

Meta-analysis of air pollution exposure association with allergic sensitization in European birth cohorts

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Background: Evidence on the long-term effects of air pollution exposure on childhood allergy is limited.

Objective: We investigated the association between air pollution exposure and allergic sensitization to common allergens in children followed prospectively during the first 10 years of life.

Methods: Five European birth cohorts participating in the European Study of Cohorts for Air Pollution Effects project were included: BAMSE (Sweden), LISApplus and GINIplus

(Germany), MAAS (Great Britain), and PIAMA (The Netherlands). Land-use regression models were applied to assess the individual residential outdoor levels of particulate matter with an aerodynamic diameter of less than 2.5 μm ($\text{PM}_{2.5}$), the mass concentration of particles between 2.5 and 10 μm in size, and levels of particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), as well as measurement of the blackness of $\text{PM}_{2.5}$ filters and nitrogen

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dioxide and nitrogen oxide levels. Blood samples drawn at 4 to 6 years of age, 8 to 10 years of age, or both from more than 6500 children were analyzed for allergen-specific serum IgE against common allergens. Associations were assessed by using multiple logistic regression and subsequent meta-analysis.

Results: The prevalence of sensitization to any common allergen within the 5 cohorts ranged between 24.1% and 40.4% at the age of 4 to 6 years and between 34.8% and 47.9% at the age of 8 to 10 years. Overall, air pollution exposure was not associated with sensitization to any common allergen, with odds ratios ranging from 0.94 (95% CI, 0.63-1.40) for a $1 \times 10^{-5} \cdot \text{m}^{-1}$ increase in measurement of the blackness of $\text{PM}_{2.5}$ filters to 1.26 (95% CI, 0.90-1.77) for a $5 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure at birth address. Further analyses did not provide consistent evidence for a modification of the air pollution effects by sex, family history of atopy, or moving status.

Conclusion: No clear associations between air pollution exposure and development of allergic sensitization in children up to 10 years of age were revealed. (J Allergy Clin Immunol 2014;133:767-76.)

Key words: Air pollution, children, cohort, IgE, sensitization, meta-analysis, European Study of Cohorts for Air Pollution Effects

Air pollution has been related to several adverse health outcomes, including childhood allergic diseases.¹⁻³ Although some epidemiologic studies suggest increased risks of allergic sensitization in relation to ambient air pollution exposure, the evidence remains inconsistent. To date, there are only a few prospective cohort studies on specific sensitization that follow children from birth to school age with assessment of exposure to air pollution on an individual level, and their results are inconclusive.⁴⁻⁷ Findings from the Swedish cohort BAMSE indicated that exposure during infancy was related to sensitization against certain allergens with a slightly different pattern at 4 and 8 years,^{5,8} whereas no association between lifetime air pollution exposure and sensitization to any allergen at the age of 9 to 10 years was seen in a cohort from Oslo.⁶ The Dutch cohort PIAMA reported an increased risk of food allergy at 4 years but not at 8 years of age.^{4,9} Statistically significant positive associations between particulate matter exposure and sensitization to inhalant allergens were shown in the southern part of the German LISA/GINI cohort at the age of 6 years⁷ but not in the northern part.¹⁰ However, these studies differed in their exposure assessment methodology, which complicates comparisons of the findings. Furthermore, only limited attention was paid to examining the importance of contextual confounders, as well as potential modifying factors (ie, sex).

This study is a part of the European collaborative European Study of Cohorts for Air Pollution Effects (ESCAPE; <http://www.escapeproject.eu>) project and aims to quantify the effect of ambient air pollution on the development of allergic sensitization in children during the first 8 to 10 years of life. We performed a meta-analysis based on health data already available from 5 European birth cohorts and applied uniform exposure assessment tools developed within the ESCAPE project. To our knowledge, no combined analysis has yet been performed on air pollution exposure and allergic sensitization in children based on prospective birth cohort studies.

Abbreviations used

ESCAPE: European Study of Cohorts for Air Pollution Effects

LUR: Land-use regression

NO_2 : Nitrogen dioxide

NO_x : Nitrogen oxides

OR: Odds ratio

$\text{PM}_{2.5}$: Particulate matter with an aerodynamic diameter of less than $2.5 \mu\text{m}$

$\text{PM}_{2.5}$ absorbance: Measurement of the blackness of $\text{PM}_{2.5}$ filters

PM_{10} : Particulate matter with an aerodynamic diameter of less than $10 \mu\text{m}$

$\text{PM}_{\text{coarse}}$: Mass concentration of particles between 2.5 and $10 \mu\text{m}$ in size

Furthermore, we examined sex-specific differences in the effects of air pollution, as well as possible confounding by area-level socioeconomic characteristics.

METHODS

Study population

Data from 5 European birth cohorts participating in the ESCAPE project were included in the current study: BAMSE (Sweden), LISApplus and GINIplus (Germany), MAAS (Great Britain), and PIAMA (The Netherlands). The cohorts were initiated in the mid-1990s, with subsequent follow-up on several occasions. Detailed descriptions of study design, recruitment, and procedures for data collection in each cohort have been provided elsewhere.¹¹⁻¹⁴ The study area of the BAMSE cohort is Stockholm County, including municipalities representing urban and suburban environments. Both LISA/GINI cohorts include smaller surrounding towns in addition to the major cities. The PIAMA cohort recruited children from a series of urban and rural communities throughout the country. The MAAS cohort is based on the Greater Manchester urban area.

For the 2 German birth cohorts LISApplus and GINIplus, which largely follow an identical design, data from the study centers of Munich and Wesel were included in the analysis and combined for each study center (Munich: LISA/GINI South; Wesel: LISA/GINI North). At the time of recruitment, parents completed a screening questionnaire on, for example, their history of asthma and allergic diseases, lifestyle and socioeconomic factors, and home environment. At the age of 4 years (5 years for the MAAS cohort and 6 years for the LISA/GINI cohorts) and 8 years (10 years for the LISA/GINI cohorts), children were invited for clinical examinations, including blood tests. Follow-up questionnaires were sent to the parents at these time points to collect information about health and various exposures for the children. All children who provided blood samples were included in the analysis. Consent for blood sampling was obtained from all parents. Ethical approval for each study was obtained from local authorized review boards.

Air pollution exposure assessment

Exposure to various air pollutants was estimated through land-use regression (LUR) models developed for each study area within the framework of the ESCAPE project. The procedures for measurements and LUR modeling have been extensively described elsewhere.¹⁵⁻¹⁷ In short, 20 sampling sites for particulate matter and 40 sampling sites for nitrogen oxides (NO_x) were selected in each study area to characterize the spatial distribution of the cohort addresses, including regional background, urban background, and traffic sites. Measurements were performed at each site 3 times during 2 weeks in the cold, warm, and intermediate seasons, and the results were averaged to estimate the annual average, adjusting for temporal variation by using a centrally located background reference site. LUR models were developed for particulate matter with an aerodynamic diameter of less than $2.5 \mu\text{m}$ ($\text{PM}_{2.5}$), measurement of

TABLE I. Population characteristics at 4 years of age

Variable	BAMSE (n = 2604)		PIAMA (n = 747)		LISA/GINI South* (n = 1670)		LISA/GINI North* (n = 1004)		MAAS* (n = 484)	
	n/N	Percent	n/N	Percent	n/N	Percent	n/N	Percent	n/N	Percent
Female sex	1281/2604	49.2	335/747	44.8	806/1670	48.3	483/1004	48.1	218/484	45.0
≥1 Allergic parent	795/2580	30.8	581/747	77.8	1179/1660	71.0	533/998	53.4	699/1058	66.1
High maternal SES†	1061/2588	41.0	284/740	38.4	1048/1662	63.1	346/1001	34.6	NA	38.6
High paternal SES†	968/2547	38.0	323/733	44.1	1180/1643	71.8	390/997	39.1	207/455	45.0
Older siblings	1244/2604	47.8	407/746	54.6	712/1668	42.7	549/1001	54.9	267/484	55.2
Breast-feeding (≥12 wk)	2414/2551	94.6	396/746	53.1	1122/1609	69.7	549/969	56.7	220/467	47.1
Mother smoked during pregnancy	323/2604	12.4	123/735	16.9	217/1640	13.2	141/988	14.3	59/458	12.9
Smoking at child's home										
Early life	528/2592	20.4	186/746	24.9	248/1646	15.1	270/986	27.4	208/457	45.5
Current	451/2587	17.4	152/720	21.1	313/1669	18.8	354/998	35.5	175/478	36.6
Use of natural gas for cooking										
Early life	294/2591	11.3	621/741	83.8	127/1653	7.7	45/980	4.6	365/459	79.5
Mold/dampness in child's home										
Early life	661/2531	25.5	218/723	30.2	425/1554	27.3	206/981	21.0	86/460	14.1
Furry pets in home										
Early life	386/2604	14.8	320/745	43.0	240/1610	14.9	156/967	16.1	166/460	36.1
Current	346/2601	13.3	315/729	43.2	385/1667	23.1	268/997	26.9	138/479	28.8
Study region‡										
I	795/2592	30.6	228/747	30.5	NA		NA		NA	
II	760/2592	29.3	285/747	38.2	NA		NA		NA	
III	664/2592	25.6	234/747	31.3	NA		NA		NA	
IV	376/2592	14.5			NA		NA		NA	
Study arm										
Observational cohort	NA		415/739	56.2	1047/1670	62.7	610/1004	60.8	421/484	87.0
Intervention group	NA		324/659	43.8	623/1670	37.3	394/1004	39.2	63/484	13.0
Moved§	1187/2580	46.0	250/741	33.7	939/1539	61.0	324/983	33.0	185/484	38.2
Birth weight (g), mean (SD), N	3521 (556)	2580	3518 (546)	744	3426 (436)	1617	3534 (495)	979	3459 (517)	1056

NA, Not applicable/not available.

*LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age.

†SES represents socioeconomic status, which is defined by education in BAMSE, LISA/GINI, and PIAMA and by income in MAAS.

‡PIAMA: I, north region; II, middle region; III, west region; BAMSE: I, Stockholm; II, Järfälla; III, Solna; IV, Sundbyberg.

§Between birth and IgE measurement.

the blackness of PM_{2.5} filters (PM_{2.5} absorbance), particulate matter with an aerodynamic diameter of less than 10 μm (PM₁₀), and mass concentration of particles between 2.5 and 10 μm in size (PM_{coarse}; ie, the difference between PM₁₀ and PM_{2.5}), nitrogen dioxide (NO₂), and NO_x based on measured annual average concentrations by using a range of Geographic Information System–derived predictor variables selected through a supervised stepwise procedure. In addition, 2 traffic variables were specified: traffic intensity, which was defined as the number of vehicles per day on the nearest street, and traffic load, representing the total traffic load on all major roads in a 100-m buffer (traffic intensity * length of all segments). Modeling was done locally at each center according to a common exposure assessment manual (<http://www.escapeproject.eu/manuals/>). The baseline air pollution exposure was estimated by assigning the LUR-modeled concentrations to the birth addresses, and the current exposure was estimated by assignment of modeled concentrations to the current addresses at the time when the blood samples were collected at 4 to 6 and 8 to 10 years of age. Routine monitoring data in the study areas were used to back-extrapolate the LUR estimates at the birth addresses. We used the absolute difference and the ratio between the routine monitoring sites' average concentration in the year before and after recruitment and in the ESCAPE monitoring year to adjust all cohort exposures (http://www.escapeproject.eu/manuals/Procedure_for_extrapolation_back_in_time.pdf). The Ruhr Area model was applied to LISA/GINI North, and the Munich/Augsburg model was applied to LISA/GINI South.

Outcome definition

Sensitization status was defined based on IgE antibody concentrations against common inhalant/food allergens. Blood samples were analyzed for

allergen-specific serum IgE to a panel of allergens, including a mix of common inhalant allergens (Phadiatop; birch, timothy grass, mugwort, cat, dog, horse, *Cladosporium herbarum*, and house dust mite [*Dermatophagoides pteronyssinus*]) and a mix of common food allergens (fx5; cow's milk, egg white, soy bean, peanut, codfish, and wheat; ImmunoCAP System, Thermo Fisher/Phadia AB, Uppsala, Sweden) or alternative test systems (ie, the RAST-like method used at the Sanquin Laboratories [Amsterdam, The Netherlands] and the CAP-RAST FEIA [Pharmacia Diagnostics, Freiburg, Germany]). Details regarding the set of allergens tested in each cohort are presented in Table E1 in this article's Online Repository at www.jacionline.org. Sensitization was defined as a positive reaction (IgE antibody level ≥0.35 kU_A/L) to any of the allergens tested. The reference group comprised subjects without sensitization to any allergen.

Statistical analyses

Associations between exposures and outcomes were analyzed by means of logistic regression at the cohort level. Air pollution concentrations were entered as continuous variables without transformation. The results are presented as odds ratios (ORs) and 95% CIs for increments of 10 μg/m³ (NO₂ and PM₁₀), 1 × 10⁻⁵ · m⁻¹ (PM_{2.5} absorbance), 5 μg/m³ (PM_{coarse} and PM_{2.5}), 20 μg/m³ (NO_x), 4,000,000 vehicles/day·m (traffic load on all major roads in a 100-m buffer), and 5,000 vehicles/day (traffic density on the nearest road), where the latter 2 were additionally adjusted for modeled background NO₂ levels in the analyses. A common set of potential individual-level confounders were defined *a priori* and included known or suspected risk factors for allergic diseases: sex, age at review, maternal smoking during pregnancy, smoking in child's home, 12 or more weeks of breast-feeding,

TABLE II. Population characteristics at 8 years of age

Variable	BAMSE (n = 2447)		PIAMA (n = 1713)		LISA/GINI South* (n = 1582)		LISA/GINI North* (n = 872)		MAAS (n = 468)	
	n/N	Percent	n/N	Percent	n/N	Percent	n/N	Percent	n/N	Percent
Female sex	1191/2447	48.7	828/1713	48.3	768/1582	50.0	437/872	50.1	211/468	45.1
≥1 Allergic parent	780/2428	32.1	978/1713	57.1	1103/1575	70.0	475/867	54.8	384/466	82.4
High maternal SES†	1026/2436	42.1	640/1707	37.5	987/1573	62.7	302/869	34.7	NA	
High paternal SES†	955/2391	39.9	710/1692	42.0	1109/1559	71.1	323/864	37.4	211/447	47.0
Older siblings	1167/2447	47.7	889/1711	52.0	686/1581	43.4	468/868	53.9	245/454	54.0
Breast-feeding (≥12 wk)	2267/2379	95.3	901/1705	52.8	1067/1522	70.1	479/829	57.8	228/454	50.2
Mother smoked during pregnancy	286/2446	11.7	260/1696	15.3	189/1548	12.2	126/861	14.6	57/467	12.2
Smoking at child's home										
Early life	499/2435	20.5	449/1712	26.2	242/1558	15.5	233/859	27.1	196/466	42.1
Current	443/2410	18.4	255/1608	15.9	201/1555	12.9	219/858	25.5	170/459	37.0
Use of natural gas for cooking										
Early life	258/2447	10.5	1380/1699	81.2	120/1563	7.7	32/855	3.7	366/468	78.2
Current	163/2440	6.7	1289/1699	75.9	126/1569	8.0	37/868	4.3	376/468	80.3
Mold/dampness in child's home										
Early life	624/2439	25.6	451/1674	26.9	415/1527	27.2	154/856	18.0	77/468	16.5
Current	237/2435	9.7	455/1597	28.5	352/1520	23.2	180/836	21.5	49/468	10.5
Furry pets in home										
Early life	350/2381	14.3	731/1710	42.7	220/1523	14.4	139/832	16.7	178/468	38.0
Current	599/2439	24.6	817/1582	51.6	544/1535	35.4	288/844	34.1	209/468	44.7
Study region‡										
I	736/2433	30.2	458/1713	26.7	NA		NA		NA	
II	714/2433	29.4	784/1713	45.8	NA		NA		NA	
III	619/2433	25.4	471/1713	27.5	NA		NA		NA	
IV	364/2433	15.0			NA		NA		NA	
Study arm										
Observational cohort	NA		1289/1706	75.6	978/1582	61.8	527/872	60.4	406/468	86.8
Intervention group	NA		417/1706	24.4	604/1582	38.2	345/872	39.6	62/468	13.2
Moved§	1557/2400	64.8	825/1703	53.9	870/1454	59.8	385/983	44.6	253/468	54.1
Birth weight (g), mean (AD), N	3536 (557)	2423	3531 (528)	1709	3422 (528)	1529	3541 (482)	841	3458 (508)	456

NA, Not applicable/not available.

*LISA/GINI: data at 10 years.

†SES represents socioeconomic status, which is defined by education in BAMSE, LISA/GINI, and PIAMA and by income in MAAS.

‡PIAMA: I, north region; II, middle region; III, west region; BAMSE: I, Stockholm; II, Järfälla; III, Solna; IV, Sundbyberg.

§Between birth and IgE measurement.

atopic mother and/or father, maternal and paternal education, mold at home, furred pets at home, older siblings, gas cooking, and study area (the latter only for the BAMSE cohort). For time-varying confounders, such as environmental tobacco smoke, use of gas for cooking, and furred pets at home, current information was used to coincide with the outcome assessment. To account for potential clustering of subjects within areas, we conducted separate analyses introducing random intercepts into the main models (BAMSE, neighborhood and community; LISA/GINI, ZIP code and community; MAAS, no area-level variable available with sufficient number of children per level; and PIAMA, neighborhood, community), as well as area-level socioeconomic indicators (eg, mean income). In addition, we expanded the main model by adding variables that could also be in the causative pathway from air pollution to sensitization, such as birth weight. Stratified analyses were performed to evaluate potential effect modifications by sex and family history of allergic disease. Sensitivity analyses evaluated the influence by change of residence after birth on the risk estimates. Also, interaction terms representing the product of air pollutant exposure and the potential modifiers were entered into the models. Also, because the main analyses were performed with exposure estimates taken directly from the ESCAPE models, additional analyses were performed with back-extrapolated exposures to NO₂, NO_x, and PM₁₀, taking into account changes in air pollution levels over time based on routine air pollution monitoring data.

Each center performed analyses locally according to the common study protocol, and cohort-specific OR estimates were subsequently meta-analyzed by using a random-effects model.¹⁸ Statistical heterogeneity among studies

was evaluated by using the I^2 statistic.¹⁹ Combined analyses were performed with STATA software (release 11.1; StataCorp, College Station, Tex).

RESULTS

The distribution of potential risk factors at 4 to 6 and 8 to 10 years of age in the 5 cohorts is presented in [Tables I and II](#). A brief description of some general characteristics related to the recruitment and follow-up of the included cohorts is provided in [Table E2](#) in this article's Online Repository at www.jacionline.org. Overall, there were no substantial differences between the subjects included in the analyses and those in the original cohorts (data not shown). However, it should be noted that in the subset of children with IgE measurements in the BAMSE cohort, the proportion of children with allergic parents was considerably lower than in the other cohorts.

The prevalence of sensitization to any inhalant or food allergens within the 5 cohorts ranged from 24.1% to 40.4% at the age of 4 to 6 years (the lowest rates were in the BAMSE cohort and the highest rates were in the PIAMA cohort) and from 34.8% to 47.9% at the age of 8 to 10 years (in the BAMSE and LISA/GINI South cohorts, respectively), as shown in [Fig 1](#).

The distribution of air pollution exposure at the birth address is displayed in [Fig 2](#). The levels of most components were lower for

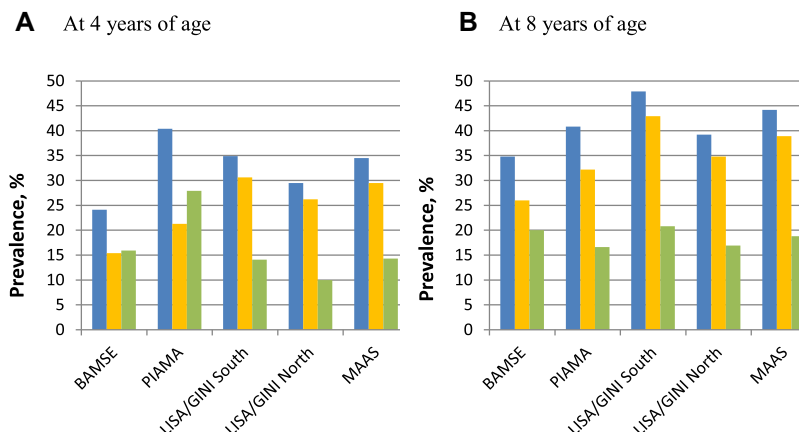


FIG 1. Prevalence of allergic sensitization at ages 4 and 8 years in 5 European birth cohorts. **A**, At 4 years of age (LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age). **B**, At 8 years of age (LISA/GINI: data at 10 years of age). *Blue bars*, Any inhalant and/or food allergen; *yellow bars*, any inhalant allergen; *green bars*, any food allergen.

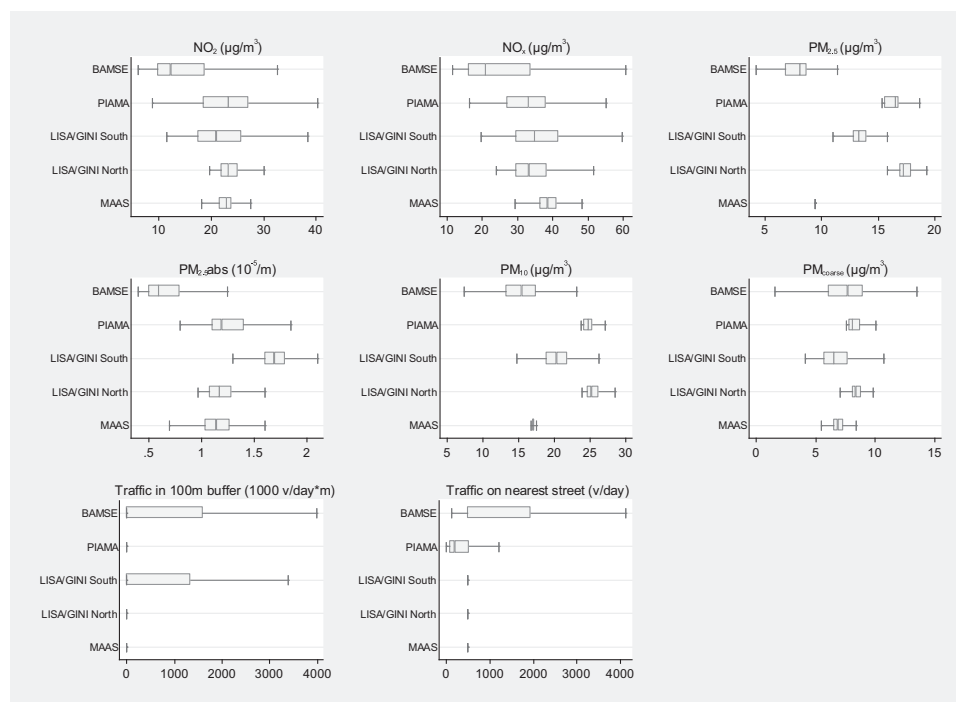


FIG 2. Air pollution exposure at birth address in 5 European birth cohorts. Each box contains the middle 50% of the data, with the upper edge (hinge) of the box indicating the 75th percentile and the lower edge indicating the 25th percentile (interquartile range). The line in the box represents the median. The ends of the vertical lines ("whiskers") indicate $1.5 \times \text{IQR}$.

the BAMSE cohort than in the other areas; however, the concentrations of coarse particles did not differ. The range of both traffic variables varied substantially between the cohorts. There was also within-area variability, which was smaller for $\text{PM}_{2.5}$ but quite substantial for $\text{PM}_{2.5}$ absorbance and NO_x values, for example. Exposure levels were similar in children with blood samples and the whole cohort (data not shown). The levels of air pollution at 4- to 6-year and 8- to 10-year addresses are summarized in Table E3 in this article's Online Repository at www.jacionline.org. There were minor changes in air pollution

levels between the current addresses at 4 to 6 and 8 to 10 years of age. Also, concentrations at the birth and current addresses were comparable for most pollutants, with slightly decreasing values over time for NO_x in the BAMSE and LISA/GINI South cohorts. In all cohorts but MAAS, NO_2 and NO_x levels for current and birth addresses were highly correlated ($r \geq 0.87$). In the BAMSE and PIAMA cohorts NO_2 and $\text{PM}_{2.5}$ absorbance values were highly correlated ($r \geq 0.90$). The lower correlations in MAAS likely reflect that the spatial variation of NO_2 and NO_x was small in that cohort. Correlations between estimated

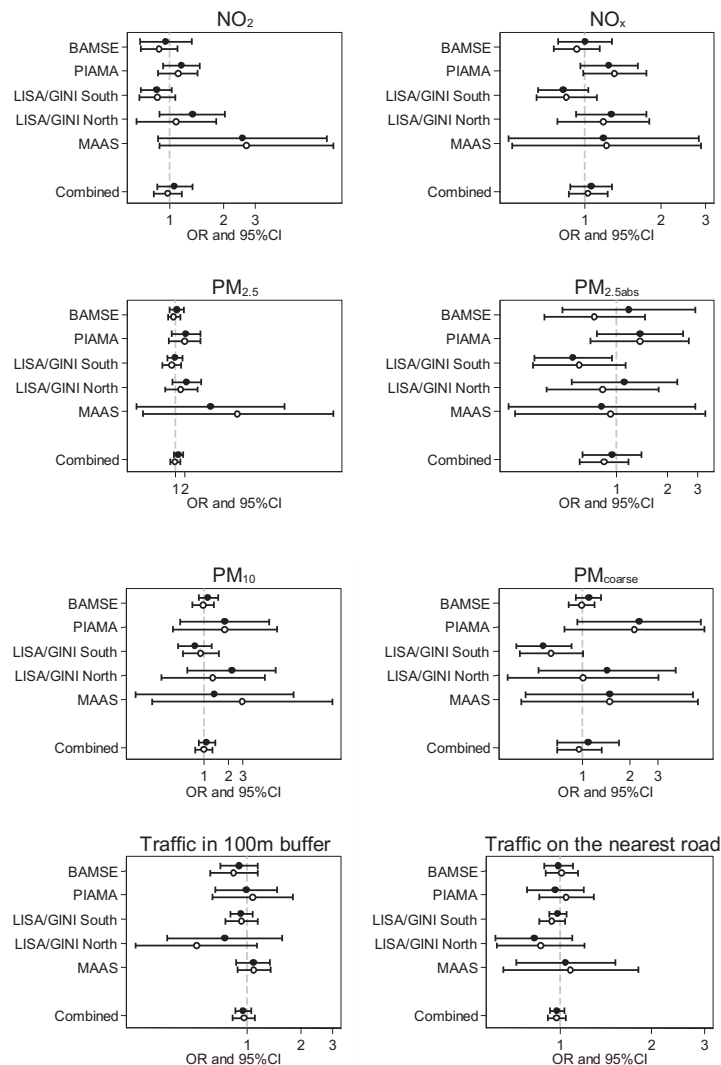


FIG 3. Meta-analyses of the associations between early-life or current air pollution exposure and sensitization to any common allergen at 4 years of age in 5 European birth cohorts. *Solid circles*, Birth address; *open circles*, current address. Cohort-specific ORs and 95% CIs were obtained by means of logistic regression and are adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breastfeeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort). Combined ORs and 95% CIs were derived by using the random-effects methods. Effects are presented for increments of $10 \mu\text{g}/\text{m}^3$ (NO_2 and PM_{10}), $1 \times 10^{-5} \cdot \text{m}^{-1}$ ($\text{PM}_{2.5}$ absorbance), $5 \mu\text{g}/\text{m}^3$ ($\text{PM}_{2.5}$ and $\text{PM}_{10\text{coarse}}$), $20 \mu\text{g}/\text{m}^3$ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day $\cdot\text{m}$ (traffic load on all major roads in a 100-m buffer). LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age; all other cohorts: data at 4 years of age.

exposures at birth and current addresses for the same pollutant were variable ($r = 0.17$ - 0.87). Correlations between pollutants and traffic indicators were moderate or low.

Cohort-specific and combined associations between exposure to air pollution and IgE outcomes at 4 to 6 and 8 to 10 years are presented in Figs 3 and 4. Low-to-moderate heterogeneity between cohort-specific effect estimates was observed. We found positive but not statistically significant associations between exposure to air pollution and sensitization to any common food allergen, inhalant allergen, or both at 4 to 6 years of age for all studied pollutants except $\text{PM}_{2.5}$ absorbance. The combined adjusted ORs for air pollution exposures at birth ranged from 0.94 (95% CI, 0.63-1.40) for a $1 \times 10^{-5} \cdot \text{m}^{-1}$ increase in $\text{PM}_{2.5}$ absorbance to 1.26 (95% CI, 0.90-1.77) for a $5 \mu\text{g}/\text{m}^3$

increase in $\text{PM}_{2.5}$ exposure. For current exposure, the combined ORs were compatible with an absence of effect. Similarly, no clear evidence was found for a negative effect of either baseline or current air pollution exposure on the development of sensitization at 8 to 10 years of age (Fig 4). The results for inhalant and food allergens separately are presented in Table E4 in this article's Online Repository at www.jacionline.org. There was a general trend of higher risk estimates for food allergens, particularly at 8 to 10 years of age.

Tables III and IV summarize results from analyses with additional adjustment for an extended set of potential confounders and analyses stratified by child's sex and parental atopy, as well as sensitivity analyses on children who either changed or did not change their baseline residence.

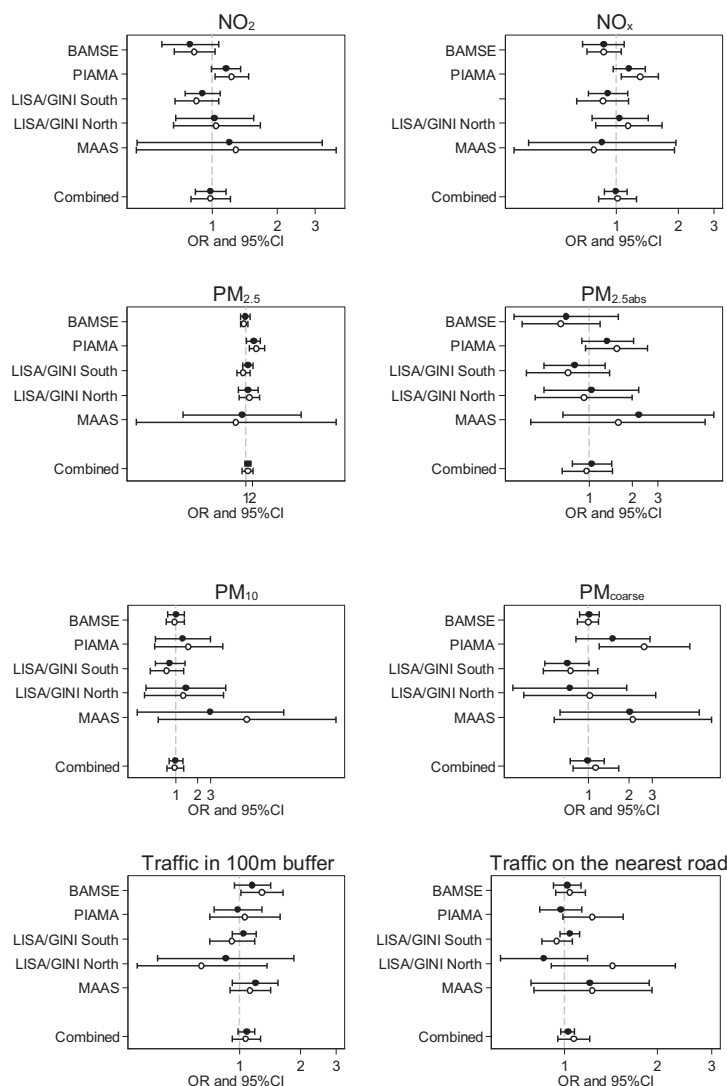


FIG 4. Meta-analyses of the associations between early-life or current air pollution exposure and sensitization to any common allergen at 8 years of age in 5 European birth cohorts. *Solid circles*, Birth address; *open circles*, current address. Cohort-specific ORs and 95% CIs were obtained by using logistic regression and are adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort). Combined ORs and 95% CIs were derived by using random-effects methods. Effects are presented for increments of $10 \mu\text{g}/\text{m}^3$ (NO_2 and PM_{10}), $1 \times 10^{-5} \cdot \text{m}^{-1}$ ($\text{PM}_{2.5}$ absorbance), $5 \mu\text{g}/\text{m}^3$ ($\text{PM}_{2.5}$ and $\text{PM}_{\text{coarse}}$), $20 \mu\text{g}/\text{m}^3$ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day*m (traffic load on all major roads in a 100-m buffer). LISA/GINI: data at 10 years of age; all other cohorts: data at 8 years of age.

First, extending the set of potential confounders, including birth weight and the study arm (where applicable), did not change the results of the main models.

Second, we computed summary estimates across sex and parental atopy strata. Although the results did not reveal clear differences between the sexes, somewhat stronger associations between air pollution exposure at birth and sensitization at 4 to 6 and 8 to 10 years of age were suggested among boys. Thus the risk estimates for the effects of a $5 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure at birth on sensitization at 8 to 10 years of age were an OR of 1.62 (95% CI, 1.05-2.50) for boys and an OR of 1.00 (95% CI, 0.63-1.58) for girls.

Third, the results of sensitivity analysis on children who did or did not move since birth also displayed some variation.

A tendency for higher risk was seen in subjects who did not change their address up to the age of 8 to 10 years, with an OR of 1.68 (95% CI, 1.03-2.75) among nonmovers and an OR of 1.02 (95% CI, 0.72-1.46) among movers for the increment of $1 \times 10^{-5} \cdot \text{m}^{-1}$ $\text{PM}_{2.5}$ absorbance exposure. Inclusion of interaction terms with child's sex, parental atopy, and moving status into the main models provided results similar to those from the stratified/sensitivity analyses. The combined interaction terms were all statistically nonsignificant (see [Tables E5 and E6](#) in this article's Online Repository at www.jacionline.org). Overall, the models did not appear sensitive to additional adjustment for area-level characteristics. Furthermore, no significant indication of area clustering in cohort-specific analyses was observed.

TABLE III. Meta-analyses of the associations between early-life or current air pollution exposure and sensitization to any common allergen at 4 years of age by child's sex, change of baseline residence, and parental atopy in 5 European birth cohorts

	Associations between exposure to traffic-related air pollution and parental atopy in European children						
	OR* (95% CI)	Moving status		Sex		Parental atopy	
		OR* (95% CI)		OR* (95% CI)		OR* (95% CI)	
		Movers	Nonmovers	Boys	Girls	Atopic	Nonatopic
Expanded model†							
Birth exposure							
NO ₂	1.06 (0.85-1.32)	0.95 (0.78-1.17)	1.05 (0.82-1.33)	1.12 (0.92-1.38)	0.96 (0.70-1.33)	1.14 (0.84-1.55)	0.98 (0.77-1.24)
NO _x	1.07 (0.88-1.29)	0.92 (0.75-1.12)	1.10 (0.90-1.34)	1.13 (0.95-1.34)	0.99 (0.72-1.37)	1.05 (0.83-1.32)	1.05 (0.85-1.31)
PM _{2.5}	1.26 (0.89-1.77)	1.56 (0.94-2.57)	1.11 (0.68-1.82)	1.51 (0.96-2.39)	1.05 (0.63-1.75)	1.42 (0.90-2.22)	1.12 (0.66-1.89)
PM _{2.5} absorbance	0.97 (0.65-1.45)	0.73 (0.45-1.18)	1.13 (0.71-1.78)	1.12 (0.73-1.70)	0.71 (0.41-1.21)	0.94 (0.56-1.58)	0.93 (0.52-1.65)
PM ₁₀	1.12 (0.80-1.57)	0.98 (0.68-1.40)	1.29 (0.93-1.78)	1.26 (0.93-1.72)	0.89 (0.62-1.29)	1.14 (0.81-1.61)	1.04 (0.75-1.44)
PM _{coarse}	1.14 (0.72-1.82)	0.97 (0.69-1.36)	1.05 (0.66-1.68)	1.13 (0.92-1.40)	1.10 (0.54-2.28)	1.20 (0.69-2.08)	1.03 (0.83-1.28)
Traffic intensity on nearest street	0.98 (0.93-1.03)	1.00 (0.93-1.07)	0.97 (0.89-1.06)	1.00 (0.94-1.06)	0.95 (0.85-1.05)	0.94 (0.87-1.01)	1.03 (0.95-1.11)
Traffic load within 100-m buffer	0.96 (0.86-1.06)	0.93 (0.80-1.08)	1.00 (0.85-1.17)	0.97 (0.85-1.10)	0.90 (0.69-1.18)	0.84 (0.72-0.99)	1.11 (0.95-1.30)
Current exposure at 4 y							
NO ₂	1.00 (0.82-1.23)	0.94 (0.75-1.19)	0.96 (0.76-1.20)	0.92 (0.73-1.15)	1.02 (0.84-1.25)	0.98 (0.77-1.25)	0.95 (0.77-1.18)
NO _x	1.07 (0.86-1.31)	1.01 (0.80-1.27)	1.02 (0.82-1.26)	0.94 (0.78-1.13)	1.12 (0.90-1.38)	1.02 (0.84-1.24)	1.10 (0.80-1.51)
PM _{2.5}	1.02 (0.72-1.44)	1.36 (0.77-2.39)	0.87 (0.57-1.34)	0.81 (0.52-1.26)	1.34 (0.81-2.23)	0.97 (0.61-1.56)	1.10 (0.59-2.05)
PM _{2.5} absorbance	0.90 (0.64-1.25)	0.77 (0.43-1.37)	0.85 (0.55-1.33)	0.72 (0.46-1.14)	1.01 (0.62-1.66)	0.76 (0.50-1.17)	0.97 (0.55-1.70)
PM ₁₀	1.02 (0.79-1.31)	0.97 (0.67-1.42)	1.05 (0.74-1.49)	0.90 (0.64-1.25)	1.17 (0.80-1.70)	1.01 (0.70-1.45)	1.02 (0.72-1.43)
PM _{coarse}	1.00 (0.70-1.43)	1.04 (0.80-1.35)	0.90 (0.63-1.29)	0.89 (0.71-1.12)	1.09 (0.69-1.72)	0.99 (0.61-1.58)	0.98 (0.78-1.23)
Traffic intensity on nearest street	0.98 (0.91-1.05)	0.99 (0.89-1.10)	0.99 (0.90-1.09)	0.98 (0.89-1.08)	0.98 (0.89-1.08)	0.97 (0.89-1.07)	0.97 (0.86-1.09)
Traffic load within 100-m buffer	0.97 (0.85-1.10)	0.89 (0.63-1.26)	0.99 (0.83-1.18)	0.94 (0.76-1.16)	0.96 (0.77-1.20)	0.83 (0.68-1.03)	1.06 (0.87-1.28)

*Combined ORs and 95% CIs were derived by using random-effects methods. Effects are presented for increments of 10 $\mu\text{g}/\text{m}^3$ (NO₂ and PM₁₀), $1 \times 10^{-5} \cdot \text{m}^{-1}$ (PM_{2.5} absorbance), 5 $\mu\text{g}/\text{m}^3$ (PM_{2.5} and PM_{coarse}), 20 $\mu\text{g}/\text{m}^3$ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day*m (traffic load on all major roads in a 100-m buffer). Results are adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort). LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age; all other cohorts: data at 4 years of age.

†Additionally adjusted for birth weight and study arm.

(data not shown). Repeating the analysis using the back-extrapolated NO_x, NO₂, and PM₁₀ concentrations did not alter the results (see Table E7 in this article's Online Repository at www.jacionline.org). Adjusting associations with current air pollution exposure (at 4-6 and 8-10 years of age) for covariates at baseline instead of at the time of the IgE measurements did not change the results (data not shown).

DISCUSSION

Our meta-analysis investigated the effect of air pollution exposure on the development of allergic sensitization to any common inhalant/food allergens in children followed from birth until 10 years of age. The combined results from the 5 birth cohort studies indicated that air pollution exposure was generally not associated with sensitization to common allergens. No consistent interaction with either sex, family history of allergic disease, or change of baseline address was found.

To our knowledge, the present study is the first to assess the effects of air pollution exposure on the development of allergic sensitization in children based on combined analyses of prospective birth cohort studies using a meta-analytic approach. Participation in the European collaborative ESCAPE project provided a unique opportunity to protocol, obtain, and use uniform exposure information at the individual level across all the included cohorts. The air pollution components under study have different origins and chemical and physical properties that might be of relevance for the health outcome under consideration. In addition, our analysis does not suffer from

some of the challenges associated with meta-analyses based on published literature (eg, publication bias).

The results indicate no overall association between exposure to the studied traffic-related air pollution components and allergic sensitization in children. Analogous conclusions have been reported in the Oslo cohort at a similar age.⁶ However, it should be noted that several of the cohorts included in our analysis have previously published cohort-specific data on allergic sensitization in relation to air pollution exposure, and these are not all consistent with the current results. This might partly be attributed to differences in the exposure assessment methodologies, as well as in analytic approaches. Thus the results from the Swedish BAMSE study suggested increased risks of sensitization both against food and pollen related to NO_x exposure during infancy but with slightly different patterns at 4 and 8 years of age.⁵ Air pollution exposure for the BAMSE cohort was assessed during different time periods by means of dispersion modeling. The Dutch cohort PIAMA reported associations between air pollution exposure to PM_{2.5}, soot, and NO₂ at birth addresses and specific sensitization to common food allergens at the age of 4 years but not at 8 years.^{4,9} Similarly, strong positive associations for any inhalant sensitization at 6 years of age in relation to PM_{2.5} and PM_{2.5} absorbance, as well as distance to the nearest main road, were found in the analysis in the LISA/GINI South cohort.⁷ In the latter 2 studies exposure to traffic-related air pollutants was estimated based on a combination of air pollution measurements in 1999-2000 and stochastic modeling procedures developed within the Traffic-related Air Pollution and Childhood Asthma project.^{20,21} Interestingly,

TABLE IV. Meta-analyses of the associations between early-life or current air pollution exposure and sensitization to any common allergen at 8 years of age by child's sex, change of baseline residence, and parental atopy in 5 European birth cohorts

	Moving status		Sex		Parental atopy		
	OR* (95% CI)	OR* (95% CI)		OR* (95% CI)			
	Expanded model†	Movers	Nonmovers	Boys	Girls	Atopic	Nonatopic
Birth exposure							
NO ₂	0.98 (0.82-1.17)	0.99 (0.86-1.14)	1.16 (0.97-1.40)	1.04 (0.84-1.29)	0.96 (0.82-1.13)	1.03 (0.85-1.26)	0.96 (0.69-1.34)
NO _x	0.99 (0.86-1.15)	0.97 (0.84-1.12)	1.17 (0.96-1.42)	1.02 (0.85-1.23)	0.98 (0.83-1.15)	1.01 (0.87-1.16)	1.05 (0.80-1.37)
PM _{2.5}	1.32 (0.92-1.91)	1.27 (0.85-1.89)	1.98 (0.77-5.07)	1.62 (1.05-2.50)	1.00 (0.63-1.58)	1.38 (0.90-2.13)	1.47 (0.64-3.36)
PM _{2.5} absorbance	1.07 (0.74-1.55)	1.02 (0.72-1.46)	1.68 (1.03-2.75)	1.20 (0.83-1.75)	0.90 (0.58-1.41)	1.04 (0.63-1.72)	1.21 (0.55-2.67)
PM ₁₀	1.01 (0.82-1.26)	0.94 (0.71-1.24)	1.41 (0.98-2.04)	1.05 (0.78-1.40)	1.00 (0.72-1.38)	1.07 (0.78-1.48)	0.97 (0.72-1.31)
PM _{coarse}	1.00 (0.73-1.35)	0.92 (0.69-1.24)	1.21 (0.92-1.59)	1.04 (0.71-1.53)	0.93 (0.74-1.16)	0.99 (0.63-1.56)	0.97 (0.80-1.18)
Traffic intensity on nearest street	1.03 (0.97-1.08)	1.03 (0.94-1.12)	1.03 (0.93-1.13)	1.03 (0.96-1.10)	1.02 (0.93-1.12)	1.02 (0.94-1.09)	1.03 (0.95-1.12)
Traffic load within 100-m buffer	1.08 (0.98-1.19)	1.11 (0.98-1.26)	1.11 (0.92-1.33)	1.09 (0.96-1.24)	1.06 (0.91-1.25)	1.02 (0.88-1.17)	1.16 (0.99-1.36)
Current exposure at 8 y							
NO ₂	1.00 (0.79-1.26)	0.94 (0.80-1.12)	1.07 (0.80-1.45)	1.08 (0.78-1.49)	0.92 (0.78-1.09)	1.00 (0.85-1.17)	1.08 (0.74-1.57)
NO _x	1.03 (0.81-1.31)	0.95 (0.73-1.24)	1.13 (0.85-1.49)	1.08 (0.77-1.49)	0.95 (0.80-1.14)	1.00 (0.85-1.18)	1.19 (0.80-1.78)
PM _{2.5}	1.31 (0.68-2.53)	0.90 (0.50-1.61)	2.06 (0.69-6.17)	1.63 (0.58-4.61)	1.02 (0.57-1.38)	1.24 (0.70-2.20)	1.48 (0.50-4.39)
PM _{2.5} absorbance	0.98 (0.63-1.50)	0.70 (0.41-1.21)	1.54 (0.74-3.19)	1.01 (0.45-2.26)	0.89 (0.57-1.38)	0.90 (0.60-1.34)	1.53 (0.53-4.37)
PM ₁₀	1.05 (0.73-1.50)	0.82 (0.38-1.77)	1.60 (0.77-3.32)	0.98 (0.63-1.52)	0.99 (0.49-2.00)	1.14 (0.80-1.64)	1.12 (0.55-2.27)
PM _{coarse}	1.17 (0.77-1.78)	1.00 (0.63-1.58)	1.25 (0.74-2.09)	1.36 (0.68-2.71)	1.10 (0.87-1.41)	1.10 (0.78-1.57)	1.45 (0.69-3.07)
Traffic intensity on nearest street	1.07 (0.95-1.20)	1.11 (0.97-1.27)	0.99 (0.88-1.11)	1.18 (0.95-1.45)	0.99 (0.90-1.09)	1.02 (0.91-1.14)	1.13 (0.91-1.39)
Traffic load within 100-m buffer	1.07 (0.90-1.27)	1.07 (0.72-1.59)	1.08 (0.88-1.33)	1.11 (0.89-1.39)	1.08 (0.82-1.43)	0.98 (0.76-1.25)	1.24 (0.96-1.60)

*Combined ORs and 95% CIs were derived by using random-effects methods. Effects are presented for increments of 10 $\mu\text{g}/\text{m}^3$ (NO₂ and PM₁₀), $1 \times 10^{-5} \cdot \text{m}^{-1}$ (PM_{2.5} absorbance), 5 $\mu\text{g}/\text{m}^3$ (PM_{2.5} and PM_{coarse}), 20 $\mu\text{g}/\text{m}^3$ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day*m (traffic load on all major roads in a 100-m buffer). Results are adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort). LISA/GINI: data at 10 years of age; all other cohorts: data at 8 years of age.

†Additionally adjusted for birth weight and study arm.

a recent study comparing LUR models used in an earlier project and ESCAPE LUR models revealed substantial improvement in the explained variance for some pollutants in certain areas (ie, 56% in Traffic-related Air Pollution and Childhood Asthma against 78% in ESCAPE for PM_{2.5} models in the Munich area and 17% to 88% in the Ruhr area).¹⁵ Although ESCAPE LUR models showed, on average, moderate-to-good explained variance, model performance varied between different areas, as well as between different pollutants (ie, the R^2 value for PM_{2.5} ranged from 35% in Manchester to 94% in Stockholm County). If early-life exposure, such as during infancy, plays an important role for the later development of sensitization, LUR models based on recent concentrations (ie, 2009 rather than 1994-1996) might not be optimal for estimating relevant exposure.

The prospective design provided a possibility for identifying potential critical time periods of susceptibility to air pollution. We assigned the exposure levels to the addresses registered at 3 different time points, including baseline addresses and those at which subjects lived at the time of clinical follow-up. The estimated air pollution level at the birth address can be considered a good proxy of early-life exposure, and it has been indicated that children tend to spend much of their time in the vicinity of their residences during infancy.^{5,6} However, for children who moved to another house, we considered only the current address at the time of clinical examination. This might have introduced some measurement error, leading to weakened associations, as shown by a tendency toward increased risks in children who never changed their residence since birth compared with those who moved. Alternatively, higher estimates

in nonmovers might also suggest that apart from early-life exposure, chronic exposure or exposure later in life might be of importance.

The issue of temporal relation between exposure and outcome deserves special consideration. In the current study air pollution modeling was based on data from the measurement campaign conducted during 2008-2009 in the framework of the ESCAPE project and thus after the outcome assessment. To account for the temporal changes, we have performed sensitivity analyses using extrapolated back in time-modeled NO_x, NO₂, and PM₁₀ concentrations; however, this did not change our main results. This is in line with the findings from the Dutch study showing that the correlation between air pollution concentrations during different years is high, even over a period of more than 10 years, largely because the major roads, which are most important for air pollution exposure, did not change.^{22,23} Similar conclusions were made in studies from Rome, Oslo, and Vancouver.²⁴⁻²⁶ However, the generalizability of these findings is uncertain because the stability of LUR models over time might be area specific.

Another potential limitation of the exposure assessment might be that air pollution concentrations were estimated only for home addresses without considering nurseries or schools, in which young children regularly spend part of their time. However, several earlier studies have found high correlations between estimated air pollution exposure estimated based on residential addresses only and those including other locations.^{5,27} To some extent, this might be explained by the fact that the majority of children attend day cares and schools near their homes. Furthermore, the modeled individual concentrations account only for outdoor air pollution and therefore

are not equivalent to personal exposure. Although misclassification of true individual exposure might affect our results, assessments of both exposure and disease were done independently from one another, making such potential bias likely nondifferential. However, we had no information on indoor allergen exposure or activity levels, and therefore we were unable to assess whether any of these biased our results.

Although different methodologies for IgE determination were used in the cohorts, all statistical analyses on relations to air pollution exposure were performed for each study separately and then combined in meta-analyses. Consequently, we do not think it is likely that the method of IgE determination would affect associations between air pollution and sensitization.

We have considered a number of potential confounders and modifiers through adjustment, stratification, and incorporation of appropriate interaction terms. Furthermore, in addition to the individual covariates, we also included area-level socioeconomic factors to account for possible contextual confounding. Still, the possibility of residual confounding cannot be ruled out. It should also be acknowledged that with 5 studies, power is limited to detect heterogeneity in results between the birth cohorts.

In conclusion, the results of this study based on the data from 5 birth cohorts did not provide clear evidence of an association between air pollution exposure and development of allergic sensitization in children up to 10 years of age.

We thank the families who participated in the included studies and the staff for their hard work and effort.

Key messages

- We studied the association between residential exposure to air pollution and allergic sensitization in combined analyses of 5 European birth cohorts with a standardized exposure assessment according to a common protocol.
- Our results do not provide clear evidence of an association between air pollution exposure and development of allergic sensitization in children up to 10 years of age.

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TABLE E1. Overview of the tested allergens in the five birth cohorts

Cohort	Test system	Tested allergens
BAMSE	ImmunoCAP System, Phadia AB, Uppsala, Sweden (Phadiatop/fx5)	Inhalant allergens: ● Outdoor: birch, timothy, mugwort ● Indoor: cat, dog, mold [<i>Cladosporium herbarum</i>], house dust mite [<i>Dermatophagoides pteronyssinus</i>] Food allergens: cow's milk, egg white, soy bean, peanut, codfish, wheat
PIAMA	RAST-like method used at Sanquin Laboratories (Amsterdam, The Netherlands)	Inhalant allergens: ● Outdoor: birch, <i>Dactylis glomerata</i> ● Indoor: cat, dog, <i>Alternaria alternata</i>, house dust mite [<i>Dermatophagoides pteronyssinus</i>] Food allergens: egg, milk
LISA/GINI South	CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany): SX1/FX1	Inhalant allergens: ● Outdoor: birch, timothy, mugwort ● Indoor: cat, dog, mold [<i>Cladosporium herbarum</i>], house dust mite [<i>Dermatophagoides pteronyssinus</i>] Food allergens: cow's milk, egg white, soy bean, peanut, codfish, rye, wheat
LISA/GINI North	CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany): SX1/FX1	Inhalant allergens: ● Outdoor: birch, timothy, mugwort ● Indoor: cat, dog, mold [<i>Cladosporium herbarum</i>], house dust mite [<i>Dermatophagoides pteronyssinus</i>] Food allergens: cow's milk, egg white, soy bean, peanut, codfish, rye, wheat
MAAS	ImmunoCAP System (Phadia AB, Uppsala, Sweden)	Inhalant allergens: ● Outdoor: Gx1 mixed grass ● Indoor: cat, dog, house dust mite Food allergens: egg, milk, peanut

TABLE E2. Description of 5 European birth cohorts included in the meta-analysis of allergic sensitization in children related to air pollution exposure

Study	Recruitment	Follow-up	At baseline	No. of subjects	
				Blood test for specific serum IgE	
				4-6 y,* no. (%)	8-10 y,† no. (%)
BAMSE, Stockholm, Sweden	1994-1996	1994-2008	4089	2604 (63)	2447 (60)
PIAMA, nationwide, The Netherlands	1996-1997	1997-2005	3963	747 (19)	1713 (43)
LISA/GINI South, Munich, Germany	1997-1999/1995-1998	1995-2006	4414	1670 (38)	1582 (36)
LISA/GINI North, Wesel, Germany	1998-1999/1995-1998	1996-2009	3390	1004 (30)	872 (26)
MAAS, Manchester, United Kingdom	1995-1997	1996-2009	1185	484 (41)	468 (39)
Total				6509	7082

*LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age; all other cohorts: data at 4 years of age.

†LISA/GINI: data at 10 years of age; all other cohorts: data at 8 years of age.

TABLE E3. Distribution of estimated annual average concentrations of air pollutants at current address at 4 and 8 years of age in 5 European birth cohorts

	4 y*						8 y†					
	Minimum	25th percentile	50th percentile	Mean	75th percentile	Maximum	Minimum	25th percentile	50th percentile	Mean	75th percentile	Maximum
BAMSE												
NO ₂ (μg/m ³)	6.0	8.4	10.5	12.3	14.3	32.9	6.0	8.2	9.9	11.9	13.6	30.5
NO _x (μg/m ³)	11.8	13.5	17.2	21.9	26.9	84.3	11.8	13.3	16.2	21.0	24.0	74.1
PM _{2.5} (μg/m ³)	4.2	6.5	7.7	7.5	8.4	11.0	4.2	6.4	7.6	7.4	8.3	11.0
PM _{2.5} absorbance (10 ⁻⁵ • m ⁻¹)	0.4	0.5	0.6	0.6	0.7	1.3	0.4	0.5	0.6	0.6	0.7	1.2
PM ₁₀ (μg/m ³)	6.0	13.3	15.5	15.4	16.6	30.9	6.0	13.4	15.6	15.3	16.6	30.9
PM _{coarse} (μg/m ³)	0.7	6.1	7.6	7.7	8.4	20.2	0.7	6.1	7.7	7.6	8.4	20.2
PIAMA												
NO ₂ (μg/m ³)	9.4	18.3	22.7	22.7	26.9	55.3	9.2	18.1	22.4	22.2	26.0	53.5
NO _x (μg/m ³)	17.0	26.4	32.4	33.6	37.8	88.1	16.5	26.1	31.7	32.4	36.3	94.3
PM _{2.5} (μg/m ³)	15.3	15.6	16.5	16.4	16.8	20.7	14.9	15.8	16.5	16.4	16.8	20.7
PM _{2.5} absorbance (10 ⁻⁵ • m ⁻¹)	0.8	1.1	1.2	1.2	1.3	2.8	0.8	1.1	1.2	1.2	1.3	2.2
PM ₁₀ (μg/m ³)	23.7	24.0	24.6	24.9	25.2	31.3	23.7	24.0	24.5	24.8	25.1	30.5
PM _{coarse} (μg/m ³)	7.6	7.8	8.0	8.3	8.6	14.0	7.6	7.8	8.0	8.2	8.4	11.4
LISA/GINI South												
NO ₂ (μg/m ³)	11.5	16.2	19.1	20.1	23.1	58.9	11.5	15.8	18.7	19.7	22.4	55.7
NO _x (μg/m ³)	19.7	27.7	32.2	33.7	38.1	114.9	19.7	27.4	31.6	33.1	37.6	110.0
PM _{2.5} (μg/m ³)	10.7	12.8	13.2	13.3	13.8	18.8	10.7	12.8	13.2	13.3	13.8	18.8
PM _{2.5} absorbance (10 ⁻⁵ • m ⁻¹)	1.3	1.5	1.6	1.7	1.7	3.4	1.3	1.5	1.6	1.6	1.7	3.4
PM ₁₀ (μg/m ³)	14.8	18.5	20.4	20.0	21.4	30.2	14.8	18.5	20.4	20.0	21.4	30.2
PM _{coarse} (μg/m ³)	4.1	5.5	6.1	6.4	17.1	13.5	4.1	5.4	6.1	6.3	17.0	13.5
LISA/GINI North												
NO ₂ (μg/m ³)	19.7	21.8	23.1	23.3	24.5	59.8	19.7	21.8	23.2	23.7	25.1	59.8
NO _x (μg/m ³)	23.9	29.3	33.0	33.4	36.5	100.3	23.9	29.6	33.2	34.5	37.9	100.3
PM _{2.5} (μg/m ³)	15.8	16.9	17.2	17.3	17.8	21.4	15.8	16.9	17.3	17.4	17.8	21.4
PM _{2.5} absorbance (10 ⁻⁵ • m ⁻¹)	1.0	1.1	1.1	1.2	1.3	3.4	1.0	1.1	1.2	1.2	1.3	3.4
PM ₁₀ (μg/m ³)	23.9	24.5	25.1	25.3	25.9	31.4	23.9	24.5	25.2	25.4	26.0	31.4
PM _{coarse} (μg/m ³)	1.9	8.1	8.4	8.5	8.7	13.8	1.9	8.1	8.4	8.4	8.7	13.8
MAAS												
NO ₂ (μg/m ³)	16.9	21.5	22.9	22.8	23.9	29.1	16.0	21.3	22.8	22.6	23.8	28.8
NO _x (μg/m ³)	26.1	36.0	38.6	38.9	40.9	77.8	26.4	35.2	38.3	38.6	41.0	77.8
PM _{2.5} (μg/m ³)	9.4	9.4	9.4	9.4	9.4	10.8	9.4	9.4	9.4	9.4	9.4	10.2
PM _{2.5} absorbance (10 ⁻⁵ • m ⁻¹)	0.7	1.0	1.1	1.1	1.2	1.7	0.8	1.0	1.1	1.1	1.2	1.7
PM ₁₀ (μg/m ³)	14.7	17.0	17.0	17.1	17.1	22.3	14.8	16.9	17.0	17.1	17.1	22.3
PM _{coarse} (μg/m ³)	5.0	6.6	6.9	7.0	7.3	11.3	5.1	6.6	6.9	7.0	7.2	11.3

Data include subjects for whom the estimated exposures were available at respective ages.

*LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age; all other cohorts: data at 4 years of age.

†LISA/GINI: data at 10 years of age; all other cohorts: data at 8 years of age.

TABLE E4. Meta-analyses of the associations between early-life or current air pollution exposure and sensitization to inhalant and food allergens at 4 and 8 years of age in 5 European birth cohorts

	4 y						8 y					
	Inhalant allergens			Food allergens			Inhalant allergens			Food allergens		
	OR* (95% CI)	I ²	P _{het}	OR* (95% CI)	I ²	P _{het}	OR* (95% CI)	I ²	P _{het}	OR* (95% CI)	I ²	P _{het}
Birth exposure												
NO ₂	1.01 (0.79-1.29)	52.6	.08	1.08 (0.91-1.27)	4.0	.38	0.98 (0.78-1.23)	63.8	.03	1.09 (0.88-1.34)	43.0	.14
NO _x	0.99 (0.81-1.20)	40.3	.15	1.09 (0.93-1.28)	0.0	.45	0.94 (0.78-1.13)	51.4	.08	1.10 (0.89-1.35)	48.1	.10
PM _{2.5}	1.14 (0.78-1.66)	0.0	.41	1.30 (0.85-1.99)	0.0	.43	1.18 (0.85-1.65)	0.0	.42	1.34 (0.74-2.44)	45.0	.12
PM _{2.5} absorbance	0.82 (0.52-1.31)	36.0	.18	1.17 (0.79-1.73)	0.0	.67	0.92 (0.60-1.42)	45.2	.12	1.36 (0.83-2.22)	43.5	.13
PM ₁₀	1.01 (0.72-1.43)	15.4	.32	1.13 (0.84-1.50)	0.0	.42	0.88 (0.70-1.12)	0.0	.60	1.42 (0.82-2.48)	54.2	.07
PM _{coarse}	1.05 (0.61-1.81)	73.2	.01	1.06 (0.78-1.45)	19.6	.29	0.90 (0.62-1.30)	59.1	.04	1.21 (0.88-1.68)	35.9	.18
Traffic intensity on nearest street	0.95 (0.90-1.01)	0.0	.94	1.01 (0.95-1.08)	0.0	.63	0.98 (0.92-1.03)	0.0	.72	1.06 (1.00-1.12)	0.0	.82
Traffic load within 100-m buffer	0.94 (0.83-1.06)	0.8	.40	0.98 (0.86-1.12)	0.0	.94	1.01 (0.91-1.11)	0.0	.77	1.15 (1.03-1.27)	0.0	.85
Current exposure												
NO ₂	0.92 (0.74-1.16)	43.4	.13	1.03 (0.84-1.26)	24.6	.26	0.96 (0.74-1.25)	70.3	.01	1.12 (0.88-1.42)	51.9	.08
NO _x	0.94 (0.76-1.17)	40.1	.15	1.09 (0.88-1.34)	25.4	.25	0.95 (0.74-1.23)	67.0	.02	1.14 (0.91-1.42)	44.9	.12
PM _{2.5}	0.87 (0.56-1.35)	14.4	.32	1.12 (0.66-1.90)	18.8	.30	1.20 (0.63-2.29)	60.4	.04	1.09 (0.46-2.59)	66.3	.02
PM _{2.5} absorbance	0.69 (0.48-1.00)	0.0	.56	0.96 (0.59-1.57)	19.2	.29	0.85 (0.52-1.40)	52.0	.08	1.13 (0.56-2.28)	63.6	.03
PM ₁₀	0.94 (0.70-1.25)	0.0	.77	1.04 (0.75-1.45)	2.5	.39	0.89 (0.66-1.21)	8.5	.36	1.40 (0.58-3.36)	75.9	.002
PM _{coarse}	0.91 (0.59-1.43)	51.6	.08	0.99 (0.81-1.22)	0.0	.68	1.10 (0.68-1.76)	63.2	.03	1.44 (0.79-2.64)	69.7	.01
Traffic intensity on nearest street	0.95 (0.87-1.03)	0.0	.10	1.00 (0.92-1.08)	0.0	.90	1.08 (0.94-1.24)	19.3	.10	1.05 (0.96-1.14)	0.0	.50
Traffic load within 100-m buffer	0.98 (0.85-1.12)	0.0	.45	0.96 (0.81-1.13)	0.0	.68	1.08 (0.92-1.27)	48.9	.29	1.14 (0.96-1.36)	9.3	.35

P_{het}, P value for heterogeneity.

*Combined ORs and 95% CIs were derived by using random-effects methods. Effects are presented for increments of 10 µg/m³ (NO₂ and PM₁₀), 1 × 10⁻⁵ · m⁻¹ (PM_{2.5} absorbance), 5 µg/m³ (PM_{2.5} and PM_{coarse}), 20 µg/m³ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day·m (traffic load on all major roads in a 100-m buffer). Results are adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort).

TABLE E5. Combined interaction terms with air pollutants and child's sex, change of baseline residence, and parental atopy included in the analyses of associations between air pollution exposure and sensitization to any common allergen at age 4 years in 5 European birth cohorts

	Interaction terms					
	Moving status		Sex		Parental atopy	
	OR* (95% CI)	P value	OR* (95% CI)	P value	OR* (95% CI)	P value
Birth exposure						
NO ₂	1.05 (0.93-1.18)	.461	1.20 (0.96-1.50)	.117	1.17 (0.89-1.54)	.270
NO _x	1.02 (0.88-1.18)	.796	1.19 (0.96-1.48)	.122	1.09 (0.86-1.38)	.270
PM _{2.5}	1.06 (0.97-1.16)	.227	1.38 (0.77-2.46)	.283	1.45 (0.77-2.73)	.247
PM _{2.5} absorbance	1.11 (0.87-1.42)	.388	1.62 (0.93-2.84)	.090	1.26 (0.64-2.48)	.514
PM ₁₀	0.95 (0.72-1.27)	.739	1.36 (0.88-2.09)	.164	1.43 (0.90-2.28)	.126
PM _{coarse}	1.07 (0.92-1.26)	.379	1.21 (0.91-1.63)	.186	1.25 (0.92-1.69)	.160
Traffic intensity on nearest street	1.04 (0.92-1.17)	.565	1.07 (0.95-1.21)	.265	0.91 (0.82-1.02)	.116
Traffic load within 100-m buffer	1.00 (0.78-1.29)	.973	1.22 (0.94-1.58)	.131	0.81 (0.64-1.03)	.087
Current exposure at 4 y						
NO ₂	1.05 (0.93-1.18)	.460	0.93 (0.73-1.19)	.546	1.08 (0.79-1.47)	.637
NO _x	1.06 (0.91-1.23)	.476	0.89 (0.69-1.14)	.348	1.03 (0.74-1.42)	.875
PM _{2.5}	1.04 (0.95-1.14)	.388	0.72 (0.39-1.33)	.298	1.10 (0.58-2.11)	.765
PM _{2.5} absorbance	1.10 (0.86-1.42)	.439	0.80 (0.43-1.51)	.495	0.79 (0.32-1.92)	.597
PM ₁₀	1.04 (0.92-1.18)	.523	0.82 (0.51-1.31)	.398	1.14 (0.69-1.88)	.619
PM _{coarse}	1.09 (0.92-1.28)	.319	0.87 (0.63-1.20)	.392	1.15 (0.82-1.62)	.420
Traffic intensity on nearest street	1.05 (0.91-1.22)	.484	0.98 (0.86-1.13)	.795	1.05 (0.90-1.23)	.508
Traffic load within 100-m buffer	1.01 (0.67-1.51)	.971	0.96 (0.73-1.27)	.797	0.82 (0.63-1.08)	.152

*Combined ORs and 95% CIs were derived by using random-effects methods adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort). Effects are presented for increments of 10 µg/m³ (NO₂ and PM₁₀), 1 × 10⁻⁵ · m⁻¹ (PM_{2.5} absorbance), 5 µg/m³ (PM_{2.5} and PM_{coarse}), 20 µg/m³ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day·m (traffic load on all major roads in a 100-m buffer). LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age; all other cohorts: data at 4 years of age.

TABLE E6. Combined interaction terms with air pollutants and child's sex, change of baseline residence, and parental atopy included in the analyses of the associations between air pollution exposure and sensitization to any common allergen at 8 years of age in 5 European birth cohorts

	Interaction terms					
	Moving status		Sex		Parental atopy	
	OR* (95% CI)	P value	OR* (95% CI)	P value	OR* (95% CI)	P value
Birth exposure						
NO ₂	0.98 (0.88-1.09)	.686	1.11 (0.92-1.33)	.290	1.07 (0.78-1.47)	.692
NO _x	0.95 (0.83-1.09)	.450	1.08 (0.90-1.31)	.408	0.97 (0.74-1.28)	.842
PM _{2.5}	0.99 (0.77-1.26)	.932	1.58 (0.92-2.69)	.096	0.88 (0.32-2.43)	.811
PM _{2.5} absorbance	0.96 (0.76-1.21)	.713	1.32 (0.81-2.16)	.261	0.81 (0.33-1.99)	.638
PM ₁₀	0.98 (0.87-1.11)	.757	1.12 (0.75-1.66)	.594	1.29 (0.84-1.97)	.238
PM _{coarse}	0.96 (0.82-1.11)	.560	1.15 (0.88-1.50)	.309	1.20 (0.90-1.59)	.209
Traffic intensity on nearest street	0.99 (0.85-1.15)	.914	1.00 (0.90-1.13)	.945	0.97 (0.84-1.13)	.719
Traffic load within 100-m buffer	1.03 (0.80-1.32)	.815	1.10 (0.90-1.35)	.351	0.90 (0.66-1.24)	.526
Current exposure at 8 y						
NO ₂	0.96 (0.85-1.08)	.453	1.17 (0.93-1.46)	.191	0.96 (0.73-1.26)	.741
NO _x	0.93 (0.76-1.15)	.504	1.14 (0.90-1.44)	.286	0.97 (0.62-1.21)	.405
PM _{2.5}	0.82 (0.46-1.45)	.493	1.47 (0.61-3.53)	.391	0.98 (0.38-2.54)	.971
PM _{2.5} absorbance	0.80 (0.50-1.26)	.328	1.28 (0.56-2.93)	.552	0.59 (0.21-1.65)	.313
PM ₁₀	0.86 (0.52-1.42)	.566	1.27 (0.50-3.24)	.616	1.26 (0.68-2.31)	.464
PM _{coarse}	0.98 (0.83-1.16)	.833	1.30 (0.62-2.70)	.487	1.18 (0.82-1.70)	.379
Traffic intensity on nearest street	1.11 (0.95-1.29)	.177	1.07 (0.92-1.25)	.362	0.97 (0.80-1.18)	.751
Traffic load within 100-m buffer	0.97 (0.63-1.48)	.869	0.98 (0.71-1.34)	.887	0.79 (0.51-1.21)	.275

*Combined ORs and 95% CIs were derived by using random-effects methods adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort). Effects are presented for increments of 10 µg/m³ (NO₂ and PM₁₀), $1 \times 10^{-5} \cdot \text{m}^{-1}$ (PM_{2.5} absorbance), 5 µg/m³ (PM_{2.5} and PM_{coarse}), 20 µg/m³ (NO_x), 5,000 vehicles/day (traffic intensity on the nearest street), and 4,000,000 vehicles/day*m (traffic load on all major roads in a 100-m buffer). LISA/GINI: data at 10 years of age; all other cohorts: data at 8 years of age.

TABLE E7. Meta-analyses of the associations between back-extrapolated early-life air pollution exposure and sensitization to any common allergens at 4 and 8 years of age in 5 European birth cohorts

	Main model		Back-extrapolated exposure			
			Ratio method		Difference method	
	OR*	95% CI	OR*	95% CI	OR*	95% CI
4 y [†]						
NO ₂	1.07	0.86-1.34	1.05	0.91-1.21	1.06	0.89-1.27
NO _x	1.06	0.88-1.28	1.04	0.93-1.16	1.05	0.89-1.23
PM ₁₀	1.08	0.86-1.37	1.04	0.86-1.24	1.04	0.84-1.29
8 y [‡]						
NO ₂	0.99	0.84-1.16	0.99	0.86-1.14	0.99	0.82-1.18
NO _x	1.00	0.88-1.13	1.00	0.92-1.10	1.01	0.89-1.14
PM ₁₀	1.01	0.81-1.26	1.00	0.85-1.18	0.99	0.81-1.20

*Combined ORs and 95% CI were derived by using random-effects methods. Effects are presented for increments of 10 µg/m³ (NO₂ and PM₁₀) and 20 µg/m³ (NO_x). Results are adjusted for sex, age at review, maternal smoking during pregnancy, anyone smoking at child's home, breast-feeding, atopic parents, parental education, mold at home, furred pets at home, older siblings, gas cooking, and region (the latter only for the BAMSE cohort).

[†]LISA/GINI: data at 6 years of age; MAAS: data at 5 years of age; all other cohorts: data at 4 years of age.

[‡]LISA/GINI: data at 10 years of age; all other cohorts: data at 8 years of age.