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9 **Association of Prenatal Exposure to Fine Particulate Matter Pollution**
10 **With Childhood Eczema**

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12 **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 10 μ m or less (PM₁₀), but not particulate matter with an aerodynamic diameter of 2.5 μ m 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

56 year of life; 41 (19.2%) during 1-2 years of age; 69 (32.4%) during 2-5 years of age; and
57 36 (16.9%) after 5 years of age. **Figure 1** depicts the main findings of this study. We
58 observed a significant association of childhood eczema with increased exposure to PM_{2.5}
59 during gestational weeks 7 to 17, with the highest risk at gestational week 12 (adjusted
60 odds ratios [AOR]=1.10 per 10 µg/m³; 95% CI=1.03-1.18) (**Figure 1**), after adjustment for
61 child's age, sex, body mass index (BMI), atopy, parental allergic disease, birth season,
62 ambient temperature and relative humidity. In gestational week 12, the
63 concentration-response relationship indicated that the AOR of childhood eczema was
64 significantly higher than 1.0 at PM_{2.5} concentrations greater than 21.2 µg/m³ (**Figure S3**).

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

73 This study has identified, for the first time, a sensitive window of exposure to PM_{2.5} at
74 gestational weeks 7 to 17 on the risk of developing childhood eczema, which may provide
75 insight into underlying mechanisms. Developmental periods of skin have been
76 documented as follows: embryonic (gestational weeks 5-8), epidermal stratification
77 (gestational weeks 9-14), follicular keratinization (gestational weeks 14-24), and
78 interfollicular keratinization (after gestational week 24) periods.⁸ The epidermal barrier
79 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/m³ 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/m³.¹¹ 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

104 detrimental effects of PM_{2.5} on human skin in children and adults. ¹¹

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

115 Our results suggest that prenatal exposure to ETS may attenuate host response to
116 fine particulate matter pollution, leading to the development of childhood eczema, as the
117 threshold of prenatal exposure to PM_{2.5} on eczema risk decreased from 21.2 µg/m³ to 12
118 µg/m³ in the presence of prenatal ETS exposure. Similar to our findings, a synergistic
119 effect of combined exposure to prenatal PM_{2.5} and postnatal ETS on eczema was
120 reported in a previous birth cohort. ³

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

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

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

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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 ($n= 912$)	<i>P</i>
Sex, boy, n (%)	632/1,128 (56.0)	121/216 (56.0)	511/912 (56.0)	0.99
Age, years (mean $\pm$ SD)	6.4 $\pm$ 0.4	6.4 $\pm$ 0.4	6.4 $\pm$ 0.4	0.35
Height, cm (mean $\pm$ SD)	118.7 $\pm$ 5.6	118.5 $\pm$ 5.9	118.7 $\pm$ 5.5	0.68
Weight, kg (mean $\pm$ SD)	22.4 $\pm$ 4.7	22.9 $\pm$ 5	22.3 $\pm$ 4.7	0.10
Body mass index, kg/m² (mean $\pm$ SD)	15.8 $\pm$ 2.4	16.2 $\pm$ 2.7	15.7 $\pm$ 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}, $\mu\text{g}/\text{m}^3$ (median/IQR)	26.1/4.3	26.7/4.6	26.0/4.3	0.08
Ambient temperature, $^{\circ}\text{C}$ (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.

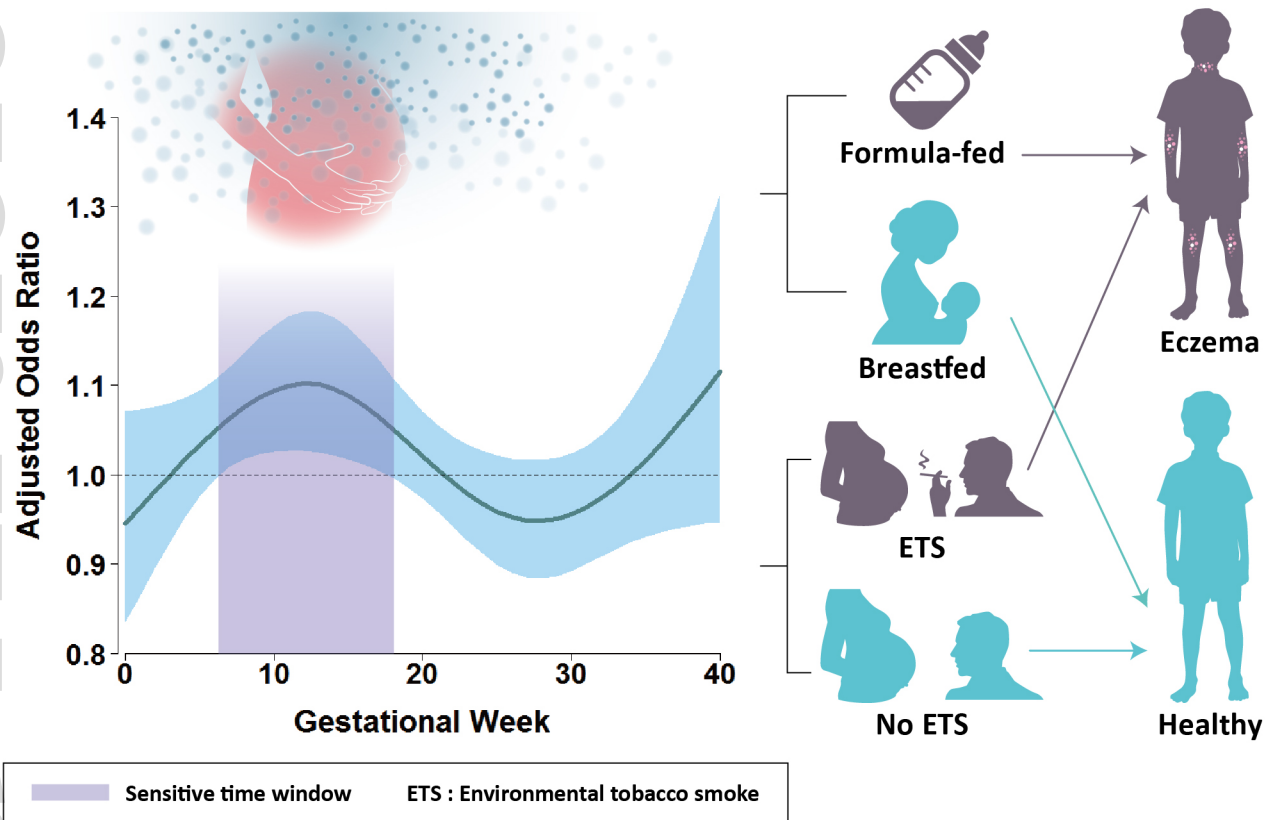
FIGURE LEGENDS

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/m³ 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.

Prenatal exposure to fine particulate matter and childhood eczema



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Supporting Information

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

DETAILED METHODS

Study Population

Study subjects were recruited from the Longitudinal Investigation of Global Health in Taiwanese Schoolchildren (LIGHTS) cohort, a prospective population-based cohort designed to longitudinally investigate the effects of prenatal and early-life exposures and genetic predisposition on childhood health outcomes, particularly allergic diseases. Among 7,053 children born between January 2010 and December 2011 at Chang Gung Memorial Hospital, a random sample of 2,500 children were invited for the 6-year follow-up visit and 1,513 children (60.5%) attended a follow-up visit between July 2016 and May 2018 at the mean age of 6.4 years; 987 children were lost to follow-up. There was no significant difference in baseline characteristics between 1,513 cohort participants and the original 7,053 subjects, indicating the sampling cohort was representative of the source population. Demographic, epidemiologic, and clinical data were collected using a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.¹ Data of anthropometric measurements, phenotyping examinations, physician interviews, and serum samples were collected under the agreement from parents/guardians of participating children. Maternal residential addresses during pregnancy were ascertained through electronic medical records (EMRs) and/or questionnaires. After excluding multiple births ($n = 162$), preterm births ($n = 343$), and missing information on exposure ($n = 8$) and outcome of interest ($n = 8$), 1,128 children were eligible for subsequent analyses. The flow diagram for subject recruitment is shown in **Figure S1**. The Institutional Review Board of Chang Gung Medical Foundation approved the study protocols (No. 2017015478B0). All parents/guardians of participating children provided written informed consents.

Exposure Assessment

Prenatal exposure to particulate matter with an aerodynamic diameter of $2.5\mu\text{m}$ or less ($\text{PM}_{2.5}$) was estimated based on data from 76 stationary automatic monitoring

stations operating by the Taiwan Air Quality Monitoring Network, Environmental Protection Administration (EPA) in Taiwan, between January 2009 and December 2011. We estimated daily data of prenatal exposure to PM_{2.5} levels using a recently developed hybrid kriging/land-use regression (LUR) model, ² which combined the strengths of kriging and LUR approaches and improved prediction performance for PM_{2.5} spatial-temporal variation, based on maternal residential addresses during pregnancy. We previously reported that the R² obtained from conventional LUR procedures was 0.66 and 0.70 for annual and monthly models, respectively, whereas the hybrid kriging/LUR model showed better explanatory power (R² of annual and monthly models: 0.85 and 0.88). ² ArcMap GIS (version 10.5) was used to construct the concentrations of air pollutants based on the developed hybrid kriging/LUR model. We calculated the prenatal weekly average PM_{2.5} concentrations based on the daily data of prenatal exposure to PM_{2.5} levels for each subject.

Outcome Definition

The primary outcome was development of eczema by 6 years of age. Current and past symptoms of eczema were assessed using a modified ISAAC questionnaire provided by parents/guardians of the study participants. ¹ An interview conducted by pediatricians was applied to all participants. Eczema was defined as having physician-diagnosed eczema and the presence of eczema in the last 12 months.

Covariates

Covariates included in subsequent analyses were listed as follows: child's age (years), gender (male or female), body mass index (BMI) (kg/m²), atopy (yes/ no), parental allergic disease (yes/ no), and birth season (spring, summer, autumn, or winter), ambient temperature [Temp] (°C), and relative humidity [RH] (%). Atopy was defined as a positive Phadiatop Infant test (≥ 0.35 PAU/L). ³ We have proposed a directed acyclic graph (DAG) to conceptualize the covariates included in the models (**Figure S5**).

We defined breastfeeding as having been exclusively breastfed during the first 3 months of life or longer. Exposure to prenatal environmental tobacco smoke (ETS) was assessed based on the questionnaire data collected by parental reports and EMRs.

Statistical Analysis

Descriptive statistics of children with and without eczema by age 6 years were reported either as mean and the corresponding standard deviation (SD); or as counts

and the corresponding percentages, respectively. Data of prenatal exposure to PM_{2.5} were treated as continuous data. We compared the difference of demographic/ clinical characteristics between subjects with or without eczema using Student's t-test for continuous variables and chi-square test for categorical variables, respectively.

To explore sensitive time-windows for the effects of prenatal exposure to PM_{2.5} on eczema in children, we applied a distributed lag non-linear model (DLNM) to examine the exposure-lag-response association between development of eczema and weekly average exposure to PM_{2.5} during gestation period,^{4,5} with adjustment of the above listed covariates. The DLNM was based on a cross-basis function simultaneously combining two dimensions: lag structure and the concentration-response relationship in the models. Specifically, we fitted the DLNM in a logistic setting:

$$\text{logit}(\pi | \mathbf{X}) = \beta_0 + s_1(\text{PM}_{2.5}, t) + s_2(\text{Temp}, t) + s_3(\text{RH}, t) + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_p X_p$$

where π was the probability of physician-diagnosed eczema given a set of covariate values ($\mathbf{X}$), and $X_1, X_2, \dots, X_p$ were the potential confounders, including child's age, gender, BMI, atopy, parental eczema, and birth season. Levels of PM_{2.5}, Temp, as well as RH were estimated on the basis of gestational week (t), and were modeled in cross-basis functions in terms of concentration-response relationship and lag effect. For the cross-basis function of PM_{2.5} exposure, Temp, and RH in this study, we set the lag scale from gestation weeks 1 to 40. If a child was born between 37 and 40 gestational weeks, PM_{2.5} exposure was set to 0 $\mu\text{g}/\text{m}^3$ from birth to 40 gestational weeks.⁶ We applied a natural spline with degree of freedom (DF) of 4 to model the potential non-linear relationship with children eczema risk, and a DF of 4 was assigned for lag time effect (0 to 40 week). To examine the modifying effect of various characteristics, we carried out subgroup analyses, stratified by breast feeding, and exposure to ETS during gestation, respectively, with and without adjustment of the above covariates.

We applied the Akaike information criterion to select the degree of freedom for the concentration-response relationship and lag effect of PM_{2.5}.⁷² A natural spline with 4 degree of freedom (df) was utilized to model the lag effect of PM_{2.5} as well as concentration-response relationship for PM_{2.5}-eczema, with a centering value set at

12 $\mu\text{g}/\text{m}^3$ based on the U.S. annual mean standard. In order to minimize the confounding due to weekly Temp and RH, we applied natural splines with 3 df for concentration-response relationship and lag-effect for both environmental factors. Estimations were robust and did not change substantially with different df of spline (df of 2 to 6) (data not shown).

Statistical significance was declared using a *P*-value less than 0.05 or 95% confidence intervals (CIs) not covering the null values. Data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R software, version 3.6.0.

DISCUSSION

Underlying Mechanisms

The underlying mechanisms of fine particulate matter affecting the development of childhood eczema have remained unclear, but some known biological mechanisms may be explained in part the observed associations. First, the fine particulate matter, $\text{PM}_{2.5}$, is a mixture of soot particles (e.g., black carbon and polycyclic aromatic hydrocarbons (PAHs)), vehicular exhaust (e.g., organic compounds, sulfates and metals) and wood smoke.^{8,9} Previous studies have demonstrated that transplacental exposure to PAHs can produce cytotoxic reactive oxygen species (ROS), which induce inflammatory and oxidative stress responses and subsequently increase the development of inflammatory skin diseases.^{10,11} Second, it is known that PAHs are ligands of the aryl hydrocarbon receptor (AhR), a transcription factor related to cytokines. It is likely that the fine particulate matter impairs function of skin barrier via activation of AhR expression upon binding to PAHs and enhancement of pro-inflammatory cytokines (e.g., interleukin 1 α , interleukin 6 and tumor necrosis factor- α etc.).¹²⁻¹⁴ Third, in addition to inducing pro-inflammatory cytokines, AhR activation induces dysregulated expression of filaggrin, an important epidermal barrier protein. Studies have shown that dysregulation of filaggrin may lead to occurrence of atopic eczema.¹⁵⁻¹⁷

Strengths and Limitations

This study has several strengths. First, we utilized the DLNM, a state-of-art methodology with better validity and robustness, to explore the critical $\text{PM}_{2.5}$ exposure window on the risk of developing eczema. Second, we applied a recently developed hybrid kriging/LUR model which combined the strengths of kriging and LUR and improved prediction performance for $\text{PM}_{2.5}$ spatial-temporal variation. Third, the EPA

in Taiwan provides comprehensive and continuous monitoring data of air pollutants across the country. Given that the concentrations of air pollutants change over time, average concentrations based on continuous monitoring provide a reliable estimation of individual exposure. However, some limitations of this study deserve mention. First, the diagnosis of eczema was based on parent-reported questionnaire which may underestimate the prevalence of eczema in children. Second, 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. Third, there remains a concern about the generalizability of our results to other populations. Further investigation will be needed to confirm the findings observed in this study.

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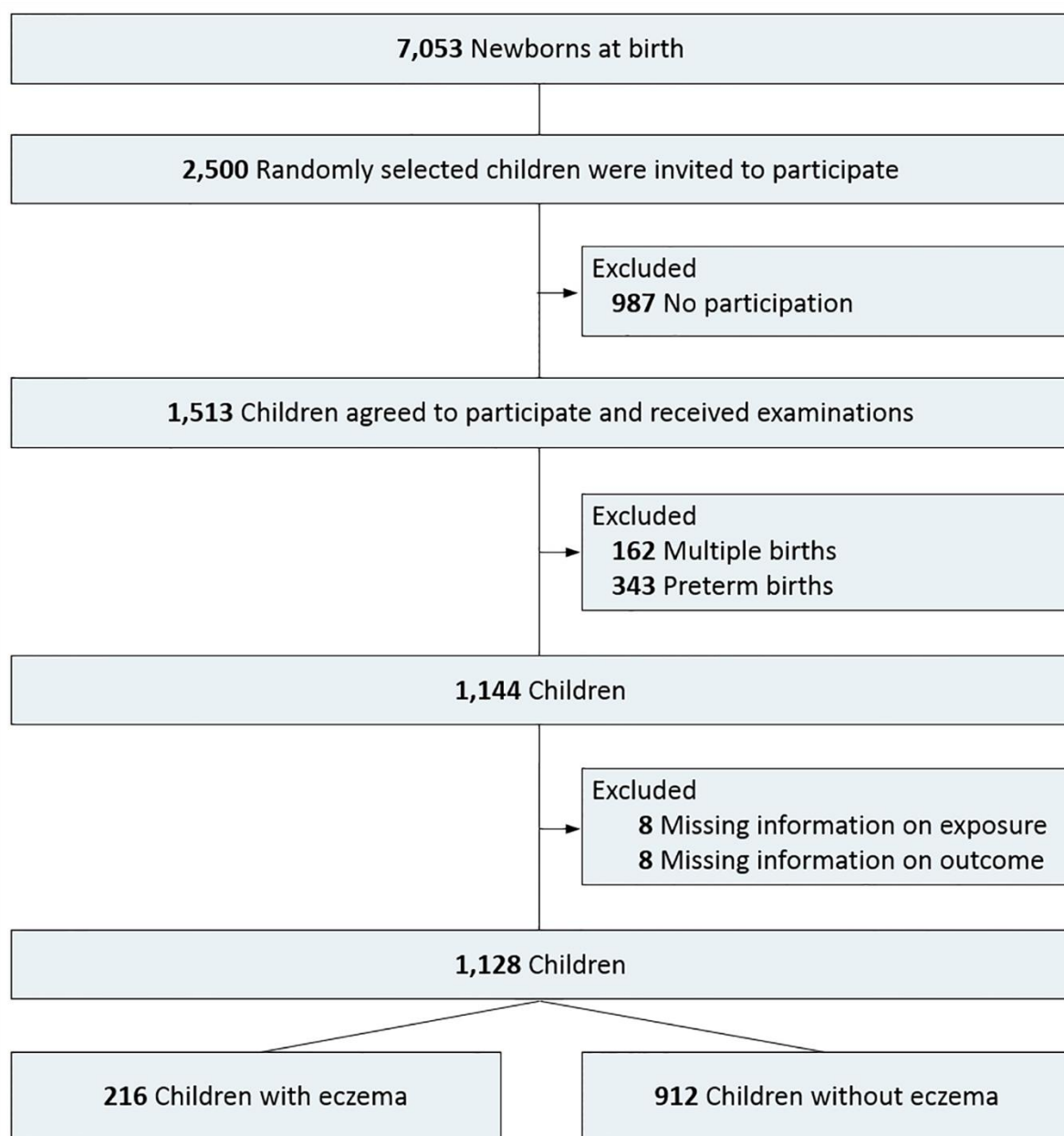
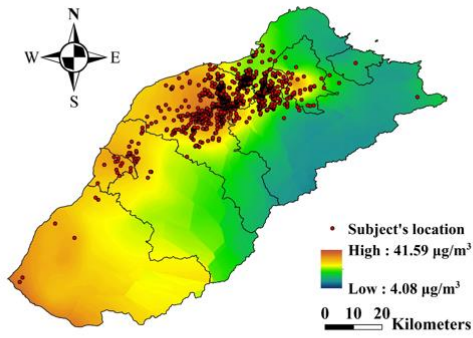
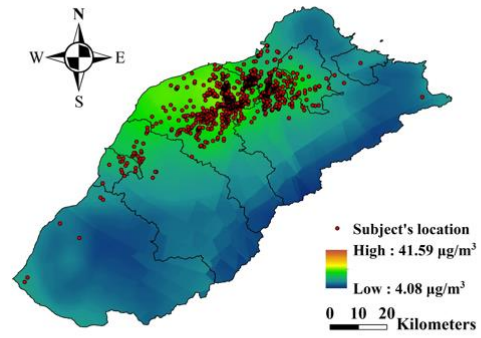


Figure S1. Flow diagram of subject recruitment process.

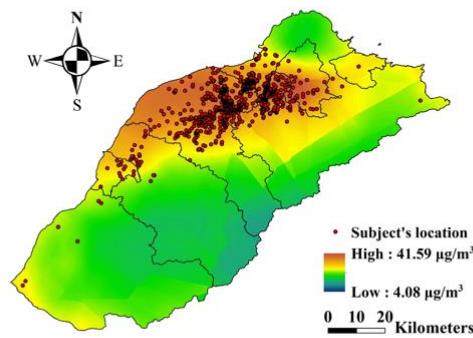
A Spring



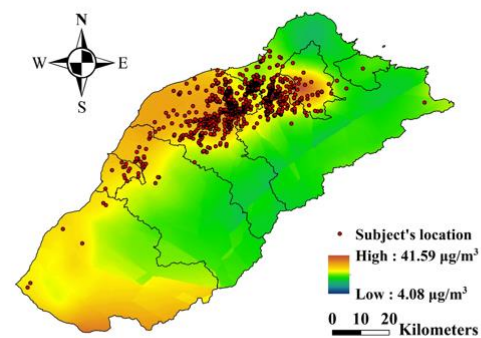
B Summer



C Fall



D Winter



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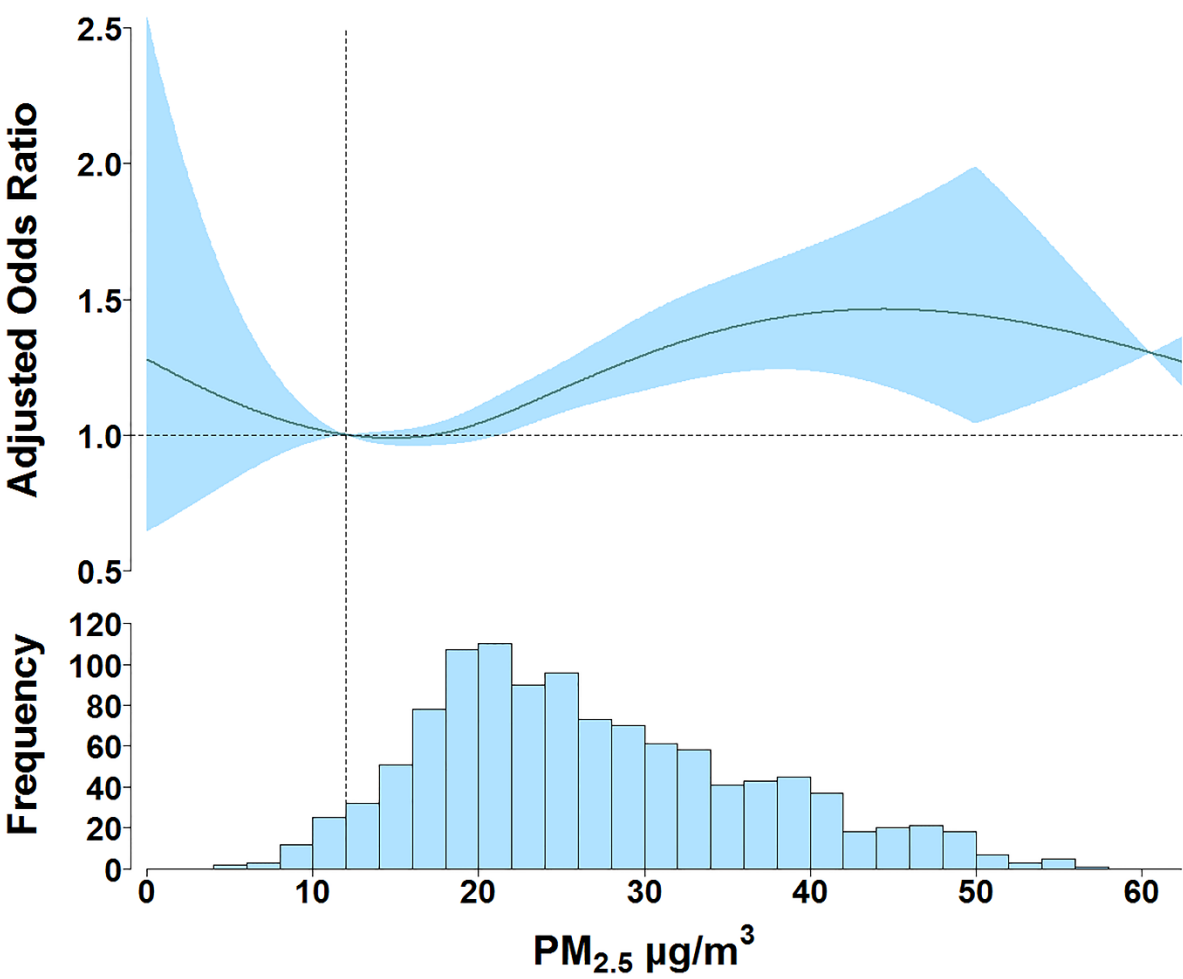
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Figure S2. Seasonal averaged PM_{2.5} concentration gradient surface maps in 2009 estimated by the hybrid Kriging/land-use regression model: (A) spring, (B) summer, (C) fall, and (D) winter.

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198

199 **Figure S3.** Exposure-response relationship between PM_{2.5} exposure at gestational
200 week 13 and development of childhood eczema. Note: The *dashed line* is the reference
201 value at 12 µg/m³ (U.S. annual mean standard). The model was adjusted for child's age, gender, body
202 mass index, atopy, parental allergic disease, birth season, ambient temperature, and relative humidity.
203 The *solid line* indicates the estimated odds ratio and the *shading area* represents the 95% confidence
204 interval. Abbreviation: **PM_{2.5}**: particulate matter with an aerodynamic diameter of 2.5 µm or less.

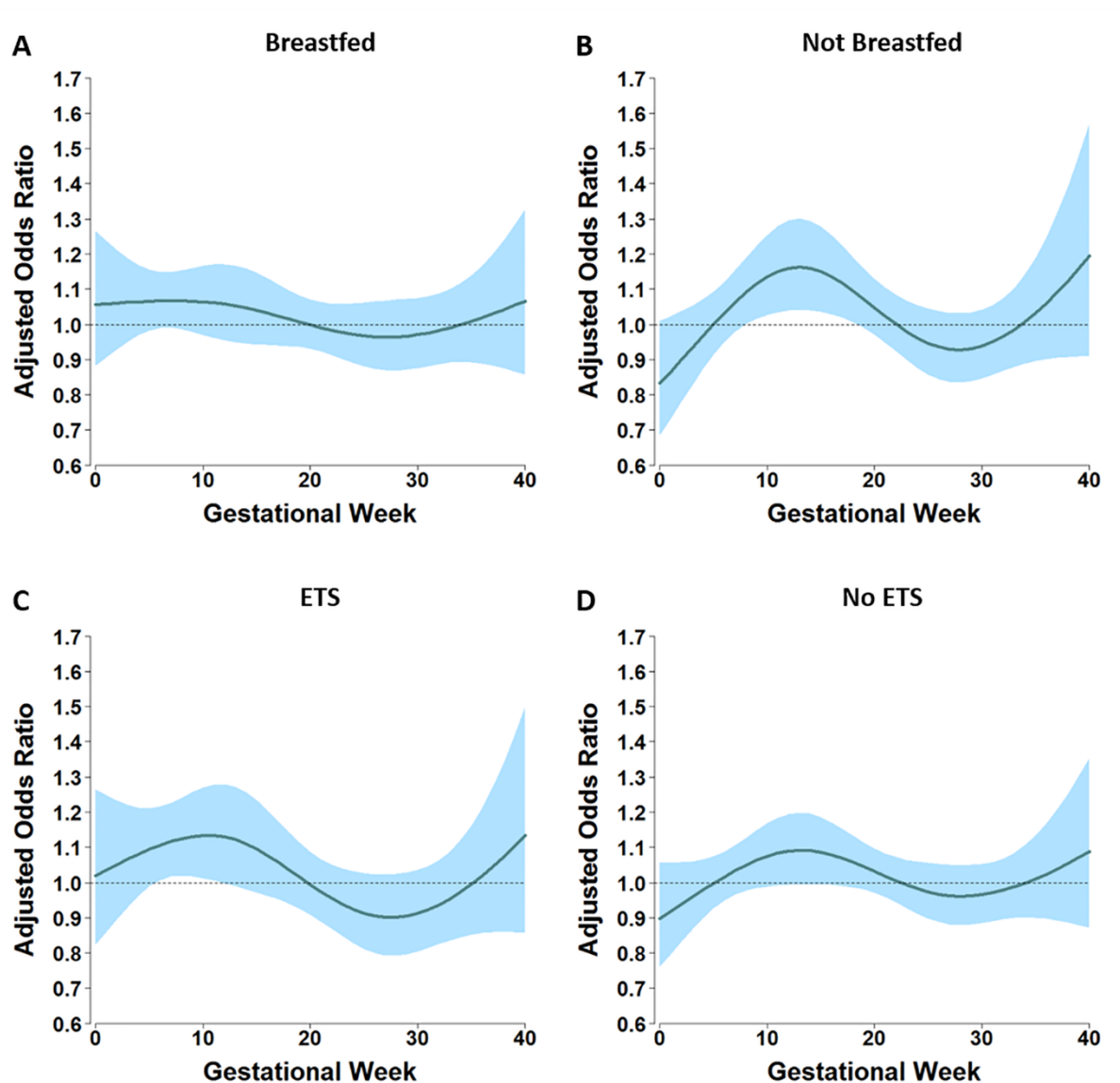


Figure S4. Associations between exposure to $\text{PM}_{2.5}$ (per $10 \mu\text{g}/\text{m}^3$ increment) during gestation and the development of childhood eczema, stratified by breastfeeding (**A**, **B**) or exposure to prenatal ETS (**C**, **D**). Note: The DLNM model was adjusted for child's age, gender, body mass index, atopy, parental allergic disease, birth season, ambient temperature, and relative humidity. The y-axis shows the odds ratio of eczema in relation to a $10 \mu\text{g}/\text{m}^3$ increase in prenatal $\text{PM}_{2.5}$ 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 adjusted odds ratio does not include 1.0. Abbreviation: **PM_{2.5}**: particulate matter with an aerodynamic diameter of $2.5 \mu\text{m}$ or less; **ETS**: environmental tobacco smoke; **DLNM**: distributed lag nonlinear model.

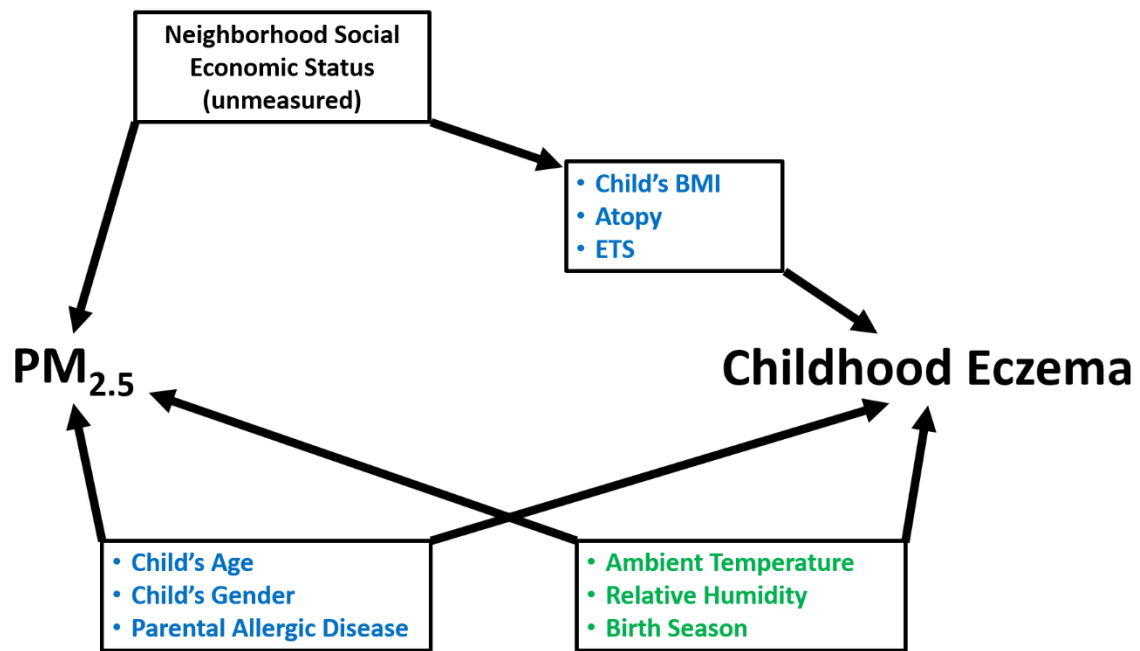


Figure S5. The directed acyclic graph (DAG) for conceptualized relation among variables included in the models. Abbreviation: **BMI**: body mass index; **ETS**: environmental tobacco smoke.