Title

Role of Air Pollution in the Development of Asthma Among Children with a History of Bronchiolitis in Infancy

Journal

Epidemiology, 34(4)

ISSN

1044-3983

Authors

Dearborn, Logan C
Hazlehurst, Marnie F
Loftus, Christine T
et al.

Publication Date

2023-07-01

DOI

10.1097/ede.0000000000001613

Peer reviewed

Role of Air Pollution in the Development of Asthma Among Children with a History of Bronchiolitis in Infancy

Logan C Dearborn,[a] *Marnie F Hazlehurst,*[a] *Christine T Loftus,*[a] *Adam A Szpiro,*[b] *Kecia N Carroll,*[c,d] *Paul E Moore,*[e] *Margaret A Adgent,*[f] *Emily S Barrett,*[g,h] *Ruby HN Nguyen,*[i] *Sheela Sathyanarayana,*[a,j,k] *Kaja Z LeWinn,*[l] *Nicole R Bush,*[m] *Joel D Kaufman,*[a,n,o] *and Catherine J Karr*[a,j,n]

Background: Infants experiencing bronchiolitis are at increased risk for asthma, but few studies have identified modifiable risk factors. We assessed whether early life air pollution influenced child asthma and wheeze at age 4–6 years among children with a history of bronchiolitis in the first postnatal year.

Methods: Children with caregiver-reported physician-diagnosed bronchiolitis were drawn from ECHO-PATHWAYS, a pooled longitudinal cohort from six US cities. We estimated their air pollution exposure from age 1 to 3 years from validated spatiotemporal models of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3). Caregivers reported children's current wheeze and asthma at age 4–6 years. We used modified Poisson regression to estimate relative risks (RR) and 95% confidence intervals (CI), adjusting for child, maternal, and home environmental factors. We assessed effect modification by child sex and maternal history of asthma with interaction models.

Results: A total of 224 children had caregiver-reported bronchiolitis. Median (interquartile range) 2-year pollutant concentrations were 9.3 (7.8–9.9) $\mu g/m^3$ $PM_{2.5}$, 8.5 (6.4–9.9) ppb NO_2, and 26.6 (25.6–27.7) ppb O_3. RRs (CI) for current wheeze per 2-ppb higher O_3 were 1.3 (1.0–1.7) and 1.4 (1.1–1.8) for asthma. NO_2 was inversely associated with wheeze and asthma whereas associations with $PM_{2.5}$ were null. We observed interactions between NO_2 and $PM_{2.5}$ and maternal history of asthma, with lower risks observed among children with a maternal history of asthma.

Conclusion: Our results are consistent with the hypothesis that exposure to modest postnatal O_3 concentrations increases the risk of asthma and wheeze among the vulnerable subpopulation of infants experiencing bronchiolitis.

Keywords: Bronchiolitis, air pollution, asthma, wheeze

(*Epidemiology* 2023;34: 554–564)

Submitted July 13, 2022; accepted March 12, 2023

From the [a]Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, WA; [b]Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA; [c]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY; [d]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, NY; [e]Division of Allergy, Immunology, and Pulmonology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN; [f]Department of Health Policy, Vanderbilt University Medical Center, Nashville, TN; [g]Department of Biostatistics and Epidemiology, Environmental and Occupational Health Sciences Institute, Rutgers School of Public Health, Piscataway, NJ; [h]Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, NY; [i]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN; [j]Department of Pediatrics, School of Medicine, University of Washington, Seattle, WA; [k]Seattle Children's Research Institute, Seattle, WA; [l]Department of Psychiatry and Behavioral Sciences, School of Medicine, University of California, San Francisco, San Francisco, CA; [m]Department of Psychiatry and Pediatrics, School of Medicine, University of California, San Francisco, San Francisco, CA; [n]Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA; [o]Department of Medicine, School of Medicine, University of Washington; Seattle, WA.

The data utilized for this study are not publicly available but de-identified data may be available on request, subject to approval by the internal review board and under a formal data use agreement. Contact the corresponding author for more information.

ISSN: 1044-3983/23/344-554-564
DOI: 10.1097/EDE.0000000000001613

This research is supported by the ECHO-PATHWAYS consortium National Institutes of Health (NIH): UG3/UH3OD023271, R01HL109977, and P30ES007033. This article has been reviewed by PATHWAYS for scientific content and consistency of data interpretation with previous PATHWAYS publications. Air pollution models were developed under a STAR research assistance agreements RD831697 (MESA Air), RD-83830001 (MESA Air Next Stage), RD83479601 (UW Center for Clean Air Research), and R83374101 (MESA Coarse), awarded by the U.S. Environmental Protection Agency with additional grants R56ES026528, R01ES023500, and R01ES02588 from NIEHS and P01AG055367 from NIA. Funding was also provided by Kresge Foundation Grant No. 243365. CANDLE is funded by the Urban Child Institute, NIH R01HL109977 and NIH R01HL132338. TIDES was funded by NIH R01ES016863, NIH R01ES25169, and UG3/UH3OD023305. M.F.H. was supported in part by the UW NIEHS-sponsored Biostatistics, Epidemiologic, and Bioinformatic Training in Environmental Health (BEBTEH) Training Grant: NIEHS T32ES015459. E.S.B. was supported in part by the NIEHS-sponsored Rutgers Center for Environmental Exposure and Disease (CEED) grant: P30ES005022. REDCap was used for some data collection and is funded by the NCATS of the NIH: UL1 TR002319. This article has not been formally reviewed by the EPA. The views expressed in this document are solely those of the authors and the EPA does not endorse any products or commercial services mentioned in this publication.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

Correspondence: Logan C Dearborn, Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, 4225 Roosevelt Way NE, Seattle, WA 98105-6099. E-mail: dearbl@uw.edu.

Bronchiolitis is a common lower respiratory tract disease in infancy and is most often associated with the respiratory syncytial virus (RSV).[1] Evaluation and care for children with more severe symptoms typically involves outpatient assessment, emergency department care, or hospitalization.[2,3] Bronchiolitis is the leading cause of hospitalization in the first year of life in the US[1,4,5] and, in the first 2 years of life, is a well-established and strong risk factor for the later development of asthma during childhood.[3,5–8] Nearly 50% of infants with severe bronchiolitis (resulting in emergency department visits or hospitalization) later receive an asthma diagnosis,[7] although it remains unclear why only some children who experience clinically significant bronchiolitis in infancy develop asthma.

We hypothesized that air pollution may play an important but understudied role in the increased risk observed for infants with bronchiolitis. In general population studies, air pollutants including particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) have been associated with childhood asthma and wheeze.[9–11] Bronchiolitis infection in infancy with subsequent postnatal exposure to air pollution may influence lung development through shared mechanisms of pulmonary injury including disruption of the epithelial barrier,[12–16] induction of pulmonary inflammatory response,[12,17,18] airway remodeling,[19,20] and reduced alveolarization.[19,21,22]

Although there are numerous studies of air pollution and pediatric asthma, the previous literature on the unique vulnerability of infants who have experienced bronchiolitis is limited. Two analyses from the Children's Health and Environmental Research cohort in the Republic of Korea assessed the independent and combined effect of air pollutants (NO_2, CO, and O_3) or proxies for traffic exposure and bronchiolitis in infancy on the development of asthma in school-aged children.[23,24] Associations between pollutants and some asthma outcomes were seen for those children with a history of bronchiolitis and higher magnitudes were observed among individuals with both higher exposure to air pollutants[23] or traffic measures[24] and a history of bronchiolitis. A multicenter US study found similar results regarding recurrent wheeze at age 3 years among children hospitalized for bronchiolitis and living less than 100 meters from a major roadway.[25] These studies suggest the potential unique susceptibility of children who have experienced bronchiolitis to postnatal air pollution.

We sought to advance understanding of the role of air pollution as a modifiable risk factor for asthma and wheeze development in children who were diagnosed with bronchiolitis in the first year of life. We conducted this study in a US population and include the most common pollutants associated with asthma in children, $PM_{2.5}$, NO_2, and O_3.[26]

METHODS

Study Population

Eligible participants were selected from the Environmental Influences on Child Health Outcomes (ECHO) PATHWAYS Consortium, which consists of three prospective pregnancy cohorts: The Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) study, the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) study, and The Infant Development and the Environment Study (TIDES). All research activities for this analysis were approved by the University of Washington and site Institutional Review Boards.

ECHO-PATHWAYS cohorts have been described previously.[27–30] In brief, CANDLE recruited women aged 16–40 years and in the second trimester with singleton, low-medical-risk pregnancies between 2006 and 2011 within Shelby County (Memphis), Tennessee.[29] GAPPS recruited women aged 18 years or older who shared demographic and health information and biospecimens with the GAPPS biorepository.[30] Participants were enrolled from 2011 to 2016 at two hospitals in Seattle, Washington and one hospital in Yakima, Washington with follow-up ending just after birth. TIDES recruited low-medical-risk pregnant women aged 18 years or older in the first trimester from obstetrical clinics located in Minneapolis, Minnesota; Rochester, New York; San Francisco, California; and Seattle, Washington between 2010 and 2012.[28] Mother–child dyads were invited to enroll into ECHO-PATHWAYS for follow-up at the time of an age 8–9-year visit in CANDLE, age 4–6-year or 8–9-year visit in GAPPS, and an age 6-year visit in TIDES.

This analysis included subjects with a valid geocoded address at age 4 who answered affirmatively to the following question: During the first 12 months of (child's name) life, did a doctor or health care provider diagnose him or her with bronchiolitis, wheezing, or "RSV" (respiratory syncytial virus)? asked retrospectively at CANDLE age 8–9, TIDES age 6, or GAPPS 4–6 year visits. Of the 246 participants with reported bronchiolitis, 9 (3.7%) were excluded for missing addresses and 13 (5.2%) for missing an airway outcome survey, leaving an analytic sample of 224.

Air Pollution Estimates

We estimated $PM_{2.5}$ ($\mu g/m^3$), NO_2 (ppb), and O_3 (ppb) exposures using predictions of outdoor pollutant concentrations at the geocoded residential address collected at the age 4 visit using a fine-resolution spatiotemporal model. In brief, a combination of external research campaigns and regulatory monitors were utilized to predict concentrations in separate spatiotemporal models via the decomposition of the space-time field. Hundreds of geographic covariates measured at regulatory monitors and residential locations were included in the models using dimension reduction via partial least squares. Spatial smoothing via universal kriging and time trends estimated from observed time series were also utilized in the construction of the models.[31–33] We estimated each child's long-term exposure to $PM_{2.5}$, NO_2, and O_3 using the address reported at the age 4 visit. Modeled pollutant concentrations at a 2-week resolution were averaged

from the date of the first birthday to the third birthday to calculate a long-term (2-year) air pollutant exposure for each participant.

Asthma and Wheeze Outcomes

We characterized childhood asthma outcomes at the CANDLE 4–6-year-old, TIDES 4-year-old, and GAPPS 4–6-year-old visit using caregiver report on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[34–37] The primary outcomes include current wheeze defined as an affirmative to both "Has your child ever had wheezing or whistling in the chest?" and "Has your child ever had wheezing or whistling in the chest in the last 12 months?" and current asthma defined as an affirmative to at least two of the following "Has your child ever had asthma, current wheeze as defined above", and/or "In the past 12 months has your child used any type of medicines, liquids, puffers, or other medication for wheezing or asthma?." In a sensitivity analysis, a stricter definition of current asthma was employed that required an affirmative to "Has your child ever had asthma?" in addition to an affirmative response to either current wheeze and/or medication use for wheeze or asthma. We approached this as a sensitivity analysis because 9 (4.0%) subjects were missing data.

Covariates

We selected confounders and precision variables a priori owing to being known risk factors for the development of asthma and harmonized them across the three cohorts. Child factors include the age at outcome assessment (years), sex assigned at birth (male/female), child race (Black or African American/White/other race), season of birth (cold as October through March/warm as April through September), preterm birth (<37 weeks/≥37 weeks), birthweight (grams), duration of breastfeeding (never/<6 months/≥6 months), and date of birth (natural splines with 1 degree of freedom for each year). We included child race to attempt to account for differences in rates of asthma among Black children in the US and to address social, economic, and structural factors linked to racial disparities in asthma including exposure to stress and environmental toxicants.[38,39] We did not perform further disaggregation of child race, as it was limited by sample size. Maternal factors include education at the age 4–6 year visit (<high school [HS]/HS or equivalent/college or technical school/some graduate work or degree), household income at 4–6 year visit (USD, adjusted for region and inflation), history of asthma at age 4–6 year visit (yes/no), and smoking during pregnancy (yes/no). Home environment factors include household size at 4–6 year visit (number of adults and children), Neighborhood Deprivation Index (age 4 year address),[40,41] pregnancy cotinine concentration (ng/mL), postnatal exposure to secondhand smoke at age 4–6 year visit (yes/no), and pets in the home during the first 12 months of life (yes/no). A recruitment site was also included to account for unmeasured confounding.

Statistical analysis

Descriptive statistics were used to explore the study population characteristics. Pearson correlations between pollutants were calculated within metropolitan areas owing to the inclusion of site as a covariate. A staged modeling approach was used with modified multivariate Poisson regression with robust standard errors to calculate relative risks (RR) and 95% confidence intervals (CI) of air pollution exposure and airway outcomes.[42] Groups were compared using interquartile range (IQR)-based effect sizes of 2-, 5-, and 2-units higher air pollution exposure for $PM_{2.5}$, NO_2, and O_3, respectively. We used substantive knowledge from existing literature to develop three stages of models to explore the influence of increasing covariate adjustment. A minimally adjusted model incorporated basic demographics: age at outcome assessment, sex, season, year of birth, and site. A main model included additional variables that were major confounders or precision variables: race, preterm birth, birthweight, maternal education, income, maternal history of asthma status, smoking during pregnancy, Neighborhood Deprivation Index, cotinine, and reported secondhand smoke exposure in addition to the variables in the minimal model. An extended model additionally included potential confounders or precision variables: duration of breastfeeding, household size, and pets in the home during the first year of life. We assessed effect modification by child sex and maternal history of asthma using multiplicative interaction terms in the main model.

Sensitivity analyses included assessing the impact of multipollutant exposures using two methods. The first approach mutually adjusted for $PM_{2.5}$, NO_2, and O_3 on the relationship between air pollution and asthma and wheeze outcomes. The second post-hoc set of multipollutant models utilized generalized additive models (GAMs) as mixture models with two- or three-way interactions to assess the joint effects of pollutants using inspection of interactions. Single pollutant GAMs were also used to assess nonlinearity. Leave one cohort or site-out analyses were utilized to assess robustness to exclusion of cohorts and sites. Another sensitivity analysis used the outcomes of strict current asthma and combined current wheeze and current asthma; as part of this sensitivity analysis, we also reanalyzed current wheeze and current asthma among the subset of participants who were not missing a response to the strict asthma variable, allowing a more appropriate comparison among these findings using the same set of participants. We conducted an additional sensitivity analysis in which we adjusted models for air pollution exposure before bronchiolitis (pregnancy to age 1 year, estimated at the address reported at enrollment). All sensitivity analyses used the same covariates as in the main model and were conducted in *R* 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 2684 PATHWAYS Mother–child dyads, caregivers of 224 children, of which 137 were from CANDLE, 47 were from GAPPS, and 40 were from TIDES, reported bronchiolitis in their child's first year of life. Most children were male (62%) and had mothers without a history of asthma (72%). The mean age at asthma assessment was 4.7 (SD 0.9) years; 36% reported current asthma and 37% reported current wheeze (Table 1).

Median (IQR) 2-year pollutant (age 1–3 years) concentrations were 9.3 (7.8–9.9) μg/m^3 $PM_{2.5}$, 8.5 (6.4–9.9) ppb NO_2, and 26.6 (25.6–27.7) ppb O_3 (Table 2). Concentrations ranged from 3.7–11.6 μg/m^3 for $PM_{2.5}$, 2.0–16.1 ppb for NO_2, and 18.6–33.9 ppb for O_3. O_3 was negatively correlated with both NO_2 and $PM_{2.5}$ whereas NO_2 and $PM_{2.5}$ were positively correlated within most sites (Table 3).

TABLE 1. Study population characteristics (N = 224)

Characteristic[a]		
History of infant bronchiolitis, n(%)	224	100
CANDLE	137	61
Memphis, TN	137	61
GAPPS	47	21
Seattle, WA	18	8
Yakima, WA	29	13
TIDES	40	18
Minneapolis, MN	16	7
Rochester, NY	7	3
San Francisco, CA	10	5
Seattle, WA	7	3
Child characteristics		
Child sex assigned at birth, n(%)		
Male	139	62
Female	85	38
Child race, n(%)		
Asian	2	1
Black or African American	99	44
Multiple race	14	55
Other	3	1
White	104	46
Year of birth, n(%)		
2007	11	5
2008	23	10
2009	38	17
2010	38	17
2011	45	20
2012	37	17
2013	20	9
2014	12	5
Season of birth, n(%)		
Cold	97	43
Warm	127	57
Preterm birth (<37 weeks), n(%)		
Yes	32	14
No	190	85
Birthweight (g), mean (SD)	3238.7	654.4
Age at age 4–6 visit (years), mean (SD)	4.7	0.9
Breastfeeding duration, n(%)		
None	57	25
<6 months	127	57
>6 months	38	17
Maternal characteristics		
Education, n(%)		
<High school diploma	12	5
High school diploma or equivalent	65	29
College or technical school	95	42
Some graduate work or degree	52	23
Income adjusted for region and inflation, mean (SD)	59068	50911
Maternal history of asthma, n(%)		
Yes	62	28
No	161	72
Smoking during pregnancy, n(%)		
Yes	15	7
No	206	92
Home environmental factors		
Household size, mean (SD)	4.5	1.4
Neighborhood Deprivation Index, mean (SD)	0.2	0.8
Cotinine (ng/mL), mean (SD)	54.3	261.3
Reported secondhand smoke exposure, n(%)		
Yes	55	25
No	168	75
Pets in home in early life, n(%)		
Yes	144	64
No	78	35
Child airway outcomes		
Current wheeze, n(%)[b]		
Yes	82	37
No	141	63
Current asthma, n(%)[c]		
Yes	80	36
No	144	64
Strict current asthma, n(%)[d]		
Yes	67	30
No	148	66
Combined current wheeze and asthma, n(%)[e]		
Yes	88	39
No	136	61

[a]Number missing for individual variables include: child race (2), preterm birth (2), birthweight (1), breastfeeding duration (2), income (6), maternal history of asthma (1), prenatal smoking (3), household size (2), cotinine (3), reported postnatal secondhand smoke exposure (1), pets in the home (2), current wheeze (1), and strict current asthma (9).

[b]Current wheeze: defined as yes to both of the following items: "Has your child ever had wheezing or whistling in the chest?" yes/no and if yes: "Has your child ever had wheezing or whistling in the chest in the last 12months?" (yes/no).

[c]Current asthma: defined as yes to at least two of the following items: Ever asthma: "Has your child ever had asthma?" (yes/no), Current wheeze (defined above), and/or Medication use: "In the past 12 months has your child used any type of medicines, liquids, puffers or other medication for wheezing or asthma?" (yes/no).

[d]Strict current asthma: defined as Ever asthma (defined above) and either Current wheeze (defined above) or Medication use (defined above).

[e]Combined current wheeze and asthma: defined as yes to either current wheeze (defined above) or current asthma (defined above).

CANDLE, Conditions Affecting Neurocognitive Development in Early Childhood; GAPPS, the Global Alliance to Prevent Prematurity and Stillbirth; TIDES, the Infant Development and the Environment Study.

TABLE 2. Median (interquartile range) of air pollution exposures by cohort and site

Study Site	N	NO_2 (ppb)	O_3 (ppb)	$PM_{2.5}$ (μg/m³)
Overall	224	8.5 (6.4–9.9)	26.6 (25.6–27.7)	9.3 (7.8–9.9)
CANDLE[a]				
Memphis, TN	137	9.3 (7.6–10.6)	27.0 (26.1–27.9)	9.7 (9.3–10.2)
GAPPS[b]				
Seattle, WA	18	7.4 (6.0–8.6)	20.5 (20.1–21.7)	5.1 (4.8–5.6)
Yakima, WA	29	4.2 (3.2–5.6)	26.7 (25.7–27.6)	6.5 (4.9–7.5)
TIDES[c]				
Minneapolis, MN	16	9.1 (7.9–9.6)	25.7 (25.2–27.3)	8.2 (8.0–8.6)
Rochester, NY	7	7.0 (6.1–7.3)	26.2 (26.0–26.5)	7.5 (7.3–7.8)
San Francisco, CA	10	8.3 (7.2–10.8)	25.8 (22.3–26.3)	9.7 (8.9–10.1)
Seattle, WA	7	9.3 (8.8–10.0)	19.7 (19.5–24.0)	6.2 (5.9–7.0)

[a]Years of exposure for the CANDLE cohort: 2008–2014.
[b]Years of exposure for the GAPPS cohort: 2012–2017.
[c]Years of exposure for the TIDES cohort: 2012–2014.
CANDLE, Conditions Affecting Neurocognitive Development in Early Childhood; GAPPS, the Global Alliance to Prevent Prematurity and Stillbirth; TIDES, the Infant Development and the Environment Study.

TABLE 3. Pearson correlation of air pollution exposures within sites

Study Site	N	Pollutant	NO_2	$PM_{2.5}$	O_3
CANDLE					
Memphis, TN	137	NO_2	1		
		$PM_{2.5}$	0.39	1	
		O_3	−0.65	−0.36	1
GAPPS					
Seattle, WA	18	NO_2	1		
		$PM_{2.5}$	0.00	1	
		O_3	−0.41	0.18	1
Yakima, WA	29	NO_2	1		
		$PM_{2.5}$	0.77	1	
		O_3	−0.49	−0.35	1
TIDES					
Minneapolis, MN	16	NO_2	1		
		$PM_{2.5}$	0.76	1	
		O_3	−0.56	−0.50	1
Rochester, NY	7	NO_2	1		
		$PM_{2.5}$	−0.85	1	
		O_3	−0.95	0.95	1
San Francisco, CA	10	NO_2	1		
		$PM_{2.5}$	0.56	1	
		O_3	−0.34	0.34	1
Seattle, WA	7	NO_2	1		
		$PM_{2.5}$	0.92	1	
		O_3	0.02	−0.17	1

CANDLE, Conditions Affecting Neurocognitive Development in Early Childhood; GAPPS, the Global Alliance to Prevent Prematurity and Stillbirth; TIDES, the Infant Development and the Environment Study.

In the main model (Figure 1), adjusted RRs for current wheeze and current asthma were 1.3 (95% CI = 1.0, 1.7) and 1.4 (95% CI = 1.1, 1.8), respectively, per 2-ppb higher postnatal O_3. A 5-ppb increase in NO_2 was inversely associated with both current wheeze (RR = 0.58; 95% CI = 0.39, 0.87) and current asthma (RR = 0.58; 95% CI = 0.41, 0.88) and the effect estimates for a 2-μg/m³ increase in $PM_{2.5}$ were imprecise (RR = 0.64; 95% CI = 0.32, 1.3 for current wheeze; RR = 0.66; 95% CI = 0.30, 1.4 for current asthma). Additional covariate adjustment did not substantially change the results.

NO_2 and $PM_{2.5}$ both showed interaction by the maternal history of asthma on child asthma outcomes (Figure 2). We observed an inverse association only among children with a maternal history of asthma; effect estimates were attenuated and CIs included the null for children without a maternal history of asthma. We observed no effect modification by the maternal history of asthma status for O_3 nor for any pollutant by child sex (Figure 3).

The results from the multipollutant models, mutually adjusted for $PM_{2.5}$, NO_2, and O_3, were similar to the main findings for O_3 but were different for $PM_{2.5}$ and NO_2. The RR for O_3 for current wheeze was 1.1 (95% CI = 0.77, 1.6) and 1.3 (95% CI = 0.87, 1.8) for current asthma. Estimated coefficients for both NO_2 and $PM_{2.5}$ were attenuated after adjustment for other pollutants; estimates for NO_2 were 0.93 (95% CI = 0.82, 1.1) for the current wheeze and 0.95 (95% CI = 0.84, 1.1) for current asthma and estimates for $PM_{2.5}$ were 0.95 (95% CI = 0.62, 1.5) for current wheeze and 1.0 (95% CI = 0.62, 1.6) for current asthma (Figure 4). No pollutants showed indication of nonlinear response in single pollutant GAMs (eFigure 1, http://links.lww.com/EDE/C24) or interactions between pairs of pollutants (eFigure 2, http://links.lww.com/EDE/C24). In contrast, the GAM assessing the 3-way interaction between the pollutants was suggestive of differences in associations between NO_2 and O_3 and current asthma, depending on the concentration of $PM_{2.5}$ (eFigure 3, http://links.lww.com/EDE/C24). When $PM_{2.5}$ was held at 4.7 μg/m³ higher levels of NO_2 and O_3 were associated with increased risk, whereas when $PM_{2.5}$ was held at 10.6 μg/m³ higher levels of NO_2 and O_3 were associated with lower risk.

Results from sensitivity analyses where one site or cohort was excluded from the main model indicate that the effect estimates were stable whereas the precision was reduced as evidenced by widened confidence intervals when CANDLE was omitted (eFigure 4, http://links.lww.com/EDE/C24).

Estimates of risk for strict current asthma as an outcome (n = 215) were imprecise whereas estimates of combined current wheeze and current asthma were similar to the main findings for O_3 but were slightly attenuated for NO_2 and $PM_{2.5}$ (Table 4). Results of current wheeze and current asthma within the subset population were near identical to the findings in the primary analysis although the strict current asthma subset results were more attenuated relative to overall current wheeze and current asthma for both NO_2 and $PM_{2.5}$ (Table 4). The additional adjustment for pregnancy and infancy concentrations of air pollution did not substantially change estimates from the main analysis (Table 4).

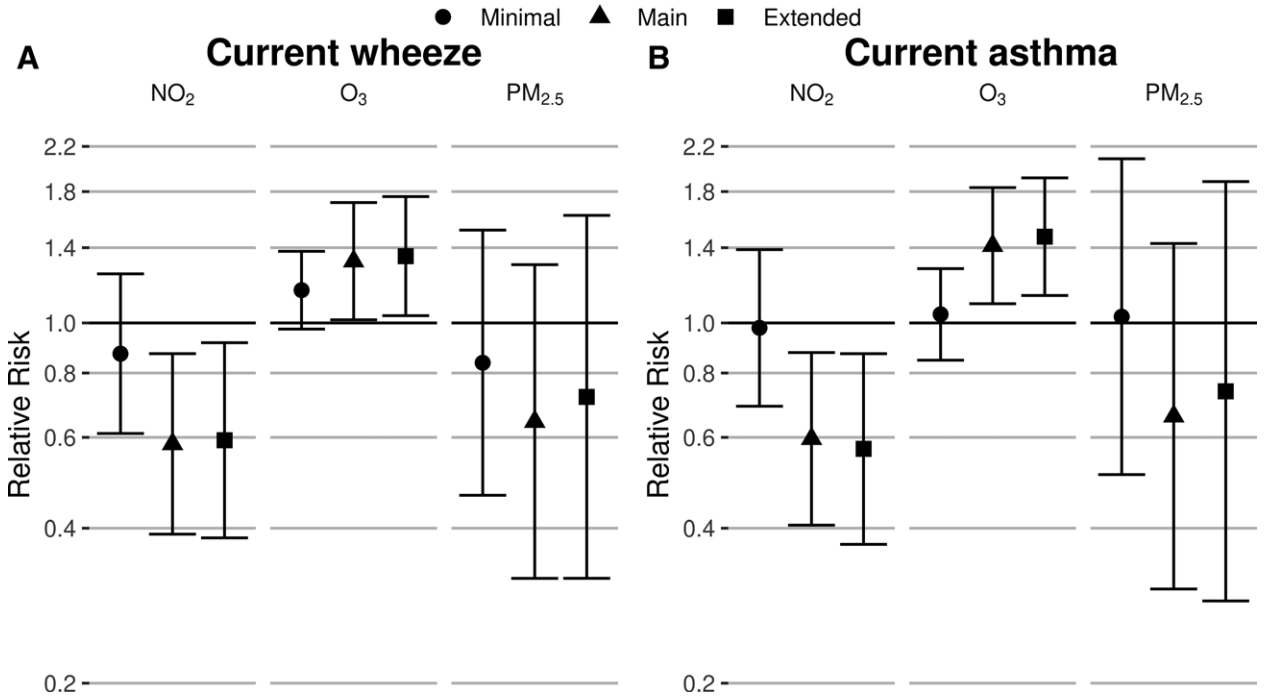

FIGURE 1. Associations between air pollution exposure and (A) current wheeze and (B) current asthma at age 4–6 years among infants with bronchiolitis in the first year of life. Relative risks and 95% confidence intervals are presented for 2-unit differences in particulate matter 2.5 ($PM_{2.5}$) and ozone (O_3) and 5-unit differences in nitrogen dioxide (NO_2). Minimal models were adjusted for age at outcome assessment, sex, season, year of birth, and site; main models additionally included race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, neighborhood deprivation index, cotinine, and reported postnatal secondhand smoke exposure; extended models additionally included duration of breastfeeding, household size, and pets in the home during the first year of life.

DISCUSSION

Bronchiolitis is common in infancy and a recognized risk factor for childhood asthma and wheeze, yet not all infants with bronchiolitis later develop asthma. Findings from this prospective cohort study among children with bronchiolitis in infancy suggest that postbronchiolitis air pollution exposure may influence the subsequent risk of wheeze and asthma in early childhood. As expected, we found a high prevalence of asthma and wheeze among our study population. We observed a higher risk for both asthma and wheeze at age 4–6 years for those with higher ambient O_3 in early childhood, consistent with our hypothesis. However, ambient $PM_{2.5}$ and NO_2 were not observed to increase the risk for either outcome in our study.

There are several potential pathways by which air pollutants may influence wheeze and asthma development after a bronchiolitis infection. Disruption of the lung epithelium after infection[12,13] alters deposition and translocation of inhaled particles that is thought to be associated with the risk of persistent wheeze.[12,14] Air pollutants have also been associated with altering barrier functions in the human lung epithelium, potentially furthering this risk.[15,16] Another pathway reflects the observed wheezy phenotype via the dysregulation of inflammation and pulmonary immune response associated with lower respiratory virus infection in early life.[12,17] This phenotype is then thought to progress to recurrent wheeze and asthma in childhood via airway remodeling and decreased alveolarization.[19] In animal models, air pollutants have also been associated with alveolar morphogensis,[21,22] airway remodeling,[20] changes in the inflammatory response,[18] and pulmonary development disruption[43] after chronic exposure, indicating that postbronchiolitis exposure may further contribute to the progression to recurrent asthma and wheeze within this vulnerable population.

Some, but not all, prior studies of general pediatric populations have identified childhood exposure to O_3 as a risk factor for asthma.[9,44–47] We found a consistently higher risk for both current wheeze and current asthma among children who had a history of infant bronchiolitis with higher exposure to O_3. All estimated O_3 concentrations were below US Environmental Protection Agency (EPA) regulatory exposure limits, with similar variability to previous studies in North America.[45,46] Kim et al.[23] also reported a higher prevalence of similar outcomes among school-aged children in Korea with both history of bronchiolitis in infancy and higher O_3, defined as above the sample mean (concentrations not provided). Their analysis included children who did not have bronchiolitis in infancy and reported a high odds ratio for children with both

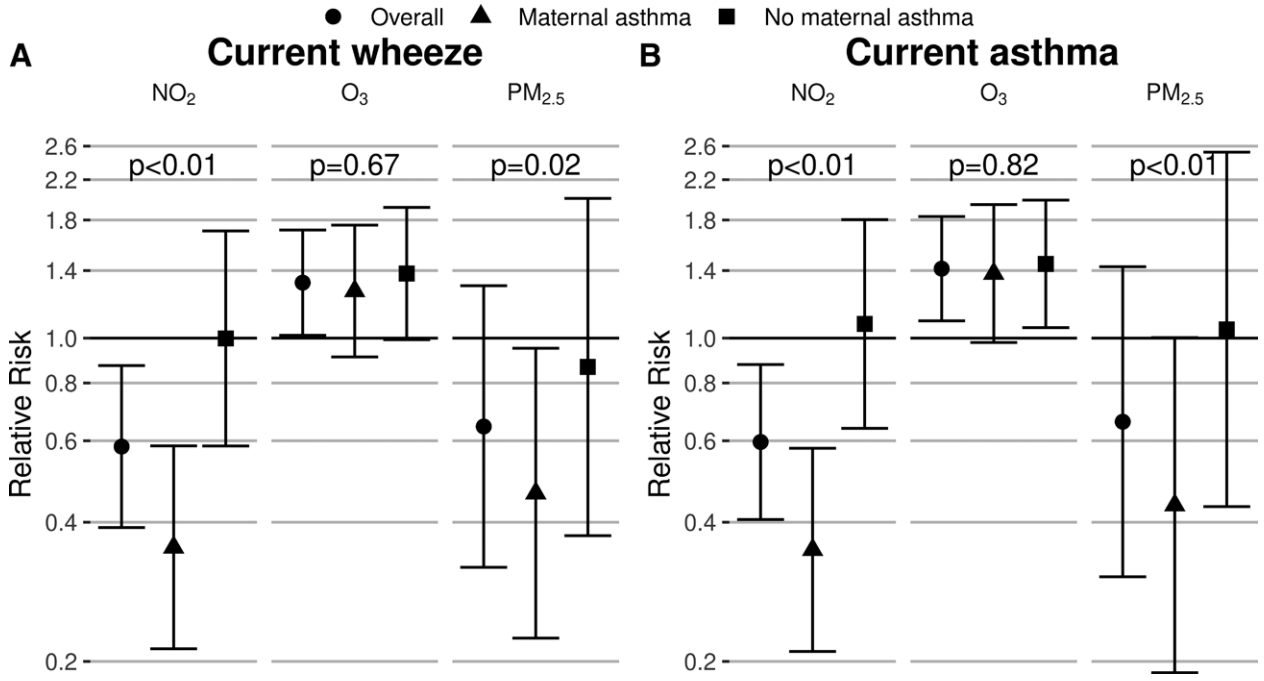

FIGURE 2. Associations between air pollution exposure and asthma risk at age 4–6 years by the maternal history of asthma status among infants with bronchiolitis in the first year of life. Relative risks and 95% confidence intervals are presented for 2-unit differences in particulate matter 2.5 ($PM_{2.5}$) and ozone (O_3) and 5-unit differences in nitrogen dioxide (NO_2). *P*-values shown are for the interaction term between air pollution and maternal history of asthma. Models were adjusted for age at outcome assessment, sex, season, year of birth, site, race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, neighborhood deprivation index, cotinine, and reported postnatal secondhand smoke exposure.

risk factors compared to those with neither current wheeze nor current asthma.[23]

We hypothesized that we would observe an adverse effect of $PM_{2.5}$ as well, given evidence for $PM_{2.5}$ on asthma risk in many general pediatric populations.[9–11,44,45,47] However, we found no association between higher $PM_{2.5}$ exposure and risk of current wheeze or current asthma at age 4–6 years among those with bronchiolitis. Our estimates contained large CIs and $PM_{2.5}$ concentrations and variability were modest and below annual EPA regulatory limits. We identified no other studies that examined the effects of exposure to $PM_{2.5}$ among children with bronchiolitis. In studies of traffic exposure, an important source of both $PM_{2.5}$ and NO_2, new wheezing and new physician diagnosis of asthma were more common among children who had both a history of bronchiolitis and traffic exposure compared with children who had neither risk factor[24] as well as among those with severe bronchiolitis who lived less than 100 meters from a major roadway with recurrent wheeze.[25] However, relatively small sample sizes of individuals with both bronchiolitis and higher air pollution lead to estimated effects with wide CIs.[23,24] Future studies with larger sample sizes and more variable exposures to $PM_{2.5}$ may offer more precise estimates for this pollutant.

In our analysis of the potential effect modification of $PM_{2.5}$ exposure on asthma and wheeze by the maternal history of asthma, we observed reduced risk among mothers with a history of asthma and null estimates among those without. A cautious interpretation is warranted owing to the small sizes of the respective groups in this exploratory analysis. In addition to unmeasured confounding, one speculation for this unanticipated observation is potential differences in behaviors between mothers based on their own asthma history. For example, those with asthma in the setting of higher air pollution exposure may be more inclined to limit their children's exposures to asthma risk factors through behaviors such as reducing indoor air contaminants that influence indoor air quality. Although we were able to control for exposure to household pets and tobacco smoke, we could not characterize cleaning products or home pesticide use, the presence of mold or moisture damage, candles or gas stove use, or cleaning practices to control dust.

Contrary to our hypothesis, we observed higher NO_2 exposure associated with a lower risk of both current asthma and wheeze in the main models. In general population studies, higher NO_2 exposure postnatally has consistently been associated with a higher risk of asthma and wheeze development.[9,11,23,44,45,47,48] Although our estimated NO_2 concentrations were all below annual EPA regulatory limits in our study, they were similar to those reported in these general population studies. Our results contrast with the Korea-based Children's Health and Environmental Research cohort, where NO_2 in the presence of bronchiolitis was associated with a higher

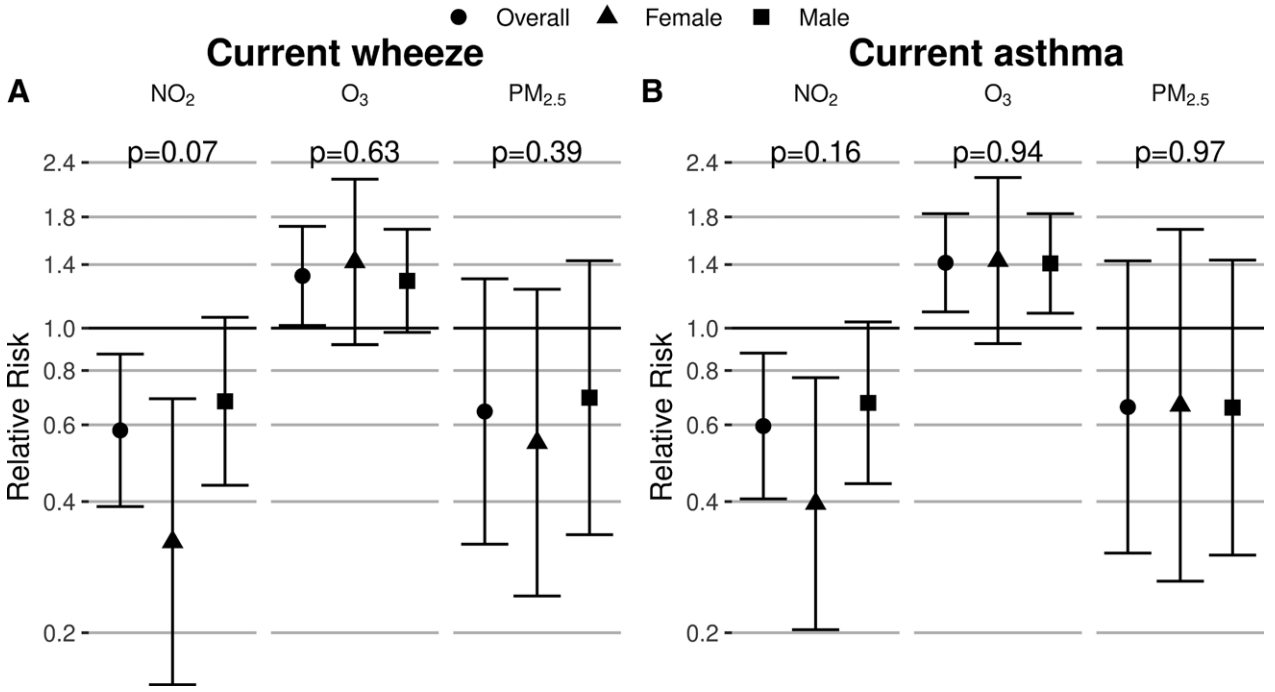

FIGURE 3. Associations between air pollution exposure and (A) current wheeze and (B) current asthma at age 4–6 years by child sex among infants with bronchiolitis in the first year of life. Relative risks and 95% confidence intervals are presented for 5-unit differences in nitrogen dioxide (NO_2) and 2-unit differences in ozone (O_3) and fine particulate matter ($PM_{2.5}$). *P*-values shown are for the interaction term between air pollution and child sex. Models were adjusted for age at outcome assessment, sex, season, year of birth, site, race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, neighborhood deprivation index, cotinine, and reported postnatal secondhand smoke exposure.

risk of asthma and wheeze.[23] We again observed reduced effect estimates only among those with a maternal history of asthma and higher NO_2. As described above, explanations for this may include unmeasured confounding as well as differences in behaviors where mothers with asthma are more precautious regarding exposure to sources of indoor air pollutants. Perhaps more importantly, concentrations of ambient NO_2 and O_3 are often negatively correlated owing to well-described atmospheric chemical reactions where NO_2 reacts and is consumed in the formation of ground-level O_3.[49] Others have observed negative correlations between NO_2 and O_3 in epidemiologic analysis[46] as well as observed effect estimates of NO_2 and O_3 in opposite directions.[44,46,50] It is possible the lower risk observed with higher NO_2 exposure reflects a proxy for the adverse impact of O_3 exposure in our study, that is, the "protective" findings of higher NO_2 may be demonstrating lesser risk for areas with lower O_3 concentrations. This is supported by our sensitivity analyses of mutual adjustment for $PM_{2.5}$, NO_2, and O_3 that resulted in a shift to null effect estimates for NO_2 whereas estimates for O_3 remain similar to the single-pollutant analysis. Additionally, the three-way interaction GAM mixture model suggested the possibility of complex interactions between exposures to $PM_{2.5}$, NO_2, and O_3, which warrant exploration in future studies. However, the sample size in this analysis limits this interpretation owing to the possibility for spurious associations. We did not detect effect modification by child sex for any pollutants.

Asthma is an imprecise diagnosis in early childhood[51] and we rely on parent report of outcomes, although using a well-validated instrument.[34] We attempt to approximate symptomatic asthma diagnosis using strictly defined current asthma, which is of major public health relevance,[52] while we examined combined asthma and wheeze owing to the overlap in characteristics between the primary outcomes in young children. In the analysis of strictly defined current asthma, which required a recognition of the term "asthma" in defining the child's health history, estimates were nearly the same for O_3 whereas were more attenuated for NO_2 and $PM_{2.5}$. Estimates of combined current wheeze and asthma were not substantially different from the primary analysis for any pollutants.

This analysis has notable strengths including the utilization of a pooled and geographically diverse population that enhances the generalizability of the results. Additionally, we estimated air pollution exposures from validated spatiotemporal models with fine-scale prediction enabling granular characterization at participant residences and consideration of timing relevant to a conceptual model of air pollution effects after bronchiolitis in the first year of life. Additionally, robust adjustment for key confounding and precision variables was possible in these well-characterized cohorts. Unlike prior

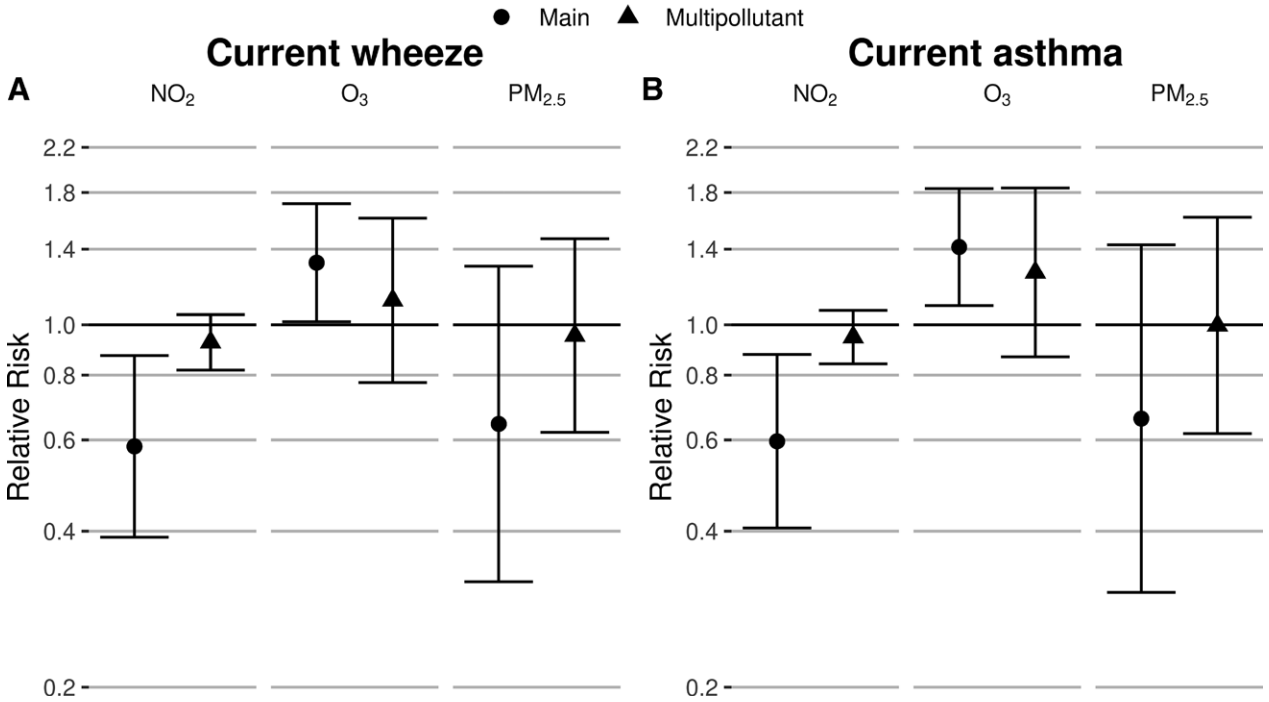

FIGURE 4. Associations between air pollutant exposure and (A) current wheeze and (B) current asthma at age 4–6 after simultaneous adjustment for nitrogen dioxide (NO_2), ozone (O_3), and fine particulate matter ($PM_{2.5}$) among infants with bronchiolitis in the first year of life. The multipollutant model simultaneously adjusted for all three pollutants. Relative risks and 95% confidence intervals for current wheeze and current asthma are reported per 5 ppb NO_2, 2 ppb O_3, or 2 μg/m^3 $PM_{2.5}$, as in the main model. Models were also adjusted for age at outcome assessment, sex, season, year of birth, site, race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, neighborhood deprivation index, cotinine, and reported postnatal secondhand smoke exposure.

TABLE 4. Sensitivity analysis of associations with air pollution exposure using strict current asthma and combined current wheeze and asthma outcomes and co-adjustment for pre-bronchiolitis air pollution

Outcome[a]	NO_2 RR (95% CI)	O_3 RR (95% CI)	$PM_{2.5}$ RR (95% CI)
Strict current asthma[b]	0.78 (0.50–1.2)	1.3 (0.97–1.8)	0.87 (0.27–2.8)
Combined current wheeze and asthma[b]	0.62 (0.42–0.90)	1.3 (1.0–1.7)	0.75 (0.40–1.5)
Current asthma[b]	0.62 (0.42–0.91)	1.4 (1.1–1.8)	0.65 (0.29–1.5)
Current wheeze[b]	0.60 (0.39–0.90)	1.3 (1.0–1.7)	0.74 (0.35–1.6)
Adjusted for pregnancy- age 1 air pollution exposure			
Current asthma[c]	0.51 (0.34–0.76)	1.3 (1.0–1.7)	0.61 (0.28–1.3)
Current wheeze[c]	0.51 (0.33–0.77)	1.3 (0.96–1.6)	0.58 (0.31–1.1)

[a]Relative risks are per 5 ppb NO_2, 2 ppb O_3, and 2 μg/m^3 $PM_{2.5}$ as in the main model and are adjusted for age at outcome assessment, sex, season, year of birth, site, race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, neighborhood deprivation index, cotinine, and reported postnatal secondhand smoke exposure.
[b]Sample restricted to participants not missing strict current asthma; sample size reduced to 215 for all outcomes.
[c]Sample using full analytic set of 224 participants.

research on air pollution and child health effects, this study focuses specifically on an important vulnerable subpopulation and allowed examination of effect modification in this group by child sex and maternal history of asthma status.

Some limitations of note include the nonspecific phrasing of the survey question used for inclusion that could conflate bronchiolitis with some non-bronchiolitis-caused wheezing as well as the lack of information on the severity of infection. This could bias results towards the null owing to the potential of not capturing exclusively those who truly had bronchiolitis or if air pollution effects were only evident among more severe infections, such as hospitalized cases. The outcome definitions, as in many studies of air pollution and child asthma, relied on caregiver report, which may have led to outcome misclassification based on the ability of a caregiver to recognize wheeze in their children or access to health care and understanding of an asthma

diagnosis. As noted above, the questions used were derived from the validated and widely applied ISAAC survey.[53] The full address history from birth to age 4 years was not available for this study sample. The inability to capture ambient exposures at all residences and nonresidential locations during the exposure window as well as potential indoor air factors and pollutants at home may additionally introduce some exposure misclassification. As previously discussed, biased exposure assessment could occur if a maternal history of asthma influences other known asthma risk factors which are not characterized. Finally, the sample size of children with bronchiolitis available in our pooled analysis, whereas greater than the prior literature, was relatively modest limiting the precision of our estimates.

In conclusion, the high burden of subsequent asthma development among infants with bronchiolitis underscores the public health importance of understanding potentially modifiable risk factors such as childhood exposure to air pollution. Despite relatively modest O_3 concentrations estimated in the study population, our results are consistent with the hypothesis that small increases in this pollutant may be of particular concern for the development of asthma among this subpopulation. Further exploration of air pollution effects on children after bronchiolitis infection is warranted and should consider modifying factors including genetic susceptibility and bronchiolitis severity.

ACKNOWLEDGMENTS

This research was conducted using specimens and data collected and stored on behalf of the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) Repository.

We acknowledge the contributions of the CANDLE, GAPPS and TIDES participants and families, the cohort research staff and Dr. Shanna Swan, and the UW data team.

REFERENCES

1. Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *Lancet*. 2017;389:211–224.
2. Respiratory Syncytial Virus (RSV). *NIH: National Institute of Allergy and Infectious Diseases*. Available at: https://www.niaid.nih.gov/diseases-conditions/respiratory-syncytial-virus-rsv. Accessed April 10, 2022.
3. Carroll KN, Wu P, Gebretsadik T, et al. The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. *J Allergy Clin Immunol*. 2009;123:1055–1061.e1.
4. Koponen P, Helminen M, Paassilta M, Luukkaala T, Korppi M. Preschool asthma after bronchiolitis in infancy. *Eur Respir J*. 2012;39:76–80.
5. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC Pediatr*. 2013;13:1–9.
6. Beigelman A, Bacharier LB. The role of early life viral bronchiolitis in the inception of asthma. *Curr Opin Allergy Clin Immunol*. 2013;13:211–216.
7. Bacharier LB, Cohen R, Schweiger T, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol*. 2012;130:91–100.e3.
8. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax*. 2010;65:1045–1052.
9. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *The Lancet*. 2014;383:1581–1592.
10. Kravitz-Wirtz N, Teixeira S, Hajat A, Woo B, Crowder K, Takeuchi D. Early-life air pollution exposure, neighborhood poverty, and childhood asthma in the United States, 1990–2014. *Int J Environ Res Public Health*. 2018;15:1114.
11. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. *Environ Int*. 2017;100:1–31.
12. Smallcombe CC, Linfield DT, Harford TJ, et al. Disruption of the airway epithelial barrier in a murine model of respiratory syncytial virus infection. *Am J Physiol Lung Cell Mol Physiol*. 2019;316:L358–L368.
13. Wong JYW, Rutman A, O'Callaghan C. Recovery of the ciliated epithelium following acute bronchiolitis in infancy. *Thorax*. 2005;60:582–587.
14. Sajjan U, Wang Q, Zhao Y, Gruenert DC, Hershenson MB. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. *Am J Respir Crit Care Med*. 2008;178:1271–1281.
15. Niu Y, Chen R, Wang C, et al. Ozone exposure leads to changes in airway permeability, microbiota and metabolome: a randomised, double-blind, crossover trial. *Eur Respir J*. 2020;56:2000165.
16. Zhao C, Wang Y, Su Z, et al. Respiratory exposure to PM2.5 soluble extract disrupts mucosal barrier function and promotes the development of experimental asthma. *Sci Total Environ*. 2020;730:139145.
17. Moreno-Solís G, Torres-Borrego J, de la Torre-Aguilar MJ, Fernández-Gutiérrez F, Llorente-Cantarero FJ, Pérez-Navero JL. Analysis of the local and systemic inflammatory response in hospitalized infants with respiratory syncitial virus bronchiolitis. *Allergol Immunopathol (Madr)*. 2015;43:264–271.
18. Gabehart K, Correll KA, Yang J, et al. Transcriptome profiling of the newborn mouse lung response to acute ozone exposure. *Toxicol Sci*. 2014;138:175–190.
19. Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF. Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol*. 2005;115:668–674.
20. Michaudel C, Fauconnier L, Julé Y, Ryffel B. Functional and morphological differences of the lung upon acute and chronic ozone exposure in mice. *Sci Rep*. 2018;8:10611.
21. Avdalovic M, Tyler NK, Putney L, et al. Ozone exposure during the early postnatal period alters the timing and pattern of alveolar growth and development in nonhuman primates. *Anat Rec (Hoboken)*. 2012;295:1707–1716.
22. de Barros Mendes LT, Groth EE, Veras M, et al. Pre- and postnatal exposure of mice to concentrated urban PM2.5 decreases the number of alveoli and leads to altered lung function at an early stage of life. *Environ Pollut*. 2018;241:511.
23. Kim BJ, Seo JH, Jung YH, et al. Air pollution interacts with past episodes of bronchiolitis in the development of asthma. *Allergy*. 2013;68:517–523.
24. Lee JY, Leem JH, Kim HC, et al. Effects of traffic-related air pollution on susceptibility to infantile bronchiolitis and childhood asthma: a cohort study in Korea. *J Asthma*. 2018;55:223–230.
25. Freid RD, Qi Y, Espinola JA, et al. Proximity to major roads and risks of childhood recurrent wheeze and asthma in a severe bronchiolitis cohort. *Int J Environ Res Public Health*. 2021;18:4197.
26. Brumberg HL, Karr CJ; Council on Environmental Health. Ambient air pollution: health hazards to children. *Pediatrics*. 2021;147:e2021051484.
27. Wilson K, Gebretsadik T, Adgent MA, et al. The association between duration of breastfeeding and childhood asthma outcomes. *Ann Allergy Asthma Immunol*. 2022;129:205–211.
28. Barrett ES, Sathyanarayana S, Janssen S, et al. Environmental health attitudes and behaviors: findings from a large pregnancy cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2014;176:119–125.
29. Sontag-Padilla L, Burns RM, Shih RA, et al. *The Urban Child Institute CANDLE Study: Methodological Overview and Baseline Sample Description*. Available at: https://www.rand.org/pubs/research_reports/RR1336.html. Accessed April 19, 2022.
30. Lewinn KZ, Karr CJ, Hazlehurst M, et al. Cohort profile: the ECHO prenatal and early childhood pathways to health consortium (ECHO-PATHWAYS). *BMJ Open*. 2022;12:e064288e064288.
31. Wang M, Sampson P, Bechle M, Marshall J, Vedal S, Kaufman J. *National PM2.5 and NO2 spatiotemporal models integrating intensive monitoring data and satellite-derived land use regression in a universal kriging*

framework in the United States: 1999-2016. ISEE Conference Abstract. Published online 2018.
32. Kirwa K, Szpiro AA, Sheppard L, et al. Fine-Scale air pollution models for epidemiologic research: insights from approaches developed in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Curr Environ Health Rep*. *2021*;8:1132113–1132126.
33. Keller JP, Olives C, Kim SY, et al. A Unified spatiotemporal modeling approach for predicting concentrations of multiple air pollutants in the multi-ethnic study of atherosclerosis and air pollution. *Environ Health Perspect*. 2015;123:301–309.
34. ISAAC. *The International Study of Asthma and Allergies in Childhood*. Available at: http://isaac.auckland.ac.nz/. Accessed April 25, 2022.
35. Adgent MA, Carroll KN, Hazlehurst MF, et al. A combined cohort analysis of prenatal exposure to phthalate mixtures and childhood asthma. *Environ Int*. 2020;143:105970.
36. Hazlehurst MF, Carroll KN, Loftus CT, et al. Maternal exposure to PM2.5 during pregnancy and asthma risk in early childhood. *Environ Epidemiol*. 2021;5:e130.
37. Rosa MJ, Hartman TJ, Adgent M, et al. Prenatal polyunsaturated fatty acids and child asthma: effect modification by maternal asthma and child sex. *J Allergy Clin Immunol*. 2020;145:800–807.e4.
38. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breysse PN. Vital Signs: asthma in children—United States, 2001–2016. *MMWR Morb Mortal Wkly Rep*. 2019;67:149–155.
39. Martinez A, de la Rosa R, Mujahid M, Thakur N. Structural racism and its pathways to asthma and atopic dermatitis. *J Allergy Clin Immunol*. 2021;148:1112–1120.
40. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health*. 2006;83:1041–1062.
41. Quraishi SM, Hazlehurst MF, Loftus CT, et al. Association of prenatal exposure to ambient air pollution with adverse birth outcomes and effect modification by socioeconomic factors. *Environ Res*. 2022;212:113571.
42. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702–706.
43. Fanucchi M, Plopper CG, Evans MJ, et al. Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. *Am J Physiol Lung Cell Mol Physiol*. 2006;291:644–650.
44. Holst GJ, Pedersen CB, Thygesen M, et al. Air pollution and family related determinants of asthma onset and persistent wheezing in children: nationwide case-control study. *BMJ*. 2020;370:2791.
45. Tétreault LF, Doucet M, Gamache P, et al. Childhood exposure to ambient air pollutants and the onset of asthma: an administrative cohort study in Québec. *Environ Health Perspect*. 2016;124:1276–1282.
46. To T, Zhu J, Terebessy E, et al. Does exposure to air pollution increase the risk of acute care in young children with asthma? An Ontario, Canada study. *Environ Res*. 2021;199:111302.
47. Dong GH, Chen T, Liu MM, et al. Gender differences and effect of air pollution on asthma in children with and without allergic predisposition: northeast Chinese children health study. *PLoS One*. 2011;6:e22470.
48. Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. *Environ Health Perspect*. 2008;116:14331433.–143311438.
49. Hagenbjörk A, Malmqvist E, Mattisson K, Sommar NJ, Modig L. The spatial variation of O_3,NO,$NO_2$and NOx and the relation between them in two Swedish cities. *Environ Monit Assess*. 2017;189:1–12.
50. Zoran MA, Savastru RS, Savastru DM, Tautan MN. Assessing the relationship between ground levels of ozone (O_3) and nitrogen dioxide (NO_2) with coronavirus (COVID-19) in Milan, Italy. *Sci Total Environ*. 2020;740:140005.
51. Bakirtas A. Diagnostic challenges of childhood asthma. *Curr Opin Pulm Med*. 2017;23:27–33.
52. Bousquet J, Bousquet PJ, Godard P, Daures JP. The public health implications of asthma. *Bull World Health Organ*. 2005;83:548–554.
53. Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. NCBI Bookshelf. Available at: https://www.ncbi.nlm.nih.gov/books/NBK7232/. Accessed April 19, 2022