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# Association of Prenatal Exposure to Fine Particulate Matter Pollution With Childhood Eczema

**Short title:** Prenatal $PM_{2.5}$ exposure and childhood eczema

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To the Editor,

Atopic eczema (or atopic dermatitis) is a chronic relapsing inflammatory skin disease affecting 15-30% of children worldwide [1]. Although previous studies have attempted to link higher prenatal exposure to particulate matter with childhood eczema, [2-6] most studies examined particulate matter with an aerodynamic diameter of 10μm or less ($PM_{10}$), but not particulate matter with an aerodynamic diameter of 2.5μm or less ($PM_{2.5}$), and yielded inconsistent results. Sensitive windows of prenatal exposure to $PM_{2.5}$ for eczema development remain unclear. Here, we aimed to explore sensitive windows for effects of weekly average $PM_{2.5}$ exposure during gestation on the development of childhood eczema.

In this case-control study, we used the data derived from the study population including 1,128 full-term children (mean age 6.4 years, 56% boys) who participated in the Longitudinal Investigation of Global Health in Taiwanese Schoolchildren (LIGHTS) cohort. Eczema was defined as having physician-diagnosed eczema and presence of eczema in the last 12 months through a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire provided by parents/guardians of the study participants. [7] We applied a distributed lag nonlinear model to examine the exposure-lag-response association of eczema with mean weekly $PM_{2.5}$ estimates using a highly spatial-temporal resolution hybrid/land-use regression model. The flow diagram for subject recruitment is shown in **Figure S1**. Seasonal averaged $PM_{2.5}$ concentrations surface maps corresponding to residential address during pregnancy are shown in **Figure S2**. Detailed methods are provided in the Supporting information.

**Table 1** shows the characteristics of 1,128 study children; 216 (19.1%) had eczema. Onset of eczema among 216 cases was reported as follows: 67 (31.5%) during the first year of life; 41 (19.2%) during 1-2 years of age; 69 (32.4%) during 2-5 years of age; and 36 (16.9%) after 5 years of age. **Figure 1** depicts the main findings of this study. We observed a significant association of childhood eczema with increased exposure to $PM_{2.5}$ during gestational weeks 7 to 17, with the highest risk at gestational week 12 (adjusted odds ratios [AOR]=1.10 per 10 μg/m$^3$; 95% CI=1.03-1.18) (**Figure 1**), after adjustment for child's age, sex, body mass index (BMI), atopy, parental allergic disease, birth season, ambient temperature and relative humidity. In gestational week 12, the concentration-response relationship indicated that the AOR of childhood eczema was significantly higher than 1.0 at $PM_{2.5}$ concentrations greater than 21.2 μg/m$^3$ (**Figure S3**).

We further stratified the analysis by breastfeeding and exposure to prenatal environmental tobacco smoke (ETS). When stratified by breastfeeding, we observed a significant sensitive exposure window between 8 and 18 gestational weeks among children who were not breastfed, but not among children who were breastfed (**Figure S4A & S4B**). Exposure to prenatal ETS might accentuate the harmful effect of $PM_{2.5}$, as a significant sensitive exposure window between 6 and 11 gestation weeks was found among children exposed to prenatal ETS, but not among children not exposed to prenatal ETS (**Figure S4C & S4D**).

This study has identified, for the first time, a sensitive window of exposure to $PM_{2.5}$ at gestational weeks 7 to 17 on the risk of developing childhood eczema, which may provide insight into underlying mechanisms. Developmental periods of skin have been documented as follows: embryonic (gestational weeks 5-8), epidermal stratification (gestational weeks 9-14), follicular keratinization (gestational weeks 14-24), and interfollicular keratinization (after gestational week 24) periods. [8] The

epidermal barrier does not form in the human fetus until 20-24 gestational weeks, [9] making the period before gestational week 20 as a critical window where the fetus may be highly vulnerable to the harmful effects of $PM_{2.5}$ diffusing into the placental barrier. The sensitive window of exposure identified in the present study coincides with the embryonic, epidermal stratification, and follicular keratinization periods of skin development, and particularly, coincides with the crucial period of vulnerability from the beginning of embryonic skin development at gestational week 5 to the initiation of epidermal barrier formation at gestational weeks 20-24. One potential explanation might be due to dysregulation of filaggrin, a key protein involved in skin barrier function and maintenance of skin integrity. Human studies have demonstrated that filaggrin expresses simultaneously with the morphologic occurrence of keratinization at gestational week 15 in follicles and gestational weeks 22-24 in the interfollicular epidermis. [8] Since the expression of filaggrin is influenced by exogenous stressors, such as systemic inflammatory mediators, oxidative stress and Th2 inflammatory responses, it is possible that filaggrin expression might be dysregulated by prenatal exposure to particulate matter during the sensitive time-window, subsequently, contributing to the development of childhood eczema. [10]

This is the first study to provide evidence linking prenatal exposure to ambient $PM_{2.5}$ above a threshold concentration of 21.2 μg/m$^3$ to the development of childhood eczema. Our results are in line with previous findings in a smaller birth cohort of 469 subjects, which showed an association of combined exposures to prenatal $PM_{2.5}$ and postnatal ETS with the development of infantile eczema. [3] In a meta-analysis of more than 46,100 subjects from 13 studies, human skin could be adversely affected when $PM_{2.5}$ concentrations reached upwards 26.04 μg/m$^3$. [11] Our findings provide further evidence for the adverse effects of particulate matter on skin in developing fetus at a slightly lower threshold concentration, compared to previously reported threshold

concentrations for the detrimental effects of $PM_{2.5}$ on human skin in children and adults. [11]

This study adds new evidence to the literature by suggesting that exclusive breastfeeding during the first 3 months of life or longer may reduce the risk of developing eczema from prenatal exposure to $PM_{2.5}$. One possible explanation is that breast milk contains many immunomodulatory factors, which may more effectively promote the programming of the infant's developing immune system than infant formula and countervail the harmful effects of air pollution. Mukherjee and colleagues have reported that breastfeeding modified the effect of smoking during pregnancy on eczema in offspring in the Isle of Wight birth cohort. [12] Zhang et al. have found that breastfeeding was associated with lower risk of lung function impairment among children exposed to air pollution. [13]

Our results suggest that prenatal exposure to ETS may attenuate host response to fine particulate matter pollution, leading to the development of childhood eczema, as the threshold of prenatal exposure to $PM_{2.5}$ on eczema risk decreased from 21.2 $\mu g/m^3$ to 12 $\mu g/m^3$ in the presence of prenatal ETS exposure. Similar to our findings, a synergistic effect of combined exposure to prenatal $PM_{2.5}$ and postnatal ETS on eczema was reported in a previous birth cohort. [3]

This study primarily focus on investigating the influence of prenatal $PM_{2.5}$ exposure on risk of childhood eczema in this study. Further investigation will be needed to uncover some important exposure windows in postnatal stage. A limitation of this study is that we did not examine the associations of prenatal exposure to $PM_{2.5}$ with severity or duration of eczema because detailed data on severity and age at onset of eczema were not available.

In conclusion, this study lends further evidence linking prenatal exposure to $PM_{2.5}$ during 7 to 17 gestational weeks to an increased risk of developing childhood

eczema by age 6 years, with the risk largely confined to children who were not breastfed or exposed to prenatal ETS.

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**Author contributions:** TCY and HJT conceptualized, designed, and supervised the study, raised funding for the study, assisted in data analysis, interpreted results, and drafted manuscript. HYH and WCP analyzed data and interpreted results. CYW, CYH, KLL, and JCC assisted in participant recruitment, cohort maintenance and acquisition of data. SYT, CLZ, CDW, and YCC assisted in data analysis and interpretation. YJH provided thoughtful input in interpretation of the results.

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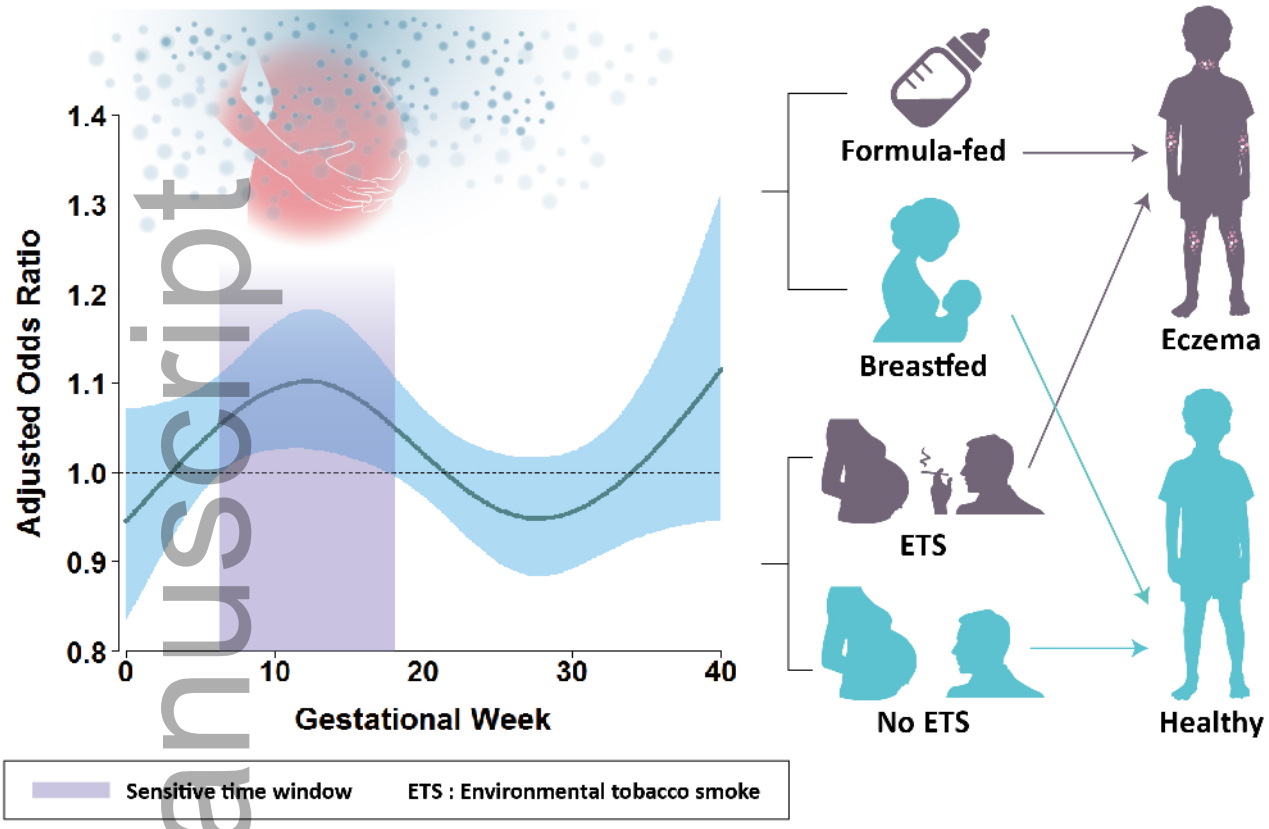
**Table 1.** Characteristics of study children in the LIGHTS cohort (*n*=1,128).

| Characteristic | All children | Eczema (*n*=216) | No eczema (*n*= 912) | *P* |
|---|---|---|---|---|
| **Sex**, boy, *n* (%) | 632/1,128 (56.0) | 121/216 (56.0) | 511/912 (56.0) | 0.99 |
| **Age**, years (mean ± SD) | 6.4±0.4 | 6.4±0.4 | 6.4±0.4 | 0.35 |
| **Height**, cm (mean ± SD) | 118.7±5.6 | 118.5±5.9 | 118.7±5.5 | 0.68 |
| **Weight**, kg (mean ± SD) | 22.4±4.7 | 22.9±5 | 22.3±4.7 | 0.10 |
| **Body mass index**, kg/m$^2$ (mean ± SD) | 15.8±2.4 | 16.2±2.7 | 15.7±2.3 | 0.01 |
| **Atopy**, *n* (%) | 716/1,089 (65.8) | 163/205 (79.5) | 553/912 (62.6) | <0.001 |
| **Breastfeeding**, *n* (%) | 566/1,128(50.2) | 114/216(52.8) | 452/912(49.6) | 0.39 |
| **Prenatal environmental tobacco smoke**, *n* (%) | 472/1,128 (41.8) | 84/216 (38.9) | 388/912 (42.5) | 0.32 |
| **Parental history of asthma**, *n* (%) | 125/1,121 (11.2) | 37/213 (17.4) | 88/908 (9.7) | 0.001 |
| **Parental history of allergic rhinitis**, *n* (%) | 715/1,127 (63.4) | 159/216 (73.6) | 556/911 (61.0) | 0.001 |
| **Parental history of atopic dermatitis**, *n* (%) | 301/1,112 (27.1) | 81/214 (37.9) | 220/898 (24.5) | <0.0001 |
| **Birth season**, *n* (%) | | | | 0.49 |
| Spring (March to May) | 257/1,128(22.78) | 52/216 (24.1) | 205/912 (22.5) | |
| Summer (June to August) | 280/1,128(24.82) | 59/216 (27.3) | 221/912 (24.2) | |
| Autumn (September to November) | 322/1,128(28.55) | 53/216 (24.5) | 269/912 (29.5) | |
| Winter (December to February) | 269/1,128(23.85) | 52/216 (24.1) | 217/912 (23.8) | |
| **$PM_{2.5}$**, μg/m$^3$ (median/IQR) | 26.1/4.3 | 26.7/4.6 | 26.0/4.3 | 0.08 |
| **Ambient temperature**, °C (median/IQR) | 22.3/2.9 | 22.4/2.9 | 22.3/3.0 | 0.95 |
| **Relative humidity**, % (median/IQR) | 76.5/1.6 | 76.6/1.8 | 76.4/1.5 | 0.33 |

Abbreviation: **SD**: standard deviation; **$PM_{2.5}$**: particulate matter with an aerodynamic diameter of 2.5 μm or less; **IQR**: interquartile range.

## FIGURE LEGENDS

**Figure 1.** Increased exposure to $PM_{2.5}$ during gestational weeks 7 to 17 was significantly associated with an increased risk of childhood eczema and this risk was largely confined to children who were not breastfed or exposed to prenatal environmental tobacco smoke. Note: A distributed lag nonlinear model was applied to explore sensitive windows for the effects of weekly average $PM_{2.5}$ exposure during gestation on the development of eczema by age 6 years, adjusting for child's age, gender, body mass index, atopy, parental allergic disease, birth season, ambient temperature, and relative humidity. The *y*-axis shows the adjusted odds ratio of eczema in relation to a 10 μg/m$^3$ increase in prenatal $PM_{2.5}$ exposure; the *x*-axis depicts gestational age in weeks. The *solid line* indicates the estimated odds ratio and the *shading area* represents the 95% confidence interval. A sensitive window is identified when the estimated pointwise 95% confidence interval of odds ratio does not include 1.0. Abbreviations: **$PM_{2.5}$**: particulate matter with an aerodynamic diameter of 2.5 μm or less.

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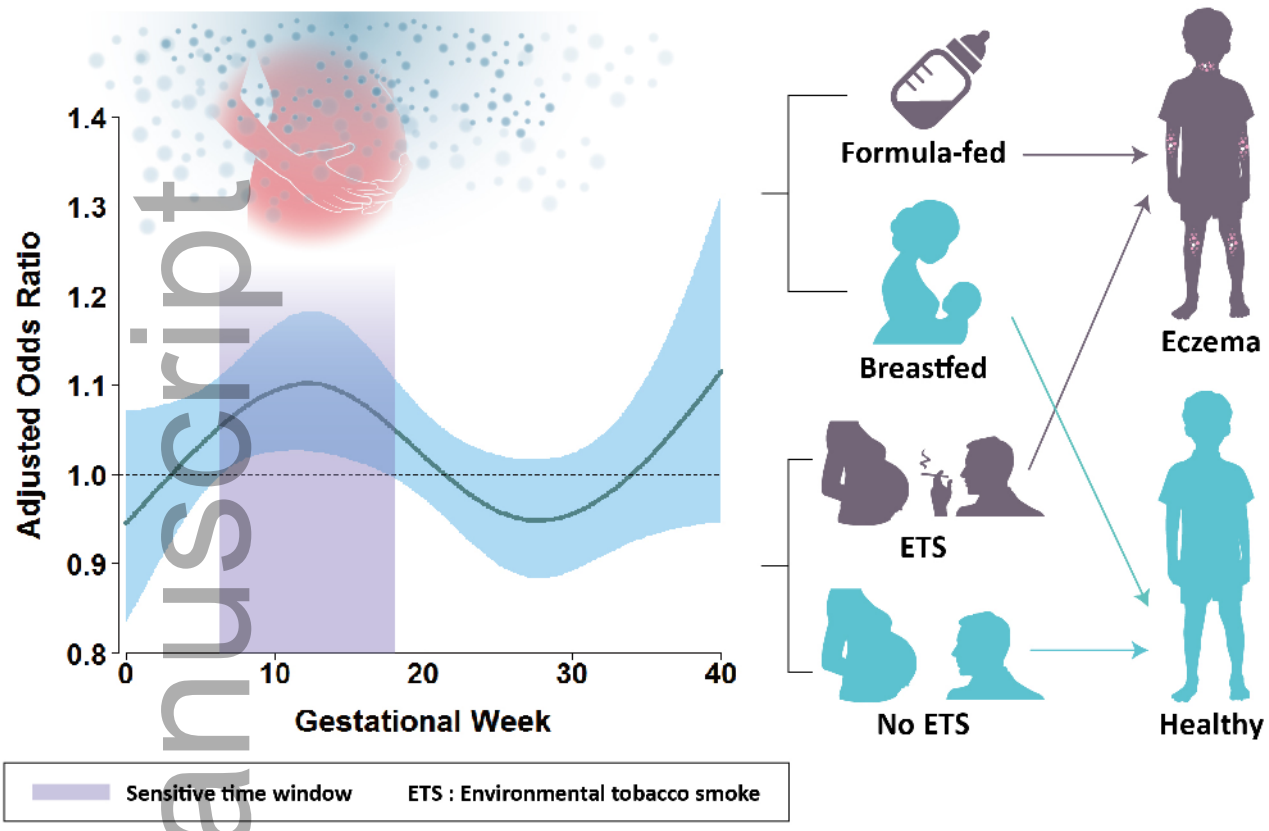


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