Traffic-related Air Pollution and the Development of Asthma and Allergies during the First 8 Years of Life

Ulrike Gehring[1], Alet H. Wijga[2], Michael Brauer[3], Paul Fischer[4], Johan C. de Jongste[5], Marjan Kerkhof[6], Marieke Oldenwening[1], Henriette A. Smit[2,7], and Bert Brunekreef[1,7]

[1]Institute for Risk Assessment Sciences, Utrecht University, Utrecht; and [2]Center for Prevention and Health Services Research, National Institute of Public Health and the Environment, Bilthoven, The Netherlands; [3]School of Environmental Health, University of British Columbia, Vancouver, British Columbia, Canada; and [4]Center for Environmental Health Research, National Institute for Public Health and the Environment, Bilthoven; [5]Department of Pediatrics, Division of Respiratory Medicine, Erasmus University Medical Center/Sophia Children's Hospital, Rotterdam; [6]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen; and [7]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Rationale: **The role of air pollution exposure in the development of asthma, allergies, and related symptoms remains unclear, due in part to the limited number of prospective cohort studies with sufficiently long follow-ups addressing this problem.**

Objectives: **We studied the association between traffic-related air pollution and the development of asthma, allergy, and related symptoms in a prospective birth cohort study with a unique 8-year follow-up.**

Methods: **Annual questionnaire reports of asthma, hay fever, and related symptoms during the first 8 years of life were analyzed for 3,863 children. At age 8, measurements of allergic sensitization and bronchial hyperresponsiveness were performed for subpopulations (n = 1,700 and 936, respectively). Individual exposures to nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}$), and soot at the birth address were estimated by land-use regression models. Associations between exposure to traffic-related air pollution and repeated measures of health outcomes were assessed by repeated-measures logistic regression analysis. Effects are presented for an interquartile range increase in exposure after adjusting for covariates.**

Measurements and Main Results: **Annual prevalence was 3 to 6% for asthma and 12 to 23% for asthma symptoms. Annual incidence of asthma was 6% at age 1, and 1 to 2% at later ages. $PM_{2.5}$ levels were associated with a significant increase in incidence of asthma (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.10–1.49), prevalence of asthma (OR, 1.26; 95% CI, 1.04–1.51), and prevalence of asthma symptoms (OR, 1.15; 95% CI, 1.02–1.28). Findings were similar for NO_2 and soot. Associations were stronger for children who had not moved since birth. Positive associations with hay fever were found in nonmovers only. No associations were found with atopic eczema, allergic sensitization, and bronchial hyperresponsiveness.**

Conclusions: **Exposure to traffic-related air pollution may cause asthma in children.**

Keywords: asthma; allergy; air pollution; cohort; traffic

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Exposure to ambient air pollution can exacerbate existing asthma. The role of exposure to ambient air pollution in the development of childhood asthma, allergy, and related symptoms, however, remains less clear due in part to the limited number of prospective birth cohort studies.

What This Study Adds to the Field

In this prospective birth cohort study, we found positive associations between traffic-related air pollution levels outside subjects' homes, and the incidence and prevalence of asthma during the first 8 years of life. Our results provide evidence that air pollution exposure may contribute to the pathogenesis of asthma in children.

Exposure to ambient air pollution can exacerbate existing asthma (1, 2). The role of exposure to ambient air pollution in the development of childhood asthma, allergy, and related symptoms, however, remains less clear (3–5) due in part to the limited number of prospective birth cohort studies addressing this problem. Studies, especially those with a focus on exposure contrasts within urban areas related to traffic, have begun to report rather consistent associations with development of asthma and asthmatic symptoms (6–10). Three European birth cohorts have so far monitored children until the age of 4 to 6 years. Results suggest positive associations with respiratory infections, allergic sensitization, symptoms of asthma, and physician-diagnosed asthma (6–8) Analyses within these studies have been cross-sectional, that is, symptoms of disease at the end of follow-up were analyzed in relation to exposure in early life. Positive associations between reports of wheeze during the first year of life and exposure to traffic-related pollutants have also been reported from a Danish birth cohort study (11). During the second and third years of life, however, the associations became less strong. Evidence of an association between air pollution and asthma initiation in older children comes from the Californian Children's Health Study (9) and a cohort study from Japan (12). In the Children's Health Study, participants exercising in communities with high levels of ozone were more likely to develop asthma (9), and residential NO_2 levels were associated with lifetime history of doctor-diagnosed asthma in a random sample of the participants (13). In the cohort study from Japan, NO_2 levels were positively associated with asthma incidence (12).

The prevalence of respiratory symptoms changes rapidly during childhood, and only a minority of children with reports of symptoms in early childhood develop asthma at school age

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Correspondence and requests for reprints should be addressed to Ulrike Gehring, Ph.D., Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80178, 3508 TD Utrecht, The Netherlands. E-mail: u.gehring@uu.nl

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(14, 15). It is therefore important to study the incidence of asthma over a sufficiently long period of time in relation to air pollution exposure, and this has not been done so far in the context of birth cohort studies.

The 8-year follow-up of the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study (16) has been completed. The follow-up is unique because of its length and the availability of annual standardized questionnaires on the respiratory health of the children and its determinants. Moreover, at the age of 8 years, a more reliable diagnosis of asthma and allergies is possible. This gives us the unique opportunity to study the association between traffic-related air pollution and the development of asthma, allergy, and related symptoms longitudinally over an 8-year period. In addition, objective measures such as allergen-specific IgE and bronchial hyperresponsiveness at age 8 are available for a subset of the population. Some of the results of this study have been previously published in the form of an abstract (17).

METHODS

Study Population

The PIAMA Study is a prospective birth cohort study (16). Women were recruited in 1996–1997 during their second trimester of pregnancy from a series of communities in the north, west, and center of The Netherlands. Nonallergic pregnant women were invited to participate in a "natural history" study arm. Pregnant women identified as allergic through the screening questionnaire were allocated primarily to an intervention arm with a random subset allocated to the natural history arm. The intervention involved the use of mite-impermeable mattress and pillow covers. The institutional review boards of the participating institutes approved the study protocol, and written informed consent was obtained from all participants.

Exposure Assessment

Air pollution concentrations at the birth address of each participant were estimated by land-use regression models described elsewhere (18). Briefly, four 2-week measurements of NO_2, fine particles ($PM_{2.5}$, particulate matter less than 2.5 μm in diameter), and "soot" (determined as the reflectance of the $PM_{2.5}$ filters) were performed at each of 40 sites within 1 year and then adjusted for temporal trends to calculate long-term average concentrations. Geographic information system (GIS) data were also collected regarding traffic, road, and population density in the vicinity of each monitoring location. Regression models were developed to relate the annual average concentrations measured at the 40 monitoring sites with the GIS variables. The models explained 73, 81, and 85% of the variability in the annual average concentrations for $PM_{2.5}$, soot, and NO_2, respectively. These models were then used to obtain a unique ambient air pollution concentration estimate at the birth address of each participant. More information about the regression models is provided in the online supplement.

Health Outcomes

Information about respiratory health and atopic eczema was obtained in yearly questionnaires that were completed by the parents approximately at the time of the child's birthday until the age of 8 years. From these questionnaires, the same health outcomes as in previous analyses (6, 19) were selected to describe asthma, allergies, and related symptoms. The exact definitions of the health outcomes studied are given in the online supplement.

At age 8 years, a blood sample was taken from all children who gave consent. Specific IgE levels for house dust mite, cat, dog, cocksfoot (*Dactylis glomerata*) and birch pollen, *Alternaria alternata*, egg, and milk were measured in blood samples by a radioallergosorbent test-like method used at the Sanquin Laboratories (Amsterdam, The Netherlands). Sensitization was defined as a positive reaction (IgE level $\geq$0.35 IU/ml) to one of the allergens tested.

At age 8 years, all children of allergic mothers and a random sample of children of nonallergic mothers were invited for a medical examination including determination of bronchial hyperresponsiveness (BHR). BHR was defined as a decrease in FEV_1 of 20% or more at a cumulative dose of methacholine bromide not exceeding 0.61 mg. More details are provided in the online supplement.

Confounding Variables

A series of potential confounding variables including sex, study arm (intervention or natural history), use of mite-impermeable mattress covers, allergies of mother and father, maternal and paternal education, maternal smoking during pregnancy, breastfeeding, presence of a gas stove in the child's home, presence of older siblings, smoking, signs of dampness and pets in the child's home, day-care attendance, and Dutch nationality were selected as in previous analyses (6, 19). High parental education was defined as having at least completed high school. Smoking was defined as any smoking at the child's home assessed by validated questionnaires completed by the parents. Confounders were defined for the first year of life to coincide as much as possible with air pollution exposure, which was estimated for addresses at birth.

Statistical Analysis

Longitudinal associations between air pollution levels at the birth address and yearly questionnaire reports of binary health outcomes at ages 1 to 8 years were analyzed by generalized estimation equations (GEE) with a logit link (20). A seven-dependent correlation matrix was chosen to account for correlations between repeated observations in the same individual at the eight different points in time. For outcomes measured at six points in time, a five-dependent matrix was chosen. Associations between air pollution and categorical outcomes that were assessed at age 8 years only were analyzed by standard logistic regression (outcomes with two categories) and polytomous logistic regression (21) (outcomes with more than two categories), respectively. Air pollution levels were entered as continuous variables without transformation in all models. All associations were calculated with and without adjustment for confounding variables. All odds ratios are presented for an interquartile range increase in estimated exposures (10.4 $\mu g \cdot m^{-3}$ for NO_2, 3.2 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, and 0.57×10^{-5} m^{-1} for soot).

Moving houses during the follow-up might have resulted in measurement error. We therefore included interaction terms between air pollution levels and moving status in the models to estimate associations between air pollution and outcomes for children who did and did not move separately.

RESULTS

General Characteristics

The study started with 3,963 newborns. For a total of 3,874 (97.8%) of these children, the parents returned at least one of the yearly questionnaires at ages 1 to 8 years. Response was high at all ages (Figure E1 in the online supplement). After exclusion of children with missing information about air pollution levels (n = 9) and all health outcomes studied (n = 2), 3,863 children remained for the final analysis. Measurements of allergen-specific IgE and BHR were available for 1,700 and 936 children, respectively. General characteristics of all children are presented in Table 1; general characteristics of the subsets of children with measurements of specific IgE and BHR are presented in Table E1 in the online supplement. By design, participants in the intervention study were overrepresented among the children with measurements of BHR and consequently the percentage of children with allergic mothers was higher in this subpopulation. In the subset of children with measurements of specific IgE, because of selective participation the proportion of children with allergic mothers was also somewhat higher than in the larger population. In addition, in both subsets the percentage of children with highly educated parents, the percentage of children who were breastfed at 3 months, and the percentage of Dutch children were somewhat higher than in the large study population; maternal smoking

TABLE 1. DESCRIPTION OF THE STUDY POPULATION

Variable	n/N	%
General Characteristics		
Female sex	1,864/3,863	48.3
Study region		
North	1,208/3,863	31.3
Middle	1,561/3,863	40.4
West	1,094/3,863	28.3
Study arm		
Natural history study	3,128/3,863	81.0
Intervention, mite impermeable mattress cover	382/3,863	9.9
Intervention, placebo mattress cover	353/3,863	9.1
Allergic mother	1,183/3,865	30.6
Allergic father	1,175/3,853	30.5
Mother's education, % high	1,328/3,796	35.0
Father's education, % high	1,491/3,752	39.7
Mother smoking during pregnancy	664/3,809	17.4
Breastfeeding at 3 mo	1,857/3,807	48.8
Gas stove*	3,158/3,821	82.6
Unvented gas water heater	152/3,509	4.3
Any other siblings (at birth)	1,942/3,861	50.3
Any smoking at home*	1,026/3,725	27.5
Signs of dampness in living room/child's bedroom*	310/3,688	8.4
Any pets in home*	1,886/3,793	49.7
Day-care attendance $\geq$ 4 h/wk*	896/3,725	24.1
Dutch nationality	3,479/3,691	94.3
Did not move house during first 8 yr of life	1,851/3,857	48.0
Health Outcomes at Age 8 years		
Wheeze phenotype		
Never	1,758/3,016	58.3
Early transient	811/3,016	26.9
Late onset	122/3,016	4.0
Persistent	325/3,016	10.8
Bronchial hyperresponsiveness	400/936	42.7
Allergic sensitization		
Any allergen positive	693/1,700	40.8
Inhalant allergens only	406/1,698	23.9
Food allergens only	144/1,698	8.5
Inhalant and food allergens	141/1,698	8.3
Atopic asthma	54/1,591	3.4
Nonatopic asthma	13/1,591	0.8

Study population (N) = 3,863.
* During the child's first year of life.

during pregnancy, smoking at the child's home, and pet ownership were less prevalent than in the large population.

Distribution of Health Outcomes

The percentage of children with questionnaire-based health outcomes that have been assessed annually are presented in Figure 1. Prevalence of health outcomes that have been assessed at age 8 years only (wheezing phenotypes, BHR, allergic sensitization, atopic and nonatopic asthma) are presented in Table 1. The annual prevalence of asthma was between 3 and 6%. The annual incidence of asthma was highest in the first year of life (6.1%) and relatively constant (1.4–2.4%) at the other ages. Prevalence of asthma-related symptoms decreased with age. The percentage of children who ever had hay fever increased from 1.2% at age 3 years to 5.1% at age 8 years. The prevalence of atopic eczema was relatively constant at all ages (14.4–18.0%).

Exposure to Air Pollutants

The distributions of annual average NO_2, $PM_{2.5}$, and soot levels at the participants' birth addresses are presented in Table 2. The estimated exposures for the various pollutants were highly correlated (r = 0.93, 0.96, and 0.97 for the correlation between NO_2 and $PM_{2.5}$, NO_2 and soot, and $PM_{2.5}$ and soot, respectively).

Associations between Air Pollution Levels and Health Outcomes

The overall associations with air pollution levels were statistically significant ($P < 0.05$) for prevalence and incidence of asthma, and prevalence of asthma symptoms, wheeze, and sneezing, runny/blocked nose during the past 12 months before and after confounder adjustment (Figure E2 in the online supplement and Figure 2, respectively). Age-specific associations from models with air pollution–age interaction terms revealed little variation of the effects of air pollution on asthma and related symptoms with age. All odds ratios (except for incident asthma at age 2 yr) were greater than one and differences in air pollution effects between ages were small with the exception of asthma incidence, for which associations became somewhat stronger at ages 6–8 years. The odds ratios for sneezing, runny/blocked nose increased with age and were greater than one from age 5 years onward. The odds ratios for atopic eczema were all close to unity. Overall, changes in odds ratio due to confounder adjustment were small (less than 10% with few exceptions). Odds ratios were similar for NO_2, $PM_{2.5}$, and soot because of the high correlation between pollutants.

Crude and adjusted associations between air pollution levels at the birth address and health outcomes, which have been assessed at age 8 years only, are presented in Table E1 and Table 3, respectively. Associations with air pollution levels were positive for all wheezing phenotypes, which is consistent with the positive associations between air pollution levels and wheeze at all ages. No association was found between air pollution levels and BHR. Air pollution levels were associated with a significantly increased risk of allergic sensitization in unadjusted analyses but the associations were somewhat reduced and no longer statistically significant after adjustment for potential confounders. When we distinguished between atopic and nonatopic asthma at age 8 years, positive associations with air pollution levels seemed to be limited to nonatopic asthma in crude analyses (crude odds ratios [95% confidence intervals] for $PM_{2.5}$, NO_2, and soot were 1.85 [0.92–3.73], 2.98 [1.21–7.37], and 2.06 [0.99–4.30], respectively, for nonatopic asthma; and 0.95 [0.64–1.40], 1.00 [0.63–1.58], and 0.97 [0.64–1.46]), respectively, for atopic asthma). Adjusted models did not converge for nonatopic asthma because of the small number of children with nonatopic asthma.

Sensitivity Analyses

We explored the possibility of regional confounding by additional adjustment for study region. Results for $PM_{2.5}$ are presented in Table 4; results for NO_2 and soot are presented in Table E3 of the online supplement. Results for the models without adjustment for study region (which are presented in Figure 2 and Table 3) are included as well in these tables to facilitate comparison. The positive associations between air pollution levels, prevalent and incident asthma, and symptoms of asthma remained stable. The association between air pollution levels and wheeze decreased to unity. Because study region is an important determinant of air pollution levels in the land-use regression models that were used to estimate exposures, the adjustment for region may be an overadjustment.

Moreover, we explored the impact of the study design (i.e., the division into an intervention arm and a natural-history study arm) by excluding the participants of the intervention study, which represent approximately one fifth of the total study population. The results remained essentially unchanged (data not shown).

Less than half the population (48.0%) still lived at their birth address at age 8 years. Children who had moved house at least

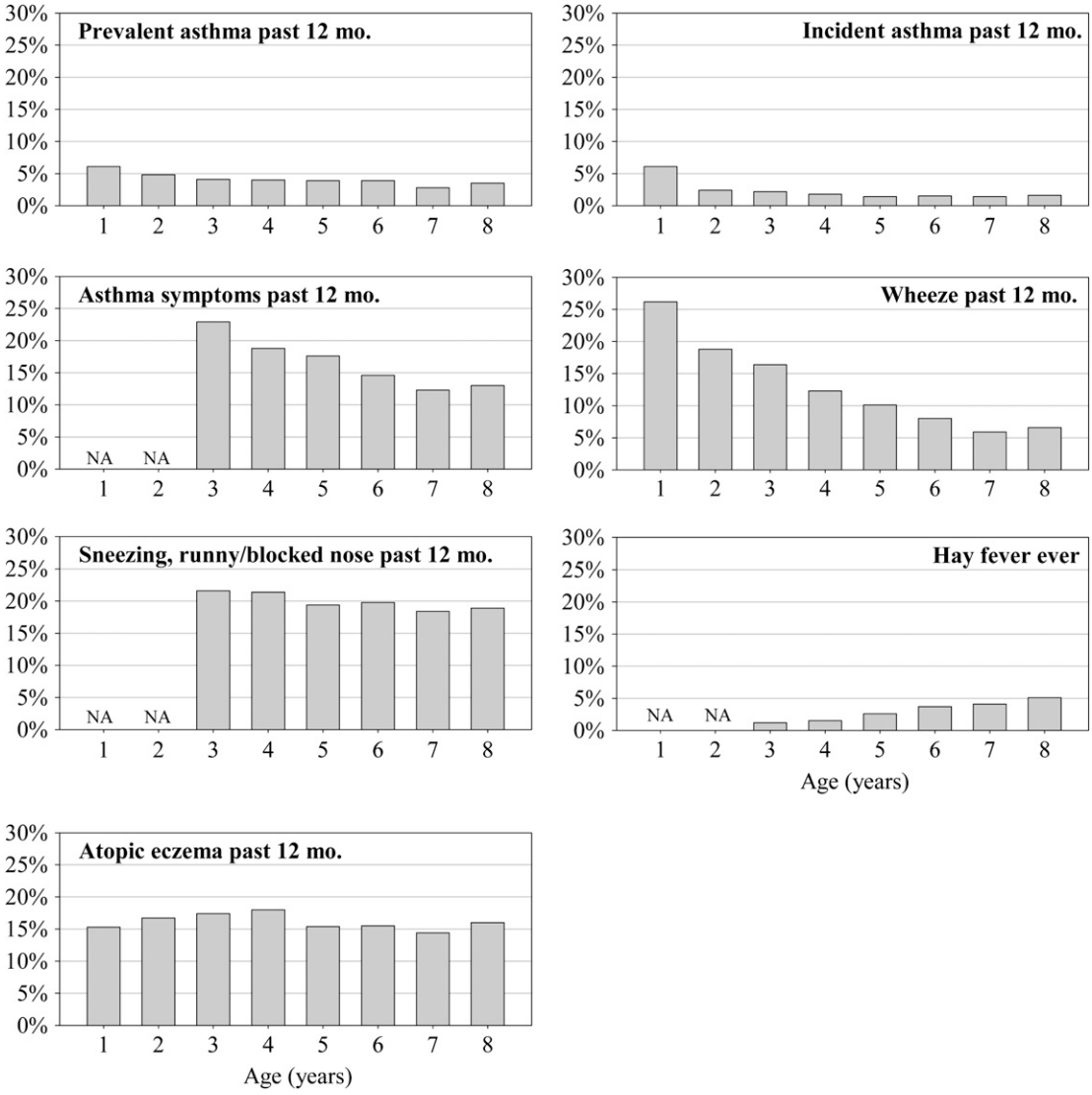

Figure 1. Percentage of children with asthma, hay fever, atopic eczema, and related symptoms at ages 1 to 8 years. NA = not available.

once during the follow-up, on average had lived at their birth address for 3.2 (SD 2.1) years before moving; 14.0% of the movers (7.3% of the total study population) moved during the first year of life. To check whether effects were different between children who did and who did not move house, we included terms for the interaction between air pollution and moving status in the models (for the repeated measures in the models for the overall effects, i.e., the models without air pollution–age interaction). Results for $PM_{2.5}$ are shown in Table 5. Results for NO_2 and soot were similar (Table E4 in the online supplement). Effects were larger and significant only for those who did not move house. There was no association between air pollution levels and hay fever in the entire study population, but there was a statistically significant positive association for children who did not move house.

DISCUSSION

We demonstrated positive associations between levels of traffic-related air pollution at the birth address and the incidence and prevalence of asthma, and the prevalence of asthma-related symptoms in children who were monitored from birth until 8 years of age. In addition, traffic-related air pollution was found to be associated with symptoms of rhinitis during the first 8 years of life. Positive associations with hay fever were found in nonmovers only.

The present work extends results from previous analyses within the same birth cohort study at ages 2 and 4 years, respectively (6, 19, 22), in several ways: first, the follow-up was extended to the age of 8 years; and second, the data were

TABLE 2. DISTRIBUTION OF ESTIMATED ANNUAL AVERAGE CONCENTRATIONS OF NO_2, $PM_{2.5}$, AND SOOT AT BIRTH ADDRESSES

	NO_2	$PM_{2.5}$	Soot
	($\mu g/m^3$)	($\mu g/m^3$)	($10^{-5}\ m^{-1}$)
Minimum	12.6	13.5	0.77
10th percentile	14.7	14.0	1.15
25th percentile	18.5	14.9	1.35
50th percentile	26.0	17.3	1.78
Mean	25.4	16.9	1.72
75th percentile	28.9	18.1	1.92
90th percentile	34.7	19.1	2.17
Maximum	58.4	25.2	3.68

Definition of abbreviation: $PM_{2.5}$ = particulate matter less than 2.5 μm in diameter.

Study population (N) = 3,863.

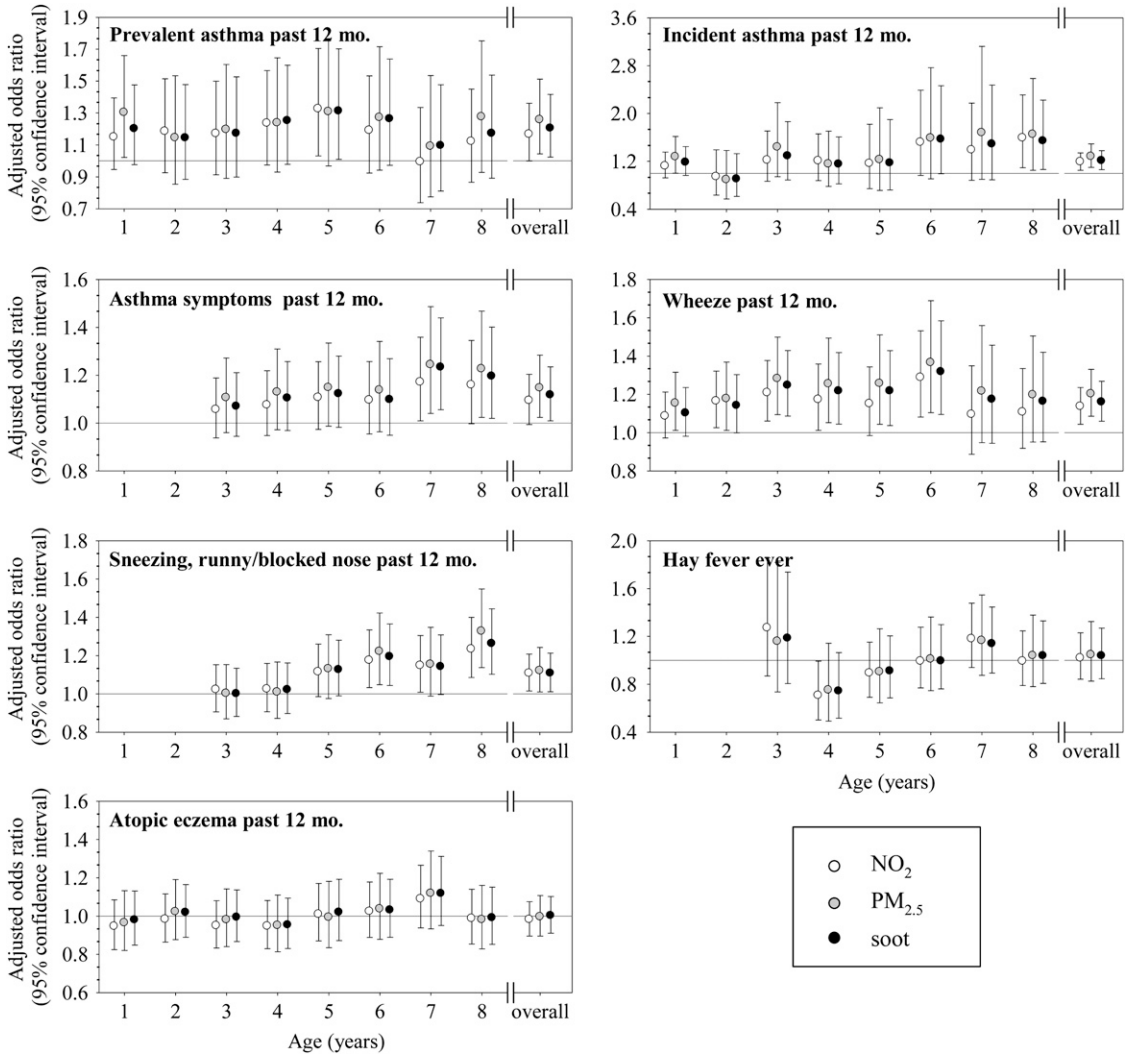

Figure 2. Adjusted overall and age-specific association between annual average levels of air pollution at the birth address and asthma, hay fever, atopic eczema, and related symptoms during the first 8 years of life. Results are presented as adjusted odds ratios (ORs) with 95% confidence intervals. We adjusted for all characteristics from Table 1 except study region. ORs were calculated for an interquartile range increase in air pollution levels (10.4 $\mu g \cdot m^{-3}$ for NO_2, 3.2 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, and 0.57 $\times$ 10^{-5} m^{-1} for soot).

analyzed longitudinally rather than cross-sectionally, making full use of the cohort design. We could show that the positive associations with wheeze and doctor-diagnosed asthma at ages 2 and 4 years persisted over time. At age 4 years, air pollution levels were associated with allergic sensitization to food allergens, but not to inhalant allergens. At age 8 years, associations with sensitization to food allergens and inhalant allergens were similar but both became nonsignificant after confounder adjustment (6). We found positive associations of air pollution levels with symptoms of rhinitis (sneezing, runny/blocked nose). Positive associations between air pollution levels and hay fever were limited to the participants who did not move house since birth. In line with our previous findings, we did not find an association between air pollution levels and atopic eczema. The relatively stable prevalence of atopic eczema in the present study is similar to the prevalence of physician-diagnosed eczema during the first 6 years of life reported from a comparable German birth cohort study (23).

One of the strengths of the present study is its prospective design with yearly questionnaire follow-ups over a period of 8 years, starting at birth. This enables us to fill the gap between those cohort studies reporting associations between traffic-related air pollution and asthma and related symptoms in early life (6, 8, 11, 19, 24) and those reporting associations with asthma prevalence and incidence at school age (9, 12). Response rates were high during the entire follow-up with 82% of the original population (3,269 of 3,963) returning the questionnaire at age 8 years. In addition, for a large subgroup of the population objective measures such as allergen-specific IgE and bronchial hyperresponsiveness at age 8 years were available. Associations with air pollution were found primarily for questionnaire-reported health outcomes. Associations with allergic sensitization became insignificant after confounder adjustment. The most important confounders were nationality, parental education, and day-care attendance: non-Dutch children, children of highly educated parents, and children attending day-care were on average exposed to slightly higher levels of air pollution and had higher rates of sensitization. Changes in the association between air pollution levels and allergic sensitization due to adjustment for single confounders were generally small (<4%), but when all confounding variables were entered into the model the associations became nonsignificant. At age 8 years, we were able to distinguish between atopic and nonatopic asthma. There was some indication that the effect might be limited to nonatopic asthma. However, because the number of children with atopic asthma, and in particular those with nonatopic asthma, were small, results must be interpreted with caution.

A potential limitation of our study may be that asthma was defined by parental reporting of physician-diagnosed asthma, rather than by direct physician diagnosis using standardized criteria such as lung function measurements and bronchial

TABLE 3. ADJUSTED ASSOCIATIONS* BETWEEN AIR POLLUTION LEVELS AT BIRTH ADDRESS AND WHEEZING PHENOTYPES, BRONCHIAL HYPERRESPONSIVENESS, AND ALLERGIC SENSITIZATION AT AGE 8 YEARS

	NO_2		$PM_{2.5}$		Soot	
	OR	95% CI	OR	95% CI	OR	95% CI
Wheeze phenotype (N = 2,668†)						
Early transient	1.17	0.97–1.41	1.29	1.04–1.62	1.22	1.00–1.48
Late onset	1.13	0.99–1.29	1.18	1.01–1.37	1.13	0.99–1.30
Persistent	1.30	0.99–1.72	1.37	0.98–1.91	1.30	0.98–1.74
Bronchial hyperresponsiveness (N = 818†)	1.04	0.85–1.28	0.98	0.76–1.24	1.04	0.84–1.29
Allergic sensitization (N = 1,499†,‡)						
Any allergen	1.11	0.95–1.30	1.16	0.96–1.39	1.12	0.95–1.32
Inhalant allergens only	1.07	0.89–1.29	1.14	0.92–1.42	1.09	0.90–1.32
Food allergens only	1.12	0.85–1.46	1.21	0.88–1.67	1.16	0.87–1.53
Inhalant and food allergens	1.17	0.89–1.56	1.09	0.78–1.52	1.10	0.82–1.48

Definition of abbreviations: CI = confidence interval; OR = odds ratio; $PM_{2.5}$ = particulate matter less than 2.5 mm in diameter.

* Associations are presented as adjusted ORs with 95% CIs. We adjusted for all general characteristics from Table 1 except study region. ORs were calculated for an interquartile range increase in annual average air pollution levels (10.4 $\mu g \cdot m^{-3}$ for NO_2, 3.2 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, and 0.57×10^{-5} m^{-1} for soot).

† Differences in numbers between crude analyses (*see* Table E1 in the online supplement) and adjusted analyses are due to missing values for one or more confounders.

‡ N = 1,497 sensitization to inhalant allergens only, food allergens only, and inhalant and food allergens due to some missing allergen-specific IgE levels.

hyperresponsiveness. Bronchial hyperresponsiveness was measured in a subset of 936 children at the age of 8 years, but no association with air pollution was found. The reason for this is not clear. The percentage of children with bronchial hyperresponsiveness in our study was relatively high among children with and without asthma (75.0 and 41.1%, respectively). This may be due to the oversampling of children with allergic mothers in the study design. The high prevalence of BHR could also imply that the cutoff at a cumulative dose not exceeding 0.61 mg of methacholine bromide was not strict enough for our population.

A potential limitation of the exposure assessment might be that exposure was defined as ambient air pollution at the participants' residential address and that exposure at nonresidential addresses such as day-care centers or schools, where participants regularly spend part of their time, was not included. Validation studies comparing personal exposures with exposures estimated from land-use regression models are scarce. A study among 62 pregnant women in Vancouver, Canada found a moderate correlation ($r = 0.49$) between short-term (48-h) personal exposure measurements of NO and NO_2 exposures estimated by land-use regression (25). The correlation was stronger in the subset of women who spent more time at home. In our birth cohort of approximately 4,000 children, personal exposure assessment was not feasible and no information was available about time–activity pattern and exposure at places other than home. However, given the age of our cohort, we believe that participants spent sufficient amounts of their time at home to yield valid exposure estimates from the land-use regression models. Apart from the sensitivity analyses on children who did/did not move house, we were not able to account for changes in residential address. This might have resulted in some measurement error, leading to attenuation of effect estimates, as indicated by the higher effects in children who did not move to another home compared with children who did move. However, in a birth cohort study from Cincinnati exposure to diesel exhaust particles was estimated by a land-use regression model as a time-weighted average of the estimated exposure at all addresses where the child spent more than 8 hours per week, that is, taking into account day-care addresses and changes in residential addresses due to moving (26). Overall, the differences between the estimated exposure at the birth record address and the time-weighted average exposure during the first 3 years of life were found to be small.

We presently know little about the relevance of the timing of the exposure in addition to the level of exposure, and it is unclear whether early life exposure at a time when the lungs are

TABLE 4. ADJUSTED ASSOCIATIONS* BETWEEN $PM_{2.5}$ LEVELS AT BIRTH ADDRESS AND HEALTH OUTCOMES WITH AND WITHOUT ADJUSTMENT FOR STUDY REGION

		Without Adjustment for Study Region		With Adjustment for Study Region	
	n†	OR	95% CI	OR	95% CI
During the first 8 years of life					
Prevalent asthma	3,184‡	1.26	1.04–1.51	1.36	0.99–1.88
Incident asthma	3,143‡	1.28	1.10–1.49	1.26	0.97–1.63
Asthma symptoms	3,156‡	1.15	1.02–1.28	1.22	0.98–1.51
Wheeze	3,184‡	1.20	1.08–1.33	1.04	0.85–1.28
Sneezing, runny/blocked nose	3,156‡	1.12	1.01–1.24	1.14	0.95–1.37
Hay fever	3,156‡	1.05	0.83–1.32	0.73	0.45–1.20
Atopic eczema	3,184‡	1.00	0.90–1.11	1.11	0.91–1.35
At age 8 years					
Bronchial hyperresponsiveness	818	0.98	0.76–1.24	1.04	0.66–1.66
Allergic sensitization	1,499	1.16	0.96–1.39	1.06	0.76–1.49

See Table 3 for abbreviations.

We adjusted for all general characteristics from Table 1 and study region as indicated. ORs were calculated for an interquartile range increase in annual average $PM_{2.5}$ level (3.2 $\mu g \cdot m^{-3}$).

* Associations are presented as adjusted ORs with 95% CIs.

† Number of subjects included in the analyses.

‡ Subjects contributed up to eight repeated observations to this longitudinal data analysis.

TABLE 5. ADJUSTED ASSOCIATIONS* BETWEEN $PM_{2.5}$ LEVELS AT BIRTH ADDRESS AND HEALTH OUTCOMES FOR CHILDREN WHO DID AND CHILDREN WHO DID NOT MOVE HOUSE DURING THEIR FIRST 8 YEARS OF LIFE

	Nonmovers			Movers		
	n†	OR	95% CI	n†	OR	95% CI
During the first 8 years of life						
Prevalent asthma	1,575‡	1.34	1.03–1.75	1,605‡	1.19	0.92–1.53
Incident asthma	1,551‡	1.36	1.09–1.69	1,588‡	1.20	0.98–1.48
Asthma symptoms	1,556‡	1.27	1.07–1.49	1,596‡	1.05	0.90–1.23
Wheeze	1,575‡	1.25	1.08–1.45	1,605‡	1.15	1.00–1.32
Sneezing, runny/blocked nose	1,556‡	1.14	0.98–1.34	1,596‡	1.09	0.95–1.25
Hay fever	1,556‡	1.43	1.01–2.04	1,596‡	0.81	0.58–1.12
Atopic eczema	1,575‡	1.03	0.89–1.21	1,605‡	0.97	0.84–1.12
At age 8 years						
Bronchial hyperresponsiveness	464	0.99	0.69–1.41	351	0.96	0.69–1.34
Allergic sensitization	617	1.25	0.96–1.61	881	1.07	0.83–1.39

See Table 3 for abbreviations.

* Associations are presented as adjusted ORs with 95% CIs. We adjusted for all general characteristics from Table 1 except study region. ORs were calculated for an interquartile range increase in annual average $PM_{2.5}$ level (3.2 $\mu g \cdot m^{-3}$).

† Number of subjects included in the analysis.

‡ Subjects contributed up to eight repeated observations to this longitudinal data analysis.

considered to be more susceptible is more important than later exposure. The estimated air pollution level at the birth address can be considered a good estimate of early life exposure for basically all participants of this study (only 7.3% of the total population moved during the first year of life). However, for children who moved house, the estimated air pollution level at the birth address is probably a poor estimate of their current exposure. The fact that effects were stronger in movers compared with nonmovers may indicate that the effects of air pollution are not due solely to early life exposure, but result at least partly from current exposure and that the relevance of early versus current exposure is not that clear. More research on this topic is needed. Moreover, the present results illustrate the impact of measurement error when relying on birth addresses alone and underline the importance of accounting for moving in this type of study.

For children who lived at their birth address during the entire follow-up, exposure might also have changed due to overall (long-term) temporal changes in air pollution levels. To investigate the long-term validity of the Traffic-related Air Pollution on Childhood Asthma (TRAPCA) model, in 2007, we went back to the original TRAPCA sites and performed four 1-week measurements (one measurement per season) of NO_2. Results indicated that the original TRAPCA model was highly predictive ($R^2 = 0.80$) of NO_2 concentrations measured at the same sites almost 10 years later. A detailed description of these measurements will be published elsewhere. Further support for the validity of the estimated air pollution levels for children who did not move house comes from the National Air Quality Monitoring Network: annual average NO_2 and PM_{10} levels were relatively stable between 2000 and 2007 (27).

An important issue regarding the present findings concerns the issue of pollutant-specific effects, that is, which (set of) pollutant(s) is responsible for the observed effects. As in our previous analyses (6, 19) it was not possible to disentangle the effects of the specific pollutants that were measured because of the high correlations among the different pollutants. In outdoor air, NO_2 often is highly correlated with other combustion products, in particular fine particulate matter (28). An expert panel reviewed the biological plausibility of epidemiological findings on criteria pollutants (29). Taking into account findings from epidemiological, human clinical, and toxicological studies, the experts concluded that NO_2 may be acting as a surrogate for a mixture of pollutants.

We conclude from our results that exposure to traffic-related air pollution may cause asthma in children monitored from birth to 8 years of age.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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