The effect of prenatal maternal trait anxiety on atopic dermatitis and immunoglobulin E level: a prospective cohort study

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The effect of prenatal maternal trait anxiety on atopic dermatitis and immunoglobulin E level: a prospective cohort study

Directed by Professor Se-Joo Kim

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ABSTRACT

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Atopic dermatitis is an inflammatory, relapsing and pruritic skin disorder and is increasing in prevalence especially in highly-developed countries. Recently, maternal distress during pregnancy is hypothesized as one of risk factors of allergic diseases. However, previous studies exhibit limitations such as outcome ascertained by maternal reports and lack of data on potential confounding factors. Moreover, the mechanism underlying the association between prenatal maternal distress and atopic dermatitis has not been investigated. The present study aimed to elucidate the effect of prenatal maternal state anxiety on the occurrence of atopic dermatitis and serum immunoglobulin E level after adjusting for postnatal depression and anxiety, and examine whether this effect was modified by nuclear factor-like 2 (*Nrf2*) gene polymorphisms. From August 2007 to November 2013, 1063 pregnant women were recruited for the study. Prenatal state anxiety levels were self-reported at 36th week of pregnancy using State-Trait Anxiety Inventory. At the time of analysis, the age of offspring ranged from 0 to 6 year-old. Atopic dermatitis was ascertained by physician diagnosis and mother's report at 6 months, 1, 2, 3, and 4 year of age. IgE level was measured from cord

blood and serum at 1st and 3rd year of age. Polymorphism in *Nrf2* (rs6726395) was genotyped by using the TaqMan assay. Cox proportional hazards model and generalized estimating equations were conducted adjusting for potential confounders, including demographic variables and postnatal depression and anxiety. Atopic dermatitis was present in 28.0% of offspring during the first year, and 16.4% at 3rd year of age. Offspring of anxious mothers were more likely to have atopic dermatitis (physician's diagnosis: HR 1.38, 95% CI 1.04-1.85; mother's report: HR 1.56, 95% CI 1.20-2.03), and the association between prenatal maternal anxiety and atopic dermatitis was significant after adjusting for postnatal depression. Offspring of anxious mothers were more likely to have elevated serum immunoglobulin E level (OR 1.46, 95% CI 1.06, 2.02). When stratified for *Nrf2* polymorphism and prenatal anxiety, offspring with *Nrf2* GG polymorphism and anxious mother showed higher risk of having atopic dermatitis level (HR 2.43, 95% CI 1.24-4.77, interaction p-value = 0.019). Prenatal maternal state anxiety were associated with atopic dermatitis and elevated immunoglobulin E level in offspring, and this effect was modified by *Nrf2* polymorphism. These findings suggest that mechanism may be mediated by reactive oxidative stress pathway. Interventions to reduce maternal anxiety during pregnancy may be helpful in preventing atopic dermatitis during infancy especially in genetically susceptible infants.

Key words: prenatal depression, prenatal anxiety, atopic dermatitis, immunoglobulin E, *Nrf*2 polymorphism

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I. INTRODUCTION

Atopic dermatitis (AD) is a type of eczema, an inflammatory, relapsing, non-contagious and pruritic skin disorder. The prevalence of atopic dermatitis has continued to escalate worldwide in the past four decades, especially in highly developed countries.[1] Pediatric allergic diseases are particularly important for society due to their chronic course and high healthcare costs.[2] Thus, efforts to reveal the etiological factors of atopic dermatitis have gained attention through recent years.

Depressive symptoms during pregnancy are common. A meta-analysis estimated that 12.0% of women in their third trimester exhibit clinically significant depressive symptoms,[3] and other study reported that 18% of women exhibit depressive symptoms prenatally.[4] Recent Korean data indicate that the prevalence of prenatal depression is as high as 20.2%.[5]

Recently, maternal prenatal distress has been hypothesized as one of the

risk factors of allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis. In one retrospective cohort study, the children of mothers who had experienced stressful life events during pregnancy were at increased risk for wheezing, asthma, allergic rhinitis, and atopic dermatitis.[6] In another cohort study, maternal psychological stress during pregnancy was significantly associated with atopic dermatitis.[7] Given the high prevalence of prenatal maternal distress[8] and heavy medical burden of atopic dermatitis[9], investigation of the association between prenatal maternal distress and atopic dermatitis in offspring, and its possible underlying mechanisms, warrants attention.

An association between inflammation and depression is gradually gaining interest over the past two decades.[10] For instance, inflammation markers are elevated in patients with depression,[11, 12] and the risk of depression increases with cytokine treatment.[13] Also, a series of studies have observed the co-occurrence of depression and inflammatory diseases.[14] ROS has also been posited as one of major mechanisms in inflammation. ROS play a key role in enhancing the inflammation through the activation of NF-kappa B and AP-1 transcription factors, and nuclear histone acetylation and deacetylation in various inflammatory diseases.[15] A growing body of evidence has suggested that reactive oxygen species (ROS) may play an important role in the pathophysiology of depression and anxiety. [16, 17] ROS are free radicals or reactive anions/ molecules containing oxygen atoms, such as hydroxyl radical, superoxide, hydrogen peroxide and peroxynitrite. ROS can cause cell damage

by enzyme inactivation, lipid peroxidation and DNA modification.[18] Oxidative stress has also been hypothesized as one of pathways in which stress and depression results in health effects. In one animal study, repeated stress promoted depressive behavior through the up-regulation of NADPH oxidase and the resultant metabolic oxidative stress.[19] In another animal study, antioxidants such as ascorbic acid was found to reverse chronic stress induced depressive-like behavior and oxidative damage.[20]

Transcription factor *Nrf2*, which is known to regulate the inducible expression of a group of detoxication enzymes, such as glutathione S-tranferase and NAD(P)H:quinone oxidoreductase, via antioxidant response elements,[21, 22] was found to coordinately regulate a group of oxidative stress-inducible genes in macrophages.[23] The cytoplasmic protein Keap1, which interacts with *Nrf2*, represses its function. The *Nrf2*-Keap1 system is now accepted as one of the key cellular defense mechanisms against oxidative and xenobiotic stresses. Also, *Nrf2*-Keap1 systems may contribute to protection against various pathogenesis, such as carcinogenesis, liver toxicity, respiratory distress and inflammation.[21] Thus, *Nrf2* gene polymorphism may be associated in the relationship between prenatal maternal distress and atopic dermatitis.

Studies of the influence of prenatal maternal distress on AD are scarce. In addition, results of studies of prenatal maternal distress and offspring health outcomes are complicated by potential confounding factors, including postnatal depression and anxiety.[24] Postnatal maternal stress may impact early

childhood environment and caregiving experience, which may in turn influence the occurrence and persistence of allergic diseases in children through change in the development of stress reactivity.[25] Since prenatal and postnatal distress are known to show high correlation,[26, 27] postnatal distress need to be adjusted in order to clarify the association between prenatal maternal distress and offspring's outcomes. Also, allergic diseases were assessed by mother's report in most extant studies, which may be affected by maternal psychological status.[28] Moreover, there are yet no data on Asian population and studies on gene-environment interactions are lacking.

In this study, we aim to examine the relation between prenatal maternal trait anxiety and AD and immunoglobulin E (IgE) level in a large sample of term infants in Korea. We also examined whether the association between prenatal maternal trait anxiety and AD and IgE level was modified by *Nrf2* gene polymorphism.

II. MATERIALS AND METHODS

1. Study participants

Data used were collected as a part of the Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study, a prospective study that aims to examine the early risk factors for childhood allergic diseases.[29-31] Women in the third trimester of pregnancy were recruited from four tertiary hospitals and eight public health centers for prenatal care located in Seoul, Korea. The recruitment took place between August 2007 and November 2013. Eligibility criteria of pregnant women included all of the followings: (1) No high-risk conditions that might have effect on the development of allergic diseases, like diabetes, preeclampsia, anemia, and severe infections, (2) plan to deliver at an affiliated medical center, and (3) residents in Seoul city. The eligibility of the baby was determined by collaborating obstetricians and pediatricians soon after delivery. Inclusion criteria of baby at birth are as follows: (1) a gestational age of ≥ 37 weeks, (2) no exclusion criteria such as major congenital anomalies or birth asphyxia.

Of 1932 women recruited, 185 who haven't given birth yet were excluded from the analysis. Among the remaining 1747 women, 274 withdrew consent and 34 were excluded due to preterm birth or congenital anomaly. Finally, 195 women with missing data on atopic dermatitis, 166 women with

missing data on prenatal trait anxiety and 15 with missing data on demographic variables were excluded, leaving 1063 mother-baby pair to be analyzed.

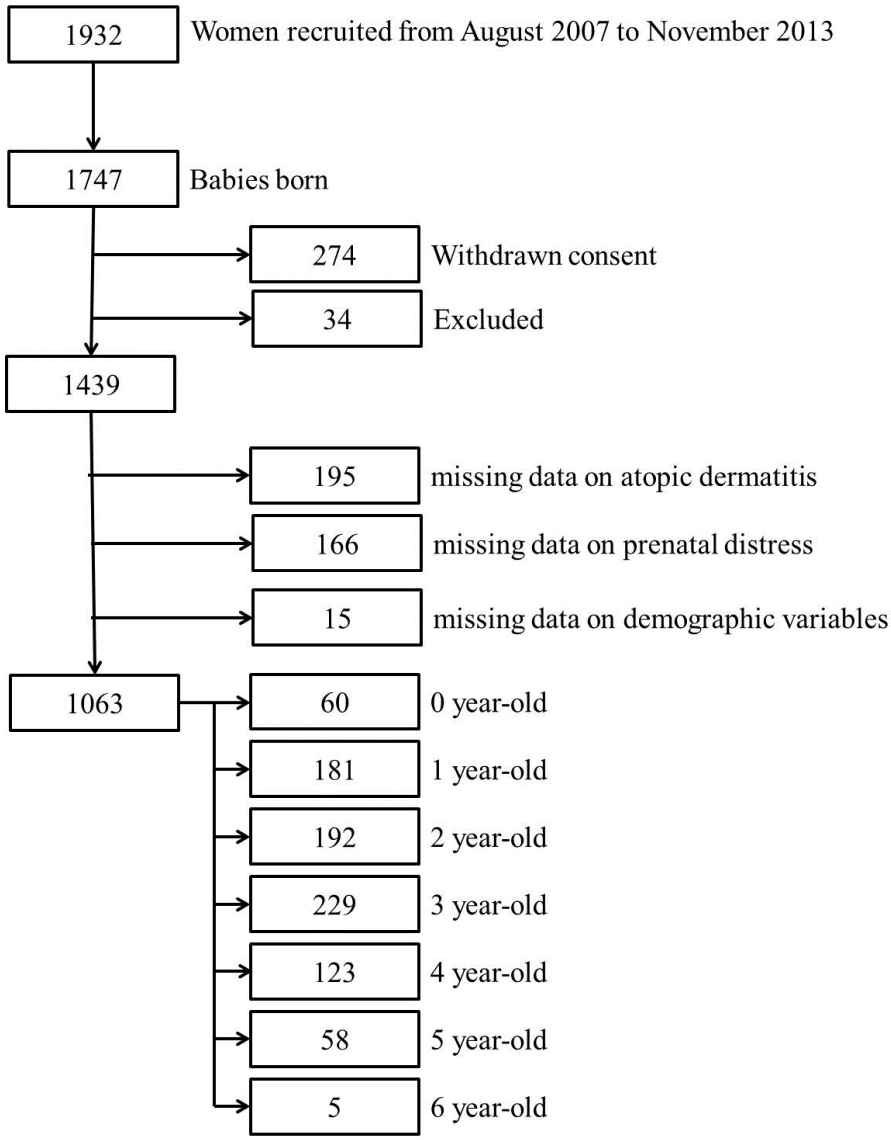

Figure 1. Flow chart of study participants.

2. Prenatal maternal trait anxiety measures

Prenatal maternal state anxiety level was evaluated by self-reported questionnaires at 36th weeks of pregnancy. State-Trait Anxiety Inventory - Trait subscale (STAI-T) was used to measure maternal state anxiety. Prenatal anxiety scores was examined as exposure variables, while postnatal depression and anxiety scores were used as potential confounders included in the multivariable analysis.

Data on prenatal anxiety were obtained by using STAI.[32] STAI consists of two subscales; State Anxiety (anxiety about an event) and Trait Anxiety (anxiety levels as a personal characteristic). Among the two subscales, Trait Anxiety subscale was used in this study, since it reflects the baseline anxiety levels of the subjects rather than a transient state. STAI-T is a 20 item questionnaire scored on a four-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. Women with STAI scores higher than median were identified as anxious. Median was used as an cut-off in this study. The Korean version of STAI has previously been shown to exhibit excellent psychometric properties and its internal consistency has been reported as having a Cronbach's alpha coefficient of 0.91.[33, 34] In this study, the reliability coefficient of STAI-T was 0.92.

3. Ascertainment of atopic dermatitis

Atopic dermatitis was ascertained by two methods at specified time points - at 6 months, 1, 2, 3, and 4 year of age. First, mothers of the offspring reported whether the baby exhibited an eczema-like symptoms suggesting atopic dermatitis. Second, atopic dermatitis was clinically diagnosed by pediatric allergy specialists using the criteria of Hanifin and Rajka. [35] At each visit, a physical examination was conducted including standard scoring for sings of eczema using the Scoring Atopic Dermatitis (SCORAD) assessment[36] in children with atopic dermatitis.

4. Blood sampling and immunoglobulin E

Blood sampling of the baby was done at birth (cord blood), 1st year, and 3rd year of age. Regarding cord blood, collaborating obstetrician was directly involved in delivery and collected the cord blood at birth following standard protocol. Samples of cord blood were obtained immediately after birth by needle aspiration from the placental end of the umbilical vein, and were collected into blood bag with CPDA1 anticoagulant, and COCOA coordinator transported them to the laboratory at main center. It is kept at room temperature pending processing within 24 hours of collection, and mononuclear cells of those are isolated by using method of density gradient

separation.

Total serum IgE concentration was measured by using a fluorescent enzyme immunoassay (AutoCAP System; Pharmacia Diagnostics AB, Uppsala, Sweden). IgE level was considered elevated if serum IgE level ≥ median. IgE level values were log-transformed for all analyses.

5. DNA isolation and genotyping of *Nrf2* gene

Genomic DNA from cord blood of the offspring was used to genotype polymorphism. The genomic DNA was extracted from the buffy coat of the cord blood using the Gentra® Puregene® Blood kit (Qiagen, Maryland, USA) as recommended by the manufacturer. The genotyping was conducted using a TaqMan assay (ABI, Foster city, CA, USA) and the assay IDs was C_155538_10 for *Nrf2* (rs6726395). Briefly, the final volume of the polymerase chain reaction was 5μL TaqMan Universal PCR Master Mix, and 0.13 μL of 40X Assay Mix. Duplicate samples and negative controls were included to ensure accuracy of genotyping.

6. Statistical analysis

Chi-square test, and univariate logistic regression analysis were performed to analyze demographic characteristics of the study participants. Participants

who withdrew their consent did not show statistical difference in demographic distribution when compared to those included in the analyses. (Supplementary Table 1)

Cox proportional hazards model was used to evaluate the association between prenatal maternal depression and anxiety and AD. Four models were used to fully examine the association: Unadjusted, Model 1: adjusted for maternal age, maternal educational level,[37] delivery method,[38] birth season,[39] parental history of allergic diseases, and child's sex, Model 2: Model 1 + postnatal depression, and Model 3: Model 1 + postnatal anxiety.

For postnatal anxiety, STAI-T was used. To assess postnatal depression level, Center for Epidemiological Studies-Depression 10 (CESD-10) was used.[40] CESD-10 is a modified version of the original 20 item full-length CESD. The CESD has been validated for use during pregnancy.[41] The score ranges from 0 to 30, with higher scores indicating more severe depressive symptoms. Consistent with previous studies, a cut-off of 10 was used to identify women with depression.[42] The internal consistency of CESD-10 in this study indicated excellent reliability (ICC = 0.785).

Generalized estimating equations model was used to evaluate the association between prenatal maternal trait anxiety and elevated serum IgE level. Four models were used to fully examine the association: Unadjusted, Model 1: adjusted for maternal age, maternal educational level,[37] delivery method,[38] birth season,[39] parental history of allergic diseases, and child's sex,

Model 2: Model 1 + postnatal depression, and Model 3: Model 1 + postnatal anxiety.

Gene-environment interaction was also examined using cox proportional hazards model including the interaction-term. To analyze the combined effect of the two factors, trait anxiety scores were divided into two levels and genetic polymorphism of *Nrf2* gene was classified to subjects with major/major (GG) allele and the rest (GA + AA).

Statistical analyses were performed on SAS version 9.3 (SAS Institute, Cary, NC). Significance was set at p-value less than 0.05.

III. RESULTS

1. Study participants

Table 1 summarized the demographic distribution of the total sample. Among 1060 mother-baby pairs included in the analysis, about half were under 32 years old (55.8%) and majority had education beyond high school (93.6%). One-fourth of the mothers underwent Caesarean section (25.8%). Of the babies born, 50.4% had at least on parent with diagnosed allergic diseases (including asthma, allergic rhinitis, atopic dermatitis or food allergy). The babies were born evenly among four seasons (spring 24.3%; summer 22.6%; autumn 24.6%; and winter 28.6%) and there were slightly more boys than girls (52.3% vs. 47.7%) (Table 1)

When the distribution of demographic variables were compared among babies with and without atopic dermatitis, boys were more likely to have atopic dermatitis compared to girls (OR 1.46, 95% CI 1.11, 1.92). Similarly, babies with parental history of allergic diseases were more likely to suffer from atopic dermatitis (OR 1.35, 95% CI 1.03, 1.78). Maternal age, maternal educational level, delivery methods, birth seasons, or *Nrf2* gene polymorphisms were not associated with development of atopic dermatitis in the offspring. (Table 2)

Table 1. Demographic characteristics of 1063 study participants

Characteristics	N (%)
Maternal age	
≤ 32 years	593 (55.8)
> 32 years	470 (44.2)
Maternal educational level	
≤ 12 years	68 (6.4)
12-16 years	759 (71.4)
> 16 years	236 (22.2)
Parental history of allergic diseases	
No	503 (49.7)
Yes	510 (50.4)
Delivery methods	
Vaginal delivery	572 (53.8)
Caesarean section	274 (25.8)
Not known	217 (20.4)
Birth season	
Spring	258 (24.3)
Summer	240 (22.6)
Autumn	261 (24.6)
Winter	304 (28.6)
Child's sex	
Girl	507 (47.7)
Boy	556 (52.3)
Nrf2 gene polymorphism	
GG genotype	313 (37.7)
GA + AA genotype	518 (62.3)

Table 2. Distribution of covariates by physician's diagnosis ever of atopic dermatitis

Characteristics	Babies with AD N (%)	Babies without AD N (%)	χ^2	p-value	OR	95% CI
Maternal age						
≤ 32 years	160 (27.3)	427 (72.7)			Ref	
> 32 years	136 (29.0)	333 (71.0)	0.392	0.532	1.09	0.83-1.43
Maternal educational level						
≤ 12 years	17 (25.0)	51 (75.0)			Ref	
12-16 years	204 (27.1)	550 (72.9)				
> 16 years	75 (32.1)	159 (68.0)	2.540	0.281	1.42	0.77, 2.61
Parental history of allergic diseases					1.11	0.63, 1.97
No	126 (25.2)	375 (74.9)			Ref	
Yes	158 (31.2)	348 (68.8)	4.590	0.032	1.35	1.03, 1.78
Delivery methods						
Vaginal delivery	170 (29.8)	400 (70.2)			Ref	
Caesarean section	70 (25.8)	201 (74.2)			0.83	0.58, 1.18
Not known	56 (26.1)	159 (74.0)	1.979	0.372	0.82	0.59, 1.14
Birth season						
Spring	77 (30.0)	180 (70.0)			Ref	
Summer	60 (25.2)	178 (74.8)			0.79	0.53, 1.17
Autumn	85 (32.8)	174 (67.2)			1.14	0.79, 1.66
Winter	74 (24.5)	228 (75.5)	6.219	0.101	0.76	0.52, 1.10

Child's sex						
Girl	121 (24.1)	382 (75.9)			Ref	
Boy	175 (31.7)	378 (68.4)	7.522	0.006	1.46	1.11, 1.92
Nrf2 gene polymorphism						
GG genotype	90 (28.9)	221 (71.1)			Ref	
GA + AA genotype	155 (30.0)	361 (70.0)	0.113	0.737	1.05	0.77, 1.44

2. Distribution of prenatal trait anxiety

Figure 2 shows the histogram of STAI scores of recruited women for anxiety at 36th week of pregnancy. The distribution of STAI scores was close to normal distribution. STAI scores were divided by median score, with 49.3% anxious prenatally.

Prenatal trait anxiety was significantly associated with postnatal depression (Chi-square 41.80, p-value<.0001) and postnatal anxiety (Chi-square 88.65, p-value<.0001). (Table 4) Also, when prenatal and postnatal CESD and STAI scores were analyzed as continuous variables, the Spearman correlation coefficient was statistically significant between prenatal trait anxiety scores and postnatal depression (Spearman correlation coefficient 0.467, p-value <.0001) and anxiety (Spearman correlation coefficient 0.629, p-value <.0001). (Figure 3)

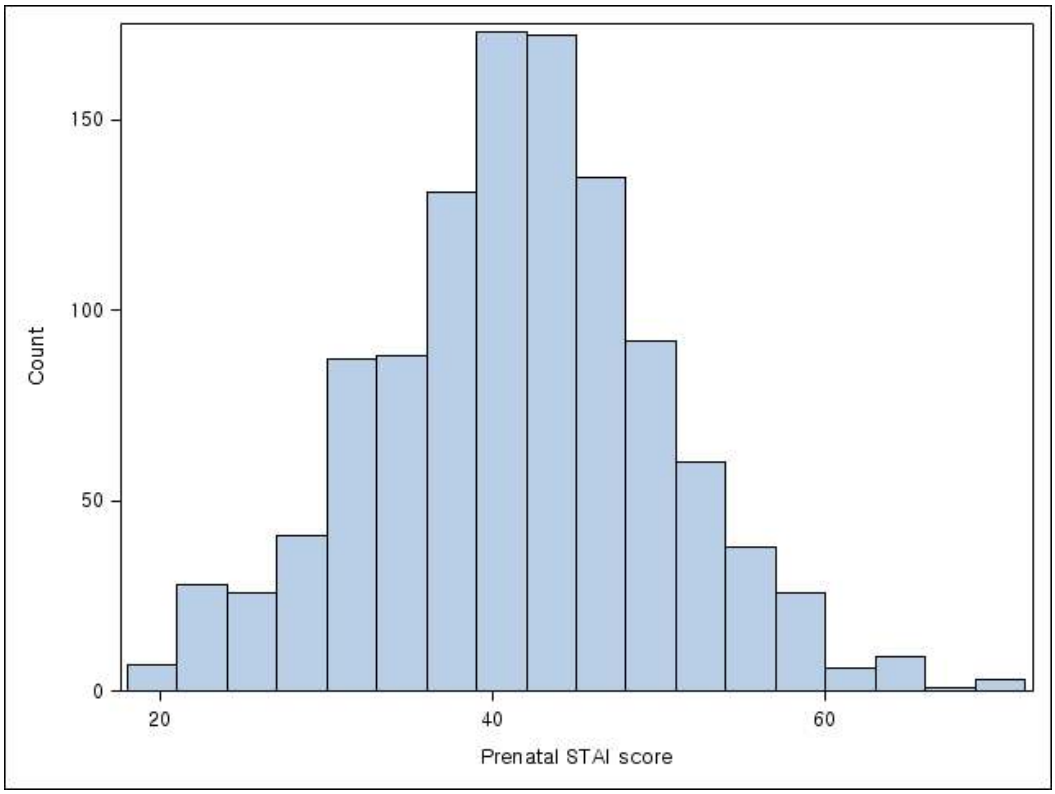

Figure 2. Distribution of prenatal trait anxiety score. STAI: State-Trait Anxiety Inventory

Table 3. Association between prenatal trait anxiety and postnatal depression and trait anxiety

		Postnatal		
		Depressed N (%)	Not depressed N (%)	Total
Prenatal	Anxious	81 (35.1)	150 (64.9)	231
	Not anxious	24 (10.1)	213 (89.9)	237
	Total	105	363	
Chi-square = 41.80 (df = 1) p-value <.0001				

		Postnatal		
		Anxious N (%)	Not anxious N (%)	Total
Prenatal	Anxious	164 (72.3)	63 (27.8)	227
	Not anxious	68 (28.6)	170 (71.4)	238
	Total	232	233	
Chi-square = 88.65 (df = 1) p-value <.0001				

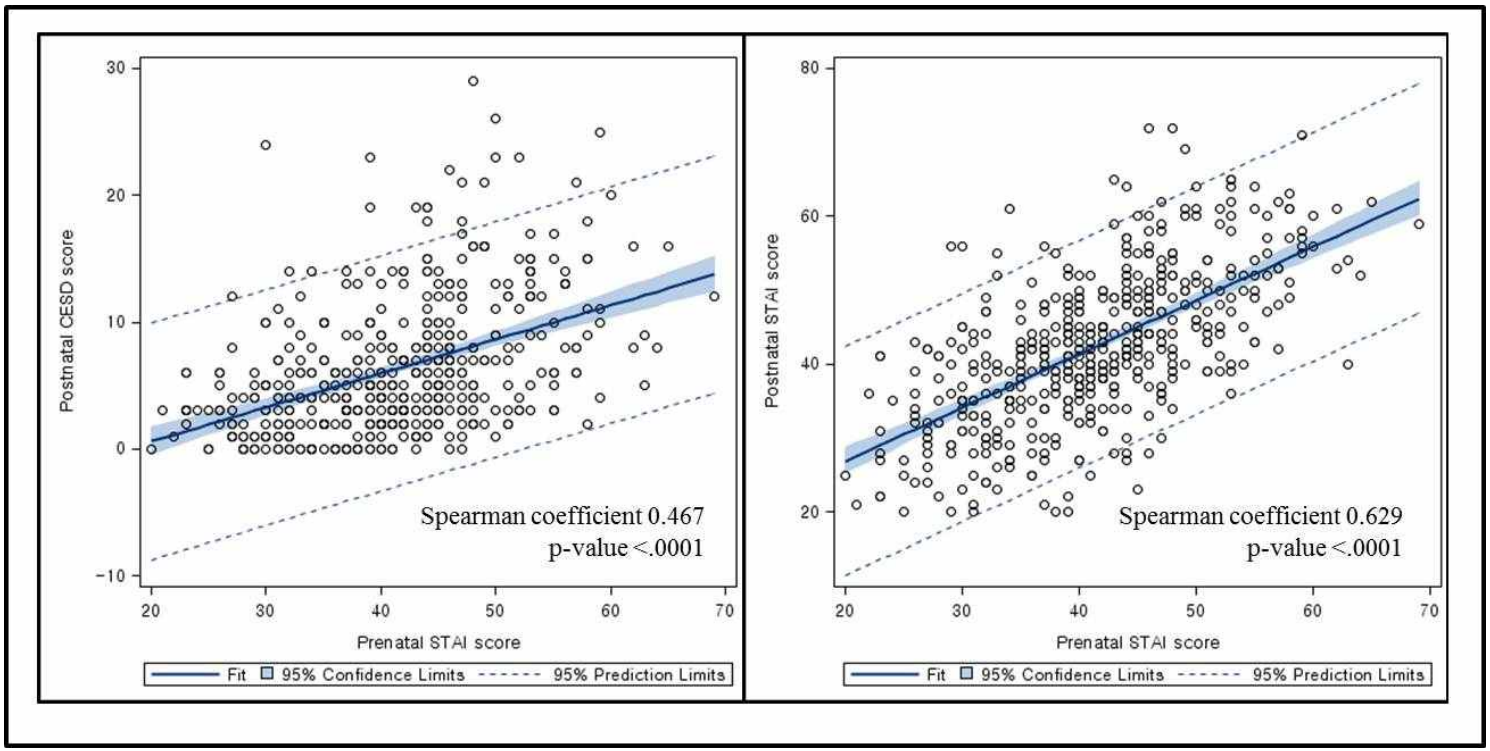

Figure 3. Correlation between prenatal trait anxiety and postnatal depression and trait anxiety. STAI: State-Trait Anxiety Inventory. CESD: Center for Epidemiological Studies - Depression.

3. Prevalence of atopic dermatitis

Regarding the prevalence of atopic dermatitis, mothers were more likely to report symptoms of atopic dermatitis compared to physician's diagnosis. Among 1056 children with at least one visit to the physician, 296 (28.0%) were diagnosed as having atopic dermatitis, while 40.1% of mothers reported their child exhibited symptoms of atopic dermatitis at least once during the follow-up period. The prevalence of atopic dermatitis at each time point is described in Table 3.

Table 4. Prevalence of atopic dermatitis

AD/ total N (%)	6 months	1 year	2 year	3 year	4 year	Ever
Physician's diagnosis	182/ 970 (18.7)	128/ 808 (15.8)	104/ 581 (17.9)	60/ 356 (16.9)	20/83 (24.1)	296/ 1056 (28.0)
Mother's report	276/ 899 (30.7)	137/ 718 (19.1)	99/ 487 (20.3)	61/ 268 (22.8)	9/65 (13.9)	389/ 969 (40.1)

4. Distribution of immunoglobulin E

Log-transformed IgE values showed normal distribution in cord blood and serum at 1st and 3rd year of age. (Figure 4) Mean and standard deviation of log-transformed cord blood IgE level were -1.339 and 1.190, respectively. Serum IgE level at 1 year and 3 year of age were 3.059 ± 1.199 and 3.870 ± 1.314, respectively.

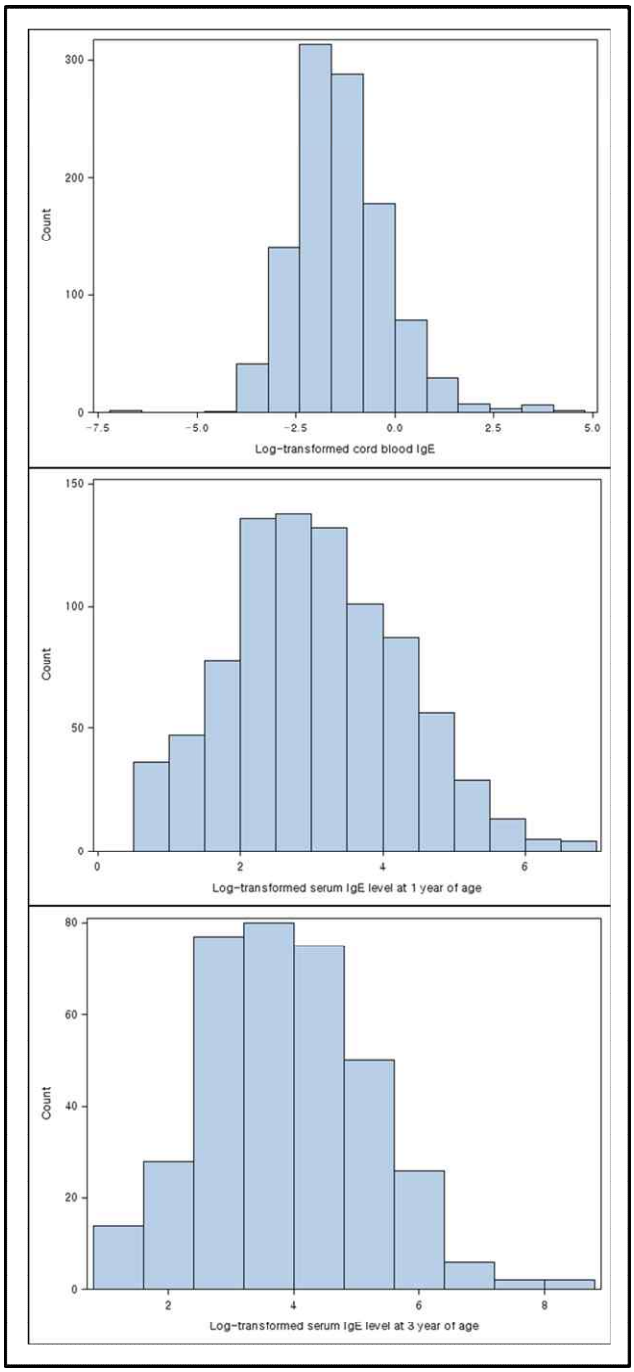

Figure 4. Distribution of Log-transformed Immunoglobulin E level of offspring

5. The association between prenatal maternal trait anxiety atopic dermatitis

Offspring of prenatally anxious mothers were more likely to have AD, whether by physician's diagnosis (HR 1.38, 95% CI 1.04-1.85) or by mother's report (HR 1.56, 95% CI 1.20-2.03). (Figure 5) The association between prenatal maternal anxiety and AD was significant after adjusting for postnatal depression (physician's diagnosis HR 1.75, 95% CI 1.18-2.59; mother's report HR 1.60 (1.13-2.27). (Table 5)

When the SCORAD score was compared to prenatal CESD and STAI scores, the correlation was significant between the severity of prenatal depression and AD severity at 1st year of age (Spearman correlation coefficient 0.186, p-value = 0.046). (Figure 5)

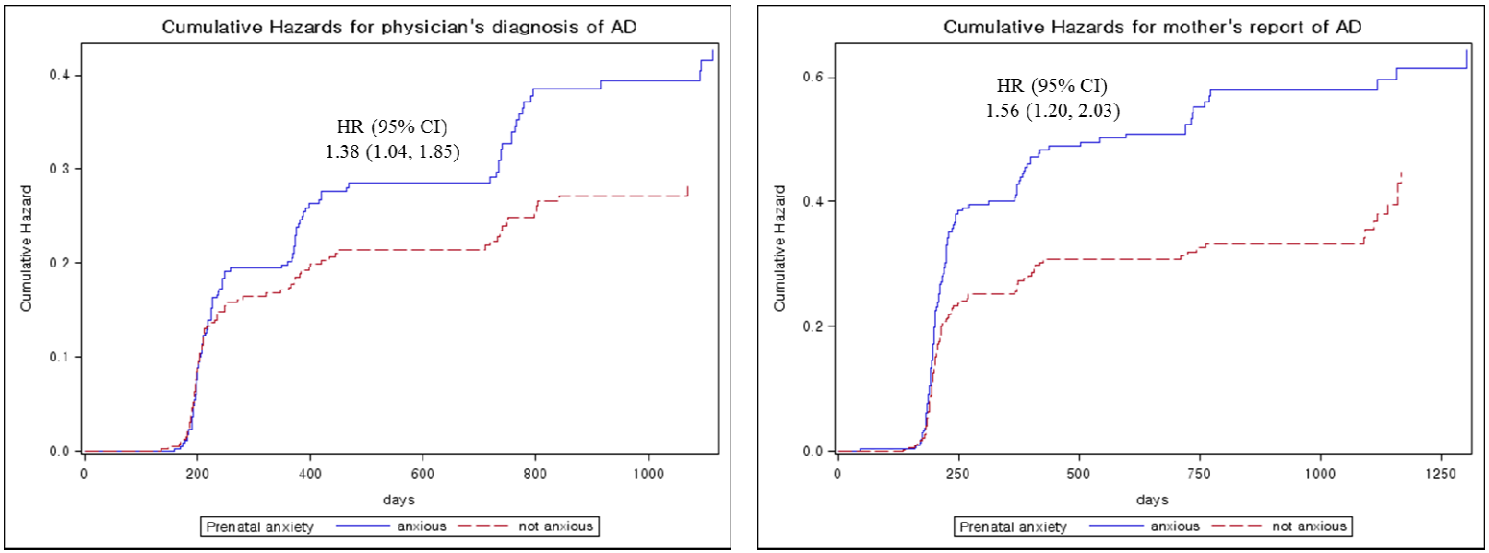

Figure 5. Cumulative hazards for physician's diagnosis and mother's report of atopic dermatitis according to prenatal maternal trait anxiety status. AD: atopic dermatitis. Adjusted for maternal age, educational level, delivery method, birth season, parental history of allergic diseases, and child's sex

Table 5. The hazard ratio and 95 % confidence interval of prenatal maternal trait anxiety and atopic dermatitis

	Unadjusted	Adjusted[1]	Additionally adjusted for	
			postnatal depression	postnatal state anxiety
Physician's diagnosis	1.38 (1.04, 1.83)*	1.38 (1.04, 1.85)*	1.75 (1.18, 2.59)*	1.51 (0.99, 2.30)†
Mother's report	1.58 (1.22, 2.03)*	1.56 (1.20, 2.03)*	1.60 (1.13, 2.27)*	1.50 (1.03, 2.18)*

[1] adjusted for maternal age, educational level, delivery method, birth season, parental history of allergic diseases, and child's sex

* p-value < 0.05

† p-value < 0.10

6. The association between prenatal maternal trait anxiety and serum Immunoglobulin E level

Offspring of anxious mothers were more likely to have elevated IgE level at the first year (OR 1.48, 95% CI 1.11-2.26), and the association between prenatal maternal anxiety and elevated IgE level was significant after adjusting for postnatal depression (OR 1.63, 95% CI 1.05-2.54). When overall IgE level was analyzed, prenatal anxiety was associated with elevated IgE level (OR 1.46, 95% CI 1.06-2.02) and the association remained significant after adjusting for postnatal depression (OR 1.57, 95% CI 1.05-2.34). (Table 6)

Cord blood IgE level was not associated with prenatal anxiety (OR 0.98, 95% CI 0.65-1.46). (Table 6)

Table 6. The odds ratio and 95% confidence interval of prenatal maternal trait anxiety and elevated elevated serum immunoglobulin E level

	Unadjusted	Adjusted[1]	Additionally adjusted for	
			postnatal depression	postnatal state anxiety
Cord blood	1.01 (0.69, 1.47)	0.98 (0.65, 1.46)		
1 year of age	1.48 (1.05, 2.07)*	1.58 (1.11, 2.26)*	1.63 (1.05, 2.54)*	1.53 (0.95, 2.46)†
3 year of age	1.30 (0.72, 2.32)	1.46 (0.77, 2.75)	2.07 (0.95, 4.53)†	1.97 (0.84, 4.62)
Overall	1.41 (1.03, 1.93)*	1.46 (1.06, 2.02)*	1.57 (1.05, 2.34)*	1.46 (0.95, 2.25)

* p-value < 0.05

† p-value < 0.10

7. Gene-environment interaction between *Nrf2* gene polymorphism and prenatal maternal trait anxiety

When stratified for *Nrf2* polymorphism and prenatal anxiety, offspring with *Nrf2* GG polymorphism and anxious mother showed higher risk of having atopic dermatitis level at 1 year of age (OR 2.431, 95% CI 1.239-4.769, interaction p-value = 0.0188). The effect of having *Nrf2* GG polymorphism and anxious mother was accentuated in AD diagnosis at 3 year of age, with OR reaching 15.788 (95% CI 2.797, 89.128, interaction p-value = 0.0115). (Table 7, Figure 6)

When interaction was examined in elevated serum IgE level, the trend was similar with offspring with *Nrf2* GG polymorphism and anxious mother showing highest odds of having elevated serum IgE level. In one year-old offspring, those with *Nrf2* GG polymorphism and anxious mother were more likely to exhibit elevated serum IgE level (OR 2.454, 95% CI 1.311-4.593). However, the interaction did not reach statistical significance (interaction p-value = 0.1031). (Table 8, Figure 7)

Table 7. Gene-environment interaction between *Nrf2* gene polymorphism and prenatal maternal trait anxiety resulting in atopic dermatitis

		Physician's diagnosis of AD	Mother's report of AD
Prenatal anxiety	*Nrf2*	HR (95% CI)	HR (95% CI)
Not anxious	GG	1	1
Not anxious	GA + AA	1.64 (0.97, 2.77)†	1.09 (0.70, 1.71)
Anxious	GG	2.13 (122, 3.73)*	1.59 (0.98, 2.57)†
Anxious	GA + AA	1.66 (0.98, 2.81)†	1.57 (1.01, 2.44)*
Interaction p-value		0.034*	0.748

Adjusted for maternal age, maternal educational level, delivery method, birth season, parental history of allergic diseases, and child's sex

AD: atopic dermatitis

* p-value < 0.05

† p-value < 0.10

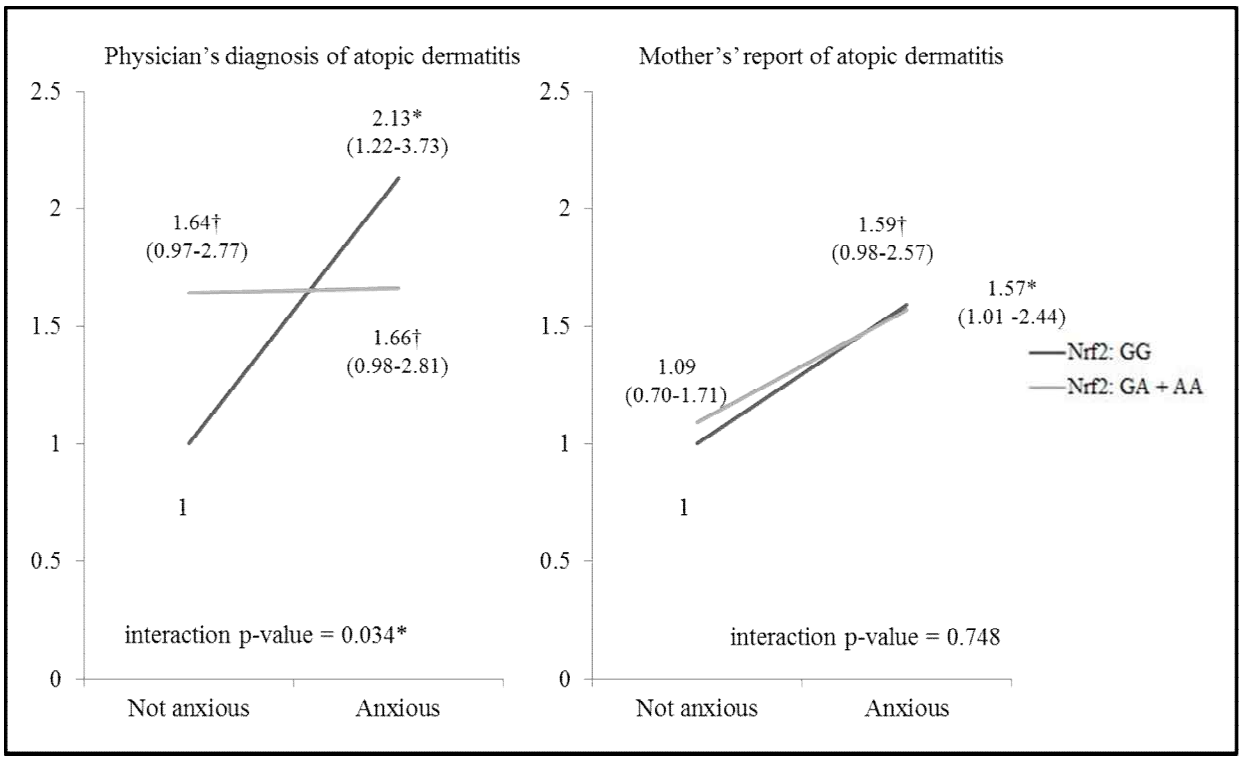

Figure 6. Gene-environment interaction between *Nrf2* gene polymorphism and prenatal maternal trait anxiety resulting in atopic dermatitis. Adjusted for maternal age, maternal educational level, delivery method, birth season, parental history of allergic diseases and child's sex. * p-value < 0.05. † p-value < 0.10.

Table 8 Gene-environment interaction between *Nrf2* gene polymorphism and prenatal maternal trait anxiety resulting in elevated immunoglobulin E level

		Cord blood	1 year of age	3 year of age
Prenatal anxiety	*Nrf2*	OR (95% CI)	OR (95% CI)	
Not anxious	GG	1	1	1
Not anxious	GA + AA	1.10 (0.62, 1.93)	1.13 (0.66, 1.93)	1.25 (0.46, 3.35)
Anxious	GG	1.15 (0.60, 2.21)	2.45 (1.31, 4.59)*	2.30 (0.75, 7.05)
Anxious	GA + AA	0.78 (0.43, 1.43)	1.45 (0.84, 2.48)	1.93 (0.74, 5.03)
Interaction p-value		0.264	0.103	0.571

Adjusted for maternal age, maternal educational level, delivery method, birth season, parental history of allergic diseases, and child's sex

* p-value < 0.05

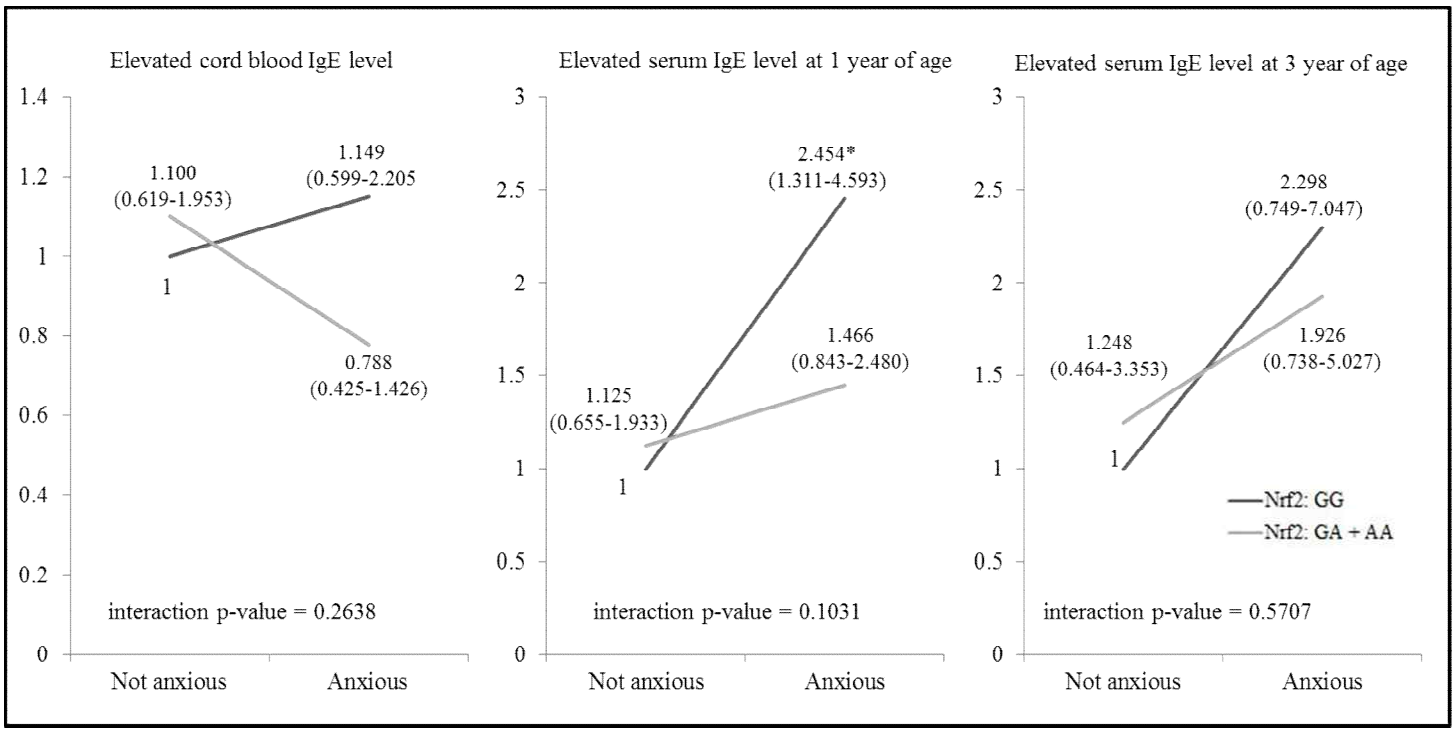

Figure 7. Gene-environment interaction between *Nrf2* gene polymorphism and prenatal maternal trait anxiety resulting in elevated immunoglobulin E level. Adjusted for maternal age, maternal educational level, delivery method, birth season, parental history of allergic diseases, and child's sex. * p-value < 0.05

IV. DISCUSSION

This is the first study to examine the association between self-reported anxiety during pregnancy and AD. Prenatal depression and anxiety was associated with physician's diagnosis of AD and elevated serum IgE level at 1st year of age, even after adjusting for potential confounders including postnatal depression and anxiety. The effect of prenatal maternal anxiety on AD was modified by genetic polymorphisms in *Nrf2* gene.

1. The relationship between allergic diseases and psychological symptoms

Allergic disease is a group including asthma, allergic rhinitis(AR) and atopic dermatitis(AD), known to be regulated through immune phenomena in which many cells (ie, mast cells, eosinophils, and T lymphocytes) and associated cytokines, chemokines, and neuropeptides play a role. Mechanisms of inflammation central to the pathophysiology of these atopic disorders overlap and involve a cascade of events that include the release of immunologic mediators triggered by both immunoglobulin E (IgE)-dependent and independent mechanisms.[43]

Clinicians have known that psychological symptoms and allergic symptoms tend to co-occur. In 1930, "allergic toxemia" was described by Rowe, a syndrome characterized by fatigue, slowed psychomotor and thought

processes, poor memory, irritability, and depression.[44] Speer[45] and Klein[46] also reported a similar phenomenon consisting of psychological symptoms and allergic diseases such as irritability, apathy, and decreased concentration., Allergic diseases were even thought as being purely psychogenic in origin before the underlying inflammatory basis of allergic diseases was discovered. Freud claimed that asthmatic symptoms were a symbolic expression of unconscious conflicts and repressed desires,[47] and Alexander included asthma and atopic dermatitis among the seven classic psychosomatic disorders.[48]

It is now increasingly clear that central pathogenesis of allergic diseases lies in interactions between the immune system and environmental exposure to allergen.[49] Studies focusing on relationship between allergic symptoms and psychological disturbances are mostly concentrating their efforts in revealing the specific relationships, between three major allergic diseases and a broad spectrum of psychological problems ranging from anxiety and depression to hyperactivity and aggression. A recent meta-analysis demonstrated a bidirectional relationship between mental health symptoms and atopic disorders.[50] There are also active attempts to understand the underlying pathophysiological mechanisms mediating such relationship.

Among allergic diseases, asthma has been most extensively studied. Patients with asthma are found to have higher prevalence of anxiety disorders,[51] and panic disorder in particular.[52-54] In pediatric population, a recent meta-analysis of 26 studies found that there was an increase in internalizing

problems among asthmatic children relative to comparison groups.[55] Strong association between pediatric asthma and psychological problems have also been replicated in longitudinal studies[56] and a nationwide mental health survey.[57]

There are fewer studies on association between AR and psychological disturbances, and most of the studies are limited to adult population. Clinical investigations suggest that AR in adult is associated with anxiety,[32] depression[58-62] and low quality of life.[63] AR is also found to be strongly associated with sleep disturbances[64, 65] and impaired cognitive functioning.[66] Mental complication of pediatric AR have been reported to include sleep disturbance[67, 68], poor school performance[69, 70] and hyperactivity.[71]

2. Extant studies on prenatal maternal status and allergic diseases

Studies of the influence of prenatal maternal distress on AD are scarce. In one retrospective cohort study, the children of mothers who had experienced stressful life events during pregnancy were at increased risk for wheezing, asthma, allergic rhinitis, and atopic dermatitis.[6] In another cohort study, maternal psychological stress during pregnancy was significantly associated with atopic dermatitis.[7]

More studies have been conducted on the effect of prenatal maternal distress on wheezing and asthma. Chiu et al. reported that maternal negative life

events during pregnancy was associated with repeated wheeze, defined as two or more episodes of wheezing during the first two years, and there was an exposure-response relationship between prenatal stress and wheezing symptoms.[72] Reyes et al. reported used Psychiatric epidemiology Research Instrument - Demoralization scale to assess prenatal maternal demoralization (e.g. psychological stress) and found that maternal demoralization was associated with overall, transient (birth to 2.5 years), and persistent wheeze (birth to 5 years).[73]

Table 1 summarizes the published studies that examined the association between prenatal maternal stress and allergic diseases in offspring. A total of nine studies were chosen: seven on wheezing/asthma, one on allergic rhinitis, and three on atopic dermatitis (One study covered all three diseases as outcomes). Although we searched for studies published from 2000 since fetal origins hypothesis began gaining strong attention during late 1990s[74] and the International Society for Developmental Origins of Health and Disease was established in 2003, the earliest report on the effect of prenatal maternal stress on allergic diseases were published in 2009. Among nine studies, four were prospectively designed while the remaining five were based on retrospective cohorts. Most studies used general population samples, although not all were nationally representative.

Prenatal maternal stress was ascertained by various methods at different time periods. Regarding assessment point, studies using negative life events

encompassed the whole pregnancy period while those using self-reported questionnaires on depression or anxiety were conducted at 2nd or 3rd trimester. All but one studies assessed maternal stress at just one time point, thus making it difficult to ascertain the critical period for the effect of prenatal maternal stress on fetal and neonatal immune development. A study conducted in UK assessed prenatal anxiety at two time points, 18 and 32 weeks of gestation, and found similar trends of positive association between prenatal anxiety and asthma at 7½ years, although the estimated parameter were larger for anxiety during 3rd trimester.[75]

In a number of studies, negative or stressful life events were used as a proxy for prenatal maternal stress. Maternal bereavements of spouse of child, which is one of the extreme trauma a person may face, was found to be significantly associated with later allergic diseases,[76, 77] and the number of stressful life events during pregnancy was also reported to show a dose-response relationship.[72] Recently, studies using validated self-reported questionnaires were also published.[24, 73] However, there are yet no studies that applied observational or objective measure to assess maternal psychological status. While there are evidences that maternal stress during pregnancy is associated with cortisol disruption,[78] the relationship between cortisol regulation and its effect on the fetus are yet to be examined.

To assess outcomes, most studies used maternal reports on child's allergic symptom.[7, 24, 72, 73] However, there is a possibility that mother's recognition and

reporting of the child's symptoms may be affected by their psychological status since depression or anxiety are known to color perception.[28] Two studies in Sweden utilized hospital records to assess the presence of asthma in a large representative general population sample.[76, 77] While hospital records provide comparatively more objective information on the medical status of subjects, register studies are limited by potential residual confounding due to factors not recorded in the registers. In one study, physician's diagnosis of allergic diseases based on maternal and child's report on symptoms were used to ascertain asthma, but no objective measurement such as pulmonary function test or methacholine challenge test were conducted.[24]

In summary, there are several limitations in extant studies to note. First, retrospective approach may result in recall bias in those with allergic diseases, thus biasing the result away from the null. Although definite life events such as death of a spouse may be more resistant to recall bias, prospective data is crucial in examining the association between more subtle psychological status and later development of diseases since symptoms like depression or anxiety are more prone to become biased. Second, data on the ascertainment of allergic diseases were collected by maternal reports in most of the studies. This may also bias the result since mood states are known to influence the perception of current situations.[28] Mothers who are depressed or anxious may be more vigilant to minimal changes in the child and thus result in the overestimation of outcome diseases. Third, the definitions of prenatal distress are inconsistent:

some studies measured one or two major life events such as bereavements or the number of stressful life events, while others used validated questionnaires. Lastly, most of the studies did not adjust for potential confounders, including risk factors for allergic diseases and postnatal maternal distress. Few studies have yet examined the effect of postnatal maternal stress on the association between prenatal maternal stress and offspring's allergic diseases. Postnatal maternal stress may impact early childhood environment and caregiving experience, which may in turn influence the occurrence and persistence of allergic diseases in children through change in the development of stress reactivity.[25] It has been reported that early-life caregiver stress is associated with repeated wheeze[79] and dysregulation in immune function[80] in a birth cohort predisposed to atopy. All the more, postnatal distress, encompassing psychological distress and negative life events, are known to show high correlation with prenatal maternal distress,[26, 27] which warrants an examination on whether any synergistic or antagonistic effect exist between prenatal and postnatal maternal stress.

These studies demonstrate that, although not yet robust, there is sufficient evidence to think that prenatal maternal stress is associated with later development of offspring's allergic diseases. Then again, most studies are focused on asthma/ wheezing, and there are scarce publication concerning other allergic diseases such as allergic rhinitis or food allergy.

Table 9. Summary of original articles published from 1 January 2000 to 30 April 2014 that examine the association between prenatal maternal stress and allergic diseases in offspring

First author (year)	Country	Design	Sample	Prenatal maternal stress assessment	Outcome assessment	Main conclusion
Wheezing and asthma						
Guxens (2014)[81]	Netherland	Prospective	4848	Brief Symptom Inventory At 20 weeks of gestation	Wheezing: maternally reported during 1-4 years annually Asthma: physician-diagnosed at 6 years	Prenatal maternal stress was positively associated with wheezing in offspring.
Mathilda Chiu (2012)[82]	US	Retrospective	653	Maternal negative life events during pregnancy	Wheezing: maternally reported during birth-2 years at 3-month interval	Exposure-response relationship between prenatal stress and child wheeze.
de Marco (2012)[6]	Italy	Retrospective	3854	Stressful Life Event during pregnancy	Wheezing/ asthma: self-reported among children aged 3-14 years	Children of exposed mothers were at increased risk of wheezing and asthma.
Khashan (2012)[76]	Sweden	Retrospective	3,200,000	Whether spouse or child died up to 6 months before or during pregnancy	Asthma: hospitalization due to asthma	Children of exposed mothers were at increased risk of being hospitalized for asthma.

Fang (2011)[83]	Sweden	Retrospective	426,334 (1-4 years old) 493,813 (7-12 years old)	Maternal bereavement shortly before and during pregnancy	Asthma: hospital contact for asthma or at least two dispenses of inhaled corticosteroids or montelukast	Exposed boys, especially those exposed during their 2nd trimester, were at increased risk of asthma.
Reyes (2011)[73]	US	Prospective	279	Demoralization scale (Psychiatric Epidemiology Research Instrument) At 3rd trimester	Wheezing: maternally reported during birth-5 years at 3 month interval (birth-2 year) and 6 month interval (2-5 year)	Prenatal maternal demoralization was associated with overall, transient, and persistent wheeze.
Cookson (2009)[75]	UK	Prospective	5810	Prenatal anxiety (Crown-Crisp Experiential index) at 18 and 32 weeks	Asthma: mother's report of doctor diagnosed asthma with current symptoms or treatment in the previous 12 months at 7½ year	Children of mothers in the higher anxiety scores were more likely to have asthma, with evidence for a dose-response.
Allergic rhinitis						
de Marco (2012)[6]	Italy	Retrospective	3854	Stressful Life Event during pregnancy	Self-reported among children aged 3-14 years	Exposed children were at increased risk of allergic rhinitis.

Atopic dermatitis						
de Marco (2012)[6]	Italy	Retrospective	3854	Stressful Life Event during pregnancy	Self-reported among children aged 3-14 years	Exposed children were at increased risk of atopic dermatitis.
Wen (2011)[7]	Taiwan	Prospective	730	Psychological stress during pregnancy	Maternally reported at 6 months and 2 years	Maternal stress during pregnancy was associated with ever having physician-diagnosed AD in 2 year old children.
Sausenthaler (2009) [84]	Germany	Prospective	3004	The presence of 2 or more stress factors of the 12 factors** (about upper 5%)	Maternally reported physician's diagnosis of AD during birth-6 years	Maternal factors during pregnancy were positively associated with childhood eczema in terms of cumulative prevalence up to the age of 2 years, but not beyond.

** psychological stress, social stress, bleeding before and after 28 weeks' gestation, placental insufficiency, premature labor, anemia, positive indirect Coombs test, risk based on other serological findings, hypertension (>140/90) and proteinuria (≥1000 mg/L), information on unwanted pregnancies

3. Possible pathways linking prenatal maternal distress and allergic diseases

It is known that psychological stress may worsen the symptoms of allergic diseases. However not many reports are available in postulating mechanisms by which prenatal maternal stress affects allergic diseases in the offspring.

The development of atopic diseases may be affected by perinatal programming - the influence of environmental or other factors in the perinatal period that imprint or organize the physiological and immunological system, which may include psychological stress.[82] Physiological systems may be altered from its normal homeostasis in response to stress. Such accommodation may be beneficial in short-term response, but not in the long-term.[81] It would be helpful to review the mechanism underlying the linkage between stress and allergy in the offspring.

Hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) are key regulatory systems activated in the neuroendocrine pathways against environmental stress. Activation of these systems can result the immunologic alteration and may cause asthma and atopic illnesses in the offspring.[85] Prenatal stress elevates the level of cortisol, persistently elevated maternal cortisol levels can influence, in the end, the developing immune system or the TH1/TH2 balance of the child.[83] Altered HPA axis can also influence the immune system of the developing fetus. Elevated cortisol may influence the fetal immune system via altered cytokine and Th1/Th2 balance.[83]

Glucocorticoids are one of the factors that are known to have effect on immune system, such as inhibition of the production IL-12, IFN-γ, Th 1 cells and up-regulation of the production if IL-4, IL-10, and IL-13 by Th2 cells.[86]

The autonomic nervous system (ANS) is also one of the key regulatory systems vulnerable to early life programming.[87] ANS activation is thought to act in a neural-immune response, meaning a bi-directional way.[88] Vagal output regulates peripheral immune response by suppressing the innate immune defense to pathogens, altering pro-inflammatory cytokine balance. On the other hand, local immune activation elevates pro-inflammatory molecular mediators, which not only influence cells of the innate/adaptive immunological system in the periphery but also activate sensory pathways that relay information to the CNS.[89]

Placenta may also play a role in the underlying mechanism linking stress and allergic diseases. Placental 11-beta hydroxy steroid dehydrogenase type II (HSD2) is known to provide a protective barrier between the fetus and mother[90] and protect the fetaus from excessive glocucorticoid delivery from the mother.[91] However, the level of HSD2 is decreased in high maternal stress situation. Additionally, CRH secretion from placenta is increased when the mother is stressed.

Epigenetic modification may also play a role. Epigenetic dysregulation of gene expression is now being focused as a programming mechanism,. A study published that there is an increased methylation at a CpG-rich region in the

promoter and exon 1F of the human glucocorticoid receptor gene (NR3C1) in infants of depressed mother.

Lastly, stress may elicit disruption of each component of interrelated systems. Alteration in autonomic, neuro-endocrinologic, and immune systems can induce the dysregulation of another system. Therefore prenatal stress in mothers may lead to increased vulnerability of disrupted stress response in their children, which in turn predisposes later expression of asthma and allergic diseases.

Further research especially on the intervention strategies that may restore altered stress response systems during the prenatal period is needed.

4. The strengths and limitations

There are strengths to be noted. First, AD was ascertained by physician's diagnosis rather than mother's report. Since there is a possibility that mother's report may be affected by their psychological status such as depression and anxiety, physician's diagnosis provide more objective measure of the AD status of the offspring. Second, the models for logistic regression were adjusted for postnatal depression and anxiety. Other strengths of this study include prospective design, large general population sample, and data on Asian population.

Limitation of this study is that maternal distress level was assessed through

self-reported questionnaires without objective biological markers such as cortisol level.

V. CONCLUSION

Prenatal maternal depression and stress was associated with AD diagnosis and elevated IgE level in offspring. This effect was modified by *Nrf2* polymorphism. These findings suggest that mechanism may be mediated by reactive oxidative stress. Reduction of prenatal maternal depression and anxiety may have impact in preventing AD during infancy. Interventions to reduce maternal anxiety during pregnancy may be helpful in preventing AD during infancy especially in genetically susceptible infants.

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APPENDICES

Supplementary Table 1. Distribution of covariates among participants included and excluded in the study

Characteristics	Mother-baby pairs included in the study N (%)	Mother-baby pairs excluded in the study N (%)	χ^2	p-value
Maternal age				
≤ 32 years	688 (85.8)	114 (14.2)		
> 32 years	540 (88.1)	73 (11.9)	1.6107	0.2044
Maternal educational level				
≤ 12 years	89 (87.3)	13 (12.8)		
12-16 years	949 (85.7)	159 (14.4)		
> 16 years	289 (87.3)	42 (12.7)	0.7074	0.7021
Parental history of allergic diseases				
No	574 (89.7)	66 (10.3)		
Yes	595 (88.2)	80 (11.8)	0.7719	0.3796
Delivery methods				
Vaginal delivery	726 (85.3)	125 (14.7)		
Caesarean section	372 (87.3)	54 (12.7)		
Not known	267 (82.4)	57 (17.6)	3.5435	0.1700
Birth season				
Spring	300 (83.3)	60 (16.7)		
Summer	321 (87.0)	48 (13.0)		
Autumn	362 (84.4)	67 (15.6)		
Winter	380 (86.2)	61 (13.8)	2.4930	0.4766
Child's sex				
Girl	646 (85.3)	111 (15.7)		
Boy	717 (85.9)	118 (14.1)	0.0910	0.7629

ABSTRACT (IN KOREAN)

산모의 산전 특성 불안이 신생아의 아토피피부염과 면역글로불린 E에 미치는 영향: 전향적 코호트 연구

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아토피피부염은 재발을 반복하는 염증성 질환으로, 선진국에서 그 유병률이 증가 추세이다. 최근 아토피피부염의 위험요인 중 하나로 산모의 산전 우울과 불안이 주목을 받고 있다. 그러나 이전 연구들에서는 아토피피부염을 부모보고로만 측정했고, 산전 불안과 높은 상관성을 보이는 산후 우울 및 불안이 보정인자에 포함되지 않았다는 제한점을 가진다. 또한 산전 특성 불안과 아토피피부염의 매개 기전 역시 아직 밝혀진 바가 없다. 이 연구의 목적은 산후 우울 및 불안을 보정한 상태에서, 산전 불안이 아동의 아토피피부염 및 혈청 면역글로불린 E의 증가에 미치는 영향을 확인하고, 이 관계가 nuclear factor-like 2 (*Nrf2*) 유전자의 다형성에 의해 교호작용을 보이는지를 검증하고자 한다. 1063명의 산모를 모집하여, 임신 36주에 State-Trait Anxiety Inventory를 사용하여 산전 특성 불안을 측정하였다. 분석 당시 아동의 나이는 0세부터 6세까지 분포하는 것으로 확인되었다. 아토피피부염은 출생 후 6개월, 1세, 2세, 3세, 그리고 4세에 소아과의사의 진단과 부모 보고의 두 가지 방식으로 확인되었다. 면역글로불린 E의 농도는 제대혈, 1세, 그리고 3세의 혈액에서 측정하였다. *Nrf2* 유전자의

다형성은 TaqMan assay를 통해 확인하였다. Cox proportional hazards model과 generalized estimating equations을 이용하여 산후 우울 및 불안을 포함한 인구학적 변인들을 통제한 상태에서 산전 특성 불안과 아토피피부염, 그리고 면역글로불린E와의 관계를 분석하였다. 우울하거나 불안한 산모의 아동의 경우, 아토피피부염을 앓는 경우가 더 많은 것으로 확인되었고 (의사진단: HR 1.38, 95% CI 1.04-1.85; 부모보고: HR 1.56, 95% CI 1.20-2.03), 이는 산후 우울을 보정한 후에도 여전히 통계적으로 유의미하였다. 또한 불안한 산모의 아동의 경우, 혈청 면역글로불린 E의 값이 증가된 경우가 더 많았다 (OR 1.46, 95% CI 1.06, 2.02). *Nrf2* 유전자의 다형성과 산전 불안으로 계층화했을 때, *Nrf2* GG 다형성과 산전 불안을 경험한 산모의 아동이 아토피피부염을 진단받는 경우가 유의하게 더 많았다 (HR 2.43, 95% CI 1.24-4.77, interaction p-value = 0.019). 산전 산모의 특성 불안은 아동의 아토피피부염 발병 및 면역글로불린 E 값의 증가와 관련이 있었고, 이 관련성은 *Nrf2* 유전자의 다형성에 의한 교호작용을 보였다. 이 결과로 미루어볼 때, 산전 우울 및 불안과 아토피피부염의 관련성은 활성산소에 의해 매개될 가능성이 있다. 산전 우울이나 불안을 감소되면 아동의 아토피피부염 발생이 감소할 수 있을 것으로 사료되며, 특히 유전적으로 취약한 아동의 경우 산전 산모의 특성 불안을 감소시키려는 개입이 아토피피부염의 예방에 도움이 될 수 있다.

핵심되는 말: 산전 우울, 산전 불안, 아토피피부염, 면역글로불린 E, *Nrf2* 유전자 다형성