

Lifetime air pollution exposure and asthma in a pediatric birth cohort



To the Editor:

Although it is clear that ambient pollution triggers symptoms among asthmatic patients, there remains uncertainty about whether long-term exposure to pollution at relatively low levels in the United States increases a child's risk of asthma. Studies have concluded generally that pollution increases asthma risk, but the duration of exposure assessment varies substantially between these studies, and few have examined lifetime exposures. Some studies have concluded that ambient pollution primarily increases the risk of early-onset (by age 3 years) asthma and wheeze,¹ whereas others have found associations that emerge later at school age.²

In Project Viva, a prebirth cohort in the Boston area with lifetime residential histories, we have found previously that living closer to a major road and lifetime exposure to particulate matter of less than 2.5 μm in diameter ($\text{PM}_{2.5}$) and black carbon (BC; a traffic-related $\text{PM}_{2.5}$ constituent) are associated with lower lung function in midchildhood.³ We hypothesized that these exposures would be associated with asthma in both early childhood and midchildhood.

Study participants were 1522 children whose mothers enrolled during their initial prenatal visit (April 1999-July 2002). Further details about the cohort, exposure and outcome assessment, and statistical analyses are described in the [Methods](#) section in this article's Online Repository at www.jacionline.org. We geocoded each participant's home address at birth and at each study visit and assigned distance to the nearest major roadway and census tract (year 2000) characteristics by using ArcGIS (ESRI, Redlands, Calif). We examined categories of distance and also the natural logarithm of proximity to major roadway. We estimated daily BC exposure at the home address using a validated spatiotemporal land-use regression model for traffic particles developed for the Boston area. We estimated daily community-level $\text{PM}_{2.5}$ levels using a hybrid model with satellite-derived measures of particle abundance and land-use terms. We calculated first year of life and lifetime BC and $\text{PM}_{2.5}$ exposure using each child's time-averaged full residential history.

The following asthma-related outcomes were ascertained using a maternal questionnaire: (1) early asthma/reactive airways

(doctor's diagnosis of asthma, wheeze, or reactive airway disease anytime between birth and the early-childhood questionnaire [age 3-5 years]); (2) recurrent wheeze at early childhood (wheezing in the past 12 months [at age 3-5 years] and wheezing at age 1 or 2 years); (3) ever asthma (doctor's diagnosis of asthma since birth reported on the midchildhood questionnaire [age 7-10 years]); and (4) current asthma in midchildhood (ever asthma and taking asthma medications or wheezing in the past 12 months).

We analyzed associations between exposures and asthma outcomes using logistic regression models, adjusting for potential confounders that we selected *a priori*. All models were adjusted for child's sex, age, race/ethnicity, parental history of asthma, breast-feeding duration, birth weight for gestational age z score, bronchiolitis in infancy, current household income and smoking, census tract income and education (using 2000 US census data), season of birth, and date of visit. We tested whether associations between pollution and asthma differed by parental atopy, child's sex and early atopic dermatitis, and individual- and neighborhood-level socioeconomic indicators, as described in the [Methods](#) section in this article's Online Repository.

Participants' characteristics and exposures are described in [Tables E1](#) and [E2](#) in this article's Online Repository at www.jacionline.org. Associations between measures of pollution exposure and asthma are shown in [Table I](#). Proximity to the roadway and exposure to BC and community-level $\text{PM}_{2.5}$ were all associated with early-childhood (age 3-5 years) asthma/reactive airways. There were log-linear associations between proximity to the roadway at birth (and also at the time of assessment) and odds of early asthma/reactive airways. Lifetime averages of BC and $\text{PM}_{2.5}$ values had greater associations with the odds of early asthma than exposures in the first year of life.

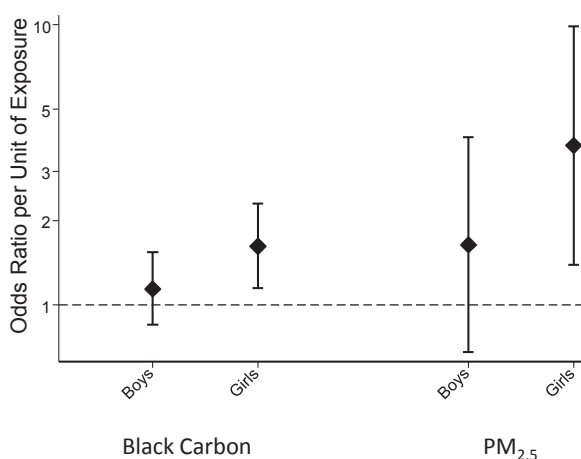
Proximity of the home to a major roadway at the time of assessment, but not birth, was associated with midchildhood (age 7-10 years) asthma overall and in sensitivity analyses confined only to those who moved (62%). There was a log-linear association of proximity to the roadway with ever asthma. Children living less than 100 m from a major road had nearly 3 times the odds of current asthma in midchildhood compared with those living more than 400 m away (odds ratio [OR], 2.86; 95% CI, 1.25-6.55; see [Table E3](#) in this article's Online Repository at www.jacionline.org). BC and $\text{PM}_{2.5}$

TABLE I. Air pollution exposures and odds of asthma in early childhood and midchildhood

	Early childhood (3-5 y), n = 1444		Midchildhood (7-10 y), n = 1242	
	Asthma/reactive airways	Recurrent wheeze	Ever asthma	Current asthma
Proximity to roadway				
At birth	1.21 (1.00-1.48)	0.97 (0.73-1.27)	1.02 (0.81-1.28)	0.99 (0.77-1.28)
At visit	1.22 (0.99-1.50)	0.88 (0.66-1.18)	1.34 (1.06-1.68)	1.16 (0.89-1.52)
BC				
First year of life	1.13 (0.93-1.38)	1.14 (0.87-1.49)	0.99 (0.80-1.23)	1.07 (0.84-1.36)
Lifetime	1.32 (1.03-1.69)	1.26 (0.91-1.74)	1.00 (0.74-1.35)	1.05 (0.75-1.46)
Community-level $\text{PM}_{2.5}$				
First year of life	2.25 (1.17-4.33)	2.62 (1.08-6.34)	0.94 (0.47-1.85)	0.95 (0.45-2.04)
Lifetime	2.35 (1.12-4.91)	2.89 (1.06-7.85)	1.03 (0.45-2.35)	0.95 (0.38-2.38)

Values are presented as ORs (95% CIs) per unit increase in exposure. Boldface values indicate confidence intervals that do not cross the null. Home address location changed at least once after birth for 46% of participants by the early-childhood visit and for 62% of participants by the midchildhood visit. Results were scaled from the 75th to 25th percentile of the log-transformed distance to a major roadway per 0.2 $\mu\text{g}/\text{m}^3$ for BC and per 2 $\mu\text{g}/\text{m}^3$ for community-level $\text{PM}_{2.5}$. Associations with $\text{PM}_{2.5}$ values are adjusted for local primary $\text{PM}_{2.5}$ generated within 100 m of home. All models were adjusted for child's age, sex, race/ethnicity, breast-feeding duration, birth weight for gestational age z score, infantile bronchiolitis, maternal and paternal asthma, household income and smoking, census tract income and education, season of birth, and date of visit.

Early Asthma/Reactive Airways (Age 3-5)



Midchildhood Current Asthma (Age 7-10)

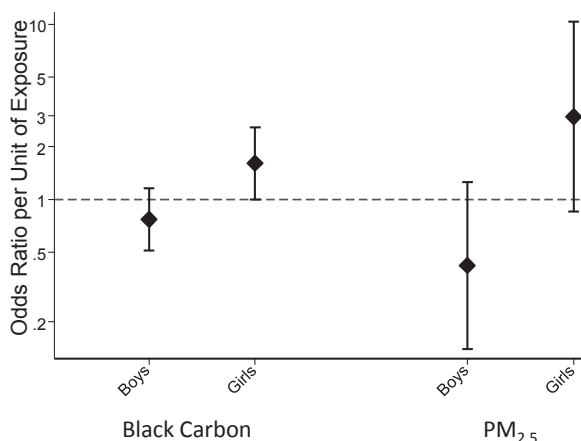


FIG 1. Sex-specific associations of lifetime pollution exposure and asthma. Results are scaled per 0.2 $\mu\text{g}/\text{m}^3$ for BC and per 2 $\mu\text{g}/\text{m}^3$ for community-level PM_{2.5}. Associations with PM_{2.5} are adjusted for local primary PM_{2.5} generated within 100 m of home. All models were adjusted for child's age, sex, race/ethnicity, breast-feeding duration, birth weight for gestational age z score, infantile bronchiolitis, maternal and paternal asthma, household income and smoking, census tract income and education, season of birth, and date of visit.

exposures were not associated with midchildhood asthma in primary analyses.

However, sex modified several associations between pollution and asthma in early childhood and midchildhood (Fig 1). Among girls, but not boys, lifetime exposures to BC and PM_{2.5} were each associated with greater odds of early childhood and midchildhood asthma. Children with parental atopy or early atopic dermatitis each had stronger associations between BC exposure and recurrent wheeze (see Fig E1 in this article's Online Repository at www.jacionline.org). Complete results of tests of effect modification and additional sensitivity analyses are shown in Table E4 and the Results section in this article's Online Repository at www.jacionline.org.

Our findings are in agreement with Brunst et al,⁴ who concluded that higher lifetime exposure to traffic-related pollution during childhood and not just early-life exposure

increases asthma risk. The large European Study of Cohorts for Air Pollution Effects (ESCAPE) study concluded that early-life exposure to ambient pollution contributes disproportionately to asthma risk² but did not account for changing pollution levels and addresses over each child's lifetime.

We found more consistent associations of pollution with early-childhood asthma/reactive airways than with midchildhood asthma. There might be less exposure misclassification for younger children, who generally spend a larger proportion of their time at home than school-aged children. Also, an inflammatory response to pollution might be more likely to produce wheeze in a younger child, whose airways are smaller. An important finding of this study is a consistent pattern of stronger associations between pollutant exposures and odds of asthma among girls compared with boys. Although some have found boys to be more likely to wheeze by age 4 years in association with pollution exposure,⁵ girls appear more likely to have asthma in association with tobacco smoke exposure.⁶ It is plausible that differences in immune responses, including more exuberant inflammatory immune responses among girls,⁷ could explain the sex differences we found. Our observation that children with a parental history of atopy are more likely to wheeze in association with air pollution is consistent with other publications.⁵

In this area, where pollution levels are relatively low and within Environmental Protection Agency standards, traffic-related pollution appears to increase the risk of pediatric asthma, especially in early childhood.

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SCCA2 is a reliable biomarker for evaluating pediatric atopic dermatitis



To the Editor:

It was claimed before that there is no reliable biomarker for atopic dermatitis (AD).¹ However, a systematic review recently showed that thymus and activation-regulated chemokine (TARC)/chemokine C-C motif ligand 17, a chemokine involved in type 2 inflammation, is the most reliable biomarker indicating the disease severity of AD.² Nevertheless, TARC has a disadvantage in that infants and children show significantly higher TARC levels than adults do; TARC levels in infants <1 year old are almost 3 times those of adults (<1367 ng/mL vs <450 ng/mL).³ This indicates that we need to evaluate serum TARC values depending on the ages of the subjects and that high pathological TARC levels may be masked in younger subjects. Therefore, a novel biomarker for AD must be found and developed that provides reliable information, particularly in younger subjects.

We previously found that 2 squamous cell carcinoma antigen (SCCA) molecules, SCCA1/SERPIN B3 and SCCA2/SERPIN B4, are downstream molecules of IL-4 and IL-13, signature cytokines of type 2 inflammation,⁴ and that SCCAs are strongly expressed in the epidermis of AD patients.⁵ We furthermore established an ELISA system to distinguish SCCA1 and SCCA2 and found that expression of SCCA2 is predominant in AD patients.⁶

In this study, we performed a multicenter analysis to compare SCCA2, TARC, and IgE, a commonly used biomarker, in the sera of children without allergies and children with AD. From 2015 to 2017, we recruited 159 subjects without allergies and 176 AD patients, including ≥10 subjects in each year of age, ≤7 years old. Selection of the subjects and the distributions of ages and clinical severities of AD are shown in the supplemental data and Table E1, which are available in this article's Online Repository at www.jacionline.org. No psoriasis patient in which we previously showed high SCCA2 levels was included.⁷ This study was conducted at 3 hospitals—Mie National Hospital, National Center for Child Health and Development, and Fukuoka National Hospital—after approval by the local institutional review boards. Measurement of SCCA2 by ELISA and preparation of recombinant SCCA2 proteins were performed as previously described, with the modification of using not biotin-conjugated, but peroxidase-conjugated, SS8G.⁶

We first examined SCCA2, TARC, and IgE in children without allergies (n = 159). Both the median values of SCCA2 and TARC decreased as the ages went up ($P < .001$), whereas the median values of IgE went up as the age increased (see Fig E1 and Table E2 in this article's Online Repository at www.jacionline.org). Both the median levels of SCCA2 and TARC were invariant in males and females.

We then compared the levels of SCCA2, TARC, and IgE in the overall group of AD children and children without allergies (Fig 1, A). SCCA2, TARC, and IgE were all significantly higher in AD children than in children without allergies (median: SCCA2: 3.90 vs 0.75 ng/mL; TARC: 1073 vs 341 pg/mL; and IgE: 807 vs 39.4 IU/mL; $P < .001$). Presence of asthma did not affect SCCA2 in AD children (data not shown). SCCA2 was well correlated with TARC ($P < .001$, $r = 0.757$), and weakly with IgE ($P < .01$, $r = 0.237$) (see Fig E2 in this article's Online Repository available at www.jacionline.org). The area under the curve (AUC) by the receiver-operating characteristic curve was higher in SCCA2 (0.929) than in TARC (0.871) and IgE (0.820) (Fig 1, B, and see Fig E3 in this article's Online Repository available at www.jacionline.org). SCCA2 showed higher AUCs than TARC did in all age groups or 3 age groups—≤1 year, 2 to 6 years, and 7 to 15 years (Fig 1, B, and see Fig E4 in this article's Online Repository available at www.jacionline.org). These results demonstrate that SCCA2 corresponded more closely to diagnosis of AD than TARC and IgE in the children overall.

We next examined the correlation of each biomarker with objective Scoring Atopic Dermatitis (O-SCORAD) (Fig 2, A). SCCA2, TARC, and IgE all showed good correlations with O-SCORAD, with the highest association in SCCA2 (SCCA2: $r = 0.622$; TARC: $r = 0.491$; IgE: $r = 0.407$; $P < .001$). To estimate the ability to reflect clinical severity, we analyzed the SCCA2 and TARC levels in 3 groups—mild (O-SCORAD: <15, n = 56), moderate (O-SCORAD: 15–40, n = 60), and severe (O-SCORAD: >40, n = 60) (Fig 2, B).⁸ Both SCCA2 and TARC increased according to the existence or the clinical severity of AD (median: SCCA2: 0.75, 2.0, 3.5, and 10.8 ng/mL; TARC: 342, 885, 897, and 2530 pg/mL). SCCA2 showed higher AUCs than TARC in all 3 comparisons—control versus mild (SCCA2: 0.864; TARC: 0.822), mild versus moderate (SCCA2: 0.671; TARC: 0.571), and moderate versus severe (SCCA2: 0.783; TARC: 0.725) (Fig 2, C). It is of note that SCCA2, but not TARC, showed a statistical significance in the comparison

METHODS

Study population

Pregnant mothers were recruited from Atrius Health, a multispecialty group practice in eastern Massachusetts, during their initial prenatal visit. Enrollment criteria have been described previously.^{E1} Exclusion criteria included multiple gestation, inability to answer questions in English, plans to move out of the area before delivery, and gestational age of greater than 22 weeks at the initial prenatal clinic appointment. Mothers were recruited during early pregnancy, and children were followed from birth. The mothers were administered annual questionnaires, and mother-child pairs were invited to an early-childhood visit (age 3-5 years) and a midchildhood visit (age 7-10 years). A total of 1522 mother-child pairs completed questionnaires, attended either the early childhood or midchildhood visit, and provided residential histories. All mothers provided written informed consent for themselves and their children. This study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard Pilgrim Health Care.

Exposure assessment

Using ArcGIS, we assigned the distance from the home address to the nearest major roadway at each study visit. A major road was defined as an A1 or A2 road based on the US Census Feature Class system. A1 roads have limited access and are primary multilane highways. A2 roads are US highways and certain state and county highways that do not have limited access. We also assigned US census data, including median household income and percentage with at least a high school education, from the tract-level 2000 US Census at each visit.

Based on published findings that traffic-related pollutants decay to background levels exponentially with distance from a freeway,^{E2,E3} we examined categories of distance (<100, 100-<200 m, 200-<400 m, and ≥400 m), as well as the natural logarithm of proximity to a major roadway. This approach is consistent with our prior work in Project Viva and other cohorts.^{E4-E6}

Daily BC exposure at the home address was estimated by using a validated spatiotemporal land-use regression model for traffic particles that was developed for the Boston area.^{E7} The BC model includes data from 148 monitoring stations operating between 1995 and 2011 and has been updated and revised from its original version.^{E7-E9} We calculated average BC exposure during the first year of life and for the child's entire lifetime from birth to the date of each visit.

Daily estimates of community-level PM_{2.5} were estimated by using a hybrid model of moderate-resolution imaging spectroradiometer satellite-derived aerosol optical depth measurements and land-use terms. Aerosol optical depth is a quantitative measure of particle abundance in the atmospheric column. The satellite model estimates were generated at 10 × 10-km resolution beginning in the year 2000.^{E10} PM_{2.5} estimation was then improved by using data from spatial predictors (eg, elevation, population density, traffic density, point and area emissions, and percentages of land use) and temporal predictors (eg, temperature, wind speed, and visibility), as described in detail in previous work.^{E10,E11} Using PM_{2.5} values measured on the ground throughout the Northeastern United States, we derived an estimate of local primary PM_{2.5} generated within 100 m of the home by traffic and the burning of heating fuel (in the winter) estimated by using a secondary land-use regression model.^{E10} All analyses of PM_{2.5} exposure were adjusted for local primary PM_{2.5} values and indicate the community-level exposure to primary and secondary PM_{2.5}, including transported air pollution from outside of the community and primary particles generated more than 100 m from the home.

We calculated average community-level PM_{2.5} exposure during the first year of life and for the child's entire lifetime from birth to the date of each visit. An updated model with satellite data at a resolution of 1 × 1 km became available in 2003^{E12} after the last year of prenatal enrollment (1999-2002) for this cohort. Therefore this model could not be used to estimate year 1 or lifetime exposure averages in this cohort. However, we calculated average PM_{2.5} exposure during the 365 days before the date of the early-childhood and midchildhood visits by using the higher spatial resolution model as an indicator of later childhood exposure and report these results as secondary analyses.

Questionnaire and interview data

Questionnaire and/or interview data were obtained from the mother at study enrollment during the first prenatal visit, by annual questionnaire, and at the early-childhood and midchildhood visits. Information was obtained about the child's health (including medication use, symptoms of wheeze, and diagnosis of asthma and early-life respiratory tract infection), parental medical history (including asthma), demographics, smoking in the household, breast-feeding, and the home environment. At each in-person visit, child height and weight were measured by a trained research assistant.

Statistical analysis

We analyzed associations between exposures and asthma outcomes using logistic regression models, adjusting for child's sex, age, race/ethnicity, parental history of asthma, breast-feeding duration, birth weight for gestational age *z* score, bronchiolitis in infancy, current household income and smoking, census tract income and education (using 2000 US Census data), season of birth, and date of visit. We used sine and cosine functions of the date of birth to estimate the amplitude and phase of the seasonal cycle. We adjusted for time as a continuous linear variable by using the visit date. We assessed the influence of day care attendance, gas stove use, and maternal vitamin D intake during pregnancy for comparison with other publications in the field.^{E13-E15} Models were fit with the PROC LOGISTIC procedure using SAS 9.3 software (SAS Institute, Cary, NC). We tested for effect modification of the associations between proximity to the major road, BC and community-level PM_{2.5}, and odds of early-childhood and midchildhood asthma by (1) risk factors or signs of allergy, (2) child's sex, (3) child's race, and (4) individual- and neighborhood-level indicators of socioeconomic position. Specifically, we assessed differential susceptibility by parental atopy by using the same definition as other investigators^{E13}: any maternal or paternal history of asthma, atopic dermatitis, or allergic rhinitis. Early atopic dermatitis was defined as any maternal report on questionnaire of eczema or atopic dermatitis on questionnaire administered at age 6 months, 1 year, 2 years, and 3 to 5 years. Child's race was defined as white versus nonwhite. We assessed the following 2 measures of socioeconomic position: self-reported household income (≤\$70,000 vs >\$70,000) at study enrollment and neighborhood education (≤20th vs >20th percentile for the percentage of census tract adults with at least a college degree) at birth.

We tested for statistical interaction of associations of the natural logarithm of distance from home to nearest major roadway and BC and PM_{2.5} exposure with odds of asthma in early childhood and midchildhood by these characteristics using cross-product terms in models, including exposure, effect modifier, and exposure-effect modifier interaction in fully adjusted models. We considered a *P* value from the Wald test of the cross-product of less than .1 as statistical evidence of effect modification. We report stratum-specific associations with pollution exposure using a model including the effect modifier and exposure-effect modifier interaction in fully adjusted models in all cases in which the *P* value for the interaction term is less than .1. When assessing effect modification by parental history of atopy, we adjust for the main effect of parental history of atopy (maternal or paternal history of asthma, atopic dermatitis, or allergic rhinitis) instead of maternal and paternal asthma as 2 covariates.

Previously, we have found that exposure to air pollution in early life is associated with risk factors for obesity^{E9,E16} and early-life respiratory tract infection^{E5} in this cohort. To evaluate whether associations between pollution and the odds of asthma might be mediated by obesity or respiratory tract infection, we adjusted additionally for body mass index *z* score at the time of the visit and examined models with and without adjustment for infantile bronchiolitis.

RESULTS

Characteristics of the study participants at the early-childhood and midchildhood visits are summarized in Table E1. The

medians and interquartile ranges of distance to the roadway and BC and community-level PM_{2.5} values for the different exposure periods are provided in [Table E2](#). The past 365-day average of PM_{2.5} values (analyzed in sensitivity analyses) was 11.1 µg/m³ at early childhood and 9.4 µg/m³ at midchildhood, which were less than the annual national ambient air quality standard of 12 µg/m³. Associations of distance to the major road in categories (<100, 100-<200, and 200-<400 m and the reference category of ≥400 m) and odds of asthma are provided in [Table E3](#). Living within 100 m of a major road at the time of assessment was associated with ever asthma and current asthma in midchildhood.

Secondary analyses

In sensitivity analyses prior 365-day community-level PM_{2.5} values (using the updated PM_{2.5} model with data beginning in 2003) had a similar association with early asthma/reactive airways: OR of 1.90 (95% CI, 1.11-3.26) per 2 µg/m³ higher prior 365-day PM_{2.5} compared with an OR of 2.35 (95% CI, 1.12-4.91) for lifetime PM_{2.5}. Adjustment for child's body mass index, day care, gas stove use, and maternal vitamin D intake during pregnancy did not affect any of the results. In models that did not adjust for the child's respiratory tract infection, associations were similar but slightly smaller in magnitude compared with the baseline model.

Results of tests of effect modification that reached statistical significance ($P_{\text{interaction}} < .1$) are shown in [Table E4](#). There was evidence of effect modification by female sex for multiple associations, including lifetime BC values with early asthma/reactive airways and lifetime and year 1 BC and lifetime PM_{2.5} values with ever and current asthma in midchildhood. There was also effect modification by early atopic dermatitis and parental history of atopy for multiple associations between BC, PM_{2.5}, or both and early-life asthma and recurrent wheeze ([Fig E1](#)). Associations of community-level PM_{2.5} exposure in the first year of life with recurrent wheeze were greater among households with an income of greater than \$70,000, and associations with early asthma/reactive airways were greater among white compared with nonwhite children. We found no evidence of effect modification of any of the associations by neighborhood-level education.

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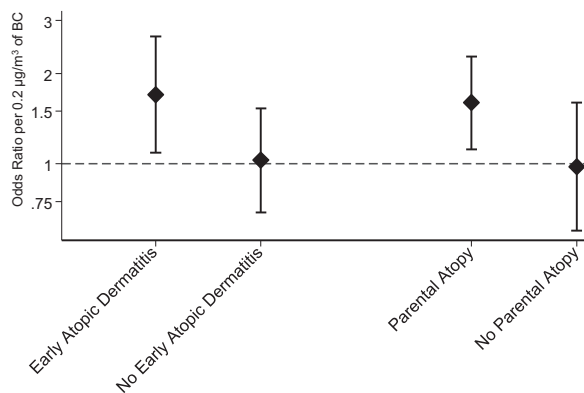


FIG E1. Lifetime BC exposure and odds of recurrent wheeze (age 3-5 years) by atopic dermatitis and parental atopy. Results were scaled per $0.2 \mu\text{g}/\text{m}^3$ of lifetime BC exposure. All models were adjusted for child age, sex, race/ethnicity, breast-feeding duration, birth weight for gestational age z score, infantile bronchiolitis, maternal and paternal asthma, household income and smoking, census tract income and education, season of birth, and date of visit. Model examining effect modification by parental atopy adjusts for parental atopy instead of maternal and paternal asthma.

TABLE E1. Characteristics of 1522 mothers and children in the Project Viva cohort with information on early-life air pollution exposure and asthma outcomes in early childhood or midchildhood

Characteristic	Early childhood (3-5 y), n = 1444	Midchildhood (7-10 y), n = 1242
Family/household		
Tobacco smoking in household (%)		
No	1139 (87.1)	1004 (88.5)
Yes	169 (12.9)	130 (11.5)
Maternal history of asthma (%)		
No	1254 (87.2)	1080 (87.4)
Yes	184 (12.8)	155 (12.6)
Paternal history of asthma (%)		
No	1239 (88.2)	1063 (88.1)
Yes	166 (11.8)	143 (11.9)
Parental history of asthma, eczema, or hay fever (%)		
No	587 (40.8)	506 (40.9)
Yes	852 (59.2)	730 (59.1)
Household income (%)		
<\$40,000	173 (13.4)	132 (11.8)
\$40,001-\$70,000	265 (20.5)	154 (13.8)
>\$70,000	853 (66.1)	830 (74.4)
Residential census tract*		
Median household income, \$10,000s	63.2 (23.2)	65.3 (24.8)
Percentage with bachelor degree or higher	40.6 (19.5)	41.6 (19.8)
Child		
Age at visit (y)	3.3 (0.4)	8.0 (0.8)
Sex (%)		
Male	742 (51.4)	625 (50.3)
Female	702 (48.6)	617 (49.7)
Race/ethnicity (%)		
Black	192 (13.3)	197 (15.9)
Hispanic	64 (4.4)	51 (4.1)
Asian	50 (3.5)	40 (3.2)
White	969 (67.1)	805 (64.9)
Other	169 (11.7)	147 (11.9)
Birth weight for gestational age z score	0.20 (0.96)	0.20 (0.97)
Breast-feeding duration (mo)	6.3 (4.6)	6.5 (4.6)
Infantile bronchiolitis		
No	1104 (86.5)	961 (87.5)
Yes	173 (13.5)	137 (12.5)
Early atopic dermatitis		
No	934 (65.0)	752 (64.9)
Yes	503 (35.0)	406 (35.1)
Outcomes†		
Early asthma or reactive airways at early childhood (%)		
No	1124 (78.3)	
Yes	312 (21.7)	
Recurrent wheeze at early childhood (%)		
No	834 (81.7)	
Yes	187 (18.3)	
Ever asthma at midchildhood (%)		
No		963 (77.5)
Yes		279 (22.5)
Current asthma at midchildhood (%)		
No		899 (80.4)
Yes		219 (19.6)

Values are presented as numbers (percentages) or means (SDs).

*Census tract data are from the year 2000 US Census for address at time of outcome assessment.

†Early asthma/reactive airways is defined as a diagnosis of asthma or wheezing/reactive airways disease assessed on the early childhood questionnaire (age 3-5 years). Early recurrent wheeze is defined as a report of wheeze symptoms at the early childhood (age 3-5 years) questionnaire and also at the 1- or 2-year questionnaire. Ever asthma by midchildhood is defined as report of a diagnosis of asthma assessed on the midchildhood (age 7-10 years) questionnaire. Current asthma at midchildhood is defined as ever asthma and a report of taking asthma medications or wheezing within the past 12 months, as assessed on the midchildhood questionnaire.

TABLE E2. Distributions of exposure averages among 1522 children with exposure and asthma outcome data

	Early childhood (3-5 y), n = 1444	Midchildhood (7-10 y), n = 1242
BC ($\mu\text{g}/\text{m}^3$)		
First year of life	0.66 (0.52-0.78)	0.68 (0.53-0.79)
Lifetime	0.59 (0.47-0.70)	0.53 (0.43-0.64)
Community-level PM _{2.5} ($\mu\text{g}/\text{m}^3$)		
First year of life	12.1 (11.6-12.5)	12.1 (11.6-12.5)
Lifetime	11.7 (11.2-12.1)	10.8 (10.4-11.2)
Distance to roadway (m)		
At time of birth (m)	1114 (464-2429)	1112 (462-2423)
Category at time of birth (%)		
<100 m	86 (6.0)	66 (5.3)
100-<200 m	87 (6.1)	82 (6.6)
200-< 400 m	138 (9.6)	123 (10.0)
≥400 m	1126 (78.4)	964 (78.1)
At time of outcome (m)	1185 (515-2700)	1349 (546-2864)
Category at time of outcome (%)		
<100 m	68 (4.9)	54 (4.6)
100-<200 m	86 (6.2)	63 (5.4)
200-<400 m	119 (8.6)	108 (9.2)
≥400 m	1106 (80.2)	949 (80.8)

Values are presented as medians (interquartile ranges) or numbers (percentages).

TABLE E3. Distance to major road in categories and odds of asthma in early childhood and midchildhood

	Early childhood (3-5 y)		Midchildhood (7-10 y)	
	Asthma/reactive airways	Recurrent wheeze	Ever asthma	Current asthma
Distance to road at birth				
<100 m	1.04 (0.53-2.06)	0.85 (0.34-2.15)	0.85 (0.38-1.88)	0.76 (0.31-1.86)
100-<200 m	1.09 (0.55-2.17)	0.64 (0.22-1.81)	1.03 (0.51-2.06)	0.89 (0.39-2.03)
200-<400 m	1.82 (1.10-3.00)	0.92 (0.44-1.96)	1.18 (0.66-2.12)	1.11 (0.57-2.16)
≥400 m	Reference	Reference	Reference	Reference
Distance to road at visit				
<100 m	1.32 (0.64-2.72)	0.80 (0.29-2.19)	3.07 (1.48-6.37)	2.86 (1.25-6.55)
100-<200 m	1.26 (0.68-2.33)	0.64 (0.23-1.73)	1.53 (0.74-3.17)	1.08 (0.44-2.63)
200-<400 m	1.57 (0.91-2.70)	0.86 (0.39-1.89)	1.40 (0.77-2.54)	0.90 (0.44-1.85)
≥400 m	Reference	Reference		Reference

ORs (95% CIs) are compared with the reference category. Boldface values indicate confidence intervals that do not cross the null. All models were adjusted for child's age, sex, race/ethnicity, breast-feeding duration, birth weight for gestational age z score, infantile bronchiolitis, maternal and paternal asthma, household income and smoking, census tract income and education, season of birth, and date of visit.

TABLE E4. Associations of air pollution exposure with asthma outcomes by effect modifiers ($P_{\text{interaction}} < .1$)

Early childhood (age 3-5 y)				
Exposure	Early asthma/reactive airways, OR (95% CI)	$P_{\text{interaction}}$	Recurrent wheeze, OR (95% CI)	$P_{\text{interaction}}$
Effect modifier				
BC, lifetime				
Female child	1.62 (1.15-2.30)	.09		.24
Male child	1.14 (0.85-1.54)			
Atopic dermatitis	1.66 (1.17-2.36)	.06	1.70 (1.09-2.66)	.07
No atopic dermatitis	1.12 (0.83-1.51)		1.03 (0.69-1.53)	
Parental atopy		.40	1.60 (1.12-2.28)	.08
No parental atopy			0.98 (0.60-1.60)	
Community-level PM _{2.5} , first year of life				
White race	3.15 (1.47-6.77)	.09		.32
Nonwhite race	1.04 (0.34-3.13)			
Household income >\$70,00		.54	4.21 (1.44-12.32)	.06
Household income <\$70,00			0.82 (0.20-3.44)	
Parental atopy		.15	4.51 (1.63-12.51)	.04
No parental atopy			0.90 (0.24-3.37)	
Midchildhood (age 7-10 y)				
	Ever asthma, OR (95% CI)		Current asthma, OR (95% CI)	
Proximity to roadway at birth				
Household income >\$70,00	1.12 (0.84-1.50)	.07	1.15 (0.83-1.59)	.05
Household income <\$70,00	0.70 (0.46-1.06)		0.66 (0.42-1.03)	
BC, first year of life				
Female child	1.25 (0.92-1.71)	.03	1.39 (0.98-1.96)	.04
Male child	0.82 (0.61-1.08)		0.87 (0.64-1.19)	
BC, lifetime				
Female child	1.46 (0.96-2.23)	.01	1.61 (1.00-2.58)	.01
Male child	0.76 (0.52-1.10)		0.77 (0.51-1.16)	
Community-level PM _{2.5} , lifetime				
Female child	2.28 (0.76-6.83)	.03	2.96 (0.85-10.36)	.01
Male child	0.56 (0.21-1.49)		0.42 (0.14-1.25)	

Results are scaled from the 75th to 25th percentile of the log-transformed distance to a major roadway per 0.2 $\mu\text{g}/\text{m}^3$ for BC and per 2 $\mu\text{g}/\text{m}^3$ for community-level PM_{2.5}. Associations with PM_{2.5} are adjusted for local primary PM_{2.5} generated within 100 m of home. All models were adjusted for child's age, sex, race/ethnicity, breast-feeding duration, birth weight for gestational age z score, infantile bronchiolitis, maternal and paternal asthma (or parental atopy when assessing for effect modification by parental atopy), household income and smoking, census tract income and education, season of birth, and date of visit. Each model adjusts for main effect of effect modifier.