“The Impact of Air Pollution Exposure in Early Childhood on Atopic Dermatitis in Preschool-Aged Children”

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Abstract

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Atopic dermatitis (AD) is a common inflammatory skin condition in children influenced by genetic and environmental factors, potentially including air pollution. While research has linked air pollution to the development of allergic diseases, such as asthma, few studies have examined AD, and none of these have been based in the United States. Understanding the role of early-life air pollution exposure in AD development could inform biological mechanisms and prevention strategies. This study evaluated associations between early-life exposure to ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$) and AD status at ages 4-6 years and explored whether associations differed by child sex. We conducted a prospective cohort study using data from 2,023 children in the ECHO PATHWAYS Consortium. Three AD outcomes were defined using caregiver report on the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire, and pollutant exposure at children's residential address during the first year was estimated using validated spatiotemporal models. Multivariable logistic regression models were used to examine associations between each pollutant and outcome, while adjusting for confounders. AD prevalence was 13-32%, with higher prevalence among non-Hispanic Black children. O_3 exposure during the first year of life was positively associated with current AD (aOR per 1-ppb increase = 1.08; 95% CI: 1.00, 1.17). No associations were observed for NO_2 or $PM_{2.5}$

exposure. Some evidence suggested sex-specific associations of NO_2, with higher NO_2 exposure associated with lower risk of AD in boys only, but the biological plausibility for protective effects is low. We conclude that early-life O_3 exposure may increase AD risk in early childhood, supporting O_3 as a potential modifiable environmental risk factor. Further studies on pollutant mixtures and biological mechanisms are needed.

Introduction

Atopic dermatitis (AD) is one of the most prevalent chronic conditions in children [1, 2]. It is an inflammatory and eczematous skin disease characterized by dry skin, recurrent erythema, itching, and scaling. Childhood AD affects between 1% and 40% of children worldwide, with AD prevalence increasing about 1.2% per decade [1,3,4]. Younger children have higher rates, with 60% of cases developing before age one and 85% by age five [2,3]. AD is generally more common in males, potentially due to biological factors [3, 5, 10]. In the U.S., about 24% of children under five had AD in 2021, with non-Hispanic Black children experiencing higher rates and greater severity compared to White children [3,5,9,10].

Currently, there is no cure for AD. Its onset often signals the beginning of the “atopic march” a sequence of allergic manifestations, with AD typically followed by asthma and rhinitis [2, 11]. AD not only impacts the quality of life for patients and their families but also generates significant healthcare costs. On average, caregivers spend more than $1000 per year out of pocket on AD-related care, and an estimated 5 billion in annual USD healthcare costs are attributed to this condition [5]. Given that AD often precedes other allergic diseases, its prevention may help reduce the risk or severity of subsequent conditions, reducing the overall public health burden.

The causes of AD are not fully understood, though multiple factors such as genetics, family history, and others are implicated [6, 12]. Differences in AD prevalence across regions have led researchers to consider environmental contributors, including air pollution. Air pollution consists as a complex mix of gases, such as ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO), particulate matter of varying sizes, including respirable particles ($PM_{2.5}$ and PM_{10}). Biological mechanisms underlying a possible link between air pollution and AD could include oxidative

stress, skin barrier dysfunction, water loss, immune dysregulation, and proinflammatory responses, among others [6, 12].

While many studies have explored the association between air pollution and childhood allergic conditions, most commonly asthma [7, 13], fewer have focused on AD. Those that did show varied results for specific pollutants. O_3 exposure has been consistently associated with increased AD risk [7, 17]. However, findings for NO_2 and $PM_{2.5}$ are mixed: some studies report positive associations [7, 12, 15, 19, 21], whereas others find no such association [7, 14]. To our knowledge, no US-based studies on the relationships between air pollution and childhood AD have been conducted.

Scarce research has evaluated whether associations between air pollution and AD vary by individual characteristics, including sex. While some studies have reported no sex-specific differences [14, 17, 18, 19], others have identified sex-related differences in the effects of nitrogen dioxide (NO_2) on AD, though not for other pollutants [15]. Child sex may modify the relationship between air pollution and AD due to biological differences in immune system development and inflammatory pathways involved in the potential toxic effects of air pollution.

Over the past few decades, global exposure to air pollution has increased, partly driven by environmental changes such as the ongoing climate crisis [12]. A warming climate exacerbates air pollution levels, with wildfire smoke contributing to rising $PM_{2.5}$ concentrations [22, 23]. Although overall air pollution trends in the USA have decreased—with ozone (O_3) and particulate matter (PM_{10}) levels showing declines in recent years—a substantial proportion of children remain exposed to pollutant levels exceeding recommended standards. The US Environmental Protection Agency has shown that more than half of US children have been exposed to O_3 over regulatory levels over the past two decades, while $PM_{2.5}$ levels have fluctuated and increased in recent years [24]. This study aims to elucidate whether exposure to early life air pollution—specifically, fine particulate matter ($PM_{2.5}$), ozone (O_3), and nitrogen dioxide (NO_2)—is associated with an increased risk of developing AD by the age of 4 to 6 years in the US-based ECHO PATHWAYS consortium as primary aim. A secondary aim is to determine whether these associations vary by child sex.

Methods

Study design

We conducted a prospective cohort study to investigate the association between exposure to air pollution during the first year of life and the diagnosis of AD in children aged 4-6 years. We analyzed three air pollutants separately: $PM_{2.5}$, NO_2, and O_3.

Study setting

Data was obtained through the ECHO PATHWAYS (ECHO Prenatal and Early Childhood Pathways to Health) Consortium, a collaboration of three pre-existing pregnancy cohorts - CANDLE, GAPPS, TIDES - representing diverse populations across the US. Starting in 2017, the consortium acquired extant data from 2,684 mother-child dyads who had previously enrolled in the three original cohorts. The consortium collected new data on the dyads under a unified protocol from 2017 through 2023. The overall goal of ECHO PATHWAYS was to examine the independent and combined impacts of pregnancy and childhood chemical exposures and psychosocial stressors on child neurodevelopment and airway health [25]. Extant data from the cohorts along with new ECHO PATHWAYS data were harmonized in one pooled dataset.

Study subjects

Eligible participants included children from all three ECHO PATHWAYS Consortium cohorts who had completed the International Study of Asthma and Allergies in Childhood (ISAAC) survey at a study visit between ages 4 and 6 years and who had complete residential address history data. This current, secondary data analysis was approved by the Institutional Review Board (IRB) at the University of Washington. All original data collection was approved by local IRBs, and all participants provided written informed consent prior to participation.

Data collection

ECHO PATHWAYS visits were conducted at child ages 4–6 years and 8–10 years, with some variations in visit protocols and timing across cohorts. During visits, caregivers completed surveys covering child and family health, behaviors and lifestyle, demographics, and other important factors to child health and development. Respiratory health and related allergic conditions were assessed using the ISAAC survey at each visit [26]. Child exams and health assessments were also collected. Residential

addresses were collected at most visits and used to develop detailed address histories for each participant, including estimated dates of moves between locations, and all addresses were geocoded.

Assessment of exposures

Weekly exposure to $PM_{2.5}$, NO_2, and O_3 was estimated at the location of each residential address in the ECHO PATHWAYS cohort using validated national spatiotemporal models [25]. We calculated average exposure levels during each child's first year of life, applying time-weighted averaging in the case of moves. Each pollutant was treated as a continuous variable in analytic models and analyzed separately.

Assessment of outcomes

AD outcomes were defined using caregiver responses to the ISAAC survey when children were 4–6 years old [26, 28]. Three AD outcomes were characterized: current AD and location specific AD as primary outcomes, and ever AD as a secondary outcome. We applied these definitions:

- Current AD as affirmative response to both questions, "Has your child ever had an itchy rash that came and went for at least 6 months?" and "Has your child had this itchy rash at any time in the past 12 months?"
- Location-specific AD as current AD plus an additional affirmative response to the question, "Has this itchy rash at any time affected any of the following areas: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?"
- Ever AD as affirmative response to the question, "Has your child ever had eczema?"

Covariates

Based on our literature review, we identified potential confounders factors that may be correlated with exposure and also affect risk of outcome, including household income, maternal race and ethnicity, and site [6, 7, 27]. We considered maternal history of asthma, history of breastfeeding, having a pet at home, secondhand smoke exposure at age 4-6, and being first born to be precision variables, related only to the outcome. Sex was evaluated as a potential effect modifier [25]. Given our assumption of an association between long-term exposure (first year of life) and outcome, we did not adjust for temperature, season, or humidity as potential confounders.

Analysis

Variables and measurements

All outcome variables, current AD, location-specific AD, and ever AD, were treated as binary. Continuous measures included air pollutants (O_3, NO_2, and $PM_{2.5}$), child age, and household income. Categorical variables included maternal race (White, Black/African American, Asian, Other [Native Hawaiian/Other Pacific Islander, American Indian or Alaska Native, Multiple Race or Other]), maternal ethnicity (Hispanic/Latino vs. non-Hispanic/Latino), and maternal education (less than high school (HS), HS general Education Development (GED), vocational, technical or associates, bachelor's and graduate or professional school). Binary covariates included firstborn status, presence of pets in the home, secondhand smoke exposure at age 4, breastfeeding history (ever or none), and history of maternal asthma.

For the analytic sample, we included participants with data on air pollution exposure and at least one AD outcome. To address missing covariate data, we applied a complete case approach, excluding individuals with missing or ambiguous responses (e.g., “unknown”) for any covariates.

Statistical methods

All analyses were conducted using R Studio version 4.4.1. We first performed descriptive analyses to provide a comprehensive overview of our dataset and characterize our study population. We calculated frequencies and percentages for all categorical variables, and for continuous variables, we summarized means (SD) and medians (IQR).

We then employed multivariate logistic regression to calculate adjusted odds ratios (OR), and 95% confidence intervals (CI) for the association between long-term exposure to each pollutant and each AD outcome. Analyses were adjusted for potential confounders and precision variables, in two stages: a minimal model, with adjustment for site and age, and a main model, with additional adjustment for maternal race, maternal ethnicity, maternal education, maternal asthma, breastfeeding, household income, pets at home, first born and secondhand smoke exposure at age 4-6. Each pollutant was analyzed separately, in single-pollutant models, and coefficients were estimated per 1 unit increase in pollutant.

For Aim 2, we added interaction terms between pollutants and child sex to evaluate whether the relationship between exposure and AD outcomes differed multiplicatively by sex. Adjustment variables were the same as the main models described above.

Results

The final analytic sample included 2,023 participants, comprising 1,126 from CANDLE, 518 from TIDES, and 379 from the GAPPS cohort. The mean age of children at the time of assessment was 4.68 years (SD = 0.75). Among mothers, 50.7% were White, 81.8% had no history of asthma, and the mean household income was $67,746 (SD = $54,660). Among children in the overall sample, 47.5% were described by caregivers as White, and 91.9% as non-Hispanic/Latino. Most caregivers (76.6%) reported breastfeeding their child any time. A majority of children were not first-born (58%) and were unexposed to secondhand smoke either in the first year or life (63.2%) or at the time of the 4-6 year study visit (78.6%). Sex was evenly distributed, and pet ownership status was similarly balanced.

Across cohorts, CANDLE had a higher proportion of Black or African American participants and greater exposure to secondhand smoke in the first year of life. Maternal education varied by cohort: CANDLE had a higher proportion of mothers with high school or GED; TIDES had more mothers with graduate education; and GAPPS had the highest proportion of mothers with a bachelor's degree. Children in the GAPPS cohort were older at the time of assessment and less likely to be first born, compared to those in the other cohorts. Other characteristics were similar between cohorts. (Table 1).

Table 1. Characteristics of the study population by cohorts.

	Total number of participants (%)	**CANDLE**	**TIDES**	**GAPPS**
Total	2023 (100)	1126 (55.6)	518 (25.7)	379 (18.7)
Sex				
Female	1014 (50.1)	561 (49.9)	267 (51.5)	186 (49.1)
Male	1008 (49.9)	564 (50.1)	251 (48.5)	193 (50.9)
Unknown	1	1	0	0
Age at assessment				
Mean (SD)	4.68 (0.75)	4.44 (0.64)	4.52 (0.34)	5.61 (0.74)
Child Race				
White	934 (47.5)	309 (28.3)	336 (66.8)	289 (78.3)

Black or African American	787 (40.1)	715 (65.5)	63 (12.7)	9 (2.4)
Asian	44 (2.2)	8 (0.7)	29 (5.8)	7 (1.9)
Other	198 (10.2)	60 (5.5)	74 (14.7)	64 (17.4)
Unknown	60	34	16	10
Child Ethnicity				
Non-Hispanic/Latino	1807 (91.9)	1055 (96.6)	447 (89.2)	305 (81.5)
Hispanic/Latino	160 (8.1)	37 (3.4)	54 (10.8)	69 (18.5)
Unknown/NA	56	34	17	5
First Born				
Yes	829 (41.1)	445 (39.5)	268 (52.6)	116 (30.7)
No	1184 (58.9)	681 (60.5)	241 (47.4)	262 (69.3)
Unknown/NA	10	0	9	1
Maternal education				
Less than HS	77 (3.9)	59 (5.3)	15 (3.2)	3 (0.8)
HS GED	507 (25.8)	446 (39.8)	29 (6.2)	32 (8.6)
Vocational, technical or associates	307 (15.6)	143 (12.8)	66 (14.0)	98 (26.2)
Bachelors	556 (28.3)	285 (25.5)	140 (29.7)	131 (35.0)
Graduate or professional school	517 (26.4)	186 (16.6)	221 (46.9)	110 (29.4)
Unknown / NA	59	7	47	5
Income				
Mean (SD)	67746 (54660)	38958 (28469)	109479 (61731)	99684 (52271)
History of maternal asthma				
Yes	365 (18.2)	197 (17.7)	101 (19.5)	67 (18.0)
No	1638 (81.8)	916 (82.3)	417 (80.5)	305 (82.0)
Unknown/NA	20	13	0	7
Pet at home				
Yes	857 (50.1)	367 (42.7)	239 (50.7)	251 (66.2)
No	853 (49.9)	493 (57.3)	232 (49.3)	128 (33.8)
Unknown/NA	313	266	47	0
Maternal Race				
White	1015 (50.7)	347 (30.8)	368 (71.7)	300 (83.1)
Black or African American	773 (38.7)	710 (63.0)	55 (11.1)	8 (2.2)
Asian	54 (2.7)	9 (0.8)	31 (6.0)	14 (3.9)
Other	156 (7.9)	60 (5.4)	57 (11.2)	39 (10.8)
Unknown / NA	25	0	7	18
Maternal Ethnicity				
Non-Hispanic/Latino	1896 (94.2)	1105 (98.1)	44 (8.6)	51 (23.6)
Hispanic/Latino	116 (5.8)	21 (1.9)	468 (91.4)	323 (86.4)
Unknown/NA	11	0	6	5
Secondhand smoke (1st year)				
Yes	246 (36.8)	214 (73.3)	0	32 (8.5)
No	423 (63.2)	78 (26.7)	0	345 (91.5)

NA	1354	834	518	2
Secondhand smoke (Visit at age 4)				
Yes	432 (21.4)	344 (30.7)	58 (11.1)	30 (7.9)
No	1587 (78.6)	778 (69.3)	460 (88.9)	349 (92.1)
NA	4	4	0	0
Breastfeeding				
Did not breastfeed	456 (23.4)	398 (35.6)	37 (8.0)	21 (5.5)
Any breastfeed	1496 (76.6)	720 (64.4)	423 (92.0)	353 (94.5)
Unknown / NA	71	8	58	5

Based on survey responses, 13.9% of participants were identified as having current AD, 11.8% as having location-specific AD, and 32.5% as having ever AD. The prevalence of current and location-specific AD varied across cohorts, with CANDLE showing higher rates compared to TIDES and GAPPS (Table 2). Differences in participant characteristics emerged by AD outcomes. Participants with current and location-specific AD were more likely to have pets at home and to have been exposed to secondhand smoke during the first year of life. In contrast, those with ever AD had lower exposure rates. Current and location-specific AD groups included a higher proportion of Black or African American children and mothers, whereas the ever AD group had a more even distribution of White and Black or African American mothers, but a higher proportion of Black or African American children Supplementary Tables 1, 2 and 3).

Table 2: Prevalence of three AD outcomes at time of 4-6 year visit by cohort. Total sample size was 2023 participants.

	Number of participants (%)			
	Total number of participants	**CANDLE**	**TIDES**	**GAPPS**
Current AD				
Yes	279 (13.9)	190 (16.9)	49 (9.6)	40 (10.7)
No	1736 (86.1)	932 (83.1)	468 (90.4)	336 (89.3)
NA	8	4	1	3
Location specific-AD				
Yes	230 (11.8)	169 (15.8)	37 (7.1)	24 (6.6)
No	1718 (88.2)	900 (84.2)	480 (92.9)	338 (93.4)
NA	75	57	1	17
Ever AD				
Yes	645 (32.5)	368 (33.1)	161 (31.2)	116 (32.8)

No	1337 (67.5)	744 (66.9)	355 (68.8)	238 (67.2)
Unknown / NA	41	14	2	25

We summarized exposure to pollutants in the first year of life by cohort and outcome (Table 3). Among children with current AD, the mean O_3 exposure during the first year of life was 26.0 (SD = 2.98) ppb, NO_2 exposure was 8.49 (SD = 2.73) ppb, and $PM_{2.5}$ exposure was 9.46 (SD = 2.12) μg/m³. For those with location-specific AD, mean exposures were 26.1 (SD = 2.90) ppb for O_3, 8.61 (SD = 2.55) ppb for NO_2, and 9.65 (SD = 2.02) μg/m³ for $PM_{2.5}$. Among children with Ever AD, mean exposures were 25.6 (SD = 3.04) ppb for O_3, 8.55 (SD = 2.81) ppb for NO_2, and 9.25 (SD = 2.15) μg/m³ for $PM_{2.5}$ Participants with current AD and location-specific AD had higher exposure to O_3 and $PM_{2.5}$ compared to those without these conditions. In contrast, participants with ever AD and those without had similar exposure levels to all three pollutants. These results suggest a potential positive crude association between O_3 and $PM_{2.5}$ exposure and current and location-specific AD, while NO_2 did not show a consistent pattern across outcomes.

Table 3. Air pollution exposure during the first year of life among those who experienced any of the outcomes.

	Mean (SD) exposure among different outcomes		
	Exposure 0_3 [ppb]	**Exposure NO_2 [ppb]**	**Exposure PM $_{2.5}$ [μg/m³]**
Current AD			
Yes	26.0 (2.98)	8.49 (2.73)	9.46 (2.12)
No	25.5 (3.09)	8.58 (2.99)	9.17 (2.07)
Location specific AD			
Yes	26.1 (2.90)	8.61 (2.55)	9.65 (2.02)
No	25.4 (3.11)	8.57 (3.01)	9.13 (2.08)
Ever AD			
Yes	25.6 (3.04)	8.55 (2.81)	9.25 (2.15)
No	25.5 (3.07)	8.59 (2.99)	9.23 (2.03)

In multivariate regression models, we observed some evidence of increased risk of AD outcomes with higher O_3 exposure in the first year of life (Figures 1-3). In the main model, the adjusted ORs per 1-ppb increase in first-year O_3 exposure were: 1.08 (95% CI: 1.00, 1.17) for current AD, 1.07 (95% CI: 0.99, 1.16) for location specific AD, and 1.00 (95% CI: 0.95, 1.06) for ever AD. Exposure to NO_2 was not

associated with AD outcomes. A 1-ppb increase in NO_2 was inversely associated with the following in main models: aOR: 0.96 (95% CI: 0.89, 1.02) for current AD, 0.97 (95% CI: 0.91, 1.04) for location-specific AD and 0.99 (95% CI: 0.94, 1.03) for ever AD. $PM_{2.5}$ was also not associated with any AD outcomes, except for a suggestion of nonsignificant negative associations for some outcomes. For $PM_{2.5}$ the effect estimates for a 1-μg/m³ increase were: OR = 0.87 (95% CI: 0.74, 1.02) for current AD, OR = 0.90 (95% CI: 0.75, 1.08) for location-specific AD and OR = 1.01 (95% CI: 0.90, 1.13) for ever AD. Effect estimates were consistent between the minimally adjusted and fully adjusted models, with no major differences observed.

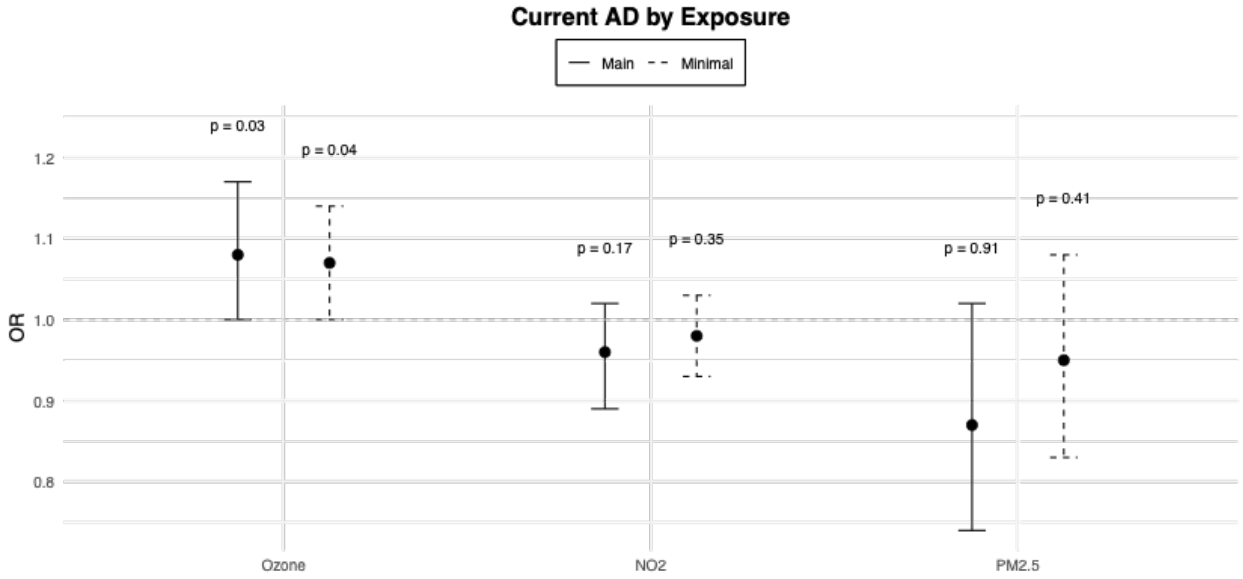

Figure 1. Associations between air pollution exposure and Current AD. Odds ratios (ORs) and 95% confidence intervals are presented for a 1-unit increase in exposure across the three outcomes. P-values correspond to each model. Minimal models were adjusted for study site and age at outcome assessment. Main models were adjusted for age at outcome assessment, study site, maternal race/ethnicity, maternal education, household income, maternal history of asthma, presence of pets at home, firstborn status, breastfeeding, and exposure to secondhand smoke.

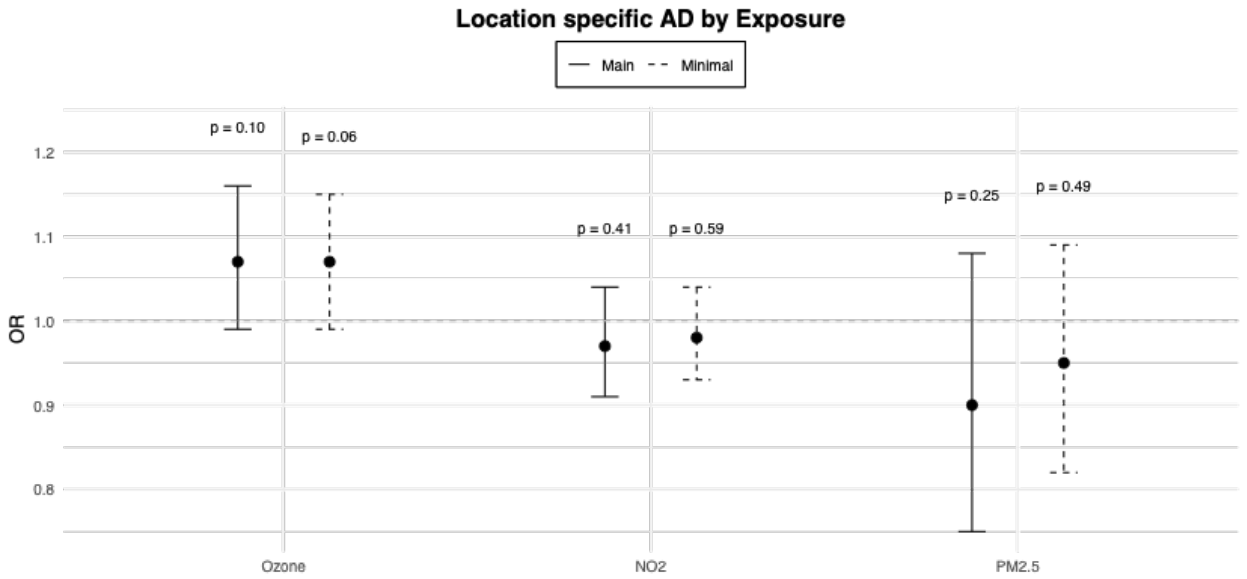

Figure 2. Associations between air pollution exposure and Location specific AD. Odds ratios (ORs) and 95% confidence intervals are presented for a 1-unit increase in exposure across the three outcomes. P-values correspond to each model. Minimal models were adjusted for study site and age at outcome assessment. Main models were adjusted for age at outcome assessment, study site, maternal race/ethnicity, maternal education, household income, maternal history of asthma, presence of pets at home, firstborn status, breastfeeding, and exposure to secondhand smoke.

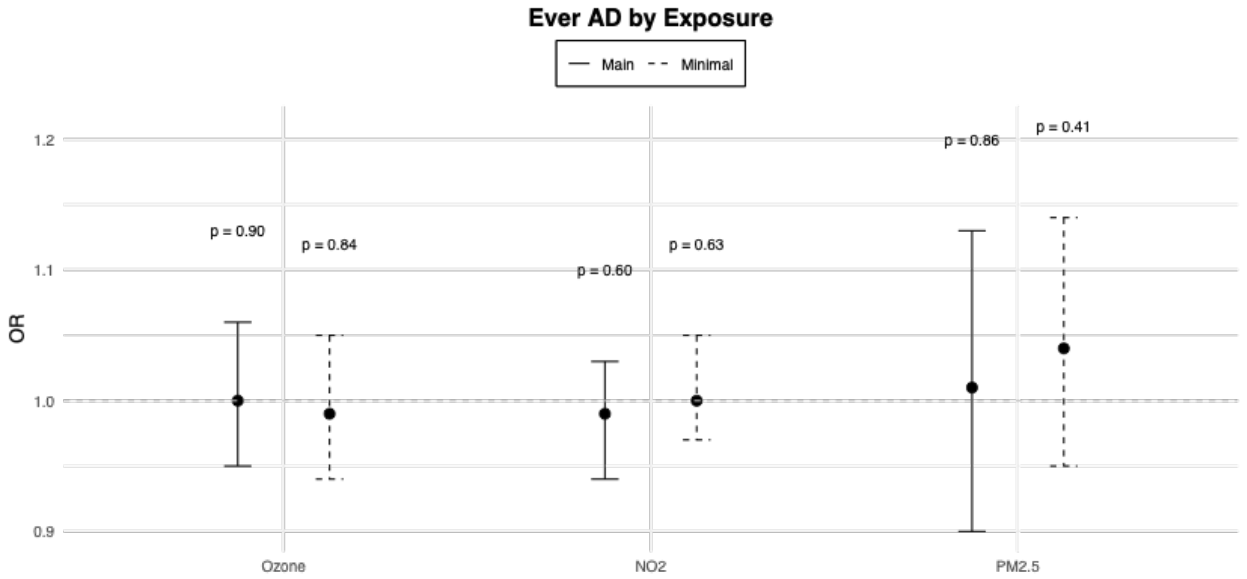

Figure 3. Associations between air pollution exposure and Ever AD. Odds ratios (ORs) and 95% confidence intervals are presented for a 1-unit increase in exposure across the three outcomes. P-values correspond to each model. Minimal models were adjusted for study site and age at outcome assessment. Main models were adjusted for age at outcome assessment, study site, maternal race/ethnicity, maternal education, household income, maternal history of asthma, presence of pets at home, firstborn status, breastfeeding, and exposure to secondhand smoke.

In a secondary analysis, we evaluated whether the association between air pollutants and AD outcomes differed by sex. Sex-specific associations of NO_2 were found for the three AD outcomes, with higher NO_2 associated with lower risk of AD in boys. No evidence of effect modification by the child's sex was observed for any of the AD outcomes for O_3 or $PM_{2.5}$. (Figure 4).

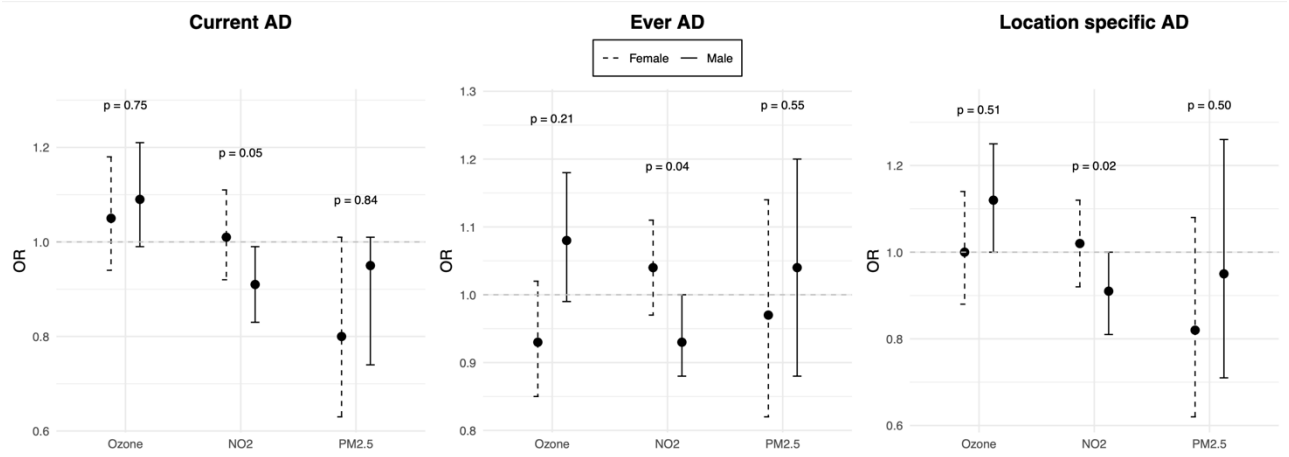

Figure 4. Associations between air pollution exposure and AD outcomes by sex. Odds ratios (ORs) and 95% confidence intervals are presented for a 1-unit increase in exposure across the three outcomes. P-values correspond to the interaction term between air pollution and child sex. Models were adjusted for age at outcome assessment, study site, maternal race/ethnicity, maternal education, household income, maternal history of asthma, presence of pets at home, firstborn status, breastfeeding, and exposure to secondhand smoke.

Discussion

We conducted an investigation of outdoor air pollution in the first year of life and AD in early childhood, adding to limited research on this topic and contributing the first US-based study of these associations, to the best of our knowledge. Notably, O_3 exposure during the first year of life was significantly associated with current AD in children at ages 4 to 6 years, and a suggestive association with location-specific AD was also evident. In contrast, no significant associations were observed between exposure to NO_2 or $PM_{2.5}$ and any of the AD outcomes. Secondary analysis provided evidence of possible modification by child sex in associations of NO_2 with outcomes, though the finding of lower risk with higher NO2 is contrary to our hypotheses and lacks biological plausibility.

Our findings were similar to those of prior research in a few ways, including the patterns of AD diagnosis. We found that the prevalence of AD ranged from 11.8% to 32.5%, with ever having AD being

the most common outcome. These findings are consistent with previous studies reporting childhood AD prevalence between 1% and 40% [1, 3, 4]. Our findings also support prior evidence that AD is more common among non-Hispanic Black/African American children. For instance, Hadi et al. (2021) estimated a 24% prevalence of AD in U.S. children under five, with non-Hispanic Black children showing higher incidence, persistence (adjusted odds ratio [aOR] 2.71), and risk (odds ratio [OR] 1.80) compared to White children, likely reflecting structural, genetic and socioeconomic factors [3, 5, 9, 10]. Although our study found no significant sex differences, previous research generally reports higher prevalence in males than females, potentially due to genetic factors [3, 5, 10].

Our results addressing the specific aims of this study—the possible associations between air pollution exposure and risk of childhood AD—showed some similarities to past studies. The association we observed linking higher O_3 exposure to an increased risk of current AD is consistent with existing literature [7, 17]. A 2024 study in China reported an OR of 1.19 (95% CI: 1.16, 1.21) per interquartile increase in the average O_3 concentration at both residential and school locations [17]. Prior studies on NO_2 and $PM_{2.5}$ exposure and their relationship with AD have shown inconsistent results. A 2019 Canadian study reported a hazard ratio (aHR) of 1.07 (95% CI 0.99–1.15) for the association between total oxidants (O_3 and NO_2) exposure at birth and AD, with a similar trend for exposure in the first 3 years of life, but no significant association for $PM_{2.5}$ exposure [7]. In contrast, a European cross-sectional study cohort found no significant association between air pollution and eczema, reporting adjusted odds ratios (aOR) of 0.94 (95% CI: 0.81–1.09) for NO_2 and 1.00 (95% CI: 0.81–1.23) for $PM_{2.5}$ [14]. We can also compare our findings to those of short-term exposure and acute health effects, such as clinic visits or hospitalization for AD, though the mechanism of adverse impacts may differ. Studies from South Africa [18], Singapore [19], Taiwan [20], and Korea [21] have yielded mixed results depending on pollutant type, exposure timeframe, and study design, with some evidence linking AD to proximity to traffic or short-term spikes in PM_{10}/$PM_{2.5}$ concentrations.

Finally, our findings show some evidence of effect modification by sex, which is consistent with some previous literature, though the majority of these studies focused on short-term exposures. Many prior studies, including a meta-analysis from Europe [14], a cross-sectional study in China [17], a time-series analysis from Singapore [19], and a prospective cohort from Taiwan [20], reported no sex-specific

differences in the association between air pollution and AD. However, a 2023 systematic review did identify a positive association between NO_2 exposure and AD specifically in females, suggesting that sex-specific effects may exist under certain conditions and warrant further investigation [15]. We observed evidence suggesting associations between NO_2 and outcomes are different, though with male-specific associations reflecting lower risk of AD with higher NO_2, contrary to hypotheses of an adverse effect. Because there is likely no support for protective effects of NO_2, it is possible that these are spurious associations.

A major strength of this study is its multicenter prospective cohort design. Unlike many prior studies, which have been limited to cross-sectional, times-series, and retrospectives cohorts, our prospective approach allows for a clearer temporal relationship between exposure and outcome. Our exposure occurred before the onset of the outcome, supporting a potential causal interpretation of the observed effects. To our knowledge, this is the first analysis evaluating the association between exposure to air pollutants and childhood AD in the U.S. This is particularly important given the high prevalence of AD, its significant impact on quality of life, and the associated burden on healthcare costs [5]. We adjusted for a suite of important potential confounding variables, as described in more detail in the Methods section—an area where control has been more limited in prior studies. Previous studies have typically restricted their consideration of confounders to a small number of environmental and demographic factors such as temperature, humidity, season, and patient age, and reported associations may be affected by confounding.

This study has several important limitations that should be considered when interpreting its findings. First, although we analyze individual air pollutants, it is important to recognize that pollutants typically exist as complex mixtures in the environment, making it difficult to isolate their specific effects. Additionally, exposure misclassification may occur due to the inability to capture ambient exposures at all residential and non-residential locations during the exposure window, as well as the exclusion of indoor air pollutants. The use of data from the ECHO PATHWAYS Consortium introduces further limitations, including potential sampling biases, since the component cohorts were not designed to be representative of their respective populations, and they contributed unequally to the pooled sample. Diagnostic inconsistencies also pose a challenge, as AD diagnoses based on caregiver reports may vary,

introducing potential for misreporting. Future studies incorporating electronic medical records (EMRs) could help improve diagnostic accuracy and reduce misclassification by providing clinically verified diagnoses. Finally, the observational design of the study precludes causal inferences, although it allows estimations of associations between early-life air pollution exposure and AD.

In conclusion, our results support the hypothesis that even small increases in early-life O_3 exposure may contribute to the onset of AD and potentially influence the development of other allergic conditions. In contrast, we found little evidence of associations between exposure to $PM_{2.5}$ or NO_2 during the first year of life. These findings underscore the need to further investigate the combined effects of multiple air pollutants and their impact on childhood allergic diseases. Given the high prevalence of AD and its substantial burden on children's health and healthcare systems, identifying modifiable environmental risk factors such as air pollution is critical. Future research should focus on exploring pollutant mixtures and their relationship with potential biological mechanisms.

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Appendix

Supplementary Table 1. Participant characteristics by status of current AD.

	Current AD status		
	Yes	No	Unknown / NA
Total	279 (13.9)	1736 (86.1)	8
Sex			
Female	141 (50.7)	866 (49.9)	7
Male	138 (49.3)	869 (50.1)	1
Unknown/NA	0	1	0
Age			
Mean (SD)	4.66 (0.75)	4.68 (0.75)	
Child Race			
White	97 (35.4)	834 (49.6)	3
Black or African American	144 (52.6)	641 (38.2)	2
Asian	9 (3.3)	35 (2.1)	0
Other	24 (8.7)	172 (10.1)	2
Unknown	7	54	1
Child ethnicity			
Non-Hispanic/Latino	254 (92.4)	1548 (92.0)	5
Hispanic/Latino	21 (7.6)	137 (8.0)	2
Unknown/NA	4	51	1
First Born			
Yes	104 (37.3)	719 (41.6)	6
No	174 (62.7)	1008 (58.4)	2
Unknown / NA	1	9	0
Maternal education			
Less than HS	10 (3.7)	67 (4.1)	0
HS GED	76 (27.8)	429 (25.4)	2
Vocational, technical or associates	56 (20.5)	248 (14.7)	3
Bachelors	74 (27.1)	480 (28.5)	2
Graduate or professional school	56 (20.9)	460 (27.3)	1
Unknown / NA	7	52	0
Income			
Mean (SD)	57177 (48338)	69456 (55431)	
History of maternal asthma			
Yes	71 (25.5)	294 (17.1)	0
No	206 (74.5)	1424 (82.9)	8
Unknown / NA	2	18	0
Pet at home			
Yes	104 (43.7)	750 (51.1)	3
No	134 (56.3)	716 (48.9)	2

Unknown / NA	41	270	2
Maternal Race			
White	109 (39.5)	901 (52.5)	5
Black or African American	138 (50.3)	633 (36.9)	2
Asian	8 (2.9)	45 (2.6)	1
Other	20 (7.3)	136 (8)	0
Unknown / NA	4	21	0
Maternal ethnicity			
Non-Hispanic/Latino	267 (99.6)	1623 (93.9)	
Hispanic/Latino	11 (0.4)	104 (6.1)	
Secondhand smoke (1st year)			
Yes	53 (53.5)	190 (33.6)	3
No	46 (46.5)	375 (66.4)	2
NA	180	1171	3
Secondhand smoke (Visit at age 4)			
Yes	82 (29.3)	345 (19.9)	5
No	197 (70.7)	1387 (80.1)	3
NA	0	4	0
Breastfeeding			
Did not breastfeed	54 (19.9)	400 (23.9)	2
Any breastfeed	217 (80.1)	1274 (76.1)	6
Unknown / NA	8	62	0

Supplementary Table 2. Characteristics of participants by status of location-specific AD.

	Location-specific AD status		
	Yes	No	Unknown / NA
Total	230 (11.8)	1718(88.2)	75
Sex			
Female	116 (50.4)	862 (50.2)	36
Male	114 (49.6)	855 (49.8)	39
Unknown/NA	0	1	0
Age			
Mean (SD)	4.59 (0.70)	4.69 (0.75)	
Child Race			
White	71 (30.9)	839 (50.5)	24
Black or African American	131 (57.2)	610 (36.7)	46
Asian	8 (3.4)	36 (2.2)	0
Other	17 (2.1)	177 (10.6)	3
Unknown	3	56	0

Child ethnicity			
Non-Hispanic/Latino	216 (95.1)	1520 (91.2)	71
Hispanic/Latino	11 (4.9)	146 (8.8)	3
Unknown/NA	3	52	1
First Born			
Yes	91 (39.7)	703 (41.1)	35
No	138 (60.3)	1006 (58.9)	40
Unknown / NA	1	9	0
Maternal education			
Less than HS	8 (3.5)	64 (3.8)	5
HS GED	67 (29.8)	415 (24.9)	25
Vocational, technical or associates	42 (18.7)	254 (15.3)	11
Bachelors	62 (27.6)	477 (28.7)	17
Graduate or professional school	46 (20.4)	454 (27.3)	17
Unknown / NA	5	54	0
Income			
Mean (SD)	54895 (48101)	69878 (55350)	
History of maternal asthma			
Yes	58 (25.4)	289 (17.0)	18
No	170 (74.6)	1412 (83.0)	56
Unknown / NA	2	17	1
Pet at home			
Yes	82 (42.4)	745 (51.1)	30
No	113 (57.6)	713 (48.9)	27
Unknown / NA	35	260	18
Maternal Race			
White	78 (34.4)	911 (53.7)	26
Black or African American	127 (55.9)	600 (35.4)	46
Asian	8 (3.5)	45 (2.6)	1
Other	14 (6.2)	140 (8.2)	2
Unknown / NA	3	22	0
Maternal ethnicity			
Non-Hispanic/Latino	224 (97.8)	1600 (93.6)	72
Hispanic/Latino	5 (2.2)	109 (4.4)	2
Unknown/NA	1	9	1
Secondhand smoke (1st year)			
Yes	51 (61.4)	182 (32.6)	13
No	32 (38.6)	376 (67.4)	15
NA	158	1153	44
Secondhand smoke (Visit at age 4)			
Yes	69 (30.0)	340 (19.8)	23
No	161 (70.0)	1375 (80.2)	51

NA	0	3	1
Breastfeeding			
Did not breastfeed	46 (20.4)	383 (23.7)	27
Any breastfeed	179 (79.6)	1271 (76.3)	46
Unknown / NA	5	64	2

Supplementary table 3. Characteristics of participants by status of ever AD

	Ever AD status		
	Yes	No	Unknown / NA
Total	645 (32.5)	1337 (67.5)	41
Sex			
Female	322 (49.9)	667 (49.9)	25
Male	323 (50.1)	669 (50.1)	16
Unknown/NA	0	1	0
Age			
Mean (SD)	4.65 (0.74)	4.67 (0.74)	
Child Race			
White	243 (38.5)	665 (51.6)	26
Black or African American	307 (48.6)	471 (36.6)	9
Asian	18 (2.8)	25 (1.9)	1
Other	64 (10.1)	129 (9.9)	5
Unknown	14	46	0
Child ethnicity			
Non-Hispanic/Latino	584 (92.4)	1186 (91.7)	37
Hispanic/Latino	48 (7.6)	108 (8.3)	4
Unknown/NA	13	43	0
First Born			
Yes	280 (43.6)	534 (40.1)	15
No	362 (56.4)	796 (59.9)	26
Unknown / NA	3	7	0
Maternal education			
Less than HS	27 (4.4)	49 (3.8)	1
HS GED	176 (28.2)	321 (24.7)	10
Vocational, technical or associates	105 (16.8)	190 (14.6)	12
Bachelors	160 (25.7)	386 (29.6)	10
Graduate or professional school	153 (24.9)	356 (27.3)	8
Unknown / NA	24	35	0
Income			
Mean (SD)	63501 (55161)	69435 (54520)	
History of maternal asthma			

Yes	147 (23.0)	213 (16.1)	5
No	492 (77.0)	1110 (83.9)	36
Unknown / NA	6	14	0
Pet at home			
Yes	245 (44.6)	586 (52.2)	26
No	304 (55.4)	536 (47.8)	7
Unknown / NA	96	215	2
Maternal Race			
White	272 (42.5)	715 (54.2)	28
Black or African American	296 (46.5)	469 (35.6)	8
Asian	21 (3.3)	33 (2.5)	0
Other	49 (7.7)	102 (7.7)	5
Unknown / NA	7	18	0
Maternal ethnicity			
Non-Hispanic/Latino	610 (95.0)	82 (6.2)	
Hispanic/Latino	32 (5.0)	1247 (93.8)	
Secondhand smoke (1st year)			
Yes	99 (43.0)	143 (34.9)	4
No	131 (57.0)	267 (65.1)	25
NA	417	927	12
Secondhand smoke (Visit at age 4)			
Yes	160 (24.8)	265 (19.9)	7
No	485 (75.2)	1068 (80.1)	34
NA	0	4	0
Breastfeeding			
Did not breastfeed	143 (23.0)	307 (23.8)	6
Any breastfeed	478 (77.0)	984 (76.2)	
Unknown / NA	24	46	1

Supplementary table 4. Mean exposure during the first year of life by participant characteristics.

	Mean (SD) exposure by patient characteristics		
	O3 [ppb]	NO2 [ppb]	PM 2.5 [µg/m³]
Total	25.5 (3.08)	8.6 (2.95)	9.2 (2.08)
Sex			
Female	25.5 (3.03)	8.5 (2.98)	9.2 (2.09)
Male	25.6 (3.13)	8.6 (2.92)	9.2 (2.07)
Child Race			
White	25.1 (3.45)	8.0 (3.31)	8.3 (2.04)
Black or African American	26.5 (1.91)	9.1 (2.21)	10.6 (1.15)
Asian	24.0 (3.34)	9.7 (3.36)	8.3 (2.08)

Other	24.1 (3.83)	8.78 (3.17)	8.2 (2.14)
Child ethnicity			
Non-Hispanic/Latino	25.6 (3.08)	8.6 (2.94)	9.3 (2.08)
Hispanic/Latino	25.2 (3.19)	7.7 (2.91)	8.4 (1.85)
First Born			
Yes	25.4 (3.21)	8.8 (2.98)	9.2 (1.94)
No	25.7 (2.96)	8.3 (2.89)	9.2 (2.17)
Maternal education			
Less than HS	25.5 (3.15)	7.96 (2.96)	10.6 (1.39)
HS GED	26.2 (1.42)	9.36 (2.15)	10.4 (1.35)
Vocational, technical or associates	24.9 (3.49)	8.69 (3.10)	8.93 (2.06)
Bachelors	25.3 (3.31)	8.39 (3.10)	8.75 (2.24)
Graduate or professional school	24.8 (3.59)	8.81 (3.31)	8.54 (2.03)
History of maternal asthma			
Yes	25.5 (3.11)	8.3 (2.92)	9.1 (2.09)
No	25.5 (3.08)	8.6 (2.96)	9.2 (2.08)
Pet at home			
Yes	25.4 (3.29)	8.1 (3.16)	8.6 (2.11)
No	25.4 (3.10)	9.0 (2.79)	9.4 (2.05)
Sites			
UTHSC (CANDLE)	26.9 (1.69)	8.5 (2.35)	10.6 (0.88)
UCSF (TIDES)	23.2 (2.30)	10.3 (2.86)	9.7 (1.23)
UMN (TIDES)	26.4 (1.87)	10.3 (2.80)	8.0 (0.57)
URMC (TIDES)	26.8 (1.39)	6.3 (1.58)	8.4 (1.02)
UW_t (TIDES)	19.8 (2.43)	10.9 (3.34)	5.8 (0.90)
Seattle_g (GAPPS)	20.2 (2.51)	9.71 (3.39)	5.8 (1.04)
Yakima (GAPPS)	26.3 (1.66)	4.8 (1.66)	7.2 (1.70)
Maternal Race			
White	25.0 (3.48)	8.1 (3.30)	8.3 (2.06)
Black or African American	26.6 (1.85)	9.1 (2.18)	10.6 (1.12)
Asian	23.0 (3.96)	10.3 (3.31)	8.2 (2.12)
Other	25.0 (3.16)	8.41 (2.98)	8.8 (2.16)
Maternal ethnicity			
Non-Hispanic/Latino	25.6 (3.07)	8.62 (2.94)	9.27 (2.09)
Hispanic/Latino	25.0 (3.12)	7.65 (2.93)	8.45 (1.74)
Cohorts			
CANDLE	26.9 (1.69)	8.5 (2.35)	10.6 (0.88)
GAPPS	23.1 (3.72)	7.4 (3.64)	6.5 (1.55)
TIDES	24.3 (3.34)	9.5 (3.24)	8.1 (1.64)
Breastfeeding			
Did not breastfeed	26.4 (1.99)	8.87 (2.48)	10.5 (1.39)
Any breastfeed	25.3 (3.27)	8.45 (3.07)	8.8 (2.12)