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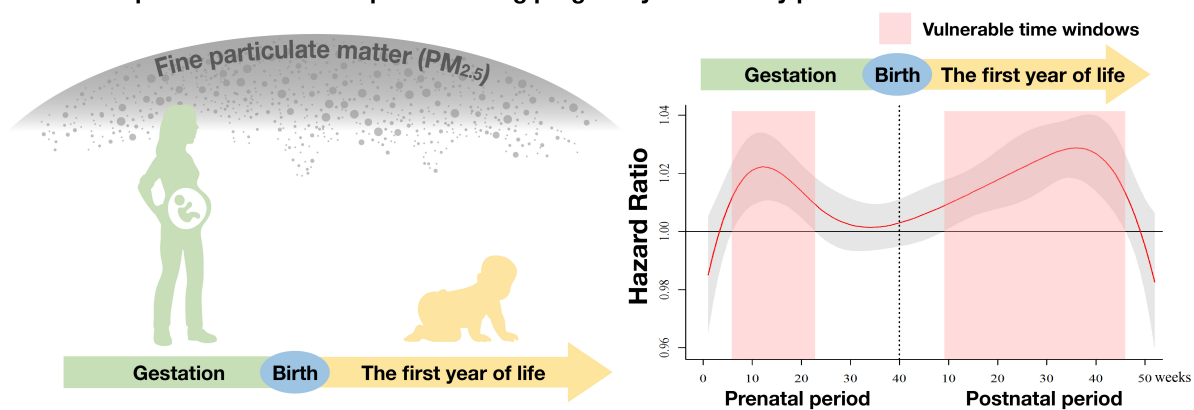
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**Fine particulate matter exposure during pregnancy and infancy
periods and incident asthma**

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competing interests.

25 Abstract

26 Background

27 Lung development is a multi-stage process from conception to postnatal period, the
28 disruption of by which air pollutants may trigger later respiratory morbidity.

29 Objective

30 To evaluate the effects of weekly average fine particulate matters (PM_{2.5}) exposure
31 during pregnancy and infancy periods on asthma, and identify vulnerable times to
32 help elucidate the possible mechanisms of the effects of PM_{2.5} on asthma.

33 Methods

34 A birth cohort study including 184,604 children born during 2004-2011 in Taichung
35 city was retrieved from the Taiwan Maternal and Child Health Database and followed
36 until 2014. A daily satellite-based hybrid model was applied to estimate PM_{2.5}
37 exposure for each subject. A Cox proportional hazard model combined with a
38 distributed lag non-linear model was used to evaluate the associations of asthma with
39 PM_{2.5} exposure during pregnancy and infancy periods.

40 Results

41 The birth cohort contained 34,336 asthma cases and the mean age of children
42 diagnosed with asthma was 3.39±1.78 years. Increased exposure to PM_{2.5} during
43 gestational weeks 6–22 and 9–46 weeks after birth were significantly associated with
44 an increased incidence of asthma. Exposure-response relationship indicated hazard
45 ratio (HR) of asthma increased steeply at PM_{2.5} exposure above 93 µg/m³ during
46 pregnancy. Additionally, the HRs remained significant with postnatal exposure to
47 PM_{2.5} between 26–72 µg/m³ (range 1.01–1.07), followed by a sharp increase in the
48 HR at PM_{2.5} exposure above 73 µg/m³.

49 Conclusion

50 Both prenatal and postnatal exposures to $PM_{2.5}$ were associated with the later
51 development of asthma. The vulnerable time windows may be within early- and
52 mid-gestation and the infancy periods.

53

54 **Key message:**

55 ▪ Prenatal and postnatal exposures to PM_{2.5} are associated with the later development
56 of asthma.

57 ▪ Increased exposure to PM_{2.5} during gestational weeks 6–22 and weeks 9–46 after
58 birth were significantly associated with increased incident asthma.

59 ▪ Hazard ratio of asthma increased steeply at PM_{2.5} exposure above 93 µg/m³ during
60 pregnancy. Additionally, the hazard ratios remained significant with postnatal
61 exposure to PM_{2.5} between 26–72 µg/m³ (range 1.01–1.07), followed by a sharp
62 increase in the hazard ratio at PM_{2.5} exposure above 73 µg/m³.

63 **Capsule summary:** Both prenatal and postnatal exposures to PM_{2.5} were associated
64 with the later development of asthma. The vulnerable time windows might be within
65 early- and mid-gestation and the first year after birth.

66 **Key words:** Asthma, air pollution, birth cohort, PM_{2.5}, prenatal, postnatal, vulnerable
67 time windows

68 **Abbreviations used**

69 AIC: Akaike Information criterion

70 AOD: Aerosol optical depth

71 CI: Confidence interval

72 Cox PH model: Cox proportional hazard model

73 DLNM: Distributed lag non-linear model

74 HR: Hazard ratio

75 ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical
76 Modification

77 IR: Incidence rate

78 IgE: Immunoglobulin E

79 NHIRD: National Health Insurance Research Database

- 80 NO₂: Nitrogen dioxide
- 81 NRD: National Registration of Death
- 82 OR: Odds ratio
- 83 PM: Particulate matter
- 84 PM_{2.5}: Particulate matter with an aerodynamic diameter less than 2.5 µm
- 85 PM₁₀: Particulate matter with an aerodynamic diameter less than 10 µm
- 86 SES: Socio-economic status
- 87 TMCHD: Taiwan Maternal and Child Health Database
- 88 TBR: Taiwan Birth Registry

89 Introduction

90 Asthma is a common, early-life onset chronic respiratory disorder that is
91 characterized by recurrent air obstruction and bronchial hyperresponsiveness.¹ More
92 than 300 million people are affected by asthma and its prevalence has increased in
93 recent decades.² An interaction between genetic and environmental factors may
94 contribute to asthma. As the genetic factors are unlikely to have changed over the last
95 few decades, the increasing prevalence of asthma is more likely due to environmental
96 factors. Since asthma is not curable following its onset, it is necessary to develop
97 asthma prevention strategies by identifying possible modifiable factors and the most
98 vulnerable time windows for asthma.

99 Increasing evidence has indicated that particulate matter (PM) and its components
100 may increase the risk of asthma and trigger acute exacerbation. Particulate matter can
101 induce free radical reactions, which may increase oxidative stress in the lungs.³
102 Oxidative damage in the airway can result in inflammation and remodeling and
103 contribute to clinical asthma.⁴ The development of the lungs is a continuous and
104 multi-stage process lasting from conception to adolescent and/or early adulthood.^{5,6}
105 The adult number of alveoli is reached at 2–3 years.⁷ Interference with any of the
106 developing stages of the lungs by environmental pollutants can lead to altered lung
107 function and an increased risk of disease later.⁵ While the lung growth from
108 conception to adolescent and/or early adulthood, the prior studies have suggested that
109 the prenatal and early postnatal periods may be particular vulnerable time windows.
110 In animal studies, the offspring of pregnant mice exposed to PM had increased serum
111 immunoglobulin E (IgE) level, pulmonary and systemic Th2 and Th17 cytokine levels,
112 and increased airway hyperresponsiveness and airway inflammation.^{8,9} An animal
113 study conducted in São Paulo, Brazil demonstrated that mice exposed to ambient
114 urban PM during both the prenatal and postnatal periods had altered lung structure

and function.¹⁰ In that study, mice exposed to PM only prenatally or postnatally did not show significant differences in structure and function compared to those in non-exposed mice.¹⁰ These results indicated that both prenatal and postnatal exposure to PM have adverse effects on respiratory health, resulting in the development of asthma.

Epidemiological studies have reported the association between postnatal exposure to air pollution and asthma^{11–13}, with the early postnatal period before 2–3 years of life a critical period for the development of asthma.^{14,15} However, only a few epidemiological studies have investigated the potential associations of prenatal exposure to PM with the later development of childhood asthma.^{16–18} These epidemiological studies have generally used average PM concentrations during the entire pregnancy or within the three trimesters as exposure matrices. It is difficult to apply the results of these kinds of studies to elucidate the plausible mechanism for PM exposure corresponding to specific stages of lung development on the later appearance of asthma owing to their lack of temporal resolution. A recent epidemiological study conducted in Boston area, a region with low pollution with a median PM with an aerodynamic diameter less than 2.5 μm ($\text{PM}_{2.5}$) concentration of 11.2 $\mu\text{g}/\text{m}^3$, of 736 full-term children provided hints to explore the possible vulnerable time windows when the fetus is susceptible to $\text{PM}_{2.5}$ based an advanced and data-driven statistical approach.¹⁹ The authors reported that prenatal exposure to $\text{PM}_{2.5}$ during gestational weeks 16–25 weeks was significantly associated with the development of asthma at 6 years of age.¹⁹ However, their study population mainly consisted of Hispanic and African Americans in the Boston area, which may not be generalizable to other populations.¹⁹ It remains unclear whether the vulnerable time window during pregnancy exists in other populations in areas with higher pollution, such as southeast Asia.

The effects of prenatal and postnatal exposures to PM_{2.5} on asthma onset have rarely been examined simultaneously. We aimed to use a large population-based birth cohort including more than 180,000 children and to apply a highly temporal resolution satellite-based hybrid model to evaluate the effects of weekly average exposure to PM_{2.5} during the prenatal and the infancy periods on asthma in a highly polluted metropolitan area with average PM_{2.5} concentrations three times the World Health Organization (WHO) air quality standard and to identify the vulnerable time windows for the development of asthma.

Methods

Study area

Taichung city is the second largest metropolitan area with approximately 2.78 million residents in a total area of 2,214 km², which is located in central-western Taiwan. There are currently 29 districts within the city. The major stationary emission sources situated in the Taichung city includes the largest coal-fired power plant in the world, a main steel plant, several industrial and science parks, and incinerators (Fig 1). As shown in Fig 1, Taichung city also has a crowded road network.

Data sources

This study was sourced from a population-based and nationwide birth cohort, the Taiwan Maternal and Child Health Database (TMCHD),²⁰ which is managed and organized by Health and Welfare Data Science Center of the Ministry of Health and Welfare. The TMCHD during 2004-2011 contained nationwide databases that could be interlinked using encrypted personal identification numbers, including the Taiwan Birth Registry (TBR) from 2004-2011, the National Registration of Death (NRD) from 2004-2014, and the National Health Insurance Research Database (NHIRD) for

outpatient visit and for inpatient visit from 2003-2014.²⁰ In Taiwan, all live births and death must be registered in the TBR within 15 days. The NHIRD covered 99.9% of the entire population in Taiwan. By interlinking with these databases, the TMCHD provides detailed information on newborn (e.g., sex, birth date, birth weight, gestational age, location of birth, single or multiple births, birth order, and Apgar score), mother (e.g., pregnancy complications, maternal age at delivery, and residential address of pregnant woman), and history of medical visits for children and their mothers (e.g., outpatient visits, hospital admissions, prescriptions and diagnosis of disease based on the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]).

This study was approved by the institutional review board of China Medical University Hospital (CMUH104-REC3-003(CR-3)) and complied with the principles outlined in the Declaration of Helsinki.

Study population

The TMCHD comprises 191,330 children born in Taichung city between January 1, 2004, and December 31, 2011, and followed-up from conception to December 31, 2014. Children were excluded from the subsequent analyses if they met the following criteria: were multiple births ($n = 5,852$), were stillbirth ($n = 7$), or who had birth defects ($n = 867$). After excluding children meeting the above criteria, the birth cohort contained 184,604 children. Children lost to follow-up was defined as those children who were withdrawn from insurance or who died during the follow-up period. The response rate of this birth cohort was 99.67% (599 children lost to follow up).

Outcome of interest

Asthma diagnoses were obtained by linking to the NHIRD. We identified

children who received at least two consistent asthma diagnosis codes (ICD-9-CM: 493) assigned by physicians between birth and December 31, 2014, in both outpatient and inpatient visit claims in the NHIRD. Incident asthma was defined as a child who received the first diagnosis of asthma (outpatient visit or inpatient visit). The diagnosis criteria for asthma please refer to the Supplementary Appendix. The asthma diagnoses from the NHIRD were confirmed in an independent study (92.0% sensitivity).²¹

Exposure assessments

A 10-km spatial resolution hybrid model that incorporated satellite-based aerosol optical depth (AOD), meteorological variables, and land-use variables was applied to estimate the ground-level PM_{2.5} concentrations in Taiwan. We previously reported the 10-km resolution hybrid model to be a reliable and validated method for estimating ground-level PM_{2.5} concentrations in Taiwan.²² We further adapted this hybrid model for environmental epidemiology. The details of the 10-km hybrid model are described in the Supplementary Appendix. The PM_{2.5} estimates were higher in the southwestern Taichung city near coastal areas (Fig 1).

We assigned daily PM_{2.5} estimates derived from the hybrid model to children according to their maternal residential address (by post-code level) and calculated the weekly average PM_{2.5} based on the daily average for each child.

Covariates

The covariates in this study include sex of children (male or female), birth weight (>2,500 or ≤2,500 g), socio-economic status (SES) derived from the insurance amount (stratified into quartiles: ≤25th percentile, 25th–50th, 50th–75th, and >75th percentile), maternal age (>30 years or ≤30 years), maternal atopy (defined as the mother having

received any diagnosis codes for asthma, allergic rhinitis, or atopic dermatitis), maternal anemia, maternal heart diseases, maternal lung diseases, mother with gestational diabetes mellitus, maternal chronic hypertension, mother with gestational hypertension, mother with preeclampsia, maternal kidney diseases, and maternal smoking status during pregnancy (yes or no).

Statistical analyses

We first utilized two separate Cox proportional hazard (PH) models to assess the associations of $PM_{2.5}$ exposure during the entire pregnancy as well as during the first year after birth with the later development of asthma. The survey time was measured from conception until the end of the study period for each child. A child was censored if they did not develop asthma until the end of the study period or was lost to follow-up. The averaged $PM_{2.5}$ concentrations during the entire pregnancy period and the first year after birth were calculated for each child and separately entered as a linear continuous variable into models for exactly how the data correction worked. In order to accommodate the non-proportional hazard of $PM_{2.5}$, we performed time transform function (*tt* function) of *coxph* (R package *survival*) to construct time-dependent covariates of $PM_{2.5}$ in the models.²³ The directed acyclic graphs (DAGs) were then used to identify confounders in the Cox PH model, we also selected confounders according to prior literature (for the detail of selection criteria for confounders, see Supplementary Appendix). Our Cox PH models were adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases. Additionally, we introduced an interaction term between the average $PM_{2.5}$ and sex into the Cox PH models for the pregnancy period and for the first year after birth, respectively, to identify any interaction between $PM_{2.5}$ and sex. In addition to separate Cox PH models, we used a mutually adjusted model to consider the correlation

between PM_{2.5} exposure during pregnancy and the first year after birth ($r = 0.52$).

Lastly, we repeated analyses with adjusting for birthweight and maternal smoking status during pregnancy as sensitivity analyses. The results are reported as hazard ratio (HR) with 95% confidence interval (CI).

To explore the vulnerable time windows, we further used a distributed lag non-linear model (DLNM) to evaluate the associations of asthma with weekly average exposure to PM_{2.5} from conception to one year after birth.²⁴ The DLNM was defined by a cross-basis function that simultaneously incorporated two dimensions, lag effect (time structure) and the exposure-response relationship. Equation of the DLNM (equation [1]) is shown below:

$$h(t, \mathbf{X}) = \alpha h_0(t) \exp[\beta_1 SES + \beta_2 M_{Age} + \beta_3 M_{Atopy} + \beta_4 M_{anemia} + \beta_5 M_{kidney\ diseases} + \delta_1 s(PM_{2.5}, t)] \dots \dots \dots [1]$$

$$\mathbf{X} = \begin{pmatrix} SES, M_{Age}, M_{Atopy}, \\ , M_{anemia}, M_{kidney\ diseases}, \\ s(PM_{2.5}, t) \end{pmatrix}$$

where $h(t, \mathbf{X})$ is the hazard function for each child with a given specification of a set of explanatory variables; $h_0(t)$ is a baseline hazard function multiplied by an exponential function, $\mathbf{X}$ is the collection of explanatory variables which contains SES, maternal age, maternal anemia, maternal atopy, and maternal kidney diseases, and $s(PM_{2.5}, t)$ is a cross-basis function to model the exposure-response relationship and lag effect for exposure to PM_{2.5} from conception until one year after birth. For the cross-basis function of PM_{2.5} exposure in this study, we set the lag scale from weeks 1–92, including 40 gestational weeks and 52 weeks after birth. If a child was born prior to 40 gestational weeks, the PM_{2.5} exposure was set to 0 µg/m³ from birth to 40 gestational weeks.²⁵ For instance, for a child born at 36 gestational weeks, we set the PM_{2.5} exposure to 0 µg/m³ for gestational weeks 37–40. α represented a

random-effect term for sex as a Gaussian distribution included in the model. The type of spline and degree of freedom for the exposure-response relationship and lag effect are selected based on the Akaike information criterion (AIC).²⁶ According to the minimum AIC, the exposure-response relationship was modeled using a b-spline with seven degrees of freedom, setting equally-spaced knots without intercept and with a centering value set at $25 \mu\text{g}/\text{m}^3$ based on the WHO 24-hr mean standard. Additionally, the lag effect was modeled using b-spline with seven degrees of freedom with equally-spaced knots with intercept. All statistical analyses were performed using R version 3.4.3 (*dlm* and *survival* packages).

Results

Within the birth cohort in Taichung city, there were 34,336 total asthma cases among 184,604 children (18.60%). The mean age at the end of follow-up was 6.35 ± 2.65 years for the total children in the birth cohort. For children with asthma, the mean age at the date of first asthma diagnosis was 3.39 ± 1.78 years (Table 1). Asthma cases tend to be male; with birth weights less than 2500 g; with a higher SES, and born to mothers with maternal atopy, younger age, with preeclampsia, without gestational diabetes, and with kidney diseases (Table 1).

The overall mean $\text{PM}_{2.5}$ concentrations during pregnancy and the first year after birth in the birth cohort were $36.2 \pm 3.5 \mu\text{g}/\text{m}^3$ (range $13.0\text{--}47.8 \mu\text{g}/\text{m}^3$) and $35.6 \pm 3.5 \mu\text{g}/\text{m}^3$ (range $12.2\text{--}45.6 \mu\text{g}/\text{m}^3$).

In the separate models, the results showed that a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during pregnancy and the first year after birth were positively associated with incident asthma (adjusted HR = 1.26, 95% CI: 1.17–1.35 and adjusted HR=1.61, 95% CI: 1.48–1.76, respectively). In the mutually-adjusted model, the association between a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during pregnancy and asthma was attenuated, but still

positive (adjusted HR = 1.04, 95% CI: 0.95–1.14). The association between a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during the first year after birth and asthma remained significant (adjusted HR = 1.55, 95% CI: 1.40–1.72). In the sensitivity analyses, we obtained similar results after adjusting for birth weight and maternal smoking status during pregnancy (Table E1).

The associations between exposure to $\text{PM}_{2.5}$ from conception to one year after birth and asthma using DLNM are presented in Fig 2. With exposure to $\text{PM}_{2.5}$ during pregnancy, we observed a significant association of asthma with a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during gestational weeks 6–22, with the highest association at gestational week 12 (Fig 2). In gestational week 12, the exposure-response relationship showed that the HR of asthma increased dramatically for $\text{PM}_{2.5}$ exposure above 93 $\mu\text{g}/\text{m}^3$ (Fig 3). Additionally, in the postnatal periods, significant associations between a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure during the first year after birth and asthma were observed for weeks 9–46 after birth, with the highest association at 36 weeks after birth (Fig 2). At 36 weeks after birth, the exposure-response relationship indicated that the HR of asthma initially remained significant at $\text{PM}_{2.5}$ exposure between 26–72 $\mu\text{g}/\text{m}^3$ (range 1.01–1.07), but increase of $\text{PM}_{2.5}$ exposure had little effect up to approximately 72 $\mu\text{g}/\text{m}^3$, followed by a sharp increase in the HR at $\text{PM}_{2.5}$ exposure above 73 $\mu\text{g}/\text{m}^3$ (Fig 3).

We did not find a statistically significant interaction between sex and $\text{PM}_{2.5}$ for the pregnancy period (p -value = 0.44 for prenatal $\text{PM}_{2.5} \times \text{sex}$). In contrast, we observed a significant interaction between sex and $\text{PM}_{2.5}$ for the first year after birth (p -value = 0.02 for the postnatal $\text{PM}_{2.5} \times \text{sex}$). We further conducted DLNM stratified by child sex to explore the effect modification by sex on the associations between $\text{PM}_{2.5}$ and asthma. However, we did not observe substantial sex differences in the effects of $\text{PM}_{2.5}$ on asthma (Fig E3).

Discussions

In this large birth cohort study, we found that increased exposure to PM_{2.5} during the prenatal and postnatal periods was significantly associated with increased incident asthma in Taichung city. The vulnerable time windows were gestational weeks 6–22 and 9–46 weeks after birth (Fig 2). The exposure-response relationships showed that maternal exposure to PM_{2.5} above 93 µg/m³ during pregnancy might increase the HR of later development of asthma in their children. Additionally, children with postnatal exposure to PM_{2.5} between 26–72 µg/m³ were associated with the increased HR of asthma (HR range 1.01–1.07), and the HR increased sharply for PM_{2.5} exposure above 73 µg/m³ (Fig 3).

The developing stages of the lungs include the embryonic (gestational weeks 4–7), pseudoglandular (gestational weeks 7–17), canalicular (gestational weeks 17–26), saccular (gestational weeks 27–36 gestational weeks), and alveolar (after 36 gestational weeks and until adolescence) stages.^{5,6} Human lungs begin to form at days 24–26 after conception.^{6,27} During the embryonic stage of lung development, the lungs appear as two outgrowths from the ventral wall of the primitive foregut, with subsequent outgrowth into the surrounding mesenchymal tissues and branching.^{5,6} The primitive foregut also divides into the esophagus and trachea during the embryonic stage.⁶ The airway epithelial tubules branch repeatedly and form terminal bronchioles during the pseudoglandular stage.^{6,28} The basal, goblet, pulmonary neuroendocrine, ciliated, and non-ciliated columnar (Clara) cells appear in the proximal airway.²⁸ In the canalicular stage, the epithelial cells would differentiate into types I and II, the alveolar epithelium comes into close contact with the mesenchymal capillaries to form the future air-blood barriers, and surfactant is produced.⁶ The saccular stage follows the canalicular stage, in which the terminal airways form

clusters of airspaces and the terminal ends widen to form saccules.⁶ A variety of antioxidant enzymes and xenobiotic metabolizing enzyme systems (e.g., superoxide dismutase, catalase, glutathione peroxidase, and the cytochrome P450 monooxygenases family) develop during late gestation to the early postnatal period.²⁹

For the pregnancy period, our results revealed that the vulnerable time windows of asthma due to PM_{2.5} exposure between gestational weeks 6–22 coincided with the embryonic, pseudoglandular, and canalicular stages of lung development. The plausible biological mechanism of the effect of PM_{2.5} during pregnancy period could be explained by PM_{2.5} inhaled by the pregnant mother penetrating the alveoli and diffusing into the placental barrier to act directly on the fetus, or the triggering systemic inflammation in the mother decreased transportation of fetal nutrients and oxygen, which influences fetal lung function.³⁰

Regarding the infancy period, we also recognized the vulnerable time windows for the effects of PM_{2.5} between 9–46 weeks after birth. Infants born within the alveolar stage. More than 85% of alveoli are formed after birth, most alveolar formation completed at around 6 months.³¹ Infants are especially susceptible to harmful effects of ambient air pollution due to their developing lungs and immature immune system.³² The respiratory epithelium in the developing lungs exhibits an increased permeability of toxicants.³² In an animal studies, mice exposure to concentrated PM_{2.5} during prenatal and early postnatal periods (40 days after birth, terminated lung alveolarization) may result in decreased alveoli number, enlarged alveolar spaces, and increased lung elastance.³³ After birth, air pollution could contribute to the development of asthma by inducing oxidative stress in the lungs, interacting with the airway wall, leading to structural changes in the airway wall, triggering inflammatory pathway and immunological effects, and enhancing respiratory sensitization to allergens.³⁴

According to previous epidemiological studies, Clark and colleagues (2010) conducted a nested case-control study of 37,401 children in southwestern British Columbia to assess the association of exposure to ambient air pollution during the entire pregnancy and the first year of life on asthma. They found that a $1 \mu\text{g}/\text{m}^3$ increase in particulate matter with an aerodynamic diameter less than $10 \mu\text{m}$ (PM_{10}) during pregnancy and the first year of life was correlated with a risk of asthma (odds ratio [OR] = 1.09, 95% CI: 1.05–1.13 and OR = 1.07, 95% CI 1.03–1.12, respectively).¹⁶ Deng and colleagues (2016) conducted a cross-sectional study in China to evaluate the associations between exposure to air pollution during the three trimesters of pregnancy and the risk of asthma in 2,598 preschool children. They found that the risk of asthma was significantly associated with exposure to nitrogen dioxide (NO_2) during the second trimester (OR = 1.72, 95% CI: 1.02–2.97).¹⁷ However, no significant association was shown between asthma and prenatal exposure to PM_{10} .¹⁷ Sbihi and colleagues (2016) performed a nested case-control study of 65,254 children, reporting a significant association of incident asthma during pre-school age (0–5-year) with perinatal exposure to PM_{10} (OR = 1.12, 95% CI: 1.05–1.19).¹⁸ No association was shown between perinatal exposure to $\text{PM}_{2.5}$ and incident asthma during pre-school age.¹⁸ Hsu and coworkers performed a prospective cohort study in the Boston area of 736 children to assess the association between prenatal exposure to $\text{PM}_{2.5}$ and asthma until six years of age.¹⁹ They reported that prenatal exposure to $\text{PM}_{2.5}$ during weeks 16–25 weeks (mid-gestation in the late pseudoglandular to canalicular stages of lung development) was significantly associated with the development of asthma at six years of age.¹⁹ Our study also found that prenatal exposure to $\text{PM}_{2.5}$ was positively correlated with asthma; although the exact periods of vulnerable time windows in the present study (gestational weeks 6–22 coinciding with the embryonic, pseudoglandular, and canalicular stages,) differed

from those reported by Hsu and colleagues (2015).¹⁹

Clark and coworkers (2010) observed that the associations between asthma and air pollution were generally stronger in women than in men during exposures both in the prenatal period and the first year after birth.¹⁶ In contrast, Hsu and colleagues (2015) reported that the associations of asthma with prenatal exposure to PM_{2.5} were specific to males.¹⁹ In this study, we observed a significant interaction between sex and PM_{2.5} for the first year after birth. While we did not observe substantial sex differences in health effects of PM_{2.5} on asthma between males and females according to the results of DLNM stratified by sex (Fig E3). Based on the developmental process, males are more likely to develop asthma than females before puberty due to differences in growth rates and sex hormones.^{35,36} The sex differences in the associations of asthma with PM_{2.5} exposures requires further investigation.

This study had two main strengths. First, this study used a large birth cohort, the TMCHD, interlinked with several country-wide registry databases in Taiwan, such as the TBR, the NRD, and the NHIRD. The TMCHD recruited all children born in Taiwan during 2004-2011 (approximately 1.6 million neonates), including more than 180,000 neonates in Taichung city. The individuals within the TMCHD can be traced from birth to death. The first diagnosis date of asthma for each child can be obtained from the database. Thus, we have a sufficient, prospective, and population-based database that allows us to examine the association of asthma with prenatal and postnatal exposures to PM_{2.5}. Secondly, we used a novel satellite-based hybrid model to integrate satellite AOD with meteorological variables and land use data with an excellent temporal resolution to estimate ground PM_{2.5} in Taiwan.²² This model allowed us to explore vulnerable time windows on a weekly basis through conception to the infancy periods.

This study also has several limitations. First, PM_{2.5} is a complex mixture of solid

and liquid aerosols. The toxicity of $PM_{2.5}$ may vary significantly due to different sources and components. The components of $PM_{2.5}$, such as black carbon, nitrate, and potassium, are associated with outpatient and inpatient visits for asthma in Taiwan.³⁷ However, we did not examine the associations of asthma with specific $PM_{2.5}$ components because of a lack of information on these components or sources. Second, we did not have data on important factors such as the activity pattern, genetic information, and nutritional status, for each child. Although we adjusted for important confounders in the models, including SES and maternal allergic diseases, we could not exclude the potential bias of confounding factors. Third, the follow-up period of our study was shorter than that of previous studies. In a Canada study, children were assessed for the incidence of asthma diagnosis up to 3–4 years of age (mean age at the end of follow-up: 48 ± 7 months).¹⁶ Children were followed up until 10 years of age in a study conducted in the greater Vancouver region of Canada.¹⁸ In addition, asthma was examined from birth up to six years of age in a study conducted in the Boston area in the U.S..¹⁹ In our study, the mean age at the end of follow-up for the whole birth cohort was 6.35 ± 2.65 years and 75% of children were followed-up for more than 4.16 years of age (Table 1). The mean age at the date of first asthma diagnosis was 3.39 ± 1.78 years. For children born in 2011, the age at the end of follow-up period (until the end of 2014) was only three years. It is possible that the first asthma diagnosis was missed within such a short period. Nevertheless, the mean age of first asthma diagnosis significantly decreased over time, to 2.6 ± 2.0 years for children born in 2000 in Canada.³⁸ We believe that the length of follow-up periods in our study are acceptable for ascertaining cases of incident asthma.

In conclusion, our findings add evidence to the growing literature indicating that prenatal and postnatal exposures to $PM_{2.5}$ are associated with the later development of asthma. For the prenatal period, the vulnerable time windows may be within the early-

and mid-gestation. Additionally, the vulnerable time windows during the postnatal period were within the first year after birth. Further studies are needed to confirm the associations between asthma and prenatal and postnatal exposures to PM_{2.5} and identify the possible vulnerable time windows. We suggest that sensitive groups, including pregnant women and children, should avoid staying outdoors or exposure to toxicants and allergens during these periods.

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Table 1. Demographic characteristics of the birth cohort in Taichung city, Taiwan from 2004-2014.

	Asthma (n=34,336)	Total (n=184,604)	Person-years at risk	Incidence rate ^a	HR (95% CI) ^b
Gestation age (weeks, mean $\pm$ SD, Q1, Q2, Q3)				38.40 $\pm$ 1.54, 38.00, 39.00, 39.00	
Age at the date of the first diagnosis of asthma (years; mean $\pm$ SD, Q1, Q2, Q3)				3.39 $\pm$ 1.78, 2.11, 3.22, 4.51	
Age at the end of follow-up (years; mean $\pm$ SD, Q1, Q2, Q3)				6.35 $\pm$ 2.65, 4.16, 6.25, 8.58	
Sex (%)					
Male	20,261 (59.01)	96,248	670,224.01	3.02	1.37 (1.34-1.40)*
Female	14,075 (40.99)	88,356	637,641.00	2.21	Reference
Birth weight (%)					
<2,500 g	2,146 (6.25)	10,057	67,556.66	3.18	1.23 (1.18-1.28)*
$\geq$ 2,500 g	32,190 (93.75)	174,547	1,240,308.35	2.60	Reference
SES (%)					
$\geq$ 33,300	6,394 (18.62)	31,603	22,7762.8	2.81	1.15 (1.12-1.19)*
20,100-33,300	8,454 (24.62)	44,489	308,537.26	2.74	1.11 (1.08-1.14)*
16,500-20,100	8,003 (23.31)	42,638	305,289.48	2.62	1.07 (1.04-1.10)*
<16,500	11,485 (33.45)	65,874	466,275.47	2.46	Reference
Maternal age, years (%)					
$\leq$ 30	19,367 (56.40)	99,383	725,000.74	2.67	1.06 (1.04-1.08)*
>30	149,69 (43.60)	85,221	58,2864.27	2.57	Reference
Maternal atopy (%)					
Yes	22,680 (66.05)	10,3421	708,025.01	3.20	1.64 (1.60-1.67)*
No	11,656 (33.95)	81,183	599,840.00	1.94	Reference
Maternal anemia (%)					
Yes	118 (0.34)	855	5,237.00	2.25	0.80 (0.67-0.96)*
No	3,4218 (99.66)	183,749	1,302,628.01	2.63	Reference
Maternal heart disease (%)					
Yes	26 (0.08)	111	725.87	3.58	1.36 (0.93-2.00)
No	34,310 (99.92)	184,493	1,307,139.14	2.62	Reference
Maternal lung disease (%)					
Yes	8 (0.02)	24	176.47	4.53	1.86 (0.93-3.72)
No	34,328 (99.98)	184,580	1,307,688.54	2.63	Reference
Gestational diabetes (%)					
Yes	124 (0.36)	672	4,295.21	2.89	1.06 (0.89-1.26)
No	34,212 (99.64)	183,932	1,303,569.8	2.62	Reference
Maternal chronic hypertension (%)					
Yes	34 (0.10)	156	921.18	3.69	1.38 (0.98-1.93)

No	3,4302 (99.90)	184,448	1,306,943.83	2.62	Reference
Gestational hypertension (%)					
Yes	262 (0.76)	1,571	10,057.29	2.61	Reference
No	34,074 (99.24)	183,033	1,297,807.70	2.63	1.05 (0.93-1.18)
Preeclampsia (%)					
Yes	168 (0.49)	750	4,873.92	3.45	1.32 (1.13-1.53)*
No	34,168 (99.51)	18,3854	1,302,991.09	2.62	Reference
Maternal kidney disease (%)					
Yes	13 (0.04)	44	278.26	4.67	1.79 (1.04-3.09)*
No	34,323 (99.96)	184,560	1,307,586.75	2.62	Reference
Maternal smoking status (%)					
Yes	13 (0.04)	68	447.89	2.90	1.11 (0.64-1.90)
No	34,323 (99.96)	184,536	1,307,417.10	2.63	Reference

Note: Q1, 25th percentile; Q2, 50th percentile; Q3, 75th percentile.

^aIncidence rate per 100 person-years

^bHazard ratios were derived by using univariate Cox proportional hazard model

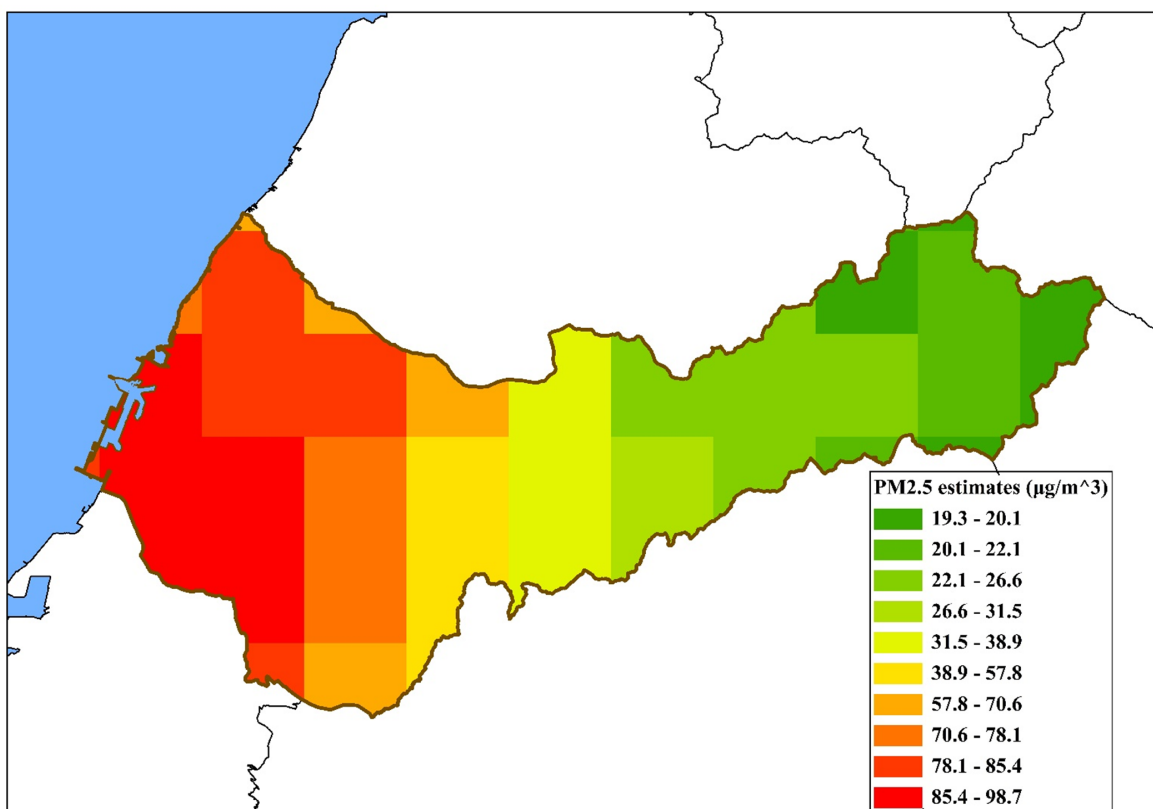
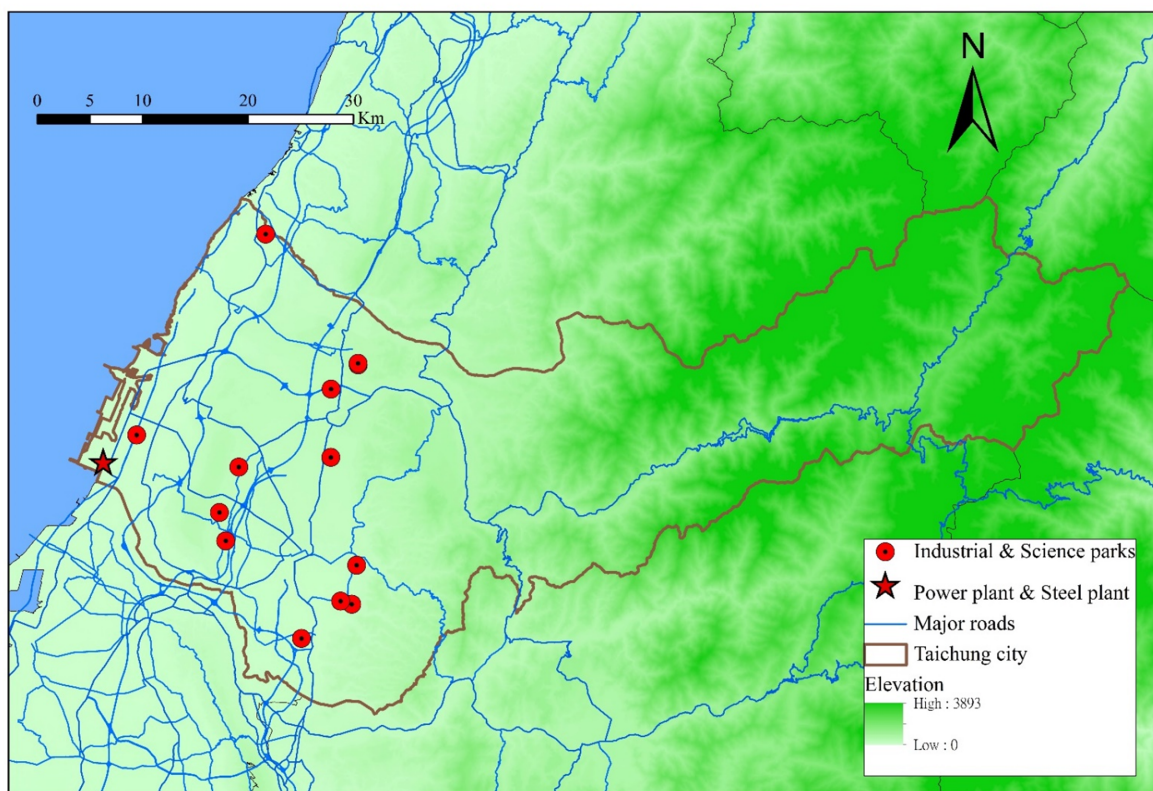
587 **Fig 1. The spatial distribution of major roads and stationary emission sources,**
588 **and average particulate matter with an aerodiameter less than 2.5 μm (PM_{2.5})**
589 **estimates in Taichung city, Taiwan between January 6–12, 2008.**
590

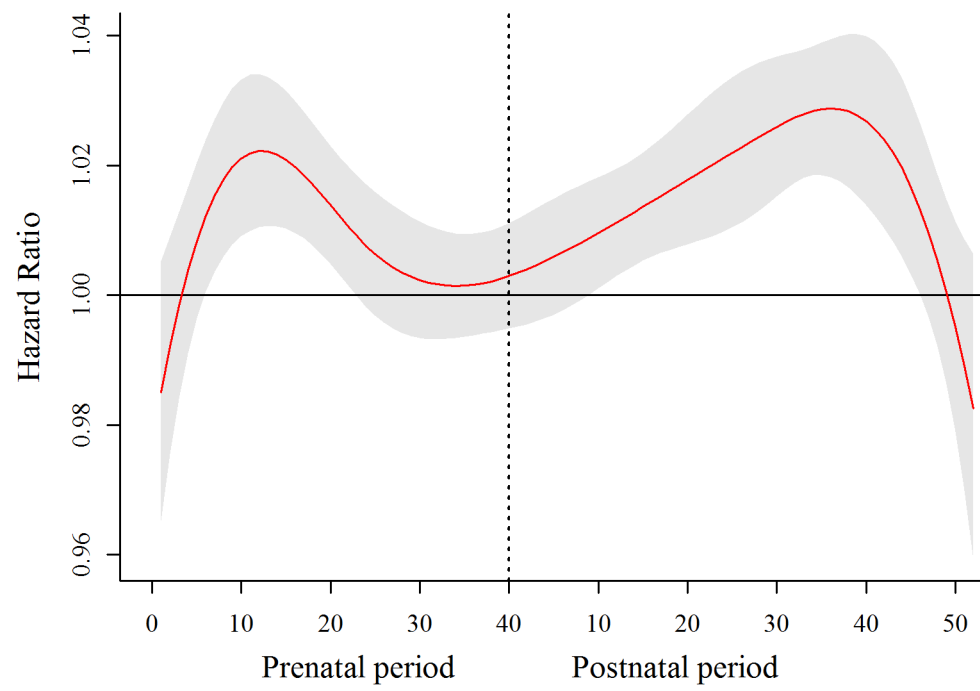
Fig 2. Adjusted hazard ratio (HR) with 95% confidence interval (grey area) of asthma with a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during the prenatal (40 weeks) and postnatal periods (52 weeks) by a Cox proportional hazard model combined with a distributed lag non-linear model.

These models were adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.

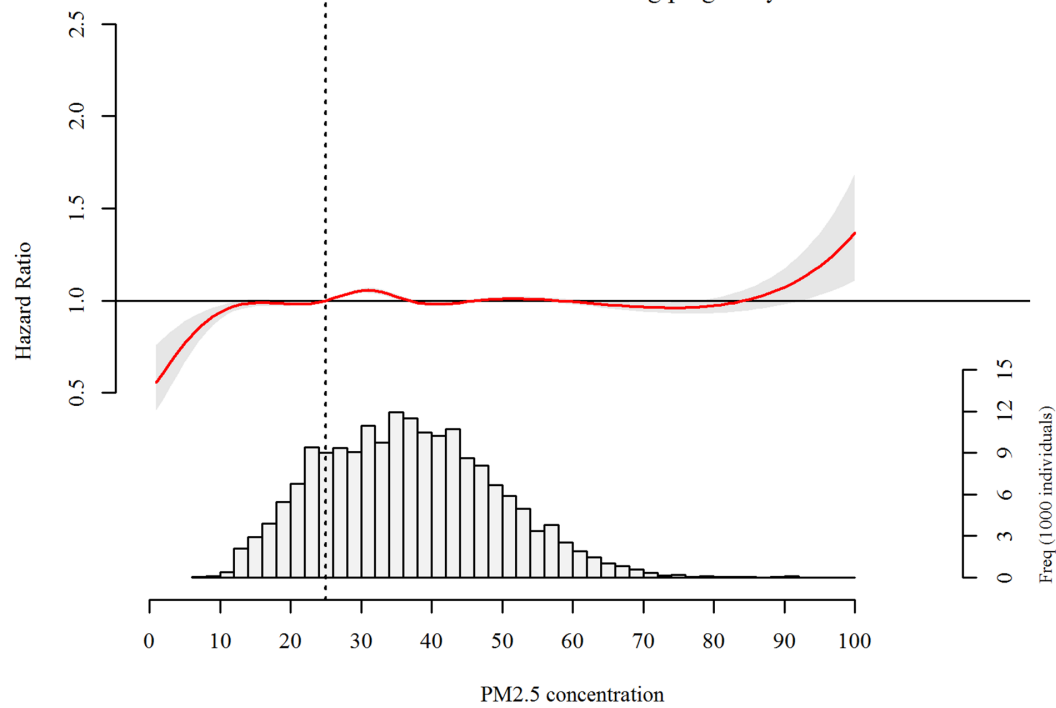
Fig 3. Exposure-response relationship between PM_{2.5} exposure and asthma in gestational week 12 (A) and 36 weeks after birth (B) represented as the hazard ratio (red line) with 95% confidence interval (grey area), as well as the corresponding PM_{2.5} concentration distributions.

The dashed line is the centering value at 25 µg/m³ (WHO 24-hr mean standard).

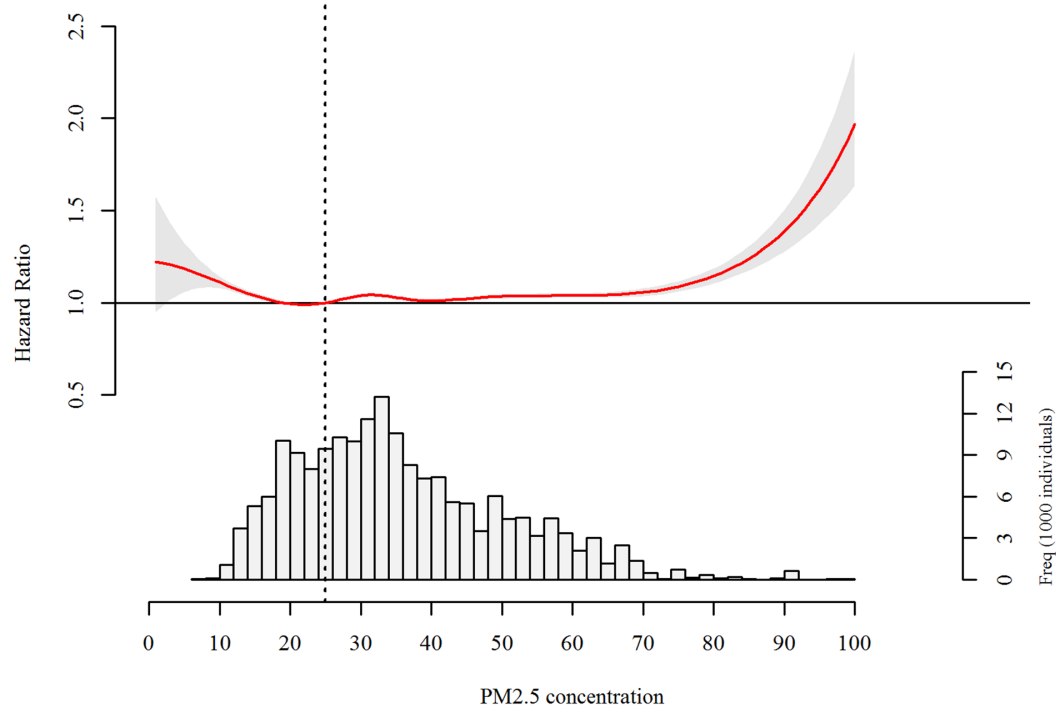


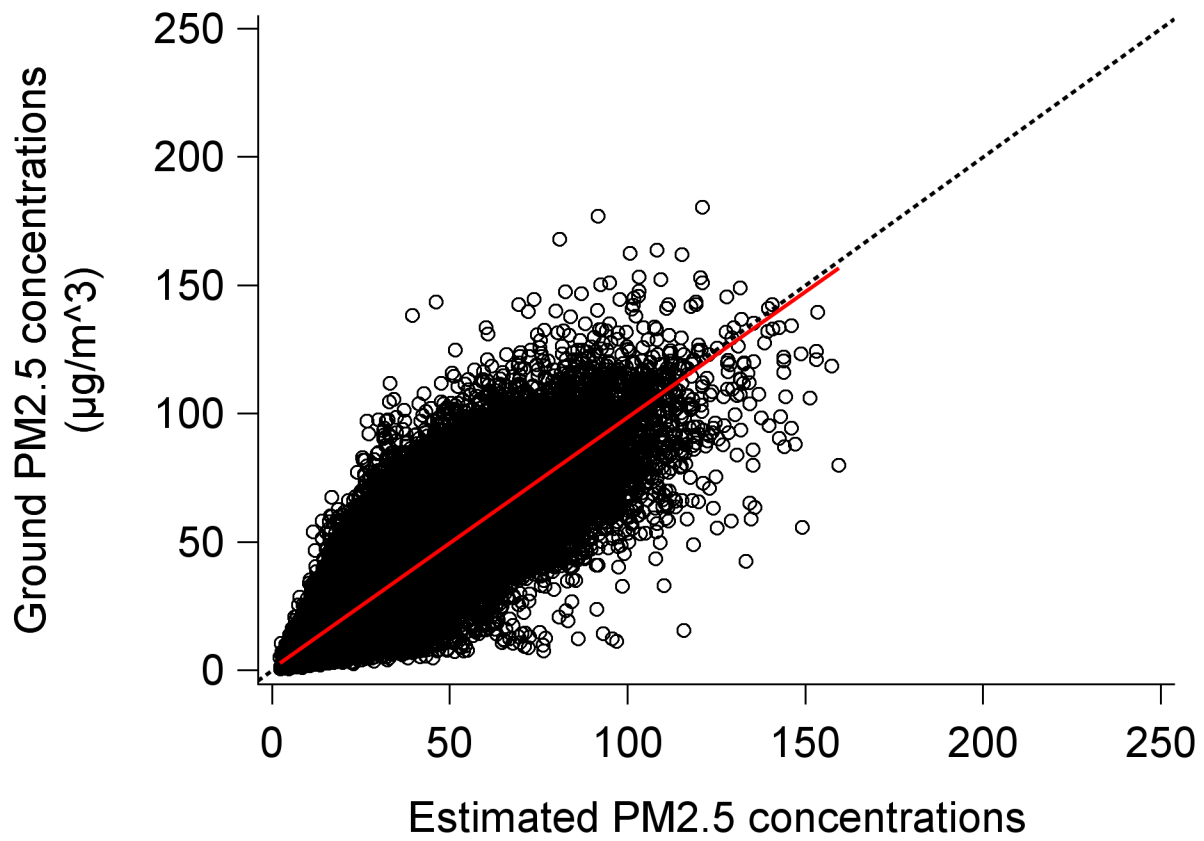


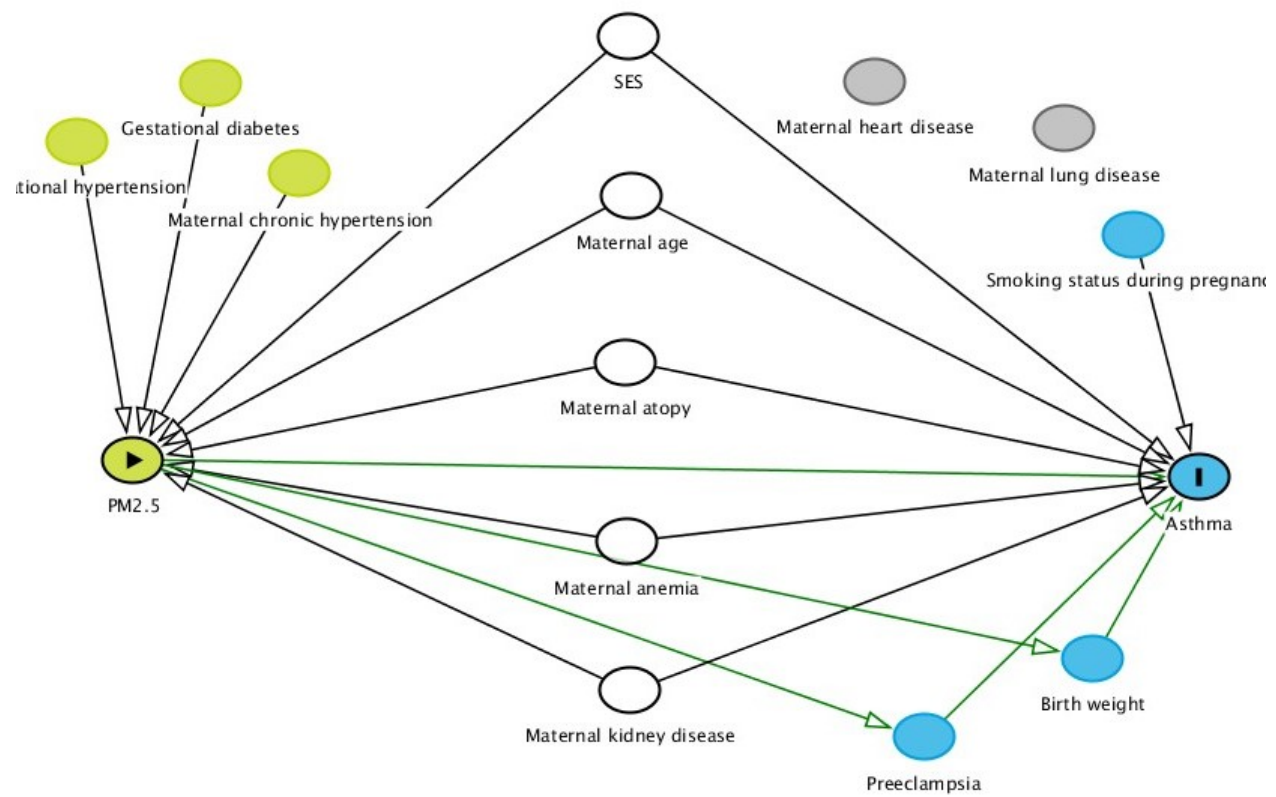
(A) Exposure-response relationship and PM2.5 distribution
Gestational week 12 during pregnancy

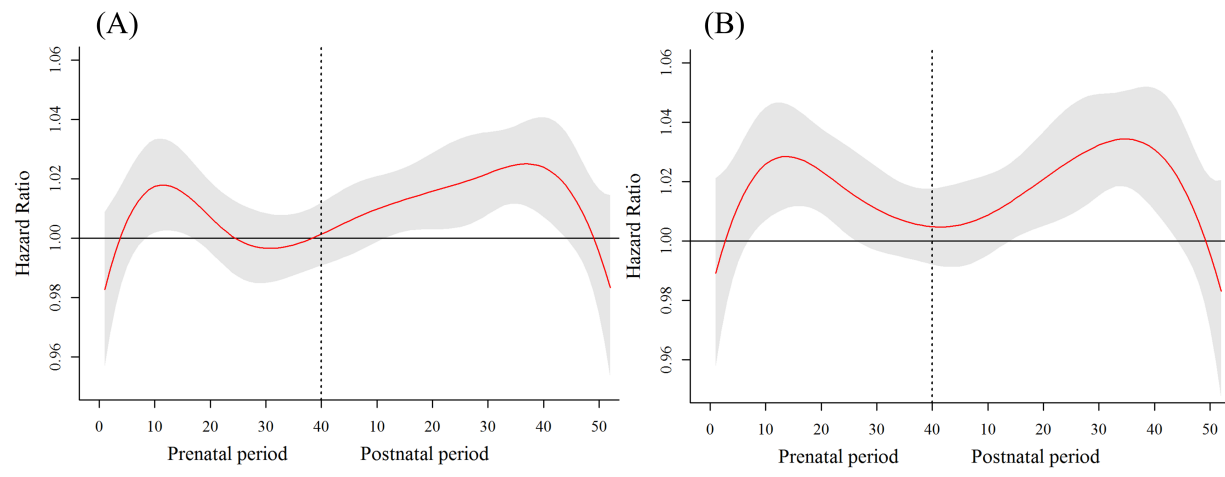


(B) Exposure-response relationship and PM2.5 distribution
36 weeks after birth









Supplementary material

**Fine particulate matter exposure during pregnancy and infancy periods
and incident asthma**

Chau-Ren Jung, PhD, Wei-Ting Chen, PhD, Yu-Hsin Tang, MSc, Bing-Fang Hwang, PhD

Diagnosis criteria for asthma

The diagnosis criteria for asthma included wheezing; cough (worse particularly at night); recurrent difficulty in breathing; recurrent chest tightness; symptoms occurring or worsening at night that awakened the patient; symptoms occurring or worsening with exercise, viral infections, inhalant allergens, irritants, change in weather, strong emotions, or menses; airflow obstruction that was at least partially reversible; diurnal variation in peak expiratory flow (PEF) of more than 20% over one to two weeks; increase of at least 12% and 200 mL in forced expiratory volume in one second (FEV₁) after bronchodilator use and reduced FEV₁ and FEV₁/forced vital capacity (FVC) ratio using spirometry.¹

The 10-km spatial resolution hybrid modeling for PM_{2.5}

The detail of the 10-km resolution hybrid model has been described previously.² In brief, the 24-hr average PM_{2.5} measurements was obtained from 73 air quality monitoring stations set by Taiwan Environmental Protection Administration (TEPA) in Taiwan. Aerosol optical depth (AOD) values at 550 nm with a 10 km spatial resolution (scientific dataset: Optical_Depth_Land_and_Ocean) from MODerate resolution Imaging Spectroradiometer (MODIS) Collection 6 Level-2 Aerosol Products (MOD04_L2 and MYD04_L2) were acquired from the Level 1 and Atmospheric Archive and Distribution System (LAADS Web; <http://ladsweb.nascom.nasa.gov>). Meteorological variables, including 2-m temperature and dew point temperature, 10-m zonal and meridional winds, surface pressure, boundary layer height, and total precipitation, were acquired from the European Centre for Medium-Range Weather Forecast (ECMWF) Re-analysis Interim (ERA-Int). The land use data were accessed from CTCI corporation and National Land Surveying and Mapping Center (NLSMC), respectively, including urban and built-up land, dryland cropland and pasture, irrigated cropland and pasture, cropland and grassland mosaic, cropland and woodland mosaic, grassland, shrub land, mixed shrub land and grassland, savanna, deciduous broadleaf forest, evergreen broad leaf forest, evergreen needle leaf forest, mixed forest, water bodies, barren or sparsely vegetate, and industrial emission sources. Elevation data was acquired from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model Version 2 (GDEM).

A novel approach—the Multiple imputation (MI) with additive regression taking cloud fraction into accounts has been conducted to fill missing AOD values.³ The cloud fraction data at 5-km spatial resolution was obtained from Terra and Aqua MODIS Collection 6 Level 2 cloud properties (MOD06_L2 and MYD06_L2). Terra and Aqua cloud fraction data were averaged to represent daily values. The equation for MI is shown below (equation [1]):

$$AOD_{ij} = s(lon_i) + s(lat_i) + s(lon_i^2) + s(lat_i^2) + s(lon_i \times lat_i) + \beta_1 CF_{ij} + \beta_2 T2M_{ij} + \beta_3 RH_{ij} + \beta_4 Elevation_i + \varepsilon_{ij} \dots \dots \dots [1]$$

where AOD_{ij} is the average AOD values at fixed grid i on day j ; lon_i and lat_i are the longitude and latitude of centroid of fixed grid i ; CF_{ij} is the daily CF at fixed grid i on day j ; $T2M_{ij}$ is the 2-m temperature at fixed grid i on day j ; RH_{ij} is the 2-m relative humidity; $Elevation_i$ is the average elevation at grid i . Then, the linear mixed effects (LME) model includes day-specific random effect and fixed effect for intercept, AOD, meteorological variables (relative humidity, surface pressure, temperature, wind direction and speed), and land use variables was performed to estimate 24-hr average $PM_{2.5}$ concentrations at grids where without air quality monitoring stations (equation [2]):

$$\begin{aligned} \log(PM_{2.5ij}) = & (\mu + \hat{\mu}) + (\beta_1 + \hat{\beta}_1)AOD_{ij} + (\beta_2 + \hat{\beta}_2)AOD^2_{ij} + (\beta_3 + \hat{\beta}_3)U_{10ij} + \\ & (\beta_4 + \hat{\beta}_4)V_{10ij} + \beta_5RH_{ij} + \beta_6T2M_{ij} + \beta_7SP_{ij} + \beta_8PREC_{ij} + \beta_9AXIS1_i + \beta_{10}AXIS2_i + \\ & \beta_{11}AXIS3_i + \beta_{12}AXIS4_i + \beta_{13}AXIS5_i + \beta_{14}AXIS6_i + \beta_{15}AXIS7_i + \beta_{16}Elevation_i + \\ & \varepsilon_{ij} \quad (\hat{\mu}\hat{\beta}_1\hat{\beta}_2\hat{\beta}_3\hat{\beta}_4) \sim N[(0,0,0,0,0), \Sigma] \dots\dots\dots [2] \end{aligned}$$

where $\log(PM_{2.5ij})$ is the logarithm of 24-hr average $PM_{2.5}$ measurements at fixed grid i on a day j ; AOD_{ij} is the average AOD value; AOD^2_{ij} is the quadratic term of AOD, the quadratic term of AOD was included in the model to depict the curvilinear relationships between AOD and $PM_{2.5}$; U_{10ij} is the 10-m zonal wind; V_{10ij} is the 10-m meridional wind; RH_{ij} is the 2-m relative humidity; SP_{ij} is the surface pressure; $T2M_{ij}$ is the 2-m temperature; $PREC_{ij}$ is the amount of total precipitation; $AXIS1_i$ - $AXIS7_i$ are axis 1 to axis 7 derived from principal component analysis that combining land use variables at fixed grid i ; $Elevation_i$ is the elevation of grid i ; μ and $\hat{\mu}$ are the fixed and day-specific random effect for intercept, respectively; β_1 - β_{16} are fixed effects for independent variables; $\hat{\beta}_1$ - $\hat{\beta}_4$ are day-specific random effects for meteorological variables; ε_{ij} is the error term; Σ is an unstructured variance-covariance matrix for day-specific random effects. The results of ten-fold cross validation R^2 for the LME model was 0.77 with a root mean square error (RMSE) of $9.0 \mu g/m^3$ (Fig E1).

Selection criteria for confounders

The directed acyclic graphs (DAGs) were used to identify confounders in the Cox proportional hazard (PH) model (Fig E2).⁴ Associations of covariates with exposure to $PM_{2.5}$ during pregnancy and the first year after birth were evaluated using univariate logistic regression. Univariate Cox PH models were conducted to assess the associations of asthma with each covariate. If a covariate was associated with asthma in the univariate Cox PH model and was associated with exposure to $PM_{2.5}$ in the univariate logistic regression but was not an intermediate variable of $PM_{2.5}$ exposure, the corresponding covariate was included in

the final model. We also selected confounders according to previous literature.⁵⁻⁸

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Table E1. Adjusted hazard ratio (HR) and 95% confidence interval of asthma with a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ with (Model I) and without adjusting for birth weight and maternal smoking status during pregnancy (Model II).

	Model I^a	Model II^b
Separate model		
$\text{PM}_{2.5}$ during pregnancy	1.258 (1.169–1.354)	1.259 (1.169–1.355)
$\text{PM}_{2.5}$ during the first year after birth	1.613 (1.479–1.759)	1.612 (1.478–1.757)
Mutually adjusted model		
$\text{PM}_{2.5}$ during pregnancy	1.038 (0.949–1.136)	1.039 (0.949–1.137)
$\text{PM}_{2.5}$ during the first year after birth	1.552 (1.397–1.723)	1.550 (1.395–1.722)

^aThese models were adjusted for socioeconomic status, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases, birth weight, and maternal smoking status during pregnancy.

^bThese models were adjusted for socioeconomic status, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.

Fig E1. The result of cross validation for the 10-km spatial resolution hybrid model.

$Y=0.9X+0.64$, cross validation $R^2=0.77$ with a root mean square of $9.0 \mu\text{g}/\text{m}^3$.

Fig E2. The directed acyclic graph (DAG) for selecting confounders in this study.

The green node with an “arrow” indicates the exposure, $\text{PM}_{2.5}$, and the blue node with the “I” indicates the outcome of interest, asthma. The white nodes indicate adjusted confounders. The green node without “arrow” is a covariate that is associated with $\text{PM}_{2.5}$ exposure but not associated with asthma. The blue node without “I” and with a green edge connection line is an intermediate variable. The blue node without “I” and with a black color connection line is a covariate that is associated with asthma but not with $\text{PM}_{2.5}$. The grey node is a variable that is neither associated with exposure nor with the outcome.

Fig E3. Adjusted hazard ratio (HR) with 95% confidence interval (grey area) of asthma with a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ during the prenatal and postnatal periods by a Cox proportional hazard model combined with the distributed lag non-linear model after stratifying by sex (male (A) and female (B)).

These models were adjusted for SES, maternal age, maternal atopy, maternal anemia, and maternal kidney diseases.