CONFLICT OF INTEREST

GdA reports advisory board and/or speaker fees from Astrazeneca, Chiesi, GSK, Napp, Boehringer Ingelheim and Teva. JK reports travel support from Teva. CR reports advisory board and/or speaker fees Astrazeneca, Chiesi, Napp, Novartis and Teva. AMN reports advisory board and/or speaker fees from Astrazeneca. DJJ reports advisory board and/or speaker fees from Astrazeneca, Chiesi, GSK, Napp, Novartis and Teva. BDK reports advisory board and/or speaker fees from Astrazeneca, Chiesi, GSK, Napp, and Novartis. No COIs are reported by the remaining authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Association of prenatal exposure to fine particulate matter pollution with childhood eczema

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 μm or less (PM_{10}), but not particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$), and yielded inconsistent results. Sensitive

Tsung-Chieh Yao and Hui-Ju Tsai contributed equally to supervision of this work.

TABLE 1 Characteristics of study children (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)	<0.001
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

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

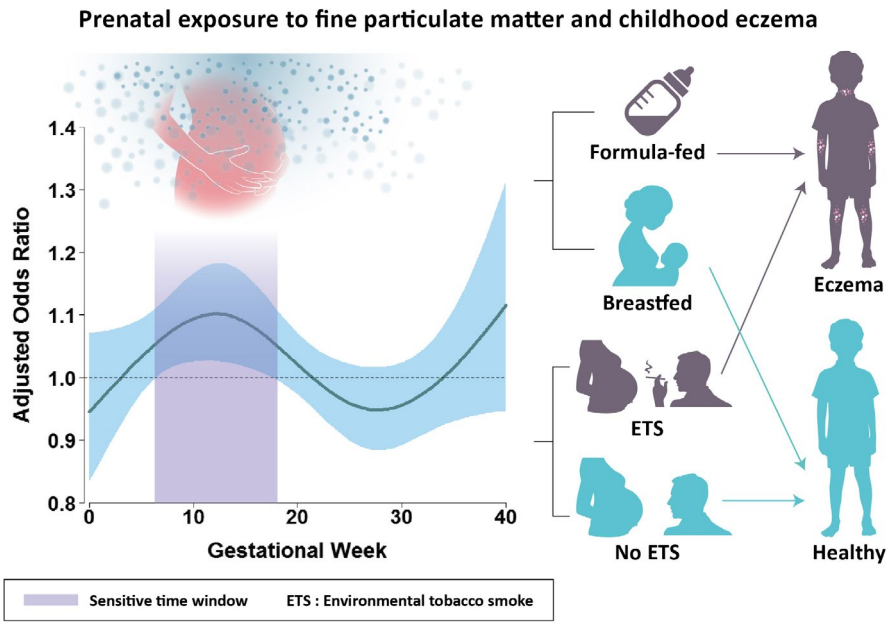

FIGURE 1 Increased exposure to $PM_{2.5}$ during gestational weeks 7 to 17 was significantly associated with an increased risk of childhood eczema and this risk was largely confined to children who were not breastfed or exposed to prenatal environmental tobacco smoke. A distributed lag nonlinear model 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. $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less

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 kriging/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. Age at onset of eczema was distributed 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 $\mu g/m^3$; 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 $\mu g/m^3$ (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 $\mu g/m^3$ to the development of childhood eczema. 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 $\mu g/m^3$.[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 the development of infantile eczema was reported in a previous birth cohort.[3]

This study primarily focuses on investigating the influence of prenatal $PM_{2.5}$ exposure on risk of childhood eczema. Further investigation will be needed to uncover sensitive windows of $PM_{2.5}$

exposure during the postnatal period. 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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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Direct activation of the aryl hydrocarbon receptor by dog allergen participates in airway neutrophilic inflammation

To the Editor,

Asthma is a chronic disorder, characterized by airway hyperresponsiveness (AHR), variable bronchial remodelling and an inflammatory process leading to fluctuating recruitment of eosinophils and neutrophils. Among asthma patients, up to 10% exhibit severe asthma and display type 2 (T2)–low and type 2 (T2)–high phenotypes. Besides T2 cytokines, Th17-type cytokines are also a driver of severe asthma pathophysiology, through induction of airway neutrophil infiltration, AHR, bronchial remodelling and corticosteroid resistance. One determinant of Th17-type cytokine production is the transcription factor aryl hydrocarbon receptor (Ahr). This receptor is activated by small molecules provided by the diet, microorganisms, metabolism and pollutants. In T cells, Ahr controls IL-17 and IL-22 transcription, but can also induce CD4 T cells with a regulatory phenotype. Depending on the Ahr ligand used, opposite results have been published in allergic airway inflammation (AAI) reporting anti- and pro-inflammatory effects.[1] The aim of this study was to develop a model of neutrophilic AAI exhibiting Th17-type features to evaluate the effect of Ahr blockade.

A mouse model of dog allergen–induced AAI was developed (Figure S1A), an allergen associated with more severe asthma in humans.[2] Dog allergen–challenged mice exhibited all the cardinal features of AAI, including increases in broncho alveolar lavage (BAL) total cell numbers, in relation to a high number of neutrophils and to a lesser extent with eosinophil and lymphocyte elevations (Figure 1A and Figure S1B), raised total and dog allergen–specific serum IgE (Figure 1B), and elevated AHR (Figure 1C). The cytokine profile of lung extracts showed that although BAL eosinophil counts were low in this model, Th2-type cytokines and chemokines *IL-4*, *IL-13*, IL-33 and CCL17 were upregulated in the lungs of dog allergen–challenged mice, as were IL-17, IL-22 and neutrophil attracting CXCL1 and CXCL2, but not IFN-γ (Figure 1D and Figure S1C). Cells known to produce IL-17 and IL-22 were analysed by flow cytometry (Figure S2). In dog allergen–stimulated groups, $CD4^+$ T cells, γδT cells and lymphoid tissue inducer cells (LTi), a subset of ILC3, appeared to be the major cell subsets expressing both IL-17 and IL-22 (Figure 1E). Other analysed cells did not significantly contribute to this cytokine production after allergen challenge (Figure S1D). These data are in agreement with other studies in lung infection models.[3] These pro-Th17 effects may relate to dog allergen composition, which includes lipocalin Can f 1, able to bind the mannose and DC-SIGN receptors that promote Th17 responses to fungal infections. Histological analysis of lung sections from dog allergen–challenged mice compared with PBS-challenged mice showed an increase in haematoxylin and eosin–stained cell infiltrates, in periodic acid-Schiff–stained mucus and in peri-bronchial collagen depots as assessed by Masson's trichrome staining, Picrosirius red staining and two-photon microscopy, as well as thicker bronchial smooth muscle cell (SMC) layer assessed by anti–α-smooth muscle actin (α-SMA) staining, and the presence of ectopic follicles resembling inducible bronchus–associated lymphoid tissue (iBALT) (Figure 1F and Figure S1E). iBALTs are tertiary lymphoid organs composed of B and T cells, and germinal centres with follicular dendritic cells (FDC). $CD21^+$FDC, $B220^+$B cells and $CD3^+$T cells were assessed by immunohistochemistry and found in the peri-bronchial ectopic follicles (Figure 1G). Total IgA and dog allergen–specific IgG1 were strongly increased in BAL from the dog allergen–challenged but not from the control group (Figure 1G). Although the presence of BALT has been observed in