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Associations of prenatal ambient air pollution exposures with asthma in middle childhood

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Disclosure of interest

The authors report there are no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114333.

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Abstract

We examined associations between prenatal fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) exposures and child respiratory outcomes through age 8–9 years in 1279 ECHO-PATHWAYS Consortium mother-child dyads. We averaged spatiotemporally modeled air pollutant exposures during four fetal lung development phases: pseudoglandular (5–16 weeks), canalicular (16–24 weeks), saccular (24–36 weeks), and alveolar (36+ weeks). We estimated adjusted relative risks (RR) for current asthma at age 8–9 and asthma with recent exacerbation or atopic disease, and odds ratios (OR) for wheezing trajectories using modified Poisson and multinomial logistic regression, respectively. Effect modification by child sex, maternal asthma, and prenatal environmental tobacco smoke was explored. Across all outcomes, 95% confidence intervals (CI) included the null for all estimates of associations between prenatal air pollution exposures and respiratory outcomes. Pseudoglandular $PM_{2.5}$ exposure modestly increased risk of current asthma (RR_{adj} = 1.15, 95% CI: 0.88–1.51); canalicular $PM_{2.5}$ exposure modestly increased risk of asthma with recent exacerbation (RR_{adj} = 1.26, 95% CI: 0.86–1.86) and persistent wheezing (OR_{adj} = 1.28, 95% CI: 0.86–1.89). Similar findings were observed for O_3, but not NO_2, and associations were strengthened among mothers without asthma. While not statistically distinguishable from the null, trends in effect estimates suggest some adverse associations of early pregnancy air pollution exposures with child respiratory conditions, warranting confirmation in larger samples.

Keywords

air pollution; asthma; Particulate matter; Developmental origins of health and disease

1. Introduction

Asthma is a leading chronic disease among children and the physical and social burden of pediatric asthma includes lost schooldays, the need for medication use and urgent medical care, and worse lung function that can persist into adulthood (Rabe et al., 2004). Child asthma is a complex disease with both genetic and environmental determinants.

The literature to date suggests a role of early childhood exposure to air pollution in the development of asthma, though fewer studies have investigated exposures beginning in utero (Khreis et al., 2017; Hehua et al., 2017). Prior literature examining the relationship between prenatal air pollution and child asthma has focused on fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2), the latter as a marker of traffic-related air pollution. Few studies have investigated these relationships with ozone (O_3) exposure in early life (Zu et al., 2018).

Exposure to air pollution during the prenatal period may be important because fetal respiratory and immune systems develop rapidly during this time. Several reviews highlight the uncertainty around windows of increased susceptibility for air pollution exposure within the in utero period (Schultz et al., 2017; Garcia et al., 2021; Bettiol et al., 2021). Some prior studies suggest a prenatal critical window in mid-gestation, when branching morphogenesis of the lung is completed with formation of the distal airways and surfactant production begins (Leon Hsu et al., 2015; Lee et al., 2018; Jung et al., 2019). However, other studies suggest a critical window later in pregnancy, when immune programming is increasing, and microvasculature maturation occurs (Hazlehurst et al., 2021).

Furthermore, asthma is a heterogenous disease with phenotypes that can shift over the course of childhood and may have differing risk factors, yet much of the current literature has examined asthma as a single outcome at a single timepoint in early childhood (Trivedi and Denton 2019). Some early life wheezing is transient, whereas persistent wheeze predicts poorer lung function and the development of asthma later in childhood and into adulthood. Furthermore, asthma diagnosis becomes more reliable later in childhood after early wheezing resolves. Understanding the role of environmental factors in the etiology of each of these asthma and wheezing phenotypes requires longitudinal data collection and these outcomes have not frequently been evaluated in prior work.

Additionally, some subgroups may be more vulnerable to the effects of prenatal environmental exposures. Exposure to toxicants such as environmental tobacco smoke may act synergistically to increase susceptibility to effects from ambient $PM_{2.5}$, NO_2, or O_3 (Rivera et al., 2021). Other factors such as maternal history of asthma may also increase susceptibility (Lavigne et al., 2018) and differences in associations between prenatal air pollution exposures and child respiratory outcomes have been observed between boys and girls (Leon Hsu et al., 2015; Lee et al., 2018).

Given that the existing literature is sparse for some pollutants and that uncertainty remains regarding potential sensitive periods, risk for specific asthma phenotypes, and susceptible subgroups, we aim to address some of these gaps using data from a prospective cohort with follow-up into middle childhood. Specifically, in this study we first examined whether specific prenatal air pollution exposures within fetal lung developmental windows were associated with increased risk of current asthma assessed in middle childhood. We hypothesized that higher exposure during these prenatal exposure windows is associated with increased risk of current asthma in middle childhood. We further explored several specific asthma case definitions, including asthma with a recent exacerbation and asthma with other atopic disease, as well as wheezing trajectories across childhood. We also investigated whether these associations varied by child sex, maternal history of asthma, or

maternal exposure to environmental tobacco smoke (ETS) during pregnancy. Based on prior studies, we hypothesized that some groups may be more vulnerable to the effects of prenatal air pollution exposures than others, including males compared to females, those with a history of maternal asthma compared to those without, and children of mothers exposed to ETS during pregnancy compared to those who were exposed to ETS.

2. Methods

2.1. Study population

This study included participants from three cohorts in the ECHO-PATHWAYS Consortium: the Conditions Affecting Neurocognitive Development and Learning in Early Childhood study (CANDLE), The Infant Development and Environment Study (TIDES), and the PATHWAYS Global Alliance to Prevent Prematurity and Stillbirth study (PATHWAYS-GAPPS or PWG). Participants were enrolled in CANDLE during mid-pregnancy in 2006–2011. Participants were required to live in Shelby County, Tennessee, have a singleton low-medical-risk pregnancy at enrollment, and have plans to deliver at one of the study hospitals. Participants in TIDES were enrolled during pregnancy, were determined to have a low-medical-risk pregnancy at enrollment, and were planning to deliver at a participating study hospital. TIDES participants were recruited from four study sites in: San Francisco, CA; Minneapolis, MN; Rochester, NY; and Seattle, WA. GAPPS participants were originally enrolled into a closed cohort during pregnancy for the purpose of developing a biorepository. Participants who previously consented to contact for future study, and whose child was eligible based on age and availability of prenatal data, were re-contacted to enroll in ECHO-PATHWAYS. Enrollment and participant characteristics for each cohort are described in detail elsewhere (LeWinn et al., 2022). Follow-up study visits for this analysis were conducted at approximately ages 4–6 years and at ages 8–9 years in all cohorts.

Mother-child dyads were included in the analysis if they completed the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire at the age 8–9 study visit and had a valid address history (defined as at least one geocoded address during pregnancy) with corresponding air pollution exposure estimates (Supplemental Fig. 1). Preterm births (<37 weeks gestation) were excluded due to the potential for different disease etiology in these children. Participants in the PWG cohort were included in this analysis if they completed the age 8–9 study visit before June 2022. Analysis of wheezing trajectories additionally required that participants had completed the ISAAC questionnaire at the age 4–6 study visit.

Women provided informed consent for themselves and their children and additionally, children assented to the age 8–9 study visit. All ECHO-PATHWAYS research activities were approved by the University of Washington Institutional Review Board (IRB, Study ID: STUDY00000638) as well as the IRB at each of the relevant partner institutions.

2.2. Prenatal air pollution exposures

Prenatal air pollutant concentrations were estimated using well-validated national spatiotemporal models, which have been described elsewhere (Keller et al., 2015; Wang et al., 2018; Kirwa et al., 2021). These models include both regulatory and scientific

monitoring data and a large suite of geographic covariates. Point-based estimates of NO_2, O_3, and $PM_{2.5}$ generated at a 2-week resolution for each participant address were averaged over the exposure window of interest. Exposure windows were specified a priori based on four biologically relevant periods of fetal morphological lung development (Pinkerton and Joad 2006; Korten et al., 2017): the pseudoglandular phase (5–16 weeks gestation), canalicular phase (16–24 weeks gestation), saccular phase (24–36 weeks gestation) and alveolar phase (36 weeks gestation to birth). Windows were calculated from date of birth and estimated gestational age at delivery. In sensitivity analyses, we additionally examined exposure averaged over the entire pregnancy or within trimesters, and models adjusted for postnatal air pollution exposure with each pollutant averaged over the residential history from birth to age 4.

2.3. Child asthma and wheezing outcomes

Asthma and wheezing outcomes were based on parent-reported answers on the well-validated ISAAC questionnaire and other study questionnaires, which were completed at the time of the age 8–9 year study visit (Asher et al., 1995). *Current asthma* was considered the primary outcome of interest and defined based on parent-report of doctor diagnosis of asthma and either recent medication use or recent wheeze, where recent medication use was defined based on the question “does the child use any medications for treatment of recurrent cough, recurrent wheezing, or asthma?”, and recent wheeze was defined as an affirmative answer to the question “has the child had wheezing or whistling in the chest in the past 12 months?”.

We examined two secondary asthma outcomes. *Current asthma with recent exacerbation* was defined as those who met the current asthma definition above and additionally reported oral steroid use, an emergency room visit, or a hospital visit, for asthma or wheezing in the last 12 months. Children were considered to have *asthma with other atopic disease* if the parent reported yes to either “has your child ever had eczema” or “has your child ever had hay fever”, in addition to meeting the criteria for current asthma.

We also examined wheezing trajectories based on ISAAC questionnaire data collected at both age 4–6 and age 8–9, regardless of asthma classification. *Early wheeze* was defined as those who reported a history of ever wheeze at the age 4–6 study visit, but did not report wheeze in the past 12 months at the age 8–9 visit. Late wheeze was defined as those who reported ever wheezing at age 8–9 but had not reported any wheeze at or before age 4–6. *Persistent wheeze* was defined as those reporting wheeze at both visits (i.e. history of ever wheeze at age 4–6 and wheeze in the past 12 months at age 8–9). Those with a response of no to wheeze at both timepoints were considered the referent group, *never wheeze*. Those who indicated “Don’t know” at either timepoint were considered missing.

2.4. Covariates and effect modifiers

Medical record abstraction was used to determine infant sex, gestational age at birth, and date of birth (used to calculate splines with 1 degree of freedom per year and birth in warm [April–September] or cold [October–March] season). Maternal education (highest level completed in 4 categories: less than high school, high school completion, graduated

college or technical school, and some graduate work or graduate/professional degree), and maternal history of asthma (yes or no) were self-reported at enrollment. Self-identified maternal race was reported as Black, White, Asian, another race, or multiple races, and collapsed into three categories (Black, White, and all other self-descriptions) due to sample size. Maternal race was considered as a proxy for social and structural factors contributing to health inequities including racial residential segregation and access to resources such as healthcare (Benmarhnia et al., 2021). Parity was used to create a binary indicator for firstborn. Pre-pregnancy height and weight reported during pregnancy were used to calculate body mass index (BMI; kg/m^2). Household income at enrollment was reported in categories; the midpoint of each category was selected, adjusted by region to reflect variation in cost of living across the study sites, and log-transformed for analysis (Quraishi et al., 2022; Bureau of Economic Analysis, 2020). Reported household count was grouped into four categories (2–3, 4, 5, and ≥6 people). The Neighborhood Deprivation Index was constructed from 5 census tract variables (% <high school education, % professional employment (reverse coded), % owner occupied housing (reverse coded), % <100% poverty, and % unemployed), combined as a continuous z-score (Messer et al., 2006; Quraishi et al., 2022). Women/caregivers reported duration of exclusive breastfeeding without formula, juices, or other foods (categorized as never, ≤6 months, >6 months) and whether there were any furry pets in the home during the child's first year of life, at the age 8–9 study visit. History of bronchiolitis in infancy (yes/no) was reported at the age 4–6 or 8–9 study visit depending on the cohort. Paternal asthma history (yes/no) was reported at the age 4 study visit. Reported postnatal child exposure to environmental tobacco smoke (ETS) during early life was dichotomized as yes/no.

Urine samples from mid to late pregnancy (mean of 22.5 weeks) were analyzed to quantify cotinine concentrations as a continuous measure (ng/mL). Participants self-reported smoking status at enrollment in early to mid-pregnancy. Participants who either self-reported smoking at enrollment or had a urinary cotinine measure above the cutoff of 200 ng/mL were considered active smokers during pregnancy (Schick et al., 2017).

Some subgroups may be more vulnerable to adverse effects of prenatal air pollutant exposure, including male fetuses and those with maternal history of asthma. We examined effect modification by child sex and maternal asthma history in the full sample. We also investigated effect modification by ETS within the subsample of non-smokers. In this subgroup, continuous urinary cotinine measures were considered as a measure of prenatal ETS.

2.5. Statistical analysis

All analyses were conducted in R 4.1 (R Foundation for Statistical Computing, Vienna, Austria). Multiple imputation by chained equations (MICE) was used to impute missing data using the *mice* R package. For analysis of asthma outcomes, we used Poisson regression with robust standard errors to estimate relative risks (RR) and 95% confidence intervals (CIs). For analysis of wheezing trajectories, we used multinomial logistic regression models to estimate odds ratios (ORs) and 95% CIs.

Potential confounders across multiple domains were identified a priori based on prior research of predictors of child respiratory health that may be correlated with pollutant exposures. Minimally-adjusted models include child age, sex, study site, and birth year. Fully-adjusted models additionally include adjustment for maternal education, race, smoking during pregnancy, and asthma history; household count by region-adjusted income; and Neighborhood Deprivation Index.

In primary analyses, exposure was averaged during phases of fetal morphological lung development. We examined associations with exposures averaged across the entire prenatal period in secondary analyses.

We assessed potential effect modifiers of the association between prenatal air pollution exposure and the primary outcome of current asthma by including a multiplicative interaction term in the model and examining p-values for the interaction term. Stratum-specific RRs were extracted from these models as well. Maternal asthma history and child sex were modeled as binary variables. Among those who were not active smokers during pregnancy, maternal ETS exposure, assessed via urinary cotinine, was first modeled as a continuous variable. Given the large proportion of subjects with urinary cotinine below the limit of detection, we also considered ETS as a binary variable comparing those in the highest quartile of urinary cotinine to those in the other three quartiles in a post-hoc analysis.

Sensitivity analyses to assess the robustness of our primary findings included: 1) a complete case analysis; 2) an extended model further adjusting for paternal asthma history, pre-pregnancy BMI, and several postnatal factors (history of bronchiolitis in infancy, breastfeeding, postnatal ETS exposure, furry pets, firstborn status, and season of birth); 3) further adjustment for early life postnatal pollutant exposures, 4) assessment of exposures in trimesters of pregnancy; 5) a multi-pollutant model simultaneously adjusting for NO_2, O_3, and $PM_{2.5}$ within the same exposure window; 6) a mutually-adjusted model adjusting for the same pollutant in other exposure windows; and 7) leaving out one of the three cohorts or one of the seven study sites at a time.

In a post hoc secondary analysis, we additionally implemented Bayesian Kernel Machine Regression (BKMR) using the *bkmr* R package (Bobb et al. 2015, 2018) to assess the relationship between prenatal air pollution and our primary outcome of current asthma at age 8, allowing for interactions between pollutant exposures (NO_2, O_3, and $PM_{2.5}$). We fit the models with 50,000 iterations of a Markov chain Monte Carlo algorithm. This secondary analysis was conducted in the subset of participants with complete data for all covariates utilized in the primary model.

3. Results

Characteristics of the sample of 1279 mother-child dyads are shown in Table 1 and by current asthma status in Supplemental Table 1. Among the women in this sample, 41.7% self-identified as Black, 49.0% as White, and 9.4% as another race or multiple races. Participants with a range of education levels were included: 8.5% had not completed high school, 34.9% completed high school, 32.4% graduated from college or technical school,

and 24.2% completed at least some graduate work or had a graduate or professional degree. Overall, 17.7% of mothers had a history of asthma.

The average age of children at outcome assessment was 8.9 years (SD 0.7); 51.4% of children were female and 48.6% were male. At the age 8–9 study visit, 119 (9.3%) of children had current asthma, 61 (4.8%) had current asthma with a recent exacerbation, and 84 (6.6%) had current asthma in addition to other atopic disease (Table 1). Some subgroups had lower rates of asthma; only 4.5% of the PWG cohort met the criteria for current asthma compared to 11.0% and 6.8% of the CANDLE and TIDES cohorts, respectively.

ISAAC questionnaire data from the age 4 study visit were available for 1192 (93.2%) children, of which 59.7% were classified as never wheeze, 21.6% as early wheeze, 11.3% as late wheeze, and 7.4% as persistent wheeze. In this sample with ISAAC data at both timepoints, 51.5% of those with ever asthma at age 4 also met criteria for current asthma at age 8 and 64.4% of children with current asthma at age 8 reported ever asthma at age 4.

Mean prenatal air pollution exposure during specified fetal lung development phases ranged from 9.4 to 9.5 $\mu g/m^3$ for $PM_{2.5}$, 8.4–9.0 ppb for NO_2, and 25.2–26.4 ppb for O_3 (Table 2). While mean levels of O_3 exposures were consistent across exposure windows, O_3 exposures tended to be negatively correlated with O_3 exposures in other exposure periods due to strong seasonal variability in this pollutant (Supplemental Table 2).

We observed null associations between prenatal air pollution and current asthma at age 8–9, asthma with recent exacerbation, and asthma with other atopic disease, for all pollutants and exposure periods (Table 3). For current asthma and asthma with other atopic disease, the largest RRs were observed for $PM_{2.5}$ exposure in the pseudoglandular phase (e.g. current asthma RR_{adj} = 1.15, CI: 0.88–1.51) though CIs still included the null. RRs for pseudoglandular O_3 and canalicular $PM_{2.5}$ exposures were elevated for asthma with recent exacerbation (RR_{adj} =1.20, CI: 0.95–1.51, and RR_{adj} = 1.31, CI: 0.91–1.87, respectively).

Further secondary and sensitivity analyses using complete case analysis, exposures averaged over trimesters, mutually-adjusted models adjusted for other prenatal exposure windows or for early postnatal exposure windows, and multipollutant models, generally produced similar results to the corresponding primary analysis of current asthma for each pollutant (Supplemental Tables 3–6). Shifts in estimated RRs were modest with additional covariate adjustment. Small differences in effect estimates, including shifts across the null, were observed in some multipollutant models (e.g. for NO_2 exposure in the saccular phase, the RR in the primary analysis was 1.03 [CI: 0.76–1.38] and in the multipollutant model was 0.97 [CI: 0.68–1.38]). However, these shifts were small and confidence intervals were nearly the same with a slight widening in the multipollutant model. When leaving out one cohort or site from the model, trends varied by pollutant. For O_3 in the canalicular window, leaving out CANDLE tended to increase RRs (RR_{adj} = 1.33, CI: 0.90–1.96) compared to the primary analysis. For $PM_{2.5}$, when CANDLE participants were removed from the sample no adverse associations were observed but when TIDES or GAPPS participants were removed from the sample the RRs tended to be higher, particularly for exposures in the canalicular

window (e.g. RR_{adj} = 1.29, CI: 0.93–1.77, when TIDES participants were left out of the sample).

Estimated ORs for wheezing trajectories with the never wheeze category as the referent, generally had confidence intervals that included the null (Table 4). For $PM_{2.5}$, ORs were elevated for persistent wheeze with exposures in pseudoglandular (RR_{adj} = 1.20, CI: 0.83–1.73) and canalicular (RR_{adj} = 1.26, CI: 0.89–1.78) phase.

No statistically significant effect modification for associations of each air pollutant with current asthma was observed by child sex or by ETS (Fig. 1, Supplemental Table 7), though there was some suggestion of an adverse association between $PM_{2.5}$ in the pseudoglandular phase and current asthma only among girls (RR_{adj} = 1.42 among girls, CI: 0.95–2.13 and RRadj = 1.03 among boys, CI: 0.76–1.40, $p_{interaction}$ = 0.13). In interaction models, some estimated RRs (e.g. for NO_2 in the saccular phase) suggest an adverse association specific to those without maternal history of asthma (RR_{adj} = 1.21, CI: 0.88–1.67), with a p-value for interaction of 0.03 (Fig. 1).

In a post hoc secondary analysis using BKMR (Supplemental Fig. 2), some patterns differed slightly from the primary analysis but confidence intervals include the null (e.g. we observed a suggestion of an association of increased risk of asthma with higher NO_2 exposure in the saccular window). No strong evidence of interaction between the pollutants was observed.

4. Discussion

In this study, estimates of associations of spatiotemporally-resolved $PM_{2.5}$, NO_2, and O_3 averaged within fetal lung developmental phases, with asthma at age 8–9 and wheezing trajectories, had confidence intervals including the null. While no statistically significant associations were identified, some trends in the magnitude of effect estimates were observed, with elevated estimates observed particularly for $PM_{2.5}$ and O_3 exposures early in pregnancy and for asthma and wheeze phenotypes with symptoms and exacerbations persisting into middle childhood. Adverse associations tended to be specific to the group without a maternal history of asthma in effect modification analyses. We found little evidence of any associations with NO_2 or for effect modification by fetal sex or ETS.

Prior epidemiologic literature on prenatal air pollution and asthma has been the most consistent for prenatal NO_2 and PM exposures (Hehua et al., 2017; Bettiol et al., 2021). Several studies have linked prenatal $PM_{2.5}$ exposures—primarily in the canalicular stage, though some in the saccular phase—with child asthma (Leon Hsu et al., 2015; Lavigne et al., 2018; Lee et al., 2018, p. 201; Jung et al., 2019; Hazlehurst et al., 2021; Chen et al., 2022). Asthma can be more difficult to diagnose at the preschool age, but prior studies have largely focused on this age group and a meta-analysis of prenatal $PM_{2.5}$ and child asthma found stronger associations for child asthma and wheezing before age 3, relative to older ages (Yan et al., 2020). In the present study of outcomes in middle childhood when asthma diagnosis is easier and cases of early wheezing may have resolved, we did not observe the same consistent associations of current asthma at age 8–9 with prenatal exposures and these results indicate that any underlying causal association in this age group may be modest.

Differences across child development may be due to less proximal exposures for asthma at age 8–9, the reduced sample size at the middle childhood (age 8–9) study visit, or different risk factors and etiologies for asthma that resolves after early childhood versus asthma that persists into or develops in middle childhood or is not well-controlled. Interventions during childhood to reduce asthma triggers and promote airway health may also buffer associations with prenatal exposures in this older age group.

In contrast to NO_2 and $PM_{2.5}$, fewer studies have examined prenatal O_3 exposure and child asthma in any age group. Some observed inverse associations between prenatal O_3 and child asthma, hypothesized to be a result of inverse correlations with traffic-related pollutant exposures, while others found an increased risk of asthma with higher O_3 exposure during the prenatal window (Clark et al., 2010; Sbihi et al., 2016; To et al., 2020). A study in China identified an association between O_3 exposure during the second trimester and child wheezing among preschool children (Zhu et al., 2022). We observed some elevated risk of both early and persistent wheezing, as well as asthma with a recent exacerbation with higher O_3 exposure.

Variability in the literature also exists across airway outcomes. Prior studies have generally identified less consistent associations with wheeze relative to asthma (Bettiol et al., 2021). A study in Mexico identified associations of wheeze with $PM_{2.5}$ only among some subgroups (Rosa et al., 2017); studies in Spain and Norway also did not observe associations between NO_2 and child wheeze (Aguilera et al., 2013; Madsen et al., 2017). In our study, ORs tended to be higher for wheezing phenotypes that begin early in life and continue throughout childhood. Further research assessing wheeze more frequently over the course of development is needed to confirm these suggested trends.

Some subgroups may be more susceptible to the effects of environmental exposures including air pollution on child asthma and wheeze. Exposure to ETS may increase susceptibility to potential adverse health effects of other inhaled pollutants; prior studies have examined interaction of these exposures during early postnatal years, and a small number have identified synergism of prenatal exposures including $PM_{2.5}$ and PAHs with ETS (Rosa et al., 2011; Rivera et al., 2021; Moore et al., 2021). In our study, we did not find evidence of effect modification by ETS. This finding differs from that of Rivera et al. who observed an association of prenatal $PM_{2.5}$ with child wheeze assessed at age 6–8 among children born to women who were exposed to ETS during pregnancy (Rivera et al., 2021). Our use of a short-term indicator, urinary cotinine, as a biomarker of ETS may not have fully captured average exposure over pregnancy or ETS exposure during the critical window of interest, preventing detection of effect modification.

While effect estimates in our study had confidence intervals including the null, prior evidence highlights potential mechanisms by which prenatal exposures may affect the developing lung in utero, resulting in impaired airway health in childhood. The trends observed in our study suggest some elevated risks of asthma and wheeze phenotypes with higher pollutant exposures early in pregnancy. Air pollution exposures early in pregnancy may disrupt cellular differentiation and branching morphogenesis via systemic inflammation, oxidative stress, and epigenetic mechanisms, while late pregnancy exposures

may interfere with structural and functional growth of the lung as well as impair maturation of the immune system through influences on immune programming (Korten et al., 2017). Toxicologic studies demonstrate that $PM_{2.5}$ exposure in mid-to-late prenatal windows causes an inflammatory response in the placenta and disrupts the lung epithelium (Yue et al., 2020), and that mitochondrial reactive oxygen species due to $PM_{2.5}$ exposure leads to mitochondrial dysfunction in the lungs (Wang et al., 2021). Animal models also indicate prenatal O_3 exposures initiate inflammatory cascades and promote oxidative stress resulting in immune dysregulation and poor airway health in offspring (Fu et al., 2020).

Several factors in this study may have limited our ability to detect associations, if true causal relationships exist. In some subgroups in the analytic sample, rates of reported asthma were low. The prevalence of asthma was lower in this sample than in several prior studies (Leon Hsu et al., 2015; Lee et al., 2018). Asthma outcomes in this study relied on participant report and may be subject to recall bias and self-reporting bias. However, these outcomes are based on standard, widely-used questionnaires; the ISAAC survey has had widespread application for characterizing asthma outcomes in this age group (Asher et al., 1995). Additionally, wheezing trajectories were defined based on only two timepoints. Exposures to ambient air pollution were estimated at the residential locations, as is commonly done in air pollution epidemiology, and did not account for potential indoor sources of exposure or exposure at other locations. Ambient air pollution levels were generally low in this sample. The limited variability for some pollutants, particularly within the Memphis study site that contributes the largest portion of the analytic sample, may further have limited our ability to observe associations in this analysis. The chemical composition of $PM_{2.5}$ may also have varied by site. A further limitation is that we were only able to adjust for early postnatal (birth to age 4) air pollutant exposures but due to data availability were not able to account for exposures in school-age windows, potentially resulting in residual confounding. Those with certain pre-existing medical conditions may be more vulnerable to the effects of air pollution exposures, but the selection of participants in this cohort included the restriction to pregnancies considered low medical risk at the time of enrollment in CANDLE and TIDES. These inclusion criteria may limit the generalizability of these findings to higher risk populations or to populations in other geographic areas.

This study had several important strengths. We utilized well-validated exposure models with point-based spatial resolution and explored associations with multiple pollutants, including O_3, which is currently understudied. Exposure windows were motivated based on our understanding of the biological phases of fetal lung development, rather than on trimesters. The sociodemographic diversity of the ECHO-PATHWAYS Consortium is also a strength of this analysis. Despite knowledge that asthma is a complex, heterogeneous disease, few studies have investigated environmental risk factors for specific asthma or wheeze phenotypes; our study examined several subgroups of asthma cases as well as wheezing trajectories across early and mid-childhood using data from two study visits. We were also able to investigate effect modification by several factors, including ETS assessed via cotinine biomarker.

5. Conclusions

Although we observed consistently null associations of prenatal air pollution with current asthma in middle childhood and therefore these results should be interpreted cautiously, trends in the effect estimates were suggestive of early developmental insults of $PM_{2.5}$ and O_3 on childhood respiratory conditions, including major public health concerns such as asthma and persistent wheezing in middle childhood. Observed associations with $PM_{2.5}$ and O_3 tended to be higher for exposures in earlier phases of fetal lung development and for respiratory outcomes that continue into middle childhood. Disaggregation of the outcome, particularly in the case of complex, heterogeneous outcomes such as asthma, allows for more precise investigation of underlying etiologies and this type of study advances clinical understanding of risk factors for various subtypes of the disease. Given the modest number of asthma cases in this study sample, future work in cohort studies with larger counts of each asthma subgroup, additional timepoints of outcome ascertainment, in settings with greater exposure variability, may further support the trends we observed in this well-characterized cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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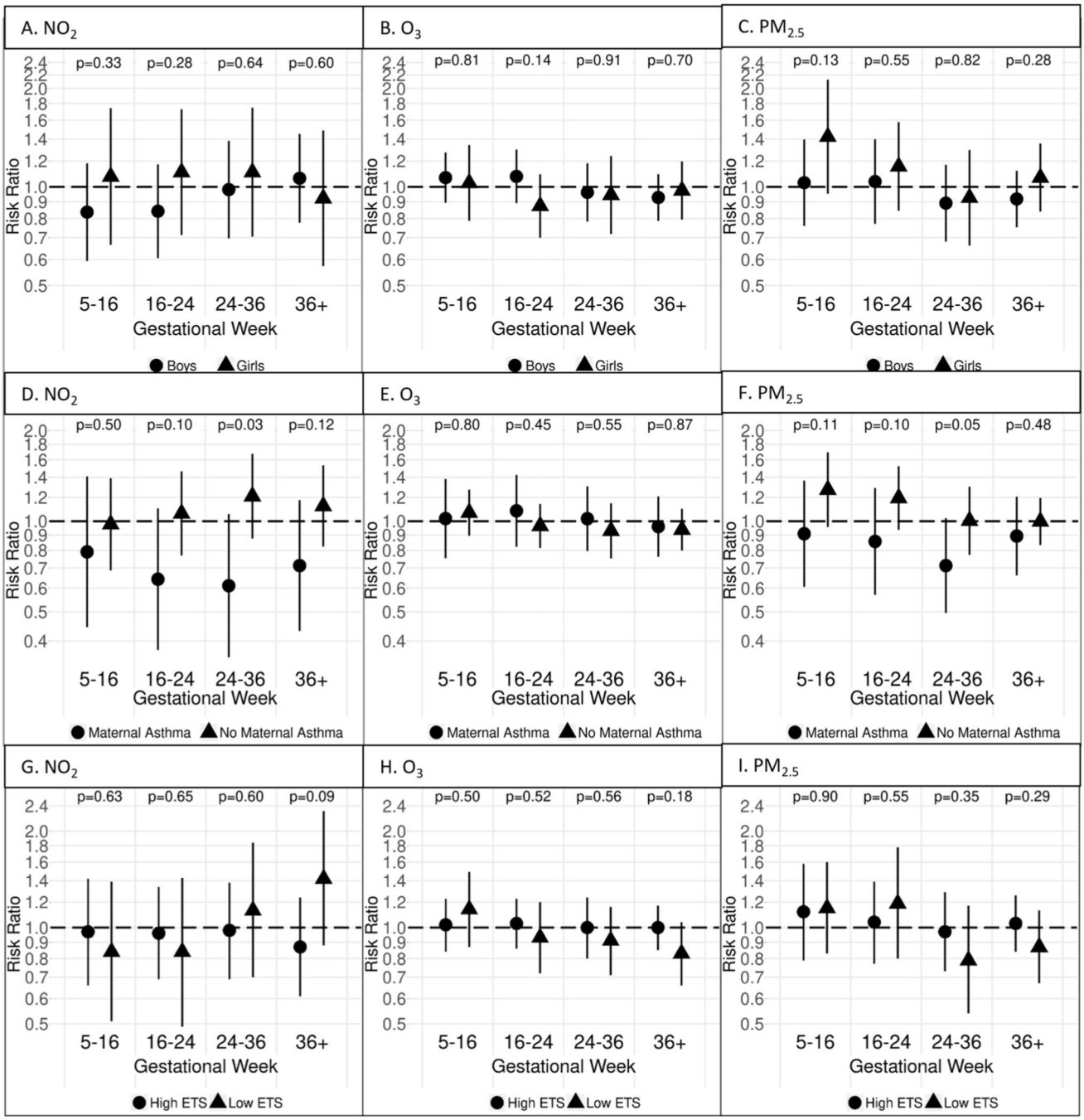

Fig. 1.

Effect modification of associations between prenatal air pollution and current asthma at age 8–9 by child sex, prenatal environmental tobacco smoke exposure, and maternal history of asthma. Risk ratios for current asthma and corresponding 95% confidence intervals are shown for associations with NO_2 in the first column (panels A, D, and G), O_3 in the second column (panels B, E, and H), and $PM_{2.5}$ in the third column (panels C, F, and I). Estimates are reported per 5 ppb NO_2, 5 ppb O_3, and 2 μg/m^3 $PM_{2.5}$. All models are adjusted for child age, sex, study site, birth year, maternal education, household income*household

count, maternal race, maternal smoking during pregnancy, maternal history of asthma, and Neighborhood Deprivation Index, as well as a product term between the air pollutant exposure and effect modifier of interest. P-values for the product interaction term are included at the top of each panel. In the first row (panels A–C), sex-specific effect estimates are shown for models including the full analytic sample (N = 1279). No evidence of effect modification by child sex was observed (all $p_{interaction}$ >0.05). In the second row (panels D–F), effect estimates are shown among those with maternal history of asthma and those without maternal history of asthma for models including the full analytic sample (N = 1279). For NO_2 and $PM_{2.5}$, those without maternal history of asthma tended to have higher risk ratios than among those with a maternal history of asthma (e.g. p-value for interaction of NO_2 in the 24–36 week window and maternal asthma = 0.03), though confidence intervals for strata-specific risk ratios all include the null. In the third row (panels G–I), effect estimates are shown for associations in a post-hoc analysis among those with high versus low environmental tobacco smoke (ETS) exposure, when the sample was restricted to non-smokers (N = 1155). High ETS was defined as participants with a urinary cotinine value in the highest quartile of the sample (>1.43 ng/mL) and low ETS was defined as participants with a urinary cotinine value in the lowest three quartiles (≤1.43 ng/mL). No effect modification by ETS was observed (all $p_{interaction}$ >0.05).

Table 1

Characteristics of the analytic sample of 1279 mother-child dyads from the ECHO-PATHWAYS Consortium.

	Analytic Sample (n = 1279) [a]	
Child age (years), mean (SD)	8.9	(0.7)
Girls, n (%)	657	(51.4)
Boys, n (%)	622	(48.6)
Maternal race, n (%)		
Asian	29	(2.3)
Black	531	(41.7)
White	624	(49.0)
Multiple races	57	(4.5)
All other self-descriptions	33	(2.6)
Maternal education, n (%)		
< High school	108	(8.5)
High school completion	445	(34.9)
Graduated college or technical school	413	(32.4)
Some graduate work, graduate/professional degree	309	(24.2)
Maternal history of asthma, n (%)		
Yes	214	(17.7)
No	995	(82.3)
Paternal history of asthma, n (%)		
Yes	177	(15.8)
No	944	(84.2)
Neighborhood Deprivation Index (NDI), mean (SD)	0.15	(0.86)
Household income (USD), mean (SD)	65200	(54000)
Household count, n (%)		
2–3 people	239	(20.1)
4 people	491	(41.4)
5 people	267	(22.5)
≥6 people	190	(16)
Birth season,[b] n (%)		
Cold	587	(45.9)
Warm	692	(54.1)
Firstborn, n (%)		
Yes	726	(57.3)
No	542	(42.7)
Breastfeeding, n (%)		
Never	290	(22.3)
≤6 months	754	(60.8)
>6 months	204	(16.9)
History of bronchiolitis in infancy, n (%)		

	Analytic Sample (n = 1279) [a]	
Yes	170	(13.7)
No	1072	(86.3)
Pre-pregnancy BMI, mean (SD)	27.4	(7.6)
Maternal smoking during pregnancy, n (%)		
Yes	124	(9.7)
No	1155	(90.3)
Urinary cotinine among non-smokers (ng/mL), mean (SD)	2.1	(8.8)
Early life environmental tobacco smoke,[c] n (%)		
Yes	240	(20.1)
No	952	(79.9)
Furry pets in early life, n (%)		
Yes	592	(47.2)
No	663	(52.8)
Recruitment site, n (%)		
CANDLE (Memphis, TN)	810	(63.3)
TIDES (San Francisco, CA)	72	(5.6)
TIDES (Minneapolis, MN)	109	(8.5)
TIDES (Rochester, NY)	109	(8.5)
TIDES (Seattle, WA)	90	(7)
PWG (Seattle, WA)	50	(3.9)
PWG (Yakima, WA)	39	(3)
Child respiratory health outcome measures, n (%)		
Current asthma[d]		
Yes	119	(9.3)
No	1160	(90.7)
Current asthma with recent exacerbation[d]		
Yes	61	(4.8)
No	1218	(95.2)
Current asthma with other atopic disease[d]		
Yes	84	(6.6)
No	1190	(93.4)
Wheezing trajectories[e]		
Never wheezing	712	(59.7)
Early wheezing	257	(21.6)
Persistent wheezing	88	(7.4)
Late wheezing	135	(11.3)

[a] Abbreviations: CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood study, TIDES = The Infant Development and Environment Study, PWG = PATHWAYS-Global Alliance to Prevent Prematurity and Stillbirth (GAPPS). Number (%) missing for individual variables include maternal race: 5 (0.3%), maternal education: 4 (0.4%), maternal asthma: 70 (5.5%), paternal asthma: 158 (12.4%), income 102 (8.0%), household count 92 (7.2%), first born 11 (0.9%), breastfeeding: 31 (2.4%), bronchiolitis: 37 (2.9%), pre-pregnancy BMI: 15 (1.2%), cotinine: 69 (5.4%), child secondhand smoke 87 (6.8%), and furry pets 24 (1.9%).

[b] Warm season was defined as April–September; cold season was defined as October–March.

[c] Environmental tobacco smoke exposure was ascertained via questionnaire at the age 4–6 study visit.

[d] Current asthma overall and with either recent exacerbation or other atopic disease were defined based on ISAAC questionnaire data collected at the age 8–9 study visit.

[e] Wheezing trajectories were defined based on ISAAC questionnaire data collected at both the age 4–6 and age 8–9 study visits. Early wheeze was defined as those who reported a history of ever wheeze at the age 4–6 study visit, but did not report wheeze in the past 12 months at the age 8–9 study visit. Late wheeze was defined as those who reported ever wheezing at age 8–9 but had not reported any wheeze at or before age 4–6. Persistent wheeze was defined as those reporting wheeze at both study visits (i.e. ever wheeze at age 4–6 and wheeze in the past 12 months at age 8–9). Those with a response of no to wheeze at both age 4–6 and age 8–9 were considered the referent group, never wheeze. Those with a response of "Don't know" at either time point were considered missing.

Table 2

Air pollution exposures.

Pollutant and Exposure Window	Mean	SD	Min.	Q1	Median	Q3	Max.
NO_2 (ppb)							
Pseudoglandular (5–16 weeks)	8.7	3.0	2.2	6.5	8.4	10.6	25.1
Canalicular (16–24 weeks)	9.0	3.8	1.5	6.1	8.5	11.5	25.5
Saccular (24–36 weeks)	8.6	3.8	1.5	5.8	8.2	11.1	31.1
Alveolar (36+ week)	8.4	3.6	1.8	5.8	7.9	10.7	28.6
Entire pregnancy	8.6	3.9	1.4	5.6	8.1	11.0	35.5
Postnatal (birth – age 4)	8.9	2.5	2.0	7.1	9.0	10.4	18.8
O_3 (ppb)							
Pseudoglandular (5–16 weeks)	25.8	3.5	13.8	23.8	26.1	28.2	36.5
Canalicular (16–24 weeks)	25.2	6.5	9.8	19.5	25.4	30.9	43.1
Saccular (24–36 weeks)	26.2	6.7	8.9	20.6	27.4	31.8	43.3
Alveolar (36+ week)	26.4	6.1	9.5	21.4	27.6	31.6	44.4
Entire pregnancy	25.8	7.2	6.2	19.3	26.5	31.9	46.5
Postnatal (birth – age 4)	26.0	2.5	16.9	25.6	26.4	27.4	35.0
$PM_{2.5}$ ($\mu g/m^3$)							
Pseudoglandular (5–16 weeks)	9.4	2.0	3.1	8.5	9.9	10.9	13.8
Canalicular (16–24 weeks)	9.4	2.4	2.3	8.2	9.7	10.7	17.0
Saccular (24–36 weeks)	9.5	2.5	2.2	8.3	9.9	10.9	22.0
Alveolar (36+ week)	9.5	2.4	2.1	8.2	9.9	10.9	16.9
Entire pregnancy	9.6	2.9	2.0	7.9	9.7	11.3	23.1
Postnatal (birth – age 4)	8.8	1.6	3.3	8.0	9.4	9.9	11.6

Abbreviations: SD = standard deviation, NO_2 = nitrogen dioxide, O_3 = ozone, $PM_{2.5}$ = fine particulate matter.

Table 3

Relative risks (95% confidence intervals) for current asthma at age 8–9 by air pollution in fetal lung development phases among 1279 mother-child dyads.

Pollutant	Model[a]	Pseudoglandular (5–16 weeks)		Canalicular (16–24 weeks)		Saccular (24–36 weeks)		Alveolar (36+ weeks)	
		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Current asthma									
NO_2	1	1.08	(0.82, 1.42)	1.04	(0.81, 1.34)	1.13	(0.87, 1.46)	1.13	(0.88, 1.45)
	2	0.92	(0.66, 1.28)	0.93	(0.70, 1.25)	1.03	(0.76, 1.38)	1.01	(0.76, 1.35)
O_3	1	1.03	(0.89, 1.21)	1.00	(0.86, 1.16)	0.95	(0.80, 1.12)	0.92	(0.80, 1.05)
	2	1.05	(0.90, 1.23)	1.00	(0.85, 1.16)	0.96	(0.80, 1.14)	0.94	(0.82, 1.08)
$PM_{2.5}$	1	1.17	(0.90, 1.52)	1.11	(0.88, 1.41)	0.99	(0.77, 1.26)	1.01	(0.85, 1.20)
	2	1.15	(0.88, 1.51)	1.08	(0.84, 1.39)	0.90	(0.70, 1.16)	0.97	(0.82, 1.15)
Current asthma with recent exacerbation									
NO_2	1	1.00	(0.68, 1.46)	1.00	(0.70, 1.41)	1.07	(0.74, 1.55)	1.15	(0.76, 1.75)
	2	0.77	(0.50, 1.18)	0.84	(0.56, 1.25)	0.92	(0.60, 1.39)	0.98	(0.64, 1.52)
O_3	1	1.16	(0.93, 1.44)	0.99	(0.80, 1.21)	0.96	(0.77, 1.20)	0.94	(0.76, 1.15)
	2	1.20	(0.95, 1.51)	0.97	(0.79, 1.20)	0.96	(0.77, 1.20)	0.96	(0.78, 1.17)
$PM_{2.5}$	1	0.97	(0.65, 1.47)	1.32	(0.94, 1.86)	1.21	(0.85, 1.73)	0.95	(0.72, 1.27)
	2	0.93	(0.59, 1.47)	1.31	(0.91, 1.87)	1.10	(0.77, 1.56)	0.89	(0.67, 1.19)
Current asthma with other atopic disease									
NO_2	1	0.93	(0.66, 1.31)	0.95	(0.69, 1.32)	0.98	(0.71, 1.36)	1.01	(0.74, 1.37)
	2	0.78	(0.52, 1.16)	0.89	(0.61, 1.29)	0.94	(0.64, 1.38)	0.91	(0.63, 1.32)
O_3	1	1.03	(0.85, 1.24)	0.97	(0.80, 1.17)	0.95	(0.78, 1.17)	1.02	(0.86, 1.20)
	2	1.04	(0.86, 1.26)	0.94	(0.78, 1.14)	0.95	(0.77, 1.17)	1.05	(0.88, 1.24)
$PM_{2.5}$	1	1.14	(0.82, 1.57)	0.99	(0.74, 1.34)	0.80	(0.59, 1.09)	0.99	(0.81, 1.22)
	2	1.18	(0.85, 1.63)	0.95	(0.69, 1.32)	0.73	(0.53, 1.00)	0.95	(0.78, 1.17)

[a]Model 1 is adjusted for child age, sex, study site, and birth year. Model 2 additionally adjusts for maternal education, household income, household count, household income*household count, maternal race, maternal smoking during pregnancy, maternal history of asthma, and Neighborhood Deprivation Index. All models include a sample size of 1279. Estimates are reported per 5 ppb NO_2, 5 ppb O_3, and 2 μg/m^3 $PM_{2.5}$. Abbreviations: RR = relative risk, CI = confidence interval, NO_2 = nitrogen dioxide, O_3 = ozone, $PM_{2.5}$ = fine particulate matter.

Table 4

Odds ratios (95% confidence intervals) for associations between prenatal air pollution and wheezing trajectories.

Pollutant	Model[a]	Pseudoglandular (5–16 weeks)		Canalicular (16–24 weeks)		Saccular (24–36 weeks)		Alveolar (36+ weeks)	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Early wheezing									
NO_2	1	0.99	(0.79, 1.24)	0.88	(0.70, 1.10)	0.86	(0.68, 1.09)	0.88	(0.70, 1.09)
	2	0.98	(0.76, 1.27)	0.86	(0.68, 1.10)	0.84	(0.65, 1.09)	0.86	(0.68, 1.08)
O_3	1	1.02	(0.90, 1.15)	1.06	(0.93, 1.20)	1.13	(0.98, 1.30)	0.99	(0.88, 1.10)
	2	1.02	(0.90, 1.16)	1.05	(0.92, 1.20)	1.13	(0.98, 1.30)	1.00	(0.89, 1.12)
$PM_{2.5}$	1	0.98	(0.80, 1.20)	1.04	(0.87, 1.25)	1.03	(0.84, 1.26)	0.97	(0.85, 1.12)
	2	1.01	(0.82, 1.24)	1.06	(0.88, 1.27)	1.03	(0.84, 1.28)	0.97	(0.84, 1.12)
Persistent wheezing									
NO_2	1	1.15	(0.80, 1.66)	0.92	(0.63, 1.33)	1.03	(0.70, 1.53)	1.13	(0.79, 1.61)
	2	0.96	(0.62, 1.49)	0.77	(0.50, 1.19)	0.92	(0.59, 1.46)	1.00	(0.66, 1.50)
O_3	1	1.08	(0.88, 1.32)	1.17	(0.95, 1.44)	1.04	(0.83, 1.30)	0.88	(0.74, 1.06)
	2	1.11	(0.90, 1.37)	1.16	(0.94, 1.45)	1.04	(0.83, 1.32)	0.91	(0.75, 1.10)
$PM_{2.5}$	1	1.17	(0.83, 1.65)	1.30	(0.94, 1.81)	1.02	(0.71, 1.49)	0.92	(0.72, 1.17)
	2	1.20	(0.83, 1.73)	1.26	(0.89, 1.78)	0.95	(0.64, 1.41)	0.86	(0.67, 1.10)
Late wheezing									
NO_2	1	1.02	(0.77, 1.34)	1.05	(0.80, 1.38)	0.89	(0.66, 1.20)	0.71	(0.53, 0.95)
	2	1.13	(0.83, 1.53)	1.17	(0.87, 1.57)	0.96	(0.70, 1.33)	0.72	(0.53, 0.99)
O_3	1	0.94	(0.81, 1.11)	0.92	(0.78, 1.07)	1.05	(0.88, 1.25)	1.06	(0.91, 1.22)
	2	0.93	(0.79, 1.09)	0.90	(0.77, 1.05)	1.04	(0.87, 1.24)	1.06	(0.91, 1.23)
$PM_{2.5}$	1	1.13	(0.88, 1.45)	0.90	(0.70, 1.15)	0.76	(0.57, 1.00)	0.97	(0.81, 1.16)
	2	1.18	(0.92, 1.52)	0.93	(0.73, 1.19)	0.77	(0.58, 1.02)	0.99	(0.82, 1.19)

[a]Model 1 is adjusted for child age, sex, study site, and birth year. Model 2 additionally adjusts for maternal education, household income, household count, household income*household count, maternal race, maternal smoking during pregnancy, maternal history of asthma, and Neighborhood Deprivation Index. All models include a sample size of 1192. Estimates are reported per 5 ppb NO_2, 5 ppb O_3, and 2 μg/m^3 $PM_{2.5}$. Abbreviations: OR = odds ratio, CI = confidence interval, NO_2 = nitrogen dioxide, O_3 = ozone, $PM_{2.5}$ = fine particulate matter.