Asan Medical Center Children's Hospital

Environmental and Genetic Risk Factors from COCOA Birth Cohort : South Korea

Soo-Jong Hong, MD, PhD
Department of Pediatrics,
Childhood Asthma Atopy Center, Environmental Health Center,
Asan Medical Center, University of Ulsan College of Medicine

Japanese Society of Pediatric Allergy and Clinical Immunology

COI Disclosure

Presenter: Soo-Jong Hong, MD, PhD

☑ The author has no conflict of interest to disclose with respect to this presentation.

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- **COCOA birth cohort study** :
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- **COCOA–AIR study** :
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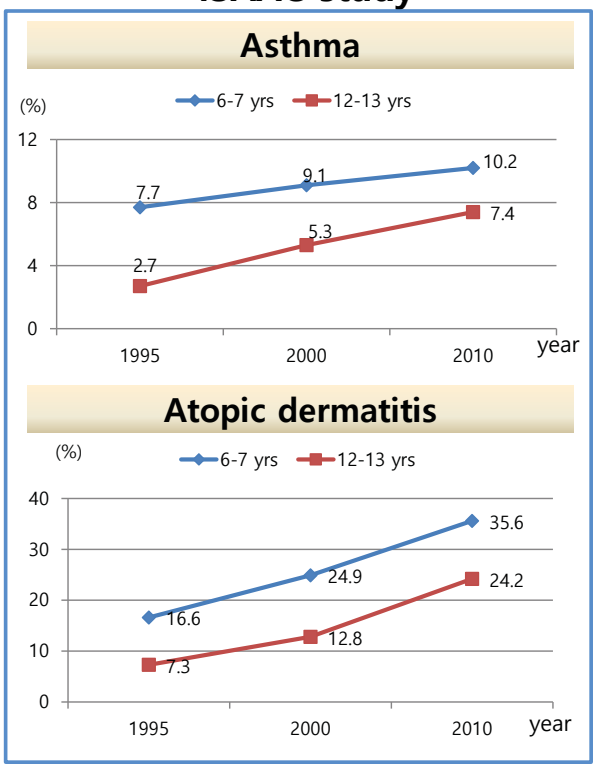
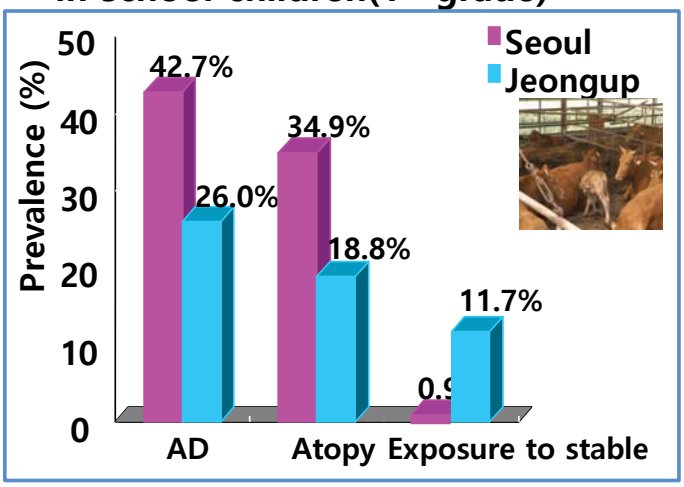
Contents

Prevalence of allergic diseases is increasing in Korean children : ISAAC study



Korean ISAAC study team, Allergy Asthma Respir Dis 2018;6:s9-20

Comparison of AD and atopy between Seoul and Jeongup area in school children(1st grade)



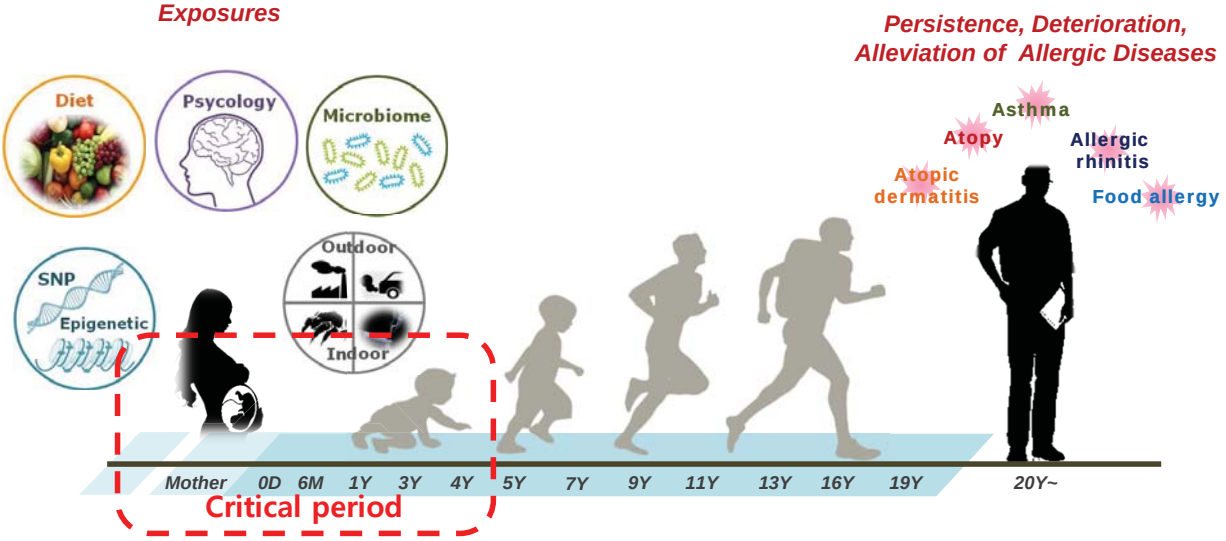
Farming environment and rural lifestyle might be associated with protective factors impacting the prevalence of allergic diseases and atopy.

Lee SY, Park KS, et al. Int Arch Allergy Immunol 2012;158:168

COCOA since 2007 (N=3004, birth = 2846)

(COhort for Childhood Origin of Asthma and allergic diseases)

Hypothesis: Development of allergic disease originates **from altered immune response to various environmental exposure during a critical period**



Aim 1: To investigate the perinatal risk factors and the critical time for the development of allergic disease
Aim 2: To investigate the gene-environment interaction for the development and natural course of allergic diseases

VIT D AND RTI, AD

VitD and allergic ds : What is already known ?

- CB vitD and child infection, allergic ds : **Protective association** between in utero vitD exposure and lower respiratory tract infection was found.
- **Protective effect of maternal intake** of each of three vitamins or nutrients (vitamin D, vitamin E, and zinc) against childhood wheeze but is inconclusive for an effect on asthma or other atopic conditions.
- Vitamin D supplementation in primary allergy prevention: **primary prevention of allergic diseases** remains uncertain.
- The health effects of vitD is **often confusing** and has led to **hot debates about the role of vitamin D, the optimal concentrations, and related guidelines for supplementation**.
- vitamin D is more likely to be a correlate **marker of overall health** and not causally involved in disease due to lack of concordance between observational studies and randomized controlled trials.

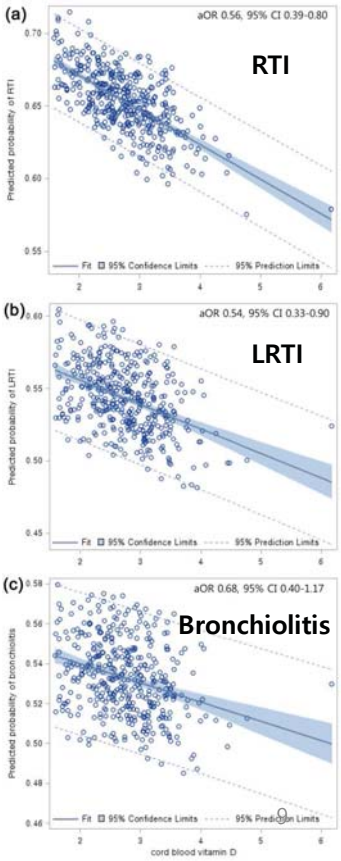
→ **Association ?** or → **Causal ?**

Association between 25(OH)vitD at birth or 1 year of age and RTIs, lower RTIs, and bronchiolitis within 1 year of age

TABLE 2. Association between cord-blood 25(OH)D concentrations or the 17q12-21 variant genotypes and respiratory-tract infections, lower respiratory-tract infections, and bronchiolitis within the first year of age, as determined by binary logistic regression model analysis[†]

Variables	N (%)			RTIs			N (%)			LRTIs			N (%)			Bronchiolitis		
	Yes	No	%	aOR* (95% CI)			Yes	No	%	aOR* (95% CI)			Yes	No	%	aOR* (95% CI)		
CB 25(OH)D																		
≥ 20 ng/mL	76	64	(54.29)	1			14	124	(10.14)	1			11	126	(8.03)	1		
< 20 ng/mL	189	88	(68.23)	2.01	(1.29	3.13)	56	210	(21.05)	2.37	(1.23	4.60)	42	224	(15.79)	2.02	(0.97	4.21)
P value				0.002						0.0104						0.0597		
25(OH)D at 1yr																		
≥ 20 ng/mL	210	126	(62.50)	1			62	265	(18.96)	1			48	278	(14.72)	1		
< 20 ng/mL	55	26	(67.90)	1.34	(0.79	2.27)	8	69	(10.39)	0.50	(0.23	1.12)	5	72	(6.49)	0.41	(0.15	1.08)
P value				0.2781						0.0936						0.0712		
17q12-21 variant genotypes																		
GG	146	76	(65.77)	1			42	175	(19.35)	1			31	186	(14.29)	1		
GA	90	66	(57.69)	0.72	(0.46	1.11)	22	131	(14.38)	0.63	(0.35	1.13)	18	134	(2.00)	0.72	(0.38	1.38)
AA	18	9	(66.67)	1.11	(0.47	2.63)	4	19	(17.39)	0.83	(0.25	2.76)	3	20	(13.04)	0.89	(0.23	3.42)
P value				0.4374						0.2175						0.4381		

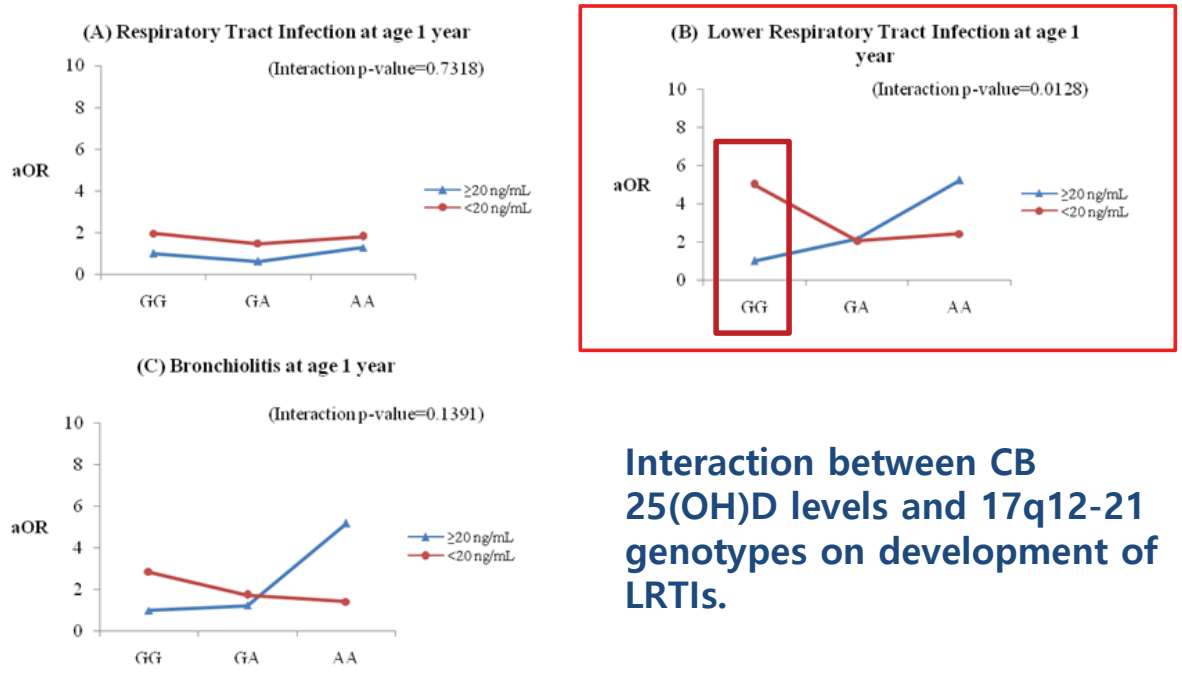
aOR: adjusted by maternal age, maternal education, maternal BMI, parental history of allergic disease, sex, gestational age, season of birth, multivitamin use



- **25(OH)D concentrations at birth (Cord-blood) are more important than those at 1 year of age.**

Shin YH, et al. Ped Pulm 2016

Effect of 17q12-21 (GSDMB) genotypes and CB 25(OH)D on RTIs, LRTIs, and bronchiolitis within 1 year of age



Interaction between CB 25(OH)D levels and 17q12-21 genotypes on development of LRTIs.

Shin YH, et al. Ped Pulm 2016

Vit D and AD from cohort studies

Reference	location	design	statistics	Main outcome measures
Jones (2012) ** Pediatrics*	Perth, Australia	Cohort 231 children (high risk)	Cord blood 25(OH)D: OR 1) 10 nmol/L increments 2) ≥75 vs <50 nmol/L	Eczema (0–1 y): (부모) 10 nmol/L increments : 0.857 (0.739-0.995) ≥75 vs <50 nmol/L : 0.38 (0.18-0.81)
Baiz (2014) ** JACI*	Nancy and Poitiers, France	Cohort 239 children	Cord blood 25(OH)D: OR 1) 12.5 nmol/L increments	Atopic dermatitis (0–5y): (부모) Early (≤2 y): 0.73 (0.62 to 0.9) Late (>2 y): 0.75 (0.60 to 0.94)
Jones (2015) ** Clin Exp Allergy*	Perth, Australia	Cohort 200 children (high risk)	Cord blood 25(OH)D: OR 1) 10 nmol/L increments	Eczema: (부모) 6 mo: 0.82 (0.70 to 0.96) 12 mo: 0.84 (0.72 to 0.99) 30 mo: 0.86 (0.72 to 1.04)
Palmer (2015) * WAO	Australian New Zealand	DOMInO Trial 270 children (high risk)	Cord blood 25(OH)D: RR 1) 10 nmol/L rise	Eczema : (의사) at 1 year of age : 0.88 (0.81, 0.96) 0.002 at 3 years of age : 0.93 (0.86, 1.01) 0.07

Limited due to **high-risk** population, **small** sample sizes, **parentally-reported** AD, **lack of both prenatal and postnatal vitD** measurement, **no mechanism study**, **no good intervention study**

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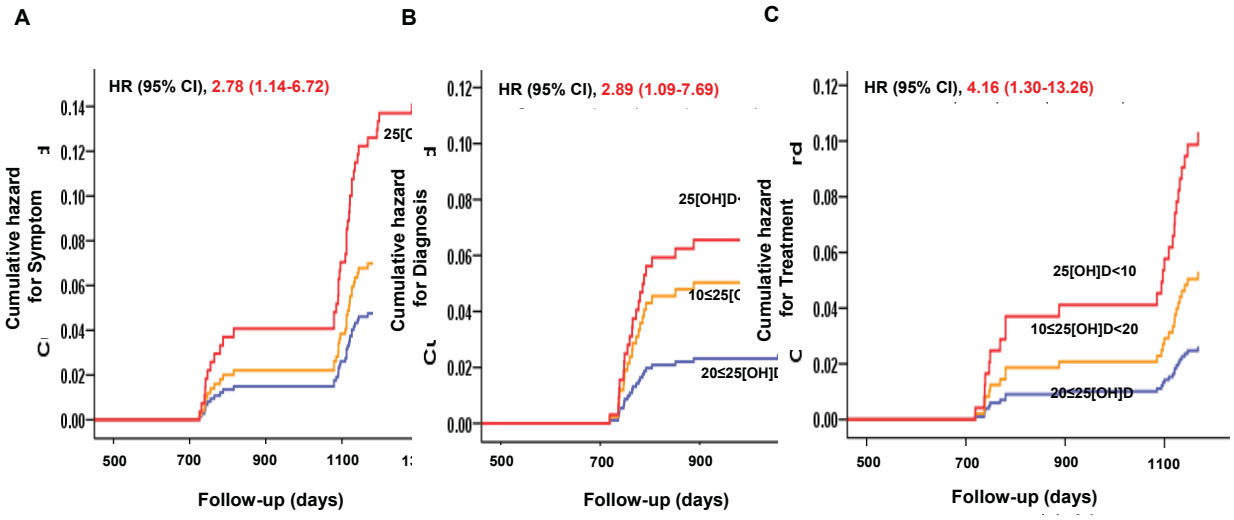
Cumulative hazard for a newly development of AD symptom, diagnosis, and treatment during follow-up period according to CB 25[OH]D



In addition, lower CB vitD linked to the reduced chances for remission of AD. But serum vitD deficiency at 1 year did not increase risk of newly development and not associated with HR(hazard ratio).

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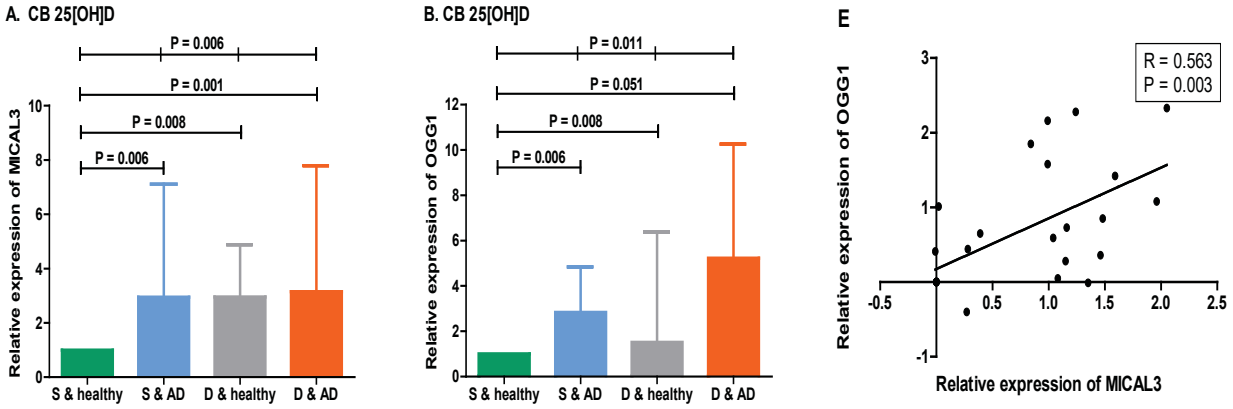
Cho HJ, Shin YH, et al. JACI 2018

Comparisons of the relative expression ratio for MICAL3 and OGG1 in placenta according to the vitamin D level of CB and AD

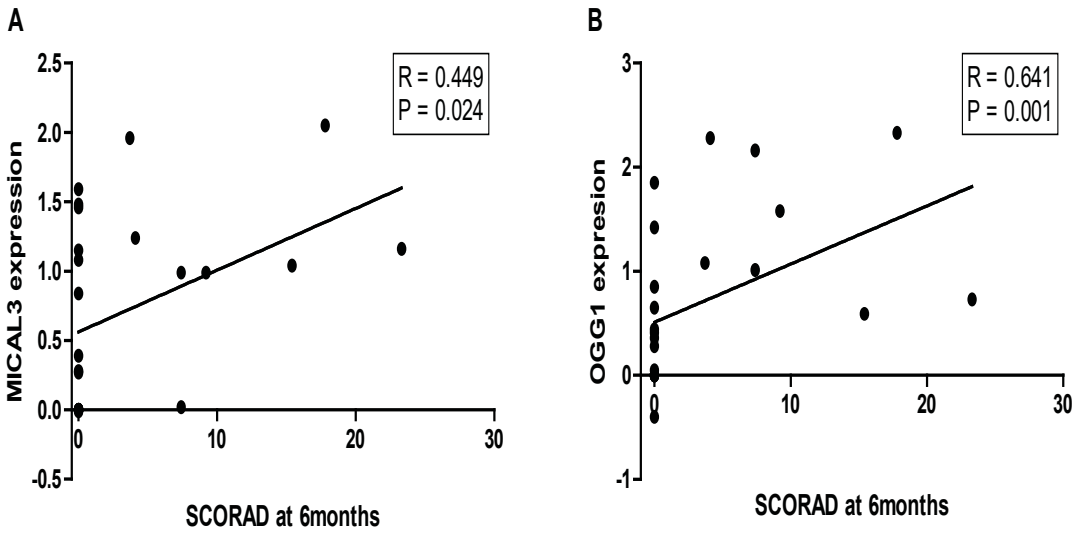
Comparison of differently methylated CpG sites among total, healthy, and AD in vitamin D deficiency : MICAL3 hypomethylation



MICAL3 : microtubule-associated monooxygenase, calponin and LIM domain containing
OGG1 : 8-oxoguanine DNA glycosylase

Cho HJ, Shin YH, et al. JACI 2018

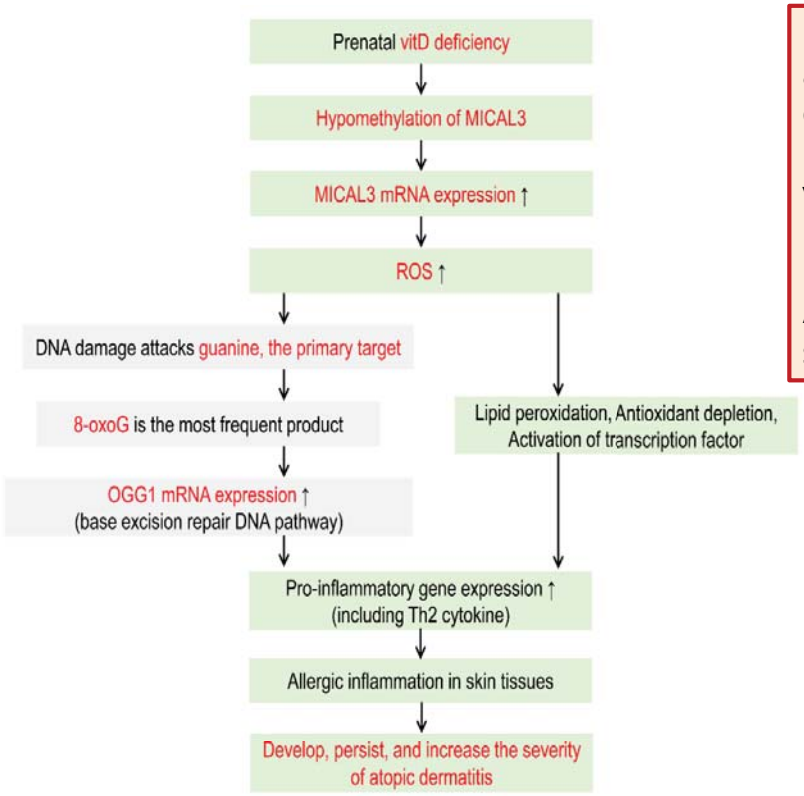
Correlation between ROS associated gene (MICAL3 (A), OGG1 (B)) and SCORAD at 6months



MICAL3 : microtubule-associated monooxygenase, calponin and LIM domain containing
OGG1 : 8-oxoguanine DNA glycosylase

Cho HJ, Shin YH, et al. JACI 2018

Proposed epigenetic mechanism through which the prenatal vitD level contributes to AD in offspring



Due to the hypomethylation and consequently increased expression of oxidative stress-promoting genes in severely vitamin D-deficient fetus, the resulting offspring is predisposed to subsequent AD development and its severity.

Cho HJ, Shin YH, et al. JACI 2018

DIET AND FA

Original Article

Maternal Perinatal Dietary Patterns Affect Food Allergy Development in Susceptible Infants

Yoon Hee Kim, MD, PhD[a,b], Kyung Won Kim, MD, PhD[b,c], So-Yeon Lee, MD, PhD[d], Kyeong Ok Koo, PhD[e], Sung-Ok Kwon, PhD[f], Ju-Hee Seo, MD, PhD[g], Dong In Suh, MD, PhD[h], Youn Ho Shin, MD, PhD[i], Kangmo Ahn, MD, PhD[j], Se-Young Oh, PhD[e], Sooyoung Lee, MD, PhD[k], Myung Hyun Sohn, MD, PhD[b,c,*], and Soo-Jong Hong, MD, PhD[d,*]
Seoul, Chuncheon, Cheonan, and Suwon, Korea

What is already known about this topic? Food allergy is caused by interactions between genes and the environment, but these interactions are not yet fully clear.

What does this article add to our knowledge? Maternal confectionary diet (high intake of baked and sugary products that may contain high trans fats) during the perinatal period may influence the development of food allergy in infants with CD14 and GST gene polymorphisms.

How does this study impact current management guidelines? Maternal dietary interventions involving reducing the consumption of confectionery (high intake of baked and sugary products) during the perinatal period should be implemented to prevent the development of food allergy, especially in genetically susceptible children.

Background: Maternal diet has emerged as an important risk factor for FA.
Objects: We aimed to evaluate the interaction between infant genetic variations and maternal dietary patterns for risk factors in the development of FA.
Methods: We used a birth cohort of 1628 infants. Maternal dietary intakes were assessed at 26 weeks of pregnancy by a food frequency questionnaire and grouped according to five dietary patterns. Infant CB samples were genotyped at 12 loci.

Kim YH, et al. JACI Practice 2019

Maternal perinatal dietary patterns affect food allergy development

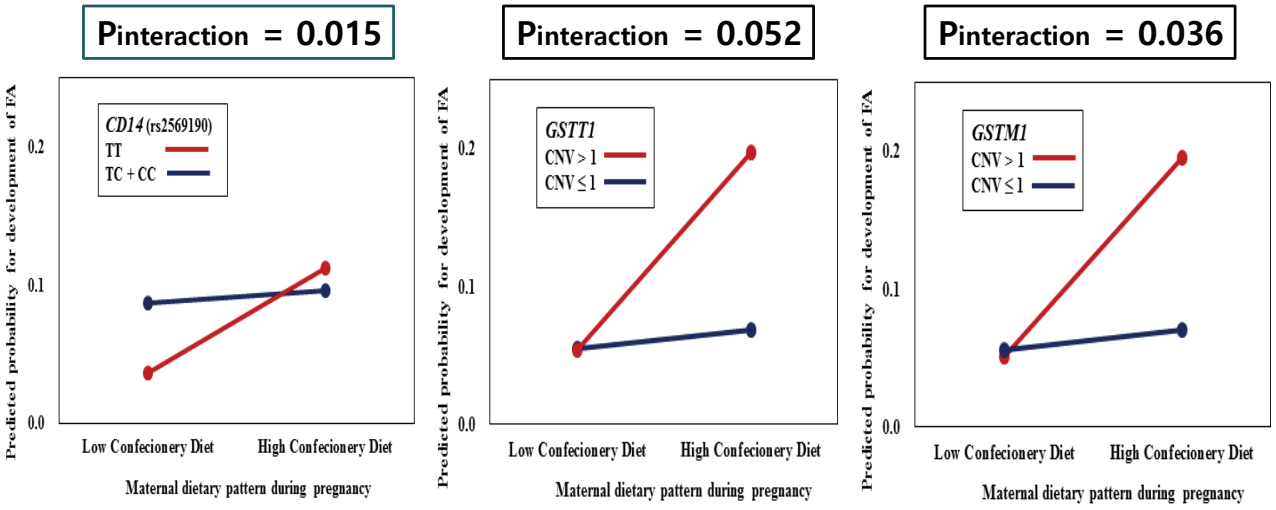
Multivariate analysis for development of FA in infant according to breast feeding period

N (FA/Total infants)	ORs of Maternal confectionary diet	95%CI	P*	Interaction P†
Total subject (147/1628)	1.517	1.017-2.147	.019	
N for breastfeeding analysis (101/1075)‡				.374
Breast feeding > 6 month (34/462)	1.792	1.053-3.048	.031	
Breast feeding ≤ 6 month (67/546)	1.219	0.594-2.501	.590	

FA, food allergy, OR, Odds ratio; CI, Confidence interval.
*P (significant in < .05) in a risk assessment of maternal confectionery dietary pattern for development of FA according to breastfeeding period. †interaction P (significant in < .10) in an interaction analysis between breastfeeding period and maternal confectionery dietary pattern for development of FA.
All analyses were adjusted for birth season, maternal allergic history, maternal age, and maternal exposure to smoking, delivery method, presence of siblings, infants' sex, and infants' development of atopic dermatitis at 6 months. ‡N (infants with FA/total infants) is a number of infant with FA and a number of infants in which the periods of breast feedings could be assessed.

Kim YH, et al. JACI Practice, 2019

Fitted predicted probability plots for development of FA in relation to maternal confectionery dietary pattern at SNP rs2569190 in *CD14* (A) and *GSTM1* (B) and *GSTT1* (C) CNVs.



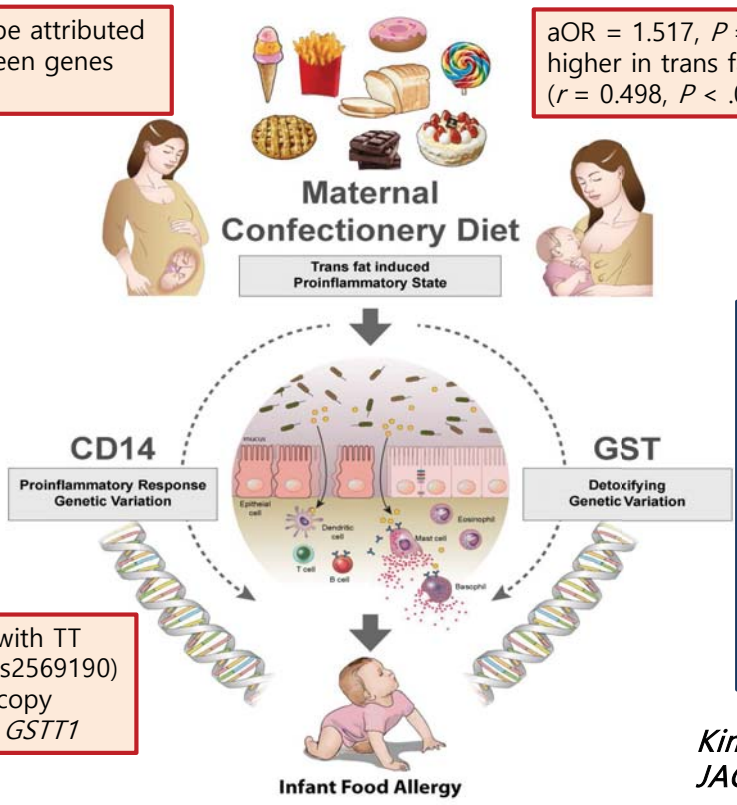
CD14 polymorphism that plays a role in increasing the proinflammatory response and polymorphisms in GST genes involved in the detoxification pathway may increase the susceptibility of infants to the influence of a maternal confectionery dietary pattern on the development of infant FA.

Kim YH, et al. JACI Practice, 2019

Maternal perinatal dietary patterns affect food allergy development in susceptible infants

Increase of FA can be attributed to interaction between genes and environment.

aOR = 1.517, *P* = .02 higher in trans fat (*r* = 0.498, *P* < .001)



significantly related with TT genotype of *CD14* (rs2569190) and more than one copy of gene *GSTM1* and *GSTT1*

Message :
Increased maternal intake of baked goods and confections during the perinatal period may increase the risk of infant food allergy, which could reflect the harmful effects of trans fatty acids derived from industrial food processing.

Kim YH, et al. JACI Practice, 2019

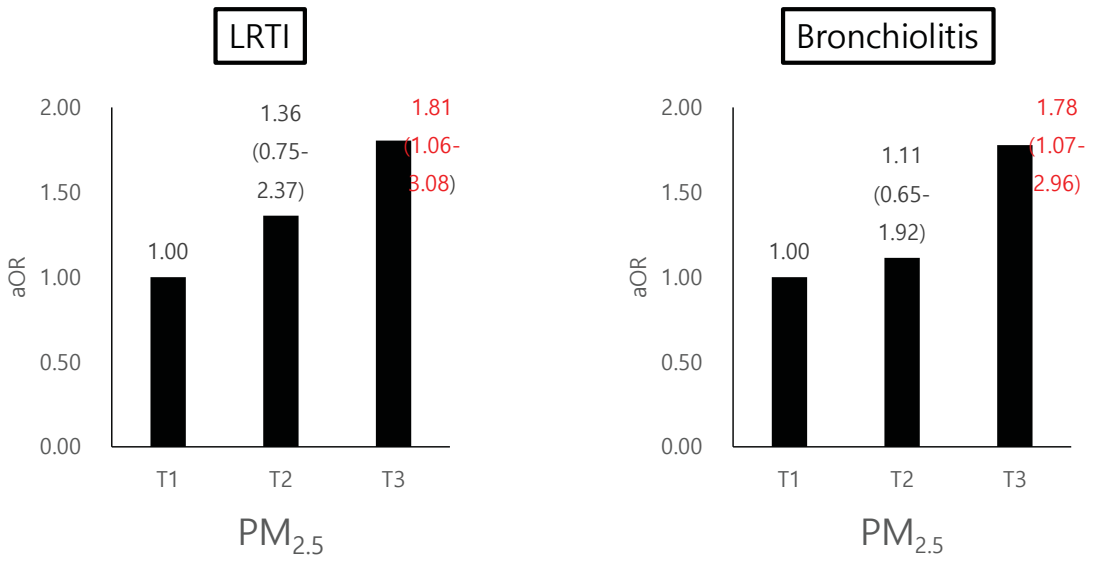
PM AND RTI

Prenatal PM vs LRTI by *GSTM1* gene : COCOA

Background: Prenatal period is considered as critical period for the effects of exposure to air pollution on development of respiratory systems. The most relevant time of particulate matter (PM) exposure during pregnancy on lower respiratory tract infections (LRTIs) in infancy is unclear.

Objects: To investigate the effect of PM according to **exposure time** during pregnancy on LRTIs and whether genetic polymorphism of *GSTM1* modify these effects of PM.

Association between $PM_{2.5}$ exposure during 3rd trimester and LRTI and bronchiolitis at age 1



Yang SI, et al. Ped Pulm 2019

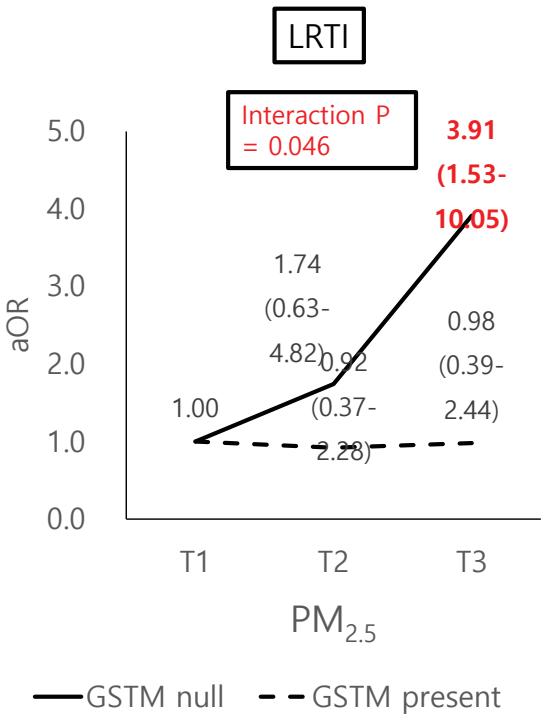
Association between $PM_{2.5}$ exposure during the third trimester and lower RTI at 1 year of age

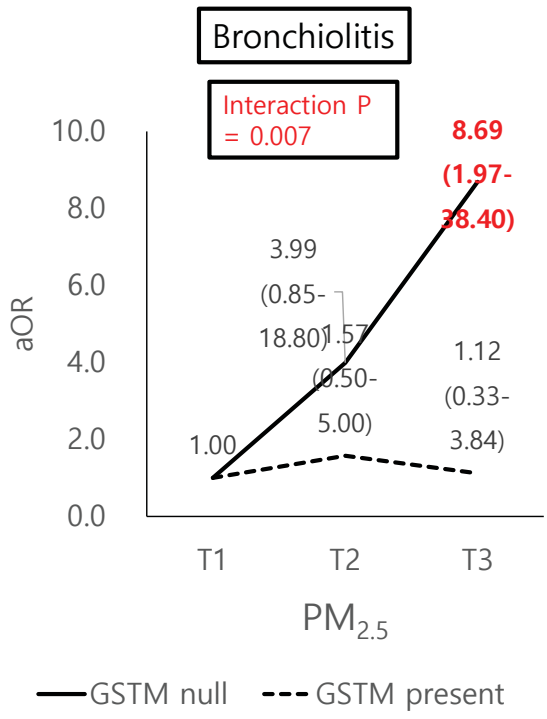
	aOR*	95% CI		p value
$PM_{2.5}$ T1	1.00			
$PM_{2.5}$ T2	1.29	0.73	2.27	0.38
$PM_{2.5}$ T3	1.84	1.04	3.26	0.04
	aOR+	95% CI		p value
$PM_{2.5}$ T1	1.00			
$PM_{2.5}$ T2	1.38	0.79	2.40	0.26
$PM_{2.5}$ T3	2.10	1.18	3.74	0.01
	aOR#	95% CI		p value
$PM_{2.5}$ T1	1.00			
$PM_{2.5}$ T2	1.52	0.85	2.73	0.16
$PM_{2.5}$ T3	2.14	1.18	3.88	0.01

*Adjusted for sex, birth weight, parental history of allergic disease, maternal education level, maternal exposure to secondhand smoking during pregnancy, presence of siblings, attendance at daycare under 1 year of age and $PM_{2.5}$ exposure during the first and second trimester, +Adjusted additionally $PM_{2.5}$ exposure during 1 year of age, #Adjusted additionally exposure to NO_2 and O_3 at the same time

Yang SI, et al. Ped Pulm 2019

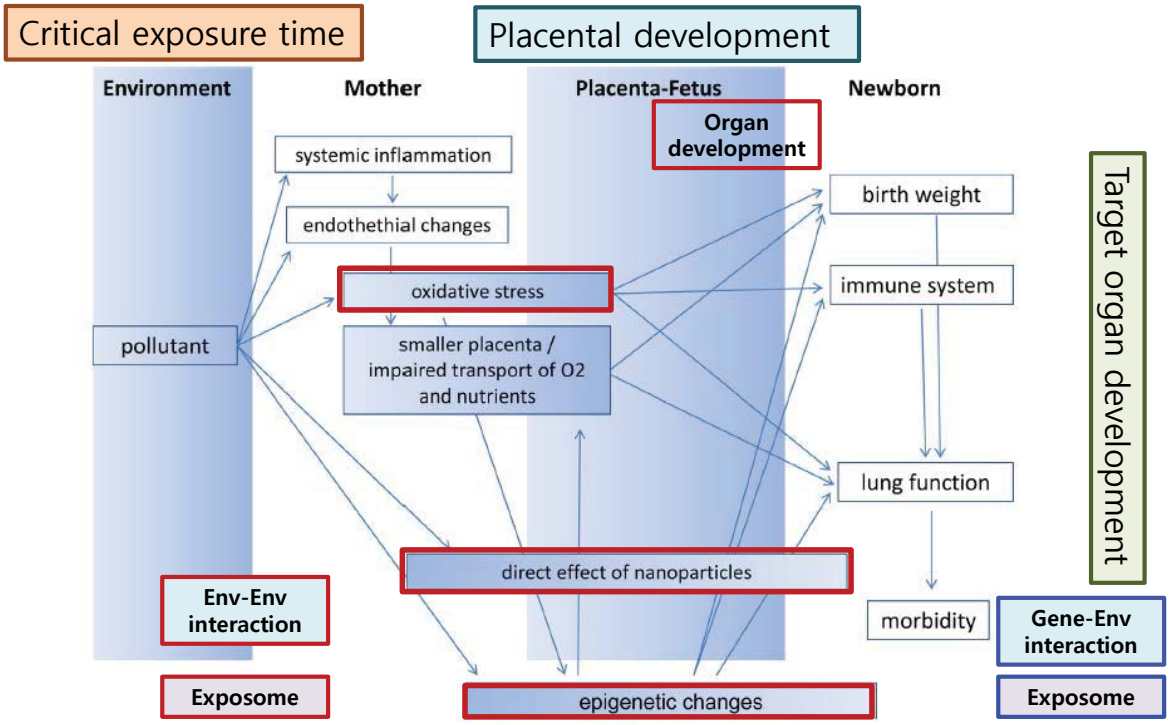
Association between $PM_{2.5}$ exposure during 3rd trimester and LRTI and bronchiolitis at age 1 by GSTM1 genotype





Yang SI, et al. Ped Pulm 2019

Direct & indirect impact of air pollution in pregnancy on adverse birth outcomes and lung development



Korten I, et al. Pediatr Respir Reviews 2017; 21:38–46 (Modification)

Conclusion :

- Prenatal vitD deficiency affects the RTI and the development and prognosis of AD, which is mediated by MICAL3 hypomethylation.
- Prenatal maternal diet may lead to development of FA in susceptible infant.
- Outdoor and indoor PM, especially in prenatal period, are very important risk factors in child lung health.
- The environmental effects may increase in the genetically susceptible individuals or be mediated by epigenetics during critical period.
- Birth cohort study and interpretation of host and environmental interaction gives light to understand these diverse environmental responsiveness and provides new individualized approaches to the prevention of diseases in children.

Acknowledgement

Advisory committee
Domestic
Yonsei Univ. Prof. Kim GE
Seoul National Univ. Prof. Ko YR
Yonsei Univ. Prof. Shin DC
National Institute of health Dr. Lee JS
Inha Univ. Prof. Lim JH
Univ. of Ulsan Prof. Goo YM
DB enterprise representative director Lee SW

International
Arizona University Prof. Martinez
Wisconsin University Prof. Lemanske
University of Western Australia Prof. Sly

Scientific committee
Sungkyunkwan Univ. Prof. Shim JY
Sungkyunkwan Univ. Prof. Ahn GM
Hallym Univ. Prof. Lee SY
Inje Univ. Prof. Kim HB
Dankook Univ. Prof. Seo JH
Soonchunhyang Univ. Prof. Yang HJ
CHA Univ. Prof. Shin YH
Seoul National Univ. Prof. Seo DI
Cheonnam Univ. Prof Lee Eun
Kwandong Univ. Prof Cho HJ

Promotion committee
Ulsan Univ. Prof. Lee SY
Yonsei Univ. Prof. Kim KW
Hallym Univ. Prof. Yang SI

Policy committee
Inje Univ. Prof. Kim HB
Cheonnam Univ. Prof Lee Eun
Kwandong Univ. Prof Cho HJ
Yonsei Univ. Prof. Kim YH

ASAN Medical Center
Hong SJ (PI)
Lee SY (Pediatrics)
Won HS (Obstetrics)
Lee MY (Obstetrics)
Choi WY (CRC)
Choi JY (CRC)
Lee SY (CRC)

Samsung Center
Ahn GM (PI)
Choi SJ (Obstetrics)
Kim EH (CRC)
Kim SY (CRC)

Severance Center
Kim KW (PI)
Kim YH (Pediatrics)
Kwon JY (Obstetrics)
Kang JI (CRC)
Lee HW (CRC)

CHA Gangnam Center
Shin YH (PI)
Kim SH (Obstetrics)
Cho YK (Obstetrics)
Yoo HJ (CRC)
Park HW (CRC)

Seoul National Center
Seo DI (PI)
Cheon JK (Obstetrics)
Seo HJ (CRC)

Central Center
Cho HJ MD
Yoon JS MD
Jung SS MD
Oh HY (program manager)
Lee SH (DataBase adiministrator)
Kim B (DataBase management)
Kim SR (DataBase management)
Kim GR (center coordinator)
Choi GY (environment coordinator)
Kim HS (biological samples)

DATA management/statistics team
Seoul National Univ. Prof. Kim H
Seoul National Univ. Prof. Won SH
Researchers : Lee MK, Kim KJ

Epidemiology team
Soonchunhyang Univ. Prof. Yang HJ
Univ. of Ulsan Prof. Kim BS

Environment team
Inha Univ. Prof. Kim HC
Hallym Univ. Prof. Yang SI
Researchers : Choi KY, Lee KW, Won YW

Genetics/epigenetics team
Ulsan Univ, Prof Kim JH
Researchers : Kang MJ, Park YH

Microbiome team
Hallym Univ. Prof. Kim BS
Cheonnam Univ. Prof. Lee E
Researchers : Park YM, Kang MJ

Metabolome team
Ulsn Univ. Prof Yoo HJ
KBSI. Nam MH

Virus team
Inje Univ. Prof. Kim HB

Biological samples Team
Ulsan Univ. Prof. Lee SY
Seoul National Univ. Prof. Kwon JW
Researcher : Kim HS, Choi YH

Functional research team
Ulsan Univ. Prof. Hong SJ
Researchers : Lee SH, Ahn JL, Ko HN

Nutrition team
Kyunghee Univ. Prof. Oh SY
Researchers : Kwon SO, Hwang HJ, Koo HO

Mental health development team
Yonsei Univ. Prof. Shin YJ
Ajou Univ. Prof. Chang HY
Hanshin Univ. Prof. Lee GS
Researcher : Choi IA, Lee MY

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Epidemiology Team

Oh HY
Lee SH
Kim SR
Lee SH
Kwon NK
Yang SH
Choi KY
Lee KW
Lee ES
Park MJ
Lee SY
Shin YH
Ahn KM
Kim KY
Seo DI

Environmental Health Center

Lee SY
Hong SB
Do KY
Jung SH
Kim HJ
Lim HY
Kang MJ
Na MR
Lee BN
Kim EM
Lee DE
Kwon MS

Research Team

Kim JH
Park YM
Lee SH
Kim HS
Park YH
Ahn JR
Go HN

CHEER study: Kwon HJ, Leem JH
COCOA-AIR Project: Kim HB, Kim HC
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Thank you for your attention !
10th Anniversary day for COCOA: 2018