Role of air pollution in development of asthma among children with a history of bronchiolitis in infancy

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Abstract

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Background

Few studies have identified potential modifiable risk factors for the development of asthma among infants who experience bronchiolitis. Air pollution has been associated with child asthma development and may be particularly important for this high-risk group.

Objectives

We assessed the role of early life air pollution on asthma and wheeze among children age 4-6 years with a history of bronchiolitis in the first year of life.

Methods

Participants were drawn from the ECHO PATHWAYS consortium, a pooled longitudinal pregnancy cohort (N=2684 mother-child dyads) from six cities across the United States. Child participants whose caregiver reported physician-diagnosed bronchiolitis in the first year of life (asked at the age 4-6 year follow up visit) were eligible for this analysis. The International Study

of Asthma and Allergies in Childhood survey (ISAAC) was also administered at this visit. Air pollution exposure from age 1 to 4 was estimated from validated spatiotemporal models of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3). Current wheeze and current asthma were derived from the ISAAC responses. We used Poisson regression with robust standard errors and models were adjusted for child, maternal, and home environmental factors. Effect modification by child sex and maternal asthma status were assessed with interaction models.

Results

Caregivers of 224 children reported bronchiolitis in the child's infancy. Mean age at asthma assessment was 4.7 (SD 0.9) years. Mean (SD) pollutant concentrations were 8.64 $\mu g/m^3$ (1.78), 8.36 ppb (2.85), and 26.41 ppb (2.62) for $PM_{2.5}$, NO_2, and O_3, respectively. Relative risk ratios for current wheeze and current asthma per 2-ppb higher postnatal O_3 were 1.32 (95% CI: 1.01-1.71) and 1.41 (1.09-1.83), respectively. NO_2 was inversely associated with current wheeze and current asthma and the effect estimate for $PM_{2.5}$ was null. NO_2 and $PM_{2.5}$ showed statistically significant interaction by maternal asthma, with evidence suggestive of inverse associations only among children without a history of maternal asthma. No effect modification by maternal asthma status was observed for O_3 nor for any pollutant by child sex.

Conclusion

Modestly higher exposure to postnatal ozone concentrations may further the risk of asthma among the vulnerable subpopulation of infants who experience bronchiolitis. The role of other common air pollutants may differ among children without a genetic predisposition based on maternal history of asthma.

Table of Contents

Background:

Bronchiolitis is a common lower respiratory tract disease in infancy[1]. Many common respiratory viruses can cause bronchiolitis although it is most often associated with respiratory syncytial virus (RSV), detected in 41-83% of patients[1]. Those with more severe symptoms typically involve outpatient assessment, emergency department care, or hospitalization[2,3]. Bronchiolitis is the leading cause of hospitalization in the first year of life in the United States[1,4,5]. Bronchiolitis in the first two years of life is a well-established and strong risk for the later development of asthma during childhood[3,5–8]. It has been estimated that 50% of infants with severe bronchiolitis (emergency department visit or hospitalization) later receive a diagnosis of asthma[7]. This relationship has been noted to decrease as children age. A meta-analysis determined the largest odds ratios for recurrent wheezing and asthma was associated with infant bronchiolitis observed among children younger than 5 years old[9]. However, it remains unclear why some children who experience clinically significant bronchiolitis in their infancy develop asthma that persists into later childhood.

One possibility is that higher postnatal exposure to air pollution contributes to risk of recurrent wheeze or asthma among children whose airways have experienced a bronchiolitis infection. Similar to bronchiolitis infections, childhood exposure to particulate matter 2.5 ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) has been associated with reductions in lung function and increases in pulmonary inflammation[10,11] as well as with the development of asthma[11–13], although the risk estimates for air pollutants are of lower magnitude. The effects of bronchiolitis infection in infancy with subsequent exposure to higher concentrations of air pollution may facilitate asthma development during an etiologically relevant time for lung development[14,15]. The alveolar stage of lung development begins late in gestation and continues at a rapid rate in early childhood and is crucial to later lung functionality[16]. Experimental models in mice demonstrate early life exposure to $PM_{2.5}$ results in reduction of alveoli number[17] while exposure

to O3 impacted airway remodeling[18], both of which are indicated as potential targets for the development of asthma and wheeze among those with a previous bronchiolitis infection[15]. Disruptions have also been noted in rhesus monkeys experimentally exposed to O_3 in infancy[19].This interruption of normal lung development presents a potential mechanism from furthered disruption of airway remodeling and alveolar multiplication resulting from post-bronchiolitis exposure to air pollution.

While 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 (CHEER) cohort in the Republic of Korea assessed the independent and combined effect of air pollution and bronchiolitis on the development of asthma[20,21]. They found statistically significant associations between higher concentrations of NO_2, CO, and O_3 and current wheezing and physician-diagnosed asthma, among those with previous bronchiolitis infections[20] as well as proxy measures for traffic exposure with newly diagnosed wheezing and asthma[21] but not among those with higher exposures without bronchiolitis. These studies suggest the potential unique susceptibility of children who have experienced bronchiolitis to post-bronchiolitis air pollution. Furthermore, neither analysis examined $PM_{2.5}$.

We sought to add understanding to the role of air pollution as a modifiable risk factor for asthma and wheeze development at age 4-6 years old among infants with bronchiolitis. Unlike prior studies, we were able estimate individual air pollution exposure based on a fine resolution temporal-spatial model for NO_2, O_3 as well as $PM_{2.5}$, an air pollutant with known pulmonary toxicity and increasing studies linking early life exposure to pediatric asthma[22]. To our knowledge this is the first analysis of this question addressing $PM_{2.5}$ and conducted in a cohort of U.S. children. Some of the results of this study have been previously reported in the form of an abstract (Pediatric Academic Societies, Denver Colorado, April 2022).

Methods

Study population

Eligible participants were selected from the Environmental Influences on Child Health Outcomes (ECHO) PATHWAYS Consortium that 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 IRB.

CANDLE recruited women aged 16-40 years and in the second trimester with singleton, low-medical-risk pregnancies. All planned to deliver at participating study hospitals[23]. Recruitment occurred between 2007 and 2011 at clinic and community locations to reflect the demographics of the study area of Shelby County (Memphis), Tennessee. Follow up commenced from birth to joining the ECHO Pathways study.

GAPPS recruited women aged 18 or older at the time of the first trimester with follow up ending just after infant birth. These participants consented to share demographic and health information as well as biospecimens with the GAPPS biorepository[24,25]. Participants enrolled from 2011-2016 at the University of Washington Medical Center, Seattle; Swedish Medical Center, Seattle; and Yakima Valley Memorial Hospital, Yakima were invited to join ECHO-PATHWAYS for postnatal follow up.

TIDES recruited low-medical-risk pregnant women aged 18 or older in the first trimester from obstetrical clinics associated with university hospitals located in San Francisco, California; Minneapolis, Minnesota; Rochester, New York; and Seattle, Washington between 2010 and 2012[26].

Participants in this study were included if they answered affirmatively to the following question regarding bronchiolitis: *During the first 12 months of _____'s 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. Additionally, only those who had a valid geocoded address history enabling air pollution estimates to be calculated were included.

Air Pollution Estimates

$PM_{2.5}$ (ug/m^3), NO_2 (ppb), and O_3 (ppb) exposures were estimated using outdoor pollutant concentrations at the geocoded residential address collected at the age 4 visit. In brief, a combination of external research campaign 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[27–29]. Estimates are made for each two-week average concentration throughout the child's life. Estimated age 1-4 years long term average $PM_{2.5}$, NO_2, and O_3 concentrations were calculated for each child's residential address collected at the age 4 study visit using the respective spatiotemporal model. This window represents the chronic air pollution exposure subsequent to the time when bronchiolitis infection was noted and coincides with the ongoing intensive airway remodeling and alveolarization stage of lung development which may be important for air pollution related influence on future lung disease[17,18].

Asthma and Wheeze Outcomes

Asthma outcomes were characterized based on parent report at the CANDLE 4-6, TIDES age 6, and GAPPS 4-6 visit using the International Study of Asthma and Allergies in

Childhood (ISAAC) questionnaire. The hierarchy of outcomes is similar to that examined in previous PATHWAYS consortium research[30–32]. 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 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 “In the past 12 months has your child used any type of medicines, liquids, puffers or other medication for wheezing or asthma?”.

Covariates

Confounders and precision variables were selected *a priori*. Variables were harmonized by the ECHO-PATHWAYS data center. Child factors include the age at outcome assessment (years), sex assigned at birth (male/female), child race (Black or African American, White or 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). Child race was categorized to account for differences in rates of asthma among Black children in the US as well as to address social, economic, and structural factors linked to racial asthma disparities including exposure to stress and environmental toxicants[33,34]. Further disaggregation of race was limited by sample size and was not performed. Maternal factors include education at 4-6 visit (<high school diploma/high school diploma or equivalent/college or technical school/some graduate work or degree), income at 4-6 visit (USD, adjusted for region and inflation), history of asthma (yes/no), and smoking during pregnancy (yes/no). Home

environment factors include household size at 4-6 visit (number of adults and children), Neighborhood Deprivation Index (long term average at age 4 address from ages 1 to 4), cotinine concentration (ng/ML), postnatal exposure to secondhand smoke (yes/no), and pets in the home during the first 12 months of life (yes/no). Recruitment site was also included to account for unmeasured confounding by geographic location (Memphis, Minneapolis, Rochester, San Francisco, Seattle-GAPPS, Seattle-TIDES, and Yakima).

Statistical analysis

Descriptive statistics were used to explore the study population. Pearson's correlations were utilized to calculate the correlation between pollutants. A staged modeling approach was used with modified multivariate Poisson regression with robust standard errors to calculate risk ratios (RR) and 95% confidence intervals (CI) of air pollution exposure and airway outcomes. Groups were compared using effect size of 2-, 2-, and 5-units higher air pollution exposure for $PM_{2.5}$, O_3, and NO_2 respectively based upon the IQR for each pollutant. A minimally adjusted model included age at outcome assessment, sex, season, year of birth, and site; the main model included race, preterm birth, birthweight, maternal education, income, maternal history of asthma, smoking during pregnancy, neighborhood deprivation index, cotinine, and reported secondhand smoke exposure in addition to the variables in the minimal model; and the extended model included duration of breastfeeding, household size, and pets in the home during the first year of life in addition to the variables in the main model. Effect modification of child sex and maternal history of asthma was assessed using multiplicative interaction terms adjusted for the same covariates as in the main model.

Performed sensitivity analyses include assessing the impact of a multipollutant model that mutually adjusts for $PM_{2.5}$, O_3 and NO_2 on the relationship between air pollution and asthma and wheeze outcomes. Additionally, a leave one cohort out and site out analysis was utilized to assess bias arising from differing geographic contexts of sites. A final sensitivity analysis

analyzed strict asthma as well as reanalyzed current wheeze and current asthma among the subset of participants who were not missing a response to the strict asthma variable, allowing comparison among these findings using the same set of participants. The strict asthma definition was performed to potentially better characterize true asthma status among participants by only considering those endorsing “a history of asthma” as having asthma at the 4-6 visit. All sensitivity analyses were tested using the same covariates as in the main model. All analyses were conducted in *R* 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Caregivers of 224 children reported bronchiolitis in the child’s infancy of which 137 were from CANDLE, 43 were from GAPPS, and 40 were from TIDES. Most children were male (62.1%) and had mothers without a history of asthma (71.9%). Mean age at asthma assessment was 4.7 (SD 0.9) years and 35.7% reported current asthma and 36.6% reported current wheeze (table 1).

Mean (SD) pollutant concentrations were 8.6 $\mu g/m^3$ (1.8), 8.4 parts per billion (PPB) (2.9), and 26.4 PPB (2.6) for $PM_{2.5}$, NO_2, and O_3, respectively. Concentrations ranged from 3.7 to 11.6 $\mu g/m^3$ for $PM_{2.5}$, 2.0 to 16.1 ppb for NO_2, and 18.6 to 33.9 ppb for O_3 (table 2). NO_2 was negatively correlated with O_3 while NO_2 and $PM_{2.5}$ and O_3 and $PM_{2.5}$ were positively correlated (table 3).

In the main model (figure 1), relative risk for current wheeze and current asthma were 1.32 (95% CI: 1.01-1.71) and 1.41 (95% CI: 1.09-1.83), 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/m^3 increase in $PM_{2.5}$ included the null (RR=0.64, 95% CI: 0.32-1.30 for current wheeze; RR=0.66, 95% CI: 0.30-1.43 for current asthma).

NO_2 showed statistically significant interaction by maternal asthma (figure 2). An inverse association was observed only among children with a history of maternal asthma; among children without maternal history of asthma, effect estimates were attenuated and confidence intervals included the null. $PM_{2.5}$ also showed statistically significant interaction by maternal asthma, with an inverse association only among children with a history of maternal asthma. No effect modification by maternal asthma status was observed 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 main findings. Although no longer statistically significant, the RR for O_3 for current wheeze was 1.11 (95% CI: 0.77-1.60) and 1.26 (95% CI: 0.87-1.84) for current asthma. The findings for both NO_2 and $PM_{2.5}$ approached the null after adjustment for other pollutants; estimates for NO_2 were 0.93 (95% CI: 0.82-1.05) for current wheeze and 0.95 (95% CI: 0.84-1.07) for current asthma, and estimates for $PM_{2.5}$ of 0.95 (95% CI: 0.62-1.47) for current wheeze and 1.00 (95% CI: 0.62-1.61) for current asthma (figure 4).

Sensitivity analyses in which one site or cohort was omitted were similar to main findings when a TIDES (Rochester, Minneapolis, Seattle, San Francisco) or GAPPS (Seattle, Yakima) site was left out for all three pollutants (figure 5). An exception is the analysis of $PM_{2.5}$ and current asthma, for which exclusion of Yakima resulted in a notable shift of results (RR:0.49, 95% CI: 0.24-0.98) relative to main findings, suggesting an inverse association. All exclusions of the CANDLE (Memphis) cohort results in greatly widened confidence intervals.

Analysis of strict asthma as an outcome (reduced sample size of 215) did not reach significance for NO_2, (RR=0.78, 95% CI:0.50-2.13), O_3 (RR=1.32, 95% CI: 0.97-1.79), nor $PM_{2.5}$ (RR=0.87, 95% CI: 0.27-2.75). Results of current wheeze and current asthma within the subset

population were near identical to the findings in Figure 1 although the strict asthma results were more attenuated relative to current wheeze and current asthma for both NO_2 and $PM_{2.5}$ (table 3).

Discussion

Bronchiolitis is highly common in infancy and a recognized risk factor for childhood asthma and wheeze, yet not all infants with bronchiolitis later develop these conditions. This analysis suggests post-bronchiolitis air pollution exposure may influence subsequent risk of wheeze and asthma in early childhood. We found higher risk for both asthma and wheeze at age 4-6 years for those with higher exposure to O_3 in early childhood, but not $PM_{2.5}$ or NO_2. Effect modification by maternal asthma status was detected for $PM_{2.5}$ and NO_2 but not O_3 where risk estimates for both $PM_{2.5}$ and NO_2 were below 1.0 for those with maternal a history of asthma and null for those without. No evidence of effect modification by child sex for any of the pollutants was found.

The biological underpinnings of our hypothesis that bronchiolitis with subsequent air pollution would increase the risk of asthma and wheeze reflected an appreciation for the bronchiolar inflammation induced by bronchiolitis[15,35] as well as also by air pollutants such as $PM_{2.5}$, NO_2, and O_3 which together may influence the increased vulnerability to recurrent asthma and wheeze. More specifically, it has been hypothesized that exposure to respiratory viruses in infancy leads to a wheezy phenotype via the dysregulation of inflammation associated with infection which is then thought to progress to recurrent wheeze and asthma in childhood via airway remodeling and decreased alveolarization associated with lower respiratory infections[15]. In mice models, $PM_{2.5}$[17] and O_3[18] have also been associated with decreased alveolarization and airway remodeling, respectively, after chronic exposure to the air pollutants, indicating that post-bronchiolitis exposure may contribute to the progression to recurrent asthma and wheeze within this vulnerable population.

Prior studies of general pediatric populations have identified childhood exposure to O_3 as a risk factor for asthma development in some but not all studies[11,36–39]. In this study, we found a consistently higher risk for both current asthma and current wheeze (RR of 1.32; 95% CI: 1.01-1.71 and 1.41; 95% CI: 1.09-1.83, respectively) among children who had a history of infant bronchiolitis in our main analysis and sensitivity analyses. *Kim et al. 2013* also report higher prevalence of similar outcomes among school aged children in Korea with both bronchiolitis and higher O_3 (defined as above mean for the sample). Their analysis included children who did not have bronchiolitis in infancy and reported a high odds ratio for children with both risk factors compared to those with neither for current wheeze and current asthma (2.73: 95% CI 1.14–6.56 and 7.54: 95% CI 2.67–21.32, respectively)[20].

We hypothesized that we would observe an adverse effect of $PM_{2.5}$ as well, given evidence for an adverse effect of $PM_{2.5}$ on asthma risk in many general pediatric populations[11–13,36,37,39]. However, in our analysis focused on infants with bronchiolitis, we found no association of subsequent higher $PM_{2.5}$ exposure and risk of current wheeze or current asthma at age 4-6 years in main models and sensitivity analyses. Our estimates contained large confidence intervals and future studies with a larger sample size may offer more precise estimates. We identified no other studies that examined effects of exposure to $PM_{2.5}$ among children with bronchiolitis. However, in the same cohort of school age children in Korea that was used for the *Kim et al. 2013* analysis noted above, exposure to traffic based on two metrics (proximity to nearest main road < 75 m or total length of roads within a 200 m buffer of the home residence) was assessed[21] and traffic is often an important source of both $PM_{2.5}$ and NO_2 in most settings. The children were followed up for two years to identify new cases of wheezing or doctor diagnosed wheezing. In contrast to our $PM_{2.5}$ findings, new wheezing and new physician diagnosis of asthma was more common among children who had a history of bronchiolitis and either of the traffic measurements compared to children who had neither risk factor. However,

these analyses reflected a relatively small sample sizes of individuals with both bronchiolitis and higher air pollution leading to estimated effects with wide confidence intervals.

In our analysis of potential effect modification of $PM_{2.5}$ exposure on asthma and wheeze by maternal asthma status, we observed a statistically significant reduced risk among mothers with a history of asthma and null estimates among those mothers without a history of asthma. A cautious interpretation is warranted due to the small sizes of the respective groups in this exploratory analysis. One potential explanation for this unanticipated observation is potential differences in behaviors between mothers based on their own asthma history such that with those with asthma in the setting of higher exposure are more likely to limit their children's exposures to asthmagens through behaviors such as reducing indoor air contaminants. While we were able to control for household pets and exposure to tobacco smoke, we did not have data to address cleaning product or home pesticide use, 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 was associated with a lower risk of both current asthma and wheeze in main models. This did not persist in sensitivity analyses where models were adjusted for the other pollutants. In general population studies, higher NO_2 exposure postnatally has consistently been associated with higher risk of asthma and wheeze development[11,13,20,36,37,39,40]. In the *Kim et al. 2013* analysis, NO2 in the presence of bronchiolitis was associated with a higher risk of asthma and wheeze. In our exploratory analysis for effect modification by maternal asthma, we observed reduced effect estimates only among those with a maternal history of asthma and not those without. Explanations for this may include consideration of the phenomenon described above where mothers who have experienced asthma are more precautionary regarding their children's exposure to traffic, gas stoves, or other sources of NO_2. In addition, concentrations of ambient NO_2 and O_3 are often negatively correlated due to well described atmospheric chemical reactions where NO_2 reacts and is quashed in the formation of ground level O_3[41]. Others have observed negative

correlations as we have between NO_2 and O_3 in epidemiological analysis[38] as well as observed effect estimates of NO_2 and O_3 in opposite directions. [38,42]. As an example, the hazard ratio (HR) of incident asthma associated with higher NO_2 and O_3 exposure were in opposite directions in a case-control study of ambient air pollution and asthma incidence in children in Denmark[36]. However, the risk estimates for higher NO_2 (HR: 1.04, 95% CI: 1.03-1.04) and higher O_3 (HR: 0.96, 95% CI: 0.95-0.97) were inconsistent with the findings of this analysis potentially due to the use of a different reference group without asthma. 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, i.e., the "protective" findings of higher NO_2 may be demonstrating lower risk for areas with lower O_3 concentrations. This is supported by our sensitivity analyses which include mutual adjustment for NO_2, O_3, and $PM_{2.5}$. This resulted in a shift to null effect estimates for NO_2 while estimates for O_3 remain similar to the single-pollutant main analysis.

Asthma is an imprecise diagnosis in early childhood[43] and we rely on parent report of outcomes, although using a well validated instrument highly employed around the world[44]. The intention of our analysis of strict asthma was to best approximate a persistent asthma diagnosis, which is of major public health relevance[45]. In the analysis of strict asthma which required a recognition of the term "asthma" in defining the child's health history in addition to endorsing current wheeze symptoms or current use of common asthma medications, estimates were nearly the same for O_3 while were more attenuated for NO_2 and $PM_{2.5}$.

Results from the sensitivity analysis where one cohort or site was excluded from the main model revealed that, overall, the effect estimates were stable while the precision of estimates was reduced as evidenced by greatly widened confidence intervals when CANDLE was omitted (figure 4). An exception is the analysis of $PM_{2.5}$ and current asthma, for which exclusion of Yakima resulted in a notable shift of results.

This analysis has notable strengths including the utilization of a pooled and geographically diverse population that enhances the generalizability of the results. Additionally,

air pollution estimates were calculated 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, quite robust control for key confounding and precision variables was possible in these well characterized cohorts. Unlike prior research on air pollution and child health effects, this study focuses specifically on an important vulnerable subpopulation and allowed examination of effect modification by sex and maternal asthma status in this group.

There are some limitations to note in this study. Firstly, the non-specific phrasing of the survey question used for study inclusion could conflate bronchiolitis with some non-bronchiolitis caused wheezing and the study did not have information on severity of bronchiolitis such as those requiring hospital care. This could bias results towards the null due to the potential of not capturing exclusively those who truly had bronchiolitis or if air pollution effects were only evident among more severe cases. These outcome definitions, as in many studies of air pollution and child asthma, relied on maternal report, which may have led to outcome misclassification based on ability of caregiver to recognize wheeze in their children or access to health care and understanding of a diagnosis of asthma. However, the questions used were derived from the validated and widely applied ISAAC survey[46]. The inability to capture all potential indoor air factors and lack of measures of air pollution concentrations indoors at home or at a child's non-residential locations such as preschool or daycare introduces exposure misclassification. As discussed above, biased exposure assessment could occur if maternal asthma status influences other asthmagen exposures. Lastly, the sample size of children with bronchiolitis available in our pooled analysis, while greater than the prior studies conducted in Korea, was relatively modest and confidence intervals were relatively wide.

In conclusion, the high rate of subsequent asthma development among infants with bronchiolitis underscores the public health importance of understanding modifiable risk factors including childhood exposure to air pollution. Despite relatively modest O_3 concentrations

estimated in the study population, we found evidence that this pollutant may be of particular concern for the development of asthma among this vulnerable population. Further exploration of the role of post-bronchiolitis air pollution is warranted in additional populations and should include considerations for other modifying factors including genetic susceptibility as well as capture effects based on bronchiolitis severity.

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Tables and Figures

Table 1: Study Population Characteristics (N=224)

		Pooled sample[a]	
History of infant bronchiolitis	Reported in the first year of life	224	100%
CANDLE		137	61.2%
	Memphis	137	61.2%
GAPPS		47	21.0%
	Seattle	18	8.0%
	Yakima	29	12.9%
TIDES		40	17.9%
	Minneapolis	16	7.1%
	Rochester	7	3.1%
	San Francisco	10	4.5%
	Seattle	7	3.1%
Child Characteristics			
Child sex assigned at birth	Male	139	62.1%
Child race	Asian	2	1.0%
	Black or African American	99	44.2%
	Multiple race	14	54.9%
	Other	3	1.3%
	White	104	46.4%
Year of birth	2007	11	4.9%
	2008	23	10.3%
	2009	38	17.0%
	2010	38	17.0%
	2011	45	20.1%

	2012	37	16.5%
	2013	20	8.9%
	2014	12	5.4%
Season of birth	Cold	97	43.3%
	Warm	127	56.7%
Premature birth	<37 weeks	32	14.2%
Birthweight	Mean (g), SD	3238.7	654.4
Age at age 4-6 visit	Mean, SD	4.7	0.9
Breastfeeding duration	None	57	25.4%
	< 6 months	127	56.7%
	> 6 months	38	17.0%
Maternal Characteristics			
Education	< High school diploma	12	5.4%
	High school diploma or equivalent	65	29.0%
	College or technical school	95	42.4%
	Some graduate work or degree	52	23.2%
Income	Mean, SD	59067.5	50910.5
Maternal history of asthma	Yes	62	27.7%
Smoking during pregnancy	Yes	15	6.7%
Home Environmental Factors			
Household size	Mean, SD	4.5	1.4
Neighborhood Deprivation Index	Mean, SD	0.2	0.8
Secondhand smoke exposure	Mean cotinine (ng/mL), SD	54.3	261.3
	Reported SHS exposure	55	24.6%
Pets in home	During first 12 months	144	64.3%

Outcomes			
Current wheeze[b]	Yes	82	36.6%
Current asthma[c]	Yes	80	35.7%
Strict asthma[d]	Yes	67	29.9%

[a]Number missing for individual variables include: child race (2), premature 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 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 asthma: defined as Ever asthma (defined above) and either Current wheeze (defined above) or Medication use (defined above).

Table 2: Air pollution Estimates

	Site	Median NO2 (IQR) PPB	Median O3 (IQR) PPB	Median $PM_{2.5}$ (IQR) µg/m3
Overall		8.5 (6.4-9.9)	26.6 (25.6-27.7)	9.3 (7.8-9.9)
CANDLE[a]				
	Memphis, TN	9.3 (7.6-10.6)	27.0 (26.1-27.9)	9.7 (9.3-10.2)
GAPPS[b]				
	Seattle, WA	7.4 (6.0-8.6)	20.5 (20.1-21.7)	5.1 (4.8-5.6)
	Yakima, WA	4.2 (3.2-5.6)	26.7 (25.7-27.6)	6.5 (4.9-7.5)
TIDES[c]				
	Minneapolis, MN	9.1 (7.9-9.6)	25.7 (25.2-27.3)	8.2 (8.0-8.6)
	Rochester, NY	7.0 (6.1-7.3)	26.2 (26.0-26.5)	7.5 (7.3-7.8)
	San Francisco, CA	8.3 (7.2-10.8)	25.8 (22.3-26.3)	9.7 (8.9-10.1)
	Seattle, WA	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

Table 3: Pearson Correlation of Air Pollution Estimates Across Sites

	NO2	O3	PM2.5
NO2	1		
O3	-0.29	1	
PM2.5	0.54	0.35	1

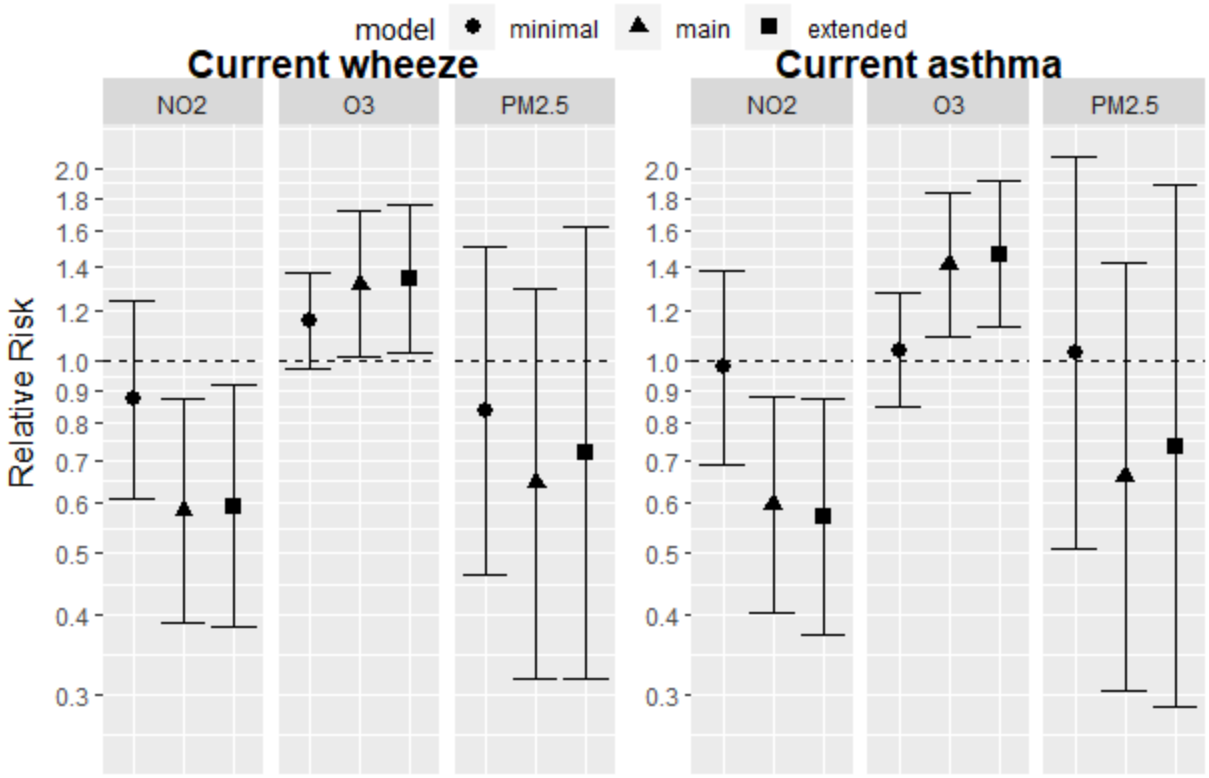

Figure 1: Minimal, Main, and Extended Models

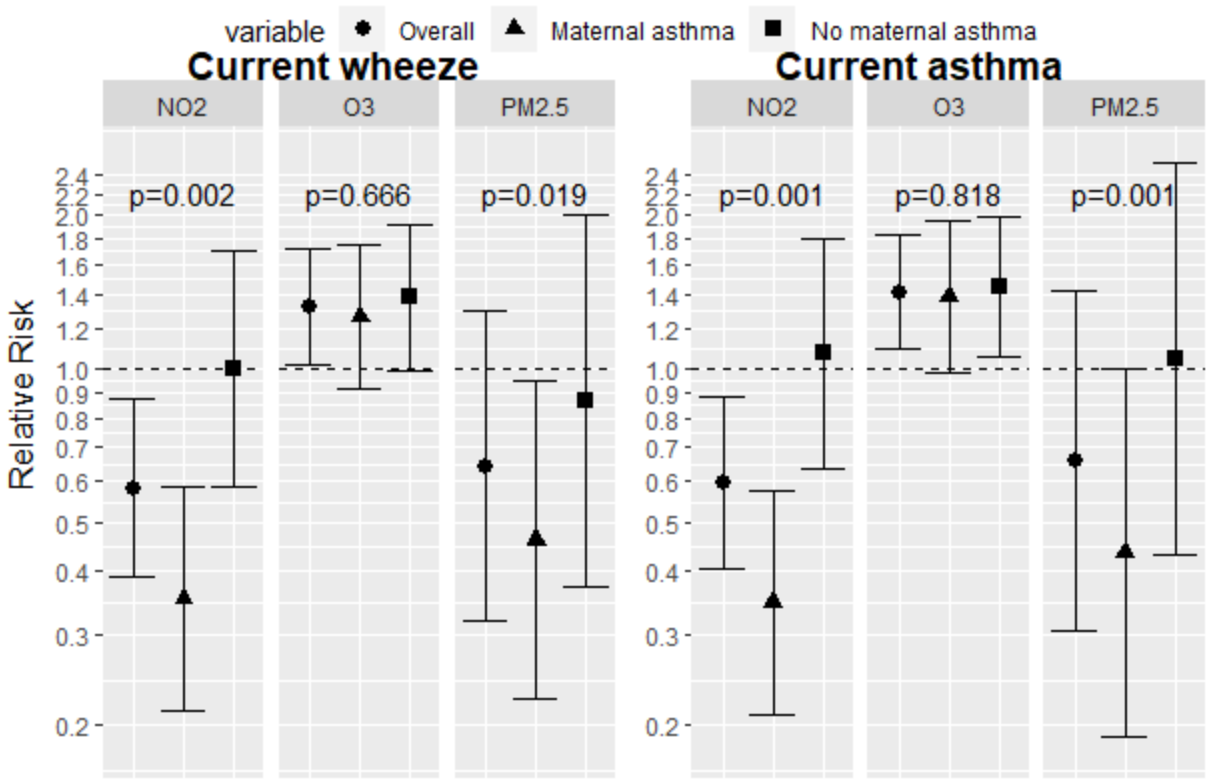

Figure 2: Effect Modification by Maternal Asthma Status

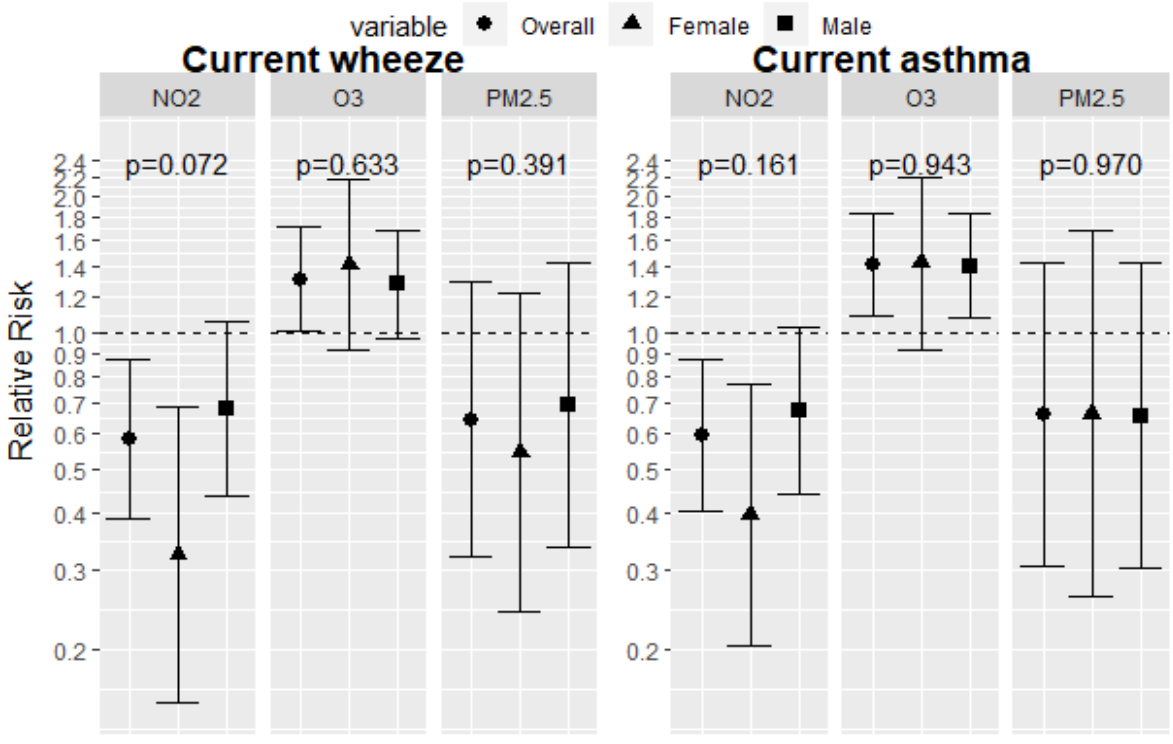

Figure 3: Effect Modification by Child Sex

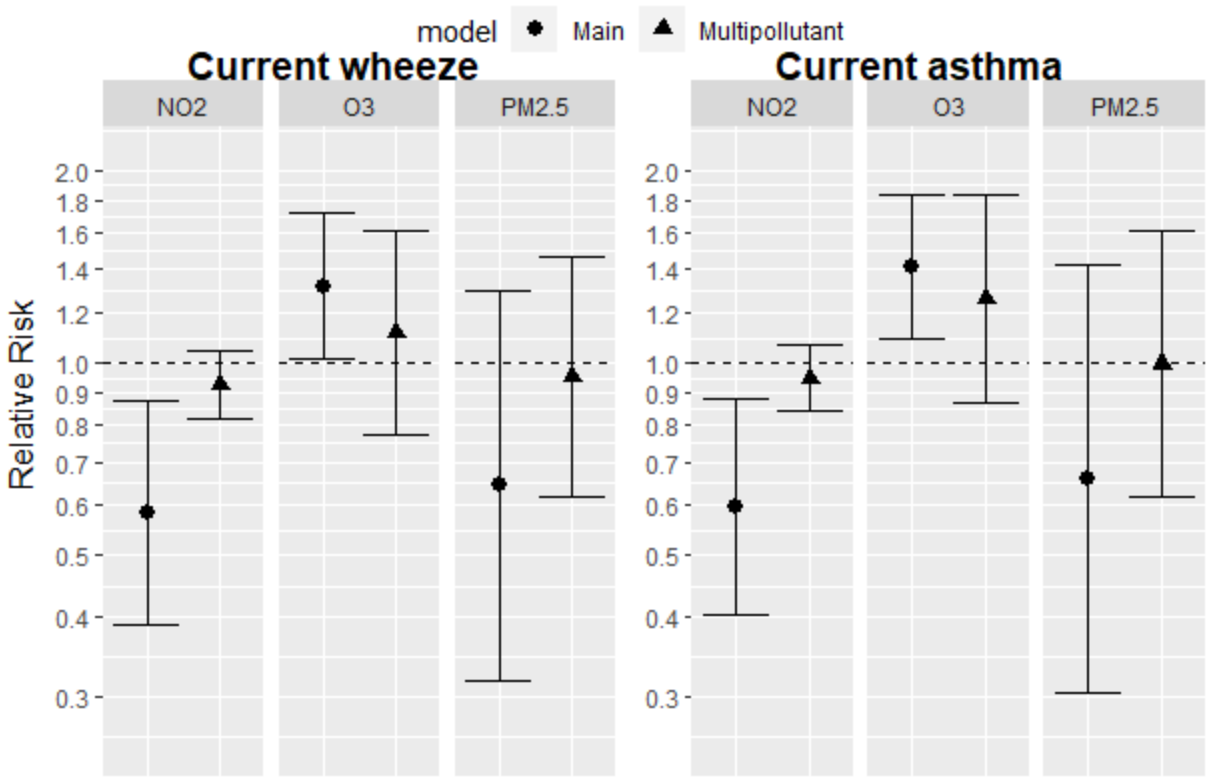

Figure 4: Multipollutant model

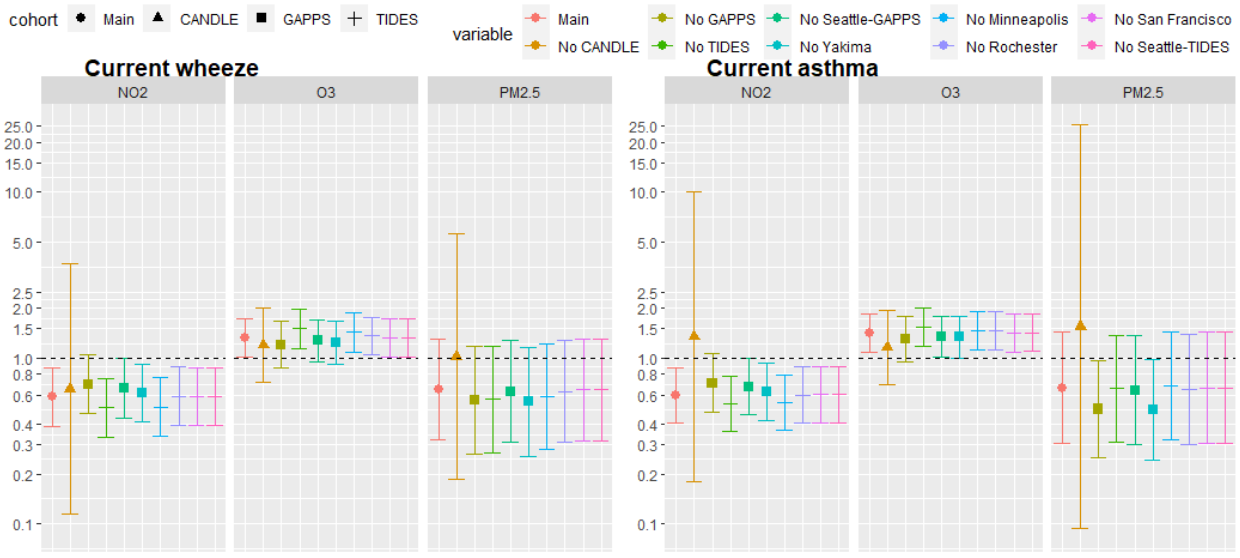

Figure 5: Leave one out

Table 4: Strict asthma analysis

	NO_2 (95% CI) RR[a]	O_3 (95% CI) RR	$PM_{2.5}$ (95% CI) RR
Strict asthma	0.78 (0.50-1.23)	1.32 (0.97-1.79)	0.87 (0.27-2.75)
Current wheeze	0.60 (0.39-0.90)	1.31 (1.00-1.73)	0.74 (0.35-1.60)
Current asthma	0.62 (0.42-0.91)	1.39 (1.06-1.82)	0.65 (0.29-1.47)

[a]Sample size reduced to 215.