Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population

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Background: Prenatal exposures to stress and physical toxins influence children's respiratory health, although few studies consider these factors together.

Objectives: We sought to concurrently examine the effects of prenatal community-level psychosocial (exposure to community violence [ECV]) and physical (air pollution) stressors on repeated wheeze in 708 urban children followed to age 2 years.

Methods: Multi-item ECV reported by mothers in pregnancy was summarized into a continuous score by using Rasch modeling. Prenatal black carbon exposure was estimated by using land-use regression (LUR) modeling; particulate matter with a diameter of less than 2.5 μm ($PM_{2.5}$) was estimated by using LUR modeling incorporating satellite data. Mothers reported child's wheeze every 3 months. The effects of ECV and air pollutants on repeated wheeze (≥2 episodes) were examined by using logistic regression. Interactions between ECV and pollutants were examined.

Results: Mothers were primarily black (29%) and Hispanic (55%), with lower education (62% with ≤12 years); 87 (12%) children wheezed repeatedly. In models examining concurrent exposures, ECV (odds ratio [OR], 1.95; 95% CI, 1.13-3.36; highest vs lowest tertile) and black carbon (OR, 1.84; 95% CI, 1.08-3.12; median or greater vs less than median) were independently associated with wheeze adjusting for sex, birth season, maternal atopy, education, race, and cockroach antigen. Associations were similar for $PM_{2.5}$ (adjusted OR, 2.02; 95% CI, 1.20-3.40). An interaction between ECV with air pollution levels was suggested.

Conclusions: These findings suggest that both prenatal community violence and air pollution can contribute to respiratory health in these urban children. Moreover, place-based psychosocial stressors might affect host resistance such that physical pollutants can have adverse effects, even at relatively lower levels. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Community violence, prenatal stress, traffic air pollution, particulate matter, repeated wheeze, prenatal exposure*

Wheezing respiratory illnesses in infancy account for significant morbidity and health care use.[1] Although the spectrum of childhood wheeze phenotypes are complex, an important step in identifying children at risk for chronic respiratory disorders (eg, poorer lung function and asthma) is characterizing risk factors that lead to and maintain this early predisposition.

The increased burden of wheezing respiratory illnesses and asthma in lower socioeconomic status (SES) urban communities might in part be related to differential environmental exposures, including psychosocial stressors and physical toxicants, which cluster in more socially disadvantaged communities.[2,3] Candidate factors receiving increasing attention include community violence and ambient air pollution.

Studies link community violence with increased asthma prevalence,[4,5] higher asthma hospitalization rates,[5] more symptom days,[6] and wheezing in 2- to 3-year-olds.[7] Higher lifetime community violence exposure was associated with increased childhood asthma risk in a prospective multilevel analysis adjusted for subject-level factors (eg, SES, race, and smoking) and neighborhood indicators (neighborhood disadvantage, social disorder, and collective efficacy).[8] Although various mechanisms might underlie this association, a leading framework conceptualizes community violence as a chronic psychological stressor taxing subjects living in high-risk communities.[9] Effects of maternal stress on respiratory outcomes might begin in pregnancy,[10] although prenatal community violence has not been studied specifically.

Studies also link ambient pollution to childhood respiratory morbidity, including wheeze, asthma, and lung function.[11-13] Evidence suggests a role for particles and other traffic-related components in particular.[14-16] Exposure to environmental toxicants, such as air pollution starting *in utero*, might alter the normal course of lung morphogenesis and affect both the structure and function of the respiratory system.[17] Studies link prenatal air pollution exposure, including fine particulate matter[18,19] and polycyclic aromatic hydrocarbons,[20] with wheeze, respiratory tract infections, and reduced lung function in children.

Studies including concurrent measures of psychosocial and physical environmental factors that might covary in lower SES urban communities are needed to assess whether they have independent effects on the child's respiratory health or whether an adverse social environment is confounded by increased physical toxicants (or *vice versa*).[21] Moreover, co-occurring

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The Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project has been funded by grants R01 ES010932, U01 HL072494, and R01 HL080674 (R.J.W.), and biostatistical support (B.A.C.) was funded by ES000002.

Disclosure of potential conflict of interest: B. A. Coull, J. Schwartz, and R. J. Wright have received grants from the National Institutes of Health. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 12, 2013; revised September 6, 2013; accepted for publication September 16, 2013.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.09.023

Abbreviations used
AOD: Satellite-derived aerosol optical depth
BC: Black carbon
BMI: Body mass index
ECV: Exposure to community violence
GAM: Generalized additive model
HPA: Hypothalamic-pituitary-adrenal
LUR: Land-use regression
NO_2: Nitrogen dioxide
OR: Odds ratio
$PM_{2.5}$: Particulate matter with a diameter of less than 2.5 μm
RERI: Relative excess risk due to interaction
SES: Socioeconomic status

psychosocial and physical exposures might combine to influence respiratory health risk. Studies examining the effects on respiratory health of interactions between community-level stress and air pollution exposures in these communities remain sparse and have focused on older children or adolescents.[22-24]

To begin to address these gaps, we examined the effects of both prenatal maternal exposure to community violence (ECV), a neighborhood-level stressor, and ambient air pollutants (black carbon [BC], a surrogate of traffic particles, and ambient particulate matter with a diameter of less than 2.5 μm [$PM_{2.5}$]) on repeated wheeze risk in urban children, adjusting for socio-demographics, potential confounders, and possible pathway variables (eg, smoking). We also examined the interactive effects of prenatal ECV and air pollution exposures on wheeze. We hypothesized that there would be independent effects of ECV and ambient pollutants on child wheeze and that those children born to mothers with higher exposure to both ECV and ambient pollutants would be more likely to wheeze compared with children born to mothers with low exposure to both factors.

METHODS

Participants were from a pregnancy cohort examining the independent and interactive effects of early-life psychosocial stress and physical toxins on urban childhood respiratory health.[25] In brief, English- or Spanish-speaking pregnant women (≥18 years old) receiving care at Brigham & Women's Hospital, Boston Medical Center, and affiliated clinics were enrolled in mid- to late pregnancy (28.4 ± 7.9 weeks' gestation) between August 2002 and December 2009. Among women approached, 989 (78.1%) of those who were eligible agreed to enroll. There were no significant differences on race/ethnicity, education, and income between women enrolled and those who declined; 955 gave birth to a live-born infant and continued follow-up. Procedures were approved by the human studies committees at Brigham & Women's Hospital and Boston Medical Center. Written consent was obtained.

ECV

Within 2 weeks of enrollment, mothers completed the My Exposure to Violence questionnaire,[26] assessing hearing gunshots and witnessing and/or experiencing fights, knife attacks, and/or shootings in their neighborhood. Acceptable internal consistency, test-retest reliability, and validity have been described.[26,27] Events reported in the past year indicated exposure proximate to and during the pregnancy, which is hereafter termed prenatal ECV. Respondents indicated the event frequency on a scale of 1 (0-1 time), 2 (2-4 times), 3 (5-10 times), or 4 (>10 times). The multi-item survey was summarized into a continuous scale by using Rasch modeling based on item response theory, as detailed previously.[28] The model was generalized to calculate conditional probabilities for each "yes" response given the presumed event severity and accounting for features theoretically influencing severity, including frequency and whether the respondent knew the victim or perpetrator.[28] Higher Rasch ECV scores indicate greater severity of violence exposure (eg, witnessing a knifing or shooting compared with pushing or shoving fights), as well as greater frequency (for more details, see the Methods section and Fig E1 in this article's Online Repository at www.jacionline.org).

Air pollution levels

Subjects' prenatal exposure to BC was estimated based on residence over the pregnancy (ie, at enrollment and updated if they moved) by using a validated spatiotemporal land-use regression (LUR) model, as detailed elsewhere.[29] In brief, the BC model was built by using data of 24-hour measures of BC based on more than 6021 pollution measurements from more than 2079 unique exposure days at 82 monitoring locations in greater Boston. Predictions were based on meteorological and other characteristics (eg, weekday/weekend of a particular day and geographic information system–based measures [eg, traffic density within 100 meters, population density, distance to major roadway, and percentage of urbanization]) and BC levels from a central monitor (representing overall area concentration on a particular day). Spline regression methods were used to allow factors to nonlinearly predict exposure, and thin-plate splines captured additional spatial variability. Separate models were fit for cold (November-April) and warm (May-October) seasons (R^2 = 0.82 for both seasons). Prenatal BC exposure across the entire pregnancy was calculated by averaging the daily BC levels derived from LUR models for each participant. The monitoring site locations that provided data for the LUR in relation to participant residence locations and their predicted prenatal BC levels are shown in Fig 1.

Prenatal $PM_{2.5}$ exposure was estimated by using a novel spatiotemporal model incorporating moderate-resolution imaging spectroradiometer satellite-derived aerosol optical depth (AOD) measurements at a 10 × 10–km spatial resolution and layering these remote sensing data with traditional LUR predictors to yield residence-specific estimates of daily $PM_{2.5}$.[30] Because the model is based on daily physical measurements of a surrogate for $PM_{2.5}$ concentrations in each grid cell, it benefits both from the spatial resolution of LUR models and the spatiotemporal resolution of satellite models. The model was run by using day-specific calibrations of AOD data with ground $PM_{2.5}$ measurements from 78 monitoring stations and LUR and meteorological variables (temperature, wind speed, visibility, elevation, distance to major roads, percentage of open space, point emissions, and area emissions). The AOD-$PM_{2.5}$ relationship was calibrated for each day by using data from grid cells with both monitor and AOD values based on mixed models with random slopes for day and nested regions. For days without AOD data (eg, because of cloud coverage and snow), the model was fit with a smooth function of latitude and longitude and a random intercept for each cell (similar to universal kriging). The "out-of-sample" 10-fold cross-validation R^2 values for daily values were 0.83 and 0.81 for days with and without available AOD data, respectively. The individual overall prenatal $PM_{2.5}$ exposure level for each participant was calculated by averaging daily levels throughout pregnancy. Predicted prenatal $PM_{2.5}$ levels at the participant's residence in relation to the 10 × 10–km grids for which the AOD data are available are shown in Fig 2.

Children's repeated wheeze

At approximately 3-month intervals starting from birth, maternally reported child wheeze was ascertained up to age 24 months through interviews. Mothers were asked the following: "*Since we last spoke with you* on (date), has your infant/child had wheezing or whistling in the chest? If so, how many times?" Therefore we captured wheeze episodes occurring during each follow-up interval. Two or more episodes constituted repeated wheeze, as in prior studies.[31,32] Of the 708 children, 449 (63.4%) never wheezed, 172 (24.3%) wheezed once, and 50 (7.1%), 25 (3.5%), 10 (1.4%), and 2 (0.3%) had 2, 3, 4, and 5 wheeze episodes, respectively. Most mothers completed 3 or more follow-up surveys, including at 2 years (88%); the

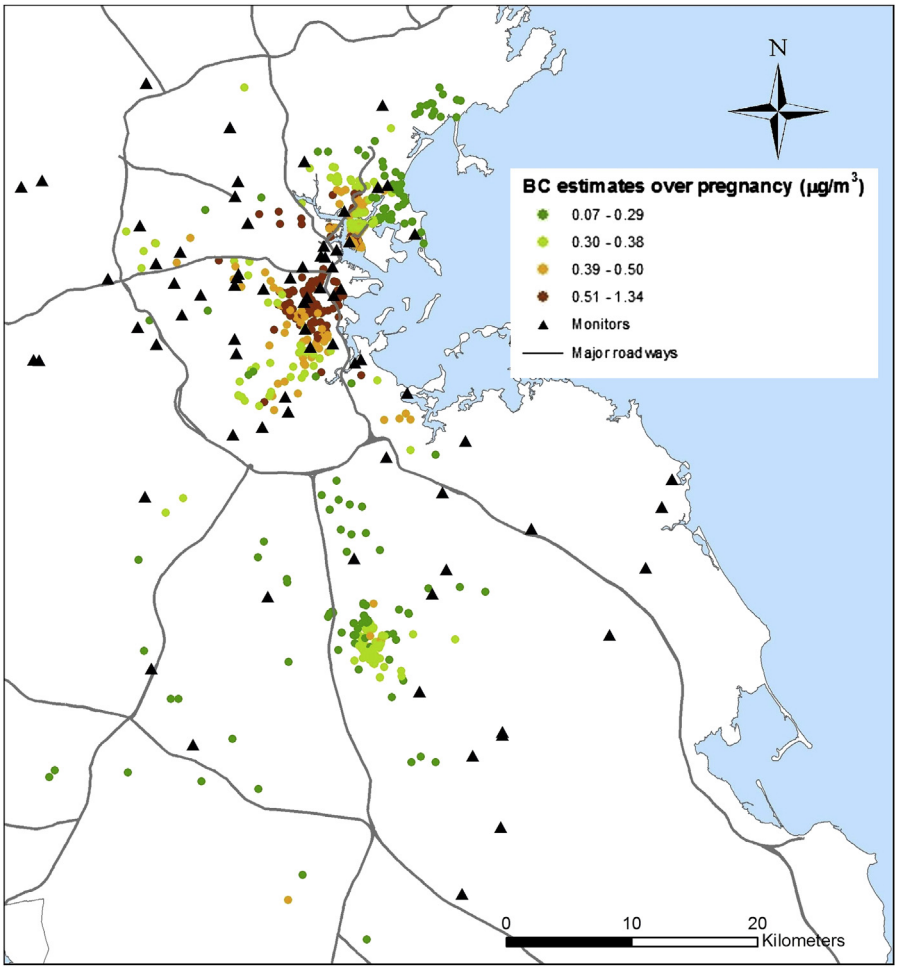

FIG 1. Predicted BC levels for ACCESS study participants during pregnancy. This figure demonstrates the predicted BC levels for study participants based on residence during the gestation period. In addition, the locations of monitoring sites used in the model to predict BC levels are presented as *black triangles*.

percentage of children with repeated wheeze was similar for those completing 3, 4, 5, 6, and 7 interviewers (16%, 17%, 19%, 22%, and 17%, respectively).

Covariates

Maternal age, race, educational status, history of atopy (ever having clinician-diagnosed asthma, eczema, and/or hay fever), and prepregnancy height and weight were ascertained at enrollment; child's sex, season of birth, and birth weight were reported postnatally. Maternal body mass index (BMI) was calculated as weight divided by height squared (in kilograms per meter squared). Given complex patterns of prenatal smoking,[33] we asked about smoking at enrollment and the third trimester; women were classified as prenatal smokers if smoking at either visit. Mothers reported postnatal smoking and whether others smoked in the home at each 3-month postpartum interview. Lower SES populations exposed to higher violence and pollution can also be exposed to increased household allergens.[34] Settled dust was collected within 2 weeks of enrollment from the mother's bedroom by using a standardized protocol.[35] Cockroach allergens (*Blatella germanica*, Bla g 1 and Bla g 2) were analyzed by using an mAb-based ELISA (Indoor Biotechnologies, Charlottesville, Va). High exposure was defined as Bla g 1 or Bla g 2 values of greater than 2 U/g.[35]

Exposures to postnatal ECV, postnatal BC, and postnatal $PM_{2.5}$ were also derived. Mothers completed the same questionnaire assessing community violence, as described above, when children were 18 to 24 months old, assessing postnatal ECV from birth. Cumulative average postnatal BC and $PM_{2.5}$ exposure from birth to age 2 years was similarly estimated as prenatal exposures.

Analysis

Those completing 2 or more postnatal interviews up to 24 months for whom air pollution indicators were derived were included in these analyses (n = 708). Characteristics of included (maternal age, 27 ± 6 years; 62% with high school education or less, 29% black, 55% Hispanic, and 52% male) versus excluded (maternal age, 26 ± 5 years; 64% with high school education or less; 38% black, 48% Hispanic; and 53% male) subjects were not significantly different. Missingness on covariates was approximately 5%, and thus missing indicators were used in analyses.

The prenatal ECV score (range, −0.68 to 3.53) was categorized as low, medium, and high based on the *a priori* decision to use cutoffs at the 33rd and 67th percentiles to address potential nonlinearity. Given some tied scores, the low (n = 358), medium (n = 149), and high (n = 201) categories were unequal. BC and $PM_{2.5}$ values were *a priori* categorized into high and low groups based on a median split because there is no established health-relevant cutoff.

In primary analyses independent effects of prenatal ECV and air pollution on the child's repeated wheeze status were examined by using multivariate logistic regression, including both in the model and adjusting for child's sex, maternal demographic variables previously correlated with community violence, pollution exposures (eg, race/ethnicity and maternal education),

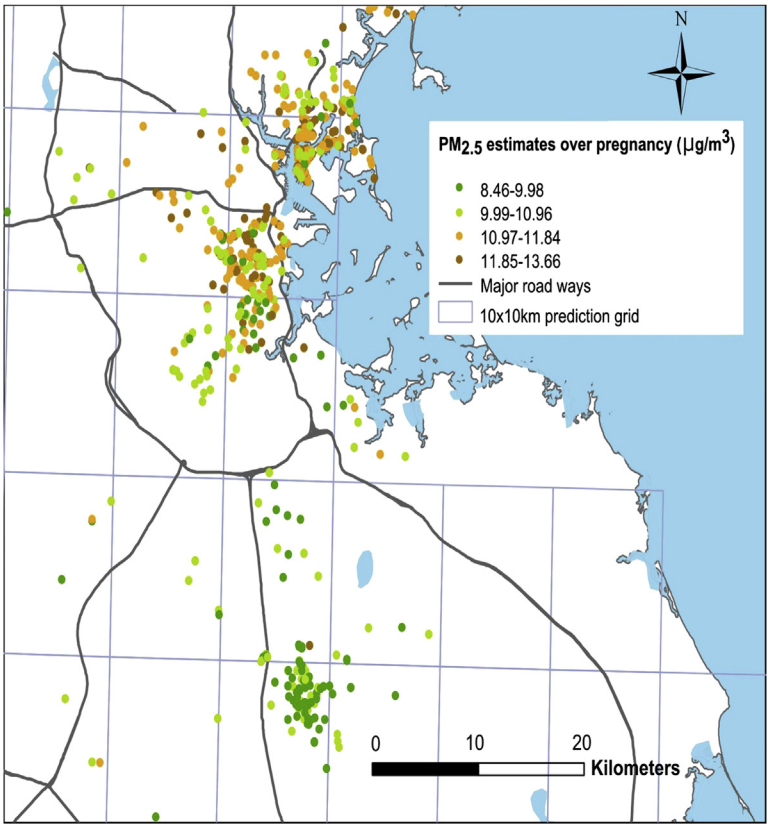

FIG 2. Predicted $PM_{2.5}$ levels for ACCESS study participants during pregnancy. This figure demonstrates predicted $PM_{2.5}$ levels for study participants based on residence during the gestation period. The 10 × 10–km AOD grid used to predict daily $PM_{2.5}$ levels is also depicted.

atopy-related factors (season of birth and maternal atopy), and cockroach exposure. Prenatal BC and $PM_{2.5}$ were considered in separate models because they were moderately correlated (Spearman $r = 0.54$). Variables that might be in the pathway between ECV, pollution, or both were considered in secondary analyses, including maternal BMI, prenatal and postnatal tobacco smoke exposure, and birth weight, adjusting for gestational age.[36] To ensure that these results were not affected by the chosen exposure cut points, we also explored exposure-response relationships using continuous exposure variables by implementing generalized additive models (GAMs) with smooth penalized spline terms for ECV, as well as air pollution indicators that allow model fitting on potential nonlinear exposure-response relationships.[37]

In stratified analyses we examined effect modification on the association between prenatal ECV and children's repeated wheeze by pollutant level. We also fit interaction terms of ECV by median split BC or $PM_{2.5}$ values to examine effects on both the multiplicative (by including a product term) and additive scales (by calculating the relative excess risk caused by interaction [RERI; RERI of 0 indicates no interaction on an additive scale] and CIs by using the bootstrap percentile method).[38] Sensitivity analyses adjusting for postnatal exposure to ECV, BC, and $PM_{2.5}$ were performed. Of note, prenatal and postnatal levels were correlated (Spearman $r = 0.72$ for prenatal/postnatal ECV, $r = 0.96$ for prenatal/postnatal BC, and $r = 0.82$ for prenatal/postnatal $PM_{2.5}$; all $P < .001$). Additional sensitivity analyses were conducted considering wheeze frequency as a multiple categorical outcome variable (eg, 0-1, 2-3, and ≥4 wheeze episodes) by using multinomial logit analyses, as well as adjacent-categories logit models (see the Methods section in this article's Online Repository). GAMs and adjacent-categories logit models were implemented by using the MGCV and VGAM packages in R (version 2.13.0). SAS software (version 9.1.3; SAS Institute, Cary, NC) was used for all other analyses.

RESULTS

Most mothers were of an ethnic minority (55% Hispanic and 29% African American) and low SES (62% having ≤12 years of education) and were nonsmokers (80%); 87 (12%) children had repeated wheeze (Table I).[26,28] Spearman correlations between ECV and pollutants were modest (Table II).[26,28]

ECV, air pollution, and wheeze

Table III summarizes results from logistic regression models. Odds ratios (ORs) for repeated wheeze comparing the high and medium with low prenatal ECV groups showed an exposure-response relationship in both the univariate model and when adjusted for prenatal BC or $PM_{2.5}$ levels. Effects of BC and $PM_{2.5}$ were borderline nonsignificant in unadjusted models. In the model adjusting for sociodemographics, atopy, and cockroach exposure, the highest level of prenatal ECV remained significantly associated with repeated wheeze, and higher-level air pollution exposures (both BC and $PM_{2.5}$) were now significantly related to wheeze. Further inclusion of potential pathway variables (eg, maternal prenatal/postnatal smoking, BMI, and gestational age–adjusted birth weight) did not alter these findings (data not shown). Other significant predictors of repeated wheeze included male sex and maternal atopy. In sensitivity analyses adjusting for postnatal exposure to ECV, the highest level of prenatal ECV remained significant in the fully adjusted BC model (OR, 1.9; 95% CI, 1.1-3.3) and the fully adjusted $PM_{2.5}$ model

TABLE I. Participant characteristics (708 mother-child pairs)

Categorical variables	No.	Percent
Repeated wheeze until age 2 y*		
No	621	87.7
Yes	87	12.3
Child's sex		
Female	343	48.5
Male	365	51.5
Maternal race/ethnicity		
Hispanic	391	55.2
Black	203	28.7
White/other	104	14.7
Missing	10	1.4
Season of birth		
Winter	190	26.8
Summer	152	21.5
Spring	155	21.9
Fall	211	29.8
Maternal education		
>12 y	233	32.9
≤12 y	442	62.4
Missing	33	4.7
Maternal atopy†		
No	429	60.6
Yes	243	34.3
Missing	36	5.1
Maternal smoking		
Never smoked	569	80.4
Smoked prenatally but not postnatally	34	4.8
Did not smoke prenatally but smoked postnatally	37	5.2
Smoked both prenatally and postnatally	68	9.6
Continuous variables		
Maternal BMI (kg/m^2; mean, SD)	28.8	6.1
Maternal age at enrollment (y; mean, SD)	27.2	6.0
Gestational age at birth (wk; mean, SD)	39.0	3.1
Birth weight percentile adjusting for gestational age (mean, SD)	43.7	31.2
ECV in past 1 y (mean, SD)‡	0.06	0.90
Prenatal BC level ($\mu g/m^3$; median, IQR)	0.38	0.30-0.50
Prenatal $PM_{2.5}$ level ($\mu g/m^3$; median, IQR)	11.22	10.25-11.89
Bla g 1 (U/g; median, IQR)	0.20	0.20-0.40
Bla g 2 (U/g; median, IQR)	0.50	0.50-0.95

*Repeated wheeze (≥2 episodes) reported by mothers at each 3-month postpartum interview up to age 2 years.
†Ever self-reported doctor-diagnosed asthma, eczema, and/or hay fever.
‡Assessed by using the My Exposure to Violence survey[26]; multi-item survey summarized into a continuous score by using Rasch modeling.[28]

TABLE II. Spearman correlations between prenatal community violence and physical environmental exposures

	Rasch ECV score*		BC level		$PM_{2.5}$ level		Household Bla g 1	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
BC level	0.14	<.001	—	—	—	—	—	—
$PM_{2.5}$ level	−0.04	.31	0.54	<.001	—	—	—	—
Household Bla g 1†	−0.04	.38	0.17	<.001	0.14	<.001	—	—
Household Bla g 2†	−0.03	.54	0.13	<.001	0.06	.19	0.78	<.001

*Assessed by using the My Exposure to Violence survey[26]; multi-item survey summarized into a continuous score by using Rasch modeling.[28]
†Household cockroach allergens (Bla g 1 and Bla g 2).

(OR, 2.1; 95% CI, 1.2-3.6), respectively. When further adjusting the BC model from Table III for postnatal BC exposure, the OR of high prenatal BC was 2.2 (95% CI, 1.1-4.2); when further adjusting the $PM_{2.5}$ model for postnatal $PM_{2.5}$, the OR of a high prenatal $PM_{2.5}$ level was 2.5 (95% CI, 1.0-6.5).

Results from the GAMs suggested that the functional form of the exposure-response relationship between wheezing status and each of the 3 exposures (ECV, BC, and $PM_{2.5}$) was approximately linear on the logit scale (Fig 3). There was some indication of a less steep relationship at higher levels for each exposure, particularly for ECV.

Finally, sensitivity analyses considering wheeze frequency as a multiple categorical outcome demonstrated that increased exposure to prenatal ECV, air pollution indictors, or both was associated with progressively increasing odds of more frequent wheeze (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). Thus these associations were robust to alternative specifications for what constituted repeated wheeze.

Stratified analyses

In analyses examining effect estimates of ECV exposure stratified by air pollution levels, we observed statistically significant associations between high prenatal ECV and increased repeated wheeze in the low BC (adjusted OR, 2.87; 95% CI, 1.33-7.32) and low $PM_{2.5}$ (adjusted OR, 3.63; 95% CI, 1.43-9.52) groups but not in the high BC (adjusted OR, 1.31; 95% CI, 0.59-2.93) or high $PM_{2.5}$ (adjusted OR, 1.51; 95% CI, 0.71-3.21) groups (Fig 4), although multiplicative interactions were not significant ($P > .20$ for both). The RERI for high ECV by low BC was 0.26 (95% CI, −0.09 to 1.83; $P = .08$), suggesting that the OR for repeated wheeze in those with high ECV and low BC is 0.26 more than if there were no interactions on the additive scale. The additive interaction between ECV and $PM_{2.5}$ was not significant ($P = .33$).

DISCUSSION

To our knowledge, this is the first prospective study to concurrently assess prenatal exposure to neighborhood-level psychosocial (ie, community violence) and physical (ie, ambient pollution) toxins in relationship to early childhood wheeze. Children born to mothers reporting higher community violence exposure prenatally were more likely to have repeated wheeze, even when adjusting for a number of subject-level (ie, sex, season of birth, and birth weight) and maternal (ie, race, education, BMI, and atopic history) factors, as well as other environmental factors (ie, ambient BC or $PM_{2.5}$, cockroach allergen, and maternal smoking). Moreover, in models considering ECV and air pollution (either BC or $PM_{2.5}$) together, increased pollution independently predicted repeated wheeze. These findings suggest that both prenatal community violence and increased air pollution contribute to respiratory health in these urban children.

These data add to growing evidence linking community violence to childhood respiratory health. Previous studies have suggested an association between community violence assessed postnatally (ie, during the child's lifetime) and heightened respiratory morbidity. Berz et al[7] found an association between witnessing violence and increased repeated wheeze by age 2 to 3 years, adjusting for sex, maternal asthma,

TABLE III. Maternal ECV and ambient air pollution during pregnancy and repeated wheeze in children: logistic regression models

	Univariate model*			Multivariate adjusted model					
				BC model†			$PM_{2.5}$ model‡		
Variables	OR	95% CI		OR	95% CI		OR	95% CI	
Community-level stress									
Prenatal community violence									
Low	Reference	—	—	Reference	—	—	Reference	—	—
Medium	1.44	0.79	2.62	1.34	0.71	2.52	1.41	0.75	2.68
High	2.08	1.25	3.46	1.95	1.13	3.36	2.15	1.24	3.71
Ambient air pollution§									
Prenatal BC exposure									
Low (≤median)	Reference	—	—	Reference	—	—			
High (>median)	1.61	0.98	2.66	1.84	1.08	3.12			
Prenatal $PM_{2.5}$ exposure									
Low (≤median)	Reference	—	—				Reference	—	—
High (>median)	1.51	0.95	2.41				2.02	1.20	3.40
Demographic characteristics									
Child's sex									
Female	Reference	—	—	Reference	—	—	Reference	—	—
Male	2.05	1.28	3.28	2.49	1.51	4.12	2.49	1.51	4.13
Maternal race/ethnicity									
Hispanic	Reference	—	—	Reference	—	—	Reference	—	—
Black	1.11	0.66	1.87	0.80	0.45	1.41	0.87	0.49	1.56
White/other	1.54	0.84	2.83	1.07	0.55	2.12	1.22	0.61	2.43
Maternal education									
>12 y	Reference	—	—	Reference	—	—	Reference	—	—
≤12 y	0.62	0.39	0.98	0.62	0.37	1.04	0.62	0.37	1.04
Atopy-related factors									
Season of birth									
Winter	Reference	—	—	Reference	—	—	Reference	—	—
Spring	1.26	0.64	2.47	1.11	0.55	2.26	1.13	0.56	2.29
Summer	1.13	0.57	2.26	1.07	0.52	2.20	1.20	0.58	2.48
Fall	1.61	0.88	2.95	1.75	0.93	3.29	1.97	1.04	3.74
Maternal atopy‖									
No	Reference	—	—	Reference	—	—	Reference	—	—
Yes	2.09	1.31	3.34	1.83	1.12	3.00	1.85	1.13	3.04
Household allergens									
Cockroach allergen level¶									
Low (≤2 U/g)	Reference	—	—	Reference	—	—	Reference	—	—
High (>2 U/g)	0.74	0.33	1.66	0.73	0.30	1.76	0.67	0.28	1.62

*Univariate (unadjusted) logistic regressions predicting repeated wheeze. Each variable listed in the table was the independent variable in a separate univariate model.
†The BC model included community violence, BC, sex, race/ethnicity, maternal education, season of birth, maternal atopy, and cockroach allergen exposure.
‡The $PM_{2.5}$ model included community violence, $PM_{2.5}$, sex, race/ethnicity, maternal education, season of birth, maternal atopy, and cockroach allergen exposure.
§BC median = 0.38 $\mu g/m^3$; $PM_{2.5}$ median = 11.22 $\mu g/m^3$.
‖Ever self-reported doctor-diagnosed asthma, eczema, and/or hay fever.
¶A high cockroach allergen level was defined as a Bla g 1 or Bla g 2 level of greater than 2 U/g.

smoking, and social support. Increased neighborhood violence exposure was associated with more symptom days among 9- to 12-year-old asthmatic patients,[6] increased asthma prevalence in school-aged children,[4] and reduced lung function at age 6 years.[39] We previously demonstrated a prospective association between higher lifetime community violence exposure and childhood asthma risk, adjusting for sociodemographics, smoking, domestic violence, neighborhood disadvantage, social disorder, and collective efficacy.[8] The current study is the first to consider prenatal ECV in relation to children's respiratory health.

Although previous studies link traffic-related air pollution assessed during early childhood (ie, postnatally) with children's asthmatic symptoms and reduced lung function,[14-16] few studies have focused on prenatal exposures.[18-20] Thus the independent effect of prenatal ambient pollution on early childhood wheeze, adjusting for community violence and other covariates, is another important finding.

Furthermore, psychosocial and physical pollutants can combine to affect health.[40,41] A few studies have assessed interactions between stress and traffic-related air pollutants and respiratory health. Notably, findings on interactions have been variable. One study of children aged 5 to 9 years suggested a stronger association between traffic-related pollution and new-onset asthma risk among children of parents reporting higher perceived stress.[24] We previously found that postnatal traffic-related nitrogen dioxide (NO_2) interacted with violence exposure to predict increased asthma risk in urban children (mean age, 6.8 years); those with both high postnatal NO_2 levels and high lifetime violence exposures were at greatest risk.[23] On the other hand, another study of asthmatic children aged 9 to 18 years found that the association between higher family stress

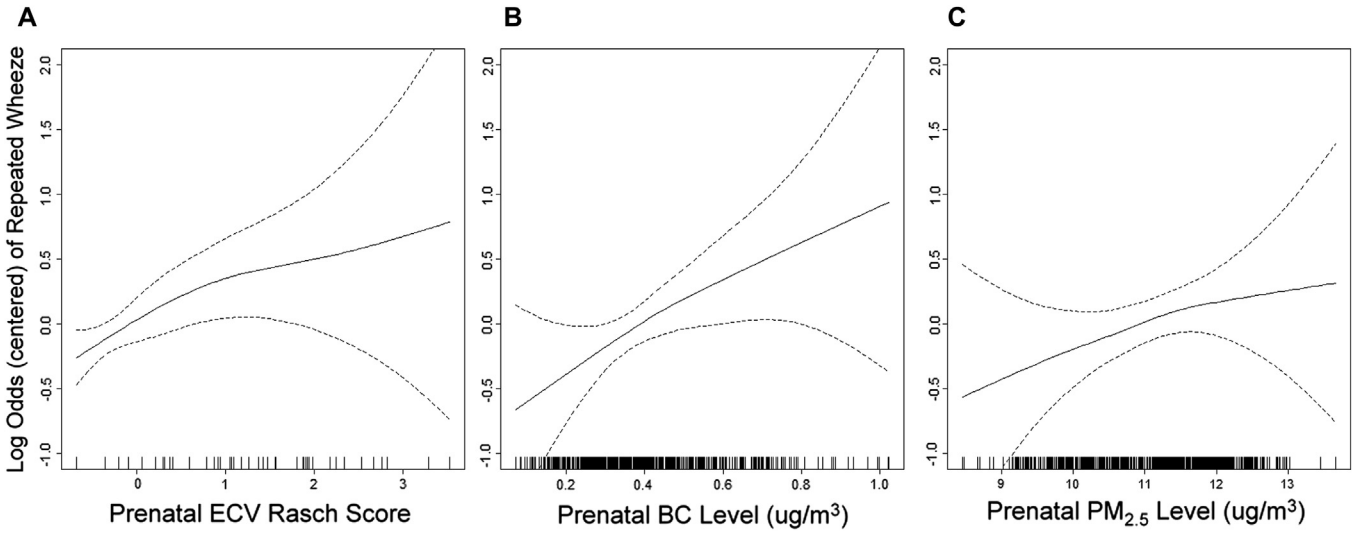

FIG 3. Exposure-response relationships of prenatal maternal ECV and prenatal air pollution indicators with children's repeated wheeze. Penalized spline curves using GAMs demonstrating the relationship of prenatal maternal ECV **(A)**, prenatal BC level (in micrograms per cubic meter; **B)**, and prenatal $PM_{2.5}$ level (in micrograms per cubic meter; **C)**, with log odds of children's repeated wheeze by age 2 years are shown. *Solid lines* depict the penalized spline curve, and *dotted lines* indicate the 95% confidence bounds. Models were adjusted for child's sex, season of birth, maternal race, education, atopy, and household cockroach allergens.

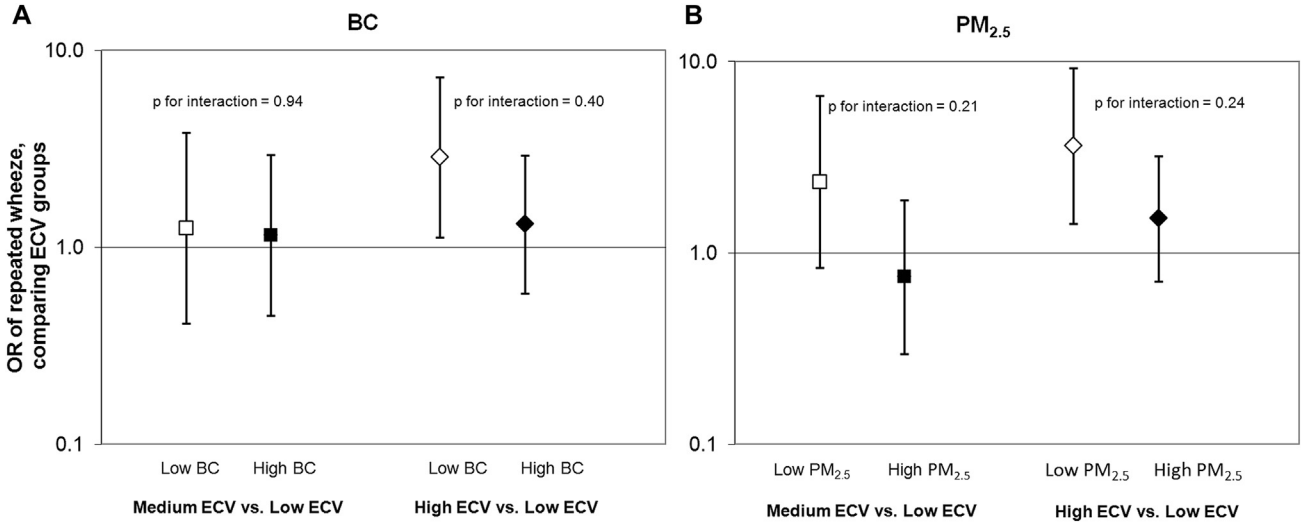

FIG 4. Associations between prenatal maternal ECV and children's repeated wheeze in analyses stratified by air pollutant levels. This figure demonstrates ORs and 95% CIs for repeated wheeze comparing medium versus low ECV groups *(squares)* and high versus low ECV groups *(diamonds)* stratified by BC median level (0.38 $\mu g/m^3$; **A)** and $PM_{2.5}$ median level (11.22 $\mu g/m^3$; **B)**. The *solid markers* indicate the ORs for participants exposed to higher levels (median or greater) of air pollution, and the *open markers* indicate the ORs for participants exposed to lower levels (less than median) of air pollution. Models were adjusted for child's sex, season of birth, maternal race, education, and atopy.

and asthma exacerbations was stronger when NO_2 levels were more modest.[22] Similar to Chen et al,[22] in this study we observed that the association between higher prenatal community violence exposure and repeated wheeze was stronger in children born to mothers with more modest prenatal air pollution exposures. There was also some indication of a negative interaction between air pollution and ECV in our data: the effect estimate of ECV in the high air pollution exposure category was less than that in the lower air pollution category. One possible explanation is that the effect of higher prenatal traffic-related air pollution exposure on childhood wheeze might be of significant magnitude to lead to a "saturation effect" such that the additional risk conferred by prenatal ECV beyond the highest level of air pollution exposure could not be detected (ie, effects of 2 factors when the effect of higher-level exposure to factor A reaches the ceiling and masks the effect of factor B). In this case the effect of factor B on the

outcome might be more apparent when the level of exposure to factor A is lower so that the effect on the outcome is not yet "saturated." On the other hand, because the 2 exposures are positively correlated, the results could be due to a less steep relationship for either exposure at higher levels. That is, this might be a result of the less steep relationship with wheeze at higher ECV exposure levels, as seen in Fig 3, so that when stratifying by those with high-level air pollution and high ECV, an association with wheeze could not be detected because of the nonlinear exposure-response function on this portion of the curve. Finally, the lack of statistical significance when testing interaction terms might be due to chance. It is also notable that the studies mentioned above varied on key aspects (eg, how and when stress and air pollution were measured and children's developmental stage [prenatal, early childhood, and adolescence]), making it challenging to compare results across studies.

Prenatal exposure to psychosocial stress[42] and ambient pollutants[11] can effect anatomy, physiological functioning, or both of the lung and interrelated systems. Programming effects can result from toxicant-induced shifts in key regulatory systems, including both central and peripheral components of neuroendocrine pathways and autonomic nervous system functioning, which in turn influence the immune system starting *in utero*. Prenatal exposure to air pollutants and stress might permanently organize these systems toward trajectories of enhanced pediatric respiratory disease risk.[43] These factors can operate through incompletely overlapping mechanisms described below that thus result in both independent and cumulative or interactive effects.

For example, prenatal stress might disrupt maternal physiology (eg, hypothalamic-pituitary-adrenal [HPA] axis and autonomic nervous system), which then might potentiate the developing fetal immune system.[44] Among various stress domains, traumatic stressors, such as community violence, might be more likely to result in lasting biobehavioral sequelae in mothers (eg, psychopathology and neurohormonal disruption) and intergenerational effects.[45] Community violence exposure is an independent predictor of anxiety and depression in urban minority women of childbearing age,[46] as well as disrupted HPA functioning in urban women[47] and children.[48] Living in a community with higher crime and violence might alter mothers' health behaviors, such as smoking,[49] which might subsequently affect childhood wheeze.[50] Both prenatal stress and ambient pollution might contribute to poor fetal growth and low birth weight,[51,52] factors linked to childhood wheeze.[53] Adjusting for birth weight and maternal smoking did not substantially affect our findings, however.

Studies have suggested that air pollution might contribute to early airway remodeling through associations with asthma development and consequent effects on lung function.[11,54,55] In addition, exposure to pollutants can be associated with airway remodeling independent of asthma.[56,57] Pathways involved in the remodeling process that might be targets of air pollution include xenobiotic metabolism,[58] mitochondrial biogenesis,[59] epithelial lung repair and regeneration,[60] and neural plasticity.[61] Ambient pollutants can also influence HPA axis functioning. HPA axis disruptions have been linked to a host of environmental chemicals (eg, carbon monoxide and metals).[62-64] Particulate matter and ozone can influence inflammatory cytokine production in the pituitary.[65] Transplacental exposure to polycyclic aromatic hydrocarbons might lead to disturbances of the pituitary-adrenocortical-placental system in pregnancy and the HPA axis over the lifecourse.[66]

The strengths of this study include the reasonably large lower SES, ethnically mixed, urban prospective cohort; the focus on the prenatal period; and available data on confounders and potential pathway variables. In addition, we used advanced methodology (ie, item response theory) to summarize the multi-item community violence measure. Our findings were consistent across 2 indicators for prenatal exposure to urban ambient particulate pollution: BC, a surrogate of traffic-related pollution, and $PM_{2.5}$, which also captures other sources. Ambient pollution was estimated by using validated, state-of-the-art, spatiotemporal LUR models adding satellite-derived AOD data when estimating $PM_{2.5}$ levels.

We also acknowledge some limitations. Mothers experiencing higher levels of community violence might be less likely to notice their children's wheeze symptoms if overwhelmed by their own stress or conversely tend to overreport children's symptoms if they are more vigilant overall. However, it is reassuring that variables related to wheeze in other studies were associated in the expected direction in our data (ie, male sex and maternal atopy). Nonetheless, it will be important to examine associations between these exposures and more definitive respiratory outcomes as we follow these children (eg, physician-diagnosed asthma and lung function) and see whether relationships hold. Future studies would also be enhanced by assessing biomarkers of potential mechanisms through which both social and physical environmental stressors might associate with respiratory health (eg, cortisol disruption, autonomic imbalance, immunomodulation, and oxidative stress). In addition, although the stratified analyses suggested a significant difference on the associations between ECV and wheeze between low versus high air pollution groups, the tests for interaction did not reach statistical significance, which might be due to the sample size and reduced power to detect interactions. Studies including larger samples might enhance the power to detect interactions between community violence and physical environmental factors, such as air pollution, in the urban environment. Although we examined other environmental factors that might covary with both ECV and ambient pollutants (eg, cockroach allergen), we cannot rule out the potential for unmeasured confounding.

In summary, we found independent effects of increased community violence and higher exposure to traffic-related air pollutants in the prenatal period on repeated wheeze in these urban children. This suggests that an adverse psychosocial environment, such as community violence exposure, might not simply be a surrogate of increased exposure to an adverse physical environment at the community level, such as ambient air pollution. Moreover, stratified analyses suggested that place-based psychosocial stressors might affect host resistance such that physical pollutants can have adverse effects, even at relatively lower levels.[21] Because these factors tend to cluster in the most socially disadvantaged communities, research that considers psychosocial stress and physical environmental toxicants concurrently, including joint effects, might better inform the cause of respiratory health disparities.

We thank Alexandros Gryparis for his contribution to the development of the BC exposure model and Steven Melly for his help creating Fig 1.

Key messages

- **These prospective analyses demonstrate independent associations of increased community violence exposure (psychosocial stressor) and higher exposure to urban ambient air pollution (physical toxicants) in the prenatal period with repeated wheeze in urban children.**
- **These findings indicate that an adverse psychosocial environment, such as community violence exposure, is not simply a surrogate marker of an adverse physical environment, such as higher levels of ambient pollution, in the urban setting with respect to children's respiratory health.**
- **Stratified analyses suggest that place-based psychosocial stressors might affect host resistance, such that physical pollutants can have adverse effects, even at relatively lower levels.**

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METHODS

Rasch modeling for ECV measurements

The multi-item My Exposure to Violence questionnaire was summarized into a continuous scale by using Rasch modeling based on item response theory, as detailed previously.[E1] A continuous ECV measure was obtained by modeling the conditional probabilities of responding "yes" to each discrete violent event on the questionnaire (eg, pushing or shoving fight, knifing, or shooting) given the severity of each event. For endorsed items, follow-up questions inquire about factors known to influence the effect of violence, including familiarity with the perpetrator or victim, events occurring more than once, and whether events occurred in the home (child's safe haven) or outside the home (eg, neighborhood violence). The model is thus generalized to account for salient features of each event, including whether the event occurred once or more than once and whether the child knew the victims or perpetrators of each discrete violent event. Models were implemented by using logistic nonlinear mixed models (NLMIXED) in SAS 9.0 software (SAS Institute, Cary, NC). A binary distribution was specified for the outcome variable, and a random effect was defined to have a known mean of 0 and a variance to be estimated as part of the model-fitting procedure. Higher Rasch ECV scores indicate greater severity of violence exposure (eg, witnessing a knifing or shooting compared with pushing or shoving fights), as well as greater frequency. Thus although the Rasch ECV scores cannot be interpreted in an absolute sense, they can be interpreted in a relative sense (eg, someone with a Rasch score of 1.2 has a lower exposure because of less severe events, less frequent occurrence of given events, or both compared with a subject with a Rasch score of 2.0).

Fig E1 shows the distribution of ECV scores derived from Rasch modeling. The graph indicates that there is a cluster for very low levels and then a right-tailed distribution for those who were exposed to ECV of increasing severity, frequency, or both.

Additional sensitivity analyses

In sensitivity analyses we assessed associations between ECV, air pollution indicators, and repeated wheeze using alternative statistical approaches that allowed us to specify the outcome of recurrent wheeze in different ways to determine whether this influenced our findings.

Table E1 demonstrates the results of multinomial logit models examining associations of prenatal ECV and prenatal air pollution exposures with wheeze outcomes as multiple categories by using the link=glogit option in PROC LOGISTIC in SAS software. We examined associations by using 2 different ways to categorize wheeze episodes: (1) outcome defined as 1 = 0 or 1 episodes, 2 = 2 episodes, and 3 = 3 or more episodes and (2) outcome defined as 1 = 0 or 1 episodes, 2 = 2 or 3 episodes, and 3 = 4 or more episodes. These analyses correspond to simultaneously fitting 2 logistic regression models comparing the odds of categories 2 and 3 to that for reference category 1 (nonrepeated wheeze category). Models were run separately for each of the air pollution indicators.

Table E2 shows the results of adjacent-categories logit models examining associations of prenatal ECV and prenatal air pollution exposures with wheeze outcomes as ordinal categories by using R statistical package VGAM.[E2] We again examined associations by using 2 different ways to categorize wheeze episodes: (1) outcome defined as 1 = 0 or 1 episode, 2 = 2 episodes, and 3 = 3 or more episodes and (2) outcome defined as 1 = 0 or 1 episode, 2 = 2 or 3 episodes, and 3 = 4 or more episodes. These analyses compare the odds of categories 2 and 3 with that for reference category 1 (nonrepeated wheeze category), assuming a linear increase in the effect estimates (on the log OR scale) with each scale increase of the ordinal outcome categories. Again, models were run separately for each of the air pollution indicators.

The results from these sensitivity analyses suggest that our findings in the main analyses (ie, that increased exposure to both increased levels of prenatal ECV and prenatal ambient air pollution indicators were associated with increased odds of more frequent wheeze) held when using alternative statistical approaches that specified frequent wheeze by using more extreme categories, although the CIs from these sensitivity analyses were wider because of smaller cell sizes.

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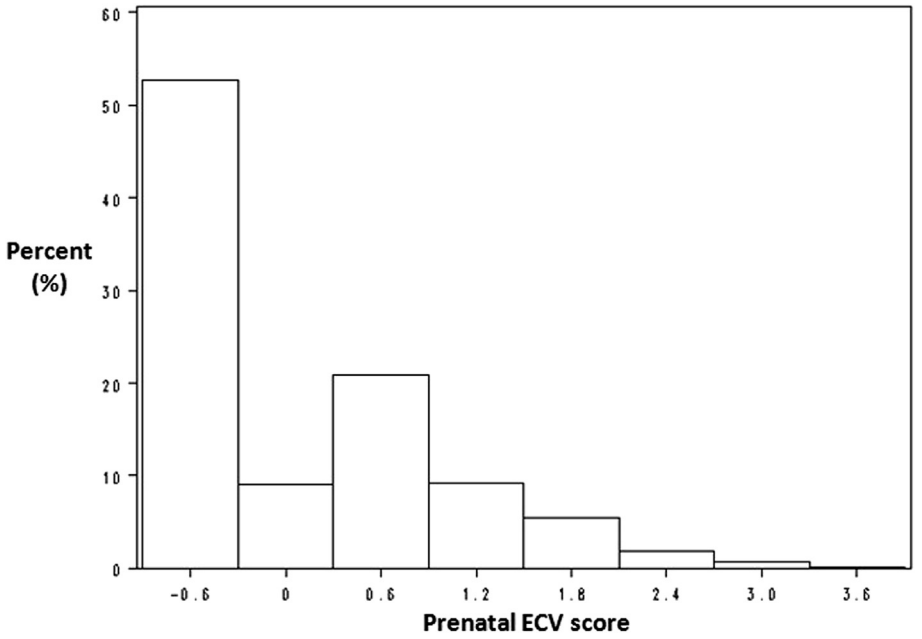

FIG E1. Distribution of ECV scores derived by using Rasch modeling among ACCESS participants.

TABLE E1. Maternal ECV and ambient air pollution during pregnancy and repeated wheeze in children: multinominal logit models

	Wheeze category: 0-1, 2, or ≥3 episodes						Wheeze category: 0-1, 2-3, or ≥4 episodes					
	$OR_{2\ vs\ 0\text{-}1}$	95% CI		$OR_{\geq 3\ vs\ 0\text{-}1}$	95% CI		$OR_{2\text{-}3\ vs\ 0\text{-}1}$	95% CI		$OR_{\geq 4\ vs\ 0\text{-}1}$	95% CI	
BC model*												
ECV												
Low	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
Medium	1.11	0.49	2.55	1.67	0.66	4.22	0.96	0.62	1.49	1.56	0.24	10.3
High	1.79	0.90	3.58	2.24	1.00	5.02	1.09	0.73	1.63	5.26	1.27	21.9
BC												
Low (≤median)	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
High (>median)	1.63	0.83	3.19	2.25	1.02	4.98	1.21	0.84	1.74	2.02	0.52	7.89
$PM_{2.5}$ model†												
ECV												
Low	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
Medium	1.16	0.51	2.67	1.78	0.71	4.50	0.99	0.64	1.53	1.90	0.28	12.8
High	1.92	0.96	3.85	2.51	1.12	5.63	1.15	0.77	1.71	8.51	1.89	38.2
$PM_{2.5}$												
Low (≤median)	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
High (>median)	2.01	1.04	3.88	2.03	0.98	4.41	1.46	1.02	2.10	15.5	2.61	92.5

*The BC model included community violence, BC level, sex, race/ethnicity, maternal education, season of birth, maternal atopy, and cockroach allergen exposure (BC median = 0.38 $\mu g/m^3$).

†The $PM_{2.5}$ model included community violence, $PM_{2.5}$ level, sex, race/ethnicity, maternal education, season of birth, maternal atopy, and cockroach allergen exposure ($PM_{2.5}$ median = 11.22 $\mu g/m^3$).

TABLE E2. Maternal ECV and ambient air pollution during pregnancy and repeated wheeze in children: adjacent-categories logit models

	Wheeze category: 0-1, 2, or ≥3 episodes						Wheeze category: 0-1, 2-3, or ≥4 episodes					
	$OR_{2\ vs\ 0\text{-}1}$	95% CI		$OR_{\geq 3\ vs\ 0\text{-}1}$	95% CI		$OR_{2\text{-}3\ vs\ 0\text{-}1}$	95% CI		$OR_{\geq 4\ vs\ 0\text{-}1}$	95% CI	
BC model*												
ECV												
Low	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
Medium	1.26	0.83	1.92	1.60	0.69	3.71	1.30	0.75	2.24	1.68	0.56	5.03
High	1.56	1.09	2.24	2.43	1.19	5.00	1.94	1.23	3.07	3.77	1.51	9.43
BC												
Low (≤median)	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
High (>median)	1.52	1.07	2.17	2.31	1.14	4.69	1.65	1.05	2.59	2.73	1.11	6.71
$PM_{2.5}$ model†												
ECV												
Low	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
Medium	1.31	0.86	2.00	1.73	0.75	4.00	1.38	0.80	2.39	1.90	0.63	5.70
High	1.66	1.16	2.39	2.76	1.34	5.70	2.13	1.34	3.39	4.53	1.79	11.46
$PM_{2.5}$												
Low (≤median)	Reference	—	—	Reference	—	—	Reference	—	—	Reference	—	—
High (>median)	1.55	1.10	2.19	2.40	1.20	4.79	2.09	1.33	3.27	4.36	1.77	10.69

*The BC model included community violence, BC level, sex, race/ethnicity, maternal education, season of birth, maternal atopy, and cockroach allergen exposure (BC median = 0.38 $\mu g/m^3$).

†The $PM_{2.5}$ model included community violence, $PM_{2.5}$ level, sex, race/ethnicity, maternal education, season of birth, maternal atopy, and cockroach allergen exposure ($PM_{2.5}$ median = 11.22 $\mu g/m^3$).