The Response of Children with Asthma to Ambient Particulate Is Modified by Tobacco Smoke Exposure

Nathan Rabinovitch[1], Lori Silveira[2], Erwin W. Gelfand[1], and Matthew Strand[2]

[1]Division of Allergy/Immunology, Department of Pediatrics, and [2]Division of Biostatistics and Bioinformatics, National Jewish Health, Denver, Colorado

***Rationale*: Ambient particulate matter concentrations have been positively associated with urinary leukotriene E_4 (LTE_4) levels and albuterol usage in children with asthma but interactions with environmental tobacco smoke (ETS) exposure have not been demonstrated despite obvious exposure to both pollutants in an urban setting.**

***Objectives*: To assess the health effects of concurrent ETS and ambient particulate matter exposure in children with asthma.**

***Methods*: Albuterol usage and LTE_4 levels were monitored in 82 urban schoolchildren with asthma over three consecutive fall to spring school periods. Concentrations of morning maximum ambient particulate matter <2.5 μm in aerodynamic diameter ($mmPM_{2.5}$) and urine cotinine levels were also measured daily.**

***Measurements and Main Results*: Albuterol usage and LTE_4 were related to $mmPM_{2.5}$ concentrations on days when urine cotinine levels were low (<10 ng/ml/mg creatinine); on these days, mean albuterol usage and LTE_4 increased up to 5 or 6% per 10 μg/m^3 increase in $mmPM_{2.5}$. In contrast, no significant relationship was observed when cotinine was high, although mean albuterol usage and LTE_4 levels were greater in this case. Model fits for LTE_4 levels as a function of $mmPM_{2.5}$ concentrations were improved when $mmPM_{2.5}$ concentrations were logged, suggesting a nonlinear dose–response relationship between particulate matter exposure concentrations and airway mediators of asthma, for which the relationship tends to flatten at higher concentrations.**

***Conclusions*: This study suggests that ETS modifies the acute effects of low-level ambient $PM_{2.5}$ exposure on childhood asthma. This negative interaction, the smaller effect of particulate matter exposure in children exposed to higher ETS, may be related to a nonlinear dose–response relationship between asthma mediators and particulate exposures.**

Keywords: air pollution; leukotriene E_4; asthma; interaction; environmental tobacco smoke

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

A number of panel studies have demonstrated a relationship between levels of airborne particulate matter less than 10 or 2.5 μm in aerodynamic diameter (PM_{10} or $PM_{2.5}$) and acute asthma severity indices including hospital admissions, declines in pulmonary function, and increases in medication use and symptoms. However, interactions between ambient $PM_{2.5}$ and environmental tobacco smoke exposures on health indicators have not been reported.

What This Study Adds to the Field

This study suggests that concurrent tobacco smoke exposure limits the increase in urinary leukotriene E_4 levels and albuterol usage in response to increases in ambient $PM_{2.5}$ concentrations.

A number of panel studies have demonstrated a relationship between levels of airborne particulate matter less than 10 or 2.5 μm in aerodynamic diameter (PM_{10} or $PM_{2.5}$) and acute asthma severity indices including hospital admissions (1–3), declines in pulmonary function, and increases in medication use and symptoms (4–12). Almost all such studies estimate ambient health effects without taking into account concurrent exposures that may impact asthma, such as environmental tobacco smoke (ETS). However, in the setting of urban asthma, where high ambient exposures are assumed, concurrent exposures to ETS are also prevalent (13–20). There are limited data on the response to ambient or indoor exposures in the typical urban environment where these concurrent exposures often occur. As such, it is unclear whether acute exposures to both ETS and ambient air pollution produce additive or synergistic effects or whether adaptive responses occur, limiting cumulative health effects from concurrent exposures.

In previous analyses involving a panel of Denver urban schoolchildren with asthma we found that morning maximum ambient particulate matter concentrations were significantly related with albuterol usage and with a mediator of bronchoconstriction and airway inflammation measured in urine, leukotriene E_4 (LTE_4) (21, 22). Not unexpectedly, many of these children continued to be exposed to ETS despite their disease. The present analysis examined how relationships between ambient $PM_{2.5}$ and albuterol use or LTE_4 were modified by cotinine, a biologic marker of ETS, to better understand how ETS and ambient particulate matter exposures interact on the health of children with mild to severe asthma. Some of these data have been previously published in abstract form (23).

METHODS

Subjects

Children aged 6–15 who attended the Kunsberg School at National Jewish Health with physician-diagnosed asthma were studied over three consecutive school periods (2002–2003, Year 1; 2003–2004, Year 2; and 2004–2005, Year 3). Pollution and health outcome data were collected in each study year from approximately October through April when children were attending school.

Ethical and scientific approval for each year was obtained from the National Jewish Health Institutional Review Board.

Ambient Air Monitoring and Meteorology

Hourly $PM_{2.5}$ concentrations were measured by a community tapered element oscillating microbalance (Rupprecht and Patashnick, East Greenbush, NY) device located approximately 3.5 miles from the

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Correspondence and requests for reprints should be addressed to Nathan Rabinovitch, M.D., National Jewish Health, 1400 Jackson Street, Denver, CO 80206. E-mail: rabinovitchn@njhealth.org

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school in downtown Denver and operated by the Colorado Department of Health Air Pollution Control Division. Morning maximum $PM_{2.5}$ ($mmPM_{2.5}$) was determined as the individual hour between 1:00 A.M. and 11:00 A.M. with the highest concentration. Temperature, relative humidity, and barometric pressure data were obtained from local Air Pollution Control Division monitoring stations. Personal $PM_{2.5}$ monitoring was also performed as previously described (24).

Albuterol Use

Daily albuterol usage during school hours (8:00 A.M. to 2:45 P.M.) was recorded by an electronic Doser (Meditrak, Hudson, MA) that records the number of metered dose inhaler (albuterol) activations (25).

Urinary Cotinine and LTE_4

Urine samples were collected from each child on up to 8 consecutive schooldays at two different periods within a study year (for up to 16 daily samples per child, per year). Urine was collected at approximately the same time each day (between 11:00 A.M. and 1:00 P.M.).

Urinary LTE_4 was measured as described by Wescott and coworkers (26). Urine LTE_4 levels were reported in picograms per milliliter and standardized per milligram of creatinine. An ELISA (OraSure Technologies Inc., Bethlehem, PA) was performed to quantify levels of urine cotinine (27). The minimum detection limit of this assay was 0.1 ng/ml. Urine cotinine levels were reported in nanograms per milliliter and standardized per milligram of creatinine.

Statistical Analyses

Daily albuterol use counts were fit using generalized linear models (log link), and log urinary LTE_4 levels were fit using linear mixed models. Models contained either individual pollutant markers ($mmPM_{2.5}$, log [$mmPM_{2.5}$], or cotinine) and covariates, or multiple pollutant markers ($mmPM_{2.5}$, cotinine, and cotinine $\times$ $mmPM_{2.5}$) and covariates as predictors. Models were fit for each study year (1–3) and lag (0, same day; 1, previous day), and for all data with a 2-day moving average of $mmPM_{2.5}$ (lag 0 and 1). Cotinine was modeled either as a binary variable (using 10 ng/ml/mg creatinine as a cut-point) or as a continuous variable, as noted in the text.

A spatial exponential covariance structure was used to account for repeated measures within subjects over time for LTE_4 models; for albuterol use, a first-order autoregressive working structure was used with generalized estimating equations (28). Covariates for albuterol use models included temperature, pressure, humidity, linear time trend, and exercise day indicator; for LTE_4, covariates were height and daily upper respiratory infection symptoms indicator. SAS (version 9.2; IBM, Chicago, IL) was used to fit all models. For more detail on statistical methods, see the online supplement.

RESULTS

Panel Characteristics

Over half the panel was African American, and most of the children had experienced an asthma exacerbation in the year before the ones in which they participated (Table 1). Based on the frequency of nighttime symptoms, most of these children were classified as moderate or severe by National Asthma, Education and Prevention Program guidelines (Table 2) (29). In each year, approximately one-third of children reported living in homes with a person who smokes, one-third reported smoking exposure from a nonhousehold member but did not live with a person who smokes, and one-third reported no regular smoking exposure (Table 2). Table 3 displays summary statistics for cotinine, LTE_4, and albuterol usage based on subject averages. There were 82 participants over 3 years who had albuterol use data collected, and 77 of these had cotinine and LTE_4 data collected; some subjects participated in multiple years.

Associations between Individual Pollutant Markers and Health Outcomes

Consistent with published literature that reports a cotinine half-life of approximately 20 hours (30), cotinine was most related with total personal $PM_{2.5}$ in the 24 hours leading up to the cotinine measurement. Mean $mmPM_{2.5}$ was 16.8, 19.5, and 22.9 $\mu g/m^3$ for the 3 consecutive study years (5th–95th percentile: 4–39, 5–46, and 7–52 $\mu g/m^3$ for Years 1 through 3, respectively).

Albuterol use was significantly and positively related to $mmPM_{2.5}$ on the same day (lag 0) in Year 1 and on the previous day (lag 1) in Year 2; no significant relationship was observed in Year 3 for lag 0 or 1. For the 3 study years combined, average albuterol use increased 2.4% per 10 $\mu g/m^3$ increase in 2-day average (lag 0 and 1) of $mmPM_{2.5}$ (95% confidence interval [CI], 1.3–3.6%; $P = 0.0005$). Effect estimates for LTE_4 generally had similar patterns and magnitudes, but usually with weaker significance (likely caused by smaller sample sizes available for analysis). Considering individual years or combined year estimates, LTE_4 was significantly and positively related to $mmPM_{2.5}$ only for lag 0 in Year 1 ($P = 0.005$). Albuterol use was 9.7% higher (95% CI, −4.2 to 25.6%; $P = 0.20$) and LTE_4 was 6.1% higher (95% CI, −0.8 to 13.3%; $P = 0.08$) for children on days when cotinine was high ($\geq$ 10 ng/ml/mg creatinine) compared with low, for the 3 study years combined.

Effect Modification of Cotinine on Relationships between Ambient $PM_{2.5}$ and Health Outcomes

Figures 1 and 2 and Table 4 demonstrate how the relationship between albuterol use or LTE_4 and $mmPM_{2.5}$ is modified by cotinine, for years and lags in which positive significant relationships existed between health outcomes and $mmPM_{2.5}$. These figures illustrate that mean albuterol use and LTE_4 levels were higher when cotinine levels were higher, but that increases in these outcomes per unit increase in $mmPM_{2.5}$ were smaller when cotinine was high. Albuterol usage and LTE_4 were both significantly or marginally significantly related to $mmPM_{2.5}$ when cotinine was low (<10 ng/ml/mg creatinine) with approximate

TABLE 1. DEMOGRAPHICS: BASIC SAMPLE CHARACTERISTICS, BY STUDY YEAR, FOR SUBJECTS WHO HAD COTININE AND LEUKOTRIENE E_4 DATA COLLECTED

Variable	Year 1 (*2002–2003*)	Year 2 (*2003–2004*)	Year 3 (*2004–2005*)
Number of children	51	41	40
Sex, female (%)	16 (31)	15 (37)	18 (45)
Mean (min, max) age, yr	10.3 (6.6, 14)	10.2 (6.2, 13)	9.8 (6.2, 13)
Mean (min, max) height, cm	140 (109, 165)	138.7 (112, 163)	138.2 (112, 163)
Number (percentage) African American	26 (57*)	29 (71)	24 (60*)
Number (percentage) of children reporting an exacerbation in the previous year	45 (88)	33 (80)	31 (78)
Number (percentage) of children using daily inhaled steroids study wide	41 (82†)	37 (90)	35 (88)

* Does not include five subjects in Year 1 and two subjects in Year 3 with mixed race but unknown origin.
† Out of 50 subjects with data.

TABLE 2. DEMOGRAPHICS: ASTHMA SEVERITY AND HOUSEHOLD SMOKING CHARACTERISTICS, BY STUDY YEAR, FOR SUBJECTS WHO HAD COTININE AND LEUKOTRIENE E_4 DATA COLLECTED

Variable	Year 1 (*2002–2003*)	Year 2 (*2003–2004*)	Year 3 (*2004–2005*)
Number (percentage) in asthma severity class*			
Mild	7 (14)	12 (29)	10 (26)
Moderate	29 (57)	17 (42)	21 (54)
Severe	15 (29)	12 (29)	8 (21)
Number (percentage) of children reporting smoking exposure at home			
Yes	19 (37)	13 (32)	16 (40)
No	32 (63)	28 (68)	24 (60)
Number reporting smoking exposure in given location (percentage)			
Inside only	1 (5)	1 (8)	0 (0)
Outside only	13 (68)	10 (77)	13 (81)
Inside and outside	5 (26)	2 (15)	3 (19)
Number reporting smoking exposure in car† (percentage, out of those that report smoking exposure)	11 (58)	6 (46)	9 (56)

*Based on National Asthma, Education and Prevention Program guidelines; one subject had unknown severity in Year 3.
† All subjects reporting smoking in car also reporting smoking inside or outside.

increases of 5%, on average, per 10 $\mu g/m^3$ increase in $mmPM_{2.5}$ for both outcomes. No significant relationships were observed when cotinine was high, for either outcome or year.

Table 5 shows slope estimates of $mmPM_{2.5}$ in albuterol use and LTE_4 models for all years and lags (0, 1 for individual years; 2-d moving average for 3-yr combined data) based on models with continuous cotinine. Related sample size information is given in Table E1. In six cases the slope estimate for "low cotinine" was positive and significant, whereas all estimates for "high cotinine" were not significantly different than 0 at the 0.1 level of significance. There were also two cases when low cotinine estimates were negative and marginally significant; however, the corresponding "combined" $mmPM_{2.5}$ effect was also negative, suggesting these results were either spurious or involved a time-varying confounder. In one case (LTE_4, Year 2, lag 1) the $mmPM_{2.5}$ effect was insignificant, but the interaction was significant.

For the combined-year data, cotinine was a marginally significant effect modifier on the relationship between albuterol use and $mmPM_{2.5}$ when cotinine was modeled as a continuous variable (the weaker significance when cotinine was modeled as a binary variable was caused by the wider confidence interval for high cotinine; see Table 4). For LTE_4, cotinine was not a significant effect modifier for the combined-year data, although the low cotinine slope estimate was still greater than for high cotinine (Table 5).

Dose–Response Relationships between Ambient $PM_{2.5}$ and Health Outcomes

In the 24 hours preceding cotinine measurements, mean total personal $PM_{2.5}$ was approximately 40% higher when cotinine was above 10 ng/ml/mg creatinine (26.8 $\mu g/m^3$) than low (19.2 $\mu g/m^3$). As such, we further examined the dose–response relationships between ambient $PM_{2.5}$ and health outcomes to determine whether there was any change in responses at higher $PM_{2.5}$ concentrations. This analysis determined that logging $mmPM_{2.5}$ yielded a better fit with LTE_4 (also modeled on the log scale) based on Akaike's Information Criterion. The combined-year model yielded Akaike's Information Criterion values of 974.6 and 980.9 when using log ($mmPM_{2.5}$) and $mmPM_{2.5}$, respectively (the lower the better). Fits were also better using the logged pollutant for individual years. For albuterol use, there was no clear advantage in using log ($mmPM_{2.5}$) or $mmPM_{2.5}$, based on

TABLE 3. SAMPLE STATISTICS FOR SUBJECT AVERAGES OF BIOMARKER AND MEDICATION USE VARIABLES, BY YEAR

Variable	Year 1 (*2002–2003*)	Year 2 (*2003–2004*)	Year 3 (*2004–2005*)
Albuterol uses per day*			
Median	1.15	0.86	1.04
5th, 95th percentiles	0.10, 1.96	0.34, 1.66	0.15, 1.76
n (subjects)	57	43	43
Median records per subject	115	142	74
Leukotriene E_4, pg/ml/mg creatinine			
Median	86.1	99.8	116.4
5th, 95th percentiles	52.7, 149.1	55, 191.6	60.2, 217.3
n (subjects)	51	41	40
Median records per subject	13	12	10.5
Cotinine, ng/ml/mg creatinine			
Median	4.44	5.44	4.54
5th, 95th percentiles	0, 40.4	0.82, 77.5	0.94, 91.7
n (subjects)	51	41	40
Median records per subject	13	12	10.5

*One use = two puffs; numbers include both pretreats and as-needed uses.

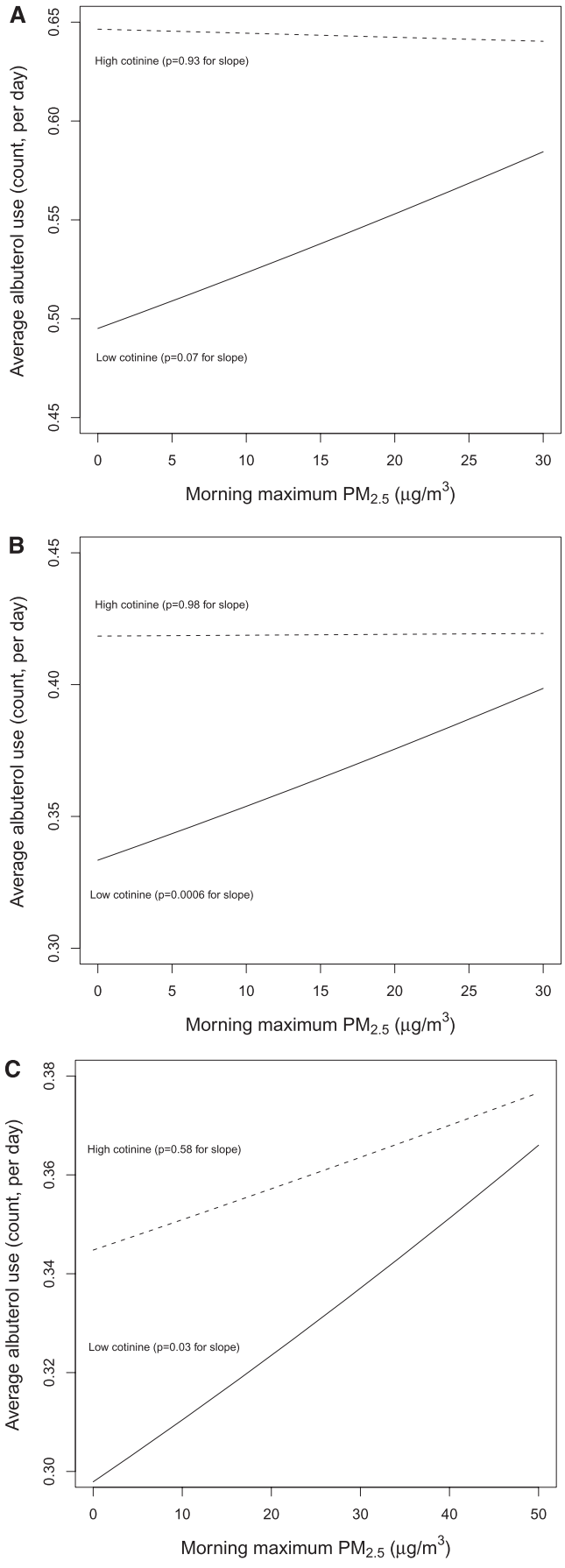

Figure 1. Estimated mean albuterol use as a function of morning maximum ambient particulate matter <2.5 μm in aerodynamic diameter ($mmPM_{2.5}$) by low (<10 ng/ml/mg creatinine) and high (≥0 ng/ml/mg creatinine) cotinine level on the same day. (*A*) Year 1, with lag 0 of $mmPM_{2.5}$ ($P = 0.23$ for cotinine × $mmPM_{2.5}$ interaction). (*B*) Year 2 with lag 1 of $mmPM_{2.5}$ ($P = 0.03$ for cotinine × $mmPM_{2.5}$ interaction). (*C*) Years 1 through 3 combined ($P = 0.54$ for cotinine × $mmPM_{2.5}$ interaction). Albuterol use plotted does not include pretreatments. See text for details of model fit.

model fits using individual years or combined years. This could be at least partially caused by the fact that albuterol counts are not continuous, like LTE_4 measurements, and so some sensitivity to modeling of the response may be lost. Figure 3 demonstrates the linear fit and loglinear fit for LTE_4 for data from the 3 study years, combined. The fit based on log ($mmPM_{2.5}$) shows that the dose–response relationship is steepest at lower values of $mmPM_{2.5}$, and it diminishes as the pollutant increases.

DISCUSSION

Over the past two decades there have been numerous studies reporting associations between low-level ambient particulate matter concentrations and acute health effects on asthma in children. Almost all of these studies did not examine interactions with other concurrent exposures prevalent in the urban environment, including ETS exposure. This 3-year study suggests that the health effects of these coexposures are not additive, but rather, the immediate biologic and physiologic health effects associated with day-to-day changes in low-level ambient particulate concentrations may be modified by recent exposure to ETS.

The evidence for the observed effect modification was seen across multiple years and outcomes. Reproducible patterns of effect modification were seen with cotinine on $mmPM_{2.5}$-related albuterol usage in 2 separate years and in a 3-year combined analysis. This physiologic effect modification was paralleled by the response to urinary LTE_4, a marker of cysteinyl leukotriene production and excretion and a mediator of asthma health effects. We primarily focused our attention to cases when the $mmPM_{2.5}$ effect itself was significant because otherwise differences between high and low cotinine are less anticipated or more difficult to interpret. For example, when the $mmPM_{2.5}$ effect itself is near 0, a significant interaction then likely requires one group (high or low cotinine) to have a positive slope between albuterol use (or LTE_4) and ambient $PM_{2.5}$, and the other negative (i.e., it requires a protective effect of ambient $PM_{2.5}$ for one of the groups). Previous research argues against such a protective effect. There were a few cases when the $mmPM_{2.5}$ effect was negative and marginally significant. These are likely either spurious results, or involve a time-varying confounder. Differences between high and low cotinine groups in these cases would be difficult to interpret even if they were real.

It is important to note that although children responded less to changes in $mmPM_{2.5}$ on days when cotinine was high, albuterol use and LTE_4 were both higher on such days. Multiple studies have reported that children exposed to ETS are at risk for developing lower lung function, increased use of rescue medications, and more frequent hospitalizations (15, 16, 31). As reported in RESULTS, averaged albuterol usage and LTE_4 levels were higher on days with higher cotinine levels but the effect of subsequent ambient pollutant concentrations was attenuated. A similar type of effect modification with tobacco smoke exposure can be inferred from some (32, 33) but not all (34) ozone challenge studies reporting greater lung function

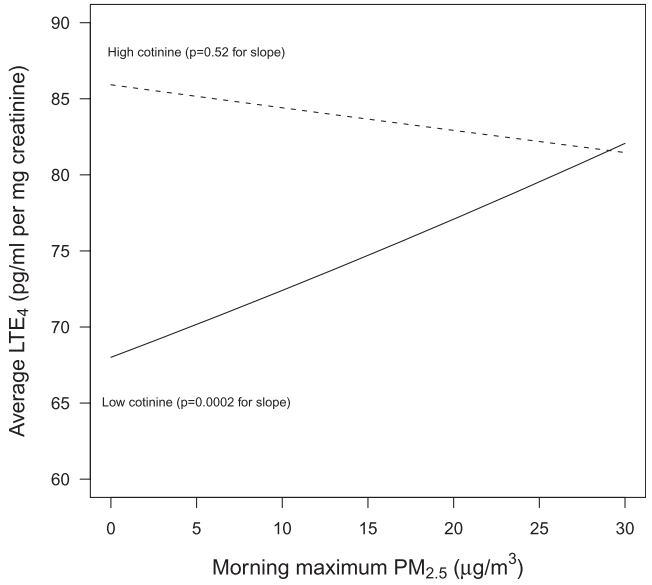

Figure 2. Estimated mean leukotriene E_4 (LTE_4) as a function of morning maximum ambient particulate matter <2.5 μm in aerodynamic diameter ($mmPM_{2.5}$) by low (<10 pg/ml/mg creatinine) and high (⩾10 pg/ml/mg creatinine) cotinine level on the same day, for Year 1, with lag 0 of $mmPM_{2.5}$ ($P = 0.01$ for cotinine × $mmPM_{2.5}$ interaction). LTE_4 was analyzed on the natural log scale; estimates were transformed back for presentation. See text for details of model fit.

and symptom responses to ozone challenge in those who do not smoke compared with those who do smoke. Although overall inflammation was similar among those who smoke and those who do not smoke exposed to ozone, there seemed to be a lower level of reactive oxygen species after ozone challenge in the subjects who smoke suggesting an up-regulation of antioxidant mediators with tobacco smoke exposure (35).

The overall pattern of biologic response to ambient $PM_{2.5}$ observed in this study may help explain some of these findings. In each of the 3 study years and in a 3-year combined analysis, a log-linear pattern for the LTE_4 response to ambient $PM_{2.5}$ with relatively greater effects at lower concentrations and flattening of the response at higher levels provided a better model fit to the data than the simple linear model. Based on this observation, we propose that children with recent ETS exposure may exhibit responses similar to children on the higher end of the dose–response curve for ambient $PM_{2.5}$. In this context, overall 24-hour averaged personal $PM_{2.5}$ exposure was approximately 40% higher on days with high compared with low cotinine levels. Additionally, there was evidence of shared biologic response pathways as LTE_4 levels increased in association with both cotinine and ambient $PM_{2.5}$ levels. Although other mechanisms are possible, these observations are consistent with the hypothesis that concurrent $PM_{2.5}$ exposures from ETS and ambient sources can act in a cumulative fashion to trigger proinflammatory pathways, such as the release of reactive oxygen species, which in turn increase cyteinyl leukotriene formation and urine LTE_4 levels. If the relationship between LTE_4 and total $PM_{2.5}$ exposure follows the same pattern that was observed between LTE_4 and ambient $PM_{2.5}$ exposure, then the response to ambient $PM_{2.5}$ for children with higher cotinine found in this study may be caused by their increased total $PM_{2.5}$ exposure. Specifically, their higher total $PM_{2.5}$ exposure may lead to the LTE_4 response that is at the higher and less steep portion of the dose–response curve, resulting in the pattern of effect modification consistently observed in this study.

Previous reports in the air pollution literature suggest that a limiting dose–response to particulate exposure might not be restricted to asthma or to children. Pope and coworkers (36) reported that relatively low levels of fine particulate exposure from either air pollution or secondhand cigarette smoke are sufficient to induce adverse biologic responses increasing the risk of cardiovascular disease mortality and that the exposure–response relationship is relatively steep at low levels of exposure and flattens out at higher exposures. Similarly, a recent article by Smith and Peel (37) reported that both ambient particulate matter and ETS exhibit nonlinear exposure–response curves with similar properties (relatively steep at low exposures and leveling off

TABLE 4. EFFECT MODIFICATION OF COTININE ON THE RELATIONSHIP BETWEEN $MMPM_{2.5}$ AND ALBUTEROL USE OR LTE_4 FOR YEARS AND LAGS IN WHICH HEALTH OUTCOMES WERE SIGNIFICANTLY AND POSITIVELY ASSOCIATED WITH $MMPM_{2.5}$

		Estimated Percentage Change in Albuterol Use Per 10 μg/m³ Increase in $mmPM_{2.5}$ (*95% CI*)†				
Variable	Year*	Combined (*model without cotinine*)	Model	Low Cotinine: <10 ng/ml/mg Creatinine	High Cotinine: ⩾10 ng/ml/mg Creatinine	*P* Value for $mmPM_{2.5}$ × Cotinine‡
Albuterol use	1	2.2§ (0.8, 3.6)	I	5.7‖ (−0.4, 12.2)	−0.3 (−6.8, 6.7)	0.23
			II	5.9‖ (0.9, 11.2)	−1.4 (−5.1, 2.5)	0.16
	2	3.2§ (1.8, 4.6)	I	6.1§ (2.6, 9.8)	0.1 (−4.9, 5.3)	0.03
			II	5.2§ (1.6, 9)	2 (−1.7, 5.8)	0.08
	3-yr combined	2.4§ (1.3, 3.6)	I	4.2‖ (0.4, 8.2)	1.8 (−4.5, 8.4)	0.54
			II	4.2‖ (0.9, 7.6)	2 (−1.2, 5.4)	0.07
LTE_4	1	4.1§ (1.2, 7.1)	I	6.5§ (3, 10.1)	−1.8 (−7, 3.7)	0.01
			II	5.2§ (2.1, 8.4)	0.6 (−3.3, 4.6)	0.02

Definition of abbreviations: CI = confidence interval; LTE_4 = leukotriene E_4; $mmPM_{2.5}$ = morning maximum ambient particulate matter <2.5 μm in aerodynamic diameter.

Model I used binary cotinine; Model II used continuous cotinine. For Model II, estimates for low and high cotinine were obtained by evaluating the continuous cotinine variable at the average cotinine value for cotinine less than 10, and cotinine at least 10 ng/ml/mg creatinine, respectively. LTE_4 was analyzed on the natural log scale; estimates were transformed back for presentation. See text for additional detail.

* In Year 1, $mmPM_{2.5}$ of current day (lag 0) was used; in Year 2, $mmPM_{2.5}$ from previous day (lag 1) was used. Selection of lags was based on when the positive and significant effects for $mmPM_{2.5}$ were observed. For the 3-year combined estimate, a 2-day moving average of the pollutant was used.

† For albuterol use, the number of subject-day records available for estimating effects were as follows: 5,977 in Year 1, 5,786 in Year 2, and 14,432 for 3 combined years for the combined effect; 613 in Year 1, 466 in Year 2, and 1,431 for 3 combined years for effects in models with cotinine. For LTE_4 (Year 1), there were 433 subject-day records available for estimating the combined effect and 430 records for estimating effects in models with cotinine.

‡ *P* values are based on Type 3 tests (*F* test for LTE_4, chi-square test for albuterol use).

§ $P \leqslant 0.01$.

‖ $0.01 < P \leqslant 0.10$.

TABLE 5. EFFECT MODIFICATION OF COTININE ON THE RELATIONSHIP BETWEEN $MMPM_{2.5}$ AND ALBUTEROL USE OR LTE_4 FOR ALL STUDY YEARS AND LAGS (0 – SAME DAY, 1 – PREVIOUS DAY, FOR INDIVIDUAL YEARS; 2-D MOVING AVERAGE FOR COMBINED DATA)

			Estimated Percentage Change in Albuterol Use Per 10 μg/m³ Increase in $mmPM_{2.5}$ (*95% CI*)			
Variable	Year	Lag	Combined* (*model without cotinine*)	Low Cotinine	High Cotinine	*P* Value for $mmPM_{2.5}$ × Cotinine†
Albuterol use	1	0	2.2‡ (0.8, 3.6)	5.9§ (0.9, 11.2)	−1.4 (−5.1, 2.5)	0.16
		1	−1.4 (−3.1, 0.4)	−0.1 (−5.3, 5.3)	3.3 (−1.4, 8.3)	0.28
	2	0	0 (−1.2, 1.2)	−2.8 (−6.8, 1.5)	−0.1 (−3.7, 3.7)	0.06
		1	3.2‡ (1.8, 4.6)	5.2‡ (1.6, 9)	2 (−1.7, 5.8)	0.08
	3	0	0.1 (−0.6, 0.9)	3.1§ (0.1, 6.1)	−2.4 (−6.3, 1.6)	0.17
		1	−0.7 (−2.3, 1)	0.7 (−3.2, 4.9)	1.7 (−2.1, 5.5)	0.54
	3-yr combined	2-d MA	2.4‡ (1.3, 3.6)	4.2§ (0.9, 7.6)	2 (−1.2, 5.4)	0.07
LTE_4	1	0	4.1‡ (1.2, 7.1)	5.2‡ (2.1, 8.4)	0.6 (−3.3, 4.6)	0.02
		1	−2.8§ (−5.8, 0.3)	−3.5§ (−6.6, −0.3)	−0.2 (−4.2, 3.9)	0.06
	2	0	−2§ (−3.9, −0.1)	−2.4§ (−4.6, −0.2)	−1.8 (−3.9, 0.4)	0.54
		1	1.4 (−1.3, 4.2)	3.1§ (−0.1, 6.3)	−0.8 (−4, 2.6)	0.03
	3	0	1 (−0.6, 2.7)	0.9 (−0.8, 2.7)	1.2 (−1.3, 3.8)	0.82
		1	1.2 (−1.3, 3.8)	1.2 (−1.4, 3.9)	1 (−1.7, 3.7)	0.80
	3-yr combined	2-d MA	0.8 (−1.4, 3.1)	1.1 (−1.3, 3.4)	0.3 (−2.1, 2.8)	0.46

Definition of abbreviations: CI = confidence interval; LTE_4 = leukotriene E_4; $mmPM_{2.5}$ = morning maximum ambient particulate matter <2.5 μm in aerodynamic diameter.

All figures are based on the model that used continuous cotinine. Estimates for low and high cotinine were obtained by evaluating the continuous cotinine variable at the average cotinine value for cotinine less than 10, and cotinine at least 10 ng/ml/mg creatinine, respectively. LTE_4 was analyzed on the natural log scale; estimates were transformed back for presentation. The number of records available for analysis corresponding to estimates presented here are shown in Table E1.

* Note that combined estimates were not always between corresponding estimates for low and high cotinine, primarily because many more records were available for analysis.

† *P* values are based on Type 3 tests (*F* test for LTE_4, chi-square test for albuterol use).

‡ $P \leq 0.01$.

§ $0.01 < P \leq 0.10$.

at higher exposures). These authors suggested that mechanism of health effects from ambient particulate matter might be similar to those from ETS as indicated by comparable dose–response characteristics. Also summarized in the article by Smith and Peel (37), an analogous type of dose–response pattern occurs not uncommonly with toxic exposures. Examples include arsenic and lung cancer (38), cigarette smoking and bladder cancer (39), and polycyclic aromatic hydrocarbon exposure and DNA adducts (40). Numerous theories have been postulated regarding the underlying mechanism leading to the nonlinear shape including exposure measurement error at higher exposure levels and biologic saturation (38, 39, 41, 42). A similar type of biologic saturation is postulated for asthma health effects from ambient $PM_{2.5}$ exposures as demonstrated in the present study by the log-linear LTE_4 response-curve and by effect modification with recent ETS exposure. For LTE_4 there seems to be consistent evidence that the log scale is better than the simple linear scale. The log scale is associated with steeper effects at lower pollution levels and tapering of effects at higher pollution levels consistent with the effect modification described in this paper. Future research will focus on the use of longitudinal nonparametric regression models to determine what the best functional relationship between $PM_{2.5}$ and LTE_4 is. This will require the development of new statistical methodologies to apply nonparametric approaches to repeated measures data.

The findings from the present study may have important implications for the research and public health community suggesting that estimates of acute ambient pollutant effects on asthma derived from time-series models may be modified by concurrent exposures. As such, it may be critically important to measure and control for differences in ETS exposures in these populations. This analysis also supports previous reports of health effects with low-level exposure to ambient particulate exposure and suggests that health benefits would accrue with reductions to $PM_{2.5}$ concentrations even at relatively low levels.

The present analysis used cotinine and ambient $PM_{2.5}$ concentrations from a fixed outdoor monitor as pollutant variables. If inference for personal exposures to ETS and ambient $PM_{2.5}$ is desired, then regression calibration for two variables including

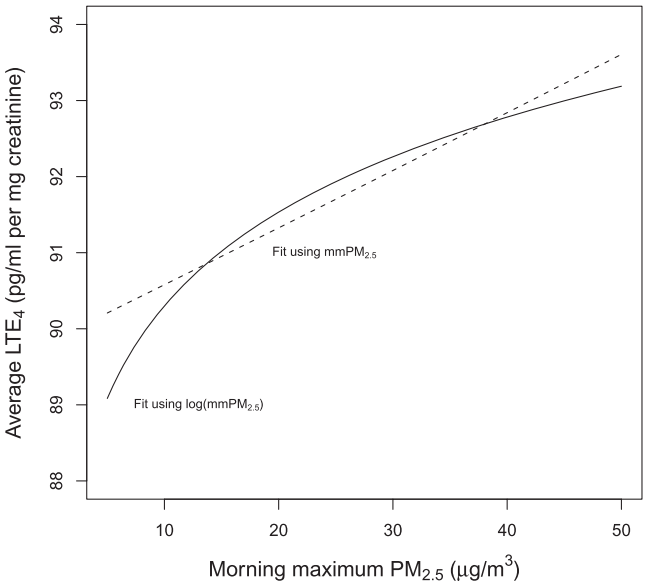

Figure 3. Estimated mean leukotriene E_4 (LTE_4) as a function of ambient particulate matter 2.5 μm in aerodynamic diameter ($PM_{2.5}$) based on models using unlogged pollutant (*dashed*) and logged pollutant (*solid*) variables, using data from the three study years combined. The Akaike's Information Criterion goodness-of-fit measure was better (lower) for the log pollutant model. LTE_4 was analyzed on the natural log scale in both cases, and estimates were transformed back for presentation. Data were not superimposed on the graph because of higher variability of the data.

interaction is one method to obtain effects of interest. If inference for personal exposures to ambient $PM_{2.5}$ is desired based on personal cotinine levels (i.e., considering biologic dose of ETS exposure as the variable of interest rather than ETS exposure itself), then a regression calibration on one variable can be performed on the ambient $PM_{2.5}$ variable. Both of these regression calibrations were performed using estimates of personal ambient $PM_{2.5}$ and ETS exposures from personal monitors, and continuous measures of cotinine for subjects and $mmPM_{2.5}$ concentrations. However, initial attempts did not yield reliable or significant results. Reasons why this may have occurred were (*1*) imprecision of estimated personal exposure concentrations from personal monitors, particularly for ETS; (*2*) the present analysis used morning maximum $PM_{2.5}$, whereas estimates of personal ambient $PM_{2.5}$ (by a method incorporating personal exposures to sulfate; *see* References 43 and 44) were only available for 24-hour time frames, and the two were significantly but only weakly correlated; and (*3*) possible violation of the critical assumption of nondifferential measurement error in the regression calibrations. Consequently, direct comparisons of effects to assess relative toxicities of ETS and ambient $PM_{2.5}$ exposures cannot be made here. However, separate analyses did show significant positive correlations between 24-hour averaged personal measurements of ambient $PM_{2.5}$ and fixed outdoor concentrations, and between estimated measures of ETS exposure using multiwavelength absorbance of personal $PM_{2.5}$ filter deposits (45) and cotinine (data not shown). Based on these observations and the overall results of the study, we anticipate a negative interaction between personal ambient $PM_{2.5}$ and ETS exposures (or cotinine, depending on which calibration is of interest) with respect to the health outcomes examined. We are continuing to explore regression calibration methods with these data.

There are also some limitations with the use of cotinine as a measure of ETS exposure. Spot cotinine levels are not tightly predicted by questionnaire measures of exposure (46) or by any particular level of smoking in the household (47), and passive smoking exposure results in very low urinary cotinine concentration. Nevertheless, cotinine levels seem to adequately categorize children into exposed and nonexposed groupings (30). There are also age-related and possibly race-related differences in cotinine metabolism. Because effect estimates in the longitudinal models used are largely based on changes within subjects, minimizing the impact of subject-specific variables, it is not surprising that estimates of interest did not change appreciably when models controlled for race and age (they were therefore dropped from final models).

In conclusion, this analysis suggests that although ETS exposures increase albuterol usage and LTE_4 in children with asthma, acute effects of daily ambient $PM_{2.5}$ exposures on LTE_4 levels and albuterol usage are limited by recent ETS exposures. These results highlight the importance of measuring ETS exposures when determining the potential health effects of ambient particulate matter in children with asthma. The modification of $mmPM_{2.5}$ by cotinine may be related to a nonlinear dose–response curve with greater effects on asthma mediators at lower levels of particulate exposure.

Author Disclosure are available with the text of this article at www.atsjournals.org.

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