이학석사 학위논문

임신 중 $PM_{2.5}$ 노출과 산모의 불안이 유아 아토피피부염에 미치는 영향: COCOA study

Effect of prenatal particulate matter 2.5 exposure and maternal anxiety on infantile atopic dermatitis: COCOA study

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이 논문을 이학석사 학위 논문으로 제출함

2021 년 02 월

울 산 대 학 교 대 학 원

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김상록의 이학석사학위 논문을 인준함

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease and mostly occurred in infants. AD in children is increasing not only in the world but also in Korea. Although the cause of AD has not clearly identified, genetic factors and environmental factors are related to the development of AD.

Objective: The aim of this study was to investigate the effect of Particulate Matter 2.5 ($PM_{2.5}$) and prenatal anxiety on AD in infant and identify the critical risk period.

Methods: The present study population was a subset of children recruited COhort for Childhood Origin of Asthma and allergic diseases (COCOA) birth cohort study. This study included 802 children who followed-up at 1 year of age and having all data used in this analysis. $PM_{2.5}$ was estimated by land-use regression models, and prenatal anxiety was measured by questionnaire. AD was diagnosed by pediatric allergy specialists at 1 year. Logistic regression analysis was used to calculate odd ratio (OR) and 95% confidence interval (CI) and Bayesian distributed lag interaction model was used to identify the critical period.

Results: Higher $PM_{2.5}$ exposure during the first trimester of pregnancy (aOR, 1.86; 95% CI, 1.08-3.19;) and higher prenatal maternal anxiety (aOR, 1.58; 95% CI, 1.01-2.47;) was associated with AD at 1 year old. Infants with both higher $PM_{2.5}$ during first trimester of pregnancy and higher maternal anxiety during pregnancy increased AD at 1 year old (aOR,

3.13; 95% CI, 1.56-6.28;). Higher $PM_{2.5}$ exposure during first trimester of pregnancy increased the risk of AD at 1 year old only in boys (aOR, 2.33; 95% CI, 1.10-4.96). In the boys exposed to higher maternal anxiety during pregnancy, exposure to $PM_{2.5}$ at 5 - 8 weeks of pregnancy is the most critical period for the development of 1-year-old AD.

Conclusion: Higher $PM_{2.5}$ exposure and maternal anxiety during pregnancy increased the risk of AD at 1 year. Boys exposed to both higher $PM_{2.5}$ during 5 - 8 weeks of gestation and maternal anxiety during pregnancy had a significantly increased risk for AD at 1 year old. Avoidance of exposure to $PM_{2.5}$ and maternal anxiety during prenatal period, especially in the first trimester, may prevent the development of infantile AD especially in boys.

Key words: particulate matter 2.5, prenatal anxiety, atopic dermatitis, critical period

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Abbreviation

AD: Atopic Dermatitis

aOR: Adjusted Odds Ratio

BDLIM: Bayesian Distributed Lag Interaction Model

CI: Confidence Interval

COCOA: The Cohort for Childhood Origin of Asthma and allergic diseases

LUR: Land Use Regression

$PM_{2.5}$: Particulate Matter 2.5

STAI: State-Trait Anxiety Inventory

Introduction

Atopic dermatitis (AD) is chronic inflammatory skin disease and mostly occurred in infants [1, 2]. AD is chronic disease which incurs many hospital which causes a great medical expense and the prevalence rate in children is and AD in children is increasing not only in the world but also in Korea [3]. When AD prevalence was compared between 2000 and 2010, the lifetime prevalence of itchy eczema in Korean children aged 6-7 years increased from 17.1% to 27.0% [4]. Although the cause of AD has not clearly identified, it is known to be related to genetic factors whereas various environmental factors reported to be related to AD risk.

Several epidemiological studies have reported that various environmental factors influence AD [5]. In particular, exposure to air pollution is reported to be one of the causes of increased AD [6, 7]. Korea is one of the countries with higher concentration of particulate matter 2.5 ($PM_{2.5}$) and exposure to higher $PM_{2.5}$ has been associated with increased AD in Korea [8]. Another study has reported that exposure to PM_{10} during pregnancy increases eczema, but decreases eczema in higher residential green space [9].

Maternal stress has been associated with increased allergic diseases such as AD, allergic rhinitis, Asthma [10]. Exposure to maternal stress affects offspirng`s AD. Maternal experiences of higher anxiety or depression during pregnancy has been reported to be associated with increased AD risk [11, 12]. Some studies have considered major life events that do not occur frequently in everyday life [13, 14]. However, it is necessary to consider maternal depression or anxiety in usual life because the experience of major life events in pregnancy is rare.

Previous studies have reported that not only outdoor air pollution but also indoor $PM_{2.5}$ and maternal diet such as vitamin D influence AD [15, 16]. Indoor $PM_{2.5}$ exposure has been associated with increased AD. Indoor $PM_{2.5}$ exposure is more vulnerable because pregnant women spend most of their time at home in pregnancy [15]. Additionally, previous study resulted that prenatal PM exposure is associated with maternal vitamin D deficiency and lower cord blood (CB) vitamin D levels [17, 18]. Co-exposure of higher indoor $PM_{2.5}$ and lower vitamin D may affect infant`s AD.

Prenatal period is susceptible to the effects of environmental exposure because their immune and organ systems are developing throughout pregnancy [19]. Prenatal PM exposure and

maternal stress induce maternal oxidative stress [20-23]. This oxidative stress is one of the important mechanisms of the pathogenesis of AD [24-26]. Epigenetic modifications mediate the effect of various environmental exposures on allergic diseases [27]. Prenatal PM and maternal stress have also been shown to modulate DNA methylation in placenta or cord blood of newborns [28-31]. Due to theses common mechanisms, synergistic effect of prenatal PM exposure and maternal stress on offspring`s AD may be possible. Several studies have shown the interactive effect of air pollution and prenatal stress on asthma in children [32-34]. However, the combined effect of these exposures on the risk of AD in offspring is not reported. Furthermore, environmental factors may afffect on the development of disease depending on the time exposed to those during fetal development stages. To the best of my knowledgy, there is no report to identify the critical exposure windows of interactive effect of prenatal $PM_{2.5}$ exposure and anxiety in pregnancy on the risk of AD in offsprings [35]. The critical exposure periods for the interactive effect of prenatal PM exposure and maternal stress also have not been examined in relation to offspring's AD.

Air pollutants and psychosocial stress can have sex-specific effects on offspring outcomes. Boys were more vulnerable to the effect of prenatal air pollution exposure on asthma development [32, 33]. Girls with higher perinatal stress had increased risks of AD compared with boys [36]. Prenatal maternal stress increased asthma in boys but no girls. But combined effect of prenatal and postnatal stress on asthma was shown only in girls [37]. The sex-specific effects of prenatal $PM_{2.5}$ and maternal stress exposure during pregnancy on the offspring's AD and their critical exposure periods remain unknown.

The aim of the study was to investigate the combined effect of prenatal $PM_{2.5}$ exposure and maternal anxiety during pregnancy on the risk of AD in infancy. In addition, this study identified the critical period in which a concurrent exposure of these environmental factors may significantly affect on the development of AD in infancy.

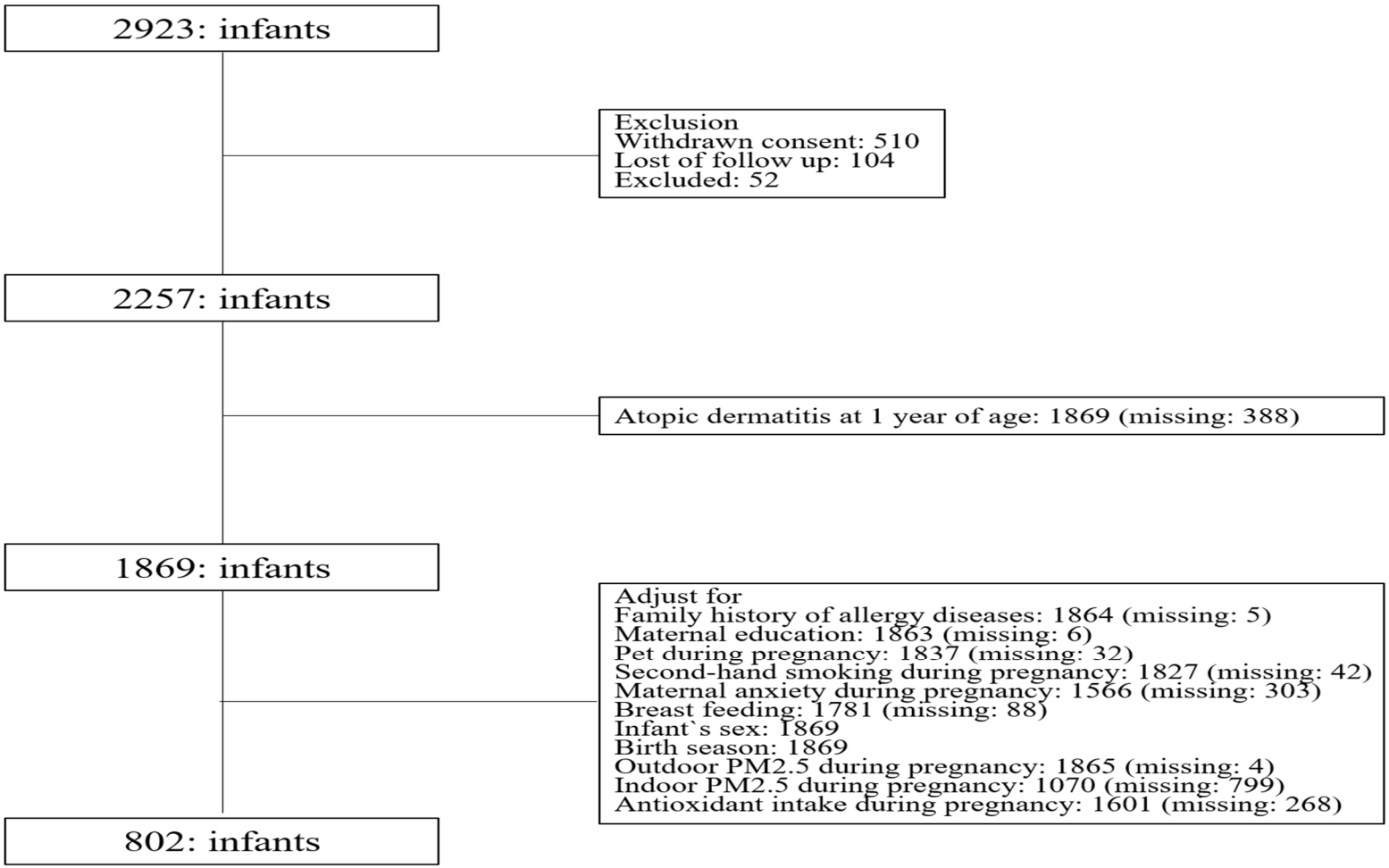
Materials and Methods

Study design and study population

The COCOA (COhort for Childhood Origin of Asthma and allergic diseases) study is a prospective birth cohort and aims to identify various environmental factors for childhood allergic diseases. Children visited the hospital according to a regular schedule to consult pediatric allergy specialists and to receive physical examinations Mother completed the questionnaires of environmental factors, such as maternal secondhand smoking, maternal anxiety, and maternal diet in pregnancy. Children regularly visited to ascertain by pediatric allergy specialist and was examined physical examination. The study has been described in detail elsewhere [38]. Of the 2,923 newborn who were recruited COCOA study, 510 withdrew consent, 52 were excluded because of preterm birth or congenital anomaly and 104 were lost to follow-up. Total 802 infants were included in this study after excluding 388 infants who did not visit the hospital at 1 year of age and did not have enough adjusted variables. Although our study was adjusted for 9 variables, the number of subjects decreased due to the many missing values for indoor $PM_{2.5}$. Therefore, 802 infants were included in this study (Figure 1).

Our present study protocol was approved by the institutional review boards of Asan Medical Center (IRB No. 2008 0616), Samsung Medical Center (IRB No. 2009 02 021), Yonsei University (IRB No. 4 2008 0588), CHA Medical Center (IRB No. 2010 010), and Seoul National University Hospital (IRB No. H 1401 086 550). Written informed consent was obtained from the parents of each child.

Figure 1. Flow chart of the study population



Definition of AD

AD was diagnosed by pediatric allergy specialists according to the basis of the criteria of Hanifin and Rajka at 1 year of age when the infants were followed-up at the hospital [38, 39].

Measurement of outdoor and indoor $PM_{2.5}$ exposure during the pregnancy

We estimated exposure to air pollutants using Land use regression (LUR) models and a regulatory monitoring network and used ambient concentrations of $PM_{2.5}$ measured at the 37 fixed monitoring station in the study area (Seoul) from the Korean Ministry of Environment (http://www.airkorea.or.kr/web). We used centrally and locally available geographic variable 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, CA, 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 the lengths of all roads, traffic intensity on nearest road, total heavy duty traffic loads of all roads, and variables representing spatial trends. The models explained 66-69% of the variability in measured $PM_{2.5}$ levels, and predicted values fitted well with the measured values, as reported in our previous study. The trimester-specific mean concentration of $PM_{2.5}$ was calculated as the mean values of pollutant concentration in each weak during each trimester. Indoor $PM_{2.5}$ levels were measured by specialists during home visit between 26 and 36 weeks of pregnancy. $PM_{2.5}$ levels were measured 3 times in the parent`s bedroom by using a particle discriminator (Model GT-331; SIBATA Co., Japan) with a laser light-scattering optical particle counter for 5 minutes. The mean value of 3 measurements was used for evaluation [15].

Measurement of maternal anxiety during pregnancy

Maternal anxiety was assessed by self-reported questionnaires at 36 weeks during pregnancy, which measures the State-Trait Anxiety Inventory-Trait subscale (STAI-T). STAI-T is a 20-item questionnaire that is scored on a 4-point Likert-type scale that reflects a general tendency to be anxious. The score ranges from 20 to 80, with a higher score

indicating a more severe anxiety level. In this study subjects with scores of greater than the 25th percentile (STAI=46) were identified as being anxious. The Korean version of STAI has previously been shown to exhibit excellent psychometric properties. In terms of internal consistency, it has been reported as having a Cronbach a coefficient of 0.91. In this study the reliability coefficient of STAI was 0.92 [11].

Statistical analysis

The associations between $PM_{2.5}$ exposure during each trimester of pregnancy and AD at 1 year of age were evaluated with logistic regression model. The prenatal period was divided into three trimesters as follows: week 1 to 13 (first), week 14 to 27 (second), and week 28 to 40 (third). $PM_{2.5}$ levels dichotomized to high or low by using the median value and dichotomized value were used in logistic regression analysis. We examined effect modification of the association of AD at 1 year of age with $PM_{2.5}$ levels by stratifying the study population according to maternal anxiety during pregnancy an infant`s sex. The results are expressed as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). BDLIM was implemented to determine the critical windows during the prenatal period for the effects of prenatal $PM_{2.5}$ in relation to AD at 1 year of age and subsequently to examine effect modification by maternal anxiety during pregnancy and infant`s sex. Significant critical windows were identified as weeks during pregnancy with a statistically significant association as previously described [40]. Potential confounder – family history of allergic diseases, maternal education, pet ownership during pregnancy, intake of antioxidants during pregnancy (the sum of daily intakes of antioxidants such as vitamin A, vitamin C, vitamin E, retinol, and carotene), second-hand smoking during pregnancy, indoor $PM_{2.5}$ during pregnancy, birth season, infant`s sex, and breast feeding until 6 months – were adjusted. Analyses were implemented in SAS statistical software (v9.4) and R statistical software (v3.6.1), with a $P < 0.05$ considered statistically significant.

Result

Characteristics of study population

Mean maternal age at delivery was 33 (Standard deviation; 3.58). The majority of mothers had an education over 13 years (95.1%) and most family earned more than 5 million wons (40.2%). More than half of the mothers were exposed to second hand smoking during pregnancy (56.9%) and more than half of infants had family history of allergic disease (55.0%). Average infant`s birth weight was 3,207 g (Standard deviation; 416.2) and gestational age was 39 weeks (Standard deviation; 1.08). The exclusive breast feeding rate was 18%. Most infants were born in winter and a partial rate of them were born in summer. Average indoor $PM_{2.5}$ was 6.35 $\mu g/m^3$ (Standard deviation; 5.307). The characteristics of study participants with and without AD at 1 year were not significantly different except for family history of allergic diseases and infant`s sex.

Table1. Characteristics of study population

		Total (N = 802) (mean ± SD or number (%))	**AD at 1 year of age (+) (n =107) (mean ± SD or number (%))**	**AD at 1 year of age (-) (n=695) (mean ± SD or number (%))**	**P-value**
Sex	Boy	420 (52.4)	66 (61.7)	354 (50.9)	**0.03**
	Girl	382 (47.6)	41 (38.3)	341 (49.1)	
Birth weight (g)		3207.7 ± 416.2	3164.7 ± 373.0	3214.2 ± 422.2	0.29
Antioxidant intakes during pregnancy		37868.6 ± 246048.45	35908.4 ± 121207.17	38170.4 ± 260056.17	0.33
Gestational age (weeks)		39.3 ± 1.08	39.3 ± 1.04	39.3 ± 1.09	0.89
Breast feeding (until 6 months)	No	658 (82.0)	90 (84.1)	568 (81.7)	0.54
	Yes	144 (18.0)	17 (15.9)	127 (18.3)	
Birth season	Spring	208 (25.9)	32 (29.9)	176 (25.3)	0.69
	Summer	171 (21.3)	20 (18.7)	151 (21.7)	
	Fall	179 (22.3)	25 (23.4)	154 (22.2)	
	Winter	244 (30.4)	30 (28.0)	214 (30.8)	

Maternal age at delivery		33.8 ± 3.58	34.3 ± 3.40	33.7 ± 3.60	0.11
Maternal education	High school	39 (4.9)	4 (3.7)	35 (5.0)	0.63
	University	585 (72.9)	76 (71.0)	509 (73.2)	
	Graduate school	178 (22.2)	27 (25.3)	151 (21.8)	
Family income (Korean million won)	< 3	154 (19.3)	20 (18.7)	134 (19.4)	0.14
	3 – 4	172 (21.5)	21 (19.6)	151 (21.8)	
	4 – 5	152 (19.0)	29 (27.1)	123 (17.8)	
	≥ 5	321 (40.2)	37 (34.6)	284 (41.0)	
Second hand smoking during pregnancy	No	346 (43.1)	51 (47.7)	295 (42.5)	0.31
	Yes	456 (56.9)	56 (52.3)	400 (57.5)	
Pet ownership during pregnancy	No	753 (93.9)	104 (97.2)	649 (93.4)	0.12
	Yes	49 (6.1)	3 (2.8)	46 (6.6)	
Family history of allergic disease	No	361 (45.0)	38 (35.5)	323 (46.5)	**0.03**
	Yes	441 (55.0)	69 (64.5)	372 (53.5)	
Indoor $PM_{2.5}$ in 36weeks of gestation (μg/m3)		6.35 ± 5.307	6.36 ± 5.184	6.35 ± 5.329	0.98

Association between prenatal $PM_{2.5}$ exposure, maternal anxiety during pregnancy, and infant`s sex with AD at 1 year of age

There was no significant association between $PM_{2.5}$ exposure during entire trimester of pregnancy and AD at 1 year of age. The association between $PM_{2.5}$ during the first trimester of pregnancy and AD at 1 year of age was significant (aOR, 1.86; 95% CI, 1.08-3.19) (Table 2). There were no significant associations between $PM_{2.5}$ exposure during second and third trimester of pregnancy and AD at 1 year of age (Table 2). AD at 1 year of age was increased in infants exposed to higher maternal anxiety during pregnancy (aOR, 1.58; 95% CI, 1.07-2.47) (Table 3). The risk of AD at 1 year of age increased in boys (aOR, 1.54; 95% CI, 1.01-2.36) (Table 4).

Table 2. Association between prenatal $PM_{2.5}$ exposure and AD at 1 year of age

		AD				
		Yes	No	aOR[a]	95% CI	
					Lower	Upper
Entire pregnancy $PM_{2.5}$	<median	54	347	ref		
	≥median	53	348	0.99	0.64	1.53
First trimester $PM_{2.5}$	<median	46	355	ref		
	≥median	61	340	**1.86**	**1.08**	**3.19**
Second trimester $PM_{2.5}$	<median	56	345	ref		
	≥median	51	350	0.84	0.51	1.41
Third trimester $PM_{2.5}$	<median	60	341	ref		
	≥median	47	354	0.62	0.37	1.04

*AD, atopic dermatitis; PM, particulate matter; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, infant`s sex, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Table 3. Association between maternal anxiety during pregnancy and AD at 1 year of age

		AD				
		Yes	No	aOR[a]	95% CI	
					Lower	Upper
STAI	<46	70	520	ref		
	≥46	37	175	**1.58**	**1.01**	**2.47**

*AD, atopic dermatitis; STAI, the state-trait anxiety inventory; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, infant`s sex, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Table 4. Association between infant`s sex and AD at 1 year of age

Sex	AD				
	Yes	No	aOR[a]	95% CI	
				Lower	Upper
Girl	41	341	ref		
Boy	66	354	**1.54**	**1.01**	**2.36**

*AD, atopic dermatitis; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Combined effect of prenatal $PM_{2.5}$ exposure, maternal anxiety during pregnancy, and infant`s sex on AD at 1 year of age

Infants with both higher $PM_{2.5}$ during first trimester of pregnancy and higher maternal anxiety during pregnancy increased AD at 1 year of age (aOR, 3.13; 95% CI, 1.56-6.28, Interaction P-value, 0.35) (Table 5). Infants with higher $PM_{2.5}$ during first trimester of pregnancy increased the risk of AD at 1 year of age in boys (aOR, 2.70; 95% CI, 1.37-5.32; Interaction P-value, 0.36) (Table 6). Higher maternal anxiety during pregnancy increased AD at 1 year of age compared to lower maternal anxiety during pregnancy in girls and lower maternal anxiety during pregnancy increased AD at 1 year of age compared to higher maternal anxiety during pregnancy in boys (Table 7).

Table 5. Association between prenatal $PM_{2.5}$ exposure and maternal anxiety during pregnancy with AD at 1 year of age

		AD					
					95% CI		
STAI	$PM_{2.5}$	Yes	No	aOR[a]	Lower	Upper	Interaction P-value
Entire pregnancy							
<46	<median	33	263	ref			
<46	≥median	37	257	1.20	0.71	2.02	0.27
≥46	<median	21	84	**2.06**	**1.12**	**3.81**	
≥46	≥median	16	91	1.43	0.73	2.80	
First Trimester							
<46	<median	31	257	ref			
<46	≥median	39	263	1.65	0.89	3.07	0.35
≥46	<median	15	98	1.29	0.66	2.54	
≥46	≥median	22	77	**3.13**	**1.56**	**6.28**	
Second trimester							
<46	<median	39	259	ref			

<46	≥median	31	261	0.76	0.42	1.37	0.410
≥46	<median	17	86	1.30	0.69	2.45	
≥46	≥median	20	89	1.45	0.73	2.87	
Third Trimester							
<46	<median	37	261	ref			
<46	≥median	33	259	0.76	0.42	1.38	0.21
≥46	<median	23	80	**2.05**	**1.13**	**3.71**	
≥46	≥median	14	95	0.88	0.42	1.83	

*AD, atopic dermatitis; PM, particulate matter; STAI, the state-trait anxiety inventory; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, infant`s sex, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Table 6. Association between prenatal $PM_{2.5}$ exposure and infant`s sex with AD at 1 year of age

		AD					
Sex	**$PM_{2.5}$**	**Yes**	**No**	**aOR[a]**	**95% CI**		**Interaction P-value**
					Lower	**Upper**	
Entire pregnancy							
Girl	<median	21	172	ref			0.98
Girl	≥median	20	169	0.97	0.50	1.89	
Boy	<median	33	175	1.52	0.84	2.76	
Boy	≥median	33	179	1.53	0.83	2.80	
First trimester							
Girl	<median	20	174	ref			0.36
Girl	≥median	21	167	1.46	0.70	3.05	
Boy	<median	26	181	1.22	0.65	2.29	
Boy	≥median	40	173	**2.70**	**1.37**	**5.32**	
Second trimester							
Girl	<median	22	175	ref			0.91

Girl	≥median	19	166	0.85	0.14	1.77	
Boy	<median	34	170	1.56	0.87	2.81	
Boy	≥median	32	184	1.31	0.68	2.54	
Third trimester							
Girl	<median	23	172	ref			0.80
Girl	≥median	18	169	0.64	0.31	1.32	
Boy	<median	37	169	1.59	0.90	2.83	
Boy	≥median	29	185	0.97	0.50	1.88	

*AD, atopic dermatitis; PM, particulate matter; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Table 7. Association between maternal anxiety during pregnancy and infant`s sex with AD at 1 year of age.

		AD					
STAI	Sex	Yes	No	aOR[a]	95% CI		Interaction P-value
					Lower	Upper	
<46	Girl	21	260	ref			
<46	Boy	49	260	**2.34**	**1.35**	**4.05**	**0.01**
≥46	Girl	20	81	**3.10**	**1.58**	**6.06**	
≥46	Boy	17	94	**2.24**	**1.12**	**4.48**	

* AD, atopic dermatitis; STAI, the state-trait anxiety inventory; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Association between prenatal $PM_{2.5}$ exposure and maternal anxiety during pregnancy with AD at 1 year of age according to infant`s sex

The risk of AD at 1 year of age increased in boys (aOR, 1.54; 95% CI, 1.01-2.36) (Table 7). Higher maternal anxiety during pregnancy increased AD at 1 year of age in girls (aOR, 3.21; 95% CI, 1.61-6.39), but not in boys (Table 8). Higher exposure of $PM_{2.5}$ during first trimester of pregnancy increased the risk of AD in boy (aOR, 2.33; 95% CI, 1.10-4.96), but not in girls (Table 8). The association between higher $PM_{2.5}$ exposure during first trimester of pregnancy and AD at 1 year of age was significant in boy with higher maternal anxiety (aOR, 5.30; 95% CI, 1.14-24.65) (Table 9).

Table 8. Association between prenatal $PM_{2.5}$ exposure and maternal anxiety during pregnancy with AD at 1 year of age according to infant`s sex

		AD								
		Boy					Girl			
		Yes	No	aOR[a]	95% CI		Yes	No	aOR[a]	95% CI	
					Lower	Upper				Lower	Upper
STAI											
	<46	49	260	ref			21	260	ref		
	≥46	17	94	0.92	0.49	1.71	20	81	**3.21**	**1.61**	**6.39**
$PM_{2.5}$											
Entire pregnancy	<median	33	175	ref			21	172	ref		
	≥median	33	179	0.98	0.55	1.73	20	169	0.96	0.48	1.92
First trimester	<median	26	181	ref			20	174	ref		
	≥median	40	173	**2.33**	**1.10**	**4.96**	21	167	1.48	0.66	3.31
Second trimester	<median	34	170	ref			22	175	ref		
	≥median	32	184	0.83	0.44	1.58	19	166	0.80	0.34	1.91
Third trimester	<median	37	169	ref			23	172	ref		
	≥median	29	185	0.62	0.31	1.23	18	169	0.63	0.28	1.38

*AD, atopic dermatitis; PM, particulate matter; STAI, the state-trait anxiety inventory; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Table 9. Association between prenatal $PM_{2.5}$ exposure and AD according to infant`s sex and maternal anxiety during pregnancy

		AD																			
		Boy and STAI (≥46)					Boy and STAI (<46)					Girl and STAI (≥46)					Girl and STAI (<46)				
		Yes	No	aOR[a]	95% CI		Yes	No	aOR[a]	95% CI		Yes	No	aOR[a]	95% CI		Yes	No	aOR[a]	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper				Lower	Upper
Entire pregnancy $PM_{2.5}$	<median	9	40	ref			24	135	ref			12	44	ref			9	128	ref		
	≥median	8	54	0.66	0.21	2.04	25	125	1.12	0.57	2.19	8	37	0.67	0.21	2.12	12	132	1.65	0.63	4.29
First trimester $PM_{2.5}$	<median	5	55	ref			21	126	ref			10	43	ref			10	131	ref		
	≥median	12	39	**5.30**	**1.14**	**24.65**	28	134	1.82	0.73	4.55	10	38	2.07	0.57	7.44	11	129	1.35	0.43	4.24
Second trimester $PM_{2.5}$	<median	9	41	ref			25	129	ref			8	45	ref			14	130	ref		
	≥median	8	53	1.09	0.32	3.71	24	131	0.81	0.38	1.74	12	36	1.71	0.38	7.62	7	130	0.57	0.16	1.98
Third trimester $PM_{2.5}$	<median	12	36	ref			25	133	ref			11	44	ref			12	128	ref		
	≥median	5	58	**0.08**	**0.01**	**0.53**	24	127	0.95	0.44	2.06	9	37	0.79	0.23	2.71	9	132	0.61	0.20	1.86

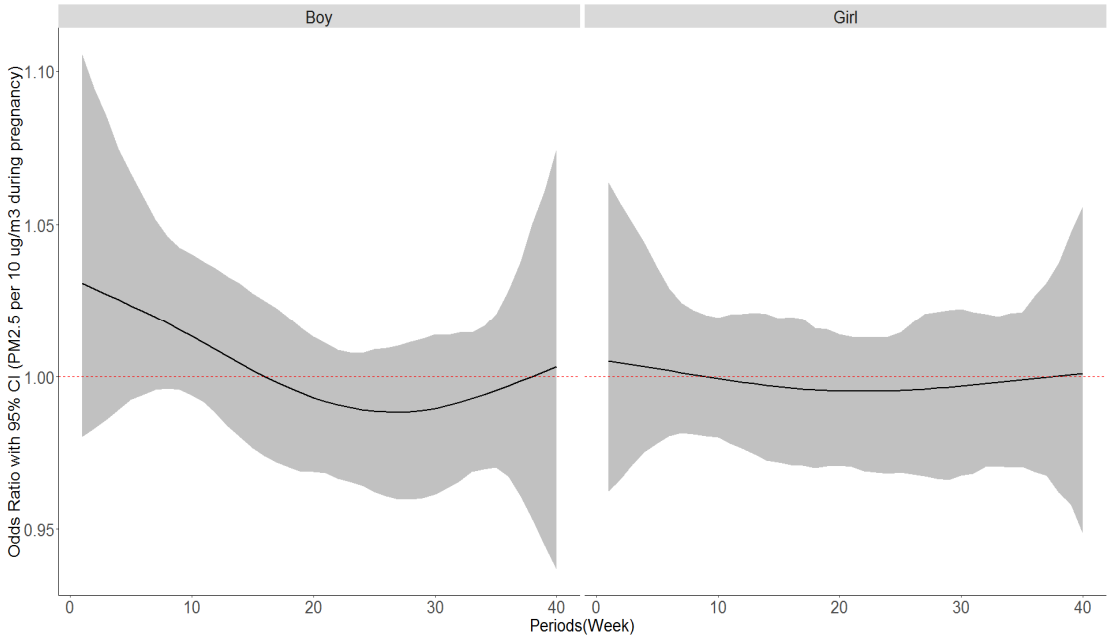
*AD, atopic dermatitis; PM, particulate matter; STAI, the state-trait anxiety inventory; aOR, adjusted odds ratio; 95% CI, 95% confidence interval

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Critical periods of prenatal $PM_{2.5}$ exposure on AD 1 year of age according to infant`s sex and maternal anxiety during pregnancy

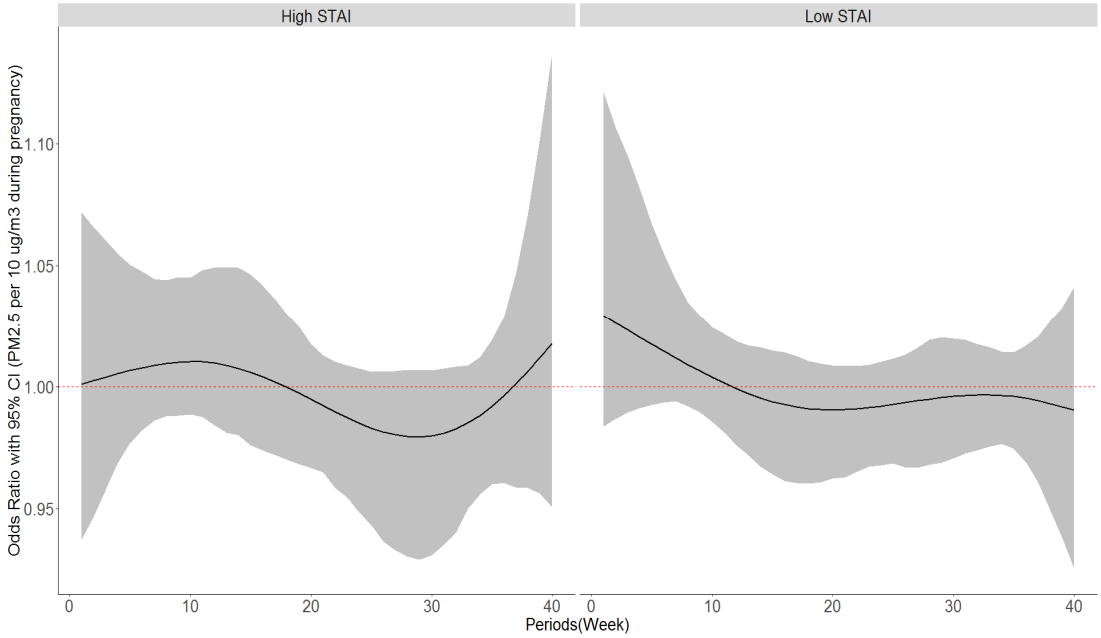
There were no critical $PM_{2.5}$ exposure periods for AD at 1 year of age in both boys and girls (Figure 2). Critical $PM_{2.5}$ exposure periods for AD at 1 year of age were not identified in infants with both higher and lower maternal anxiety during pregnancy (Figure 3). However, when examining the modification effect according to sex and prenatal maternal anxiety, during 5 - 8 weeks of gestation was significant critical periods of $PM_{2.5}$ exposure during pregnancy on AD at 1 year of age in boys with higher maternal anxiety during pregnancy (Figure 4).

Figure 2. Association between prenatal $PM_{2.5}$ exposure and AD at 1 year of age accoridng to infant`s sex



[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

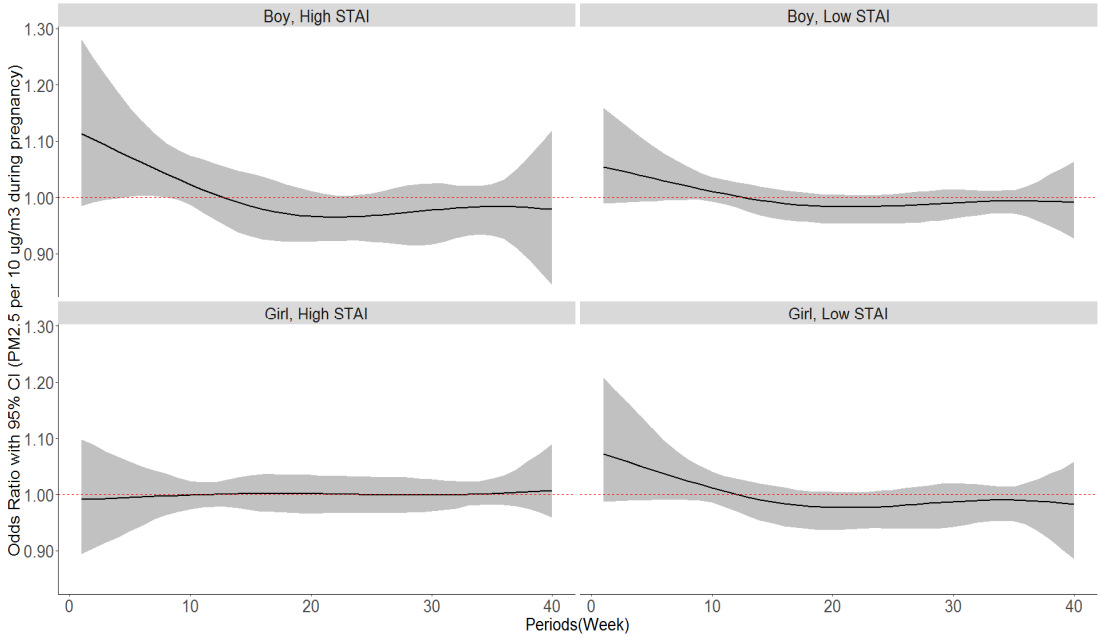
Figure 3. Association between prenatal $PM_{2.5}$ exposure and AD at 1 year of age according to maternal anxiety during pregnancy



* STAI, the state-trait anxiety inventory

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, infant`s sex, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Figure 4. Association between prenatal $PM_{2.5}$ exposure and AD at 1 year of age according to infant`s sex and maternal anxiety during pregnancy



* STAI, the state-trait anxiety inventory

[a]Adjusted for family history of allergy diseases, maternal education, pet ownership during pregnancy, antioxidant intake during pregnancy, second-hand smoking during pregnancy, birth season, breast feeding, and indoor $PM_{2.5}$ exposure at any time in 26 ~ 36 weeks

Discussion

We evaluated the effect of prenatal $PM_{2.5}$ exposures and maternal anxiety on AD at 1 year of age. We found independent effect of $PM_{2.5}$ exposures during the first trimester of pregnancy and maternal anxiety during pregnancy on the risk of AD at 1 year of age. And infants who were concurrently exposed to higher $PM_{2.5}$ during the first trimester of pregnancy and higher maternal anxiety during pregnancy increased the risk of AD at 1 year of age. Boys were more vulnerable to co-exposure to $PM_{2.5}$ and maternal anxiety than girls. $PM_{2.5}$ exposure during 5 - 8 weeks of gestation was associated with AD in boys with higher maternal anxiety during pregnancy. These results suggest that the development of AD may be affected from the exposure of $PM_{2.5}$ during first trimester of pregnancy. Avoidance of $PM_{2.5}$ exposure and maternal anxiety during the first trimester of pregnancy should be critical to prevent AD development.

Exposure to ambient air pollution during the prenatal period associated with childhood AD. Higher NO_2 exposure during the first trimester increased the risk of eczema in children aged 3-6 years in a prospective cohort study in China [41]. PM_{10} and CO exposure during the first trimester of pregnancy also increased the risk of AD in 6 month old children [9, 42]. In addition to ambient air pollution, prenatal maternal stress associated with AD in the offsprings. $PM_{2.5}$ exposure during the first trimester of pregnancy may be affected AD at 1 year.

Previous COCOA study showed that both prenatal maternal depression and anxiety increased predicted probability of AD [11]. Recent systematic review also showed that prenatal maternal stress was associated with increased risk of AD in the offsprings [10]. Previous studies showed that maternal anxiety during pregnancy was associated with AD, especially in the second and third trimesters.

Our previous COCOA study resulted that indoor $PM_{2.5}$/ETS exposure and vitamin D deficiency is associated with infant`s AD [15, 16]. Pregnant women who spend most of their time at home might be affected by indoor $PM_{2.5}$ which was associated with lower maternal plasma and CB vitamin D [15, 17, 18]. Other study resulted that higher vitamin D was associated with adverse effects of indoor air pollution among obese children with asthma [43].

Therefore, pregnant women were more vulnerable to co-exposure of higher indoor $PM_{2.5}$ and lower vitamin D.

Maternal exposure to $PM_{2.5}$ and psychosocial stress during pregnancy is positively associated with oxidative stress [20, 22, 44]. Oxidative stress may play role in the pathogenesis of offspring`s AD. Increased oxidative stress during pregnancy may affect fetal development and growth [20, 21]. Oxidative stress could also modulate T-cell polarization toward a T helper 2 (Th2) cellular subset and alter the release of cytokines. Furthermore, oxidative stress can alter the physiologic functioning of the hypothalamic–pituitary–adrenal axis and induce damage in keratinocytes [25].

Oxidative stress can be affected different effects according to specific sex. The levels of oxidative stress markers are higher, and the makers related to antioxidant capacity are lower in boys compared to girls during the neonatal period [45]. Sex differences in oxidative stress may make boys more susceptible to the effects of prenatal $PM_{2.5}$ and maternal anxiety during pregnancy.

Epigenetic mechanisms could explain the effect of prenatal environmental factors on disease development in offsprings [27]. Prenatal exposure to $PM_{2.5}$ influence placental adaptation by DNA methylation [28]. Maternal distress during pregnancy can also alter DNA methylation patterns that is associated with increases allergy risk in newborns [31, 46].

Prenatal air pollution exposure and prenatal maternal stress may affect DNA methylation by sex, but results are inconsistent and vulnerable sex has not yet been identified [45, 47, 48]. Further study is needed to evaluate sex- specific epigenetic changes and whether these epigenetic changes are related to later differences in disease development among boys and girls.

As both prenatal air pollution and maternal stress may have common oxidative and epigenetic mechanistic pathways, it is plausible that co-exposures of air pollution and maternal stress could have effects on AD in the offspring. Previous studies showed that higher prenatal stress modifies the impact of ambient pollutants on asthma in children [32-34]. However, no study has examined the interaction between prenatal $PM_{2.5}$ exposures and maternal stress in relation to childhood AD development. Furthermore, prenatal $PM_{2.5}$ exposure and maternal stress showed sex specific effect on the outcome of offspring. Boys

are more vulnerable to the effects of prenatal air pollution and stress exposure [11, 49]. Whether sex-specific effect exists for the effects of prenatal $PM_{2.5}$ exposure and maternal stress on AD in offspring remains unknown. In our study, co-exposure to $PM_{2.5}$ during 5-8 weeks of gestation and higher maternal anxiety during pregnancy increased AD in 1 year of age in boys, not in girls. Our results suggest that combined effect of prenatal $PM_{2.5}$ and prenatal maternal anxiety on offspring's AD and boys are more vulnerable to the effect of exposure to air pollution and stress during pregnancy on offspring's AD.

Our finding that first trimester of pregnancy is critical periods of $PM_{2.5}$ exposure for AD at 1 year of age is consistent with our previous studies [50, 51]. The development of antioxidant enzyme systems begins during mid to late gestational periods and continue to mature through to early postnatal years [52]. Thus, before these enzyme systems are established, early pregnancy is more susceptible to oxidative stress produced by $PM_{2.5}$ and stress exposure. $PM_{2.5}$ and PM_{10} exposure could have a significant impact on placental DNA methylation patterns from the first trimester of pregnancy [28, 29, 53]. Alterations of DNA methylation in placenta influence placental development. As the placental function is important in fetal programming, placental DNA methylation is associated with abnormal fetal development [54]. Especially, the fetal skin structure develops rapidly during the first trimester of pregnancy [9]. Therefore, the first trimester of pregnancy is a critical period for the effects of $PM_{2.5}$ exposure to AD.

Our study has several strengths. First, our study is prospective birth cohort. We can generalize our results with general population. In our study, AD was investigated by pediatric allergists, and more valid measures of maternal prenatal distress was collected by pediatric psychiatrist and developmental psychologist. Secondly, we adjusted the data for not only common confounding factors but also indoor $PM_{2.5}$ and antioxidant intake during pregnancy. Several factors such as sex, other environmental factors, dietary factors, and psychological stress can interact with air pollutants to enhance or mitigate adverse effects [19]. In stratification analysis by sex and maternal anxiety, we evaluated modifying effect of sex and maternal anxiety for prenatal $PM_{2.5}$ induced AD at 1 year of age. Pregnant women tend to spend more time indoors than outdoors, so we adjusted second-hand smoke and indoor $PM_{2.5}$ during pregnancy. Antioxidant intake during pregnancy was also adjusted because the role of diet and antioxidants was presented in mitigating the effects of air pollution [55]. Therefore, we could more accurately identify the effect of prenatal $PM_{2.5}$ exposure and its critical

periods on offspring's AD. Thirdly, we used valid self-reported questionnaires that is suitable measure of usual distress during pregnancy than major life events that occur rarely. Finally, this is the first study to consider the sex-specific effects of co-occurring $PM_{2.5}$ and maternal anxiety exposures on infant`s AD risk.

Our study has several limitations. First, we used exposure modeling to estimate the concentrations of $PM_{2.5}$, which is widely used in epidemiologic studies to estimate exposure levels [9, 33, 34, 49, 51]. Some misclassification of $PM_{2.5}$ exposures is possible with this system but it is not feasible to use individual and continuous direct pollutant monitoring in a large general population. So far we have not collected individually direct exposure, but we are currently collecting direct exposure for children. Secondly, prenatal maternal anxiety was collected by questionnaire, structured-interviews were not conduct and we don`t have stress related biomarker such as cortisol. Prenatal maternal anxiety was measured from 26 weeks to 36 weeks of pregnancy. Gestation and may not reflect the entire duration of pregnancy. Thirdly, we didn`t adjusted for other air pollution. Previous studies have shown that not only PM but also other air pollution such as NO_2 affect AD. Fourth, we adjusted for indoor $PM_{2.5}$, but many subjects were excluded. So this study may occur selection bias.

Our present findings demonstrated that $PM_{2.5}$ exposure during the first trimester of pregnancy and maternal anxiety during pregnancy increased the risk of AD at 1 year of age. Boys born to mothers exposed to both increased $PM_{2.5}$ during 5 - 8 weeks of gestation and anxiety during pregnancy were at elevated risk for AD at 1 year of age. Avoidance of exposure to $PM_{2.5}$ and maternal anxiety during prenatal period, especially in the first trimester, may prevent the development of infantile AD.

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국문요약

배경: 아토피피부염은 만성 염증 피부 질환으로 주로 유아에게서 발생한다. 유아 아토피피부염은 의료 비용 지출 부담을 증가시키고 전 세계 유병률뿐만 아니라 국내 유병률 또한 증가하는 추세이다. 아토피피부염의 원인은 명확하지 않지만 유전적 요인과 관련이 있는 것으로 알려져 있으며 다양한 환경적 요인과 관련되어 있다고 보고되었다.

목적: 본 연구의 목적은 임신 중 산모의 $PM_{2.5}$ 노출과 산모의 불안이 유아 아토피피부염에 미치는 상호작용을 평가하고 임신 기간 중 질병 위험에 가장 분명한 영향력을 발휘하는 중요한 시기를 찾고자 한다.

방법: 소아 호흡기 알레르기질환 장기추적 코호트 (COCOA)에 등록된 영유아 중 연구 조건을 만족하는 총 802명의 영유아가 본 연구에 포함되었다. $PM_{2.5}$ 노출은 Land-use regression model을 이용하여 추정하였고, 산전 불안은 설문지를 이용하여 수집하였다. 1세 아토피피부염은 소아 알레르기 전문의에 의해 진단되었다. Logistic regression을 사용하여 오즈비와 95% 신뢰구간을 확인하였고 Bayesian distributed lag interaction model을 사용하여 중요한 시기를 확인하였다.

결과: 임신 첫 삼 분기 동안의 $PM_{2.5}$ 노출과 산모의 불안이 1세 유아 아토피피부염과 관련이 있었다 (각각, aOR, 1.86; 95% CI, 1.08-3.19; aOR, 1.58; 95% CI, 1.01-2.47). 첫 삼 분기 동안의 높은 $PM_{2.5}$ 노출과 임신중 높은 산모 불안이 1세 유아 아토피피부염과 관련이 있었다 (aOR, 3.13; 95% CI, 1.56-6.28). 첫 삼 분기 동안의 높은 $PM_{2.5}$ 노출이 1세 남자아이의 아토피피부염을 증가시켰다 (aOR, 2.33; 95% CI, 1.10-4.96). 산모의 높은 불안에 노출된 남자아이에게는 임신 5 – 8주 동안의 높은 $PM_{2.5}$ 노출이 1세 유아 아토피피부염 발병에 가장 중요한 시기였다.

결론: 임신 동안의 높은 $PM_{2.5}$ 노출과 산모의 불안은 1세 유아 아토피피부염 위험을 증가시켰다. 산모의 높은 불안에 노출된 남자아이는 임신 5 – 8 주 동안에 높은 $PM_{2.5}$ 노출이 될 경우 1세 유아 아토피피부염 위험을 증가시켰다. 이상의 결과로 미루어, 임신 초기에 산모의 $PM_{2.5}$ 노출을 줄이고 임신중 산모의

불안을 낮추면 유아 아토피피부염의 발병을 예방할 가능성이 있음을 시사한다.
중심 단어: 임신, $PM_{2.5}$, 불안, 아토피피부염, Bayesian distributed lag interaction model, 유아