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Altered pulmonary function in children with asthma associated with highway traffic near residence

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Cross-sectional analyses were conducted to evaluate the effects of exposure to highway traffic on pulmonary function in Fresno, California. Traffic and spirometry data were available for 214 children (enrollment ages six to 11 years). Multiple linear regression was used to evaluate the relations between pulmonary function and traffic parameters. Heavy-duty vehicle count was used as a surrogate measure for diesel-related exposures. Pulmonary function was non-significantly associated with longer distance-to-road and non-significantly associated with higher traffic intensity. Evaluation of effect modification by $FEF_{25–75}/FVC$ (a measure of intrinsic airway size) showed that all pulmonary function measures of flow were significantly inversely related to a traffic metric that incorporates traffic intensity and roadway proximity. The results indicate that residence proximity to highway traffic is associated with lower pulmonary function among children with asthma, and smaller airway size is an important modifier of the effect of traffic exposure on pulmonary function and a marker of increased susceptibility.

Keywords: asthma; children; traffic; pulmonary function; air pollution

Introduction

Transient changes in pulmonary function measures have been associated with short-term exposure to traffic-related pollutants, e.g. nitrogen dioxide (NO_2), fine particulate matter (i.e. particles $\leq$2.5 microns in aerodynamic diameter, $PM_{2.5}$), or daily traffic counts (Gauvin et al. 2001; Steerenberg et al. 2001; Delfino et al. 2003; Burr et al. 2004). In a cross-sectional analysis of data from a school-based study of children in six communities in the Netherlands, lower pulmonary function was associated with automobile and truck traffic (Brunekreef et al. 1997). In support of the link between altered pulmonary function and traffic-related pollutants was the observation that community-monitor-based estimates of long-term exposures to NO_2, $PM_{2.5}$, as well as acid vapor (a secondary pollutant) were associated with reduced lung function growth over an eight-year period (Gauderman et al. 2004) and

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that pollutant markers of traffic exposure, that included NO_2 and five particulate matter (particles <2.5 microns in aerodynamic diameter) ($PM_{2.5}$), near residences, also were associated with impaired lung function growth (Gauderman et al. 2007).

Independent of air pollution exposures, children with asthma have been observed to have lower pulmonary function, with more severe asthma being associated with greater deficits (Weiss et al. 1992), especially in measures of small airways function (Berhane et al. 2000). Furthermore, atopy and allergic sensitization have been associated with more severe asthma and greater deficits in lung function in children with asthma (O'Connor et al. 1989). Chronic inflammation, recognized as a hallmark of asthma, involves large and small airways (Martin 2002) and provides a mechanistic link between allergy, asthma severity, and deficits in lung function. Plausibly, the adverse effects on pulmonary function of traffic-related air pollution, which is known to cause airway inflammation (Larsson et al. 2007), may be enhanced in children with more severe asthma, with atopy, or those with greater impairment of small airways.

The Fresno Asthmatic Children's Environment Study (FACES) is a longitudinal cohort study of children with asthma initiated in 2000 in Fresno, California to evaluate the relationship between short-term air pollution exposure-response patterns and the longer-term natural history of asthma. A unique aspect of FACES is the availability of detailed information on each child's respiratory and overall health, the child's medical history and status, such as asthma severity, medications used, and allergen sensitivity based on skin-prick tests, as well as family medical information, demographic data and a variety of potential environmental exposures.

We report on cross-sectional analyses of the associations between several surrogate measures of background exposure to traffic near primary residences and baseline measures of pulmonary function. A central hypothesis of FACES is that, among children with asthma, there are subgroups that are especially susceptible to the adverse effects of respiratory environmental exposures. Based on a priori considerations, we tested hypotheses that asthma severity, atopic status, and distal airways size modify the relation between highway traffic and pulmonary function.

Methods

Study sample

A convenience sample of children with asthma was recruited between September 2000 and October 2004. Eligibility criteria included: (1) age, six to 11 years old; (2) a physician-diagnosis of asthma; (3) active asthma indicated by current use of asthma medication, asthma symptoms or asthma-related healthcare utilization in the 12 months prior to enrollment; (4) lived in primary residence for a minimum of 3 months prior to study entry with no plans to move in next 2 years; (5) the primary residence is within a 20 km radius of the US Environmental Protection Agency (EPA) air quality monitoring "Supersite" located in Fresno, CA; and (6) absence of any other physical or mental conditions that could impair completion of the study protocol. Medical conditions that excluded a child from participation in the study included those that might have affected performance of spirometry by the child such as cognitive impairments, thoracic cage deformities, and neuromuscular disorders, etc.

Upon entry to the study, a questionnaire was administered in-person and health evaluations were conducted (spirometry, skin-prick allergen-sensitivity tests). Clinic-based spirometry is repeated and an update questionnaire administered at 6-month

intervals after the baseline visit. The study protocol was approved by the Committee for the Protection of Human Subjects of the University of California, at Berkeley. Written informed consent was obtained from parents/legal guardians.

Spirometry

The Forced Vital Capacity maneuver was demonstrated; each child was allowed three practice blows before testing. Spirometry was obtained with a dry rolling-seal spirometer (Spiroflow; P.K. Morgan Instruments, Andover, MA, USA) with the child seated and wearing nose-clips. Up to eight attempts were allowed to obtain three acceptable tracings as described previously (Mortimer et al. 2003).

The 1994 American Thoracic Society (ATS) spirometry performance criteria (ATS 1995) were modified to allow for forced expiratory times of two seconds or greater. Reproducibility criteria were: (i) 10% for Forced Expiratory Volume in 1 sec (FEV_1) and Forced Vital Capacity (FVC); and (ii) 20% for Peak Expiratory Flow Rate (PEFR). Standing height and weight were obtained in stocking-feet with a wall-mounted stadiometer and a digital scale, respectively.

Pre-bronchodilator pulmonary function measures were used in this analysis to reflect the usual state of the child's functional status: measures included FVC, FEV_1, FEV_1/FVC ratio (as a percent), PEFR, Forced Expiratory Flow between 25% and 75% of Vital Capacity ($FEF_{25–75}$), and the ratio of $FEF_{25–75}$ to FVC ($FEF_{25–75}$/FVC). The $FEF_{25–75}$/FVC ratio has the interpretation of the reciprocal of the time constant of the lung (Tager et al. 1986), similar to Meade's $Vmax_{50}$/(VC * $Pst(L)_{50}$) (i.e. instantaneous flow at 50% divided by vital capacity times elastic recoil pressure at 50% of vital capacity) and reflects intrinsic airway size (Mead 1980). For each measure (FVC, FEV_1, PEFR, $FEF_{25–75}$), the mean of the best three (but not less than two) acceptable tracings was calculated. Consistent with many studies of asthma, FVC, FEV_1, FEV_1/FVC%, PEFR and $FEF_{25–75}$ percent-of-predicted (%predicted) values were used: i.e. the pulmonary function test result as a percent of the ''predicted values'' for persons of similar characteristics. The small sample size of the FACES cohort precluded development of internal reference equations. Therefore, we computed sex and race/ethnicity-specific %predicted values for FVC, FEV_1, PEFR and $FEF_{25–75}$ based on reference equations for African American, Mexican-American or Caucasian males <20 years of age or females <18 years of age, from the third National Health and Nutrition Examination Survey (NHANES III) (Hankinson et al. 1999). The NHANES III sex- and race/ethnicity specific reference equations available for FEV_1/FVC% were applicable to all persons aged eight to 80 years (Hankinson et al. 1999). Reference equations are not used for $FEF_{25–75}$/FVC; therefore, the raw data for $FEF_{25–75}$/FVC were used in all analyses.

Skin-prick tests and designation of atopic status

Skin-prick allergen sensitivity tests were performed with the MultiTest device (donated by Lincoln Laboratory, Decateur, IL, USA). Saline and histamine controls, and 14 antigens (Hollister-Stier, Spokane, WA, USA) relevant to the Fresno environment were evaluated. Atopy was defined as one or more positive skin tests. A test was classified as negative for the purpose of this analysis if a subject failed to respond to any antigen and the histamine control was positive. Not all

children completed skin tests; therefore an additional measure of atopy was defined based on *ever* having been diagnosed by a physician as having hay fever or allergic rhinitis. The two variables for atopy were evaluated independently.

Interview-based information

Trained interviewers administered a standardized questionnaire to the child's parent/guardian to ascertain demographic data (e.g. race/ethnicity, family income, etc.); the child's medical history, asthma risk factors and symptoms and medication use; family risk factors for asthma; and information on home characteristics and the child's activity patterns. The parent/guardian identified medications from a chart with color photographs of commonly prescribed asthma medications, and staff recorded prescription information from medication containers.

Children's personal smoking was evaluated without parents' presence. No children were active smokers; only one child had tried to smoke but had smoked less than 10 cigarettes in the past.

The symptom/disability-based criteria of the Global Initiative for Asthma (GINA) asthma severity classification scheme (National Institutes of Health 2002) and parental report of symptom frequency were used to designate the asthma severity status of each child at baseline.

Traffic data

The location of the children's primary residence relative to the closest highway (Functional Roadway Class 1) and the motor vehicle activity on that road were used as markers of their potential exposures to vehicle emissions. The roadway locations were based on the TeleAtlas MultiNet^{TM} USA (TAMN) roadway database. This database contains detailed roadway and address information, with high positional accuracy (TeleAtlas 2004). The locations of the subjects' residences on the TAMN were determined by submission of their standardized baseline addresses to the TeleAtlas Eagle Geocoding Technology Service. Traffic volumes for the year 2000 were obtained from the California Department of Transportation (CALTRANS). The data included annualized average daily traffic (AADT) count and the fraction of that count made up of heavy-duty vehicles (HDV, vehicles with six or more axles). Most HDV are diesel-powered. ArcInfo (Environmental Systems Research Institute, Inc. [ESRI]) was used to preprocess the roadway segment and traffic count data. Each direction-of-travel was represented as a separate roadway segment with half of the total AADT for the highway segment. ArcGIS software (ESRI, Inc.) was used to calculate the distance from each child's primary residence to the nearest highway segment in the TAMN. The inverse-distance-weighted annual average daily traffic count (IDWT) was computed (AADT/distance). A surrogate measure of potential diesel exhaust exposure was computed by multiplication of the IDWT by the HDV fraction (IDWTH).

A variable (comprised of three dummy variables) was created based on self-report of residence proximity to "the nearest freeway, major highway, major intersection, or street with heavy traffic". Response options included: immediately in front, behind, or beside residence; one block away; $>$1–3 blocks away; $>$4 blocks away. The reference group was set as those $>$4 blocks way.

Ambient air quality and meteorological data

To account for variation in pulmonary function measurements related to short-term pollutant levels and weather conditions on the day of and prior to lung function testing, the current and prior-day average 24-h average O_3, NO_2, $PM_{2.5}$, and particulate matter between 2.5 and 10 microns ($PM_{25–10}$), or day-of-test 24-hour average temperature and relative humidity were evaluated in candidate models. Daily pollutant and meteorological data collected at the Fresno "Supersite" were obtained from the California Air Resources Board. Based on an evaluation of meteorological and air pollution patterns in the Fresno region, three distinct seasons were defined: Spring (February–May), summer (June–September), winter (October–January).

Statistical analyses

Multiple linear regression was used to evaluate the associations between pre-bronchodilator pulmonary function measures and traffic-related exposures at the children's primary residence. The analyses were restricted to 214 Hispanic, African American, and Caucasian children for whom traffic and spirometry data, as well as daily central-site ambient air quality data were available. For each pulmonary function measure, a series of linear regressions were implemented to identify an appropriate model. Initially, backwards and forwards stepwise linear regressions were used to evaluate a priori potential confounders or effect-modifiers of associations between traffic exposure and pulmonary function measures (summarized in Tables 1 and 2). The %predicted values used in the analyses were based on sex- and race/ethnicity specific external reference equations that included terms for age, age-squared and height-squared (or in the case of FEV1/FVC% only a term for age). Because %predicted values used in the analyses were not generated from the study population, to account for residual between-subject variation in pulmonary function associated with sex, race/ethnicity, age, and height, we included these variables in candidate models. A number of time-independent markers of

Table 1. Baseline anthropometric and spirometric data.

	All children ($n = 214$)	Girls ($n = 94$)	Boys ($n = 120$, 56.1%)
Age, yr	8.75 (1.64)	8.74 (1.55)	8.75 (1.71)
Height, cm	133.0 (11.7)	132.4 (10.7)	133.5 (12.5)
Weight, kg	34.3 (12.7)	33.7 (11.2)	34.9 (14.1)
FVC, %predicted	101.7 (16.3)	101.6 (18.3)	101.8 (14.6)
FEV_1, %predicted	97.1 (17.4)	97.2 (16.6)	97.0 (18.1)
FEV_1/FVC%, %predicted	93.2% (8.8%)	93.4% (8.2%)	93.2% (9.3%)
PEFR, %predicted	107.8 (22.3)	109.5 (21.9)	106.4 (22.6)
$FEF_{25–75}$, %predicted	92.6 (36.9)	92.1 (36.0)	92.9 (37.7)
$FEF_{25–75}$/FVC	0.921 (0.307)	0.963 (0.296)	0.890 (0.313)

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; $FEF_{25–75}$, forced expiratory flow between 25 and 75% of vital capacity. *A prediction equation was not available for $FEF_{25–75}$/FVC; therefore observed values were used. †The values are mean and standard deviation (in parentheses); due to missing values there are small differences in sample sizes for some pulmonary function measures. ‡No statistically significant difference between sexes was observed for any function measure.

Table 2. Baseline distributions of independent variables.

Characteristic	*n* (%)
Race/ethnicity	
White	93 (43.5)
Black	27 (12.6)
Hispanic	94 (43.9)
Household education:	
Both parents < HS graduate	24 (11.2)
Either parent some college	86 (40.2)
Household income level	40 (18.7)
Low income: <$15k $15k to $50k	115 (53.7)
High income: >$50k	54 (25.2)
Health insurance	
None	11 (5.1)
Work, self, other non-government coverage	133 (62.2)
Government	70 (32.7)
Own home	115/198 (53.7)
In home at least 1 year (Median = 3 yrs)	191 (89.3)
Mother smoked during pregnancy	19/201 (9.5)
Low birth weight (<2500 g) or premature (by ≥3 weeks)	26/212 (12.3)
Early diagnosis with asthma, i.e., at ≤age 2 years	87/210 (41.4)
GINA-symptom-based asthma severity classification[†]	
Step 1	60 (28)
Step 2	104 (48.6)
Step 3	44 (20.6)
Step 4	6 (2.8)
By self-report: ≤2 wks prior to testing occurrence ≥1 of:	
Runny nose	65 (30.4)
Cough	74 (34.6)
Wheeze	74 (34.6)
The condition made asthma worse	50 (23.4)
Any asthma medication used ≤2 wks of PFT	92 (43)
Rescue medication used ≤1 month of PFT	148 (69.2)
Controller medication ≤1 month of PFT	109 (50.9)
Doctor diagnosis of allergies	61/194 (28.5)
Positive skin-prick test (≥1)	118/191 (55.1)
History of eczema	28/213 (13.2)
Study year ([2002 + 2003]: reference 2001)	101 (47.2)
Season of PFT[‡]	
Spring (February–May)	87 (40.7)
Summer (June–September)	83 (38.8)
Winter (October–January)	44 (20.6)
Home completely closed in month of/prior to testing	56 (26.2)
Mother or father currently smokes in home	17 (7.9)
Child: SHS exposure in ≥1 home/car microenvironment	20 (9.3)
Any months home completely closed	132/211 (61.7)
Any pests seen in home (rodents, roaches, etc.)	98 (45.8)
Any fur-bearing pets (cats, dogs, rodents)	87 (40.7)
At least one natural gas appliance inside home	129/213 (60.6)
Garage attached	126/213 (58.9)
Water damage to home	54/213 (25.2)
Mold or mildew visible	119/199 (55.6)
Air conditioning in summer (almost always use)	102/213 (47.7)

(*continued*)

Table 2. (*Continued*).

Characteristic		*n* (%)
Ambient air quality and meteorological measurements[§]	*n*	Mean (SD)
O_3, ppb	214	34.7 (16.4)
NO_2, ppb	213	19.3 (8.4)
$PM_{2.5}$, $\mu g/m^3$	198	20.3 (13.7)
$PM_{2.5-10}$, $\mu g/m^3$	177	26.1 (13.3)
Temperature, °C	214	51.6 (18.7)
Relative humidity, %	212	20.5 (7.3)

PFT, pulmonary function test; SHS, second hand smoke; O_3, ozone; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter of aerodynamic diameter $\leq$2.5 microns; $PM_{2.5-10}$, particulate matter of aerodynamic diameter $>$2.5 microns and $\leq$10 microns. *Unless otherwise noted, number (percent of respondents) is shown. [†]Step 1 = mild intermittent, Steps 2, 3, 4 = mild, moderate, and severe persistent asthma, respectively. [‡]Three distinct seasons exist in Fresno region. [§]Mean of 24-hour averages for days on which PFTs were conducted.

socioeconomic status were considered: home ownership (versus renter), years in residence (a potential marker of family stability and potential exposure duration), a derived variable for "crowding" (number rooms in the residence/number of persons in the residing in the home), income, employment (by mother, father or both), education (mother, father). In addition, maternal smoking during pregnancy and markers of second hand smoke exposure in the home, e.g. current parental smoking inside home (mother, father, both), and total number of smokers in home. Time-dependent variables (e.g. an acute respiratory illness, asthma-related symptoms, or rescue medication use within the two weeks prior to the date-of-examination or season in which examination occurred) were considered, because participants were recruited over several years.

A best subsets selection method was then used to identify the optimum subset of candidate covariates; model selection was based on minimization of the Akaike's Information Criterion (AIC). This step was repeated with the time-dependent daily pollutant (O_3, NO_2, $PM_{2.5}$, $PM_{2.5-10}$) and meteorological (temperature, humidity) variables added one at a time; these variables were not included in the stepwise selection step due to their relatively high colinearity. Candidate covariates with partial R^2 of <0.01 (and $p > 0.05$), or with a large number of missing observations were removed from the model if this did not result in a $>15\%$ change in the IDWT effect estimate and the standard error of that estimate was unaltered.

The residuals from the final model for each pulmonary function measure were checked to verify that model assumptions were met. For mean FEF_{25-75}/FVC, a natural log transformation was required. Possible effect modifiers considered were asthma severity, atopic status and FEF_{25-75}/FVCratio (as an indicator of small airways size). All continuous independent variables (except traffic measures) were centered on their population means. Statistical Analysis System (SAS) software (version 8.2; SAS Institute, Cary, NC) was used for all analyses.

Results

Anthropometric and spirometric data are summarized in Table 1; other covariates are summarized in Table 2. Children of Asian ($n = 2$) or "other" ($n = 8$) race/ethnicity were excluded because pulmonary function reference equations were not available.

Pulmonary function measures for the children in our study did not differ by sex (Table 1). Participants were more likely to be boys (56%) (Table 1), and to have mild–intermittent or mild–persistent asthma (77%) (Table 2). Sixty-one (28%) of the children were reported to have a physician diagnosis of allergies, while 118 (55%) tested positive to at least one antigen on the skin-prick tests (of these children, 73 (61%) did not have a physician diagnosis of allergies).

The spatial distribution of participants' residences and their position in relation to the four highways in the study region are shown in Figure 1. Between-individual IDWT varied substantially (coefficient of variation, computed as standard deviation divided by the mean; CV = 174%), with greater variation contributed by distance-to-roadway (CV = 80%) than by AADT counts (CV = 58%) (Table 3). The traffic count (AADT) ascribed to Highway 168 was the same over the entire length of the roadway, and there was little inter-individual variation in the AADT for Hwy 180. There also was little inter-individual variation in the HDVf, because three of the four highways were each assigned a single value over their entire length (Hwy 168 HDVf = 0.0092; Hwy 180 HDVf = 0.0125; Hwy 99 HDVf = 0.1777). For Highway 41, the HDVf ranged from 0.0143–0.1777 (mean = 0.021; standard deviation 0.022). Only the HDVf for Highway 99 is based on actual weigh-in motion scale data.

The associations between pulmonary function and measures of traffic on highways closest to residences are shown in Table 4. Traffic regression coefficients (and 95% confidence intervals (CI)) are scaled to the respective interquartile range

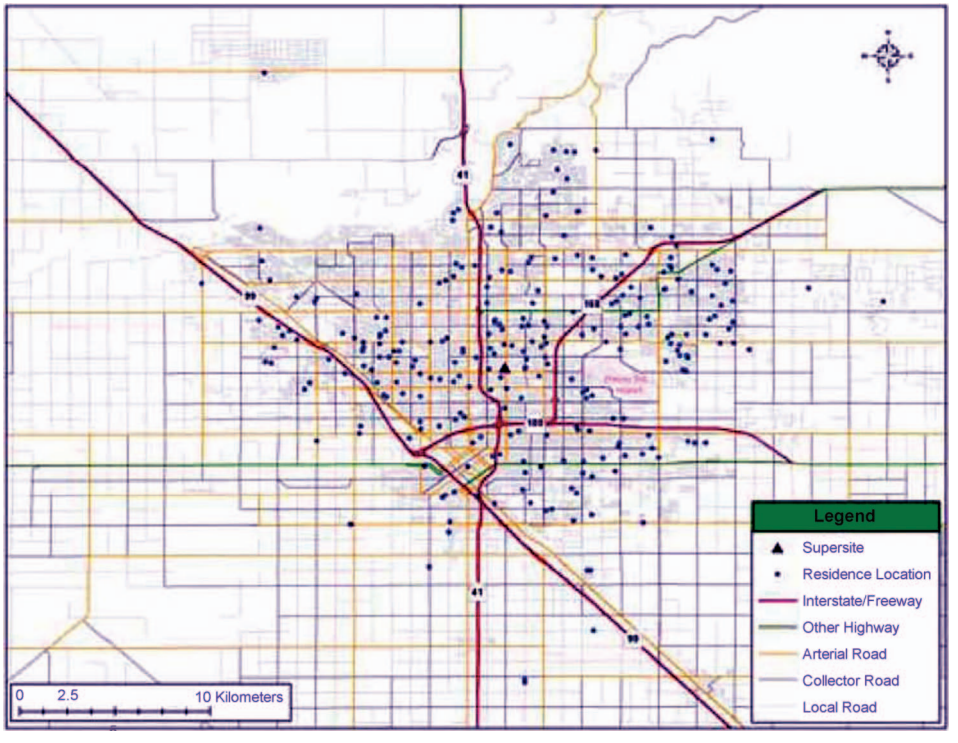

Figure 1. Spatial distribution of participants' baseline residences and their position in relation to the four highways in the Fresno Asthmatic Children's Environment Study region.

Table 3. Distributions of traffic measures on highways closest to baseline residences.

Variable	Mean	SD	IQR	Min.	Percentiles					Max.
					5th	25th	Median	75th	95th	
IDWT ([#/day]/m)	84.6	146.7	73.72	1.27	3.24	17.4	41.7	90.2	302	1,243
AADT (#/day)	52,869	30,214	44,911	5,776	5,776	30,964	54,996	75,875	113,600	113,600
Distance (m)	1,566	1,232	1,439	58.4	221	645	1,275	2,073	4,246	6,293
HDV fraction	0.05	0.07	0.17	0.01	0.01	0.01	0.01	0.03	0.18	0.18
IDWTH ([#/day]/m)	5.85	17.6	4.90	0.02	0.05	0.18	0.85	4.49	26.8	203

IDWT, inverse-distance-weighted annual average daily traffic (AADT) count; HDV fraction, heavy-duty vehicle fraction of total count; IDWTH, the IDWT scaled by the heavy duty vehicle fraction; IQR, Interquartile range.

Table 4. Effect of highway traffic on pre-bronchodilator measures of pulmonary function.

	Coefficient 95% (CI)
FVC %Predicted	
IDWT	0.75 (−0.24, 1.73)
AADT	−0.46 (−3.63, 2.71)
Distance to road	−0.70 (−3.41, 2.02)
IDWTH	0.07 (−0.46, 0.60)
FEV_1 %Predicted	
IDWT	−0.11 (−1.14, 0.92)
AADT	−0.72 (−4.04, 2.61)
Distance to road	−0.01 (−2.85, 2.84)
IDWTH	−0.05 (−0.61, 0.52)
FEV_1/FVC% %Predicted	
IDWT	−0.57 (−1.13, −0.02)
AADT	−1.67 (−3.39, 0.05)
Distance to road	0.84 (−0.53, 2.22)
IDWTH	−0.21 (−0.52, 0.10)
PEFR %Predicted	
IDWT	−1.01 (−2.45, 0.43)
AADT	−1.81 (−6.65, 3.04)
Distance to road	0.30 (−3.77, 4.38)
IDWTH	−0.44 (−1.22, 0.33)
$FEF_{25–75}$ %Predicted	
IDWT	−1.58 (−3.64, 0.48)
AADT	−3.62 (−9.87, 2.63)
Distance to road	1.77 (−3.35, 6.88)
IDWTH	−0.40 (−1.54, 0.73)
$FEF_{25–75}$/FVC Percent difference	
IDWT	−2.63 (−4.79, −0.47)
AADT	−8.31 (−15.23, −1.40)
Distance to road	4.13 (−1.46, 9.71)
IDWTH	−1.06 (−2.25, 0.13)

For definition of abbreviations see Tables 1 and 3. *Mean value of $FEF_{25–75}$/FVC, natural log transformed, used in analyses; results are in terms of percent difference. †Regression coefficients are scaled to the interquartile range for each traffic measure as follows: 73.7 AADT/meter for IDWT; 44,911 vehicles/day for AADT; 1,439.2 m for Distance to road; and 4.89 for IDWTH. ‡Models adjusted as follows: FVC: weight, height, race/ethnicity, own home, asthma worse due to symptom ≤2 wks prior to PFT, doctor diagnosis of allergies, study year. FEV_1: weight, height, early diagnosis of asthma, own home, runny nose ≤2 wks prior to PFT, wheeze ≤2 wks prior to PFT, doctor diagnosis of allergies, history of eczema, study year. FEV_1/FVC: race/ethnicity, mother smoked during pregnancy, early diagnosis, in residence ≥1 year, cough ≤2 wks prior to PFT, asthma worse due to symptom. PEFR: weight, height, mother smoked during pregnancy, early diagnosis, own home, asthma worse due to symptom ≤2 wks prior to PFT, doctor diagnosis of allergies, study year. $FEF_{25–75}$: weight, height, either parent current smoker, early diagnosis, in residence ≥1 year, own fur-bearing pet, asthma symptom (cough, wheeze) ≤2 wks of PFT, history of eczema. $FEF_{25–75}$/FVC: height, age at time of PFT, race/ethnicity, mother smoked during pregnancy, early diagnosis, in residence ≥1 year, runny nose ≤2 wks prior to PFT, asthma worse due to symptom ≤2 wks prior to PFT, atopic (based on skin-test).

(IQR). Adjustment covariates included in the final analysis models varied by pulmonary function measure (Table 4, footnote). FEV_1/FVC%, PEFR, and $FEF_{25–75}$ %predicted and $FEF_{25–75}$/FVC tended to be associated positively with longer distance-to-road and associated negatively with traffic measures that capture traffic intensity (AADT, IDWT, and IDWTH); however, the estimates were relatively imprecise (i.e. only two were statistically significant at $p < 0.05$). The coefficients for

$FEF_{25–75}$/FVC were the most precisely estimated. Over a 73.7 IQR in IDWT, the %predicted FEV_1/FVC% was diminished by 0.6% (95% CI: −1.13, −0.02), and there was a −2.6% difference in $FEF_{25–75}$/FVC (95% CI: −4.79%, −0.47%). The AADT (IQR = 44911) was associated with a deficit in $FEF_{25–75}$/FVC (−8.31%: 95% CI: −15.23%, −1.40%). Although not statistically significant, the association between pulmonary function and the heavy-duty vehicle fraction (surrogate for diesel trucks) of traffic intensity also was estimated most precisely for $FEF_{25–75}$/FVC (−1.06; 95% CI: −2.25, 0.13). Of note, self-report of residence proximity to a major roadway was not associated with any pulmonary function measure (results not shown).

There was a significant interaction between the $FEF_{25–75}$/FVC ratio and IDWT for all measures of pulmonary function, except FVC %predicted, for all children combined and for both sexes (Table 5). For comparison purposes, regression coefficients are scaled to the population interquartile ranges of 73.7 AADT/m for IDWT and 68.0 for $FEF_{25–75}$/FVC*IDWT; however, the observed IQR in IDWT was larger for boys (77.5 (#/day)/m)) than girls (62.7). Higher levels of $FEF_{25–75}$/FVC ratio were associated with a diminished association between traffic measures and %predicted FEV_1, FEV_1/FVC%, PEFR and $FEF_{25–75}$. Except for FVC, the deficits in all pulmonary function measures were similar for girls and boys (when proportional airway size was considered).

Sensitivity analyses were conducted to assess whether observed effects were due to uncontrolled spatial confounding related to roadway patterns and socioeconomic clustering around specific roads. In these analyses each road was treated as a potentially unique subpopulation (community) by addition of a fixed effect categorical variable for that road in the regression models used in the main analyses (see Table 4, footnote) (Pattenden et al. 2000). None of the road indicator variables were significant, nor did their inclusion change the traffic effect estimates (results not shown).

Evaluation of modification of the traffic-exposure-response relationships by atopic status (based on skin-prick tests or on physician diagnosis of allergies), or by asthma severity (GINA symptom/disability-based classification) did not yield any consistent patterns (results not shown).

Discussion

Several surrogate measures of motor vehicle emission (MVE) exposures were used to evaluate the effects of MVE on pulmonary function among 214 children with asthma ages six to 11 years. IDWT, which includes both the traffic counts on the highway closest to the primary residence and the distance to that residence, was most consistently associated with lower pulmonary function (Table 4). For all pulmonary function measures, except FVC, we observed a significant interaction between IDWT and $FEF_{25–75}$/FVC ratio in both sexes (Table 5). This is consistent with the our *a priori* hypothesis that children with asthma who have worse small airway function are most sensitive to the effects of mobile source pollutants and follows from the fact that smaller airway caliber affects airways resistance that, in turn, leads to greater response to bronchoconstrictor stimuli such as air pollutants. In contrast, the main effect of pulmonary function was not associated consistently with variables for vehicle count (AADT) or distance-to-road although the direction of the relationships tended to be as expected (Table 4). In all cases, the magnitudes of the

Table 5. Effect of traffic on measures of pulmonary function with consideration of effect modification by the $FEF_{25–75}$/FVC ratio.

%Predicted	All children combined coefficient (95% CI)	Girls coefficient (95% CI)	Boys coefficient (95% CI)
FVC			
IDWT	−0.97 (−3.97, 2.04)	−4.44 (−9.83, 0.95)	0.12 (−3.36, 3.61)
$FEF_{25–75}$/FVC * IDWT	2.50 (−1.65, 6.66)	6.30 (−0.90, 13.50)	0.52 (−4.37, 5.41)
FEV_1			
IDWT	−7.00 (−10.00, −4.00)	−7.92 (−13.54, −2.31)	−6.75 (−10.71, −2.79)
$FEF_{25–75}$/FVC * IDWT	10.02 (5.89, 14.16)	11.12 (3.82, 18.43)	9.49 (3.91, 15.06)
FEV_1 /FVC%			
IDWT	−5.38 (−6.70, −4.06)	−5.73 (−8.25, −3.24)	−5.55 (−7.12, −3.98)
$FEF_{25–75}$/FVC * IDWT	6.69 (4.98, 8.41)	7.28 (3.88, 10.61)	6.87 (4.84, 8.84)
PEFR			
IDWT	−11.1 (−15.2, −6.93)	−8.44 (−15.91, −0.96)	−12.13 (−17.27, −6.99)
$FEF_{25–75}$/FVC * IDWT	14.8 (9.04, 20.6)	11.26 (1.24, 21.29)	16.00 (8.70, 23.30)
$FEF_{25–75}$			
IDWT	−22.3 (−27.9, −16.8)	−17.0 (−27.4, −6.6)	−23.9 (−31.0, −16.9)
$FEF_{25–75}$/FVC * IDWT	29.5 (22.0, 36.9)	22.5 (9.1, 35.9)	31.3 (21.6, 41.0)

*Effect estimates are adjusted for the covariates listed in Table 4 footnote. †For comparison purposes, all regression coefficients are scaled by the interquartile range (IQR) for IDWT (IQR = 73.7 AADT/meter) and for FEF25-75/FVC * IDWT (IQR = 68.0); however, the IQR for IDWT differed for girls (62.7 AADT/m) and boys (77.5 AADT/m).

associations were small. For example, over the interquartile range in IDWT (73.7) there was a decrease in FEV_1/FVC% of 0.6% of predicted (Table 4). The association with IDWT was significant for $FEF_{25–75}$/FVC, a measure that reflects intrinsic small airways size and function.

The traffic intensity data available to construct the IDWT was an annualized average of daily traffic count; therefore, the IDWT reflects residence-specific background, longer-term traffic-related exposures rather than short-term variation (hourly or daily) in traffic-related pollutants near the residence. Thus, the current analyses are not comparable to studies that have examined short-term effects of traffic-related pollutants or daily traffic counts on transient changes in lung function (e.g. PEFR variability) (Gauvin et al. 2001; Steerenberg et al. 2001; Delfino et al. 2003; Burr et al. 2004). Nonetheless, the effects we observed could be a function of the cumulative impacts of transient responses to higher pollutant levels that exist near homes during daily peak travel periods, such as commute times, as well as the potentially higher average long-term exposures near roadways.

An important limitation of this analysis is the presence of only four roads in the highway category in the study region (see Figure 1) and the minimal variation in the road-specific AADT and HDVf traffic data available from CALTRANS, which together would lead to reduced inter-individual variation in exposure and diminished sensitivity of the analyses. Use of the distance-weighted measure (IDWT) both increased the inter-individual variation in traffic-exposure estimates and potentially reduced measurement error related to distance-to-source; this likely contributed to the more consistent associations between IDWT and pulmonary function. Information on important predictors of MVE near a residence (e.g. whether the home was up-wind or down-wind of the road, and prevailing wind direction) was not available at the time of this analysis.

In their study of children, Brunekreef et al. (1997) reported larger deficits in lung function (FEV_1, PEFR) related to truck traffic as compared to automobile traffic (not restricted to those with asthma) in six communities in The Netherlands. The relative impacts of automobiles versus trucks cannot be determined from our study for which there were no statistically significant associations with the surrogate measure of truck traffic used in these analyses – i.e. the heavy-duty vehicle fraction of the IDWT (Table 4). As more sensitive markers of diesel exposure become available for the FACES cohort, we will further investigate the important issue of which type of vehicle emissions potentially pose greater risk to children's respiratory health.

The limitations of the exposure data make the observed traffic-associated deficits in pulmonary function all the more striking, particularly the effect modification by $FEF_{25–75}$/FVC. Inclusion of the interaction term for IDWT and $FEF_{25–75}$/FVC revealed a significant inverse relationship between IDWT and all pulmonary function measures of flow for all children combined and for both sexes (Table 5), effects not as clearly evident from results of analyses without the interaction term (Table 4). Moreover, we observed that for all pulmonary function measures, except FVC, with a measure of distal small airways size ($FEF_{25–75}$/FVC) included in the models, the effect estimates were similar for girls and boys. Interestingly, among girls, %predicted FVC was inversely associated with traffic (not significant), while there was no apparent affect among boys (Table 5); this pattern is similar to that seen by Brunekreef et al. (1997).

Tager et al. (1986) demonstrated that the ratio of $FEF_{25–75}$ to FVC can be used to approximate the $Vmax_{50}/(VC*Pst(L)_{50}$, a measure of distal small airways resistance (Mead 1980). Relevant to asthma, it was also observed that children with a lower $FEF_{25–75}$/FVC ratio were more likely to respond to a non-specific bronchial challenge (cold air), an effect most evident in children with larger FVC (Tager et al. 1986). O'Connor et al. (2000) also observed the $FEF_{25–75}$/FVC ratio to be a sensitive and consistent indicator of the state of the airways in children with asthma.

Asthma has been shown to influence lung function growth. Weiss et al. (1992), in a longitudinal study, observed that both girls and boys with active asthma had lower %predicted $FEF_{25–75}$. Girls with asthma had lower average %predicted FEV_1, as compared to a non-asthmatic reference group. Similarly, boys with active asthma had larger average %predicted FVC. Similar observations have been made in other studies, although the sex-specific effects differed somewhat depending on the study (Merkus et al. 1993; Berhane et al. 2000; O'Connor et al. 2000). Since $FEF_{25–75}$, to some degree reflects small airways function, it is possible that the chronic inflammation and airway remodeling that characterizes asthma (Bousquet et al. 2000; Jeffrey 2001) contributes to greater air pollution sensitivity among children with asthma through a reduction in airway size. Chronic exposure to air pollutants also induces airway inflammation; this could exacerbate the preexisting asthma-related remodeling with subsequent further reduction in airway size. Thus, $FEF_{25–75}$/FVC would reflect the degree of structural and functional change related to inflammation in the peripheral airways, which is an important marker of disease severity and determinant of disease progression in asthma (Bousquet et al. 2000; Jeffrey 2001).

A core hypothesis of FACES is that children who are more susceptible to the effects of short-term exposures, as indicated by greater frequency and severity of symptoms, medication use, or larger transient declines in pulmonary function are at greater risk of more severe asthma and permanent deficits in pulmonary function over the longer-term, as compared to children less responsive to short-term exposures. It cannot be determined from this cross-sectional analysis whether more severe asthma leads to larger traffic effects, or traffic exposure altered severity, which in turn influenced traffic effects on lung function, or a combination of both scenarios. We will be able to evaluate this complex timing-dependent interplay between responsiveness, exposure and response when these analyses are extended to the longitudinal FACES data.

Conclusion

Among a cohort of children with asthma in Fresno, California, traffic intensity on highways closest to their residence was inversely but non-significantly related to all pulmonary function measures of flow (FEV_1, FEV_1/FVC, PEFR, and $FEF_{25–75}$) at baseline. However, higher traffic exposure was associated with a statistically significant lower ratio of $FEF_{25–75}$ to FVC; the ratio reflects distal small airway size (relative to lung size). This ratio was found to be an important modifier of the effect of traffic on pulmonary function and a marker of greater susceptibility.

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Appendix

Partial correlations of pre-bronchodilator pulmonary function measures[a] with covariates in final analysis models.

Variable	FVC	FEV_1	FEV_1/FVC	PEFR	$FEF_{25–75}$	$FEF_{25–75}$/FVC
Weight at time of PFT	0.23**	0.28**		0.21**	0.17*	
Height at time of PFT	−0.40**	−0.46**		−0.36**	−0.35**	−0.22**
Age at time of pulmonary function test						0.15‡
Race/ethnicity						
Black vs. white	−0.18*		−0.24**			−0.20*
Hispanic vs. white	0.06[c]		−0.05[c]			0.05‡
Either parent current smoker					−0.13‡	
Mother smoked during pregnancy			−0.16*	−0.15‡		−0.16*
Diagnosis of asthma at ≤2 years		−0.21**	−0.24**	−0.13‡	−0.18*	−0.27**
Own home	0.22**	0.18*		0.15‡		
In home at least 1 year			−0.19*		−0.15*	−0.20*
Fur-bearing pet (cat, dog, rodent)					0.20**	
≤2 wks prior to PFT occurrence of:[d]						
Runny nose		−0.23**				
Cough			0.14‡			0.18*
Wheeze		0.13‡				
The condition made asthma worse	−0.12‡		−0.14‡	−0.14‡		−0.21**

(*continued*)

Appendix. (*Continued*).

Variable	FVC	FEV_1	FEV_1/FVC	PEFR	$FEF_{25–75}$	$FEF_{25–75}$/FVC
Asthma symptom (cough, wheeze) $\leq$2 wks of PFT					−0.14*	
Doctor diagnosis of allergies	0.20*	0.17*		0.11[e]		
Atopic (at least 1 + response on skin-prick test)						−0.08[e]
History of eczema		−0.21**			−0.18**	
Study year (2nd (2002 + 2003) vs. 1st year (2001))	0.17*	0.23**		0.22**		

[a]Prediction equation not available for $FEF_{25–75}$/FVC; therefore raw values used. Natural log transformation used in main effects analyses. Variables that were considered but were not selected into any model were: income (3 levels), education (mother, father, separately and as household), mother employed, father employed, relative crowding (defined as number of people/rooms; similar to census SES variable); any health insurance. We also evaluated a number of potential housing characteristics that might have influenced exposure, such as attached garage, presence of air conditioning, pets, pests (rodents, roaches), mildew, etc. [b]Covariate partial correlations are adjusted for other variables included in the model, including IDWT. [c]Hispanic race not significantly different from white at the 0.15 level; it is included as part of the set of 'dummy' variables for race. [d]Variable required to meet model assumptions; $^{\#}p < 0.15$; $^{*}p < 0.05$; $^{**}p < 0.01$.