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Particulate matter exposure during pregnancy increases risk of childhood asthma: modified by gender and *NRF2* genotype

Hyo-Bin Kim,[1] Hyeyeun Lim,[2]* Sangrok Kim,[2] So-Yeon Lee,[2] Hwan-Cheol Kim,[3] Mi-Jin Kang,[2] Minjee Park,[2] Sungsu Jung,[4] Jisun Yoon,[5] Hyun-Ju Cho,[6] Song-I Yang,[7] Soo-Jong Hong[2]*

Abstract

Background: Exposure to particulate matter (PM) has been known to develop asthma in children and the oxidative stress-related mechanisms are suggested. For the development of asthma, not only the exposure dose but also the critical window and the risk modifying factors should be evaluated.

Objective: We investigated whether prenatal exposure to PM_{10} increases the risk of childhood asthma and evaluated the modifying factors, such as gender and reactive oxidative stress-related gene.

Methods: A general population-based birth cohort, the Panel Study of Korean Children (PSKC), including 1572 mother-baby dyads was analyzed. Children were defined to have asthma at age 7 when a parent reported physician-diagnosed asthma. Exposure to PM_{10} during pregnancy was estimated by land-use regression models based on national monitoring system. TaqMan method was used for genotyping *nuclear factor, erythroid 2-related factor, NRF2 (rs6726395)*. A logistic Bayesian distributed lag interaction model (BDLIM) was used to evaluate the associations between prenatal PM_{10} exposure and childhood asthma by gender and *NRF2*.

Results: Exposure to PM_{10} during pregnancy was associated with the development of asthma (aOR 1.03, 95% CI 1.00-1.06). Stratifying by gender and *NRF2* genotype, exposure to PM_{10} during 26-28 weeks gestation increased the risk of childhood asthma, especially in boys with *NRF2 GG* genotype.

Conclusion: A critical window for PM_{10} exposure on the development of childhood asthma was during 26-28 weeks of gestation, and this was modified by gender and *NRF2* genotype.

Key words: asthma, gender, gene, *NRF2*, particulate matter, pregnancy

Affiliations:
[1] Department of Pediatrics, Inje University Sanggye Paik Hospital, Seoul, Korea
[2] Department of Pediatrics, Childhood Asthma Atopy Center, Environmental Health Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3] Department of Occupational and Environmental Medicine, Inha University School of Medicine, Incheon, Korea
[4] Department of Pediatrics, Pusan National University Yangsan Hospital, Yangsan, Korea
[5] Department of Pediatrics, Chung-Ang University Gwang-Myeong Hospital, Chung-Ang University College of Medicine, Gwang-Myeong, Korea
[6] Department of Pediatrics, International St. Mary's Hospital, Catholic Kwandong University Hospital, Incheon, Korea
[7] Department of Pediatrics, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

* These authors contributed equally to this work and should be considered co-first authors.

Corresponding author:
Soo-Jong Hong
Department of Pediatrics, Childhood Asthma Atopy Center, Environmental Health Center, Asan Medical Center, University of Ulsan College of Medicine,
88 Olympic-ro-43-gil Songpa-gu, Seoul 05505, Republic of Korea
E-mail: sjhong@amc.seoul.kr

Introduction

Epidemiologic studies support that particulate matter (PM) increases the risk of asthma development and exacerbation.[1] Emerging evidence highlights the importance of prenatal and early life exposure to fine particulates and childhood asthma.[2-4] Maternal exposure to particulate air pollution induces fetal oxidative stress and influences gene expression that is crucial for lung maturation to result in childhood asthma.[5]

Asthma is a chronic respiratory disorder that is incurable after development, so prevention strategies before onset are required. It is important to identify the critical window of exposure and the most susceptible subpopulation to prevent asthma from PM exposure.

Reports have shown sex differences in the development of asthma with PM exposure. Due to differences in growth rates, hormonal status, and activity patterns, boys are more likely to develop asthma in early childhood than girls.[6] In a Danish population study of asthma risk factors, women had higher enzyme activities of most antioxidant enzymes than did men, and sex-differences were found in the association between markers of antioxidative defense and asthma.[7]

Genetic factors also inevitably affect susceptibility. Nuclear factor erythroid 2-related factor (Nrf2) is a major up-regulator of antioxidant response element (ARE)-mediated expression of antioxidant enzymes and cytoprotective proteins.[8] Nrf2 activation has protective effects against lung injury. Genetic polymorphisms or epigenetic change in *NRF2* have been reported in a cohort study of respiratory diseases.[9]

Herein, we evaluated the association of prenatal exposure to PM with diameter less than 10 micrometers (PM_{10}) and childhood asthma at age 7 to estimate the critical windows of vulnerability and to identify susceptible populations. With the recent development of statistical methods, it is available to estimate the critical windows of prenatal PM exposure associated with the adverse childhood respiratory health, with considering multiple modifying factors.[10] Modified susceptibility was assessed by differences in gender and oxidative stress-related polymorphisms in *NRF2*.

Materials and Methods

Study population

Participants were from the Panel Study of Korean Children (PSKC), a nationwide general population-based birth cohort consisting of 1,572 mother-baby pairs followed up from 2008 to 2015. A total of 2,150 mothers were recruited from nationwide thirty obstetric clinics selected by random sampling. A series of questionnaires on mother and child lifestyles were fulfilled at 36 weeks of gestation and every subsequent yearly scheduled visit. Among the enrolled participants, children of 1,572 were followed up at 7 years of age and 565 children were analyzed with full data of genetic, questionnaire and PM_{10} exposure data (**Figure 1**). Subject recruitment and study procedures have been described previously.[11]

Detailed patient history and physical examinations were obtained by pediatric allergists at each regional study hospital. Asthma was assessed in 2015 when children were about 7 years old with the following question: "Has your child been diagnosed with asthma by a physician at any time during his/her lifetime?"

The Institutional Review Board of Asan Medical Center reviewed and approved the current study protocol (IRB No. 2015-0907). Written consent was obtained from all parents and guardians following detailed explanation of the study.

Exposure assessments

Exposure to PM_{10} at residential addresses was estimated by land-use regression (LUR) models using a previously described standardized method.[12] The concentrations of ambient air pollutants in various areas at various times were compiled using air monitoring data that are routinely recorded by monitoring stations operated by the Department of Environment, Republic of Korea. Each monitoring station measures PM_{10} hourly. Centrally and locally available geographic variables were used as potential predictors. Predictor variables, such as traffic indicators, surrounding-land usage, topography, and spatial trends, were computed at each location using ArcGIS version 9.3 (ESRI, Redlands, WA, USA). Multiple linear regression models were built using a supervised forward stepwise procedure. Predictor variables used in the final LUR model for air pollution included lengths of all roads, traffic intensity on nearest roads, total heavy-duty traffic loads of all roads, and a variable representing spatial trends. Each mother was assigned an average PM_{10} exposure value for each week of pregnancy based on the predicted value at her address of residence.

Genotyping

Genomic DNA was prepared from heparinized blood samples using a G-DEX II kit (Intron, Seoul, Korea). *NRF2* (rs6726395) polymorphisms were genotyped using a TaqMan assay (ABI, Foster City, CA, USA).

Statistical analysis

Bayesian distributed lag interaction models (BDLIM) were used to assess whether the critical window of prenatal PM_{10} exposure was associated with childhood asthma. To evaluate the modifying effect of gender and *NRF2* genotype, BDLIM was performed after stratifying the population by gender and

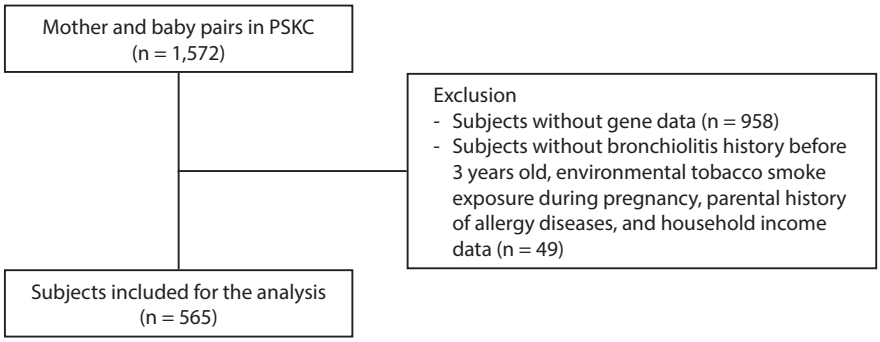

Figure 1. Flow chart of participants in Panel Study of Korean Children

genotype and was adjusted for bronchiolitis history before 3 years old, environmental tobacco smoke exposure during pregnancy, parental history of allergy diseases, and household income. All analyses were implemented with R statistical software (v3.3.1, Vienna, Austria).

Results

Characteristics of participants are presented in **Table 1**. A total of 6.7% (38/565) of participants had physician-diagnosed asthma in this study. Asthma was more prevalent in boys than girls (10.1% vs 3.0%, $P < 0.001$). Children with a history of bronchiolitis before 3 years old were more likely to have asthma than children without a history of bronchiolitis (16.5% vs 3.5%, $P < 0.001$). Exposure to environmental tobacco smoke during pregnancy, parental history of allergic diseases, and household income were not associated with asthma development.

The overall association between a 10 μ/m^3 increase in PM_{10} exposure throughout pregnancy and childhood asthma was statistically significant (aOR 1.03, 95% CIs 1.00-1.06) (**Figure 2A**), and higher PM_{10} exposure at 36 to 37 weeks of gestation was associated with increased risk of asthma at 7 years old (**Figure 2B**). Gender and *NRF2* genotype did not separately interact with the association between prenatal PM_{10} exposure and childhood asthma (**Figure 2C-D**). However, after stratifying the group by gender and *NRF2* genotype, BDLIM demonstrated associations between higher PM_{10} exposure at 26 to 28 weeks of gestation and increased odds of asthma at 7 years old only in males with *NRF2 GG* (26 weeks of gestation: aOR 1.01, 95% CI 1.00-1.02; 27 weeks of gestation: aOR 1.01, 95% CI 1.00-1.02; 28 weeks of gestation: aOR 1.01, 95% CI 1.00-1.02 per 10 μ/m^3 increase in PM_{10}) (**Figure 3**).

Table 1. Characteristics of participants according to physician-diagnosed asthma at 7 years old

	Control (n = 527)		Asthma (n = 38)		*P*-value
	n	%	n	%	
Gender					
Female	259	49.1	8	21.1	< 0.001
Male	268	50.9	30	78.9	
Bronchiolitis history before 3 years old					
Yes	116	22.0	23	60.5	< 0.001
No	411	78.0	15	39.5	
Environmental tobacco smoke exposure during pregnancy					
Yes	335	63.6	25	65.8	0.08
No	192	36.4	13	34.2	
Parental history of allergic diseases					
Yes	361	68.5	30	78.9	0.20
No	166	31.5	8	21.1	
Household income (KW)					
< 1 Million	15	2.9	1	2.6	0.22
1-3 Million	196	37.2	20	52.6	
3-5 Million	214	40.6	14	36.8	
≥ 5 Million	102	19.4	3	7.9	
Prenatal PM_{10} level (μ/m^3), range (mean)	28.9-91.2 (56.4)		43.8-73.2 (59.5)		> 0.05

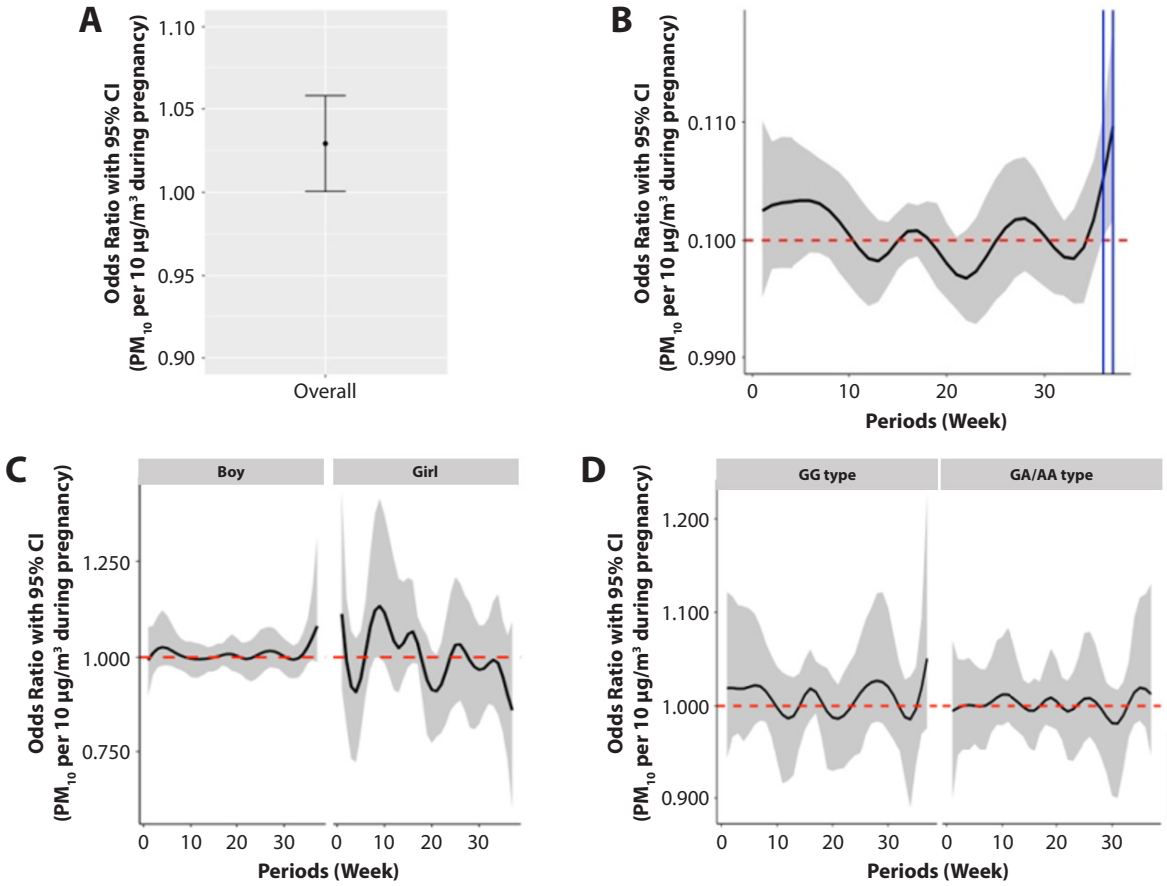

Figure 2. Association between overall pregnancy and weekly prenatal PM_{10} exposure and childhood asthma: BDLIM model. (A) Overall pregnancy PM_{10} exposure per 10 μ/m³ increase was significantly associated with childhood asthma (aOR 1.03, 95% CIs 1.00-1.06). (B) Higher PM_{10} exposure at 36 to 37 weeks of gestation was associated with increased odds of asthma (36 weeks gestation: aOR 1.00, 95% CI 1.00-1.01; 37 weeks gestation: aOR 1.01, 95% CI 1.00-1.02). Association between weekly prenatal PM_{10} exposure and childhood asthma interacted by gender (C) and *NRF2* genotype (D) was not significant.
*Adjusted for bronchiolitis history before 3 years old, environmental tobacco smoke exposure during pregnancy, parental history of allergic diseases, and household income.

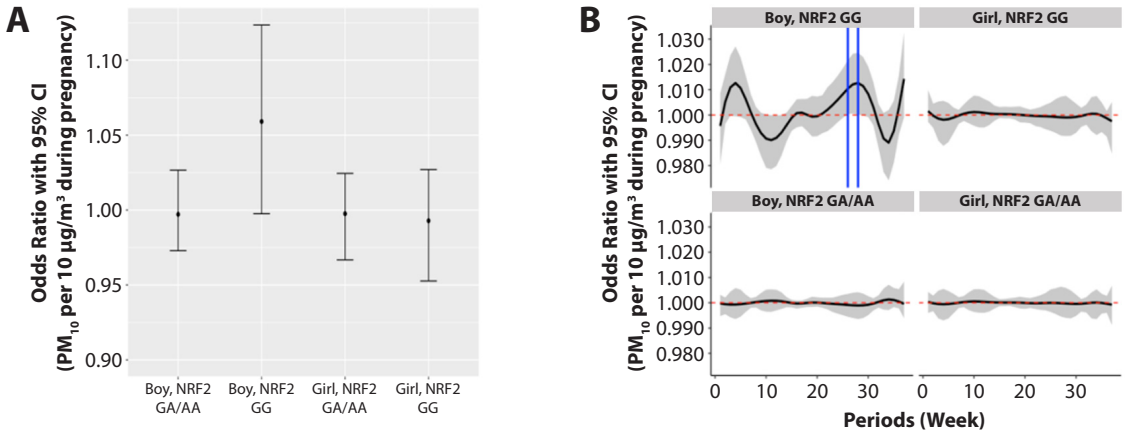

Figure 3. Association between overall pregnancy and weekly prenatal PM_{10} exposure and childhood asthma by gender and *NRF2* genotype. (A) Overall pregnancy PM_{10} exposure per 10 μ/m³ increase was not associated with childhood asthma in each group (boys with *NRF2 GA+AA*: aOR 0.99, 95% CIs 0.97-1.03; boys with *NRF2 GG*: aOR 1.06, 95% CIs 0.99-1.12; girls with *NRF2 GA+AA*: aOR 0.99, 95% CIs 0.97-1.02; girls with *NRF2 GG*: aOR 0.99, 95% CIs 0.95-1.03). (B) When stratifying groups by gender and *NRF2* genotype, higher PM_{10} exposure at 26 to 28 weeks of gestation was associated with increased odds of asthma at 7 years old only in boys with *NRF2 GG* (26 weeks gestation: aOR 1.01, 95% CI 1.00-1.02; 27 weeks gestation: aOR 1.01, 95% CI 1.00-1.02; 28 weeks gestation: aOR 1.01, 95% CI 1.00-1.02 per 10 μ/m³ increase in PM_{10}).
*Adjusted for bronchiolitis history before 3 years old, environmental tobacco smoke exposure during pregnancy, parental history of allergic diseases, and household income.

Discussion

We found that high level of exposure to PM_{10} during pregnancy was significantly associated with childhood asthma at 7 years of age. To evaluate the critical window of the prenatal PM_{10} exposure on childhood asthma, an advanced statistical modeling, BDLIM, was applied and prenatal PM_{10} exposure during 26-28 weeks of gestation was associated with childhood asthma, modified by male gender and genetic factor, *NRF2 GG*, which could be considered as susceptible subpopulation to prenatal PM_{10} exposure.

Previous epidemiological studies reported the association between prenatal exposure to air pollution and childhood asthma, yet the results are various depending on the factors, such as area, race, the kind of air pollution, and the period of exposure, etc.[13] In the children born in southwestern British Columbia in 1999 and 2000, increased exposure to in utero traffic-related pollutants were associated with high risk of asthma; a 1 μ/m^3 increase in PM_{10} during pregnancy was associated with asthma risk (OR 1.09, 95% CI 1.05-1.13).[14] One reported that exposure to nitrogen dioxide during the second trimester was significantly associated with asthma in preschool children, and prenatal PM_{10} exposure did not,[15] whereas a birth cohort study during 2004-2011 in Taichung City showed the both prenatal and postnatal exposure to $PM_{2.5}$ were associated with preschool asthma.[4] Our study group previously reported in the other cohort study that prenatal PM_{10} exposure is associated with an increased risk of asthma in schoolchildren.[16] In the animal studies, PM exposure effects on airway inflammation through the production of Th2 cytokines,[17] and moreover ultrafine PM exposure during pregnancy effects on pulmonary immunosuppression in offspring and increases the childhood susceptibility to respiratory health.[18] Therefore, prenatal period should get the attention for the strategies of asthma prevention regarding to the PM exposure. These days, many studies are more focusing on searching the vulnerable exposure windows during pregnancy to the air pollution for the asthma development in the birth cohort studies.[2-4] In our study, we also found that PM_{10} exposure during pregnancy was associated with childhood asthma development.

The impact of the exposure to air pollution on respiratory system may depend on the window of exposure. Asthma is associated with structural changes in the airways and airway remodeling, which occur during the saccular (27-36 weeks of gestation) and alveolar stages (36 weeks of gestation-2 years after birth) of fetal lung development.[19] These stages could be the vulnerable windows for the childhood asthma development with exposure to air pollution. In the Asthma Coalition on Community, Environment and Social Stress (ACCESS) project, a hospital-based urban ethnically-diverse pregnancy cohort, increased $PM_{2.5}$ exposure at 16-25 weeks of gestation was associated with the development of childhood asthma,[2] and exposure at 35-40 weeks of gestation was associated with decreased lung function.[20] Mouse models showed significant alterations in alveolar structure and elasticity with prenatal $PM_{2.5}$ exposure.[21] We found that 26 to 28 weeks of gestation may be a critical window for asthma development with PM_{10} exposure in boys with *NRF2 GG* in Korean children. Evaluation of the association between prenatal PM_{10} exposure and bronchial hyperreactivity via provocholine challenge test was not significant (data not shown).

There were reports showing sex difference in the development of asthma with PM exposure. One reported that girls exposed to perinatal period were strongly associated with asthma than boys[14] and several others reported the prenatal particulate exposure was associated with preschool and early school-aged asthma in boys.[2-4,6,22] Males with more vulnerable genetic susceptibility to prenatal oxidant injury may have an exaggerated response to in utero air pollution exposure.[5] Oxidative stress induced by air pollution exposure mediates asthma development and *GSTP1* controls enzymes, glutathione-S-transferase (GST), involved in the detoxification of ROS.[23] Children with *GSTP1* variants can be more susceptible to develop asthma.[20] In this study, the analysis was performed to evaluate the association between *GSTP1* and childhood asthma, but there was no association. In addition, *GSTP1* did not have a modifying effect on the association between prenatal PM_{10} exposure and childhood asthma (data not shown). It is thought that further studies with more subjects should be conducted in the future.

Nrf2 is a major regulator of ARE-mediated cytoprotective protein expression, which indicates that this is an upstream regulator of antioxidant responses which were occurred by detoxifying enzymes such as GST isozymes to maintain cellular redox homeostasis and reduces severe oxidative damage. We, herein, investigated the *NRF2*. Under stressed conditions caused by constant highly oxidative environments, including exposure to air pollutions, the Nrf2-antioxidant pathway is activated to protect cells and tissues from oxidative stress injury.[8] *NRF2* deletion causes high susceptibility for various respiratory diseases, including bronchopulmonary dysplasia, respiratory infections, and asthma.[24,25] The developing fetus is especially prone to oxidative stress, and genetic susceptibility resulting from *NRF2* polymorphism may have a strong impact on lung development with a high level of PM_{10} exposure during the critical window.

The strength of this study is the use of a large general population-based birth cohort that enrolled participants nationwide. Second, allergy specialists evaluated the development of asthma with a well-defined assessment. Third, a new updated analysis method, BDLIM, was used to evaluate the critical windows for PM_{10} exposure and their association with asthma. BDLIM accounts for both the time-varying sensitive window and the within-window effects throughout the pregnancy.[2,10] Using mean PM_{10} over the full gestation period or a selected trimester can result in biased estimates and can identify incorrect critical windows. In contrast, BDLIM, data-driven methods that use temporally resolved exposure data, are generally unbiased. By sharing information across subgroups on the timing of window and the within-window effects, BDLIM provides a more powerful method of detecting windows of vulnerability and transient effects under interaction. Fourth, this is the first study considering an oxidative stress-related gene with a gender difference as a modifying factor on childhood asthma development with PM_{10} exposure

during the critical period. Nrf2 plays a crucial role in the host defense mechanism against oxidative stress, and the enhanced antioxidative capacity of estrogen in females might account for the gender difference. Estrogen-dependent Nrf2 expression may contribute to protection against the development of diseases via oxidative stress in females, which could make the difference in gender.[26,27]

There are some limitations of this study as well. Although a large population was enrolled, the analysis was performed in a small subgroup with gene data due to limited samples, which may lead to selection bias. However, there was no significant differences in gender, bronchiolitis history before 3 years old, exposure to environmental tobacco smoke during pregnancy, parental history of allergic diseases, and household income between total study population and study participants (**Table 2**).

Table 2. Demographic characteristic of total population and study participants in Panel Study of Korean Children

	Total population (N = 1,572)		Study participants (N = 565)	
	N	%	N	%
Gender				
Female	765	48.7	267	47.3
Male	807	51.3	298	52.7
Gestational age				
< 37 weeks	51	3.2	16	2.8
≥ 37 weeks	1,470	93.5	549	97.2
Breast feeding				
Yes	942	59.9	345	61.1
No	585	37.2	220	38.9
Delivery method				
Vaginal delivery	844	53.7	331	58.6
Cesarean section	683	43.4	234	41.4
Bronchiolitis history before 3 years old				
Yes	326	20.7	139	24.6
No	1,242	79.0	426	75.4
Environmental tobacco smoke exposure during pregnancy				
Yes	961	61.1	560	73.2
No	611	38.9	205	26.8
***NRF2* (rs6726395)**				
GG			359	63.8
GA+AA			204	36.2
Age of mother at delivery				
20–29 years old	484	31.7	178	31.5
30–39 years old	1,015	66.5	378	66.9
≥ 40 years old	27	1.8	9	1.6
Parity				
First birth	712	45.3	278	49.2
≥ Second	810	51.5	287	50.8
Maternal education level				
< High school	473	30.1	163	28.8
College	473	30.1	174	30.8
≥ University	622	39.6	228	40.4
Region				
Seoul	218	13.9	77	13.6
Gyeonggi/Incheon	503	32.0	159	28.1
Daejeon/Chungcheong/Gangwon	204	13.0	77	13.6
Daegu/Gyeongbuk	184	11.7	75	13.3
Busan/Ulsan	286	18.2	111	19.6
Gyeongnam/Gwangju/Jeolla	177	11.3	66	11.7
Household income (KW)				
< 1 Million	88	5.6	16	2.8
1-3 Million	559	35.6	216	38.2
3-5 Million	609	38.7	228	40.4
≥ 5 Million	316	20.1	105	18.6
Parental history of allergic diseases				
Yes	979	62.3	391	69.2
No	504	32.1	174	30.8
Averaged prenatal PM_{10} level (μ/m^3), median (SD)	57.70 (8.7)		56.8 (8.7)	

In conclusion, revealing the critical window of PM_{10} exposure on the development of childhood asthma is important for the prevention of asthma. In this study, 26 to 28 weeks of gestation was a critical window of prenatal PM_{10} exposure and this was modified by gender and *NRF2* genotype. For the asthma prevention strategy, identifying susceptible subjects and critical windows to PM_{10} exposure could be helpful to make targeted action plans.

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Conflicts of interest

The authors declare no competing interests pertaining to this article.

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