

Traffic-related Exposures, Airway Function, Inflammation, and Respiratory Symptoms in Children

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Rationale: Traffic-related emissions have been associated with respiratory symptoms in some studies. However, there is limited information on how traffic-related emissions relate to lung function and airway inflammation.

Objectives: To determine the differential association of traffic-related exposures with exhaled nitric oxide (NO) and lung volumes and symptoms in children with and without asthma.

Methods: We performed a longitudinal study of 200 children from ages 6 to 12 years of whom half had physician-diagnosed asthma. Two-week NO₂ and 48-hour average levels of elemental carbon and particulate matter of less than 2.5 μm (PM_{2.5}) were measured at participating schools. Road and traffic densities were determined at schools and at each participant's house.

Measurements and Main Results: In children with asthma, an interquartile increase in road density within the 50-, 100-, and 200-m home buffer areas was associated with increased exhaled NO (50 m: 28%; $P = 0.03$; 95% confidence interval [CI], 3–60; 100 m: 27%; $P = 0.005$; 95% CI, 8–49; 200 m: 17%, $P = 0.09$, 95% CI, –2 to 40), and reduced FEV₁ (50 m: –0.091 L; $P = 0.038$; 95% CI, –0.174 to –0.007; 100 m: –0.072 L, $P = -0.028$, 95% CI, –0.134 to –0.009; 200 m: –0.106 L, $P = 0.002$, 95% CI, –0.171 to –0.041). Exposure to NO₂ at schools was marginally associated with reduced FEV₁ (–0.020; $P = 0.060$; 95% CI, –0.042 to 0.001). We did not observe significant associations with PM_{2.5} or elemental carbon on exhaled NO. We did not observe significant reductions in lung volumes or changes in exhaled NO among healthy children.

Conclusions: Vehicular traffic exposures are associated with increased levels of exhaled NO and reduced lung volumes in children with asthma.

Keywords: air pollution; traffic; asthma; exhaled nitric oxide

Outdoor air pollution can increase the risk for developing adverse respiratory health outcomes in children with asthma (1), yet this risk varies depending on the association with different outdoor emission sources. For example, vehicular emission exposure is associated with higher rates of adverse respiratory health outcomes in comparison with background air pollution exposure (2–6). This phenomenon may be explained by the pollutant mix properties near vehicular emission sources, including larger concentration of fine and ultrafine particles (7),

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Traffic-related exposures are associated with increased asthma severity.

What This Study Adds to the Field

Traffic-related exposures are associated with increased airway inflammation and reduced lung volumes. Children with asthma are more susceptible than healthy control subjects.

higher concentrations of carbon monoxide, and higher nitrogen dioxide levels (8). Although there is not a clear consensus on what constitutes exposure to vehicular-related emissions, the majority of studies have found that the rate of adverse respiratory health effects seems to increase proportionately in relation to road proximity (1) and with increasing traffic density (9). Proximity to major traffic roads and traffic density has been associated with higher rates of wheezing (5), atopy (10, 11), respiratory symptoms, and health care use in children (12–14). However, whether or not exposure to traffic-related emissions can adversely affect respiratory health remains controversial because other studies have failed to show significant associations (15–17).

The objectives of this study were to determine if exposure to traffic-related emissions is associated with increased airway inflammation and reductions in lung function in children and to characterize the differential effects related to the exposure among children with and without asthma. To test this hypothesis, we determined the association between traffic-related exposures with exhaled nitric oxide (NO), a sensitive biomarker for airway inflammation (18), respiratory symptoms, and exhaled lung volumes, in a cohort of 100 school-age children with asthma and 100 age- and sex-matched nonasthmatic children. This study was conducted as part of the United States-Mexico Border 2012 program, which aims to improve and measure environmental health in border communities (19).

METHODS

Study Population

This study consisted of school children with and without physician-diagnosed asthma from 6 to 12 years of age. Children without asthma were age and sex matched and attended the same schools as the children with asthma (Figure 1).

During the initial visit, study participants underwent baseline spirometry and allergy skin testing (Alerquim, Mexico) and answered questionnaires regarding past medical history, use of asthma medications, respiratory symptoms, and environmental tobacco exposure. During follow-up, participants from schools in each zone were monitored

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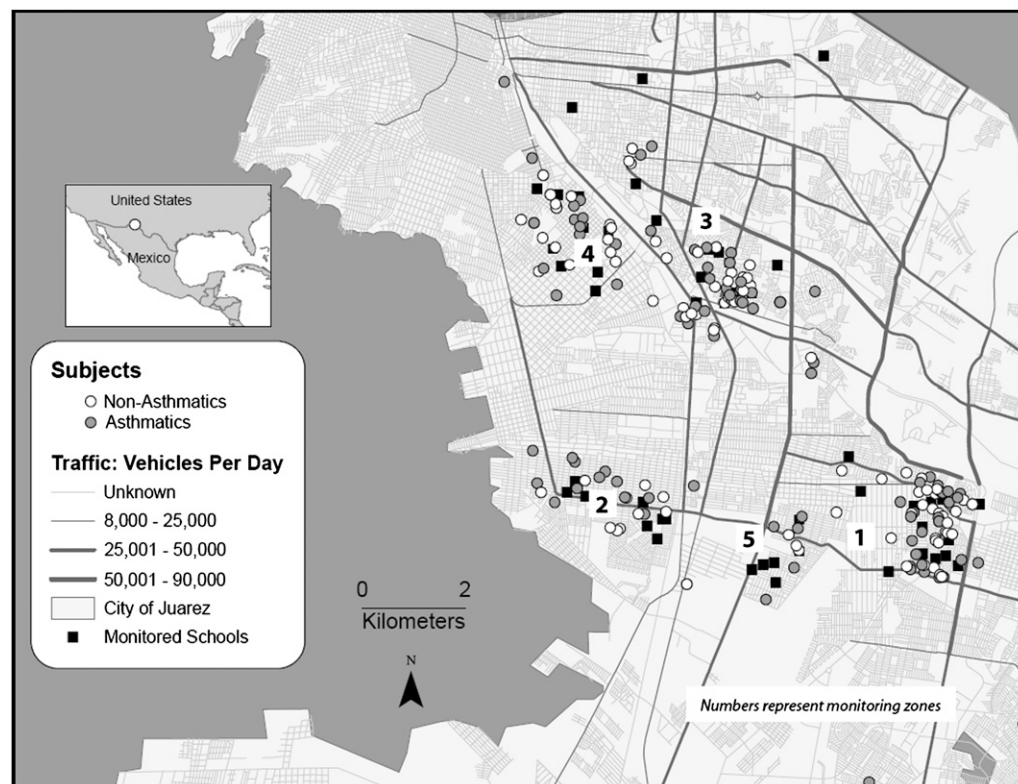


Figure 1. Map of Ciudad Juarez, Mexico, illustrating the location of the subjects' homes, road with average traffic densities, and schools in each study area; Ciudad Juarez, Mexico, 2001–2002.

consecutively for 4 months. Follow-up consisted of biweekly visits to the research center for measurements of exhaled NO, spirometry, and a daily respiratory symptom questionnaire.

Exhaled NO and spirometry were determined following the American Thoracic Society guidelines (20, 21). Daily respiratory health questionnaires were administered by parents and checked for consistency during the biweekly visits.

Air pollution measurements were monitored in the schools at each study zone during follow-up (monitoring schedule by zone and school is provided in Figures E1–E3 in the online supplement). Air pollutants measured in the study included 48-hour average particulate matter of less than 2.5 μm ($\text{PM}_{2.5}$) determined by gravimetric analysis using Mini-Vol portable air samplers (version 4.2; Air Metrics, Eugene, OR) with 47-mm Teflon filters (Pall Gelman Laboratories, Vancouver, WA) and flows set at 5 L/minute. Elemental carbon (EC) was determined by using light absorption on Teflon filters (Desert Research Institute, Reno, NV). NO_2 was measured weekly by using passive Ogawa samplers (Pompano Beach, FL; samples processed at the Harvard School of Public Health in Boston, MA).

To assess the health effects of traffic-related exposures, we used landscape-level variables obtained through a geographic information systems (GIS) analysis using ArcGIS 9.1 (Environmental Systems Research Institute, Redlands, CA). GIS variables included road density (amount of road length in kilometers in each buffer) and traffic density (vehicle-km/h) within buffer areas around study schools and subject homes. These variables did not vary longitudinally.

Statistical Analysis

We evaluated the effects of measured air pollutant concentrations at schools (NO_2 , $\text{PM}_{2.5}$, and EC) (longitudinal component) and traffic-related landscape variables on measured pulmonary function (NO , FEV_1 , and FVC) and self-reported pulmonary symptoms (spatial component). We developed a flexible, mixed-modeling framework that can incorporate three levels of aggregation: school, subject, and subject-time. In all cases, models were fitted using the restricted maximum likelihood estimation technique via R statistical software (R development core team 2006, Vienna, Austria) using the linear and nonlinear mixed effects models (R package version 3.1) and modern applied statistics with S (MASS) packages (22). Symptoms were a binary response

defined as the self-reported occurrence of cough, wheeze, or phlegm. All models were adjusted for sex, age, body mass index, day of the week, season, total number of years of maternal education, total number of years of paternal education, and passive smoking. Children with and without asthma were modeled separately. School and subject (nested within school) were modeled as random intercepts. All models were adjusted to represent change in the response relative to an interquartile change in the predictor. Exhaled NO levels were log-transformed results are presented as a percentage change. FEV_1 and FVC were not transformed and are presented as unit (liter) changes and change in symptoms; a binary response is given as an odds ratio. A full description of the methods and analysis, is given in the online supplement.

RESULTS

Study Population

Table 1 presents the general characteristics of the study population. Out of a total of 225 children who were interviewed to participate in the study, 200 were recruited, and 196 completed the study protocol. Four participants withdrew for reasons unrelated to the study protocol. The median distance between the children's homes and their respective schools was 397 m (interquartile range [IQR], 239–692).

Participants with asthma had higher average levels of exhaled NO and had a higher frequency of respiratory symptoms (Table 1). The lung volumes were similar across both groups, although participants with asthma were more likely to show some degree of airway obstruction. At the beginning of the study, 78% of the subjects with asthma were classified as mild intermittent, 13% were mild persistent, 8% were moderate persistent, and 1% were severe according to GINA (Global Initiative for Asthma) guidelines (23). Of the subjects with asthma, 16% used a short-acting β -agonist, 9% used an inhaled corticosteroid, 3% used oral antihistamines, and 18% were prescribed antibiotics in at least one occasion during follow-up.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

Variables	Subjects with Asthma (n = 95)	Subjects without Asthma (n = 99)	P Value
Female	31	41	
Male	64	58	
Age, yr	9.0 (± 1.7)	9.0 (± 1.6)	
Weight, kg	37.4 (± 14)	38 (± 13)	0.2
Atopy, %	58	37	0.02
FeNO, ppb	5.6 (± 4.5)	3.1 (± 3)	<0.01
Cough rate*	0.108	0.065	<0.01
Wheeze rate	0.021	0.002	<0.01
Phlegm rate	0.090	0.034	<0.01
Albuterol use rate	0.083	0	<0.01
Overall symptoms rate	0.302	0.102	<0.01
FEV ₁ , L	1.70 (± 0.51)	1.95 (± 0.49)	<0.01
FEV ₁ , % predicted	89.6 (± 17)	98.1 (± 15)	0.2
FVC, L	2.25 (± 0.70)	2.23 (± 0.63)	0.7
FEV ₁ /FVC	76 (± 11)	83 (± 12)	<0.01

* Rates: number of positive entries/100 questionnaire entries.

Subjects with asthma were more likely to have atopy (58%, n = 53) when compared with the subjects without asthma (37%; n = 36) ($P < 0.05$). Subjects with and without atopic asthma had higher levels of exhaled NO when compared with patients with nonatopic asthma and nonatopic nonasthmatic subjects (6.14 vs. 4.9 ppb [$P < 0.05$] and 4.43 vs. 2.4 ppb [$P < 0.05$], respectively).

Environmental Exposure Data

During the study period, the mean ($\pm$ SD) levels of PM_{2.5}, EC, and NO₂ were 17.5 $\mu\text{g}/\text{m}^3$ (± 8.9), (24-h PM_{2.5} standard: 35 $\mu\text{g}/\text{m}^3$), 3.05 $\mu\text{g}/\text{m}^3$ (± 4), and 18.2 ppb (± 9.6) (NO₂ annual standard: 53 ppb), respectively. The correlation of PM_{2.5} and EC was $r = 0.64$ ($P < 0.01$), and the correlations of NO₂ with PM_{2.5} and EC were $r = 0.30$ ($P < 0.01$) and $r = 0.49$ ($P < 0.01$), respectively. Figure 2 shows the distribution of pollutants during the study period and showed larger concentrations of pollutants during the winter months. The average traffic (vehicle-km per hour/zone

area in km²) in zones 1 through 5 was 1,439, 1,658, 3,933, 1,057, and 1,560, respectively. The average GIS road density (roads in km/zone area in km²) in study zones 1 through 5 were 17.4, 23.9, 18.4, 15.1, and 14, respectively.

Association between Exhaled NO, Lung Volumes, and Respiratory Symptoms with Traffic-related Exposures at Schools

Air pollutant exposures were not associated with respiratory outcome (Figure 3) but were suggestive of a reduction in FEV₁ associated with NO₂ exposures in both groups. An IQR increase in road density within the 50- to 200-m buffer was associated with a nonsignificant increase in exhaled NO in subjects with and without asthma. An IQR increase in road density in these buffers was associated with a nonsignificant reduction in FEV₁ and FVC in nonasthmatic children (Figure 4). We did not observe significant associations between respiratory symptoms with the road densities. There were no significant associations of the traffic counts with any of the study outcomes (data not shown).

Association between Exhaled NO, Lung Volumes, and Respiratory Symptoms with Traffic-related Exposures at Participants' Homes

Exposure to an IQR road density increase in the 50-, 75-, and 200-m buffers was associated with a significant or near significant increase in exhaled NO in patients with asthma only (Figure 5). In addition, an IQR increase in road density in these buffers was associated with a significant reduction in FEV₁ and with a reduction in FVC in the 200-m buffer. For all three of these outcomes there was a statistically significant trend with road density where the strongest effects were observed in buffers closer to the participants' homes (Figure 6). Subjects with asthma exhibited a significant OR for having respiratory symptoms only in the 50-m buffer (odds ratio [OR], 1.58; 95% confidence interval [CI], 1.05–2.38). There were no significant associations for respiratory symptoms in subjects without asthma. There were no significant associations between traffic

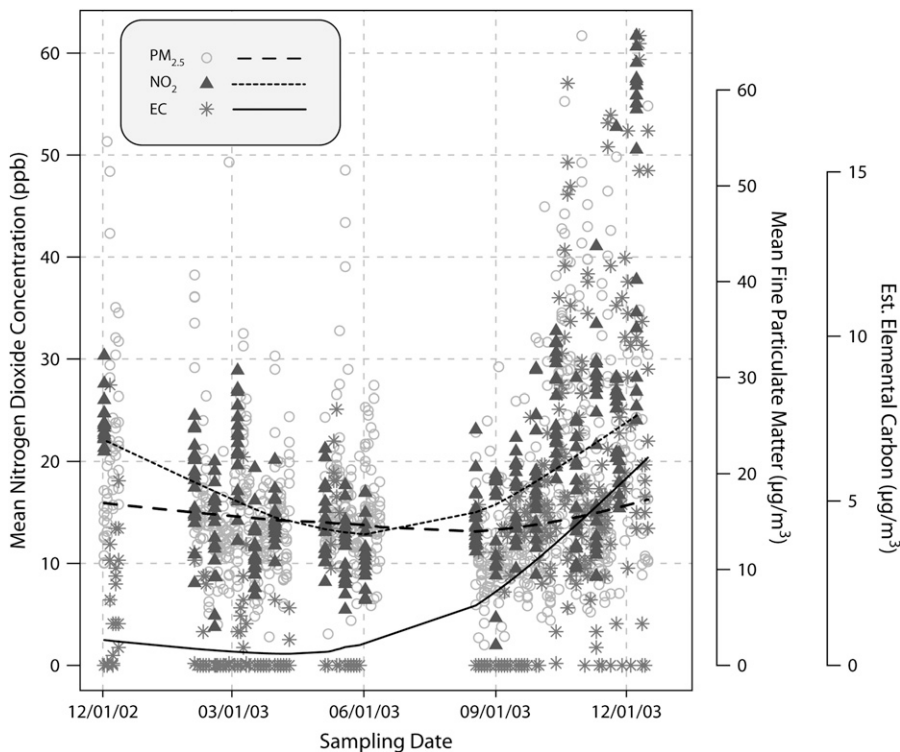


Figure 2. Average air pollutant levels monitored at schools, Ciudad Juarez, 2002–2003. EC, elemental carbon; PM_{2.5}, particulate matter <2.5 μm .

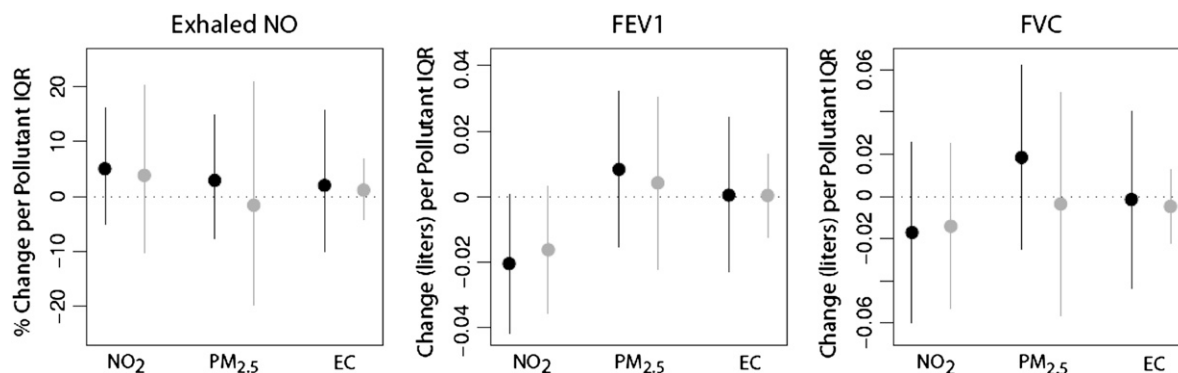


Figure 3. Association of exhaled NO, FEV₁, and FVC in children with and without asthma with exposure to air pollutants measured at participating schools. Shaded dots represent children without asthma; solid dots represent children with asthma. Dots represent the adjusted β -coefficient and standard error for the percentage change in NO or the change (in liters) of FEV₁ and FVC for an interquartile range (IQR) increase in air pollutant concentration (IQRs for NO₂, particulate matter <2.5 μ m [PM_{2.5}] and elemental carbon [EC] are 12.3–2.6 ppb, 12.6–17.7 μ g/m³, and 0–5.1 μ g/m³, respectively). Models were adjusted for sex, age, body mass index, day of the week, season, total number of years of maternal education, total number of years of paternal education, and passive smoking.

counts with respiratory symptoms, exhaled NO, or lung volumes (data not shown).

DISCUSSION

In this panel study of children with and without asthma, traffic-related exposures were estimated by measuring outdoor levels of NO₂, EC, and PM_{2.5} at schools and by measuring road and traffic densities at schools and at the subject's homes. We observed significant associations between exhaled NO in children with asthma and the IQR increase in road density in the 50-m (28% increase per IQR; 95% CI, 3–60), 75-m (27% increase per IQR; 95% CI, 27–49), and 200-m (17% increase per IQR; 95% CI, –2 to 40) buffer areas of each participant's homes. Exposure to road density in these buffer areas was associated with reduced FEV₁ (50 m: –0.091 L; 95% CI, –0.174 to –0.007; 100 m: –0.071 L; 95% CI, –0.134 to –0.009; 200 m: –0.106 L; 95% CI, –0.171 to –0.041). Exposure to NO₂ at schools was marginally associated with reduced FEV₁ (–0.020; 95% CI, –0.042 to 0.001) in subjects with asthma. Exposure to the 50-m buffer road density in relation to the subject's home was also associated with increased OR for respiratory symptoms

in children with asthma (OR, 1.53; 95% CI, 1.02–2.29). In contrast, there was an unexpected positive association between FEV₁ and the 400-m road density buffer among children without asthma that was not a significant trend.

Outdoor air pollution studies have largely relied on the use of central monitoring stations to estimate the health effects related to the exposure. Although this method offers the advantage of simultaneously studying a large number of subjects, it is limited by predominantly estimating background air pollution, which may differ from traffic-related exposures. Exposure to outdoor levels of NO₂ and residential distance to a freeway have been associated with increased odds for asthma and respiratory symptoms in children, yet few studies have addressed potential mechanisms that could explain why traffic exposure is related to increased respiratory events. Steerenberg and colleagues have shown that in children who live in an urban area characterized by moderate traffic, exposure to ambient NO, PM₁₀, and black smoke was associated with increased exhaled NO (24). In contrast, suburban children only showed consistent associations with ambient NO. Short-term variations in ambient PM_{2.5} have also been associated with increased exhaled NO in a small panel of children with asthma in Seattle, Washington

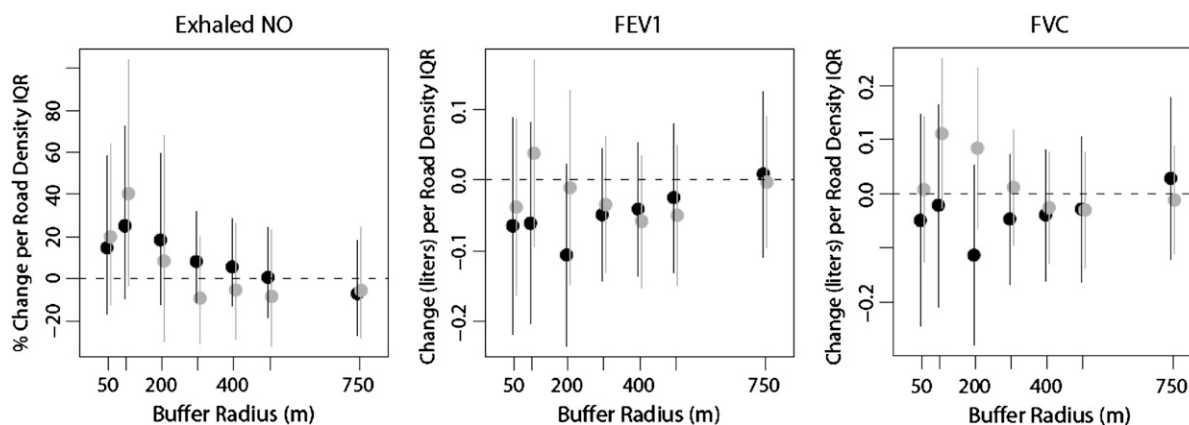


Figure 4. Association between exhaled NO, FEV₁, and FVC in children with and without asthma and the road density exposure in each participating school. Shaded dots represent children without asthma; solid dots represent children with asthma. Dots represent the adjusted β -coefficient and standard error for the percentage change in NO or the change (in liters) of FEV₁ and FVC for an interquartile range (IQR) increase in road density exposure in each corresponding buffer area. Models were adjusted for sex, age, body mass index, day of the week, season, total number of years of maternal education, total number of years of paternal education, and passive smoking.

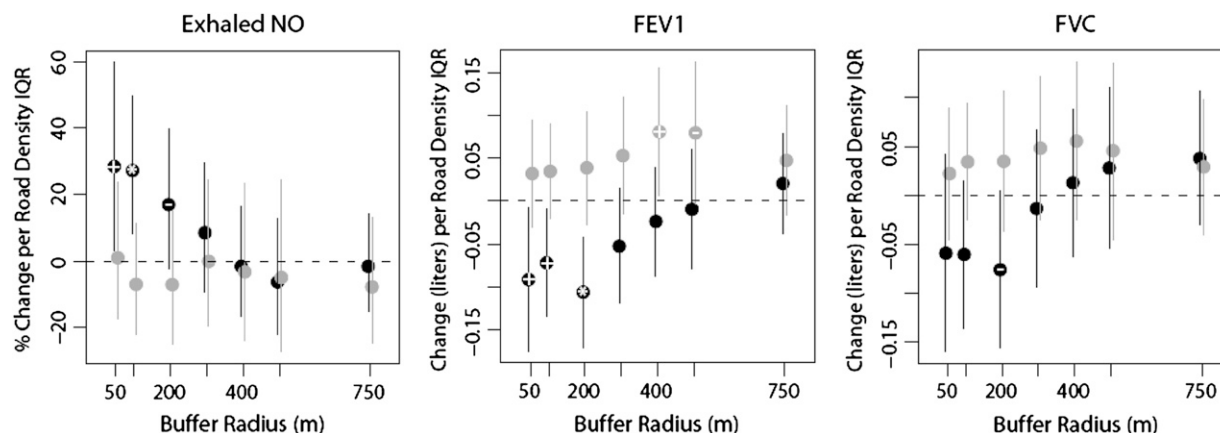


Figure 5. Association between NO, FEV₁, and FVC in children with and without asthma and the road density exposure in each participant's home. Shaded dots represent children without asthma; solid dots represent children with asthma. Dots represent the adjusted β -coefficient and standard error for the percentage change in NO or the change (in liters) of FEV₁ and FVC for an interquartile range (IQR) increase in road density exposure in each corresponding buffer area. Models were adjusted for sex, age, body mass index, day of the week, season, total number of years of maternal education, total number of years of paternal education, and passive smoking. * $P < 0.01$; + $P < 0.05$; - $P < 0.10$.

(25). However, these studies used ambient air pollutant data and did not directly assess traffic exposure. In a more recent study, Delfino and colleagues showed that short-term exposure to personal levels of PM_{2.5}, EC, and NO₂ were associated with increased exhaled NO in 45 children with asthma followed for 10 days (26). Although Delfino and colleagues evaluated the association of exhaled NO with pollutants using personal exposure measurements, this study was limited by a relatively small sample of participants who were followed for a short period. In contrast, our study followed a large group of children with and without asthma for 1 year and estimated the exposure to traffic-related emissions directly by measuring the concentration of NO₂, PM_{2.5}, and EC in schools situated in close proximity to major traffic roads (see Figure 1) and indirectly by using the GIS variables of traffic and road density. Our study found that exposure to NO₂, but not ambient PM_{2.5} or EC, was marginally associated with reduced lung function; however, none of the pollutants measured was associated with exhaled NO. Whether exposure to NO₂ in itself can be deleterious to patients with asthma is debatable (27). Our study, without more information on exposure sources, can only evaluate NO₂ exposure as a surrogate marker for traffic-related emissions. Our inability to detect associations with EC and PM_{2.5} exposure

could be related to a lack of adequate exposure assessment (i.e., our ambient monitors for PM_{2.5} levels lacked the exposure resolution required to detect the exposure associated with changes in airway inflammation in children with asthma). This is supported by the study of Delfino and colleagues, which showed that the association between ambient PM_{2.5} and exhaled NO was weaker than personal PM_{2.5}, thereby suggesting that ambient mass-based methods alone may not be sufficiently representative of the relevant pollutant components when assessing the effects of particulate air pollutants on airway inflammation (26).

Our study found significant associations with exhaled NO and lung volumes in children with road density as a proxy to traffic exposure. Other studies have also shown proximity to traffic-related exposures as a risk factor for reductions in lung volumes in children. In preschool healthy children, Fritz and colleagues have shown spatial variation in lung volumes with relation to traffic exposure; in this study, children exposed to heavier vehicular traffic and/or domestic heating showed more reductions in FEV₁ and FVC (28). Gauderman and colleagues showed that children who lived within 500 m of a freeway had substantial deficits in 8-year growth of FEV₁ compared with children who lived at least 1,500 m from a freeway (29). These

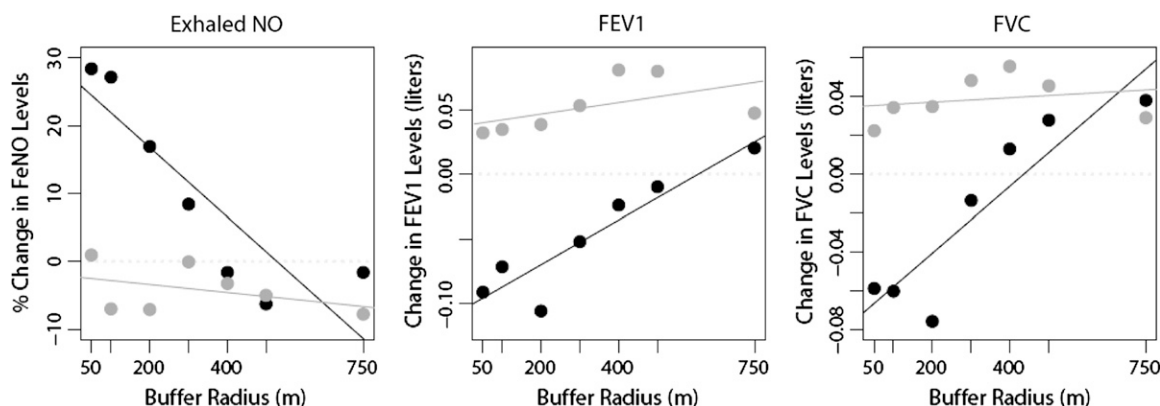


Figure 6. Linear trend of the change of exhaled NO, FEV₁, and FVC in relation to road density in each buffer area for children with and without asthma. Shaded dots represent children without asthma; solid dots represent children with asthma. Exhaled NO: asthma trend, $P = 0.008$; no asthma trend, $P = 0.36$. FEV₁: asthma trend, $P = 0.003$; no asthma trend, $P = 0.21$. FVC: asthma trend, $P = 0.005$; no asthma trend, $P = 0.6$.

results, in addition to ours, suggest that there is a chronic respiratory effect associated with exposure in close proximity to roads.

To our knowledge, using road density as a GIS-related exposure variable has not been used in other asthma studies to evaluate the association to traffic emissions sources. The majority of studies have used traffic density measures and distance to roads as proxies for traffic emissions. Our study was underpowered to detect associations with traffic density given that we only had traffic information on 212 km out of 3,951 km of road grid involved in the study. Furthermore, traffic counts relied on weekly averages obtained on site at each monitoring area during the study; therefore, our measurements lacked the necessary resolution to detect significant associations. Using road density as an exposure measure of road proximity may be useful only when dealing with large cities that have dense road grids where exposure within a 50-m buffer can be estimated with adequate resolution. Our study suggests that road density may be a reasonable alternative to obtaining adequate traffic density measures, which, in many cities, particularly in developing countries, may be difficult to obtain.

We observed increased odds for having respiratory symptoms in children with asthma only in association with the road density of the 50-m buffer of each participant's home; however, we failed to detect significant associations with any of the air pollutants measured in our study. This could be partly explained by our study being underpowered and by the fact that our asthmatic population was characterized by children with mild intermittent and mild persistent asthma.

Many cities in international border crossings are characterized by having significant problems with vehicular emissions due to traffic directed across the border. In the case of Ciudad Juarez, for example, a significant amount of border-crossing traffic must go through the city before reaching El Paso, Texas. Other studies have also found significant associations with asthma and air pollution in cities with border crossings. A clear example is the clustering of asthma cases located downwind of the Peace Bridge Complex and the freeways (main crossing site for the United States and Canada) in Buffalo, New York (30, 31).

Significant limitations must be taken into consideration when interpreting the results of this study. First, EC- and PM_{2.5}-monitored days were considerably less than the monitored days available for NO₂ (see online supplement); these differences could partly explain why we only observe significant associations with NO₂. Second, some degree of exposure misclassification could have hampered our ability to adequately estimate the effects of EC and PM_{2.5} on exhaled NO. Air pollutant exposure assessment using 48-hour averages may not accurately represent the PM_{2.5} or EC critical window of exposure at the time of exhaled NO collection or may fail to detect the right exposure window that is associated with changes in exhaled NO. Third, air pollution exposure was limited to the school level; therefore, our study cannot provide information on air pollutants measurements at the children's homes. Fourth, using road density as a measure of traffic-related exposures may be confounded by other unmeasured factors such as noise (32, 33) and variations in socioeconomic status (SES) (34); these and other unmeasured factors may lead to substantial residual confounding in our results. We tried to limit potential confounding from SES by recruiting our participants from the same public school system and by adjusting our models for parental education as a proxy for SES (35). Fifth, the study did not adjust for ozone exposure; however, given that ozone is more homogeneously distributed across large areas, we would not expect it to confound the association between NO₂ or traffic density within different buffer areas. Also, our study found associations during high- and low-

ozone periods. Last, even though our models adjusted for seasonality, we did not control for any residual seasonal effects resulting from changes in the prevalence of respiratory viral infections that could have increased the levels of exhaled NO among patients with asthma, especially during the winter months when the prevalence of viral infections peaks and the concentration of pollutants are higher.

An additional concern with respect to seasonality and longitudinal changes in respiratory symptoms is the possible confounding effects of medication use by asthmatics. To address this concern, we ran the models discussed previously with an additional covariate representing seasonal medication use by subject (we summed the number of days a subject used albuterol by season). Adding this covariate had a small effect on the results. For example, the OR for the effect of road density in the 50-m buffer on symptoms changed from 1.58 ($P = 0.03$; 95% CI, 1.05–2.38) to 1.51 ($P = 0.04$; 95% CI, 1.00–1.27). Results from our study provide further evidence that traffic-related exposures are associated with increased airway inflammation and reduced lung function in children with asthma. This finding could have significant public health policy implications because a significant proportion of schools in many countries (36) are located in close proximity to major roads.

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

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