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Asthma Morbidity and Ambient Air Pollution

Effect Modification by Residential Traffic-Related Air Pollution

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Background: Ambient air pollution has been associated with asthma-related hospital admissions and emergency department visits (hospital encounters). We hypothesized that higher individual exposure to residential traffic-related air pollutants would enhance these associations.

Methods: We studied 11,390 asthma-related hospital encounters among 7492 subjects 0–18 years of age living in Orange County, California. Ambient exposures were measured at regional air monitoring stations. Seasonal average traffic-related exposures ($PM_{2.5}$, ultrafine particles, NO_x, and CO) were estimated near subjects' geocoded residences for 6-month warm and cool seasonal periods, using dispersion models based on local traffic within 500 m radii. Associations were tested in case-crossover conditional logistic regression models adjusted for temperature and humidity. We assessed effect modification by seasonal residential traffic-related air pollution exposures above and below median dispersion-modeled exposures. Secondary analyses considered effect modification by traffic exposures within race/ethnicity and insurance group strata.

Results: Asthma morbidity was positively associated with daily ambient O_3 and $PM_{2.5}$ in warm seasons and with CO, NO_x, and $PM_{2.5}$ in cool seasons. Associations with CO, NO_x, and $PM_{2.5}$ were stronger among subjects living at residences with above-median traffic-related exposures, especially in cool seasons. Secondary analyses showed no consistent differences in association, and 95% confidence intervals were wide, indicating a lack of precision for estimating these highly stratified associations.

Conclusions: Associations of asthma with ambient air pollution were enhanced among subjects living in homes with high traffic-related air pollution. This may be because of increased susceptibility (greater asthma severity) or increased vulnerability (meteorologic amplification of local vs. correlated ambient exposures).

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Studies have shown acute adverse changes in respiratory outcomes among children with asthma from short-term increases in exposure to ambient air pollutants, including particulate matter ≤2.5 mm ($PM_{2.5}$), ozone (O_3), and nitrogen dioxide (NO_2).[1] Among these are time series studies in which aggregate counts of emergency department visits or hospital admissions for asthma have been related to ambient air pollution measured at regional locations. Generally, all subjects in a geographic region are assigned the same exposures. This can result in exposure error—for example, owing to variability of air pollution from local sources such as traffic. We have shown in cohort panel studies of pediatric asthma that personal exposure to markers of traffic-related air pollution (elemental carbon and NO_2) was more clearly associated with acute asthma outcomes than were the same air pollutants measured at ambient sites.[2,3]

Adverse respiratory effects of traffic-related air pollution are supported by experimental studies showing that organic chemicals from fossil fuel combustion (eg, polycyclic aromatic hydrocarbons) increase airway inflammation through oxidative stress mechanisms.[4] These organic chemicals are enriched in ultrafine particles (<0.1 μm) that are emitted at high concentration near traffic sources[5] and are expected to aggravate asthma symptoms, induce airway inflammation,[6,7] and decrease lung function, especially with heavy diesel traffic exposure.[7] High traffic density near home or school has been associated with the incidence and prevalence of diagnosed asthma and increased asthma morbidity.[8–10]

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We hypothesized that the relationship between daily ambient air pollution and daily hospital morbidity for asthma in individual children will be enhanced by higher chronic exposures to traffic-related air pollution near the subjects' homes. This effect modification is anticipated because daily increases in ambient air pollution may be accompanied by much higher excursions in traffic-related air pollution exposures near homes with high traffic density. For example, region-wide increases in ambient air pollutants may result from meteorologic conditions, such as air stagnation, and may be correlated with increased concentrations of air pollutants near ground level, leading to higher risks of hospital admissions for asthma.[11] Homes near busy traffic are expected to be the most affected under these and other meteorologic conditions (such as high photochemical activity) that are generally reflected by background increases in ambient $PM_{2.5}$.[12] In addition to being more vulnerable to short-term air pollutant elevations, chronic exposures to traffic-related air pollution may increase susceptibility to short-term exposures via chronic changes in underlying airway inflammation or other mechanisms.

The present study evaluated this potential effect modification using a case-crossover design. We analyzed individual-level hospital patient data for asthma in relation to daily ambient exposures and their interaction with individual-level traffic-related air pollution exposures based on each subject's residential address. This analysis enables an assessment of the risk of hospital utilization from both spatial and temporal differences in air pollutant exposures. Like time series studies, the case-crossover design is an approach to assess acute effects of air pollutants on hospital utilization events. Each subject acts as their own control by comparing exposure near event periods to exposure during nonevent periods. Despite the availability of individual data, the case-crossover design has been underused in the study of effect modification of air pollution exposures by spatial variation in individual exposures.[13] However, several recent case-crossover studies have evaluated whether other individual characteristics are effect modifiers of air pollutant associations with cardiorespiratory outcomes.[14–17]

METHODS

Population

We extracted hospital data from billing records at two hospitals 2.5 km apart (eFigure 1, http://links.lww.com/EDE/A731), the Children's Hospital of Orange County (~90% of subjects) and the University of California Irvine Medical Center in Orange County, California. Records were extracted for hospital encounters (hospital admissions and emergency department visits) with a primary diagnosis of asthma (*International Classification of Disease, 9th revision Clinical Modification* 493) from 2000 through 2008 among persons 0–18 years of age living in Orange County. Collected data include age, sex, health insurance (private, government sponsored, uninsured, or unknown), race/ethnicity, and residential address. We removed 218 encounters among 194 subjects because they were recurrences within 7 days of the first encounter and could be the same episode of asthma. In addition, we observed 254 encounters for persons whose residences could not be geocoded, leaving 11,177 encounters among 7492 unique subjects for analysis (Table 1). The Institutional Review Boards of the

TABLE 1. Demographic Characteristics of the Hospital Data, 2000–2008

	No. Hospital Encounters			
Subject Characteristics (%)	**Emergency Department Visits (n = 8,088)**	**Hospital Admissions (n = 3,089)**	**Total Hospital Encounters[a] (n = 11,177)**	**No. Unique Subjects (n = 7,492)[b]**
Boys	63	61	63	62
Age (years)				
0–4	52	62	55	55
5–12	38	32	36	36
13–18	10	6	9	9
Race/ethnicity				
White non-Hispanic	36	35	36	36
White Hispanic	54	53	54	52
African American	3	4	3	3
Asian	3	4	3	4
Other/unknown	4	4	4	5
Source of payment				
Private insurance	36	41	37	38
Government sponsored or uninsured	62	53	60	58
Unknown	2	6	3	4

[a]Total encounters is the sum of emergency department visits and hospital admissions.
[b]Number of unique subjects is the subject count excluding recurrent encounters.

Children's Hospital of Orange County and the University of California Irvine approved the study protocol.

Exposures

Subject addresses were geocoded using the TeleAtlas Geocoding Service and then linked to local traffic data and to the nearest ambient air monitoring station data (2000–2008) from the US Environmental Protection Agency's Air Quality System (eFigure 2, http://links.lww.com/EDE/A731). Criteria pollutant gas data were available from four air monitoring stations (average distance to monitors ~7,800 m). Daily $PM_{2.5}$ was available only at the station in Anaheim, California, near the two hospitals (~10,000 m).

We used a modified CAlifornia LINE Source Dispersion Model, version 4 (CALINE4) to estimate traffic-related NO_2, NO_x ($NO + NO_2$), CO, $PM_{2.5}$, and particle number concentrations (dominated by ultrafine particles) at each residence, as previously described[18,19] (eAppendix, http://links.lww.com/EDE/A731). The model is generally based on the principle that wind patterns influence the direction and dispersion of pollutants from their traffic sources, and thus, exposures at residences depend on their location upwind versus downwind of local roadways. The dispersion-modeled pollutant variables are considered surrogate indicators of traffic-related air pollution (a mixture of particles and gases). Model inputs were based on local traffic emissions of gasoline vehicles and diesel trucks within a 500-m radius buffer and included traffic volumes, roadway geometry, vehicle emission rates, and meteorology. We selected 500 m a priori because causal pollutant components are enriched near roadways. We performed sensitivity analyses of asthma associations using a wider 1500-m buffer. The study area (~1000 km^2) and spatial distribution of dispersion-modeled NO_x are shown in eFigure 3 (http://links.lww.com/EDE/A731).

Because dispersion-modeled inputs generally enable the prediction of long-term local exposures[20,21] (eAppendix, http://links.lww.com/EDE/A731), we used models estimate average exposures around each subject's residence for 6-month seasonal periods (warm season, May–October; cool season, November–April). Analysis stratified by season is justified, given that air pollution composition can vary with meteorologic influences, and, thus, effects can vary.[22] Dispersion-modeled data provide for analyses of effect modification by seasonal residential exposure to traffic-related air pollution of relations between daily ambient air pollution and asthma morbidity.

To capture more diverse sources of air pollution (traffic and other) from distances ≤15 km around each subject's residence, we also estimated NO_2 and NO_x using land-use regression models.[21] We developed these models separately to predict season-specific concentrations (no annual variance) based on actual measurements at over 240 sampling locations (eAppendix, http://links.lww.com/EDE/A731), as previously described.[23] The final model predicted seasonal NO_2 and NO_x concentration surfaces well, with cross-validation R^2 values from 0.88 to 0.92.

Analysis

We evaluated associations of asthma-related hospital morbidity with air pollution exposure using a case-crossover design with parameter estimates obtained via conditional logistic regression. In this design, each person acts as their own control because exposures are sampled from that person's time-varying distribution of exposure. Exposure at a time just before the event (lag day 0) is compared with a set of referent times representing the expected distribution of exposure for nonevent follow-up times. Time-invariant subject-specific characteristics (such as socioeconomic status or race/ethnicity) are controlled for by design, and using sufficiently narrow referent windows avoids bias in the presence of seasonal confounding.[24,25]

We used the semisymmetric bidirectional referent selection design,[26] with modification.[27] Exposures of interest are those just before each subject's hospital encounter over the previous 7 days (exposure period). These exposures are then compared with the subject's exposure at other nearby times (referent periods) when the subject was not in the hospital (eFigure 4, http://links.lww.com/EDE/A731). To reduce serial correlation and avoid confounding from temporally adjacent exposures, we did not select referent days within 7 days of the exposures of interest. Specifically, the control (referent) days came from the same days of the week when subjects were not seen in hospital (7–14 days before lag day 6 or 7–14 days after lag day 0). To avoid overlap bias, if another hospital encounter occurred within one of the two 7-day referent periods, we used the other event-free referent exposure and used an offset term ($\log_e 2$, otherwise 0).[27] The offset also indicated if there was only one available referent. Among 170 subjects (2%), there were 111 hospital encounters (1%) where one of the two referent periods had another encounter and 65 encounters (0.6%) where one referent period was missing at the beginning and end of the time series. If another encounter occurred in both referent periods (nine encounters, 0.1%), then the encounter was not analyzed, but this did not alter results. If no encounter occurred in either referent period, then one of the referents was randomly selected.[26] Incorporating an offset term yields a localizable and ignorable design, such that the likelihood that incorporates the referent window selection reduces to the conditional logistic regression likelihood, yielding an unbiased estimating equation, as discussed by Janes et al.[27] As a sensitivity analysis, we also tested the time-stratified method, the other localizable and ignorable design.[27] Results were qualitatively the same, and our conclusions were unaltered.

Given that some subjects have repeated hospital encounters, within-subject correlation was present in the data. To adjust for this, the standard errors of parameter estimates were obtained using a robust variance estimator with clustering on subject.[28]

We tested regression estimates for current-day exposures (lag 0), as well as for 6 lagged days that were averaged with lag 0 to estimate possible cumulative acute effects of multiday exposures (2-day through 7-day averages). For simplicity, we present models for 1-day (lag 0), 3-day, 5-day, and 7-day averages. The same averaging time was used for control exposure periods in each model.

Associations of ambient air pollutants with emergency department visits and with hospital admissions were first tested in separate models and found to have consistent effect estimates but with differing precision. Emergency department visit regression coefficients had smaller standard errors, likely because of greater sample size. Therefore, we combined the two asthma encounter types ("asthma-related hospital morbidity") as previously.[9,10] We adjusted for 24-hour mean temperature and relative humidity of the same lag average as air pollutants. Model fit did not improve with smoothed penalized spline terms to adjust for nonlinear effects of temperature. Weather had a nominal impact on associations (≤7% change).

To test effect modification by 6-month seasonal average residential air pollution, subjects were stratified above and below median dispersion-modeled and land-use regression-modeled exposures to provide sufficient sample size. We hypothesized that increases in asthma morbidity from daily elevations in ambient air pollution would be modified by higher chronic exposures to traffic-related pollution near subjects' homes. Product terms of ambient pollutants with binary traffic exposure group were considered to most clearly indicate effect modification at a nominal $P < 0.1$. For greater interpretability, regression results were standardized to interquartile range (25th to 75th percentile) increases in each ambient air pollutant. There was little difference between estimates for ambient air pollution interactions with dispersion-modeled residential CO, NO_2, or NO_x, and so we present results only for dispersion-modeled NO_x and for dispersion-modeled $PM_{2.5}$ and particle number.

Although fixed subject characteristics cannot confound associations of hospital morbidity with air pollution in case-crossover models, it is possible that residential dispersion-modeled strata could function as a surrogate of demographic differences that vary with traffic. This is possible because poorer and minority children are more likely to live near higher density traffic,[29] and in the present study, this population is more likely to lack private health insurance.[30] Therefore, we conducted a secondary analysis to assess the influence of race/ethnicity or health insurance status on differences in association with traffic-related air pollution strata. In these models, effect modification by dispersion-modeled exposures was estimated within race/ethnicity and insurance strata using multiplicative interaction models.

RESULTS

Descriptive Statistics

Table 1 shows the distribution of subject data. Substantial proportions of children were Hispanic and had no private health insurance. Descriptive results for air pollutant exposures are shown in Table 2 and eTable 1 (http://links.lww.com/EDE/A731).

Spearman correlations of ambient air pollutants (eTable 2, http://links.lww.com/EDE/A731) showed moderate-to-strong positive correlations among the traffic-related gases (NO_2, NO_x, and CO), and the gases were weakly to moderately correlated with $PM_{2.5}$ (stronger in cool seasons). In cool seasons, O_3 was inversely correlated with traffic-related gases and $PM_{2.5}$, partly because of air stagnation periods as reflected by correlations of these air pollutants with wind speed (positive with O_3 and negative with traffic-related gases and $PM_{2.5}$).

Regression Analysis of Ambient Air Pollution

We found many positive associations of ambient air pollution with asthma-related hospital morbidity (Figures 1 and 2, "All Subjects"). In general, associations strengthened from the 1-day average to longer air pollutant averaging times. Associations with NO_2, NO_x, and CO are stronger and 95% confidence limits tighter in cooler seasons (Figure 1), whereas associations for $PM_{2.5}$ up to the 5-day average are stronger in warmer seasons (Figure 2). However, when using a season-specific interquartile range to express the magnitude of association, associations for $PM_{2.5}$ are stronger in cooler seasons, whereas the stronger associations in cooler seasons for NO_2, NO_x, and CO remained (eTable 3, http://links.lww.com/EDE/A731). Higher $PM_{2.5}$ mass concentrations in the cooler seasons are likely accompanied by differences in pollutant composition and toxicity.[22]

Expected positive associations are seen with O_3 in the warm season (Figure 2). The standard error of estimates for 24-hour average O_3 was lower than 8-hour maximum O_3 (not shown). We observed a previously reported but biologically implausible inverse association with O_3 in the cool season similar to hospital time series studies.[22] This paradoxical association could be because of negative correlations of O_3 with $PM_{2.5}$, NO_2, NO_x, and CO that were positively associated with asthma morbidity. Seasonal differences in association led to weaker associations for O_3, NO_x, and CO in models combining seasons (not shown). Positive associations with $PM_{2.5}$ were seen in both seasons.

Regression Analysis of Effect Modification by Traffic-related Air Pollution

For cool season models, associations of asthma morbidity with daily ambient CO, NO_x, NO_2, and $PM_{2.5}$ (especially 7-day averages) were generally stronger among subjects living at residences with greater than median dispersion-modeled NO_x, $PM_{2.5}$, and particle number (Figure 1). The main exceptions to these findings were for ambient $PM_{2.5}$ and NO_2 by dispersion-modeled NO_x and particle number strata, where there was little or no difference. Eight of 48 product terms for dispersion-modeled pollutants reached $P < 0.1$ for cool season ambient CO, NO_2, NO_x,

TABLE 2. Seasonal Distribution of Ambient Air Pollution and Traffic-related Air Pollution Exposures Estimated by Dispersion (CALINE4) and Land-use Regression Models[a]

Exposure	Season	No.[b]	Mean (SD)	Median	Interquartile Range[c]	Minimum	Maximum
Ambient							
$PM_{2.5}$ (μg/m^3)	Cool	5,755	19.0 (13.8)	14.5	15.4	2.54	113.9
	Warm	4,421	16.0 (9.5)	14.1	7.77	3.09	115.5
NO_2 (ppb)	Cool	6,347	26.6 (12.5)	25.4	15.9	1.74	84.2
	Warm	4,978	16.1 (10.5)	13.7	13.7	1.52	67.1
NO_x (ppb)	Cool	6,349	65.3 (51.4)	52.2	64.4	0.70	393.6
	Warm	5,018	23.4 (21.6)	16.1	21.7	0.14	158.3
CO (ppm)	Cool	6,353	0.81 (0.59)	0.66	0.69	0.01	4.40
	Warm	5,034	0.36 (0.28)	0.30	0.29	0.01	2.29
O_3 (ppb)	Cool	6,355	20.0 (11.2)	18.2	16.8	0.01	58.4
	Warm	5,032	34.0 (10.4)	33.9	14.5	1.00	71.0
Temperature (°F)	Cool	6,358	58.8 (5.81)	58.5	7.00	22.6	83.0
	Warm	5,032	69.3 (5.69)	69.1	7.25	0.01	88.0
Relative humidity (%)	Cool	6,287	62.7 (20.9)	67.3	28.6	1.92	100.0
	Warm	5,034	71.1 (14.8)	72.9	17.2	0.50	99.0
Dispersion model[d]							
$PM_{2.5}$ (μg/m^3)	Cool	5,399	0.55 (0.79)	0.281	0.349	0.00	7.09
	Warm	4,222	0.55 (0.84)	0.269	0.355	0.00	8.07
NO_x (ppb)	Cool	5,399	1.65 (2.36)	0.854	1.18	0.00	18.7
	Warm	4,222	1.51 (2.30)	0.744	1.06	0.00	25.7
Particle number (no./cm^3)	Cool	5,399	1,984 (3,689)	761	1,266	0.00	34,247
	Warm	4,222	1,646 (3,101)	594	1,041	0.00	30,647
Land-use regression model							
NO_x (ppb)	Cool	5,396	53.4 (11.2)	57.2	12.4	1.29	71.3
	Warm	4,222	19.1 (6.6)	18.6	9.0	0.60	44.1

[a]The ambient exposures are for daily 24-hour mean measurements on event days, whereas the exposures computed from the dispersion and land-use models are for 6-month seasonal averages by subject.

[b]The number of observations is based on each event of a hospital encounter in the case-crossover analysis where ambient air pollution and residential air pollution data are available.

[c]The overall across-season interquartile ranges were used in the within-season regression analyses in Figures 1 and 2 to express magnitudes of association as follows: 11.1 μg/m^3 for $PM_{2.5}$, 18 ppb for NO_2, 52.5 ppb for NO_x, 0.55 ppm for CO, and 20.2 ppb for O_3.

[d]See Methods section for details on CALINE4. Because CALINE4 estimates are only from local traffic within 500 m of the home (left-skewed from little nearby traffic), CALINE4 pollutant concentrations are considerably lower than ambient levels and lower than NO_x estimated by land-use regression.

and $PM_{2.5}$ (primarily 5-day and 7-day ambient air pollution averages). The strongest effect modification was with dispersion-modeled $PM_{2.5}$, especially with ambient CO and NO_x. For example, among subjects living in the upper half of dispersion-modeled $PM_{2.5}$ during the cool season, the estimated percentage change in hospital encounters in relation to an interquartile increase in 7-day average ambient NO_x (52.5 ppb) was 29% (95% confidence interval = 10 to 52) compared with 5% (–6 to 18) for those living in the lower half of dispersion-modeled $PM_{2.5}$ (test for interaction, $P < 0.02$).

In warm seasons, associations of ambient $PM_{2.5}$ with asthma-related hospital morbidity tended to be stronger and with tighter confidence intervals for subjects in the upper median of dispersion-modeled NO_x, $PM_{2.5}$, and particle number (Figure 2). Results were similar for ambient CO. Overall, seven of 48 product terms for dispersion-modeled pollutants reached $P < 0.1$ for warm season ambient CO, NO_2, NO_x, and $PM_{2.5}$. Associations for ambient O_3 in warm seasons were more strongly positive in subjects with dispersion-modeled pollutants at or below the median, although only two product terms reached $P < 0.1$.

Sensitivity analysis results for dispersion-modeled data using a much wider 1500-m buffer (not shown) were consistent with the above results using a 500-m buffer, but differences in asthma associations above and below the median dispersion-modeled strata were smaller and confidence intervals wider.

We discuss secondary analyses of demographic factors in the eAppendix (http://links.lww.com/EDE/A731). In brief, Hispanic and African American subjects, as well as subjects without private insurance, were more likely to live in residences with higher dispersion-modeled traffic-related air pollution (eTable 4, http://links.lww.com/EDE/A731). Associations with all ambient air pollutants in the cool season were stronger among Hispanic whites compared with non-Hispanic whites, and there were isolated stronger associations with ambient $PM_{2.5}$ in the warm season among subjects without

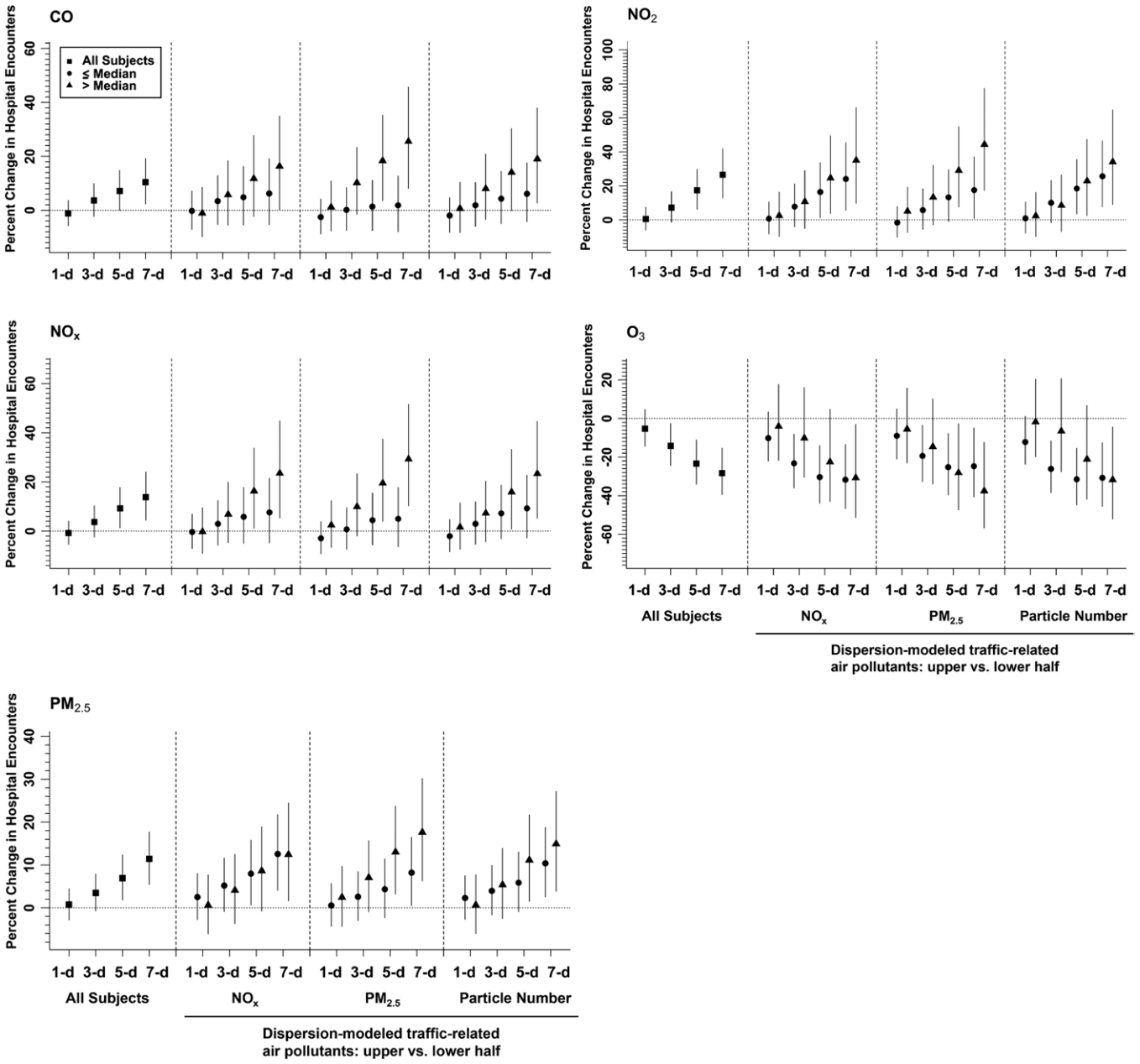

FIGURE 1. Associations between pediatric asthma hospital morbidity and ambient air pollution (CO, NO_2, NO_x, O_3, and $PM_{2.5}$) in the cool season. Effect modification by dispersion-modeled traffic-related air pollution above and below median levels. All exposures are for the 24-hour daily average concentrations. Percentage change in hospital encounters and 95% CI are for an interquartile increase in the ambient air pollutant (Table 2, footnote c), adjusted for temperature and relative humidity of the same averaging time.

private health insurance (eTable 5, http://links.lww.com/EDE/A731). In most cases, there was no consistent evidence of effect modification of associations of asthma morbidity with ambient air pollution by dispersion-modeled exposure within race/ethnicity and insurance strata, and confidence limits were wide, indicating a lack of precision for estimating these highly stratified association estimates (eTable 6, http://links.lww.com/EDE/A731).

Regression Analysis of Effect Modification by Land-use Regression-estimated NO_2/NO_x

There were no clear differences in associations above or below the median of land-use regression-estimated NO_2 (not shown). Associations with asthma hospital morbidity in the cool seasons were slightly stronger and confidence intervals narrower for 5-day and 7-day averages of ambient NO_2, NO_x, CO, and $PM_{2.5}$ among subjects in the upper half of land-use

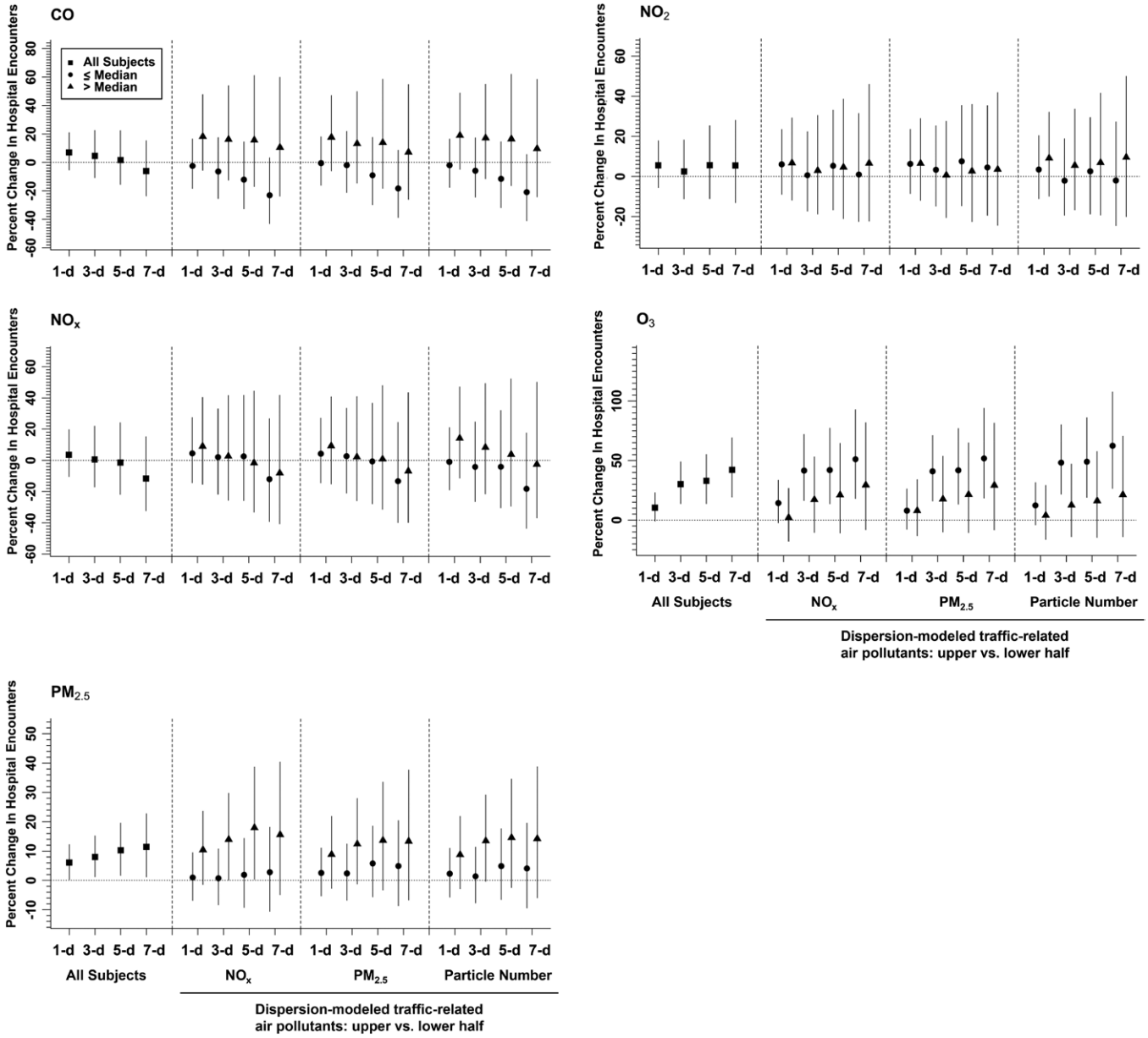

FIGURE 2. Associations between pediatric asthma hospital morbidity and ambient air pollution (CO, NO_2, NO_x, O_3, and $PM_{2.5}$) in the warm season. Effect modification by dispersion-modeled traffic-related air pollution above and below median levels. All exposures are for the 24-hour daily average concentrations. Percentage change in hospital encounters and 95% CI are for an interquartile increase in the ambient air pollutant (Table 2, footnote c), adjusted for temperature and relative humidity of the same averaging time.

regression-modeled NO_x (eTable 7, http://links.lww.com/EDE/A731). However, confidence intervals among land-use regression estimates overlapped considerably. For land-use regression models during the warm seasons, there was less evidence of a difference in associations.

DISCUSSION

We found that emergency department visits and hospital admissions for asthma were positively associated with ambient air pollution, including $PM_{2.5}$ and O_3 in the warm season and $PM_{2.5}$, CO, NO_2, and NO_x in the cool season. This is consistent with many previous epidemiologic time series and case-crossover studies. To our knowledge, this is the first study to show that associations of daily ambient air pollution with asthma-related hospital morbidity are stronger among subjects living at residences with higher predicted levels of air pollution from traffic sources. We expected amplification in traffic-related air pollution exposures during days with higher

ambient air pollutant concentrations, especially during cooler periods with lower mixing heights and air stagnation.[31,32] Traffic-related particulate matter exposures can be more prooxidant per unit mass than background ambient particulate matter exposures.[5] This would lead to greater airway oxidative stress and inflammation (one hallmark of the asthma phenotype). All in all, our findings suggest that exposure error from the use of ambient air pollution data may be diminished using the present approach of analyzing interaction between long-term spatial exposure and short-term ambient air pollution exposure. It is also possible that findings of effect modification were observed because subjects who lived near traffic had greater levels of chronic airway inflammation as a result of their persistently elevated exposures and were thus more vulnerable to short-term increases in ambient background air pollution. The strongest associations were for 5-day and 7-day average air pollutant concentrations, likely the result of cumulative effects.

Effect modification by residential traffic-related air pollution was observed for the air pollutant gases representing pollutants from primary combustion sources (CO, NO_2, and NO_x). $PM_{2.5}$, on the contrary, represents both primary and secondary chemical constituents (from photochemical processes). It is possible that the effect modification by residential traffic-related air pollution observed for ambient $PM_{2.5}$ was from increases in primary traffic-related PM, with photochemically generated components important as well during warmer periods (Figure 2, $PM_{2.5}$). Although the expectation was that dispersion-modeled particle number should have best represented this, dispersion-modeled $PM_{2.5}$ showed similar or stronger effect modification.

Overall, differences using land-use regression-modeled NO_x data were far less clear than traffic-related air pollution estimated by dispersion models within close proximity of subject residences (500 m). This finding is consistent with the wider confidence intervals for dispersion-modeled data based on a larger 1500-m buffer. Dispersion-modeled NO_x at 500 and 1500 m were not correlated with land-use regression-modeled NO_x (eFigures 5–6, http://links.lww.com/EDE/A731), suggesting that in our study region they represent different exposures (local traffic only vs. all sources, respectively). It is likely that causal pollutant components are enriched near roadways. Previous findings indicate that particle number and CO concentrations decrease in an exponential fashion by downwind distance from freeways and reach near-background levels at 200 m during daytime hours (10:00–18:00)[33] and up to 2000 m during the pre-sunrise hours (04:00–07:30).[34] An exponential decay of NO_x is also observed, reaching near-background levels at around 500 m from a freeway.[35] Therefore, a 500-m cut point for dispersion-modeled data likely captures many primary pollutants from traffic sources.

Ozone is an identified trigger of asthma.[1] Associations of asthma with ambient O_3 in warm seasons were nominally stronger among subjects with lower dispersion-modeled pollutant exposures (≤median). A possible explanation is that subjects in high traffic areas were less exposed to O_3 than subjects in low traffic areas because of the well-known reduction in O_3 by traffic-generated NO.[35] This again supports the view that exposure error is diminished with the present approach of combining spatial and temporal data.

We are aware of only one other case-crossover study that has evaluated both population-based asthma morbidity events and air pollution on a residential spatial scale.[36] That study (conducted in France) examined telephone calls to an emergency medical system for asthma exacerbations. Air pollutants were modeled for census blocks using deterministic models, including emission inventories, meteorology, and background pollutant levels. Nominally positive associations with asthma exacerbations were found for spatially resolved PM_{10}, NO_2, and sulfur dioxide.

Our secondary analyses showed that associations with ambient $PM_{2.5}$, NO_2, and CO in the cool season were nominally stronger among Hispanics compared with non-Hispanic whites, but there were no consistent differences for health insurance status. Three-way product-term models did not suggest that dispersion-modeled traffic-related air pollution strata are acting as surrogates of racial/ethnic or health insurance differences in geographic areas. However, this analysis was limited by the fact that the only available individual-level socioeconomic data were health insurance status. Unmeasured demographic and socioeconomic factors may confound the observed effect modification, but we were unable to fully account for this after stratification by race/ethnicity and insurance status. As with any stratified analysis, the smaller sample sizes within subgroups likely limited the statistical power to detect potential interactions and confounding.

Additional limitations include the use of long-term average estimates of traffic-related air pollution (6-month) from dispersion and land-use regression models with inputs having low temporal resolution. Nevertheless, our main objective was to estimate asthma risk from daily ambient air pollution by relative spatial variability in traffic-related air pollution exposure. In addition, chronic exposure to traffic-related air pollution may increase susceptibility in some fundamental way, including chronic effects on airway caliber.[37] A further limitation is that we have no direct information on the causal air pollutant constituents represented by the dispersion-modeled data. Future research is needed to address this uncertainty in pollutant variables that are likely acting as surrogates for causal components.[38] This is reflected in an expected similar pattern of association across strata of different dispersion-modeled pollutants, given their common sources and predictive inputs. Nevertheless, we did find nominal differences in traffic-related air pollution exposure classification because 79% and 77% of the subjects in the upper median of dispersion-modeled NO_x were in the upper median dispersion-modeled $PM_{2.5}$ and particle number, respectively, whereas 86% of the subjects in the upper median of dispersion-modeled particle number were in

the upper median dispersion-modeled $PM_{2.5}$. Additional exposure error is expected because subjects spend time at nonresidential locations, including school, for which air pollution data were not available. Finally, only one station was available for $PM_{2.5}$ versus four for gases (see eAppendix, http://links.lww.com/EDE/A731; for sensitivity analyses).

The results presented here imply that associations of asthma-related hospital morbidity with ambient CO, NO_2, NO_x, and $PM_{2.5}$—particularly during the colder seasons—are enhanced among subjects living in areas with high traffic-related air pollution near the home (≤500 m), including ultrafine and fine particles. This suggests that associations reported in the time series literature may underestimate effects of ambient air pollutants on asthma morbidity for pediatric populations so exposed as a result of acutely increased vulnerability or chronically increased susceptibility. Previous work has shown that, during cooler periods of air stagnation, particle size distribution drifts toward higher levels of ultrafine particles[32] and toward higher concentrations of polycyclic aromatic hydrocarbons that are not reflected by particle mass concentrations.[39] This could have greater effects per unit particle mass on asthma.[6] These findings point to the need for research that assesses the importance of air pollutant chemistry and sources in asthma exacerbations.[38]

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