Atopic Diseases, Allergic Sensitization, and Exposure to Traffic-related Air Pollution in Children

Verena Morgenstern[1], Anne Zutavern[1,2], Josef Cyrys[1,3], Inken Brockow[4], Sibylle Koletzko[2], Ursula Krämer[5], Heidrun Behrendt[6], Olf Herbarth[7,8], Andrea von Berg[9], Carl Peter Bauer[4], H.-Erich Wichmann[1,10], and Joachim Heinrich[1], for the GINI and LISA Study Groups

[1]Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich, Germany; [2]Ludwig-Maximilians University of Munich, Dr. v. Hauner's Children's Hospital, Munich, Germany; [3]University Augsburg, WZU–Environmental Science Center, Germany; [4]Technical University Munich, Children's Hospital, Munich, Germany; [5]Institut für Umweltmedizinische Forschung, Working Area Epidemiology, Düsseldorf, Germany; [6]Technical University Munich, Division of Environmental Dermatology and Allergy, ZAUM–Center for Allergy and Environment, Munich, Germany; [7]UFZ–Human Exposure Research and Epidemiology at the UFZ Leipzig-Halle, Leipzig, Germany; [8]Faculty of Medicine, Environmental Medicine and Environmental Hygiene, University of Leipzig, Leipzig, Germany; [9]Marien-Hospital Wesel, Wesel, Germany; and [10]Ludwig-Maximilians University of Munich, Institute of Medical Data Management, Biometrics and Epidemiology, Munich, Germany

***Rationale*: *In vitro* studies, animal experiments, and human exposure studies have shown how ambient air pollution increases the risk of atopic diseases. However, results derived from observational studies are inconsistent.**

***Objectives*: To assess the relationship between individual-based exposure to traffic-related air pollutants and allergic disease outcomes in a prospective birth cohort study during the first 6 years of life.**

***Methods*: We studied 2,860 children at the age of 4 years and 3,061 at the age of 6 years to investigate atopic diseases and allergic sensitization. Long-term exposure to particulate matter ($PM_{2.5}$), $PM_{2.5}$ absorbance, and nitrogen dioxide (NO_2) was assessed at residential addresses using geographic information systems based regression models and air pollution measurements. The distance to the nearest main road was used as a surrogate for traffic-related air pollutants.**

***Measurements and Main Results*: Strong positive associations were found between the distance to the nearest main road and asthmatic bronchitis, hay fever, eczema, and sensitization. A distance-dependent relationship could be identified, with the highest odds ratios (ORs) for children living less than 50 m from busy streets. For $PM_{2.5}$ absorbance, statistically significant effects were found for asthmatic bronchitis (OR, 1.56; 95% confidence interval [CI], 1.03–2.37), hay fever (OR, 1.59; 95% CI, 1.11–2.27), and allergic sensitization to pollen (OR, 1.40; 95% CI, 1.20–1.64). NO_2 exposure was associated with eczema, whereas no association was found for allergic sensitization.**

***Conclusions*: This study provides strong evidence for increased risk of atopic diseases and allergic sensitization when children are exposed to ambient particulate matter.**

Keywords: air pollution; GIS; allergic sensitization; allergy

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Epidemiologic investigations on exposure to traffic-related air pollutants and atopic outcomes have found inconsistent results.

What This Study Adds to the Field

This study provides strong evidence for the adverse effects of traffic-related air pollutants on atopic diseases, as well as on allergic sensitization, when individual-based exposure assessment strategies are applied.

The prevalence of allergic diseases has increased in Europe during the past decades (1), with the increased exposure to traffic-related air pollutants as one speculative reason for this rise in allergic disease. According to the latest assessment of air quality conducted in January 2005 by the European Commission, high concentrations of particulate matter (PM) led to approximately 348,000 premature deaths in the European Union in 2000, despite projected significant reductions in annual PM impact between 2000 and 2020 (2). According to the World Health Organization (WHO), life expectancy is reduced by 8.6 months in the European Union and by 10.2 months in Germany by adverse effects from current levels of PM concentrations (3).

The literature is inconclusive regarding the interaction between traffic-related air pollutants and allergic sensitization. For example, a study in Switzerland found increased allergic sensitization to pollen allergens in adults living close to a major road for more than 10 years (4). However, in another study in Germany, such associations were not observed (5). A number of pediatric studies found inconsistent associations between allergic diseases and exposure to air pollutants (6). Even the use of the highly standardized outcome assessment of the International Study of Asthma and Allergies in Childhood (ISAAC) in two cities in Germany led to conflicting results on the link between hay fever and exposure to traffic-related air pollutants (7, 8). The WHO's review on the health effects of transport-related air pollution (9) concluded that substantial evidence from controlled human exposure studies (10) and animal experiments (11, 12) indicates that transport-related air pollution can increase the risk of allergy development and exacerbate allergic reaction. However, there is no evidence from long-term clinical trials and only weak evidence from epidemiologic studies to support this conclusion. Due to inconsistent results from available epidemiologic studies (6, 9), it is clear that further research is needed. One possible reason for the inconsistent findings in studies investigating allergies and

(*Received in original form January 8, 2007; accepted in final form March 12, 2008*)

Supported by grants from the BMU (for the Institut für Umweltmedizinische Forschung; FKZ 20462296) and the Federal Ministry for Education, Science, Research, and Technology (no. 01EG9705/2 and 01EG9732). The determination of specific IgE antibodies was financially supported by the Child Health Foundation (Stiftung Kindergesundheit).

A listing of the participants in the GINI and LISA study groups may be found before the REFERENCES.

Correspondence and requests for reprints should be addressed to Joachim Heinrich, Helmholtz Zenrum München, German Research Center for Environmental Health, Institute of Epidemiology, Ingolstaedter Landstrasse 1, D-85764 Neuherberg, Germany. E-mail: joachim.heinrich@helmholtz-muenchen.de

Am J Respir Crit Care Med Vol 177. pp 1–7, 2008
Originally Published in Press as DOI: 10.1164/rccm.200701-036OC on March 12, 2008
Internet address: www.atsjournals.org

traffic-related air pollutants could be insufficient exposure assessment (6). Traditionally, data from the nearest air pollution–monitoring site were used to estimate exposure in these studies. In the present study, however, individual estimated exposure levels were derived with GIS (geographical information systems)–based modeling. Only a few studies have combined geographic data with concentration measurements to calculate individual exposure (14–18); yet, they have provided good approximations of long-term average exposures. We applied this exposure model to two Munich birth cohorts: the GINI (German Infant Nutritional Intervention) study and the LISA (Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in East and West Germany) cohorts.

Data regarding allergy-related health effects to the age of 2 years from these cohorts have previously been published (16, 19). However, children of this age were too young to study asthma and hay fever outcomes. The purpose of this study is to analyze longitudinally the effects of individual-based exposure to traffic-related air pollutants on respiratory and allergic health outcomes. Preliminary results were published as an abstract (20).

METHODS

Study Area

This study was conducted in the Munich metropolitan area. In December 2005, the city of Munich had a population of approximately 1.29 million (21) covering an area of 310 km^2. The newborns were recruited in obstetric hospitals in the city of Munich. Because several families had moved outside the city boundaries, we extended the study area to the Munich metropolitan area. This includes the surrounding suburbs (Munich rural, Ebersberg, Fürstenfeldbruck, Starnberg, Freising, Erding, and Dachau) covering approximately 1,200 km^2. For more details, *see* Morgenstern and colleagues (16).

Study Population

The study population consists of two prospective birth cohort studies (GINI and LISA) in the Munich metropolitan area. Detailed descriptions of the design of these cohort studies have been published elsewhere (22, 23). Briefly, 2,300 children from the GINI birth cohort were selected from the Munich metropolitan area; 1,714 children could be followed up for the first 3 years, 1,900 children within the first 6 years (*see* Figure 1). The LISA cohort consists of 1,286 children living in the Munich metropolitan area. At 2 years of age, the data of 1,146 children were still in the study and at 6 years 1,166 children were still in the study. Between the second/third year and the sixth year, some children, mainly from the GINI cohort, reentered the study, and for the second/third year some addresses were not available.

According to the availability of the children's addresses, exposure assessment was calculated at three different time points (birth, 2 or 3 years, and 6 years). The estimated individual air pollution levels at the different time points were then linked with the outcome variables shown in Table 1. The studies were approved by the Bavarian Medical Association (Landesärztekammer Bavaria) and were performed in accordance with the institutional guidelines for the protection of human subjects. Informed consent was obtained from all parents of the participating children.

Questionnaire Data

All data on health outcomes and potential confounding variables were obtained through questionnaires that were completed by the parents. The parents from the LISA cohort members received questionnaires when the children were 6 months, 1 year, 1.5 years, 2 years, 4 years, and 6 years old. In the GINI cohort, the questionnaires were distributed at 1, 2, 3, 4, and 6 years of age. For the investigation at 6 years of age for both the GINI and LISA cohort, the aforementioned ISAAC questionnaires were used.

Definition of the Outcomes

Parents were asked the following: "Has a physician diagnosed any of the following diseases during the past year of life: . . . asthmatic/spastic/obstructive bronchitis, asthma, hay fever, allergic/eczema?" If the parents selected yes, the child was defined to have "physician-diagnosed disease," which was the primary outcome parameter.

The symptoms were obtained using the following question: "Did your child have . . . wheezing attacks, sneezing attacks during the past year of life?" An asthmatic/spastic/obstructive bronchitis/asthma symptom was defined by wheezing, hay fever symptom by sneezing/running/stuffed nose without a cold, and eczema symptom (at 6 yr of age) as ever having itchy skin lesions that lasted for at least 6 months or were present in the preceding 12 months. At 4 years of age, the eczema symptom was defined as having itchy skin during the last 12 months and lasting for at least 2 weeks. For the analysis, the outcomes asthma and asthmatic/spastic/obstructive bronchitis were combined into the variable asthmatic/spastic/obstructive bronchitis.

Assessment of Allergic Sensitization

Specific IgE against common food allergens and inhalant allergens was determined at 6 years of age by standardized methods with CAP-RAST FEIA (Pharmacia Diagnostics, Freiburg, Germany). A screening test for atopy was used to detect specific IgE antibodies against inhalant allergens (SX1: timothy grass, rye, birch, mugwort, house dust mite, cats, dogs, and molds) in the serum. The children who had positive results for

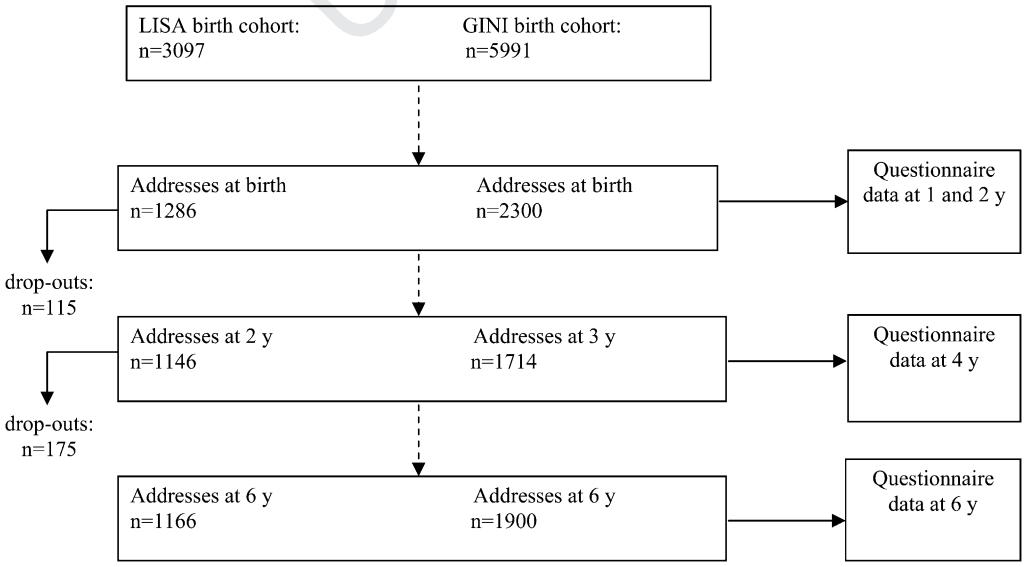

Figure 1. Timing of exposure assessment and available questionnaire data. *Results published in Reference 16.

TABLE 1. DESCRIPTION OF THE STUDY COHORT

	Frequency			
	Age 4 yr		Age 6 yr	
Variable	n/Total n	%	n/ Total n	%
Diseases and symptoms*				
Doctor-diagnosed asthmatic/spastic/ obstructive bronchitis/ asthma	277/2,545	10.9	187/2,817	6.6
Doctor-diagnosed hay fever	72/2,776	2.6	162/2,807	5.8
Doctor-diagnosed allergic/atopic eczema	281/2,696	10.4	257/2,814	9.1
Symptom for asthmatic/spastic/ obstructive bronchitis/ asthma	284/2,686	10.6	234/2,626	8.2
Symptom for hay fever	278/2,696	10.3	452/2,862	15.8
Symptom for eczema	432/2,786	15.5	120/2,453	4.9
Allergic sensitization ⩾ 0.35 kU/L				
Inhalant sensitization†	NA	NA	489/1,554	31.5
Outdoor positive‡	NA	NA	287/1,352	21.2
Indoor positive§	NA	NA	186/1,352	13.8
Confounding variables				
Female sex	1,398/2,693	51.6	1,486/2,881	51.6
Parental atopy	1,484/ 2,810	52.8	1,385/3,061	45.3
ETS at home	545/2,631	20.7	573/2,881	19.9
Maternal education				
Less than 12 grades	1,894/2,696	70.3	1,909/2,725	70.1
12 or more grades	1,058/2,696	39.2	1,074/2,725	39.4
Siblings	1,165/2,652	43.9	2,223/2,867	58.6
Use of gas for cooking	228/2,674	8.5	222/2,861	7.8
Home dampness	183/2,676	6.8	89/2,861	3.1
Indoor molds	817/2,675	30.5	415/2,755	15.1
Keeping of pets	555/2,666	20.8	856/2,873	29.8
Cat	246/2,660	9.3	346/2,869	12.1
Dog	132/ 2,660	5.0	196/2,869	6.8

Definition of abbreviation: ETS = environmental tobacco smoke.

* Doctor-diagnosed diseases refer to parental reports of doctors' diagnoses, whereas symptoms refer to parental reports only.

† Including timothy grass, rye, birch, mugwort, house dust mite, cat, dog, and molds.

‡ Including timothy grass, rye, birch, and mugwort.

§ Including house dust mite, cat, dog, and molds.

SX1 were tested for single specific allergens. Sensitization to pollen allergens (outdoor) included timothy grass, rye, birch, and mugwort, and sensitization to indoor allergens included house dust mite, cats, dogs, and molds. Inhalant sensitization and specific allergen sensitization were defined as any specific IgE antibody value of 0.35 kU/L or greater.

Air Pollution Measurements and Exposure Assessment

Details about the air pollution measurements have been described elsewhere (24, 25).

Briefly, 40 measurement sites for PM and NO_2 were selected within the city of Munich. Four measurements were taken at each of the 40 sites so that each site was measured in each season once. All measurements were made during 2-week intervals between March 1999 and July 2000. Sampling periods were approximately 14 days, during which the air was sampled for 15 minutes every 2 hours for a total of approximately 42 hours per sampling period. $PM_{2.5}$ (PM of 2.5 μm in diameter and smaller) was assessed using Harvard impactors; $PM_{2.5}$ absorbance from the reflectance of the PM filters (25) and NO_2 were measured using Palmes tubes (26).

Because it is not feasible to measure personal exposure to traffic-related air pollutants for all study subjects, exposure modeling was used. For each pollutant, a linear model was fitted with a subset of the following characteristics as covariates: distance to different types of roads, length of each type of road within various buffers, land coverage, population, and household density (within a postcode area). The model precision was estimated by cross-validation (16). The same models were then applied to the addresses at birth (GINI and LISA), at 2 years (LISA) or 3 (GINI) years, and at 6 years (GINI and LISA). The distance to the nearest main road was assigned as the minimum distance to the next motorway, federal road, or state road. We also looked at the association between living close to a main road and the allergic disease outcomes. The cutoff for the variable "living close to main road" was 50 m. This was based on the hypothesis that the largest contribution from main streets to the air pollution is expected at short distances. Afterward, we categorized this variable as <50 m, 50–250 m, 250–1,000 m, and >1,000 m to investigate the dose–response relationship in more detail.

Statistical Analysis

We analyzed the association between individual exposure to the traffic-related air pollutants $PM_{2.5}$, $PM_{2.5}$ absorbance, and NO_2, and the development of allergic symptoms and diseases with marginal logistic regression models (generalized estimating equations) adjusting for potential confounding factors. The association between the pollutants and allergic sensitization was assessed using multiple logistic regression models. The individual confounders that were used were identified in our previous studies (16, 19). These were sex, parental atopy, parental education, siblings, environmental tobacco smoke at home, use of gas for cooking, home dampness, indoor molds, and keeping of pets. Because measurements on the same experimental unit are likely to be correlated, repeated measurements analysis must account for that correlation. One way of doing this is modeling the covariance structure of an individual's response. The first-order autoregressive covariance structure models so that the covariance of measurements that are close together in time are higher than the covariance for measurements further apart. In addition, the age of the child as a continuous variable was entered into the models to remove the confounding effects of growth of the child on the health–exposure relationship.

Using this approach allows to adjust the individual-based air pollution estimates at three different time points (the birth addresses [GINI and LISA], the 2- [LISA] or 3- [GINI] year addresses, and 6-year addresses [GINI and LISA]). All odds ratios (ORs) are presented as an interquartile range increase in air pollution concentration. Statistical significance was defined by a two-sided α level of 5%, and thus 95% confidence intervals (CIs) were given. All statistical analyses were performed using SAS version 9.01 (SAS Institute, Cary, NC).

RESULTS

Study Population

The characteristics of the study population are summarized in Table 1. The frequency of hay fever and its symptoms increased between the fourth and sixth years of age, whereas the frequency of asthmatic/spastic/obstructive bronchitis and its symptoms and eczema decreased.

The prediction models were applied to the addresses available at the different time points. For descriptive statistics of the individual-based estimated levels of the air pollutants at the two relevant time points, *see* Table 2. Nearly a quarter (24.4%) of our study population lived less than 50 m from a major street, 37.0% lived between 50 and 250 m, and 9% lived between 250 and 1,000 m from a major street.

Between the 2-/3-year and the 6-year estimates, no considerable changes in air pollution exposure levels were observed.

Relationship between Ambient Air Pollutant Exposure and Allergic Diseases and Symptoms and Allergic Sensitization

The associations between exposure to air pollutants and asthmatic and allergic outcomes are given in Table 3. The associations between exposure to the air pollutants and allergic sensitization are shown in Table 4. After controlling for individual confounders, statistically significant positive associations were found between the pollutant $PM_{2.5}$ absorbance and asthmatic/spastic/obstructive bronchitis and hay fever. NO_2 was positively associ-

TABLE 2. ANNUAL AVERAGE CONCENTRATIONS FOR $PM_{2.5}$, $PM_{2.5}$ ABSORBANCE, AND NO_2 ESTIMATED FOR THE RESIDENTIAL ADDRESSES

	Min	10th	25th	50th	Mean	75th	90th	Max
At 2 or 3 yr of age								
$PM_{2.5}$, $\mu g/m^3$	1.3	6.5	8.3	12.4	11.1	13.1	13.7	15.0
$PM_{2.5}$ absorbance, 10^{-5} m^{-1}	1.1	1.5	1.6	1.7	1.7	1.8	2.0	3.3
NO_2, mg/m^3	8.0	28.4	31.4	34.5	34.7	37.8	39.3	58.4
At 6 yr of age								
$PM_{2.5}$, $\mu g/m^3$	9.2	10.2	10.5	11.0	11.1	11.5	12.0	13.0
$PM_{2.5}$ absorbance, 10^{-5} m^{-1}	1.1	1.5	1.6	1.7	1.7	1.8	2.0	2.9
NO_2, mg/m^3	16.0	29.3	32.2	34.0	34.6	37.7	40.5	73.7

ated with eczema. Distance to main roads and asthmatic/spastic/obstructive bronchitis (symptoms and diseases) were significantly associated (Table 3).

When we additionally investigated the association between the pollutants and atopic dermatitis (eczema and sensitization), the effect estimates became even higher. Further sensitivity analyses for distance to main roads (categorized in <50 m, 50–250 m, 250–1,000 m, and >1,000 m) resulted in clear distance-dependent effect estimates (*see* Figure 2). Children living closer than 50 m to a busy street had the highest probability of getting allergic symptoms compared with children living further away than 50 m, 250 m, and 1,000 m (reference category). In general, the effects were stronger for the doctor-diagnosed outcomes than for the symptoms, but the corresponding diagnoses and symptoms showed corresponding values (Figure 2).

The results for allergic sensitization showed significant associations between sensitization to outdoor allergens (pollen) and $PM_{2.5}$, $PM_{2.5}$ absorbance, and distance to nearest main road (Table 4). Neither the pollutants nor the distances had any associations with indoor allergens. A clear dose–response relationship was seen for sensitization to inhalant allergens and pollen allergens. For the indoor allergens, however, the dose–response relationship was less clear (*see* Figure 3).

DISCUSSION

We assessed the association between long-term exposure to traffic-related air pollutants and atopic diseases and allergic sensitization in a cohort of young children. We additionally analyzed the association between living close to main roads and allergic outcomes. We consistently found strong associations between the distance to the nearest main road and the allergic disease outcomes. Statistically significant effect estimates for the association between $PM_{2.5}$, $PM_{2.5}$ absorbance, and sensitization to inhalant allergens and pollen were found. For the variable "living close to main roads," a clear dose–response relationship could be identified with the highest effect estimates for children living less than 50 m from busy streets (*see* Figure 2).

Previous analyses of the LISA and GINI cohorts at age 1 and 2 years showed significant associations between the air pollutants $PM_{2.5}$, $PM_{2.5}$ absorbance, and NO_2, and cough without infection, dry cough at night, and otitis media. At age 2 years, these effects were attenuated (19, 27). The same analyses were conducted in a larger geographical area and thus in a larger cohort using different models for the same pollutants (16). We previously concluded that these adverse health effects should be confirmed when the children are older and further outcomes like asthma or hay fever should be included. These outcome parameters can only be assessed beyond the second year of life. Therefore, we used data from the same ongoing cohorts when the children were 4 and 6 years of age.

The results, taken together with the findings from Wyler and colleagues (4), suggest that living on busy roads is associated with a higher risk for sensitization to pollen and could be interpreted as an indication for interaction between pollen and air pollutants and the effect of this interaction on the human immune response. This argument is strengthened by the altered morphology of pollen in polluted areas (28). Furthermore, other investigations of dust samples from highly polluted areas in Germany showed a significant degree of particle agglomeration on the surface of pollen grains (29). For all inhalant allergens, we found strong, statistically significant associations with the pollutants, although they were the lowest for NO_2. A positive association between the increase in PM and an increased prevalence of respiratory and atopic indicators was found in a study conducted in six French cities (30). Within the Dutch PIAMA cohort, several positive associations between the traffic-related air pollutants and wheezing, asthma diagnosis, and respiratory infections such as flu or serious colds, and ear, nose, throat infection were observed. In addition, positive associations were found between air pollution and specific sensitization to common food allergens. This study, however, does not use the advantages of the longitudinal design of their cohort and thus used multiple logistic regression models (15). A study in a cohort of Southern California schoolchildren (5–7 yr of age) also indicates that residence near a major road is associated with asthma (18).

A cross-sectional study in Dutch schoolchildren found that sensitization to pollen increased with relation to truck but not car traffic counts (32). With the data from our study, this differentiation is not possible. As a marker for diesel exhaust particles, we

TABLE 3. ASSOCIATION (ODDS RATIOS) BETWEEN AN INCREASE (PER INTERQUARTILE RANGE) IN THE POLLUTANT AND PREVALENCE OF ASTHMATIC AND ALLERGIC SYMPTOMS

	Doctor-diagnosed Diseases			Parental Reports of Symptoms		
Exposure Variable	Asthmatic/Spastic/Obstructive Bronchitis or Asthma (*n = 2,436*)	Hay Fever (*n = 2,488*)	Eczema (*n = 2,430*)	Symptoms for Asthmatic/Spastic/Obstructive Bronchitis or Asthma (*n = 2,496*)	Symptoms for Hay Fever (*n = 2,508*)	Symptoms for Eczema (*n = 2,495*)
$PM_{2.5}$ (per 1.0 $\mu g/m^3$)	1.12 (0.94–1.29)	1.01 (0.91–1.12)	1.00 (0.97–1.04)	0.97 (0.91–1.02)	1.02 (0.96–1.08)	1.05 (0.90–1.37)
$PM_{2.5}$ abs (per 0.2*10 – 5 m^{-1})	**1.56 (1.03–2.37)**	**1.59 (1.11–2.27)**	1.03 (0.86–1.24)	0.96 (0.83–1.11)	1.11 (0.93–1.31)	1.05 (0.93–1.47)
NO_2 (per 6.4 $\mu g/m^3$)	1.04 (0.67–1.39)	1.05 (0.77–1.45)	**1.18 (1.00–1.39)**	1.03 (0.90–1.17)	1.07 (0.94–1.22)	1.11 (0.98–1.50)
Distance to nearest main road <50 m (yes vs. no)	**1.66 (1.01–2.59)**	1.16 (0.67–2.00)	0.96 (0.72–1.11)	**1.24 (1.01–1.52)**	0.96 (0.78–1.20)	0.99 (0.87–1.35)

Definition of abbreviation: abs = absorbance.

Values are adjusted for sex, age, parental atopy, maternal education, siblings, environmental tobacco smoke at home, use of gas for cooking, home dampness, indoor molds, keeping of dogs and cats.

TABLE 4. ASSOCIATION (ODDS RATIOS) BETWEEN AN INCREASE (PER INTERQUARTILE RANGE) IN THE POLLUTANT AND ALLERGIC SENSITIZATION AT 6 YEARS OF AGE

Exposure Variable	Any Inhalant Sensitization* (*n = 1,353*)	Outdoor Positive* (*n = 1,351*)	Indoor Positive* (*n = 1,352*)
$PM_{2.5}$ (per 1.5 μg/m³)	**1.45 (1.21–1.74)**	**1.52 (1.23–1.87)**	0.92 (0.66–1.46)
$PM_{2.5}$ abs (per 0.4*10^{-5} m^{-1})	**1.40 (1.20–1.64)**	**1.36 (1.14–1.63)**	0.92 (0.69–1.50)
NO_2 (per 8.5 μg/m³)	1.03 (0.86–1.25)	1.00 (0.81–1.23)	0.95 (0.66–1.42)
Distance to nearest main road <50 m (yes vs. no)	**1.30 (1.02–1.66)**	**1.33 (1.00–1.78)**	1.07 (0.88–1.90)

Definition of abbreviation: abs = absorbance.

Positive = IgE antibodies ⩾ 0.35 kU/L. Values are adjusted for sex, age, parental atopy, maternal education, siblings, environmental tobacco smoke at home, use of gas for cooking, home dampness, indoor molds, keeping of dogs and cats.

* Defined as in Table 1: any inhalant sensitization (outdoor positive or indoor positive) outdoor positive (timothy grass, rye, birch, mugwort) indoor positive (house dust mite, cat, dog, molds).

measured $PM_{2.5}$ absorbance. We were unable to differentiate between heavy- and light-duty vehicles. Several other studies have shown that trucks (most often fueled with diesel) are associated with reduced lung function and increased prevalence of chronic respiratory symptoms (33, 34). In general, our findings concerning respiratory illness and their symptoms are consistent with the literature (35–39).

Because our GIS-based models comprise mainly broad-scale predictors (17), we could more accurately determine the local associations using the distance measurements. This allowed us to assess exposure to a less diluted aerosol and to a fresh motor vehicle–originated aerosol. Traffic-related particles coagulate and condensate within seconds after emission. The composition and the particle distribution change greatly with increasing distance to major roads (40, 41). Those living very close to a major road are likely to be exposed not only to a higher amount of traffic-derived particles and gases but also to a more freshly emitted aerosol, which may be more toxic. This assumption is strengthened by the strong dose–response relationship, which has been found in our study. Our study, however, could not disentangle the effects between the distances to the roads and the pollutants, because a major component of the modeled pollutants is the distance to the different road types.

Because we assessed the individual-based exposure models to the addresses at three different time points and built longitudinal models, we could incorporate the residential history of the study participants very precisely and we did not have to exclude children who moved within the first 6 years of life in the Munich metropolitan area. Moreover, these data were advantageous because we could track the children's living habits and use this information for more detailed analyses. Furthermore, we took residual confounding into account. However, the building structure in old European cities like Munich showed that a substantial fraction of the Munich population is living rather close to busy roads and living close to busy roads is not restricted to less advantaged people (42). Income turned out not to be a confounding factor in the present analyses. As in most epidemiologic studies, looking at confounding factors was limited to the questionnaire-derived variables. One has to bear in mind that confounding and exposure misclassifications are limitations of this study.

In conclusion, our findings provide strong evidence for the adverse effects of traffic-related air pollutants on atopic diseases as well as on allergic sensitization. The results regarding allergic symptoms contribute substantially to the current knowledge of traffic exposure and allergic sensitization (4–9, 30–39). We found negative effects for children living closer than 50 m from a busy road, with declining effects for children living farther

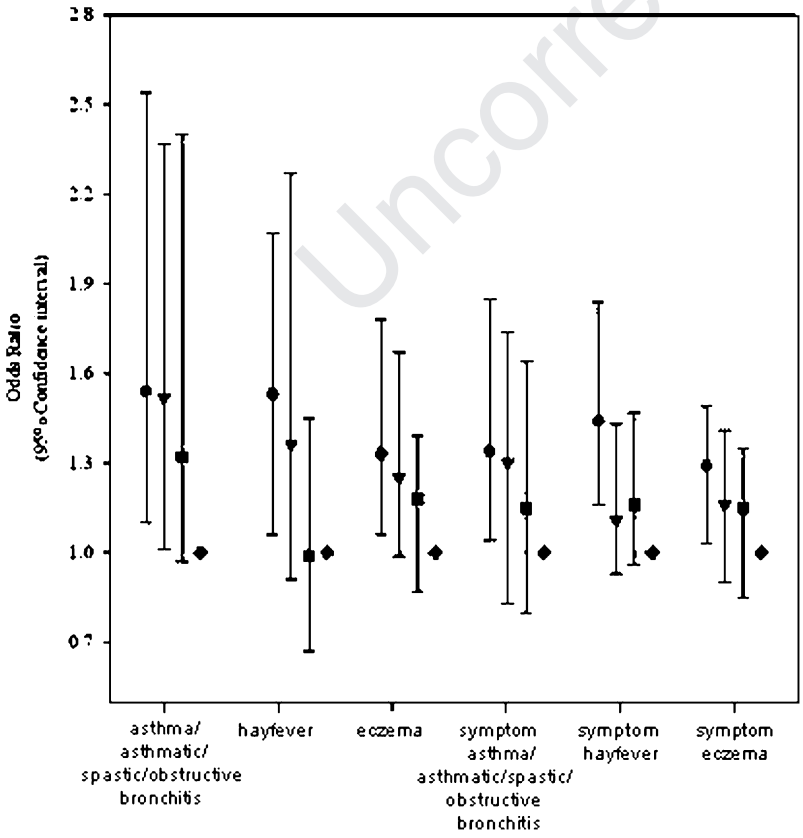

Figure 2. Association (odds ratios) between distance to nearest road (reference, >1,000 m) and prevalence of asthmatic and allergic symptoms. #Adjusted for sex, age, parental atopy, maternal education, siblings, environmental tobacco smoke at home, use of gas for cooking, home dampness, indoor molds, keeping of dogs and cats. *Circles*, distance to nearest main road <50 m; *inverted triangles*, distance to nearest main road 50–250 m; *squares*, distance to nearest main road 250–1,000 m; *diamonds*, distance to nearest main road >1,000 m.

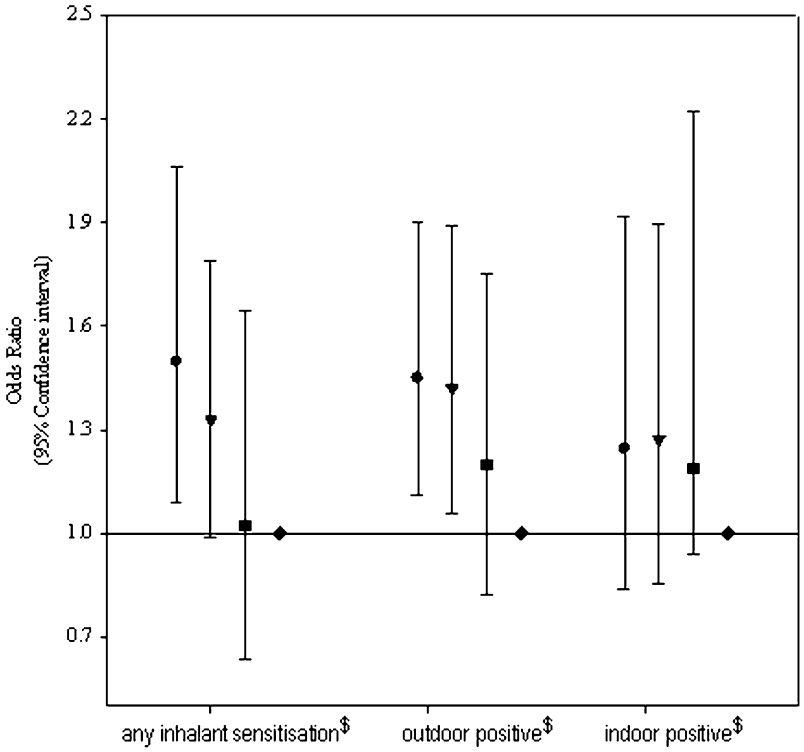

Figure 3. Association (odds ratios) between distance to nearest road (reference, >1,000 m) and allergic sensitization at 6 years of age. #Adjusted for sex, age, parental atopy, maternal education, siblings, environmental tobacco smoke at home, use of gas for cooking, home dampness, indoor molds, keeping of dogs and cats. $Defined as in Table 1: any allergic sensitization (outdoor positive or indoor positive); outdoor positive (timothy grass, rye, birch, mugwort); indoor positive (house dust mite, cat, dog, molds). *Circles*, distance to nearest main road <50 m; *inverted triangles*, distance to nearest main road 50–250 m; *squares*, distance to nearest main road 250–1,000 m; *diamonds*, distance to nearest main road >1,000 m.

away, and speculate that this reflects exposure to a traffic-related aerosol.

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.

The GINI study group consists of the following members: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (H. E. Wichmann, J. Heinrich, A. Schoetzau, M. Mosetter, J. Schindler, A. Höhnke, K. Franke, B. Laubereau, S. Sausenthaler, A. Thaqi, A. Zirngibl, A. Zutavern); Department of Pediatrics, Marien-Hospital, Wesel (D. Berdel, A. von Berg, C. Scholten, C. Bollrath, I. Groß, M. Möllemann); Department of Pediatrics, Ludwig Maximilians University, Munich (S. Koletzko, D. Reinhard, H. Weigand, I. Antonie [formerly I. Jesch], B. Bäumler-Merl, C. Tasch, R. Göhlert); Department of Pediatrics, Technical University, Munich (C. P. Bauer, I. Brockow, A. Grübl, P. Bartels, I. Brockow, A. Fischer, U. Hoffmann, F. Lötzbeyer, R. Mayrl, K. Negele, E.-M. Schill, B. Wolf); Institut für Umweltmedizinische Forschung, Düsseldorf (U. Krämer, E. Link, U. Ranft, R. Schins, D. Sugiri); Department of Dermatology, Technical University, Munich (J. Ring, J. Grosch, U. Darsow, S. Weidinger); Centre for Allergy and Environment, Technical University, Munich (H. Behrendt, A. Kasche, J. Buters, C. Traidl-Hoffmann); Pediatric Immunology, Ludwig Maximilians University, Munich (S. Krauss-Etschmann).

The LISA study group consists of the following members: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (H. E. Wichmann, J. Heinrich, G. Bolte, P. Belcredi, B. Jacob, A. Schoetzau, M. Mosetter, J. Schindler, A. Höhnke, K. Franke, B. Laubereau, S. Sausenthaler, A. Thaqi, A. Zirngibl, A. Zutavern); Department of Pediatrics, University of Leipzig (M. Borte, R. Schulz, G. Sierig, K. Mirow, C. Gebauer, B. Schulze); Department of Pediatrics, St. Georg Hospital, Leipzig (M. Borte, U. Diez, S. Straub); University of Leipzig, Institute of Clinical Immunology and Transfusion Medicine, Leipzig (I. Lehmann, U. Sack); Department of Pediatrics, Marien-Hospital, Wesel (A. von Berg, C. Scholten, C. Bollrath, I. Groß, M. Möllemann); Bad Honnef (B. Schaaf); Department of Human Exposure Research and Epidemiology, UFZ–Center for Environmental Research Leipzig-Halle (O. Herbarth, M. Bauer, U. Franck, C. Graebsch, A. Mueller, M. Rehwagen, M. Richter, S. Roeder, U. Rolle-Kampczyk, U. Schlink, S. Albrecht, A. Jorks); Department of Environmental Immunology, UFZ–Center for Environmental Research Leipzig-Halle (I. Lehmann, G. Herberth, C. Daegelmann); Department of Pediatrics/Infectious Diseases and Immunology, Ludwig Maximilians University, Munich (M. Weiss, M. Albert); Institute of Clinical Immunology, Friedrich-Schiller-University, Jena (B. Fahlbusch); Institute of Social, Occupational, and Environmental Medicine (W. Bischof, A. Koch); Institut für Umweltmedizinische Forschung, Düsseldorf (U. Krämer, E. Link, U. Ranft, R. Schins, D. Sugiri); Department of Pediatrics, Technical University, Munich (C. P. Bauer, I. Brockow, A. Grübl); Department of Dermatology, Technical University, Munich (J. Ring, J. Grosch, U. Darsow, S. Weidinger); Center for Allergy and Environment, Technical University, Munich (H. Behrendt, A. Kasche, J. Buters, C. Traidl-Hoffmann); CCG Pediatric Immunology, Ludwig Maximilians University, Munich, and Helmholtz Zentrum München, German Research Center for Environmental Health, Munich (S. Krauss-Etschmann); Institute of Social Medicine, University of Luebeck, Luebeck (T. Schäfer).

Acknowledgments: The authors acknowledge Marie Cox for her help with editing. The authors thank all families for their participation in the LISA and GINI studies.

References

1. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
2. Pye S, Watkiss P. CAFE CBA: baseline analysis 2000 to 2020. AEAT/ED51014/Baseline Issue 2. 2005.
3. Amann M, Bertok I, Cofala J, Gyarfas F, Heyes C, Klimont Z, Schöpp W, Winiwarter W. Baseline Scenarios for the Clean Air for Europe (CAFE) programme: final report. 2005.
4. Wyler C, Braun-Fahrlander C, Kunzli N, Schindler C, Ackermann-Liebrich U, Perruchoud AP, Leuenberger P, Wuthrich B. Exposure to motor vehicle traffic and allergic sensitization. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Epidemiology* 2000;11:450–456.
5. Heinrich J, Topp R, Gehring U, Thefeld W. Traffic at residential address, respiratory health, and atopy in adults: the National German Health Survey 1998. *Environ Res* 2005;98:240–249.
6. Heinrich J, Wichmann HE. Traffic related pollutants in Europe and their effect on allergic disease. *Curr Opin Allergy Clin Immunol* 2004;4:341–348.
7. 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.
8. 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;21:956–963.
9. Krzyzanowski M, Kuna-Dibbert B, Schneider J, editors. World Health Organization: health effects of transport-related air pollution. 2005.
10. Svartengren M, Strand V, Bylin G, Jarup L, Pershagen G. Short-term exposure to air pollution in a road tunnel enhances the asthmatic response to allergen. *Eur Respir J* 2000;15:716–724.

11. Sagai M, Furuyama A, Ichinose T. Biological effects of diesel exhaust particles (DEP). III. Pathogenesis of asthma like symptoms in mice. *Free Radic Biol Med* 1996;21:199–209.
12. de Haar C, Hassing I, Bol M, Bleumink R, Pieters R. Ultrafine but not fine particulate matter causes airway inflammation and allergic airway sensitization to co-administered antigen in mice. *Clin Exp Allergy* 2006;36:1469–1479.
14. Hochadel M, Heinrich J, Gehring U, Morgenstern V, Wichmann HE, Kuhlbusch T, Link E, Krämer U. Predicting long-term average concentrations of traffic-related air pollutants using GIS-based information. *Atmos Environ* 2006;40:542–553.
15. Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS, Kerkhof M, Brunekreef B. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007;5:879–888.
16. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Gehring U, Koletzko S, Bauer CP, Reinhardt D, Wichmann HE, Heinrich J. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. *Occup Environ Med* 2007;64:8–16.
17. Briggs DJ, Collins S, Elliot P, Fischer P, Kingham S, Lebret E, Pryl K, Reeuwijk vH, Smallbone K, Van der Veen A. Mapping urban air pollution using GIS: a regression-based approach. *Int J Geogr Inf Sci* 1997;11:699–718.
18. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, Künzli N, Gauderman J, Avol E, Thomas D, Peters J. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect* 2006; 114:766–772.
19. 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;19:690–698.
20. Morgenstern V, Heinrich J, Zutavern A, Cyrys J, Brockow I. Atopic diseases, allergic sensitization, and individual estimate exposure to traffic-related air pollutants in children. *Epidemiology* 2007; 18(Suppl): S10.
21. Landeshauptstadt München SA. Munich facts and figures. 2001. [Internet]. Available from: http://www.muenchen.de/Wirtschaft/15/index.html
22. Filipiak B, Zutavern A, Koletzko S, von Berg A, Brockow I, Grubl A, Berdel D, Reinhardt D, Bauer CP, Wichmann HE, *et al*; GINI Group. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. *J Pediatr* 2007;151:352–358.
23. Zutavern A, Brockow I, Schaaf B, Bolte G, von Berg A, Diez U, Borte M, Herbarth O, Wichmann HE, Heinrich J. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006;117:401–411.
24. Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewne M, Gehring U, Bellander T, Fischer P, Vliet PP, Brauer M, *et al.* Comparison between different traffic-related particle indicators: elemental carbon (EC), PM(2.5) mass, and absorbance. *J Expo Anal Environ Epidemiol* 2003;13:134–143.
25. Hoek G, Meliefste K, Cyrys J, Lewne M, Bellander T, Brauer M, Fischer P, Gehring U, Heinrich J, Van Vliet P, *et al.* Spatial variability of fine particle concentrations in three European areas. *Atmos Environ* 2002; 36:4077–4088.
26. Cyrys J, Heinrich J, Richter K, lke G, Wichmann HE. Sources and concentrations of indoor nitrogen dioxide in Hamburg (west Germany) and Erfurt (east Germany). *Sci Total Environ* 2000;250: 51–62.
27. Brauer M, Gehring U, Brunekreef B, de Jongste J, Gerritsen J, Rovers M, Wichmann HE, Wijga A, Heinrich J. Traffic-related air pollution and otitis media. *Environ Health Perspect* 2006;114:1414–1418.
28. Traidl-Hoffmann C, Kasche A, Menzel A, Jakob T, Thiel M, Ring J, Behrendt H. Impact of pollen on human health: more than allergen carriers? *Int Arch Allergy Immunol* 2003;131:1–13.
29. Behrendt H, Becker WM, Friedrichs KH, Darsow U, Tomingas R. Interaction between aeroallergens and airborne particulate matter. *Int Arch Allergy Immunol* 1992;99:425–428.
30. Penard-Morand C, Charpin D, Raherison C, Kopferschmitt C, Caillaud D, Lavaud F, Annesi-Maesano I. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. *Clin Exp Allergy* 2005;35:1279–1287.
31. Oftedal B, Brunekreef B, Nystad W, Nafstad P. Residential outdoor air pollution and allergen sensitization in schoolchildren in Oslo, Norway. *Clin Exp Allergy* 2007;37:1632–1640.
32. 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;111:1512–1518.
33. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, Van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. *Epidemiology* 1997;8:298–303.
34. Van Vliet P, Knape M, de Hartog J, Janssen N, Harssema H, Brunekreef B. Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environ Res* 1997;74:122–132.
35. Gordian ME, Haneuse S, Wakefield J. An investigation of the association between traffic exposure and the diagnosis of asthma in children. *J Expo Sci Environ Epidemiol* 2006;Jan 16(1):49–55.
36. Bayer-Oglesby L, Grize L, Gassner M, Takken-Sahli K, Sennhauser FH, Neu U, Schindler C, Braun-Fahrlander C. Decline of ambient air pollution levels and improved respiratory health in Swiss children. *Environ Health Perspect* 2005;113:1632–1637.
37. Bayer-Oglesby L, Schindler C, Hazenkamp-von Arx ME, Braun-Fahrlander C, Keidel D, Rapp R, Kunzli N, Braendli O, Burdet L, Sally Liu LJ, *et al.* Living near main street and respiratory symptoms in adults: the Swiss Cohort Study on Air Polution and Lung Diseases in Adults. *Am J Epidemiol* 2006;164:1190–1198.
38. Livingstone AE, Shaddick G, Grundy C, Elliott P. Do people living near inner city main roads have more asthma needing treatment? Case control study. *BMJ* 1996;312:676–677.
39. Holguin F, Flores S, Ross Z, Cortez M, Molina M, Molina L, Rincon C, Jerret M, Berhane K, Romieu I. Traffic-related exposures, airway function, inflammation and respiratory symptoms in children. *Am J Respir Crit Care Med* 2007;19:S1073–449X.
40. Gilbert NL, Goldberg MS, Beckerman B, Brook JR, Jerrett M. Assessing spatial variability of ambient nitrogen dioxide in Montreal, Canada, with a land-use regression model. *J Air Waste Manag Assoc* 2005;55:1059–1063.
41. Zhu Y, Hinds WC, Kim S, Sioutas C. Concentration and size distribution of ultrafine particles near a major highway. *J Air Waste Manag Assoc* 2002;52:1032–1042.
42. Heinrich J, Gehring U, Cyrys J, Brauer M, Hoek G, Fischer P, Bellander T, Brunekreef B. Exposure to traffic related air pollutants: self reported traffic intensity versus GIS modelled exposure. *Occup Environ Med* 2005;62:517–523.

AUTHOR QUERIES

1 Au: Please spell out WZU, ZAUM, and UFZ in Affiliations.

2 Au: Please add city name for Environmental Science Center.

3 Au: Please spell out BMU and check expansion of IUF.

4 Au: Please provide professional degree for corresponding author.

5 AU: "Long-term exposure to particulate matter ($PM_{2.5}$), $PM_{2.5}$ absorbance, and long-term exposure to nitrogen dioxide... were assessed" intended? Please check wording.

6 Au: Delete "data of" here?

7 Au: "or" ok as added? Or please amend to clarify.

8 Au: Please spell out CAP and FEIA in CAP-RAST FEIA.

9 Au: Please spell out SX1.

10 Au: PM2.5 ok as defined?

11 Au: Please supply name/location of manufacturers for Harvard impactors and Palmes tubes.

12 Au: GEE ok as expanded?

13 Au: Please provide expansion for PIAMA.

14 Au: Do edits for wording "A study in" preserve your intent?

15 Au: More information available for Bad Honnef (eg, city name, department)?

16 Au: Text in ref 2 appears to be a website address; however, link not found. Please clarify and, if web address, please also supply date on which site was accessed.

17 Au: Please provide name/location of publisher (or website address and date of access) for ref 3.

18 Au: In ref 9, please provide name/location of publisher.

19 Au: In ref 17, please check author's first-name initials "vH"?

20 Au: Web site from 2001 correct? Also, please add date on which site was accessed, in Ref 21.

21 Au: Volume number ok as edited in ref 31?

22 Au: Please clarify journal volume number in ref 35.

23 Please verify the page numbers (S1073-449X) (in reference 39 "Holguin, Flores, Ross, Cortez, Molina, Molina, Rincon, Jerret, Berhane, Romieu, 2007").

24 Au: Please provide asterisk callout symbol in Figure 1 art, to correspond with footnote in legend.

25 Au/Editor: Note that Figs 2 and 3 were supplied as low-resolution art.

26 Au: Footnote callout symbol does not appear to be present in Fig 2 art. Please check. Please also check Fig 3.

27 Au: Should there be a multi dot (or other) between 10^{-5} and m^{-1} in table? Please check throughout.

28 Au; Please clarify significance of asterisk (is this a math symbol here?), and supply missing symbol(s) in 10 – $5m^{-1}$. Please also check Table 4.

29 Au: Please explain significance of values in bold face, in table footnote, for Tables 3 and 4.

30 Au: Please supply correspond footnote callout in table body to correspond to table footnote, if necessary, and add symbol to footnote. See also Table 4.

31 Au: Note that Ref 13 is missing in References and in text. Please add missing reference, or if References are numbered incorrectly, please renumber here and in text accordingly.