

Maternal Perinatal Dietary Patterns Affect Food Allergy Development in Susceptible Infants



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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: The increasing incidence of food allergy (FA) can be attributed to interactions between genes and the environment, but these interactions are not yet fully clear.

OBJECTIVE: We aimed to evaluate the interaction between infant genetic variations and maternal dietary patterns to identify risk factors in the development of FA.

METHODS: We used the Cohort for Childhood Origin of Asthma and allergic diseases birth cohort of 1628 infants, born between 2007 and 2015. Maternal dietary intakes were assessed at 26 weeks of pregnancy using a food frequency questionnaire and grouped according to 5 dietary patterns. Infant cord blood samples were genotyped at 12 loci.

RESULTS: Among 1628 infants, 147 (9.0%) were diagnosed with FA based on history. A maternal confectionary diet characterized by a higher intake of baked and sugary products during pregnancy was associated with a higher prevalence of FA (adjusted odds ratio [OR] = 1.517, $P = .02$); this dietary

pattern tended to be higher in trans fat ($r = 0.498$, $P < .001$). Development of FA was associated with longer periods of breastfeeding (adjusted OR = 1.792, $P = .03$), and this dietary pattern was more significantly related to the development of FA in infants with the homozygous TT genotype of *CD14* (rs2569190) and more than 1 copy of *GSTM1* and *GSTT1*. **CONCLUSIONS:** A maternal confectionary diet during pregnancy that majorly consists of baked and sugary products, combined with a longer ensuing period of breastfeeding, may lead to the development of FA, suggesting a harmful effect of trans fats in the infant. Polymorphisms in *CD14* and *GST* in the infant influence FA susceptibility. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2337-47)

Key words: *CD14*; Confectionary; Dietary pattern; Fatty acids; Food allergy; Genetics; *GST*; Infant; Perinatal; Polymorphism

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Abbreviations used

AD- Atopic dermatitis
 CNV- Copy number variation
 COCOA- COhort for Childhood Origin of Asthma and allergic diseases
 FA- Food allergy
 FFQ- Food frequency questionnaire
 GST- Glutathione S-transferase
 LPS- Lipopolysaccharide
 MFDS- Ministry of Food and Drug Safety
 OR- Odds ratio
 rTFA- Ruminant TFA
 SFA- Saturated fatty acid
 SNP- Single nucleotide polymorphism
 TFA- Trans fatty acid
 TLR- Toll-like receptor

Food allergy (FA) is known to be caused by environmental triggers in genetically susceptible individuals and usually occurs in early childhood.¹⁻³ Maternal diet during pregnancy and breastfeeding is considered an important environmental factor in allergy programming.^{4,5} Determining maternal dietary patterns by assessing total food intake is considered preferable to measuring a single nutrient, food, or food groups because dietary patterns vary among cultures and regions.⁶

Studies of genes that influence susceptibility to allergic diseases, such as asthma and atopic dermatitis (AD), have improved our understanding of the mechanism of allergy through shared genetic loci and related phenotypes.⁷ Many genetic variants, known as single nucleotide polymorphisms (SNPs), have been suggested to affect susceptibility, not just to asthma but to atopy and AD.⁸ However, genetic variants associated with FA are largely unknown because the prevalence of FA is lower than those of asthma and AD and because the phenotypic heterogeneity of FA makes diagnosis difficult.^{9,10} Genetic variation is also influenced by ethnicity and area of residence.¹¹

Several birth cohort studies have been established to disentangle the contributions of genetic and environmental factors to allergic diseases. These cohorts are designed to accurately reflect the characteristics of the population from which they are derived.^{12,13} In 2007, we established a prospective birth-cohort study in Korea called the COhort for Childhood Origin of Asthma and allergic diseases (COCO) to investigate the individual and interactive effects of genetics and environmental factors on the development of allergic diseases in Korean children.¹⁴ In this study, we aimed to determine the contribution of maternal dietary patterns to the development of FA in infants and to identify potential interactions between maternal dietary patterns and known genetic susceptibility loci for asthma and atopy.

METHODS**Subjects**

The COCO study¹⁴ is an ongoing prospective birth cohort study carried out in 5 Korean hospitals. Recruitment took place from November 2007 to April 2015. Detailed descriptions of this study

are provided in the [Supplementary Methods](#) (available in this article's Online Repository at www.jaci-inpractice.org).

Definition of FA based on history

All mothers were asked to complete a questionnaire regarding FA in their children at 1 year of age to determine the following: (1) any diagnosis of FA, (2) any symptoms of FA, (3) causative foods, (4) time from food ingestion to symptom development, (5) repetition of adverse reactions, (6) avoidance of causative foods, and (7) whether any medications had been prescribed. All children at 1 year of age visited an allergy clinic at one of the institutions and were examined for the presence of FA by a pediatric allergy specialist. If there was a positive response to any of the 7 questions above, the pediatric allergy specialists asked more detailed questions to verify that the allergic symptoms, including the organs affected, timing from ingestion to symptom onset, and the exact foods involved in the reaction that were subsequently avoided, fulfilled the definition of FA based on history. This is explained in detail below. FA was reported as the presence of definite allergic symptoms after ingestion of a specific causative food with a time interval of 4 hours or less from food ingestion to symptom awareness,¹⁵ followed by repeated allergic symptoms from the same definitive causative food or the complete avoidance of the definitive causative food after the development of allergy. Allergic symptoms included skin rash or wheal or gastrointestinal, respiratory, or cardiovascular symptoms.¹⁶

For focusing on IgE-mediated FA and excluding non-IgE-mediated FA, if allergic symptoms were reported as gastrointestinal (vomiting, diarrhea, bloody stool, etc.), the presence of associated symptoms, such as skin symptoms (wheals, rash, or edema), respiratory symptoms, or cardiovascular symptoms, was also required for diagnosis of FA based on history.^{17,18}

Maternal dietary patterns during pregnancy

A semiquantitative food frequency questionnaire (FFQ) was self-administered at 26 weeks of pregnancy to assess maternal dietary intake. This questionnaire was previously validated and included 120 food items.^{19,20} For the clustering of dietary patterns, our analysis consisted of 35 foods/food groups (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). We calculated trans fat intake based on information supplied by Food Safety Korea (<http://www.foodsafetykorea.go.kr/>), which is administered by the Ministry of Food and Drug Safety (MFDS) in Korea. The maximum and minimum trans fat amounts per gram of various foods corresponding to each of the 35 foods/food groups were used.

Dietary patterns were classified into 5 groups derived from clustering analysis and named according to the foods/food groups with the most positive factor loadings in the pattern ([Table 1](#)). The 5 groups consisted of the "traditional," "confectionery," "meat," "processed," and "coffee and milk" patterns. Details for maternal dietary pattern analysis are provided in the [Supplementary Methods](#) (available in this article's Online Repository at www.jaci-inpractice.org).

Assessment of infant genetic variation

For the evaluation of the interaction between maternal dietary patterns and infant genetic variation, we obtained DNA extracted from infant cord blood samples. The collaborating obstetricians in the COCO study were directly involved in the delivery and collected the cord blood at birth according to a standard protocol.¹⁴ Cord blood samples obtained from the infants were genotyped at 12

TABLE I. Major foods/food groups according to maternal dietary patterns (N = 1628)

	Traditional	Confectionery	Meat	Processed	Coffee and milk
Major food/food group*	Vegetables	Bread	Chicken	Fast food	Coffee
	Seaweed	Potatoes	Beef	Noodle	Milk
	Fruits	Rice cake	Fresh fish	Ramen	
	Anchovies	Sweets	Pork	Fat	
	Beans	Fat	Processed fish	Cheese	
	Kimchi	Ice cream	Processed meat		
		Cereal			
		Chocolate			
		Sweet bread			

*Major foods/food groups were defined as those ≥ 0.3 factors loading through factor analysis.

genetic loci considered to be important in the development of allergic diseases, as shown in Table II. Details for the assessment of genetic variation are provided in the [Supplementary Methods](#) (available in this article's Online Repository at www.jaci-inpractice.org).

Statistical analysis

Maternal and infant characteristics were compared between infants with and without FA. Maternal characteristics (maternal age, allergic history, and smoking history including indirect contact and delivery methods) and infant characteristics (birth season, sex, presence of siblings, and AD at 6 months) were used as potential confounding variables in the multivariable analysis. Maternal allergic history was considered positive when asthma, allergic rhinitis, or AD was diagnosed.

For assessing the influence of the maternal dietary pattern on the development of infant FA, each dietary pattern was divided into high (Q3-Q4) and low (Q1-Q2) intake groups according to the quartiles of the dietary pattern scores, and the groups were compared for the number of infants with and without FA. Each dietary pattern was assessed by multivariable analysis for the development of FA after adjustment with the confounders mentioned above. The amounts of energy and nutrients consumed, including trans fat, were compared amongst the different dietary patterns.

All homozygous and heterozygous SNP genotypes and copy number variations (CNVs) of more than 1 copy were evaluated using multiple logistic regression models with an added "interaction term" to identify candidate SNPs that interact with maternal dietary patterns in the development of infant FA. The *P* value of the additional interaction term was derived from the logistic model, representing the interaction *P*. Correction for multiple comparisons was carried out using the Benjamini-Hochberg false discovery rate method.²¹

We conducted a stratified analysis using logistic regression to investigate the effects of the risk associated with maternal dietary patterns within each genotype group separately, and we produced plots of the predicted probabilities for the development of FA between high- and low-risk maternal dietary patterns to display the results graphically. All *P* values $< .05$ and interaction *P* values $< .10$ were considered statistically significant.^{22,23} SPSS version 23 statistical software (IBM Corp., Armonk, NY) was used for all analyses.

RESULTS

Maternal/infant characteristics and incidence of infant FA based on history

Of the 2512 women who were recruited, 1628 mother-infant pairs were analyzed finally in this study, which is summarized in Figure 1.

Among the 1628 infants, 147 (9.03%) were diagnosed with FA based on history. Table III shows a comparison of maternal and infant characteristics between infants with and without FA. Mothers of infants with FA were more likely to have a history of allergy, whereas other maternal characteristics showed no differences between the 2 groups.

The most frequent food allergens were eggs (61 infants, 41.5%) and milk (43 infants, 29.3%). There were 34 infants with more than 1 causative food, and 1 infant exhibited allergic symptoms in response to eggs, milk, and wheat concomitantly. The most common symptoms were skin rashes and wheals, which were reported in 129 infants (88%), followed by facial swelling (35 infants, 24%) and gastrointestinal symptoms (17 infants, 12%). The causative food allergens and allergic symptoms are shown in Figures E1 and E2 (available in this article's Online Repository at www.jaci-inpractice.org). Of the total subjects, 1300 were sampled for serum and total IgE. Infants with FA had significantly higher IgE levels than those without (Table III and Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Maternal dietary patterns during pregnancy associated with infant FA

Table III shows the distribution of the 5 maternal dietary patterns in infants with and without FA and the results of the multivariable analysis for the development of FA. For each dietary pattern, the percentage of individuals in the upper intake group (Q3-Q4) was compared between the infants with and without FA. The percentage of individuals in the upper intake groups (Q3-Q4) for the maternal confectionery dietary pattern was higher among infants with FA than among those without, whereas the other dietary patterns showed no significant differences between the groups. On multivariable analysis and adjusting for possible confounding factors, the maternal confectionery diet was found to be significantly associated with the development of infant FA (odds ratio [OR] = 1.517, *P* = .019).

Daily intakes of nutrients, such as protein, fat, vitamins, folate, and fatty acids, were compared between the low and high confectionery diet intake groups (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Because the confectionery diet was characterized by higher intake of baked goods and sugary products, we also compared trans fat intakes. When considering each food/food group for maximal trans fat intake, a higher confectionery intake was associated with higher trans fat intake (56.6 g of trans fat in upper [Q3-Q4] quartiles vs 39.8 g in lower [Q1-Q2] quartiles). According to the

TABLE II. Screening of infant genetic variations for interaction effects between maternal confectionery dietary pattern and infant development of food allergy

	ORs of maternal confectionery diet	95% CI	<i>P</i> *	FDR <i>P</i> †	Interaction <i>P</i> ‡	FDR interaction <i>P</i> §
Single nucleotide polymorphisms, N (infants with FA/total infants)¶						
Total infants (147/1628)	1.517	1.017-2.147	.019			
IL 13, rs20541 (129/1512)						
GG (66/744)	1.891	1.106-3.234	.020	.021	.345	.376
AA+AG (63/768)	1.311	0.775-2.216	.313	.327		
CD14, rs2569190 (129/1508)						
TT (39/528)	3.418	1.608-7.266	.001	.001	.015	.016
CC+CT (90/980)	1.133	0.731-1.755	.578	.578		
TLR4, rs1927911 (130/1508)						
CC (48/555)	1.663	0.903-3.065	.103	.107	.817	.891
TT+TC (82/953)	1.465	0.919-2.337	.109	.114		
GSDMB, rs4794820 (126/1492)						
GG (66/784)	1.679	0.991-2.844	.054	.056	.570	.622
AA+AG(60/708)	1.381	0.801-2.380	.245	.256		
GSDMB, rs7216389 (128/1506)						
TT(72/830)	1.495	0.908-2.461	.114	.119	.990	.994
CC+CT(56/676)	1.526	0.867-2.687	.143	.149		
GR, rs41423247 (130/1511)						
GG(87/918)	1.530	0.972-2.409	.066	.069	.898	.979
CC+CG(43/593)	1.390	0.730-2.650	.314	.328		
BDNF, rs6265 (129/1512)						
GG(37/440)	2.235	1.075-4.647	.031	.032	.185	.202
AA+AG(92/1072)	1.314	0.850-2.030	.219	.229		
Nrf2, rs6726395 (129/1510)						
GG(52/562)	1.516	0.838-2.743	.169	.176	.994	.994
AA+AG(77/948)	1.620	1.000-2.625	.050	.052		
NAT2, rs4271002 (129/1505)						
GG(82/883)	1.496	0.941-2.380	.089	.093	.691	.754
CC+CG(47/622)	1.504	0.805-2.810	.200	.209		
GSTP1, rs1695 (130/1511)						
AA(93/1001)	1.295	0.839-2.000	.243	.254	.153	.167
GG+GA(37/510)	2.367	1.121-4.998	.024	.025		
Copy number variations, N (infants with FA/total infants)¶						
GSTM1 (77/1031)						
CVN ≤ 1(53/836)	1.287	0.724-2.286	.390	.407	.048	.052
CVN > 1(23/191)	4.235	1.429-12.555	.009	.009		
GSTT1 (77/1031)						
CVN ≤ 1(51/820)	1.279	0.710-2.306	.413	.431	.033	.036
CVN > 1(25/209)	4.258	1.546-11.730	.005	.005		

BDNF, Brain-derived neurotrophic factor; *CD14*, cluster of differentiation 14; *CI*, confidence interval; *CVN*, copy number variation; *FA*, food allergy; *FDR*, false discovery rate; *GSDMB*, Gasdermin-B; *GSTM1*, glutathione *S*-transferase mu; *GSTP1*, glutathione *S*-transferases pi; *GSTT1*, glutathione *S*-transferase theta; *GR*, glucocorticoid receptor; *NAT2*, N-acetyltransferase 2; *Nrf2*, nuclear factor erythroid 2-related factor 2; *OR*, odds ratio; *TLR4*, Toll-like receptor 4.

All analyses were adjusted for birth season, maternal allergic history, maternal age, maternal exposure to smoking, delivery method, presence of siblings, infants' sex, and infants' development of atopic dermatitis at 6 months.

**P* (significant if < .05) in a risk assessment of the maternal confectionery dietary pattern for the development of FA according to homozygous dominant and the other SNP genotypes.

†FDR *P* and §FDR interaction *P* (significant if < .10) in a false discovery rate correction of interaction *P*.

‡Interaction *P* (significant if < .10) in an interaction analysis between infant genetic variation and maternal confectionery dietary pattern for the development of FA.

¶N (infants with FA/total infants) refers to the number of infants with FA and the number of infants whose cord blood could be assessed for a genetic variation.

correlation analysis, confectionery diet factor scores were significantly correlated with the maximal trans fat intake ($r = 0.498$, $P < .001$). No other nutrients were significantly correlated with confectionery diet factor scores, and neither total calorie intake

nor gestational weight gain differed between the upper and lower confectionery diet intake groups.

A correlation matrix was used to assess the correlations between the other dietary patterns and trans fat intake (Figure 2).

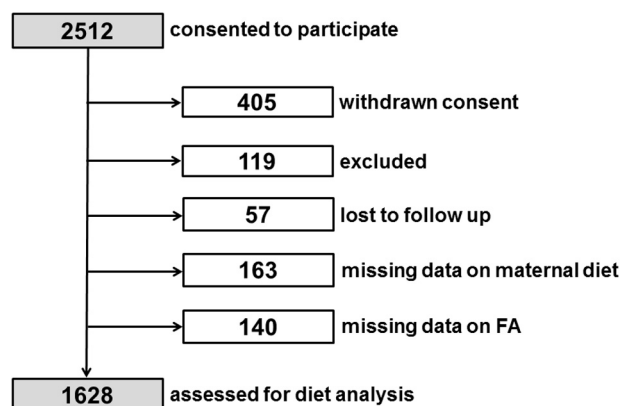


FIGURE 1. Flowchart of study subjects. Of the 2512 women, 405 withdrew consent and 57 lost to follow-up. Another 119 were excluded because of infants with preterm or congenital anomaly. Finally, 163 women with missing data on maternal diet and 140 babies with missing data on diagnosis of FA were excluded, leaving 1628 mother-infant pairs for diet analysis. FA, Food allergy.

The meat dietary pattern factor score also showed a meaningful correlation with the minimal trans fat intake, whereas the factor scores of the traditional, processed, and coffee and milk patterns did not show any correlations with trans fat intake.

Effect of breastfeeding

Because breastfeeding has been found to be an important factor in the development of allergy and as it also connects maternal diet to the nutrients that the infant receives, we evaluated the influence of breastfeeding on the maternal confectionery diet and the development of infant FA. A total of 1075 subjects answered the questions about breastfeeding period, among whom 101 had infants diagnosed with FA based on history. In infants with more than 6 months of breastfeeding, maternal confectionery diet was significantly associated with the development of FA (OR = 1.792, $P = .031$). This dietary pattern was not related to the development of FA in infants with less than 6 months of breastfeeding (OR = 1.219, $P = .590$), as shown in Table IV. However, the interaction between the breastfeeding period and the influence of the maternal dietary pattern on the development of FA was not statistically significant

TABLE III. Demographics and maternal dietary patterns during pregnancy between infants without and with FA and multivariable analysis for FA (N = 1628)

	Without FA (n = 1481)	With FA (n = 147)	ORs	95% CI
Maternal characteristics				
Age, y, m (IQR)	33 (31-35)	33 (31-35)	0.981	0.933-1.034
History of allergic disease*, n (%)	421 (28.4)§	58 (39.5)	1.652¶	1.160-2.350
Smoking exposure†, n (%)	840 (56.7)	80 (54.4)	0.872	0.618-1.232
Cesarean section, n (%)	538 (36.3)	47 (32.0)	0.831	0.572-1.207
Birth season, n (%)				
Spring	353 (23.8)	36 (24.5)		
Summer	319 (21.5)	37 (25.2)	1.116	0.684-1.822
Autumn	382 (25.8)	30 (20.4)	0.706	0.422-1.182
Winter	427 (28.8)	44 (29.9)	0.984	0.615-1.573
BMI before pregnancy, m (IQR)	20.2 (19.0-22.0)	20.0 (18.8-21.5)		
Gestational weight gain, kg, m (IQR)	13.0 (10.0-16.0)	12.12 (10.2-15.7)		
Infants' characteristics				
Male sex, n (%)	696 (47.0)	69 (46.9)	0.968	0.685-1.367
Presence of siblings, n (%)	608 (41.1)	58 (38.5)	0.906	0.632-1.300
Gestational age, wk, m (IQR)	39.1 (38.3-40.0)	39.4 (38.4-40.0)		
Birth weight (mg), m (IQR)	3190 (2920-3450)	3175 (2905-3490)		
Birth height (cm), m (IQR)	49.5 (48.0-51.0)	49.3 (48.0-50.2)		
Atopic dermatitis‡ at 6 mo, n (%)	213 (14.4)§	34 (23.1)	1.849¶	1.214-2.818
Atopic dermatitis‡ at 1 y, n (%)	193 (13.0)§	40 (27.2)		
Serum total IgE, m (IQR)	0.0 (0.0-1.0)§	1.0 (0.0-2.0)		
Maternal dietary pattern during pregnancy, n (%)				
Traditional	740 (50.0)	74 (50.3)	1.034	0.732-1.459
Confectionary	727 (49.1)§	87 (59.2)	1.517¶	1.070-2.150
Meat	743 (50.2)	71 (48.3)	0.885	0.626-1.249
Processed	740 (50.0)	74 (50.3)	0.981	0.695-1.386
Coffee and milk	738 (49.8)	76 (51.7)	1.026	0.726-1.449

BMI, Body mass index; CI, confidence interval; FA, food allergy; IQR, interquartile range; m, median; OR, odds ratio.

Data are expressed as median (interquartile range) or number (percentages). Multivariable analysis adjusted for birth season, maternal allergic history, age, smoking history, delivery method, presence of siblings, infants' sex, and atopic dermatitis at 6 months.

*History of allergic disease was assessed with asthma, allergic rhinitis, and atopic dermatitis.

†Smoking exposure includes maternal and family members who live together smoking history during pregnancy.

‡Doctor diagnosed atopic dermatitis.

§ $P < .05$ between infants without and with FA.

¶ $P < .05$ of ORs in multivariable analysis.

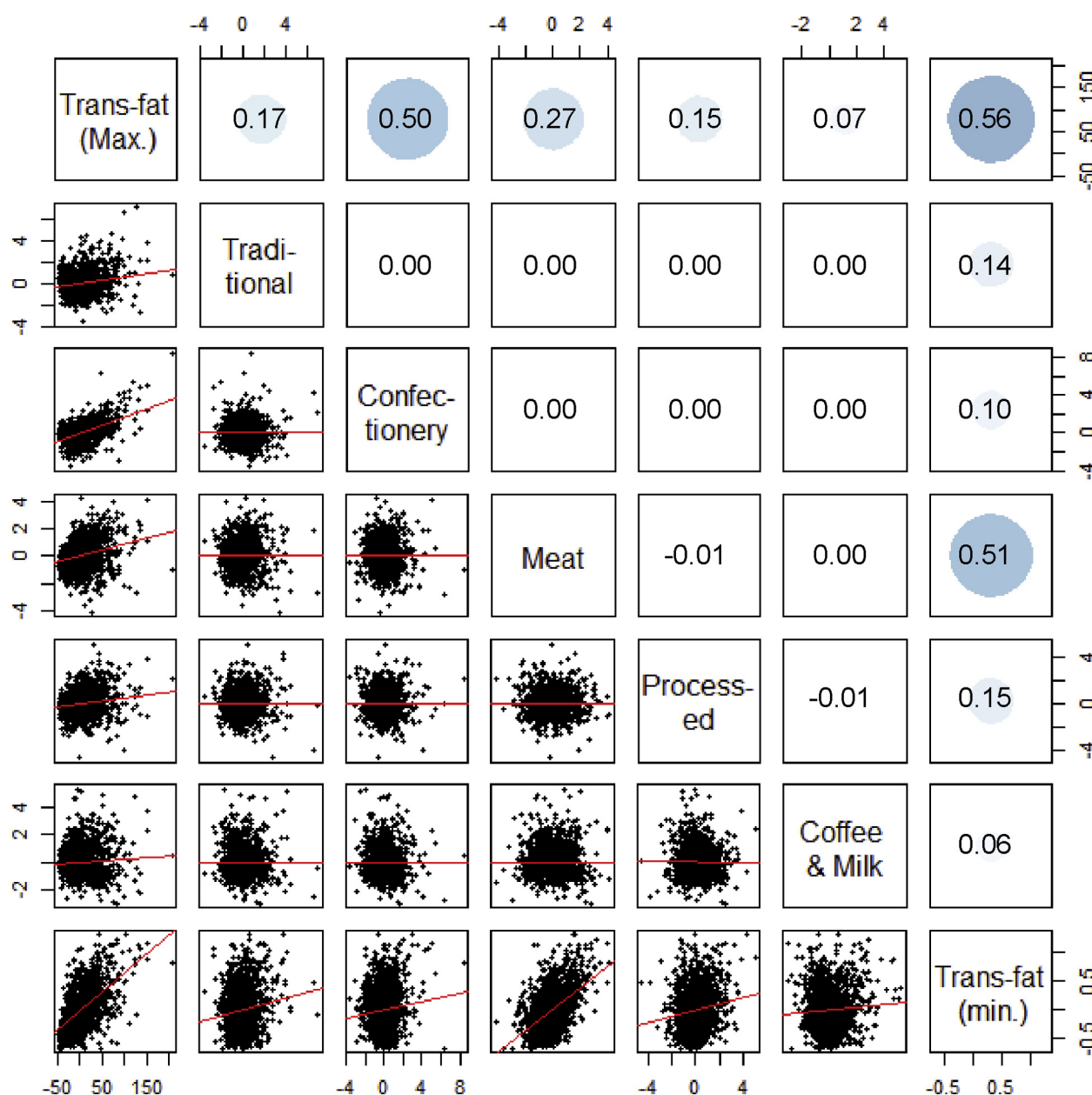


FIGURE 2. Correlation matrix between maximal and minimal trans fat intakes and 5 maternal dietary patterns.

(interaction $P = .374$). There was no significant difference in the duration of breastfeeding between infants with and without FA (data not shown).

Interactions between infant genetic variants and maternal dietary patterns in the development of infant FA

Interaction analysis was performed to identify infant genetic variants that interact with the maternal confectionery dietary pattern in the development of infant FA (Table II). After correction for multiple testing, *CD14*, *GSTM1*, and *GSTT1* genetic variants showed significant interactions with the maternal confectionery dietary pattern (interaction

$P = .015$ for *CD14*, $.052$ for *GSTM1*, and $.036$ for *GSTT1*). These results were based on 1508 infant cord blood samples that were assessed for the SNP in *CD14* and 1031 infant samples assessed for the CNVs of *GSTM1* and *GSTT1*. High maternal confectionery diet intake tended to increase the risk of developing FA among infants with the TT genotype at SNP rs2569190 in *CD14* but not in C-allele carriers, as shown in Figure 3, A. High maternal confectionery diet intake tended to increase the risk of developing FA in infants with more than 1 CNV of *GSTM1* or *GSTT1* but not in other infants, as shown in Figure 3, B and C. In the analysis using recessive models, no genetic variant showed a significant interaction (data not shown).

TABLE IV. Multivariable analysis for the development of FA in infants according to breastfeeding 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 mo (34/462)	1.792	1.053-3.048	.031	
Breast feeding ≤ 6 mo (67/546)	1.219	0.594-2.501	.590	

CI, Confidence interval; FA, food allergy; OR, odds ratio.

All analyses were adjusted for birth season, maternal allergic history, maternal age, maternal exposure to smoking, delivery method, presence of siblings, infants' sex, and infants' development of atopic dermatitis at 6 months.

*P (significant if <.05) in a risk assessment of the maternal confectionary dietary pattern for the development of FA according to breastfeeding period.

†Interaction P (significant if <.10) in an interaction analysis between breastfeeding period and maternal confectionary dietary pattern for the development of FA.

‡N (infants with FA/total infants) refers to the number of infants with FA and the number of infants in which the periods of breastfeeding could be assessed.

DISCUSSION

During the first and second trimester of pregnancy, a maternal dietary pattern that is high in baked and sugar products also referred to as confectionery can be linked to the higher likelihood of the development of FA in infants; this confectionery dietary pattern is correlated with higher trans fat intake. The association is more prominent in infants who breastfeed from their mothers for longer periods. For infants with genetic variations of homozygous TT in *CD14* (rs2569190) and infants with more than 1 CNV of *GSTM1* or *GSTT1*, a maternal confectionery dietary pattern is more significantly related to the development of FA.

Maternal diet in pregnancy encompasses more than food intake alone because high food quality and adequate nutrient intake during the perinatal period are critical for maternal and infant health.^{24,25} A "Western" diet, which is generally poor in fiber and rich in saturated fats and carbohydrate sweeteners, is considered to be an environmental risk factor, increasing the prevalence of FA.^{9,26} Moreover, high trans fat intake, as a typical part of the "Western" diet, was suggested to play a role in the development of childhood asthma, AD, and sensitization in a previous study that did not assess dietary patterns or FA.²⁷ In addition, several studies have reported that high margarine consumption and energy-dense dietary patterns, such as increased consumption of fast food, high-fat snacks, and candy, may affect the development of eczema and asthma, but these studies did not assess trans fat intake or FA.^{28,29} Here, we assessed trans fat intake in connection with a related dietary pattern and assessed its role in the development of allergy, specifically FA.

Trans fatty acids (TFAs) may induce various pathological conditions through direct effects related to inflammation and indirect effects related to gut microbiota dysbiosis, known as TFA lipotoxicity.^{30,31} TFAs induce a proinflammatory response that may disrupt the intestinal barrier and increase intestinal permeability; the subsequent penetration of food allergens through the disrupted intestinal barrier could be a cause of allergic reactions.^{32,33}

Most studies on the relationship between a "Western" diet and the development of asthma and atopy have focused on excessive weight gain, especially during pregnancy, and this relationship is explained by the inflammatory response of adipose tissue macrophages.^{34,35} However, in our study, mothers with high intake of a confectionery diet did not exhibit increased weight gain compared with the other mothers (Table E3,

available in this article's Online Repository at www.jaci-inpractice.org). This shows that TFA lipotoxicity can influence human health without causing excess weight gain.³¹

TFAs used in confections are usually industrial TFAs, produced during the partial hydrogenation of unsaturated fatty acids in vegetable oils, with concentrations as high as 60%.³⁰ In contrast, ruminant TFAs (rTFAs) are produced naturally from the bacterial metabolism of unsaturated fatty acids in the rumens of cows, sheep, and goats, with maximal concentrations of 6%.³⁰ This is why the meat dietary pattern was associated with minimal intake of trans fat, whereas the confectionery dietary pattern was associated with maximal intake of trans fat in the correlation matrix. The maternal meat dietary pattern was not associated with the development of infant FA, which may indicate that rTFAs in meat are not harmful to human health and may play a role in protecting against allergy development.^{30,36,37}

Exclusive breastfeeding is recommended in high-risk infants to prevent FA.³⁸ In this study, the maternal confectionery dietary pattern was found to have a greater influence on the development of infant FA in mother-baby pairs with longer breastfeeding periods. The FFQ includes dietary questions that encompass the previous year, and it is commonly used in diet research under the assumption that individual dietary habits do not change easily or quickly.^{39,40} Thus, if maternal dietary patterns are generally consistent throughout pregnancy and the first 6 months of breastfeeding, the harmful effects of the maternal confectionery diet may be passed to the infant through breastfeeding, and this may add to the *in utero* effect of maternal diet that occurs during pregnancy.²⁵

CD14 is a lipopolysaccharide (LPS)-binding protein that induces the production of innate immune cells through the Toll-like receptor (TLR) signaling pathway by recognizing bacterial lipoglycans, primarily LPS.⁴¹ In addition to LPS, saturated fatty acids (SFAs) can be recognized by the CD14-TLR4 complex and trigger inflammatory pathways, exacerbating many chronic diseases.^{42,43} The T allele at the *CD14* rs2569190 polymorphism can induce higher expression of *CD14* and increased monocyte cytokine production,^{44,45} leading to an excessive inflammatory response.⁴⁶ Assuming that TFAs result in a similar lipotoxic mechanism as SFAs,^{31,43} an increase in the proinflammatory response through high consumption of TFAs associated with the maternal confectionery dietary pattern could exacerbate the effects of the T allele in *CD14*, thus resulting in the significant interaction observed in our study. The T allele in *CD14* has been

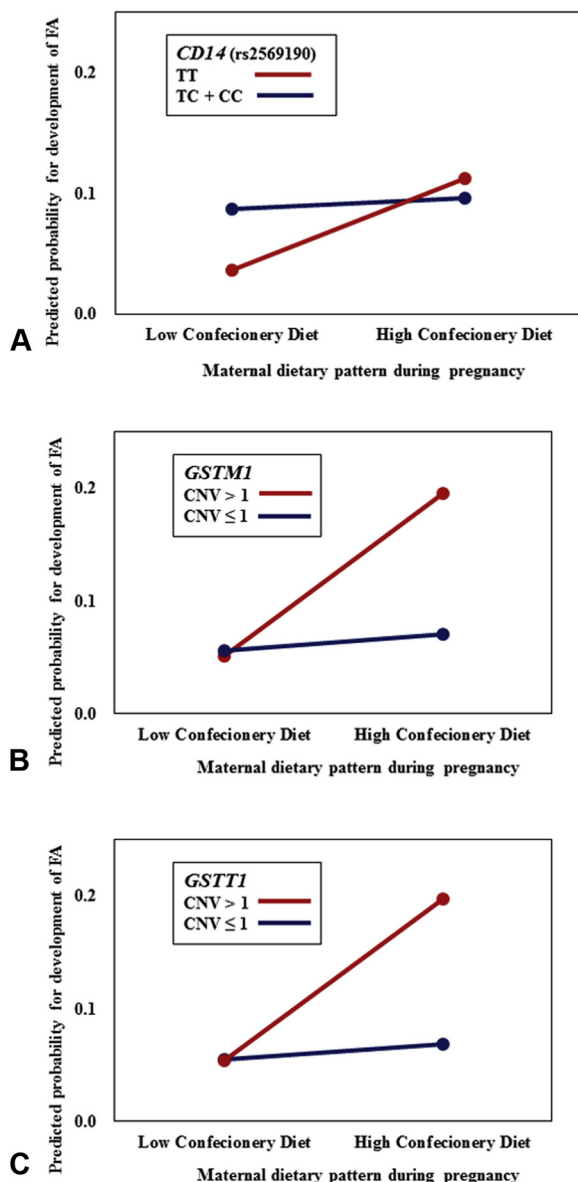


FIGURE 3. Fitted predicted probability plots for the development of food allergy in relation to the maternal confectionery dietary pattern in infants with different genotypes at SNP rs2569190 in *CD14* (A) and more than 1 copy of the *GSTM1* (B) and *GSTT1* (C) CNVs. CNV, Copy number variation; FA, food allergy; SNP, single nucleotide polymorphism.

previously reported to be a risk allele for the development of FA at 1 year of age, and this may reflect enhanced sensitization to food allergens through an increased proinflammatory response.⁴⁷

Glutathione S-transferases (GSTs) play a role in the detoxification enzymatic pathway and protect humans from various environmental hazards, such as air pollution, carcinogens, and xenobiotics.⁴⁸ A possible explanation for the effect of the interaction between infant GST variation and maternal confectionery

dietary pattern in our study may be that TFAs are inducing pathological responses similar to those induced by toxic xenobiotics.⁵¹ A *GSTM1* polymorphism has been reported to increase the potential protective role of the “Korean traditional healthy” diet against AD, and a *CD14* polymorphism was also shown to influence the effect of prenatal antioxidant intake on infant respiratory infections in Korean children.^{49,50} The “Korean traditional healthy” diet consists of rice, soup, and side dishes based on vegetables and a variety of food groups such as other grains, fruit, eggs, fish, and milk.⁵¹ Thus, these *CD14* and *GST* gene polymorphisms may be important concerning the Korean population and diet.^{52,53}

This study has some limitations that should be considered. First, the diagnosis of FA was based only on clinical symptoms and characteristics, and no objective tests such as provocation tests, serum-specific IgE, or skin test were performed. This may have caused an overestimated prevalence rate in our study compared with other reports.^{54,55} However, the definition of FA used here was not only based on self-reporting but also on the existence of a definitive causative food, the period to the development of symptoms, and the accompanying allergic skin symptoms for the exclusion of non-IgE-mediated FA as assessed by allergy specialists. Second, we calculated the minimal and maximal trans fat contents instead of using mean values. In Korea, the MFDS reported TFAs in processed foods for the first time in 2005 and has since been trying to reduce them. However, we could not ensure that all foods consumed were subjected to national regulations or labels. Therefore, we thought that there may be considerable variation in trans fat amounts in domestic foods and that the minimal and maximal values would better reflect this reality. There may be another limitation in assessing maternal diet during pregnancy because the third trimester was not encompassed in the initial plan of the cohort, in spite of the assumption that individual dietary habits do not change easily or rapidly.⁴⁰ Lastly, we evaluated only 12 genetic polymorphisms, rather than conducting a genome-wide association study. However, these genetic polymorphisms are considered to be important for allergic diseases in the Korean population, as shown in our previous studies.^{49,50,52,56-58}

To the best of our knowledge, this study is the first to assess the relationship between infant genetic variations and maternal dietary patterns on the development of infant FA in a birth cohort. In addition, unlike other studies of dietary patterns associated with allergy development, we suggested a possible mechanism for the relationship between the maternal confectionery dietary pattern and FA, namely the lipotoxic effect of TFAs. Moreover, we suggested candidate risk polymorphisms for the development of infant FA, specifically focusing on the interactions of these polymorphisms with maternal, perinatal dietary patterns. The implications of this study should be addressed via food safety and regulatory standards.

In conclusion, maternal dietary patterns that involve high intake of confectionery during periods of pregnancy and prolonged breastfeeding can lead to the development of FA in the infant, and this type of FA may reflect the harmful effects of TFAs produced during industrial food processing.

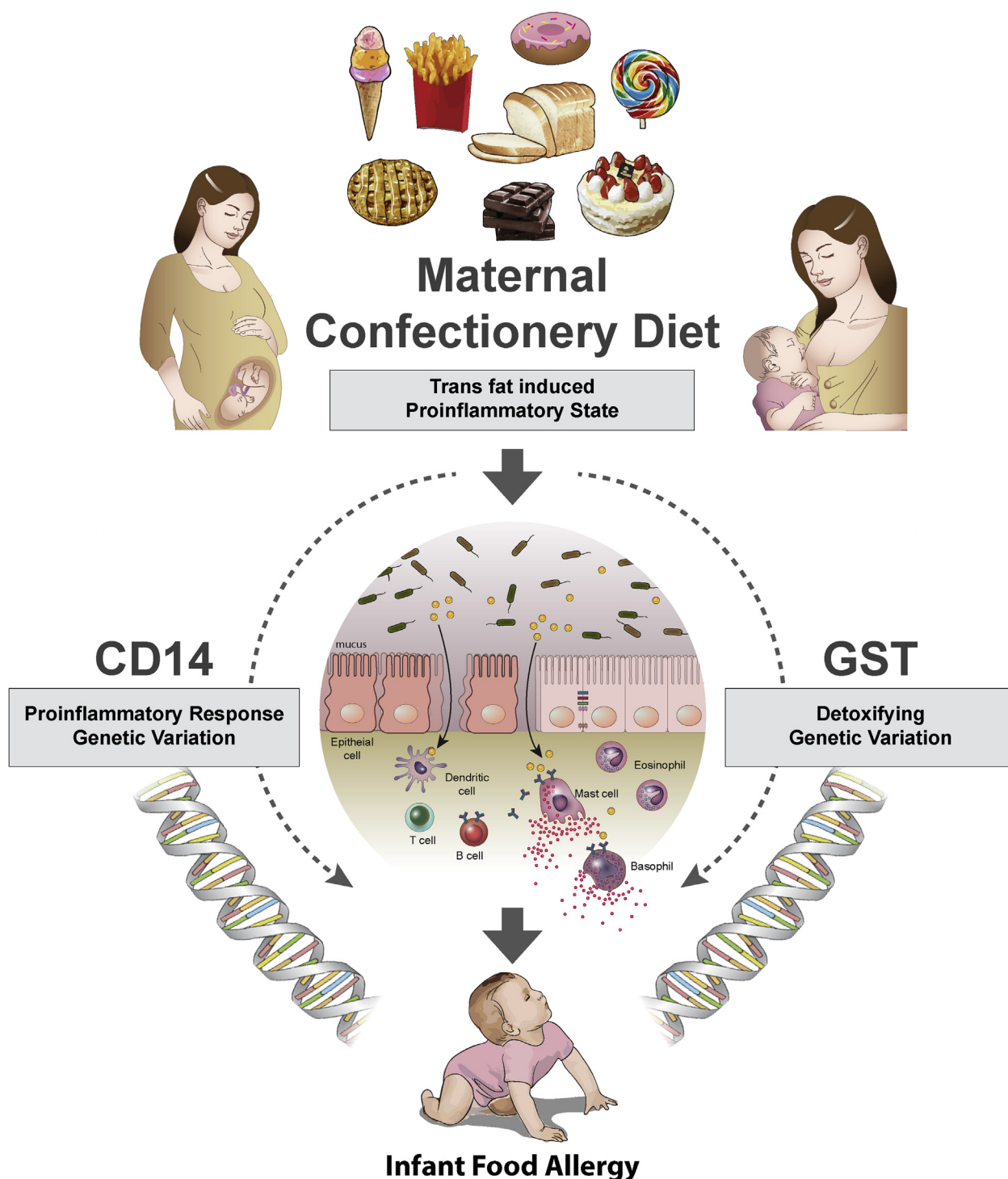


FIGURE 4. Maternal confectionery diet (high intake of baked and sugary products which may contain high trans fats) during the perinatal period may influence the development of food allergy in infants with *CD14* and *GST* gene polymorphisms.

Polymorphisms of *CD14* that play a role in increasing the proinflammatory response as well as polymorphisms in *GST* that play a role in detoxification pathways may increase the susceptibility to FA in infants whose mothers' diets are rich in confectionery, as summarized in Figure 4. Maternal dietary interventions involving reducing the consumption of confectionery during the perinatal period should be implemented to

prevent FA development, especially in genetically susceptible children.

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REFERENCES

1. Tan TH, Ellis JA, Saffery R, Allen KJ. The role of genetics and environment in the rise of childhood food allergy. *Clin Exp Allergy* 2012;42:20-9.
2. Tham EH, Leung DYM. How different parts of the world provide new insights into food allergy. *Allergy Asthma Immunol Res* 2018;10:290-9.
3. Lee SE, Kim H. Update on early nutrition and food allergy in children. *Yonsei Med J* 2016;57:542-8.
4. Grieger JA, Clifton VL, Tuck AR, Wooldridge AL, Robertson SA, Gatford KL. *In utero* programming of allergic susceptibility. *Int Arch Allergy Immunol* 2016;169:80-92.
5. Lockett GA, Huoman J, Holloway JW. Does allergy begin in utero? *Pediatr Allergy Immunol* 2015;26:394-402.
6. Venter C, Brown KR, Maslin K, Palmer DJ. Maternal dietary intake in pregnancy and lactation and allergic disease outcomes in offspring. *Pediatr Allergy Immunol* 2017;28:135-43.
7. Bonnelykke K, Sparks R, Waage J, Milner JD. Genetics of allergy and allergic sensitization: common variants, rare mutations. *Curr Opin Immunol* 2015;36:115-26.
8. Portelli MA, Hodge E, Sayers I. Genetic risk factors for the development of allergic disease identified by genome-wide association. *Clin Exp Allergy* 2015;45:21-31.
9. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011;22:155-60.
10. Shu SA, Chang C, Leung PS. Common methodologies in the evaluation of food allergy: pitfalls and prospects of food allergy prevalence studies. *Clin Rev Allergy Immunol* 2014;46:198-210.
11. Barnes KC. Genomewide association studies in allergy and the influence of ethnicity. *Curr Opin Allergy Clin Immunol* 2010;10:427-33.
12. Jackson DJ, Gern JE, Lemanske RF Jr. Lessons learned from birth cohort studies conducted in diverse environments. *J Allergy Clin Immunol* 2017;139:379-86.
13. Hahn EL, Bacharier LB. The atopic march: the pattern of allergic disease development in childhood. *Immunol Allergy Clin North Am* 2005;25:231-246, v.
14. Yang HJ, Lee SY, Suh DI, Shin YH, Kim BJ, Seo JH, et al. The Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study: design, rationale and methods. *BMC Pulm Med* 2014;14:109.
15. McWilliam VL, Koplin JJ, Field MJ, Sasaki M, Dharmage SC, Tang MLK, et al. Self-reported adverse food reactions and anaphylaxis in the SchoolNuts study: a population-based study of adolescents. *J Allergy Clin Immunol* 2018;141:982-90.
16. Frazier AL, Camargo CA Jr, Malspeis S, Willett WC, Young MC. Prospective study of pre-pregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. *JAMA Pediatr* 2014;168:156-62.
17. Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol* 2015;135:1114-24.
18. Nowak-Węgrzyn A, Spengel JM. Food protein-induced enterocolitis syndrome: Not so rare after all! *J Allergy Clin Immunol* 2017;140:1275-6.
19. Lim Y, Oh S-Y. Development of a semi-quantitative food frequency questionnaire for pre-school children in Korea. *Korean J Community Nutr* 2002;7:58-66.
20. Oh S-Y. Reproducibility and validity of a semiquantitative food frequency questionnaire to assess dietary intakes for the Korean elderly. *Ecol Food Nutr* 2002;41:533-47.
21. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 1995;57:289-300.
22. Martin M, Segui MA, Anton A, Ruiz A, Ramos M, Adrover E, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. *N Engl J Med* 2010;363:2200-10.
23. Hovi P, Andersson S, Eriksson JG, Jarvenpää AL, Strang-Karlsson S, Makitie O, et al. Glucose regulation in young adults with very low birth weight. *N Engl J Med* 2007;356:2053-63.
24. Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *PLoS Med* 2018;15:e1002507.
25. Danielewicz H, Myszczyński G, Debinska A, Myszkal A, Boznanski A, Himle L. Diet in pregnancy—more than food. *Eur J Pediatr* 2017;176:1573-9.
26. Lambrecht BN, Hammad H. The immunology of the allergy epidemic and the hygiene hypothesis. *Nat Immunol* 2017;18:1076-83.
27. Weiland SK, von Mutius E, Husing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. ISAAC Steering Committee. *Lancet* 1999;353:2040-1.
28. Sausenthaler S, Kompauer I, Borte M, Herbarth O, Schaaf B, Berg A, et al. Margarine and butter consumption, eczema and allergic sensitization in children. The LISA birth cohort study. *Pediatr Allergy Immunol* 2006;17:85-93.
29. Lee SC, Yang YH, Chuang SY, Liu SC, Yang HC, Pan WH. Risk of asthma associated with energy-dense but nutrient-poor dietary pattern in Taiwanese children. *Asia Pac J Clin Nutr* 2012;21:73-81.
30. Stender S, Astrup A, Dyerberg J. Ruminant and industrially produced trans fatty acids: health aspects. *Food Nutr Res* 2008;52:10.3402/fnr.v52i0.1651.
31. Estadella D, da Penha Oller do Nascimento CM, Oyama LM, Ribeiro EB, Damaso AR, de Piano A. Lipotoxicity: effects of dietary saturated and trans fatty acids. *Mediators Inflamm* 2013;2013:137579.
32. König J, Wells J, Cani PD, Garcia-Rodenas CL, MacDonald T, Mercenier A, et al. Human intestinal barrier function in health and disease. *Clin Transl Gastroenterol* 2016;7:e196.
33. Carvalho G, Moura CS, Roquette AR, Barrera-Arellano D, Yamada AT, Santos AD, et al. Impact of trans-fats on heat-shock protein expression and the gut microbiota profile of mice. *J Food Sci* 2018;83:489-98.
34. Harpsøe MC, Basit S, Bager P, Wohlfahrt J, Benn CS, Nohr EA, et al. Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: a study within the Danish National Birth Cohort. *J Allergy Clin Immunol* 2013;131:1033-40.
35. Camargo CA Jr. Gestational weight gain and offspring asthma: a novel opportunity for primary prevention research. *Clin Exp Allergy* 2015;45:544-6.
36. Ooi EM, Watts GF, Ng TW, Barrett PH. Effect of dietary fatty acids on human lipoprotein metabolism: a comprehensive update. *Nutrients* 2015;7:4416-25.
37. Thijs C, Muller A, Rist L, Kummeling I, Snijders BE, Huber M, et al. Fatty acids in breast milk and development of atopic eczema and allergic sensitization in infancy. *Allergy* 2011;66:58-67.
38. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;69:590-601.
39. Ishihara J. Challenges in dietary exposure assessment in epidemiology: research trends. *J Nutr Sci Vitaminol (Tokyo)* 2015;61(Suppl):S33-5.
40. Willet W. *Nutritional Epidemiology*. New York: Oxford University Press; 2012.
41. Di Gioia M, Zanoni I. Toll-like receptor co-receptors as master regulators of the immune response. *Mol Immunol* 2015;63:143-52.
42. Rocha DM, Caldas AP, Oliveira LL, Bressan J, Hermsdorff HH. Saturated fatty acids trigger TLR4-mediated inflammatory response. *Atherosclerosis* 2016;244:211-5.
43. Jin C, Flavell RA. Innate sensors of pathogen and stress: linking inflammation to obesity. *J Allergy Clin Immunol* 2013;132:287-94.
44. Du J, Zhang Z, Ge Y, Zhen J, Leng J, Wang J. VKORC1 and CD-14 genetic polymorphisms associate with susceptibility to cardiovascular and cerebrovascular diseases. *Int J Clin Exp Med* 2015;8:20444-53.
45. LeVan TD, Bloom JW, Bailey TJ, Karp CL, Halonen M, Martinez FD, et al. A common single nucleotide polymorphism in the CD14 promoter decreases the affinity of Sp protein binding and enhances transcriptional activity. *J Immunol* 2001;167:5838-44.
46. Lin J, Yao YM, Yu Y, Chai JK, Huang ZH, Dong N, et al. Effects of CD14-159 C/T polymorphism on CD14 expression and the balance between proinflammatory and anti-inflammatory cytokines in whole blood culture. *Shock* 2007;28:148-53.
47. Woo JG, Assa'ad A, Heizer AB, Bernstein JA, Hershey GK. The -159 C→T polymorphism of CD14 is associated with nonatopic asthma and food allergy. *J Allergy Clin Immunol* 2003;112:438-44.
48. Hollman AL, Tchounwou PB, Huang HC. The association between gene-environment interactions and diseases involving the human GST superfamily with SNP variants. *Int J Environ Res Public Health* 2016;13:379.
49. Chung J, Kwon SO, Ahn H, Hwang H, Hong SJ, Oh SY. Association between dietary patterns and atopic dermatitis in relation to GSTM1 and GSTT1 polymorphisms in young children. *Nutrients* 2015;7:9440-52.
50. Hong SA, Lee E, Kwon SO, Kim KW, Shin YH, Ahn KM, et al. Effect of prenatal antioxidant intake on infants' respiratory infection is modified by a CD14 polymorphism. *World J Pediatr* 2017;13:173-82.

51. Song Y, Joung H. A traditional Korean dietary pattern and metabolic syndrome abnormalities. *Nutr Metab Cardiovasc Dis* 2012;22:456-62.
52. Hong SJ, Kim HB, Kang MJ, Lee SY, Kim JH, Kim BS, et al. TNF-alpha (-308 G/A) and CD14 (-159T/C) polymorphisms in the bronchial responsiveness of Korean children with asthma. *J Allergy Clin Immunol* 2007;119:398-404.
53. Lee SY, Yu J, Ahn KM, Kim KW, Shin YH, Lee KS, et al. Additive effect between IL-13 polymorphism and cesarean section delivery/prenatal antibiotics use on atopic dermatitis: a birth cohort study (COCOA). *PLoS One* 2014;9:e96603.
54. Renz H, Allen KJ, Sicherer SH, Sampson HA, Lack G, Beyer K, et al. Food allergy. *Nat Rev Dis Primers* 2018;4:17098.
55. Min TK, Pyun BY, Kim HH, Park Y-M, Jang GC, Kim H-Y, et al. Epidemiology of food allergy in Korean children. *Allergy Asthma Respir Dis* 2018;6:4-13.
56. Yang SI, Kim BJ, Lee SY, Kim HB, Lee CM, Yu J, et al. Prenatal particulate matter/tobacco smoke increases infants' respiratory infections: COCOA study. *Allergy Asthma Immunol Res* 2015;7:573-82.
57. Lee E, Chang HY, Lee KS, Suh DI, Yu HS, Kang MJ, et al. The effect of perinatal anxiety on bronchiolitis is influenced by polymorphisms in ROS-related genes. *BMC Pulm Med* 2014;14:154.
58. Yu J, Ahn K, Shin YH, Kim KW, Suh DI, Yu HS, et al. The interaction between prenatal exposure to home renovation and reactive oxygen species genes in cord blood IgE response is modified by maternal atopy. *Allergy Asthma Immunol Res* 2016;8:41-8.

ONLINE REPOSITORY

METHODS

Subjects

The Cohort for Childhood Origin of Asthma and allergic diseases^{E1} study is an ongoing prospective longitudinal study. This study was approved by the Institutional Review Boards of Asan Medical Center (IRB No. 2008-0616), Samsung Medical Center (IRB No. 2009-02-021), Severance Hospital (IRB No. 4-2008-0588), the CHA Medical Center (IRB No. 2010-010), and the Seoul National University Hospital (IRB No. H-1401-086-550). Written informed consent was obtained from the parents of each infant. A woman was recruited if she (1) lacked high-risk conditions that could affect the development of allergic diseases in the child (eg, diabetes, preeclampsia, anemia, and severe infection) and (2) planned to deliver at an affiliated medical center. The eligibility of the baby was determined soon after delivery by the collaborating obstetrician and pediatrician. Babies were excluded at birth if (1) their gestational age was less than 37 weeks or (2) they had any major congenital anomalies or birth asphyxia that required oxygen supplementation.

All subjects were sampled for serum total IgE and specific IgE for egg and milk at age 1. After sampling, the sera were kept in -70°C refrigerator. Total serum IgE concentration was measured using a fluorescent enzyme immunoassay (AutoCAP System; Pharmacia Diagnostics AB, Uppsala, Sweden). The IgE antibodies specific for cow's milk and egg white were measured using the Phadia ImmunoCAP system (Phadia, Uppsala, Sweden).

Maternal dietary patterns during pregnancy

To assess maternal dietary intake, a semiquantitative food frequency questionnaire was self-administered at 26 weeks of pregnancy. This questionnaire was validated previously and included 120 food items with 9 nonoverlapping intake frequencies (ranging from "rarely eaten" during the preceding year to "eaten more than 3 times per day") and 3 portion sizes (small, average, or large).^{E2,E3} For clustering of dietary patterns, our analysis consisted of 35 food/food groups based on nutrient profiles of each food item (Table E1).

The energy and nutrient intake of a diet was calculated using CAN-Pro 3.0 nutrient-intake assessment software (CAN-Pro 3.0; Korean Nutrition Society, Seoul, Korea). Because CAN-Pro 3.0 does not handle trans fat amount, we calculated trans fat intake based on information supplied by the Ministry of Food and Drug Safety in Korea at Food-Safety-Korea (<http://www.foodsafetykorea.go.kr/>). The maximum and minimum trans fat amounts per gram of each of the 35 food/food groups were used.

For the 35 food/food groups (Table E1), using daily intake frequency values per 1000 kcal, we performed factor analysis followed by varimax rotation to dietary group patterns. In accordance with the eigenvalue (>1.0), scree plots, and interpretability of factors, eigenvalues ended in an abrupt slop down at 5 component points (Figure E3),^{E4} and therefore 5 dietary patterns were classified (Table E2). For investigating whether the 5 dietary patterns yielded stable, we qualified this result by Kaiser-Meyer-Olkin and Bartlett methods. Kaiser-Meyer-Olkin

measure for sampling adequacy was 0.780 and P value in Bartlett methods was $<.001$.^{E5,E6}

We calculated factor loadings for each food/food group across the 5 dietary patterns. Then, for the evaluation of each mother's diet, we obtained for her a factor score in each dietary pattern; the factor score was determined by weighing the mother's intake of the 35 food/food groups with their respective factor loadings in the pattern, and then summing together.

We named the 5 dietary patterns based on the food/food groups with the most positive factor loadings in the pattern (Table 1). The "traditional" pattern consisted of relatively higher intakes of vegetables, seaweeds, fruits, anchovies, beans, and kimchi. The "confectionery" pattern was of higher intakes of baked goods, including breads, rice cakes, cereals, and sweet breads, in addition to sugar confections such as ice cream and chocolate and other foods high in sweets and fats. The "meat" pattern was of higher intakes of chicken, beef, fresh fish, pork, and processed meat and fish. The "processed" pattern was of higher intakes of fast food, noodles, and Ramen. The "coffee and milk" pattern was of higher intakes of coffee and milk.

Assessment of infant genetic variation

For the evaluation of the interaction between maternal dietary patterns and infant genetic variation, we obtained DNA extracted from infant cord blood samples.

Cord blood samples obtained from the infants were screened for single nucleotide polymorphisms (SNPs) in interleukin 13 (*IL-13*, rs20541), cluster of differentiation 14 (*CD14*, rs2569190), and Toll-like receptor 4 (*TLR4*, rs1927911), which have been reported to be related to immune functions; samples were screened for Gasdermin-B (*GSDMB*, rs4794820, rs7216389), glucocorticoid receptor (*GR*, rs41423247), and brain-derived neurotrophic factor (*BDNF*, rs6265), which are related to pediatric asthma; samples were screened for nuclear factor erythroid 2-related factor 2 (*Nrf2*, rs6726395), N-acetyltransferase 2 (*NAT2*, rs4271002), and glutathione *S*-transferases pi (*GSTPI*, rs1695), which are related to antioxidant response.^{E7,E8} Because the glutathione *S*-transferase (*GST*) superfamily has been known to play a role in the gene-environment interaction, copy number variations (CNVs) of glutathione *S*-transferase mu 1 (*GSTM1*) and glutathione *S*-transferase theta 1 (*GSTT1*) were also screened^{E9}; accordingly genotypes of *GSTM1* and *GSTT1* were coded as categorical variables by these CNVs, that is, as having more than 1 copy of the genes or not. Only 1508 cord blood samples could be assessed for the SNPs; only 1031 samples could be assessed for CNVs of *GSTM1* and *GSTT1*.

Genomic DNA was extracted from the buffy coat of the cord blood samples by using the Gentra Puregene Blood Kit (Qiagen, Germantown, Md), as recommended by the manufacturer. Genotyping was conducted using a TaqMan assay (ABI, Foster City, Calif), and the endpoint fluorescent readings were performed on an ABI 7900 HT Sequence Detection System. Duplicate samples and negative controls were included to ensure the accuracy of genotyping. Distributions of these polymorphisms were in Hardy-Weinberg equilibrium ($P > .1$).

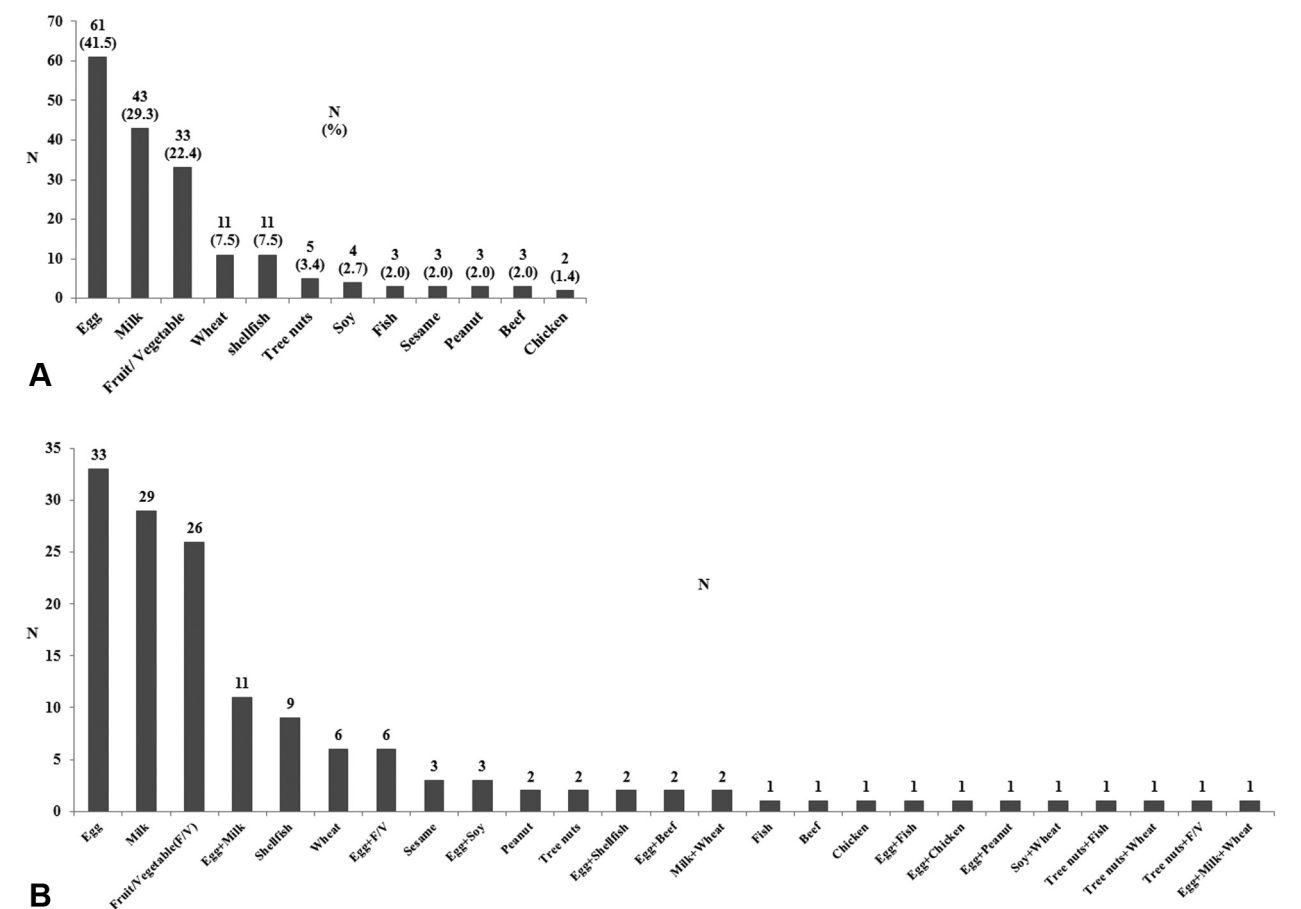


FIGURE E1. A, Causative food allergens in total infants with food allergy based on history. **B,** Causative food allergens in individual subjects with food allergy based on history.

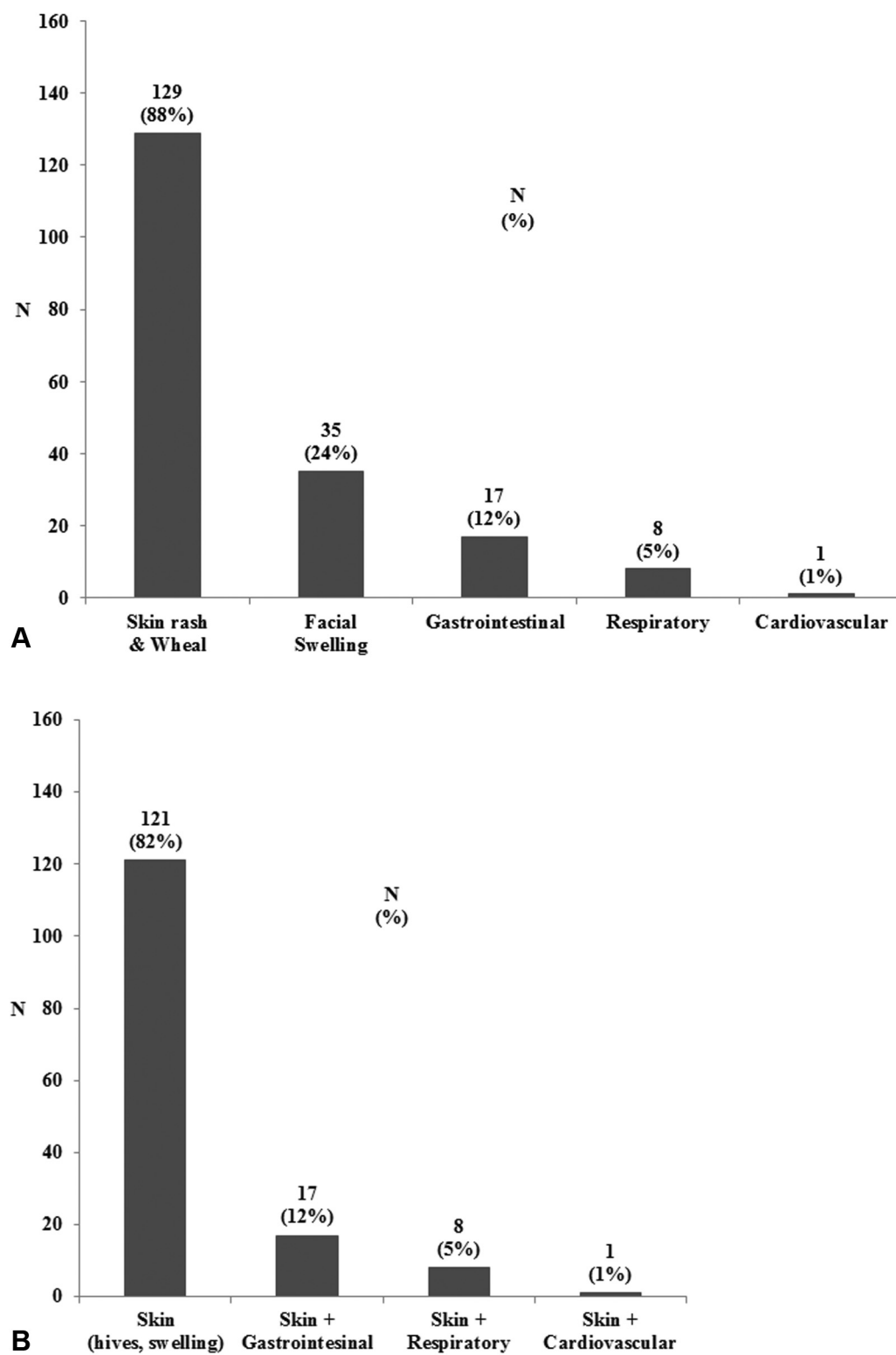


FIGURE E2. **A**, Food allergy symptoms in total infants with food allergy based on history. **B**, Food allergy symptoms in individual subjects with food allergy based on history.

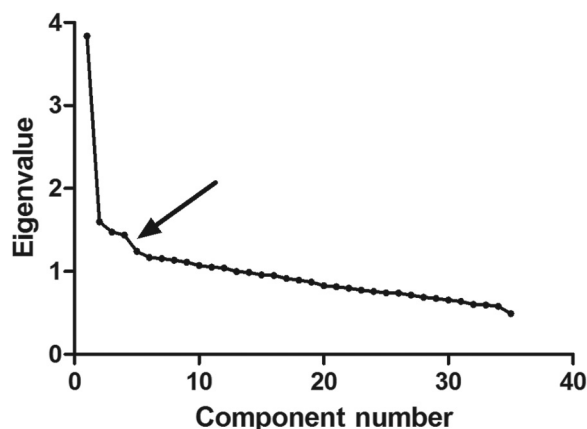


FIGURE E3. Scree plot of factor analysis for the maternal dietary pattern. The arrow shows that eigenvalues ended in an abrupt slop down at the 5 component points.

TABLE E1. Thirty-five food groups used in statistical analyses with factor analysis

Food/food group	Food
Alcohol	Wine, beer, Korean traditional alcohol (fermented rice alcohol), fermented fruit alcohol, etc.
Beans	Soybean curd (tofu)/curd residue, soybean (boiled with soy sauce), soymilk
Beef	Sliced beef with sauces (Galbi, Bulgogi), beef (loin, tender loin), beef soup/beef broiled down in soy
Bread	White and dark breads
Cereals	Breakfast cereals
Cheese	Cheese
Chicken	Chicken (fried), chicken (boiled, braised)
Chocolate	Chocolate
Coffee and tea	Coffee, tea, green tea
Eggs	Eggs
Fast food	Hamburgers, pizza, French fries
Fats	Butter/margarine, mayonnaise
Fresh fish	White fish (pan fried, fried), white fish (grilled, broiled down in soy) blue fish (pan fried, fried), blue fish (grilled, broiled down in soy), squid/octopus, shrimp, clams/oysters
Fruit juice	Orange juice, tomato juice, other fruit juices
Fruits	Strawberries, apples, pears, mandarins/oranges, tomatoes, bananas, melons/muskmelons, watermelons, peaches/plums, grapes
Ice cream	Ice cream
Kimchi	Korean cabbage kimchi/seasoned cubed radish roots/young radish kimchi, other kinds of kimchi
Milk	Whole milk, flavored milk, low fat milk
Mulchi	Anchovy (stir-fried)
Noodles and dumplings	Korean style noodles, spaghetti/bean sauce noodles, dumplings
Nuts	Nuts
Pork	Pork (loin, tender loin, shoulder), pork (belly)
Potatoes	Potatoes, sweet potatoes (not fried)
Processed fish	Canned tuna, fish paste
Processed meat	Ham/sausage
Ramen	Ramen
Rice	White rice, other grains
Rice cake	Rice cakes
Seaweeds	Dried laver, sea mustard
Snacks	Chips, crackers
Sweet bread	Sweet bread, pastries
Sweet drinks	Cocoa, soft drinks, sport drinks, traditional sweet drinks
Sweets	Candies, jam
Vegetables	Lettuce/cabbage (raw), lettuce/cabbage (cooked), radish, bean sprout/mungbean sprout, cucumber, spinach, perilla leaves, unripe hot pepper, onion, carrots, squash, mushrooms, roots of balloon flower/fernbrake
Yogurt	Yogurt, yogurt drinks

TABLE E2. Factor-loading matrix for defining dietary patterns by factor analysis using 35 food/food group variables (N = 1628)

Food/food group	Traditional	Confectionery	Meat	Processed	Coffee and milk
Vegetables	0.585	0.118	0.26	0.112	−0.002
Seaweed	0.54	−0.081	−0.012	0.076	0.005
Fruits	0.501	0.108	−0.019	0.141	0.151
Mulchi	0.494	−0.028	0.133	−0.261	0.053
Beans	0.48	0.078	0.123	0.187	0.056
Kimchi	0.451	0.138	0.025	−0.095	0.087
Fruit juice	0.297	0.139	0.074	0.178	0.172
Alcohol	0.286	−0.271	−0.078	0.242	0.172
Eggs	0.244	0.141	0.012	−0.007	−0.12
Nuts	0.236	0.181	−0.005	0.196	−0.05
Yogurt	0.232	0.216	0.056	0.115	0.017
Sweat drink	0.226	0.044	0.15	0.221	0.148
Bread	−0.025	0.507	0.062	0.011	−0.013
Potatoes	0.121	0.503	0.205	−0.072	−0.051
Rice cake	0.013	0.417	0.104	0.022	−0.062
Sweet	0.037	0.38	0.031	0.205	0.205
Fat	0.24	0.377	0.112	0.322	−0.081
Ice cream	0.19	0.374	−0.064	−0.057	0.142
Cereal	−0.166	0.342	−0.003	0.247	0.196
Chocolate	0.143	0.339	0.055	0.158	0.094
Sweet bread	0.286	0.326	−0.033	−0.058	−0.024
Snack	0.224	0.297	−0.182	0.156	−0.03
Rice	0.044	0.129	−0.111	−0.004	0.06
Chicken	0.002	0.168	0.639	−0.147	0.044
Beef	0.04	0.098	0.562	0.056	0.197
Fresh fish	0.273	0.055	0.484	−0.046	−0.053
Pork	0.026	0.094	0.483	0.286	0.03
Processed fish	0.158	−0.034	0.453	0.169	−0.056
Processed meat	−0.004	−0.045	0.432	0.286	0.071
Fast food	−0.079	0.016	0.14	0.584	0.02
Noodles and dumplings	0.105	0.111	0.208	0.516	0.097
Ramyeon	0.118	−0.035	0.017	0.407	−0.065
Cheese	0.044	0.254	−0.069	0.321	0.087
Coffee and tea	0.098	0.03	0.064	0.081	0.799
Milk	0.102	0.057	0.081	−0.036	0.799

TABLE E3. Daily nutrients and trans fat intakes according to the maternal confectionery dietary pattern

Confectionery diet	GWG (kg)	Calorie (kcal)	Animal protein (g)	Plant protein (g)	Animal fat (g)	Plant fat (g)	Vitamin A (µg, RE)	Retinal (µg)
Comparison between low (Q1-Q2) and high (Q3-Q4) confectionery diet group								
Low (Q1-Q2)	13.0 (10.0-16.0)	1839 (1480-2191)	21.2 (17.4-24.9)	18.8 (16.9-20.7)	13.8 (11.3-16.8)	14.5 (12.1-17.0)	445.9 (357.3-558.6)	91.2 (69.6-119.1)
High (Q3-Q4)	12.8 (10.0-16.0)	1818 (1422-2382)	22.0 (18.4-25.9)	18.9 (17.1-20.7)	14.3 (11.9-17.4)	14.4 (12.1-16.7)	462.5 (360.5-597.2)	92.5 (71.9-115.4)
P	.630	.196	.001	.621	.030	.842	.036	.600
Correlation analysis with confectionery diet factor score								
r	−0.022	0.001	0.039	0.069	−0.005	−0.005	0.051	−0.056
P	.440	.956	.120	.005	.849	.853	.040	.023
β-Carotene (µg)	Vitamin C (mg)	Folate (µg)	Vitamin E (mg)	SFAs (g)	MFAs (g)	PUFAs (g)	Trans fat (Max.) (g)	Trans fat (Min.) (g)
Comparison between low (Q1-Q2) and high (Q3-Q4) confectionery diet group								
2055 (1554-2745)	58.6 (46.4-75.0)	284 (248-334)	10.2 (8.7-11.7)	7.0 (5.5-8.6)	7.4 (6.1-8.8)	5.8 (4.8-6.9)	39.8 (30.0-56.2)	0.64 (0.41-0.86)
2146 (1594-2983)	61.8 (46.6-78.1)	294 (247-345)	10.4 (8.8-11.9)	7.2 (5.8-8.7)	7.6 (6.3-9.1)	5.9 (4.9-7.2)	56.6 (37.2-82.3)	0.65 (0.39-0.93)
0.040	0.094	0.065	0.115	0.385	0.122	0.009	<0.001	0.484
Correlation analysis with confectionery diet factor score								
0.063	0.051	0.017	0.040	−0.039	−0.004	0.052	0.498	0.104
0.011	0.041	0.506	0.111	0.118	0.879	0.036	<0.001	<0.001

GWG, Gestational weight gain; MFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SD, standard deviation; SFA, saturated fatty acids; *Trans fat (Max.)*, maximal intakes of trans fat; *Trans fat (Min.)*, minimal intakes of trans fat.

Data expressed as mean ± SD or median (interquartile range).

All nutrients were adjusted with calorie intake except for the calorie variable. Correlation analysis was adjusted with calories and maternal age.

TABLE E4. Specific IgE of egg and milk in egg and milk allergy

Egg specific IgE (sIgE) in egg allergy (45 egg allergy/1300 total subjects with blood sampling)	
Egg sIgE, median (min/25th/75th/max) (IU/mL)	1.15 (0.00/0.27/3.84/100.01)
Egg sIgE, mean $\pm$ SD (IU/mL)	4.57 $\pm$ 14.9
Egg sIgE $\geq$ 0.35 IU/mL	33/45 (73.3%)
Egg sIgE $\geq$ 0.1 IU/mL	38/45 (84.4 %)
Milk specific IgE in milk allergy (35 egg allergy/1300 total subjects with blood sampling)	
Milk sIgE, median (min/25th/75th/max) (IU/mL)	0.40 (0.00/0.06/1.42/24.6)
Milk sIgE, mean $\pm$ SD (IU/mL)	1.70 $\pm$ 4.3
Milk sIgE $\geq$ 0.35 IU/mL	17/35 (48.6%)
Milk sIgE $\geq$ 0.1 IU/mL	29/35 (82.9 %)

SD, Standard deviation.

Data expressed as median (minimum/interquartile range/maximum) or (number of subjects/number of total subjects) or number (percentage).

REFERENCES

- E1. Yang HJ, Lee SY, Suh DI, Shin YH, Kim BJ, Seo JH, et al. The Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study: design, rationale and methods. *BMC Pulm Med* 2014;14:109.
- E2. Lim Y, Oh S-Y. Development of a semi-quantitative food frequency questionnaire for pre-school children in Korea. *Korean J Community Nutr* 2002;7: 58-66.
- E3. Oh S-Y. Reproducibility and validity of a semiquantitative food frequency questionnaire to assess dietary intakes for the Korean elderly. *Ecol Food Nutr* 2002;41:533-47.
- E4. Gaskin CJ, Happell B. On exploratory factor analysis: a review of recent evidence, an assessment of current practice, and recommendations for future use. *Int J Nurs Stud* 2014;51:511-21.
- E5. Cerny BA, Kaiser HF. A study of a measure of sampling adequacy for factor-analytic correlation matrices. *Multivariate Behav Res* 1977;12: 43-7.
- E6. Brown TA. *Confirmatory Factor Analysis for Applied Research*. New York: Guilford Publications; 2014.
- E7. Bonnelykke K, Sparks R, Waage J, Milner JD. Genetics of allergy and allergic sensitization: common variants, rare mutations. *Curr Opin Immunol* 2015;36: 115-26.
- E8. Portelli MA, Hodge E, Sayers I. Genetic risk factors for the development of allergic disease identified by genome-wide association. *Clin Exp Allergy* 2015; 45:21-31.
- E9. Hollman AL, Tchounwou PB, Huang HC. The association between gene-environment interactions and diseases involving the human GST superfamily with SNP variants. *Int J Environ Res Public Health* 2016;13:379.

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