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Windows of susceptibility and joint effects of prenatal and postnatal ambient air pollution and temperature exposure on asthma and wheeze in Mexican children

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109122.

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Abstract

Introduction: Prenatal and early-life exposure to air pollution and extreme temperatures are associated with childhood asthma and wheeze. However, potential windows of susceptibility and their sex-specific and interactive effects have not been fully elucidated. We aimed to identify critical windows of susceptibility and evaluate sex-specific effects in these associations, and evaluate exposure interactions.

Methods: We analyzed data from 468 mother–child pairs enrolled in the PROGRESS birth cohort in Mexico City. Daily residential levels of $PM_{2.5}$, NO_2, and temperature were generated from our validated spatiotemporally resolved models from conception to age 4 years. Childhood asthma and wheeze outcomes were collected at 4–6 and 7–8 years. Distributed lag nonlinear models (DLNMs) were used to identify susceptible windows for prenatal weekly-specific and postnatal monthly-specific associations of air pollution and temperature with respiratory outcomes adjusting for covariates. To evaluate sex-specific effects, DLNMs were stratified. Joint effects were assessed using relative excess risk due to interaction and attributable proportion.

Results: Mid-gestation was a critical window for both $PM_{2.5}$ (weeks 20–28, cumulative OR: 1.18 [95% CI: 1.01, 1.37]; weeks 19–26, cumulative OR: 1.18 [95% CI: 1.02, 1.36]) and NO_2 (weeks 18–25, cumulative OR: 1.16 [95% CI: 1.02, 1.31]) exposure, associated with higher odds of wheeze. Postnatal exposure to $PM_{2.5}$ and NO_2 during the first year of life was also linked to higher odds of wheeze. The warmer and colder temperatures showed mixed effects on respiratory outcomes. We observed a synergistic interaction between high $PM_{2.5}$ and high temperature exposure during the first year of life, associated with higher odds of current wheeze. The associations of prenatal air pollution and temperature exposure with respiratory outcomes were more pronounced in males.

Conclusions: Early-life air pollution exposure contributes to the development of childhood asthma and wheeze, while exposure to temperature showed mixed associations with respiratory outcomes.

Keywords

Air pollution; Temperature; Asthma; Wheeze; Susceptible window

1. Introduction

Asthma and wheeze are chronic respiratory conditions that significantly impact the health and quality of life of children worldwide. Childhood asthma is a major public health concern, affecting approximately 14 % of children globally (Asher and Pearce, 2014).

Wheezing refers to whistling-like sounds during exhalation and is a common symptom of asthma. Wheezing can also be indicative of other respiratory conditions (Ducharme et al., 2014) such as lower airway infections. Recurrent wheeze is characterized by breathlessness and coughing, which can impair a child's physical activity, sleep quality, and overall well-being (Nurmagambetov et al., 2018). Over the past decades, the prevalence of childhood asthma has seen a substantial rise, with indications of stabilization in some developed areas (Khreis et al., 2017). However, low- and middle-income nations have experienced a sharp increase in recent times (Asher et al., 2006; Song et al., 2022). Although the precise drivers behind these trends remain largely unidentified, scientists postulate that simultaneous shifts in environmental exposures could be significant contributors (Gaffin et al., 2014).

There is increasing evidence suggesting that pre- and postnatal exposure to environmental stressors may play a significant role in the etiology of childhood asthma and wheeze. Air pollution and temperature have been linked to the onset and exacerbation of childhood respiratory conditions (Cisneros et al., 2021; Hertz-Picciotto et al., 2007; Hu et al., 2022; Ibrahim et al., 2021; Khreis et al., 2017; Liu et al., 2016; Parker et al., 2009). Consistent evidence has linked air pollutants, such as nitrogen dioxide (NO_2) and particulate matter ≤ 2.5 μm in diameter ($PM_{2.5}$), to an elevated risk of asthma and wheeze in children (Anenberg et al., 2022; Brunst et al., 2015; Gehring et al., 2015). Moreover, exposure to extreme temperatures and temperature fluctuations have been associated with adverse respiratory outcomes (Hu et al., 2022; Xu et al., 2012). The fetal and early life periods represent crucial developmental windows, during which environmental insults can disrupt the normal maturation of the respiratory system inhibiting growth and predisposing the child to respiratory disease later in life (Kajekar, 2007; Wright, 2010). Although several studies have reported significant associations of prenatal exposure to air pollution with higher odds of childhood asthma and wheeze (Clark et al., 2010; Leon Hsu et al., 2015; Pedersen et al., 2023; Tian et al., 2024), other studies have reported null or even protective effects (Aguilera et al., 2013; Fuertes et al., 2013; Hazlehurst et al., 2024; Madsen et al., 2017). Furthermore, most previous studies have relied on trimester averages of air pollution and temperature exposure, while the true susceptible window could be shorter (e.g., weekly specific) and warrants more precise definition (Wilson et al., 2017). The auto-correlation of air pollution and temperature across adjacent periods also presents a challenge in accurately identifying a true sensitive window. In addition to the necessity of identifying susceptible windows of prenatal exposure, Bettiol et al. (2021) emphasized the need to confirm vulnerable time windows after birth through studies with more precise exposure assessment.

Furthermore, the joint effects of air pollutants and temperature remain largely unexplored (Buckley and Richardson, 2012; Hu et al., 2022). Previous research (D'Amato et al., 2010) has identified a link between air pollution and ambient temperature, indicating potential temperature–pollutant interactions (Reinmuth-Selzle et al., 2017). Given the potential for synergistic interactions between these environmental factors, it is essential to investigate their combined effects on childhood asthma and wheeze (Lu et al., 2023; Lu et al., 2022). To date, evidence on associations of pre- and postnatal air pollution and temperature exposure with childhood asthma and wheeze in Mexico City is limited. This megacity, where air pollution levels routinely exceed World Health Organization (WHO) guidelines, offers a unique study environment. Its geographical location in a valley exacerbates pollution,

especially during cold weather thermal inversions. These factors, along with the distinct climate and socio-demographic profile, highlight the need for investigations in populations with specific environmental conditions, potentially informing targeted interventions in highly polluted urban areas. Additionally, males and females exhibit distinct patterns in lung growth and airway development (Bolte et al., 2021; Carey et al., 2007b; Torday et al., 1981), suggesting differential responses to environmental stressors may be operating (Guilbert et al., 2023b; Hsu et al., 2015). Therefore, investigating sex-specific windows of susceptibility to these exposures is critical.

We leveraged an ongoing longitudinal birth cohort study with highly temporally and spatially resolved air pollution and temperature data to identify prenatal and postnatal windows of susceptibility to these exposures and odds of asthma and wheeze in childhood, and explore sex-specific effects. We additionally investigated potential joint effects of air pollution and temperature.

2. Materials and methods

2.1. Study population

The ongoing prospective birth cohort, Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS), was initiated in Mexico City in 2007 (Burris et al., 2013). From July 2007 to February 2011, pregnant women who were receiving prenatal care through the Instituto Mexicano del Seguro Social (IMSS), the Mexican Social Security Institute, were enrolled in the study. Eligibility criteria for participation included: gestational age less than 20 weeks, aged 18 or older, completion of primary education, intention to reside in Mexico City for the following 3 years, access to a telephone, and absence of a history of kidney or heart disease, daily alcohol consumption, or use of steroid or anti-epilepsy medications. In Mexico, ultrasounds are not routinely performed as standard of care, therefore gestational age was based on last menstrual period (LMP) and by a standardized physical examination to determine gestational age at birth (Capurro et al., 1978). If the physical examination assessment of gestational age differed by more than 3 weeks from the gestational age based on LMP, the physical exam gestational age was used instead of the gestational age determined by LMP. The study protocol was approved by the institutional review boards of the Mexican National Institute of Public Health and the Icahn School of Medicine at Mount Sinai. All participants provided written informed consent during the study visits. Among the 948 mothers who gave birth to a live infant, 681 mother–child pairs were followed longitudinally. The selected sample included children with gestational ages ≥ 37 weeks and with complete exposure, outcome and covariate data. A flow diagram is provided in Supplemental Fig. S1. No material differences were seen between the excluded and included subsamples (Supplemental Table S1).

2.2. Ambient air pollution and temperature exposure assessment

Validated hybrid spatiotemporal resolved model, previously described in detail (Gutiérrez-Avila et al., 2022; He et al., 2023; Just et al., 2015), were employed to estimate prenatal and postnatal air pollutant concentrations to $PM_{2.5}$ and NO_2. For $PM_{2.5}$ we used both extreme gradient boosting and inverse-distance weighting techniques that incorporate aerosol optical

depth, meteorology, and land-use variables to generate daily residence predictions at 1 km resolutions. For NO_2 we applied a unique hybrid ensemble model which incorporates machine-learning (XGBOOST, RF), geo-statistics and remote sensing approaches. Daily temperature data were obtained using a calibrated model that integrated satellite-derived surface temperature readings with ground-based air temperature measurements, employing land use regression techniques for adjustment (Gutiérrez-Avila et al., 2021; Politis et al., 2024). Model performance was assessed using monitor-level leave-one-out cross-validation. The R^2 values ranged from 0.64 to 0.86 for $PM_{2.5}$ and 0.78 to 0.95 for temperature across years. For NO_2, the cross-validated R^2 of RF and XGBOOST models were 0.75 and 0.86, respectively, indicating strong predictive performance across all parameters. Daily estimates of $PM_{2.5}$, NO_2, and temperature were generated at a 1 × 1 km spatial resolution from conception up to 4 years postnatal at each participant's address obtained at enrollment and updated following any relocation. For prenatal models, daily exposures were averaged into weekly measures and for postnatal models, daily measures were averaged into monthly measurements (Daouda et al., 2024; Guilbert et al., 2023a). Additionally, exposure was averaged into clinically relevant exposure periods: (1st trimester: 1–13 weeks, 2nd trimester: 14–27 weeks, 3rd trimester: 28 weeks–delivery) (McGuinn et al., 2020; Rosa et al., 2019). For the postnatal exposure assessment, air pollutant concentrations were averaged: from birth to 12 months (the first year of life), from birth to 24 months (the first 2 years of life), and from birth to 48 months (the first 4 years of life) (Tian et al., 2024).

2.3. Child asthma and wheeze outcome assessment

At the 4–6 and 7–8 years of age visits, the validated Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was administered (Mata Fernández et al., 2005). During both visits, the respiratory outcomes including ever wheeze, current wheeze, and asthma were assessed. Ever wheeze was defined as a caregiver's affirmative response to the question, "Has your child ever experienced wheezing or whistling in the chest at any time in the past?" Current wheeze was determined based on the caregiver's response to the question, "In the past year, did your child have chest wheezing or whistling?" Asthma was defined by asking caregivers, "Has your child ever had asthma in their life?".

2.4. Covariates

Covariates were considered based on previous research of factors influencing child respiratory health, which might be associated with air pollution and temperature exposures but not on the causal pathway (for instance, gestational age or birth weight). The selection of covariates was confirmed using a Directed Acyclic Graph (DAG; Supplemental Fig. S2). The main models were adjusted for the minimally sufficient adjustment sets, which included maternal age (continuous, years), pre-pregnancy body mass index (BMI) (continuous, kg/m^2), education level (< high school, high school, > high school), parity (primiparous vs. multiparous), environmental tobacco smoke (ETS) (yes vs. no), child sex and age (continuous, years) at the time of visit, and seasonality of $PM_{2.5}$, NO_2, temperature exposure, which was defined as sine and cosine of time of year (Rice et al., 2016; Stolwijk et al., 1999). Information on maternal age, education level, and parity was gathered via questionnaires administered at enrollment. ETS was defined as the presence of any

household smoker reported during the second or third trimester of pregnancy. Child sex was obtained from delivery records. Women's pre-pregnancy BMI (kg/m^2) was estimated as previously described (Soria-Contreras et al., 2020). Socioeconomic status (SES) was assessed using a six-level index developed by the Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública (AMAI), which was based on 13 variables obtained from the prenatal questionnaire (Politis et al., 2024). These levels were then grouped into lower, medium, and higher SES categories (Rosa et al., 2019). The season of visit and birth was defined according to weather patterns in Mexico City as dry cold (January–February; November–December), dry warm (March–April), and rainy (May–October) (Politis et al., 2024). Information on maternal asthma history (yes vs. no) was also collected at the time of enrollment.

2.5. Statistical analysis

Summary statistics were calculated for all sociodemographic characteristics and respiratory outcomes, and the continuous variables were evaluated for normality using visual inspection of histograms. For normally distributed variables, we reported mean values with standard deviations (SD); for skewed distributions, we presented medians and interquartile ranges (IQR). Categorical data were summarized as counts (n) and percentages (%). Spearman's correlations between different time periods for $PM_{2.5}$, NO_2, and temperature measures were calculated.

To assess the exposure-lag-response associations and identify susceptibility windows, distributed lag nonlinear models (DLNMs) were applied (Gasparrini, 2014). The exposure period was set from the 1st to 37th gestational weeks (the minimum gestational age of term births) to facilitate the assessment of prenatal susceptible windows according to previous studies (Chen et al., 2023; Yitshak-Sade et al., 2021). For each respiratory outcome and exposure indicator, two exposure periods were examined separately: (1) prenatal exposure, in weeks, from the 1st to 37th gestational weeks; and (2) postnatal exposure, in months, from the 1st to 48th months postpartum. The analysis was restricted to full-term births (Carlson et al., 2023). All DLNMs were adjusted for maternal age, pre-pregnancy BMI, education level, parity, ETS, child sex and age, seasonality of exposure, and the same exposure indicator in the other exposure period. We modeled $PM_{2.5}$ and NO_2 effects on respiratory outcomes assuming linear relationships, employing natural cubic splines with varying degrees of freedom (2–6) for the lag function (Jakpor et al., 2020). Given the often non-linear nature of temperature-respiratory outcome associations (Agache et al., 2024), we modeled the exposure–response association using natural cubic splines with knots positioned at the 10th, 50th, and 90th percentiles of the temperature distribution for each relevant lag period. For the lag-response association, we applied natural cubic splines with one knot centered on the full lag period specific to each outcome. We compared warmer (95th percentile) and colder (5th percentile) temperatures exposure against median temperature exposure, plotting lag response curves with odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) (Guilbert et al., 2023b). The optimal degrees of freedom for $PM_{2.5}$ and NO_2 were determined by minimizing the Akaike Information Criterion (AIC). Effect estimates were presented as ORs and 95 % CIs by using logistic regression models combined with DLNMs per 5 $\mu g/m^3$ increment in $PM_{2.5}$ and 5

ppb increment in NO_2. Susceptible exposure windows were identified as the weeks/months during which the 95 % CI did not include 1. DLNM also enables for the estimation of cumulative effects of exposure across several weeks/months by summing the coefficients from individual time intervals (lags) within the specified period (Carlson et al., 2023). We computed the cumulative effect of weekly/monthly increases in each exposure for significant windows. We then examined effect modification by stratifying DLNMs by sex.

Additionally, multivariable logistic regression models were employed to investigate the associations of air pollution and temperature exposure with childhood asthma and wheeze across various time windows after adjusted the aforementioned covariates. For logistic regression models without time series data, seasonality was accounted for by incorporating season of visit in prenatal models and season of birth in postnatal models. Associations were calculated as ORs with 95 % CIs for each 5 $\mu g/m^3$ increase in $PM_{2.5}$, 5 ppb increase in NO_2, and per 1 °C increase in temperature. We assessed effect modification by including an interaction term between exposure variables and child sex in our models. To investigate potential sex-specific effects of air pollution and temperature exposure on childhood asthma and wheeze, we added a cross-product term between each exposure variable and child sex, considering interactions with $p < 0.10$ as statistical significance (Tillaut et al., 2023). Subsequently, we conducted sex-stratified analyses to examine whether the observed associations were qualitatively similar between males and females.

To investigate potential additive interactions between $PM_{2.5}$, NO_2, and temperature exposure on the risk of childhood asthma and wheeze, these exposures were dichotomized within each exposure window based on their median values. Exposures were categorized as high (1) if they exceeded the median, and low (0) if they were less than or equal to the median (Chen et al., 2023; Lu et al., 2022; Xiao et al., 2024). Dummy variables were created by combining the two air pollutants with temperature (P_1T_0/N_1T_0: exposure to high $PM_{2.5}/NO_2$ and low temperature; P_0T_1/N_0T_1: exposure to low $PM_{2.5}/NO_2$ and high temperature; P_1T_1/N_1T_1: exposure to high $PM_{2.5}/NO_2$ and high temperature), with P_0T_0/N_0T_0 as the reference. The relative excess risk due to interaction (RERI) and attributable proportion (AP) were calculated to assess the joint effects of exposures. A positive RERI indicates synergistic effects, while a negative RERI suggests antagonistic effects. AP, calculated as RERI divided by the OR of co-exposure, represents the proportion of the risk attributable to the interaction. The absence of interactions is indicated by an RERI or AP equal to zero. Logistic regressions were fitted, and ORs with corresponding 95 % CIs were calculated using the bootstrap percentile method (Chen et al., 2023).

To evaluate the stability of our main results, we performed additional sensitivity analyses including: 1) an expanded model incorporating additional adjustments for maternal asthma history and SES; 2) a multi-exposure model simultaneously adjusting for $PM_{2.5}$, NO_2, and temperature within the same exposure window; 3) a model adjusting for the same exposure in other exposure windows; 4) considering the causal relationships among temperature, $PM_{2.5}/NO_2$, and respiratory outcomes, previous research has indicated that ambient temperature influences $PM_{2.5}/NO_2$ concentrations, rather than the reverse (Buckley et al., 2014). Therefore, we additionally adjusted for weekly temperature when examining the associations between prenatal $PM_{2.5}$ and NO_2 exposure and childhood asthma and

wheeze; and 5) a model using natural cubic splines with degrees of freedom selected based on the AIC for both exposure–response and lag-response relationships in prenatal temperature exposure analyses.

All statistical analyses were performed using R software (version 4.3.3), with the DLNM implemented via the “dlnm” package (version 2.4.7).

3. Results

3.1. Characteristics of the study participants

Characteristics of the study population are presented in Table 1. Mothers’ mean age (SD) was 27.6 (5.63) years, with a pre-pregnancy BMI of 26.5 (4.17) kg/m^2. Maternal education levels varied: 40.4 % had not finished high school, 37.8 % had completed high school, and 21.8 % had attained more than a high school degree. A total of 324 (69.2 %) mothers did not report ETS. Among the mothers, 282 (60.3 %) were primiparous, and 186 (39.7 %) were multiparous. Overall, only three (0.6 %) mothers had a history of asthma. Child sex was evenly split with 235 (50.2 %) males and 233 (49.8 %) females. Child age was 4.8 (0.55) and 6.7 (0.54) years at 4–6 years and 7–8 years study visits, respectively. At the 4–6 years of age study visit, 123 (26.3 %) children had ever wheeze, 60 (12.8 %) had current wheeze, and 14 (3.0 %) had asthma. The distribution of respiratory outcomes at the 7–8 years of age study visit was as follows: 75 (16.0 %) were classified as ever wheeze, 27 (5.8 %) as current wheeze, and 21 (4.5 %) as asthma.

The mean prenatal and postnatal ambient air pollution and temperature exposures during the whole pregnancy, specific trimesters, first year, first two years, and first four years of life ranged from 22.4 to 23.2 $\mu g/m^3$ for $PM_{2.5}$, 32.4 to 33.6 ppb for NO_2, and 14.8 to 15.2 °C for temperature (Table 2). There was a moderate to high correlation between the different exposure time periods of exposure measures (Supplemental Fig. S3).

3.2. Windows of susceptibility of prenatal and postnatal $PM_{2.5}$, NO_2, and temperature

As shown in Fig. 1, prenatal $PM_{2.5}$ exposure (per 5 $\mu g/m^3$ increase) was associated with higher odds of ever wheeze at 4–6 years of age during the 20th to 28th gestational weeks (Fig. 1A) and ever wheeze at 7–8 years of age during the 19th to 26th gestational weeks (Fig. 1D). The cumulative ORs for the sensitive windows were 1.18 (95 % CI: 1.01, 1.37) and 1.18 (95 % CI: 1.02, 1.36) for ever wheeze at 4–6 and 7–8 years of age, respectively. Prenatal NO_2 exposure during the 18th to 25th gestational weeks (per 5 ppb increase) was associated with higher odds of ever wheeze at 7–8 years of age (Fig. 2D). The cumulative OR for the sensitive windows was 1.16 (95 % CI: 1.02, 1.31). Prenatal warmer temperature exposure was associated with higher odds of current wheeze at 4–6 years of age during the 27th to 37th gestational weeks and ever wheeze at 7–8 years of age during the 26th to 37th gestational weeks, with cumulative OR of 20.01 (95 % CI: 1.35, 295.98) and 21.04 (95 % CI: 1.42, 312.46) respectively (Fig. 3B and 3D). However, no susceptible windows were observed for colder temperature exposure (5th percentile of temperature, 11 °C) with respiratory outcomes compared to the median temperature (50th percentile of temperature, 15 °C) (Fig. 4).

For postnatal exposure, $PM_{2.5}$ (per 5 μg/m^3 increase) exposure during the early months of life was associated with higher odds of wheeze (Fig. 5). Exposure during the 1st to 19th months postpartum was associated with higher odds of ever wheeze at 4–6 years of age (cumulative OR: 2.55, 95 % CI: 1.25, 5.20) (Fig. 5A), while exposure during the 1st to 6th months postpartum was associated with higher odds of ever wheeze at 7–8 years of age (cumulative OR: 1.62, 95 % CI: 1.12, 2.34) (Fig. 5D). Additionally, exposure during the 1st to 10th months (cumulative OR: 8.05, 95 % CI: 2.75, 23.60) and the 41st to 48th months (cumulative OR: 4.98, 95 % CI: 1.33, 18.56) postpartum was associated with higher odds of current wheeze at 7–8 years of age (Fig. 5E).

Postnatal NO_2 exposure (per 5 ppb increase) was associated with higher odds of wheeze at various exposure windows (Fig. 6). Exposure during the 1st to 10th months postpartum was associated with higher odds of ever wheeze at 4–6 years of age (cumulative OR: 1.74, 95 % CI: 1.14, 2.65) (Fig. 6A). Similarly, exposure during the 15th to 25th months postpartum was associated with higher odds of current wheeze at 4–6 years of age (cumulative OR: 1.23, 95 % CI: 1.03, 1.46) (Fig. 6B). Postnatal NO_2 exposure showed divergent associations with ever wheeze at 7–8 years of age. Higher exposure was linked to increased odds during the 1st to 8th months (cumulative OR: 1.83, 95 % CI: 1.18, 2.83), but decreased odds during the 21st to 36th months postpartum (cumulative OR: 0.44, 95 % CI: 0.23, 0.83) (Fig. 6D). The odds of current wheeze at 7–8 years of age was increased by exposure during two periods: the 2nd to 14th months (cumulative OR: 6.29, 95 % CI: 2.19, 18.09) and the 43rd to 48th months (cumulative OR: 4.99, 95 % CI: 1.54, 16.14), while they decreased during the 25th to 37th months postpartum (cumulative OR: 0.14, 95 % CI: 0.04, 0.51) (Fig. 6E).

Postnatal temperature exposure analysis revealed temperature-dependent associations with respiratory outcomes. Warmer temperature, compared to the median, during the 12th to 23rd months postpartum were associated with lower odds of current wheeze at 4–6 years of age (cumulative OR: 0.09, 95 % CI: 0.01, 0.89) (Fig. 7B). Similarly, colder temperature during the 15th to 27th months postpartum were associated with lower odds of ever asthma at 7–8 years of age (cumulative OR: 0.01, 95 % CI: 0.00, 0.53) (Fig. 8F).

Sex-stratified analyses of prenatal exposure to $PM_{2.5}$, NO_2, and temperature revealed evidence of effect modification by child sex. The results indicated that the majority of significant associations were observed in males versus females. Specifically, prenatal $PM_{2.5}$ exposure was significantly associated with increased odds of ever wheeze at both 4–6 and 7–8 years of age exclusively in males. Prenatal NO_2 exposure was linked to higher odds of ever wheeze at 7–8 years of age in both sexes, albeit with differing windows of susceptibility. Regarding temperature effects, warmer temperature exposure was associated with higher odds of ever wheeze at 7–8 years of age in males, while colder temperature exposure was associated with lower odds of ever asthma at 4–6 years of age, also in males. (Supplemental Fig. S4–S7).

3.3. Associations of average air pollution and temperature measures with childhood asthma and wheeze

Temperature exposure during the whole pregnancy (OR: 1.20, 95 % CI: 1.00, 1.43), first trimester (OR: 1.12, 95 % CI: 1.00, 1.25) and second trimester (OR: 1.14, 95 % CI: 1.00,

1.29) was associated with higher odds of ever wheeze at 4–6 years of age (Supplemental Fig. S8). No associations were found between exposure to $PM_{2.5}$, NO_2, or temperature at any period and either current wheeze or asthma at 4–6 years of age (Supplemental Fig. S8). For respiratory outcomes at 7–8 years of age, $PM_{2.5}$ exposure during the first year (OR: 6.65, 95 % CI: 2.34, 22.95), first two years (OR: 8.08, 95 %CI: 1.46, 44.33), and first four years (OR: 7.27, 95 %CI: 1.08, 47.45) of life, as well as NO_2 exposure during the first years of life (OR: 1.56, 95 %CI: 1.09, 2.24), were linked to higher odds of current wheeze at 7–8 years of age (Supplemental Fig. S9).

We observed statistical interactions between child sex and average $PM_{2.5}$ exposure during the whole pregnancy ($P_{interaction}$ = 0.09) in association with ever asthma at 7–8 years of age, NO_2 exposure during the first four years of life ($P_{interaction}$ = 0.07) in association with ever wheeze at 7–8 years of age, and temperature exposure during the third trimester ($P_{interaction}$ = 0.05) in association with current wheeze at 7–8 years of age. Furthermore, sex-stratified analyses of the associations between air pollution exposure at various exposure windows and outcomes of interest provided evidence of sex-specific effects, indicating that these effects were more evident in males. For instance, $PM_{2.5}$ exposure during the first year, first two years, and first four years of life were associated with higher odds of current wheeze at 7–8 years of age, in males but not for females. Similarly, NO_2 exposure during the first year of life was linked to higher odds of current wheeze and ever asthma at 7–8 years of age for males, but not for females (Supplementary Fig. S10–S11). Temperature exposure during the first trimester was found to be associated with higher odds of ever asthma at 7–8 years of age in females only (Supplementary Fig. S12).

3.4. Additive interactions between $PM_{2.5}$, NO_2, and temperature on childhood asthma and wheeze

No significant additive interaction patterns were observed for the majority of the air pollutant/temperature-outcome-exposure window combinations (Supplemental Table S2–S7). However, a significant additive effect was found for high $PM_{2.5}$ exposure and high temperature during the first year postpartum (OR: 7.02, 95 % CI: 2.24, 27.51; RERI: 5.32, 95 % CI: 0.10, 36.90; AP: 0.76, 95 % CI: 0.01, 1.07) on current wheeze at 7–8 years of age.

3.5. Sensitivity analysis

In sensitivity analyses, models additionally incorporating adjustments for alternative prenatal exposure windows or postnatal exposure periods, as well as multipollutant models, generally yielded results consistent with the primary analysis (Supplemental Table S8–S13). Our prenatal air pollution exposure analyses when included weekly temperature as a covariate showed similar shapes but associations are attenuated with the inclusion of weekly temperature measures (Supplemental Fig. S13–S14). We additionally found that prenatal colder temperature exposure was associated with lower risk of ever wheeze at 7–8 years of age, while no sensitive windows were identified for prenatal warmer temperature exposure in comparison with our main analyses when modeled the dose–response and lag-response relationships using natural cubic splines with degrees of freedom selected based on the AIC (Supplemental Fig. S15–S16).

4. Discussion

In this prospective birth cohort study, we identified windows of susceptibility during mid-gestation and early postnatal life for exposure to $PM_{2.5}$ and NO_2, and higher odds of wheeze in early and mid-childhood. Late-gestation was identified as a susceptibility window for warmer temperature, primarily linked to increased odds of childhood wheeze. In contrast, exposure to warmer and colder temperatures around 2–3 years of age was associated with lower odds of wheeze and asthma, respectively. In addition, there was evidence of an interaction between $PM_{2.5}$ exposure and temperature, with higher exposure to both during the first year of life being associated with higher odds of current wheeze in mid-childhood. Our results also indicated sex-specific effects of prenatal air pollution exposure, with $PM_{2.5}$ and NO_2 both associated with higher odds of ever wheeze in males, while NO_2 exposure was additionally linked to higher odds of asthma in males.

We found consistent associations with wheeze outcomes but not with asthma. These results were in line with the Hong Kong Chinese Birth Cohort study, which found that NO_x exposure in utero, 0–2, and 3–8 years of age, were also associated with wheezing but not asthma at ~17.5 years (He et al., 2019). Additionally, a previous *meta*-analysis found that NO_2 exposure during the entire pregnancy was associated with higher risk of wheezing, but not asthma, in offspring (Hua et al., 2023). One plausible explanation is that some early life wheezing can be temporary in nature, while persistent wheeze is indicative of impaired lung function and a higher risk of developing asthma later in childhood (Hazlehurst et al., 2024). Moreover, our asthma outcome was based on ever report and was not based on physician diagnosis which might differ from other studies (Lee et al., 2018; Zanobetti et al., 2024). The identified critical windows at mid-gestation for $PM_{2.5}$ and NO_2 exposure are in line with prior studies (Jung et al., 2019; Lavigne et al., 2018; Lavigne et al., 2019; Lee et al., 2018) that focused on the effects of $PM_{2.5}$ and NO_x exposure during pregnancy on childhood asthma development. Exposure to both $PM_{2.5}$ and NO_2 during the first year of life was identified as a consistent critical window of exposure across multiple outcomes. These results were partly supported by previous studies, such as Rancìere et al. (2017) and Nordling et al. (2008) found NO_x exposure during the first year of life was linked to higher risk of persistent wheezing at 4 years; Gehring et al. (2010) observed annual average $PM_{2.5}$ exposure estimated at birth address was linked to higher risk of early transient and late onset wheezing.

In contrast to $PM_{2.5}$ and NO_2, relatively few studies have investigated the long-term effect of temperature extremes, especially for the prenatal period on childhood asthma and wheeze (D'Amato et al., 2010; Hu et al., 2022). Previous time-series studies often focused on postnatal exposure and assessed the short-term effect of temperature on asthma hospital admissions or outpatient/emergency department visits (Agache et al., 2024; Qiu et al., 2015). Temperature extremes showed complex associations with wheeze outcomes in this study, varying by timing and intensity of exposure. While increased average temperature exposure during pregnancy generally increased the odds of ever wheeze, both warmer and colder temperatures exposure during late-gestation was linked to higher odds of wheeze outcomes. Postnatal exposure to warmer temperature was linked to lower odds of current wheeze, while exposure to colder temperature was linked to lower odds of ever asthma. We

acknowledge that the linear assumption for temperature in our logistic regression models is a simplification that may not fully capture complex non-linear relationships. Our main findings from non-linear DLNM analyses should be considered more representative of the true temperature-health associations. These findings generally indicate that the relationship between temperature and respiratory health in children is not linear and depends on the specific developmental window of exposure. Our warmer temperature (19 °C) is similar to the Generation R study (Granés et al., 2024) with heat exposure of 20.2 °C and ENVIRONAGE birth cohort study (Martens et al., 2019) with heat threshold of 19.5 °C. This is consistent with previous studies suggesting a non-linear relationship between temperature and respiratory health, with both extreme cold and heat potentially having adverse effects on the respiratory system (Hu et al., 2020; Xu et al., 2013). Several recent literature reviews (Hu et al., 2022; Xu et al., 2012) indicated that exposure to temperature extremes, both cold and heat, could increase asthma risk through various biological pathways including cold temperatures can induce bronchoconstriction and increase airway inflammation, while heat can lead to dehydration of the airways, altering mucus properties and potentially triggering bronchospasms. Additionally, both extremes can affect the immune system, increasing susceptibility to respiratory infections and allergens, which are known asthma triggers. Complementing these findings, experimental research using a mouse model of asthma revealed a U-shaped relationship between temperature and inflammatory markers. The study observed peak levels of immune proteins and pro-inflammatory factors at 24 °C, suggesting that temperatures deviating from this point in either direction could exacerbate airway inflammation (Deng et al., 2020). Overall, human epidemiological and animal experimental evidence indicates that there exists an optimum range within which the impact of temperature on respiratory health is minimal.

Lung growth and development is a critical process that starts as early as 3–4 weeks of gestation and progresses into early adulthood, with the most rapid growth occurring during the early stages of life, highlighting the crucial role of early lung development in shaping future respiratory health (Martinez, 2016; Stocks et al., 2013). The potential mechanisms explaining the association between early life environmental stressors, such as air pollution and temperature, and childhood asthma and wheeze may be attributed to multiple factors. Firstly, exposure to air pollutants and extreme temperatures during the critical developmental period of the lungs in infancy and early childhood may alter lung function and structure, leading to increased susceptibility to respiratory disorders (Bose et al., 2018; Cai et al., 2020; Guilbert et al., 2023b). Secondly, these environmental stressors may trigger oxidative stress and inflammatory responses in the airways, which are key pathways in the development of asthma and wheeze (Lu et al., 2023; Riedl, 2008; Xu et al., 2023). Moreover, air pollution and temperature variations may modulate the immune system, influencing the balance between T-helper cell types and promoting allergic sensitization (Aguilera et al., 2023; Glencross et al., 2020; Morgenstern et al., 2008; Sampath et al., 2023; Tuazon et al., 2022). Early-life environmental influences may induce epigenetic modifications, including alterations in DNA methylation patterns and histone modifications, potentially contributing to the development of respiratory conditions like asthma and wheeze in children (Ji et al., 2016a; Yang et al., 2017). Lastly, the interaction between environmental factors and genetic predisposition likely plays a role in how early

life environmental stressors affect respiratory health outcomes in childhood (Gref et al., 2017; Ji et al., 2016b; Peden, 2005).

The observed sex-specific effects of air pollution and temperature exposure on respiratory outcomes may be attributed to inherent differences in fetal lung development between males and females, which are largely influenced by sex hormones (Guilbert et al., 2023b). These differences are characterized by distinct patterns of pulmonary growth and airway formation. Specifically, female fetuses typically develop smaller lungs and alveolar surface areas compared to males, but possess larger-caliber airways (Carey et al., 2007a; Liptzin et al., 2015). Furthermore, lung surfactant production begins earlier in female fetuses than in males. This advanced surfactant development may contribute to higher airflow rates and lower airway resistance in girls (Carey et al., 2007a). These physiological distinctions could potentially explain the differential susceptibility to environmental exposures observed between sexes during critical periods of lung development. The identified prenatal sensitive window aligns with the canalicular phase of fetal lung development, a critical period for tissue formation and functional differentiation (Hsu et al., 2015). During this stage (weeks 17–26), significant changes occur, including continued airway development, emergence of capillaries and alveolar structures, and the initiation of type II to type I cell differentiation, leading to surfactant production (Burri, 1984; Kajekar, 2007; Miller and Marty, 2010). The airway epithelium formed in this phase plays a crucial role in innate immunity, potentially influencing later respiratory conditions like asthma and wheezing (Kato et al., 2007). The sensitivity observed in the first year of life may be attributed to infants' heightened vulnerability to environmental factors (Zhao et al., 2021). This susceptibility stems from their unique physiological characteristics, including higher oxygen needs, proportionally smaller lung surface area, more permeable airways, and still-developing pulmonary defense mechanisms (Salvi, 2007).

This study had several strengths. The PROGRESS cohort study included a relatively large sample size of mother–child dyads with longitudinal data collected rigorously over several years, allowing us to assess childhood asthma and wheeze at 4–6 and 7–8 years of age study visits using a well-validated instrument (Mallol et al., 2010). We employed validated exposure models with high spatial and temporal resolution and investigated associations of respiratory outcomes with two air pollutants, temperature, and their interaction effects. Exposure windows were assessed based not only on the biological stages of prenatal lung formation and clinically defined trimesters but also confirmed using the flexible DLNMs. We considered exposure in both prenatal and postnatal periods, covering the first 1000 days of life (from conception to the 2nd year of life), which might be particularly relevant for understanding the long-term impact of environmental stressors on child health.

We also acknowledged potential limitations. Following standard practices in air pollution research, we estimated personal exposure to air pollutants and temperature based on residential addresses. This approach does not account for indoor environments or time spent at non-residential locations. As with most similar studies, we cannot rule out exposure misclassification or confounding by indoor air, which may have attenuated the reported results. Nevertheless, the mild climate in Mexico City led to nearly all participants (≥ 94 %) keeping their windows open throughout the day, reducing the potential for indoor-outdoor

pollution/temperature ratio discrepancies that often pose a challenge in studies conducted in developed countries (Hsu et al., 2024). The respiratory outcomes we studied were based on caregiver reports, which may introduce potential recall bias. Nevertheless, it is worth noting that parent-reported asthma and wheeze are a common and accepted practice in epidemiological research on childhood respiratory health (Hazlehurst et al., 2024; Zhang et al., 2021). We acknowledge that some effect estimates for late pregnancy, although not reaching statistical significance, were notably strong. This pattern warrants careful interpretation. The widening of confidence intervals at the extremes of the exposure period is a known limitation of DLNM, which may reduce statistical power to detect significant associations in early and late pregnancy. The potentially important role of late pregnancy exposures should not be overlooked. However, we did not find significant associations for third trimester air pollutant exposure. These findings highlight the complex nature of fetal development and underscore the need for future studies with larger sample sizes to better characterize exposure impacts across different gestational periods. As with any observational study, residual confounding due to unmeasured factors that could confound and/or modify the effect of air pollution and temperature exposure on childhood wheeze and asthma cannot be completely ruled out. Finally, given the extensive number of models fitted, it is plausible that some of the observed associations could be attributable to chance. Instead of applying corrections for multiple testing, which might increase the risk of type II error, we chose to concentrate on identifying consistent patterns of relationships across the various analyses (Althouse, 2016; Fandiño-Del-Rio et al., 2022).

5. Conclusions

Our results provide evidence that exposure to air pollution and temperature, in utero and in early life is associated with childhood asthma and wheeze. We identified susceptibility windows primarily during mid-gestation and early postnatal life for air pollution and late-gestation and 2–3 years for warmer and colder temperatures. We also found the effect estimates were more evident in males versus females. Furthermore, interactions were observed between high $PM_{2.5}$ exposure and high temperature during the first year of life, resulting in a significantly increased odds of wheeze outcome. The implications of these findings, in conjunction with existing evidence, suggest that reducing early life air pollution exposure could potentially lower the risk of developing childhood asthma and wheeze.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that has been used is confidential.

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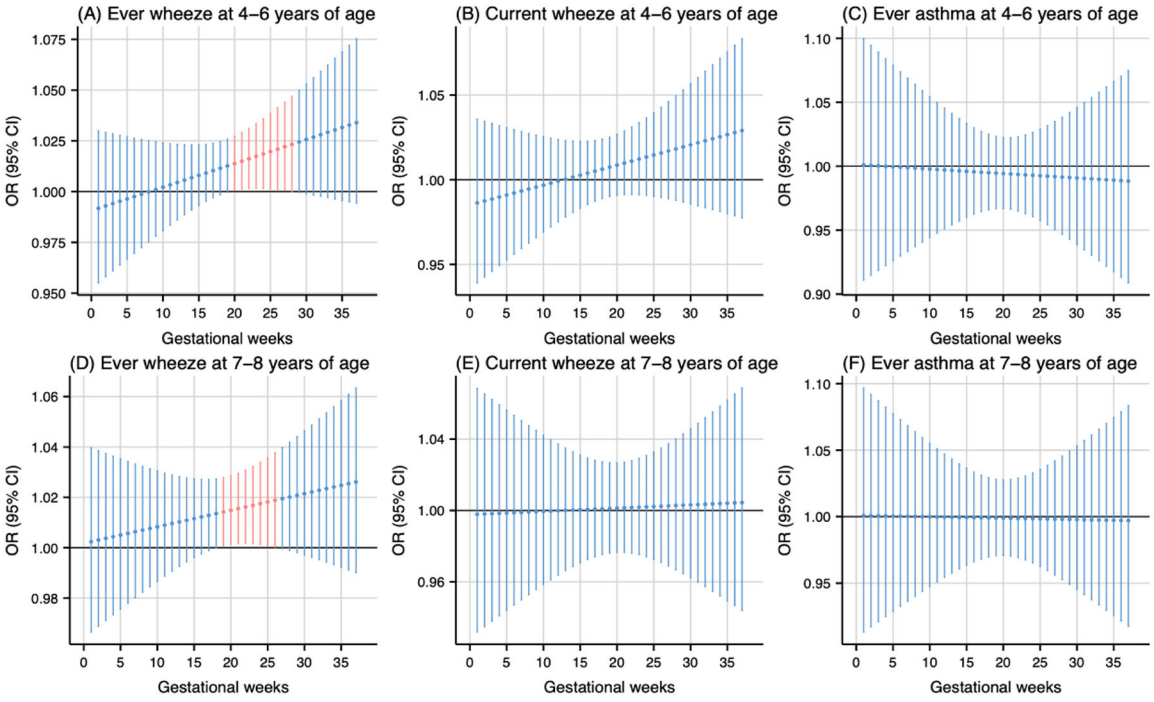

Fig. 1.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with weekly-specific $PM_{2.5}$ exposure during 1–37 weeks of pregnancy. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and postnatal year 4 average $PM_{2.5}$.

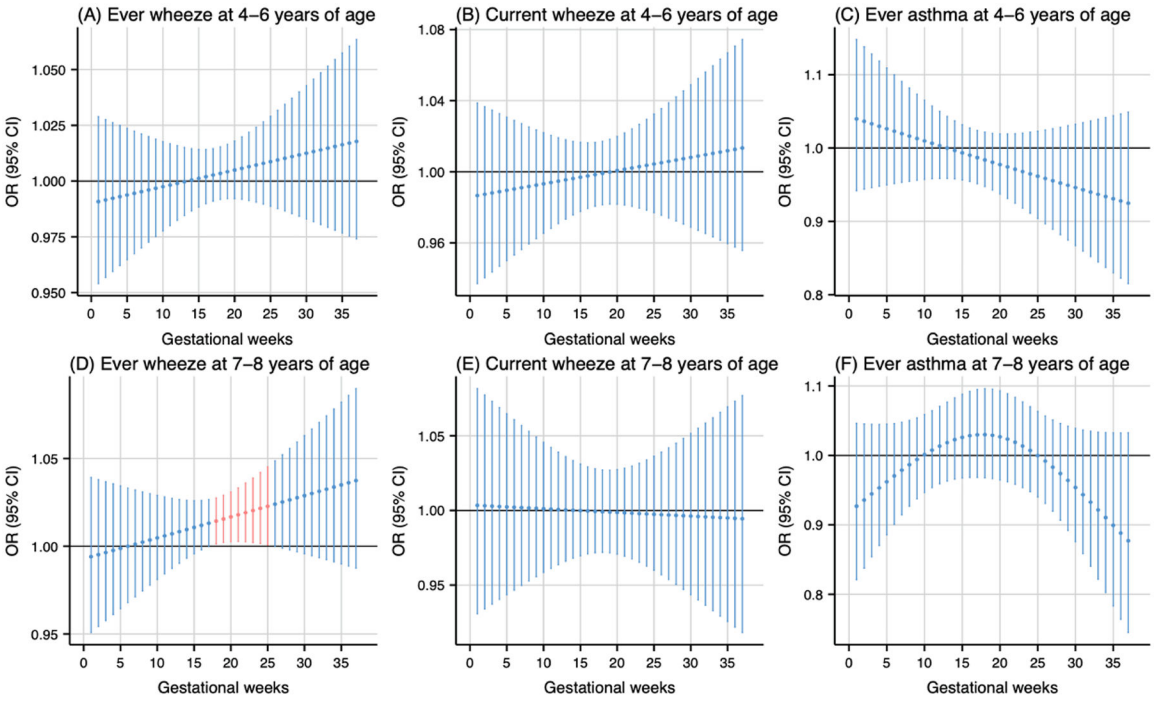

Fig. 2.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with weekly-specific NO_2 exposure during 1–37 weeks of pregnancy. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and postnatal year 4 average NO_2.

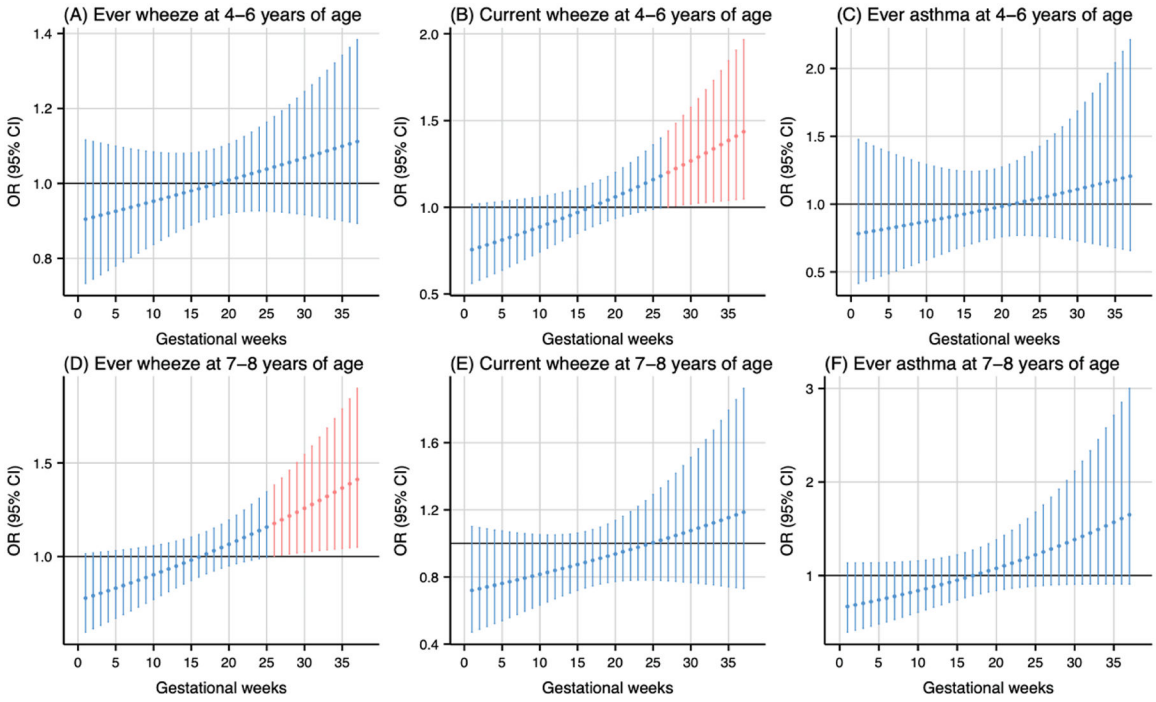

Fig. 3.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with temperature at 95th percentile (19 °C), relative to the 50th percentile (15 °C) during 1–37 weeks of pregnancy. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and postnatal year 4 average temperature.

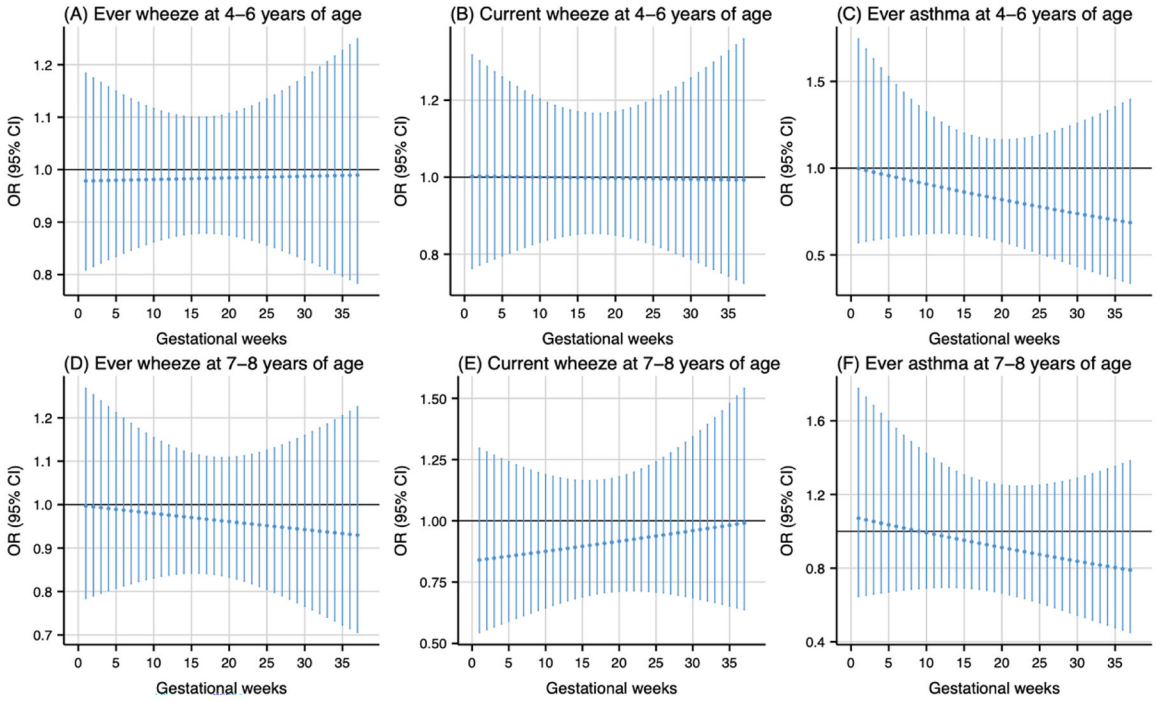

Fig. 4.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with temperature at 5th percentile (11 °C), relative to the 50th percentile (15 °C) during 1–37 weeks of pregnancy. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and postnatal year 4 average temperature.

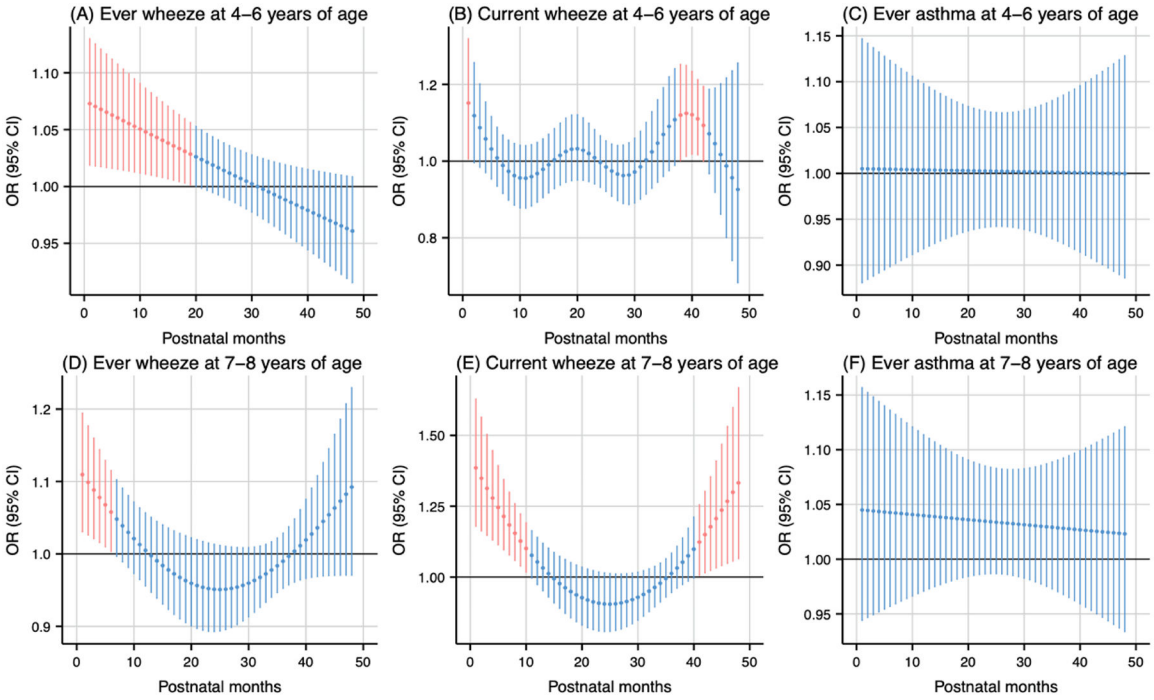

Fig. 5.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with monthly-specific $PM_{2.5}$ exposure during postpartum 1–48 months. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and prenatal average $PM_{2.5}$.

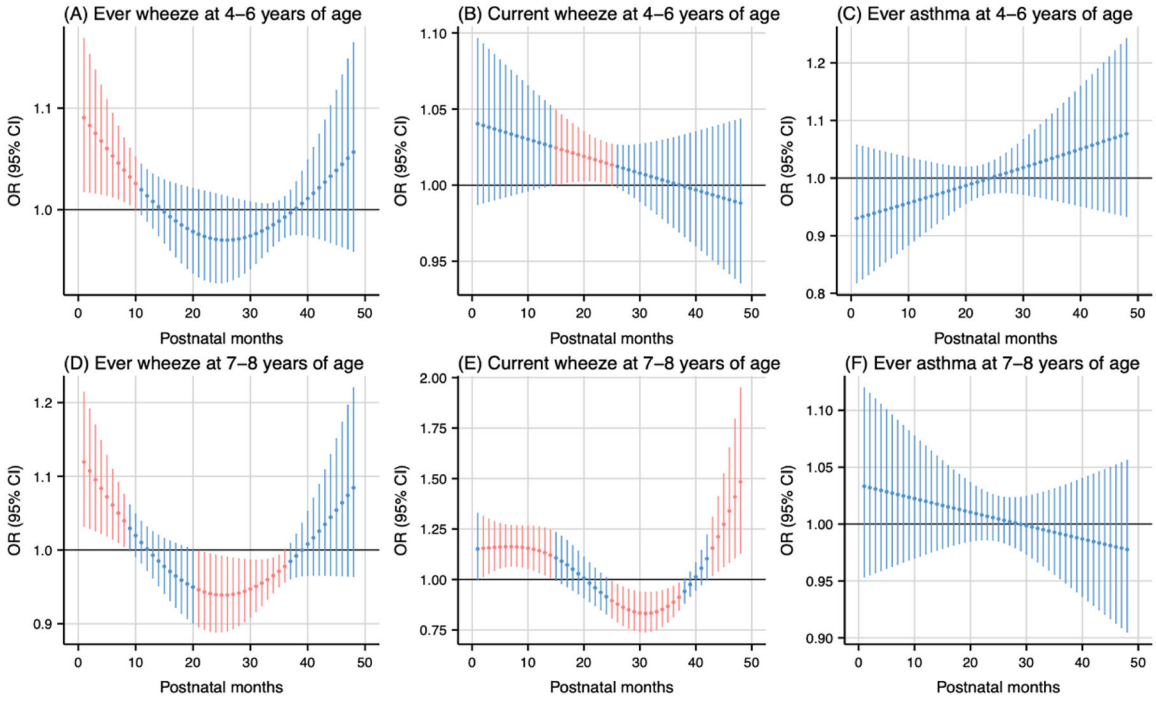

Fig. 6.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with monthly-specific NO_2 exposure during postpartum 1–48 months. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and prenatal average NO_2.

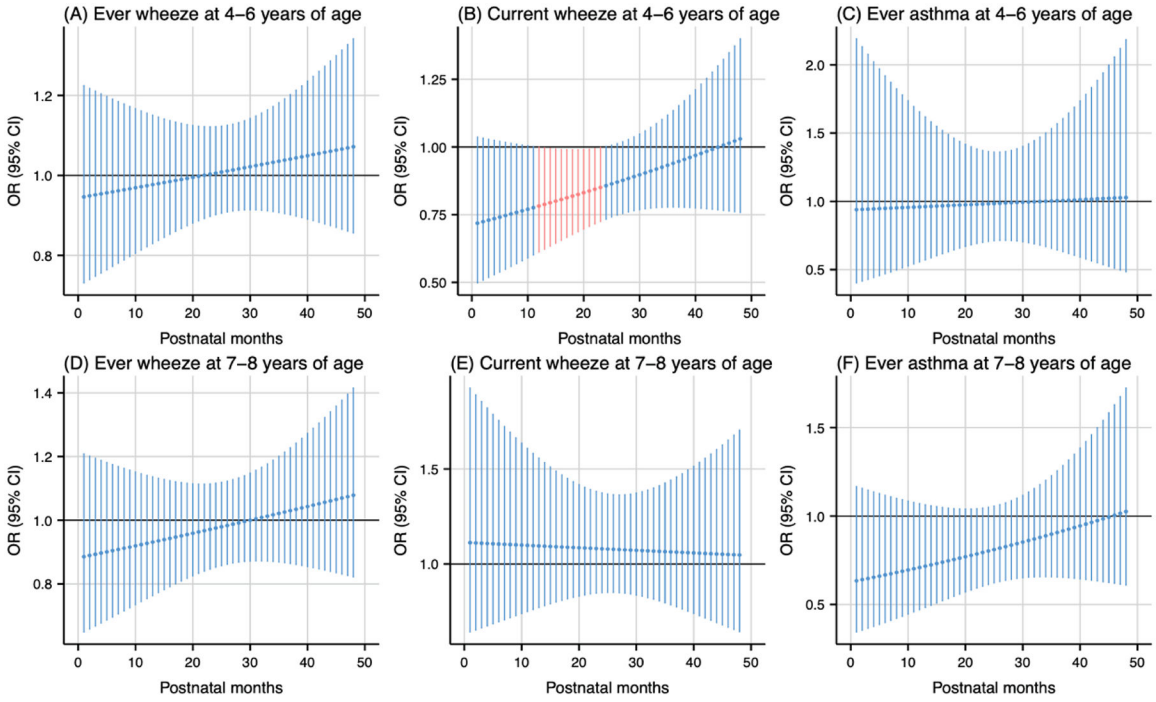

Fig. 7.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with temperature at the 95th percentile (19 °C), relative to the 50th percentile (15 °C) during postpartum 1–48 months. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and prenatal average temperature.

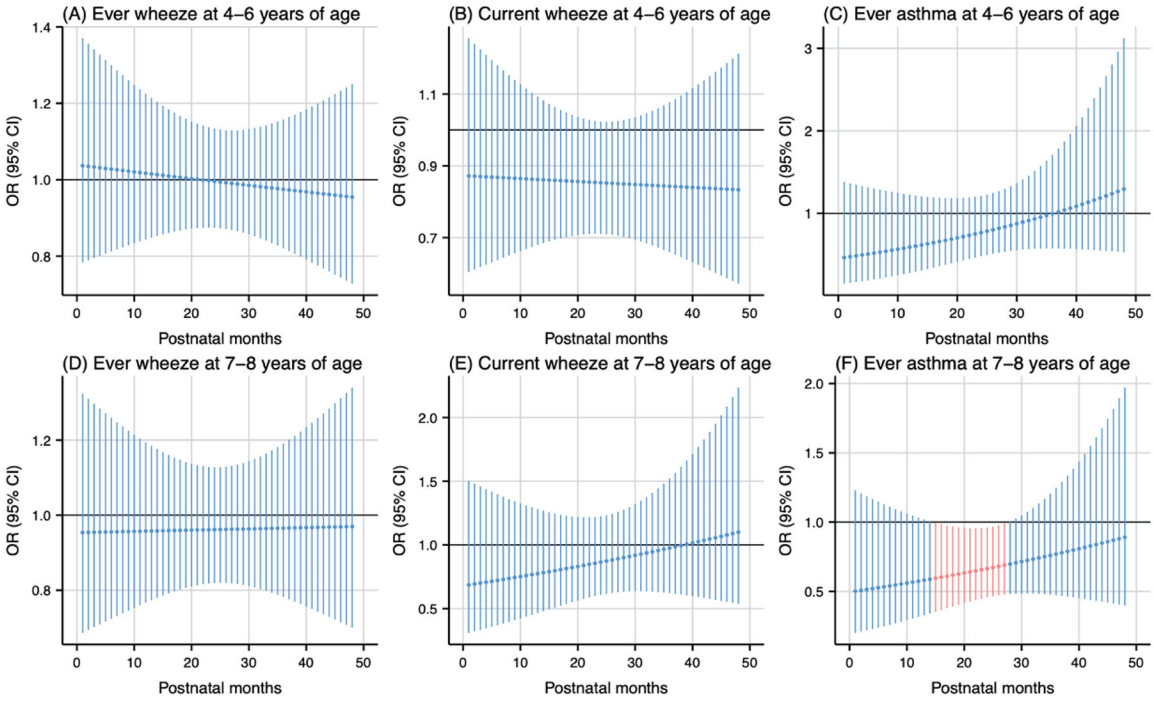

Fig. 8.

Odds ratio (95 % CI) of childhood asthma and wheeze in association with temperature at the 5th percentile (11 °C), relative to the 50th percentile (15 °C) during postpartum 1–48 months. Critical windows are highlighted in red. Models were adjusted for maternal age, pre-pregnancy body mass index, education level, parity, environmental tobacco exposure, child sex and age, seasonality, and prenatal average temperature.

Table 1

PROGRESS participant characteristics (N = 468).

Characteristics	Total sample	Males (n = 235)	Females (n = 233)
Maternal age (years), mean (SD)	27.6 (5.63)	27.9 (5.46)	27.2 (5.78)
Maternal education, n (%)			
< High school	189 (40.4)	103 (43.8)	86 (36.9)
High school	177 (37.8)	82 (34.9)	95 (40.8)
> High school	102 (21.8)	50 (21.3)	52 (22.3)
Maternal ever asthma, n (%)			
Yes	3 (0.6)	2 (0.9)	1 (0.4)
No	465 (99.4)	233 (99.1)	232 (99.6)
ETS, n (%)			
Yes	144 (30.8)	72 (30.6)	72 (30.9)
No	324 (69.2)	163 (69.4)	161 (69.1)
Maternal pre-pregnancy BMI, mean (SD)	26.5 (4.19)	26.8 (4.05)	26.1 (4.30)
Parity, n (%)			
Primiparous	282 (60.3)	148 (63.0)	134 (57.5)
Multiparous	186 (39.7)	87 (37.0)	99 (42.5)
Child age at 4–6 years visit, mean (SD)	4.8 (0.55)	4.8 (0.54)	4.8 (0.56)
Child age at 7–8 years visit, mean (SD)	6.7 (0.54)	6.7 (0.55)	6.7 (0.53)
Respiratory outcomes			
(4–6 years of age), n (%)			
Ever wheeze	123 (26.3)	68 (28.9)	55 (23.6)
Current wheeze	60 (12.8)	37 (15.7)	23 (9.9)
Ever asthma	14 (3.0)	8 (3.4)	6 (2.6)
Respiratory outcomes			
(7–8 years of age), n (%)			
Ever wheeze	75 (16.0)	41 (17.4)	34 (14.6)
Current wheeze	27 (5.8)	16 (6.8)	11 (4.7)
Ever asthma	21 (4.5)	14 (6.0)	7 (3.0)

Abbreviations: SD, standard deviation; ETS, environmental tobacco smoke; BMI, body mass index.

Table 2

Distribution of ambient air pollution and temperature.

Exposure and window	Mean	SD	Min.	Q1	Median	Q3	Max.
PM2.5 ($\mu g/m^3$)							
Whole pregnancy	22.8	2.9	16.4	20.4	23	24.9	30.3
First trimester	22.8	4.9	12.6	18.8	21.8	26.8	34.3
Second trimester	22.4	5.1	11.5	18	21.3	26.9	32.8
Third trimester	23.2	5.8	11.9	18.1	22.5	28.3	37.5
First year	22.6	2.5	17.6	20.3	23.4	24.6	26.7
First two years	22.4	1.2	20.5	21.6	22.3	23	26.1
First four years	22.5	1	20	21.7	22.2	23.3	26.3
NO_2 (ppb)							
Whole pregnancy	33.1	5.6	17.8	29	31.9	36.9	49.7
First trimester	33.1	7.7	16.6	27.1	31.1	37.5	60.7
Second trimester	32.8	7.2	20.1	27	31.7	36.9	56.5
Third trimester	33.6	7.6	16.4	27.7	33.1	38.2	63.7
First year	32.7	5.4	17.7	28.6	30.4	37	48.9
First two years	32.4	5.2	17.3	28.5	30.3	36.1	46.9
First four years	32.1	5.2	17	28.4	30	35.6	46.5
Temperature (°C)							
Whole pregnancy	15	1.3	11.6	14.2	15	16	18
First trimester	15.2	2	10	13.9	15.3	16.6	19.5
Second trimester	15	2.1	10.1	13.6	14.9	16.6	19.2
Third trimester	14.8	2.2	9.3	13.2	14.7	16.5	20.6
First year	15.1	1.2	11.5	14.2	15.2	16.1	17.8
First two years	15.2	1.2	11.6	14.4	15.2	16.2	17.7
First four years	15.2	1.2	11.5	14.4	15.2	16.2	17.6

Abbreviations: SD, standard deviation; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤ 2.5 μm in diameter.