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Air Pollution and the Development of Asthma, Allergy and Infections in a Birth Cohort

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ABSTRACT

Few studies have addressed associations between traffic-related air pollution and respiratory disease in young children. We assessed the development of asthmatic/allergic symptoms and respiratory infections during the first four years of life in a birth cohort study (n~4,000).

Outdoor concentrations of traffic-related air pollutants (NO_2, $PM_{2.5}$ and "soot") were assigned to the birthplace home addresses with a land-use regression model. They were linked by logistic regression to questionnaire data on doctor-diagnosed asthma, bronchitis, influenza and eczema and to self-reported wheeze, dry nighttime cough, ear/nose/throat infections and skin rash. Total and specific IgE to common allergens were measured in a subgroup (n=713).

Adjusted odds ratios per interquartile pollution range were elevated for wheeze (1.2, 95% CI=1.0–1.4 for "soot"), doctor-diagnosed asthma (1.3, 1.0–1.7), ear/nose/throat infections (1.2, 1.0–1.3) and flu/serious colds (1.2, 1.0–1.4). No consistent associations were observed for other endpoints. Positive associations between air pollution and specific sensitization to common food allergens (1.6, 1.2-2.2 for "soot"), but not total IgE, were found in the subgroup with IgE measurements.

Traffic-related pollution was associated with respiratory infections and some measures of asthma and allergy during the first four years of life.

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INTRODUCTION

Many studies have demonstrated that exposure to outdoor air pollutants can exacerbate pre-existing asthma [1,2], but it is less clear whether outdoor air pollutants increase the incidence of asthma or allergic diseases in children. While a limited number of studies have described associations between asthma and ozone [3,4] there is growing evidence that air pollutants that are specifically associated with traffic exposure may be of greater importance to asthma and allergic disease development [5-18]. Specifically, a number of recent studies have reported associations between concentrations of air pollution arising directly from motor vehicle emissions and asthma or asthmatic symptoms [5,6]. Cross-sectional studies have found lung function to be reduced [7] or the prevalence of respiratory symptoms [8-14] to be elevated for individuals living or attending schools close to high traffic roads. Several case control studies have also found associations between measures of traffic intensity and respiratory outcomes such as wheeze [14], asthma [15] hospitalization for wheezing bronchitis (4 – 48 month old children) or asthma (children under five years) [16-17]. Despite the fact that the majority of these studies relied on distance to major roads or on measures of traffic intensity as a proxy for exposure to air pollutants these studies suggest that living near busy roads leads to adverse respiratory health effects. A more limited number of studies included direct measurements or modeled concentrations of air pollution. For example, two recent analyses suggest associations between asthma and several measures of highway pollutants in California [18, 19], and a cross-sectional study in Germany in which air pollution concentrations were estimated for all home and school addresses found an association with prevalence of cough and bronchitis but not with atopy in children [11]. A study that used an emissions model to estimate exposures showed an association between several traffic-related pollutants and current wheeze or asthma but not with allergic sensitization [20]. A series of studies completed in the Netherlands indicated that children living near roads with high truck traffic intensity have lower lung function and more chronic respiratory symptoms compared to children living on roads with less truck traffic [21]. A similar relationship was found between measures of respiratory health of schoolchildren with levels of traffic-related air pollutants, especially measures specific to trucks, measured in their schools [22, 23]. Several studies have also suggested that traffic-related air pollution may be associated with increased respiratory symptoms in young

children [24-26] although data regarding associations with respiratory infections, especially from cohort studies, are lacking.

We previously reported on the relationship between traffic-related air pollution and the development of asthmatic symptoms, allergic diseases and respiratory infections at age two in a birth cohort study in the Netherlands [26]. In that study exposure to air pollution was estimated for an existing birth cohort study (PIAMA) [27,28]. A unique aspect of the study was the use of individual exposure estimates for each cohort member derived from a land use regression model [29-31]. Individual estimates of exposure to traffic related air pollution were computed using a validated model based on geographic data and air pollution measurements of NO_2, $PM_{2.5}$ and filter reflectance, a measure of particulate elemental carbon. Significant positive associations between traffic-related air pollutants and especially wheeze at age two were reported. A related study conducted in Munich and using the same exposure assessment approach found associations between traffic related air pollutants and cough, but concluded that the young age of the cohort (2 years) precluded conclusions related to asthma [32]

Although our previous analysis suggested associations of traffic-related air pollution with asthma and respiratory infections at age two, the implication of wheeze or asthma reported at these very young ages is somewhat unclear. Therefore we extended the previous analysis of the same birth cohort to assess the association between individual-level estimates of exposure to traffic-related air pollution with respiratory symptoms and measures of allergy reported at age four. At age four reporting of asthma and symptoms of wheeze have a clearer implication, although diagnoses of asthma are still not definitive. In addition, the association between air pollution and objectively measured sensitization to common allergens was analyzed in a subset of the cohort.

METHODS

Study population

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) prospective birth cohort study had initial enrollment of 4,146 children recruited during the second trimester of pregnancy from a series variable size communities in the Netherlands [27-28]. The study protocol was approved by the Institutional Review Boards of each participating institute, and informed consent was obtained from all participants in writing. At inception, the study included two groups of about 400 'high risk' children randomly allocated to control and intervention groups in which allergen-free mattress covers were used. In addition, the study population included a 'natural history' group of approximately 2,900 children, including 400 high-risk children. 'High risk' children were identified before birth by obtaining information regarding self-reported allergy or reporting of physician-diagnosed allergy to house dust, house dust mite, pets or hayfever/rhinitis) in the (expecting) mothers. This analysis included all children (natural history and intervention who remained in the cohort at age 4 (see Results for more detailed description).

Exposure Assessment

Details of the exposure assessment have been reported elsewhere. Briefly, air pollution concentrations at the home address at birth were calculated by a model combining air pollution measurements with a Geographic Information System (GIS) [29-31, 33]. Fine particles ($PM_{2.5}$), NO_2, and "soot," measured as the reflectance of the $PM_{2.5}$ filters, were measured at 40 sites, designed to capture the maximum variability in pollution from traffic sources. At each location, measurements were conducted for four two-week periods dispersed throughout one year (March 1, 1999 - April 20, 2000, corresponding to a period when the cohort was, on average 2 – 3 years old) and then adjusted for temporal trends to calculate long-term average concentrations. This adjustment was based on the calculation of an annual average for a single reference site where 14-day integrated samples were made for the entire study period, calculating for this reference site the difference between the annual average and the measurements for each 2-week sampling period at all other sites, addition of this

difference for each sampling period to the measured concentrations at each site during this period and calculation of an annual average from these adjusted values [31]. This exposure assessment approach therefore emphasizes spatial contrasts in long-term average concentrations during the first four years of life that we hypothesized to have greater relevance for development of chronic respiratory disease than would short term temporal variation in concentrations. At the same locations, GIS data was also collected regarding traffic in the vicinity of each monitoring location and regression models were developed to relate the annual average concentrations measured at the 40 monitoring sites with the GIS variables. For example, the number of high traffic roads within a 250 meter radius of a location, the presence of a major road within a distance of 50 meters, the density of buildings (addresses) within a 300 meter radius and an indicator for the region of the country were used in the model to predict "soot" concentrations. Models with similar variables describing traffic intensity were developed for $PM_{2.5}$ and NO_2. These models explained 73, 81 and 85% of the variability in the annual average concentrations for $PM_{2.5}$, "soot' and NO_2, respectively [29-31]. These models were then applied to the same GIS variables measured at the home addresses of each cohort member to obtain individual long-term ambient air pollution exposure estimates. Exposure was assessed for the address at birth to reflect our interest in the effects of early life exposures on respiratory health.

Questionnaire data

From questionnaires completed by the parents of cohort members, we selected the same health outcomes as in our previous analysis to describe symptom frequencies and physician diagnoses for indicators of asthma, allergic disease and infections (Table 1). Questionnaires were completed during pregnancy, at the time the child was 3 months old, and at the time of the child's first, second, third and fourth birthday. Each questionnaire contained a core set of questions that were supplemented with additional questions as the cohort aged. To the current analysis we added additional variables describing wheeze and asthma development (Table 2). The Appendices lists the symptoms, diagnoses and exact questions as well as definitions of early-onset transient, late-onset, and persistent wheeze as

well as a definition of "Possible / Probable asthma" based upon reported symptoms and other conditions. The definition was developed in the PIAMA project according to guidelines of the Dutch General Practitioners Association with the relevant questions identical to those of ISAAC [34]. Analyses were conducted with the same potential confounding variables as in our previous study (Table 3). The data for these variables were selected from the earliest questionnaire available, to coincide with the estimated exposures for birth addresses. Details are presented in the legend of Table 3.

Sensitization data

A blood sample was taken at age four in a total of 713 children who also had a home visit at age 3 months, who completed the year 4 questionnaire and whose parents consented to blood sampling. Blood sampling was offered to children participating in the intervention study, and those children in the 'natural history' part of the cohort who had had a home visit at age 3 months [35] Specific IgE levels for house dust mite, cat, dog, Dactylium, birch pollen, Alternaria, egg and milk and as well as total IgE were measured. IgE was determined by a RAST-like method according the Standard Operating Procedure used at the Sanquin Laboratories. Positive reactions were those with IgE levels > 0.35 IU/ml. Sensitization was defined as elevated IgE to any of the measured allergens, to any indoor allergens, any of the outdoor allergens or any of the food allergens.

Statistical analysis

The association between exposure and health outcomes was analyzed by multiple logistic regression, adjusting for confounders. Sensitivity analyses were conducted for the subset of the cohort who remained at the birth address at age four and those who remained at the same address since their first birthday. While our primary analysis was focused on the relationship between health outcomes at age four and risk factors in the first year of life, we also conducted separate analyses including risk factors information (gas stove, pets, siblings and home dampness), from the 4-year questionnaire. Odds ratios are presented for an interquartile range increase in air pollutant concentrations equivalent to 3.3 $\mu g/m^3$ for $PM_{2.5}$, $0.58*10^{-5}$ m^{-1} for "soot" (corresponding to 0.84 $\mu g/m^3$ elemental carbon) [30] and

10.6 μg/m^3 for NO_2. We also performed a stratified analysis on the subset of the population with sensitization measurements to assess whether the association between air pollution and symptoms was stronger in children who were sensitized.

RESULTS

Prevalence of health outcomes

At the time of the first questionnaire (3 months), 212 children had dropped out of the study (N=3,934). At one year the cohort size was 3,745 (401 missing) and 3,730 at two years (416 missing). At four years, data were collected from 3,538 children (608 missing), corresponding to 85.3% retention. Of those children remaining in the study population at age 4, 608 (17.2%) were in the intervention arm, representing a slightly lower proportion (19.3%) than at the initiation of the cohort. The main reasons for dropout were due to subjects' loss of interest or available time and subjects moving and becoming untraceable. Although complete data was not available for any of the covariates, subjects who dropped out (Online Supplementary Material - Table A1) of the study had were more likely to have allergic mothers, parents with less than a medium level professional education, mothers who smoked during pregnancy and were more likely to live in homes with a smoker, mold, and an unvented gas heater. These subjects also were less likely to have been breastfed at 3 months of age, were born to younger mothers and were more likely to live in the western part of the Netherlands. Finally, those subjects that dropped out had higher estimated exposures to traffic related air pollutants.

Health outcomes are presented separately for those defined by the questionnaire or sensitization measurements conducted at age 4 (and referring to diagnoses and symptoms experienced in the fourth year of life) (Table 1) and cumulative indicators of disease (Table 2) based on the experiences during the first four years of life. The highest prevalence of symptoms at age four was found for ear/nose/throat infections (Table 1). The prevalence of wheeze was about three times higher than doctor diagnosed asthma.

From the 3,538 subjects with completed 4-year questionnaires, 1,836 (52%) subjects resided in the same house since birth and 2,497 (71%) resided in the same house from age 1 to age 4 years. Prevalences of the health outcomes were very similar for these subsets of the cohort (data not shown) relative to the full cohort. Slightly elevated prevalences for early wheeze were observed in the subset remaining at the birth address (23.6%) and those residing at the same address since age 1 (22.7%) relative to the full cohort (21.8%).

The prevalence of sensitization to any allergen was high and primarily due to sensitization to food allergens (28.1%), with relatively few children being sensitized to outdoor allergens yet (8.2%). Note that these prevalences cannot be compared with the very low prevalence of self-reported allergy in Table 2 because the sensitization data were available for a subgroup of children in which children born to allergic mothers were overrepresented [35]. As a result, the subpopulation with blood sampling differed from the full cohort in some respects. Tables A2 and A3 in the Online Supplementary Material present prevalences of the health outcomes and potential confounders for this subpopulation. At age four, these children reported significantly higher prevalence of wheeze, physician-diagnosed asthma, cough, bronchitis, itchy rash and physician-diagnosed eczema in the past 12 months than did the full cohort. Further, this subpopulation was more likely to be female, to have older siblings, to have been breastfed for at least 3 months and to have a lower prevalence of smoking during pregnancy, smoking in the home, pets in the home and fathers with less than a medium level professional education. These differences suggest that the subset was likely at greater risk of developing allergic disease but were more aware of relevant risk factors and took steps to minimize such risks. The tendency for families with children at increased risk for the development of allergic diseases, based on maternal allergy status, to avoid known risk factors has been reported previously for this same cohort (25).

Prevalence of potential counfounders

Table 3 lists the distribution of potential confounders in the study population. Prevalence of smoking was 24%. Most households used gas for cooking (79%). Unvented gas water heaters were present in

only 3% of the homes. Virtually all children were of Dutch ethnicity. There were no major differences in the prevalence of potential confounders between the full cohort and the subset who remained at the birth address.

Exposure to air pollutants

Exposures were successfully calculated for the home addresses of 3,532 of the 3,538 children (99.8%) and are summarized in Table 4. For 6 subjects, exposures were not calculated due to an inability to geocode their home addresses or an error in the GIS calculation of one variable. The exposure estimates for the different pollutants were very highly correlated. The correlation between 'soot' and NO_2 was 0.96 and between 'soot and $PM_{2.5}$, 0.97. The correlation between NO_2 and $PM_{2.5}$ was 0.93. There were only very minor differences in exposure (< 2% for median or 90^{th} percentile exposures) between the full cohort and those subsets who remained at the birth address. Given the similarities in exposure, prevalence of potential confounders and health outcomes between the full cohort and those who did not move, we did not conduct any sensitivity analyses of the associations between air pollution exposure and the main outcomes for these groups. Such sensitivity analyses were performed for the sensitization relationships given the small size of the group with sensitization measures.

Associations between air pollution exposure and health outcomes

The association between exposure to air pollution and development of respiratory symptoms and sensitization is reported in Tables 5-7. Before adjustment for confounders, air pollution was associated with increased incidence of wheeze, dry cough at night, ear/nose/throat infections and flu/serious colds (Table 5) based on responses referring to the fourth year of life only. After adjustment for the full set of confounders the associations between air pollution and increased risk of wheeze (e.g OR =1.18, 95% Confidence Interval = 0.98 – 1.41 per interquartile range increase in "soot"), ear/nose/throat infections (e.g. for 'soot' OR=1.15, 1.01-1.31) and flu/serious colds (e.g. for 'soot' OR=1.18, 1.02-1.36) remained elevated, but the odds ratios for dry cough at night was somewhat decreased (e.g. for 'soot' OR=1.13, 0.97-1.30). Sample sizes for the adjusted odds ratios were reduced due to incomplete questionnaires for some of the confounding variables. When analyses

were restricted to adjustment for early life risk factors, results were similar with somewhat elevated odds ratios for ear/nose/throat infections (e.g. for 'soot' OR=1.16, 1.03-1.31), flu/serious colds (e.g. for 'soot' OR=1.19, 1.04-1.37) and physician-diagnosed asthma (e.g. for 'soot' OR=1.30, 0.98-1.71) (Table 5).

Sensitization to any common allergen was positively associated with air pollution, both before and after adjustment, with substantially elevated Odds Ratios (e.g. adjusted OR for 'soot' =1.45, 1.11-1.91) (Table 6). The association between sensitization and air pollution was only present for food allergens. As indicated above, this subset was composed of children with higher familial risk of allergy but lived in lower-risk home environments. Air pollution exposures for the subset did not differ from those of the full cohort.

Table 7 presents the results of analyses in which information from different years was combined to produce cumulative measures of disease status. In the unadjusted analysis, significant associations were found between air pollution exposure and any reporting of wheeze ('wheeze ever') and with probable asthma while there were also indications of associations with physician-diagnosis of asthma and with persistent wheeze. In the adjusted analysis, the sample size was substantially reduced as only those subjects who completed all questionnaires during the four years of follow-up were included (n~2500). After adjusting for potential confounders, the relationship with 'wheeze ever' remained significant (e.g. for 'soot' OR=1.18, 1.04-1.34) and a significant association with physician-diagnosis of asthma was observed (e.g. for 'soot' OR=1.26, 1.02-1.56). The association with probable asthma observed in the unadjusted analysis disappeared, while a relationship with early-onset transient wheeze emerged. Associations with persistent wheeze remained borderline significant. No associations were found with doctor diagnosis of bronchitis, eczema or reported itchy rash.

Symptom Odds Ratios for non-sensitized and sensitized children were very similar. Since air pollution exposures were assessed only for the birth addresses, we also conducted sensitivity analyses by restricting to those subjects who remained at the birth address until age four. Adjusted OR for

sensitization to food allergens were somewhat reduced, but still greatly elevated for those who had never moved and similar to the full cohort for those who had not moved since age 1.

DISCUSSION

In this prospective cohort study we observed several positive associations of traffic-related air pollutants with wheeze, asthma diagnosis, respiratory infections and sensitization to food allergens. These findings extend observations made at age 2 in the same cohort [26]. Odds ratios were not altered to any great extent by the inclusion of potential confounding variables in the regression models or in sensitivity analyses that evaluated inclusion of confounders measured early rather than later in life. Our indications of associations between exposure to traffic-related air pollutants and respiratory symptoms in children are consistent with results reported elsewhere, although few cohort studies to date have evaluated effects on young children.

A limitation of our earlier analysis [26] relates to the validity of the specific health outcome variables for disease diagnosis at very young ages. Interestingly, the associations we reported earlier with wheeze largely remained, whereas at age 4 the reporting of current wheeze can be assumed to have more validity as an indicator of asthma than at age 2. This suggests that air pollutants contributed similarly to the incidence of the different phenotypes in early life. Future studies, including longitudinal analyses of this cohort, will also help to reveal whether these early life exposures also affect asthma at older ages. Additionally, these analyses refer to health outcomes derived from questionnaires and responses were not verified by objective measures in most cases. One exception is the demonstration in this cohort, that the measure of physician asthma diagnosis, but not reporting of wheeze was been associated with higher levels of exhaled nitric oxide [36]. An additional limitation is that exposures are based upon outdoor concentrations estimated for the home address at birth and do not consider personal exposures directly. Recent work has, however, shown that personal exposures are related to measures of traffic proximity and broadly support the validity of the exposure assessment applied here [37,38]. Balanced against these limitations is the large size of this birth cohort and the individual-level exposure assessment.

The finding of a positive association between air pollution and objectively measured sensitization to common allergens supports the findings of subjectively reported symptoms. Sensitization data were available for a subgroup of the full cohort, with an overrepresentation of children born to allergic mothers. The association with sensitization appeared to be limited to food allergens, whereas an association with indoor or outdoor aeroallergens seems more plausible. In early childhood, however, sensitization manifests itself first as sensitization towards food allergens, especially milk allergen. In this cohort at age four, the prevalence of food allergen sensitization was about twice that of indoor allergens and more than three times that of outdoor allergens. Food allergy in early childhood may develop into allergy towards aeroallergens later. It would therefore be of interest to study whether the associations between air pollution and sensitization shift towards aeroallergens at older ages. The low prevalence of especially sensitization to outdoor allergens limits the interpretation of the Odds Ratios, evidence by the large confidence intervals. Surprisingly, the association of air pollution and total IgE did not support at all the association for sensitization to 'any allergen'. It has been reported before that total IgE and IgE towards specific allergens are associated with different clinical presentations and may be determined by different mechanisms [39,40].

Early childhood respiratory effects may develop into chronic respiratory impairment later in life, and for this reason it is important to identify modifable determinants of adverse respiratory outcomes in the first years of life [41,42]

This analysis utilized a unique approach to calculate individual air pollution concentrations for the home addresses of each cohort member and therefore has distinct advantages over ecological analyses that assign single air pollution concentrations to all individuals living in certain areas [29]. In particular, the exposure model was developed to incorporate the impact of traffic sources on air pollution concentrations and to therefore capture the variability in exposure to traffic-related air pollution. This represents a major difference from the more typical use of government monitoring network data to estimate exposures in epidemiological studies. Most network monitors are located in

order to measure urban or regional background air pollution concentrations and therefore to specifically not reflect the influence of local traffic. As the cohort was drawn from throughout the Netherlands and included individuals living in urban and rural areas there was significant variability in exposure to traffic-related pollutants, but the magnitude of exposure differences was relatively small compared to between-city or longitudinal comparisons.

As in our earlier analysis we did not observe consistent differences in associations with health outcomes between the three pollutant measures given the high correlation between the pollutants. The high correlations among the different pollutants that were measured precluded analysis of the impact of specific pollutants or indicators of specific components (heavy duty vehicles for example) of traffic-related air pollution. The geographic variables, which were used to estimate exposure, were selected as surrogates for exposure to traffic sources in general.

In summary, we examined the relationship between traffic-related air pollution and the development of asthmatic/allergic symptoms, respiratory infections and sensitization in a large birth cohort (N~ 4,000) study in the Netherlands. A validated model was used to assign outdoor concentrations of traffic-related air pollutants (NO_2, $PM_{2.5}$ and "soot") at the home addresses of the cohort. Questionnaire-derived data on self-reported wheeze, dry nighttime cough, ear/nose/throat infections, skin rash and physician diagnoses of asthma, bronchitis, influenza and eczema at age four were analyzed in relation to air pollutants. Adjusted odds ratios for wheeze, doctor-diagnosed asthma, ear/nose/throat infections and flu/serious colds indicated positive associations with air pollutants. No associations were observed for eczema and bronchitis. These findings at age four years confirm earlier observations made at age 2 in the same cohort [26]. The finding of a positive association between air pollution and objectively measured sensitization to common allergens supports the findings of subjectively reported symptoms. The association with sensitization was limited to food allergens, with no indication of an association with indoor or outdoor aeroallergens, probably reflecting the low sensitization prevalence at this age.

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REFERENCES

1. Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. J Allergy Clin Immunol. 2005 Apr;15:689-99.

2. Von Mutius E. The environmental predictors of allergic disease. J Allergy Clin Immunol 2001;105:9-19.

3. Hwang BF, Lee YL, Lin YC, Jaakkola JJ, Guo YL. Traffic related air pollution as a determinant of asthma among Taiwanese school children. Thorax. 2005; 60:467-73.

4. McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. Lancet. 2002; 359:386-91.

5. Heinrich J, Wichmann HE. Traffic related pollutants in Europe and their effect on allergic disease. Curr Opin Allergy Clin Immunol. 2004;4:341-8.

6. Brunekreef B, Sunyer J. Asthma, rhinitis and air pollution: is traffic to blame? Eur Respir J. 2003; 21:913-5.

7. Wjst M, Reitmeir P, Dold S, Nicolai T, Von Loeffelholz Colberg E, Von Mutius E. Road traffic and adverse effects on respiratory health in children. Br Med J 1993; 307:596-600

8 Oosterlee A, Drijver M, Lebret E, Brunekreef B. Chronic respiratory symptoms of children and adults living along streets with high traffic density. Occup Environ Med 1996; 53:241-247

9. Weiland SK, Mundt KA, Ruckmann A, Keil U. Self reported wheezing and allergic rhinitis in children and traffic density on street of residence. Ann Epidemiol 1994; 4:243-247

10. English P, Neutra R, Scalf R, Sullivan M, Waller L, Zhu L. Examining associations between childhood asthma and traffic flow using a geographic information system. Environ Health Perspect 1999; 107:761-767.

11. Hirsch T, Weiland SK, von Mutius E, Safeca AF, Grafe H, Csaplovics E, Duhme H, Keil U, Leupold W. Inner city air pollution and respiratory health and atopy in children. Eur Respir J 1999; 14:669-677.

12. Kim JJ, Smorodinsky S, Lipsett M, Singer BC, Hodgson AT, Ostro B. Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. Am J Respir Crit Care Med. 2004;170:520-6.

13. Shima M, Nitta Y, Adachi M. Traffic-related air pollution and respiratory symptoms in children living along trunk roads in Chiba Prefecture, Japan J Epidemiol. 2003;13:108-19.

14. Venn AJ, Lewis SA, Cooper M, Hubbard R, Britton J. Living near a main road and the risk of wheezing illness in children. Am J Respir Crit Care Med. 2001; 164:2177-80.

15. Zmirou D, Gauvin S, Pin I, Momas I, Sahraoui F, Just J, Le Moullec Y, Bremont F, Cassadou S, Reungoat P, Albertini M, Lauvergne N, Chiron M, Labbe A; Vesta Investigators. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. J Epidemiol Community Health. 2004;58:18-23.

16. Pershagen G, Rylander E, Norberg S, Eriksson M, Nordvall SL. Air pollution involving nitrogen dioxide exposure and wheezing bronchitis in children. Int J Epidemiol 1995; 24:1147-1153.

17. Edwards J, Walters S, Griffiths RK. Hospital admissions for asthma in pre-school children: relationship to major roads in Birmingham, United Kingdom. Arch Environ Health 1994; 49:223-227.

18. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, Kuenzli N, Gauderman J, Avol A, Thomas D, Peters J. Traffic, Susceptibility, and Childhood Asthma. Environ Health Perspect. 2006; 114:766-72.

19. Gauderman WJ, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J, McConnell R. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology. 2005; 16:737-43.

20. Nicolai T, Carr D, Weiland SK, Duhme H, von Ehrenstein O, Wagner C, von Mutius E. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. Eur Respir J. 2003;21:956-63.

21. Brunekreef B, Janssen NAH, de Hartog J, Harssema H, Knape M, van Vliet P. Air Pollution from traffic and lung function in children living near motorways. Epidemiology 1997; 8:298-303.

22. van Vliet P, Knape M, de Hartog J, Janssen NAH, Harssema H, Brunekreef B. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. Environmental Research 1997; 74:122-132.

23. Janssen NA, Brunekreef B, van Vliet P, Aarts F, Meliefste K, Harssema H, Fischer P. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. Environ Health Perspect. 2003; 111:1512-8.

24. Braun-Fahrlander C, Ackermann-Liebrich U, Schwartz J, Gnehm HP, Rutishauser M, Wanner HU. Air pollution and respiratory symptoms in preschool children. Am Rev Respir Dis 1992; 145:42-7.

25. von Mutius E, Sherrill DL, Fritzsch C, Martinez FD, Lebowitz MD. Air pollution and upper respiratory symptoms in children from East Germany. Eur Respir J 1995; 8:723-8.

26. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. Am J Respir Crit Care Med 2002; 166:1092-8.

27. Wijga A, Smit HA, Brunekreef B, Gerritsen J, Kerkhof M, Koopman LP, Neijens HJ. Are children at high familial risk of developing allergy born into a low risk environment? The PIAMA Birth Cohort Study. Prevention and Incidence of Asthma and Mite Allergy. Clin Exp Allergy 2001;31:576-81.

28. Koopman LP, Smit HA, Heijnen M-L A, Wijga A, van Strien RT, Kerkhof M, Gerritsen J, Brunekreef B, de Jongste JC, Neijens HJ. Respiratory infections in infants: interaction of parental allergy, childcare, and siblings-the PIAMA study. Pediatrics. 2001; 108:943-8.

29. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer P, Gehring U, Heinrich J, Cyrys J, Bellander T, Lewne M, Brunekreef B. Prediction of long term average particulate air pollution concentrations by traffic indicators for epidemiological studies. Epidemiology, 2003;14:228–239.

30. Lewné M, Cyrys J, Meliefste K, Brauer M, Fischer P, Gehring U, van Vliet P, Heinrich J, Brunekreef B, Bellander T. Spatial variation of outdoor nitrogen dioxide in Munich (Germany), the Netherlands and Stockholm County (Sweden). Science of the Total Environment. 2004; 332: 217-230.

31. Hoek G, Meliefste K, Cyrys J, Lewné M, Brauer M, Fischer P, Gehring U, van Vliet P , Heinrich J, Bellander T, Brunekreef B. Spatial variability of fine particle concentrations in three European countries. Atmospheric Environment 2002; 36:4077-4088.

32. Gehring U, Cyrys J, Sedlmeir G, Brunekreef B, Bellander T, Fischer P, Bauer CP, Reinhardt D, Wichmann HE, Heinrich J. Traffic-related air pollution and respiratory health during the first 2 yrs of life. Eur Respir J. 2002;19:690-8.

33. Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewné M, Gehring U, Bellander T, Fischer P, van Vliet P, Brauer M, Wichmann H-E, Brunekreef B. Comparison between different traffic related particle indicators: elemental carbon (EC), $PM_{2.5}$ mass and absorbance. J Exposure Anal Environ Epidemiol. 2003; 13:134–143.

34. Weiland SK, Bjorksten B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. Eur Respir J. 2004; 24:406-12.

35 Brussee JE, Smit HA, van Strien RT, Corver K, Kerkhof M, Wijga AH, et al. Allergen exposure in infancy and the development of sensitization, wheeze, and asthma at 4 years. J Allergy Clin Immunol 2005;115:946-52.

36. Brussee JE, Smit HA, Kerkhof M, Koopman LP, Wijga AH, Postma DS, Gerritsen J, Grobbee DE, Brunekreef B, de Jongste JC. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. Eur Respir J. 2005; 25:455-61.

37. Wichmann J, Janssen NAH, van der Zee S, Brunekreef B. Traffic-related differences in indoor and personal absorption coefficient measurements in Amsterdam, the Netherlands. Atmos Environ. 2005; 39: 7384-7392.

38. van Roosbroeck S, Wichmann J, Janssen NA, Hoek G, van Wijnen JH, Lebret E, Brunekreef B. Long-term personal exposure to traffic-related air pollution among school children, a validation study. Sci Total Environ. 2006; 368:565-73.

39. Sunyer J, Anto JM,Castellsague J, Soriano JB, Roca J. Total serum IgE is associated with asthma independently of specific IgE levels. The Spanish Group of the European Study of Asthma. Eur Respir J 1996; 9:1880-1884.

40. Sinclair D, Peters SA. The predictive value of total serum IgE for a positive allergen specific IgE result. J Clin Pathol 2004; 57:956-959.

41. Lau S, Nickel R, Niggemann B, Gruber C, Sommerfeld C, Illi S, et al. The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). Paediatr Respir Rev 2002;3:265-72.

42. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? Paediatr Respir Rev 2002;3:193-7

Variable	N*	Prevalence (%)
Wheeze	429 (3,528)	12.2
Doctor diagnosed asthma	144 (3,533)	4.1
Dry cough at night w/o cold	782 (3,537)	22.1
Doctor diagnosed bronchitis	214 (3,501)	6.1
Itchy rash	906 (3,537)	25.6
Doctor diagnosed eczema	503 (3,518)	14.3
E,N,T infections	1047 (3,549)	29.5
Doctor diagnosed flu, serious cold	760 (3,521)	21.6
Any positive sp IgE	277 (713)	38.8
Any indoor positive sp IgE	118 (713)	16.5
Cat allergen positive	44 (708)	6.2
Dog allergen positive	26 (706)	3.7
Dust mite allergen positive	101 (713)	14.2
Any outdoor positive sp IgE	57 (698)	8.2
Dactylium positive	47 (698)	6.7
Birch positive	16 (696)	2.3
Alternaria positive	11 (680)	1.7
Any food positive sp IgE	194 (689)	28.1
Milk allergen positive	182 (689)	26.4
Egg allergen positive	51 (681)	7.5
Total IgE > 100 IU/ml	186 (713)	26.1

Table 1. Prevalence of selected health outcomes at age 4 in the full cohort and of sensitization to specific allergens based on IgE measurement in cohort subset (age 4 yr.) All outcomes refer to incidence or diagnoses within the past 12 months, the period between 3 and 4 years of age (Online Supplementary Material - Appendix 1). * number (total valid in parentheses, based on completion of year 4 questionnaire and allergy testing where applicable) of subjects with the symptom, condition or positive IgE reaction to a specific allergen. E,N,T = ear, nose, throat. Sp IgE = specific serum IgE.

Variable	N*	Cumulative Incidence (%)
Wheeze ever	960 (3,530)	27.2
Doctor diagnosed asthma ever	258 (3,534)	7.3
Possible asthma†	52 (3,549)	1.5
Probable asthma†	516 (3,549)	14.5
Possible or probable asthma†	568 (3,549)	16.0
Early wheeze†	843 (3,872)	21.8
Late wheeze†	72 (3,872)	1.9
Persistent wheeze†	333 (3,872)	8.6
Early frequent wheeze†	353 (3,872)	9.1
Late frequent wheeze†	47 (3,872)	1.2
Persistent frequent wheeze†	58 (3,872)	3.0
Doctor diagnosed bronchitis ever	628 (3,481)	18.0

Doctor diagnosed eczema ever	974 (3,470)	28.1
Itchy rash (Eczema)[†]	1438 (3,873)	37.1
Allergic	106 (3,542)	3.0

Table 2. Cumulative incidence of selected health outcomes in the full cohort (at age 4 yr.). All outcomes refer to cumulative incidence or diagnoses within the first 4 years of life based on the 4 year questionnaire, unless indicated otherwise[†] in which cases the outcome is based upon all questionnaires (Online Supplementary Material - Appendix 2). * number (total valid in parentheses) of subjects with the symptom / condition.

Variable	N*	Prevalence (%)
[a]Mother smoking during pregnancy	583 (4,079)	14
[b]Smoking in home	1,121 (3,903)	29
[e]Smoking in home	847 (3,532)	24
[a]Intervention study	855 (4,146)	21
[a]natural history study	3,291 (4,146)	79
[a]Mattress cover (allergen-free)	416 (4,146)	10
[c]Mother ≤ Medium level professional education	1,743 (3,709)	47
[c]Mother ≥ High school education	1,966 (3,709)	53
[c]Father ≤ Medium level professional education	1,816 (3,546)	51
[c]Father ≥ High school education	1,730 (3,546)	49
[b]Male	2,035 (3,934)	52
[b]Female	1,899 (3,934)	48
[b]Gas stove	3,236 (3,911)	83
[e]Gas stove	2,545 (3,218)	79
[b]Gas water heater (unvented)	192 (3,760)	5
[e]Gas water heater (unvented)	102 (3,312)	3
[b]Any other siblings	1,986 (3,919)	51
[e]Any other siblings	2,972 (3,495)	85
[d]Netherlands ethnicity	3,478 (3,690)	94
[d]Other ethnicity	212 (3,690)	6
[b]Any breastfeeding at 3 months	1,827 (3,883)	47
[c]Any mold in home	1,215 (3,704)	33
[e]Any mold in home**	1,297 (3,523)	37
[b]Any pets in home	2,011 (3,905)	51
[e]Any pets in home***	1,864 (3,456)	54
[a]Allergic mother	1,281 (4,114)	31
[b]Allergic father	1,172 (4,051)	29
[a]Residence in North region of country	1,275 (4,146)	31
[a]Residence Middle region of country	1,647 (4,146)	40
[a]Residence in West region of country	1,224 (4,146)	29

Table 3. Prevalence of selected potential confounders in the cohort. Data collected from [a]pregnancy, [b]3 month, [c]1 year, [d]2 year, [e]4 year questionnaires (shaded rows). * Number / prevalence of subjects with the characteristic **Includes presence of molds, water damage and visible moisture in any of four specified rooms. ***"Any pet" refers to cats, dogs, rodents or birds. Prevalence of pets, gas water heater and gas stove at year 4 may not be completely accurate due to incomplete data (questions at each year are asked only for cases in which there was a change since previous year's questionnaire) which leads to a slight increase in missing values.

	$PM_{2.5}$ ($\mu g/m^3$)	Soot (filter absorbance, $10^{-5}\ m^{-1}$)	NO_2 ($\mu g/m^3$)
Minimum	13.5	0.77	12.6
10^{th} percentile	14.0	1.15	14.7
25^{th} percentile	14.8	1.33	18.2
50^{th} percentile	17.3	1.78	26.0
Mean	16.9	1.71	25.2
75^{th} percentile	18.1	1.91	28.8
90^{th} percentile	19.0	2.16	34.4
Maximum	25.2	3.68	58.4

Table 4. Summary statistics of estimated annual average air pollution concentrations for the home (birth) addresses of the full cohort (including only those 3,538 subjects for whom the 4 year questionnaire was completed and with estimated exposures, n = 3,532).

	Unadjusted			Adjusted*			Adjusted – early life**		
	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N
Wheeze									
$PM_{2.5}$	1.20	1.02 - 1.42	3,522	1.23	1.00 - 1.51	2,577	1.20	0.99 - 1.46	2,825
"soot"	1.19	1.03 - 1.38	3,522	1.18	0.98 - 1.41	2,577	1.18	1.00 - 1.40	2,825
NO_2	1.14	0.99 - 1.31	3,522	1.13	0.95 - 1.34	2,577	1.16	0.98 - 1.36	2,825
Asthma doctor diagnosis									
$PM_{2.5}$	1.21	0.92 - 1.60	3,527	1.15	0.82 - 1.62	2,575	1.32	0.96 - 1.83	2,826
"soot"	1.23	0.97 - 1.56	3,527	1.15	0.85 - 1.55	2,575	1.30	0.98 - 1.71	2,826
NO_2	1.20	0.96 - 1.51	3,527	1.12	0.84 - 1.49	2,575	1.29	0.99 - 1.69	2,826
Dry cough night									
$PM_{2.5}$	1.19	1.04 - 1.36	3,531	1.11	0.94 - 1.31	2,578	1.14	0.98 - 1.33	2,830
"soot"	1.19	1.06 - 1.34	3,531	1.13	0.97 - 1.30	2,578	1.14	1.00 - 1.31	2,830
NO_2	1.17	1.05 - 1.30	3,531	1.11	0.97 - 1.28	2,578	1.11	0.97 - 1.26	2,830
Bronchitis doctor diagnosis									
$PM_{2.5}$	0.96	0.77 - 1.21	3,496	0.88	0.66 - 1.18	2,559	0.86	0.66 - 1.11	2,807
"soot"	0.98	0.80 - 1.20	3,496	0.90	0.69 - 1.16	2,559	0.88	0.69 - 1.11	2,807
NO_2	0.97	0.80 - 1.17	3,496	0.90	0.70 - 1.15	2,559	0.89	0.71 - 1.12	2,807
E,N,T infections									
$PM_{2.5}$	1.11	0.98 - 1.25	3,543	1.13	0.98 - 1.31	2,587	1.17	1.02 - 1.34	2,839
"soot"	1.12	1.00 - 1.24	3,543	1.15	1.01 - 1.31	2,587	1.16	1.03 - 1.31	2,839
NO_2	1.13	1.03 - 1.25	3,543	1.17	1.03 - 1.32	2,587	1.18	1.05 - 1.32	2,839
Flu/serious cold doctor diagnosis									
$PM_{2.5}$	1.17	1.02 - 1.33	3,515	1.21	1.02 - 1.42	2,572	1.25	1.07 - 1.46	2,820
"soot"	1.16	1.03 - 1.30	3,515	1.18	1.02 - 1.36	2,572	1.19	1.04 - 1.37	2,820
NO_2	1.13	1.01 - 1.27	3,515	1.14	1.00 - 1.31	2,572	1.17	1.02 - 1.33	2,820
Itchy rash									
$PM_{2.5}$	1.07	0.95 - 1.22	3,531	0.96	0.82 - 1.11	2,582	0.98	0.85 - 1.14	2,832
"soot"	1.06	0.95 - 1.18	3,531	0.94	0.82 - 1.08	2,582	0.97	0.85 - 1.10	2,832
NO_2	1.05	0.95 - 1.17	3,531	0.95	0.83 - 1.08	2,582	0.97	0.86 - 1.10	2,832
Eczema doctor diagnosis									
$PM_{2.5}$	1.10	0.97 - 1.25	3,464	1.00	0.83 - 1.21	2,571	0.98	0.82 - 1.17	2,819
"soot"	1.09	0.98 - 1.22	3,464	0.99	0.84 - 1.17	2,571	0.97	0.83 -1.14	2,819
NO_2	1.06	0.95 - 1.17	3,464	1.00	0.85 - 1.17	2,571	0.97	0.83 - 1.14	2,819

Table 5. Association between exposure to air pollution and infections, asthmatic and allergic symptoms at age four for full cohort based on recent and early life risk factors. Crude and adjusted odds ratios and 95% Confidence intervals. *OR and 95% CI adjusted for confounders in Table 3 and mothers' age at time of birth, but not region and **with confounders from earliest year available instead of year 4 for shaded variables in Table 3. OR are calculated for an interquartile range increase in annual average concentration at birth address.

	Unadjusted			Adjusted*		
	OR	95% CI	N	OR	95% CI	N
Any allergen positive						
$PM_{2.5}$	1.46	1.13 - 1.88	704	1.55	1.13 - 2.11	502
"soot"	1.37	1.09 - 1.71	704	1.45	1.11 - 1.91	502
NO_2	1.27	1.03 - 1.55	704	1.32	1.03 - 1.70	502
Any indoor allergen positive						
$PM_{2.5}$	1.14	0.82 - 1.57	732	1.03	0.69 - 1.55	524
"soot"	1.12	0.85 - 1.49	732	1.02	0.71 - 1.46	524
NO_2	1.01	0.78 - 1.32	732	0.97	0.69 - 1.36	524
Any outdoor allergen positive						
$PM_{2.5}$	0.92	0.59 - 1.44	685	0.93	0.54 - 1.58	488
"soot"	0.91	0.62 - 1.36	685	0.95	0.59 - 1.52	488
NO_2	0.94	0.66 - 1.36	685	0.92	0.59 - 1.43	488
Any food allergen positive						
$PM_{2.5}$	1.59	1.20 - 2.11	708	1.75	1.23 - 2.47	506
"soot"	1.50	1.18 - 1.92	708	1.64	1.21 - 2.23	506
NO_2	1.41	1.13 - 1.76	708	1.49	1.13 - 1.97	506
Total IgE > 100 IU/ml						
$PM_{2.5}$	0.99	0.75 - 1.30	738	0.84	0.59 - 1.18	529
"soot"	0.95	0.75 - 1.21	738	0.80	0.59 - 1.09	529
NO_2	0.97	0.77 - 1.21	738	0.81	0.60 - 1.09	529

Table 6. Association between term exposure to air pollution and allergen sensitivity age four for subset of cohort with blood samples, based on early life risk factors. Crude and adjusted odds ratios and 95% Confidence intervals. *OR and 95% CI adjusted for confounders listed in Table 3 (with confounders from earliest year available instead of year 4 for shaded variables in Table 3) and mothers' age at time of birth, but not region. OR are calculated for an interquartile range increase in annual average concentration at birth address.

	Unadjusted			Adjusted*		
	OR	95% CI	N	OR	95% CI	N
Wheeze (ever)						
$PM_{2.5}$	1.15	1.02 - 1.31	3,524	1.22	1.06 - 1.41	2,575
"soot"	1.13	1.02 - 1.26	3,524	1.18	1.04 - 1.34	2,575
NO_2	1.11	1.00 - 1.23	3,524	1.19	1.05 - 1.34	2,575
Asthma doctor diagnosis (ever)						
$PM_{2.5}$	1.17	0.95 - 1.45	3,528	1.32	1.04 - 1.69	2,575
"soot"	1.16	0.96 - 1.39	3,528	1.26	1.02 - 1.56	2,575
NO_2	1.16	0.98 - 1.38	3,528	1.28	1.04 - 1.56	2,575
Probable asthma						
$PM_{2.5}$	1.18	1.01 - 1.38	3,543	1.08	0.90 - 1.30	2,588
"soot"	1.16	1.01 - 1.33	3,543	1.06	0.90 - 1.24	2,588
NO_2	1.12	0.98 - 1.27	3,543	1.04	0.89 - 1.22	2,588
Early wheeze						
$PM_{2.5}$	1.05	0.92 - 1.19	3,863	1.16	1.00 - 1.34	2,588
"soot"	1.02	0.91 - 1.14	3,863	1.11	0.97 - 1.26	2,588
NO_2	1.03	0.93 - 1.15	3,863	1.13	1.00 - 1.28	2,588
Persistent wheeze						
$PM_{2.5}$	1.19	0.99 - 1.43	3,863	1.19	0.96 - 1.48	2,588
"soot"	1.17	1.00 - 1.38	3,863	1.18	0.98 - 1.42	2,588
NO_2	1.10	0.94 - 1.28	3,863	1.13	0.94 - 1.35	2,588
Early frequent wheeze						
$PM_{2.5}$	1.15	0.96 - 1.39	3,863	1.19	0.96 - 1.47	2,588
"soot"	1.12	0.95 - 1.31	3,863	1.14	0.95 - 1.37	2,588
NO_2	1.09	0.94 - 1.27	3,863	1.14	0.95 - 1.36	2,588
Bronchitis doctor diagnosis (ever)						
$PM_{2.5}$	0.99	0.86 - 1.14	3,475	0.96	0.81 - 1.13	2,543
"soot"	0.99	0.87 - 1.12	3,475	0.95	0.82 - 1.10	2,543
NO_2	0.96	0.85 - 1.08	3,475	0.94	0.82 - 1.08	2,543
Itchy rash (Eczema)						
$PM_{2.5}$	1.04	0.93 - 1.16	3,864	0.99	0.88 - 1.13	2,588
"soot"	1.03	0.94 - 1.14	3,864	0.99	0.89 - 1.11	2,588
NO_2	1.01	0.93 - 1.11	3,864	0.98	0.88 - 1.09	2,588
Eczema doctor diagnosis (ever)						
$PM_{2.5}$	1.10	0.97 - 1.25	3,464	0.98	0.85 - 1.13	2,536
"soot"	1.09	0.98 - 1.22	3,464	0.99	0.87 - 1.12	2,536
NO_2	1.06	0.95 - 1.17	3,464	0.97	0.86 - 1.10	2,536

Table 7. Association between exposure to air pollution and cumulative lifetime indicators of asthma and allergy status symptoms at age four for full cohort members with estimated exposures and completed year 4 questionnaire, based on early life risk factors. Crude and adjusted odds ratios and 95% Confidence intervals. *OR and 95% CI adjusted for confounders in Table 3 (with confounders from earliest year available instead of year 4 for shaded variables in Table 3) and mothers' age at time of birth but not region. OR are calculated for an interquartile range increase in annual average concentration at birth address.