., 2020). Disruption of the gastrointestinal epithelial barrier due to the air pollution exposure can in turn cause an inflammatory response and leave the deeper tissue and blood stream vulnerable to exposure to allergens (Peters et al., 2022).

#### 4.2. Two-pollutant exposure models

Generally, the independence of health effects of UFP remains inconclusive partly due to the lack of studies including multipollutant models (Ohlwein et al., 2019). In our study we adjusted for major co-pollutants. The positive associations that we observed between UFP exposure and food allergen sensitization were reduced to essentially unity after the addition of co-pollutants in the models. Additionally, associations between NO<sub>2</sub>, PM<sub>2.5</sub> absorbance and PM<sub>2.5</sub> exposure with sensitization to food allergens remained significant in models that included UFP exposure, indicating that these associations were independent of UFP exposure. Disentangling the health effects of different air pollution components remains a challenge due to often high correlations between most pollutants. In our study, UFP was highly correlated with NO<sub>2</sub>, PM<sub>2.5</sub> absorbance and PM<sub>10</sub>.

The absence of associations between sensitization and UFP and the presence of associations with co-pollutants could be related to differences in the exposure models or true differences in health effects. One potential explanation is the larger time span between development of exposure models and health outcome assessment for UFP. The UFP exposure models were developed based on measurement data from the year 2016–2017 and applied to predict exposure from 1996/1997 to 2012/2013, potentially leading to exposure misclassification. This

limitation applies less to associations with health data from the 12 and 16 year follow-ups than to associations with health data from the 4 and 8-year follow-ups. The comparison of estimated UFP exposure levels from the models with independent long-term measurements in two major cities, Amsterdam and Utrecht in 2014 had an R<sup>2</sup> ranging from 0.52 to 0.60 (Kerckhoffs et al., 2021). Another Dutch study used UFP models to predict UFP measurements collected ten years previously and found an R<sup>2</sup> value of 0.36 (Montagne et al., 2015). Therefore, there is some support that recent models can predict spatial variation of UFP levels for periods of 10 years moderately well. This is corroborated by the relatively small trend in particle number concentrations seen at a background measurement location in the Netherlands over a period of 8 years, from 2008 to 2015 (Mamali et al., 2018). Similarly, we used LUR models based on measurements from 2008 to 2010 for the co-pollutants. Previous studies have found good stability of spatial contrasts of NO<sub>2</sub> for periods of 8–12 years (Cesaroni et al., 2012; Eeftens et al., 2011). For UFP, we did not have sufficient data for back-extrapolation. For the co-pollutants, back-extrapolation was feasible (Strak et al., 2021) but deemed unnecessary due to the temporal alignment with the follow-up period and the aforementioned stability of spatial contrasts.

A second potential explanation is differences in performance of the UFP and co-pollutant exposure models, as models have been developed with different monitoring strategies. We cannot quantitatively compare model performance as the performance of these models was assessed with different internal validation datasets.

Our finding of persistent associations between NO<sub>2</sub> and sensitization independent of UFP is corroborated by experimental studies showing that particle-depleted diesel exhaust is associated with increased allergen response, indicating NO<sub>2</sub> as an important factor in allergic sensitization (Bosson et al., 2019; Wooding et al., 2019).

#### 4.3. Comparing exposure model algorithms

Estimated UFP levels from the different exposure models, based on the use of different algorithms, were highly correlated. We furthermore found that differences in the association estimates with allergic sensitization were small. Kerckhoffs et al. (2021) found small differences in model performance based on correlation and external validation between development algorithms, but deemed the deconvolution method to be the most appropriate model based on physical principles (Kerckhoffs et al., 2021). The findings of this study and the Kerckhoffs study together indicate that the algorithm used for model development did not substantially influence model performance in terms of explained spatial variation or health effect estimates.

#### 4.4. Strengths and limitations

Strengths of this study include its prospective design, the possibility to adjust for many potential (time-varying) confounders and the availability of annual average UFP exposure data from a national model,

allowing analysis of a cohort with residential addresses spread over the Netherlands. Most previous studies were based on single city analyses (Ohlwein et al., 2019).

A limitation of this study is that we could assess UFP exposure only based on recent measurements. The study population included slightly more participants with highly educated parents compared to the PIAMA baseline population, mostly at age 16. Additionally, the percentage of participants with at least one atopic parent is relatively high at age 4 due to the overrepresentation of children with atopic mothers in the study design. However, as no age-specific associations were found at age 4, it seems unlikely that this biased the main analyses. It does not limit the generalizability of our findings to the PIAMA cohort and the general population.

In conclusion, we found no evidence that annual average UFP exposure was associated with allergic sensitization in children up to 16 years of age. Association estimates did not differ between exposure models based on different algorithms.

### Author contributions

GH and UG designed the study and secured funding. FB performed the formal analysis and wrote the initial manuscript under the supervision of GH and UG. 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 the manuscript, (iii) approved the final version, and (iv) agreed to be accountable for all aspects of the work.

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### Ethics approval

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.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data availability

The authors do not have permission to share data.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2022.115102>.

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