Maternal perinatal dietary patterns affect food allergy development in susceptible infants

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Maternal perinatal dietary patterns affect food allergy development in susceptible infants

Directed by Professor Myung Hyun Sohn

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Yoon Hee Kim

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This certifies that the Doctoral Dissertation of Yoon Hee Kim is approved.

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Food. Before I went to a medical school, I had believed that it could be a cause for all kinds of human diseases and at the same time, it could be a key of overcoming them because we have food everyday for a lifetime. But after acquiring a vast amount of medical knowledge and a large variety of drugs, I forgot my ideas about food. In this dissertation, I tried to verify the role of food in infant food allergy and I realized which area and how I should focus on to solve food allergy.

I would like to express my gratitude to Prof. Myung Hyun Sohn for guiding me throughout this dissertation. He was always supportive when overcoming many hurdles during this work and this dissertation would not have been possible without him. I also owe gratitude to Prof. Sooyoung Lee for her vast experiences and knowledge of food allergy in children. I would also like to thank Prof. Hyeyoung Kim and Prof. Changsoo Kim for their critical comments with advanced knowledge about food,

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Above all, I am deeply grateful for my husband, Hyukjin Shin for his love and support, and also my children Heeon and Gaeon for giving me strength. Finally, I dedicated this dissertation to my parents who have always given me unconditional and unlimited supports.

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ABSTRACT

Maternal perinatal dietary patterns affect food allergy development in susceptible infants

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The increasing incidence of food allergy (FA) can be attributed to interactions between genes and environment, but these interactions are not yet fully clear. We aimed to evaluate the interaction between infant genetic variations and maternal dietary patterns for risk factors in the development of FA. We used COCOA birth cohort of 1628 infants, born between 2007 and 2015. Maternal dietary intakes were assessed at 26 weeks of pregnancy by a food frequency questionnaire and grouped according to five dietary patterns. Infant cord blood samples were genotyped at 12 loci. Gut microbiota in infants' stools at 6 months was analyzed. Among 1628 infants, 147 (9.0%) were diagnosed with FA. A maternal diet characterized by higher intake of confectioneries during pregnancy was associated with greater prevalence of FA [adjusted odds ratio (OR) = 1.517, P = .02]; such dietary pattern tended to be higher in trans-fat (r = 0.498, P < .001); such development of FA was associated with longer periods of breast feeding (adjusted OR = 1.792, P = .03), and this dietary pattern was more significantly related to development of FA in infants with homozygous TT genotype of CD14 (rs2569190) and more than one copy of GSTM1 and GSTT1.

The synergic effect of high maternal confectionery dietary pattern and SNPs of CD14 or GSTM1 induced gut microbiota alterations including decreased alph diversity and increased Firmicutes or Verrucomicrobia. A maternal diet during pregnancy that majorly consists of confectionery products, combined with a longer ensuing period of breastfeeding may lead to development of FA, which may be a harmful effect of trans fat in the infant; and the polymorphisms in *CD14* and GST of the infant play a role in that susceptibility to FA. This synergic interaction of perinatal dietary pattern and infant genetic variation might induce infant gut microbiota dysbiosis which could development infant FA.

Key words : CD14, dietary pattern, fatty acids, food allergy, genetics, GST, infant, microbiome, perinatal

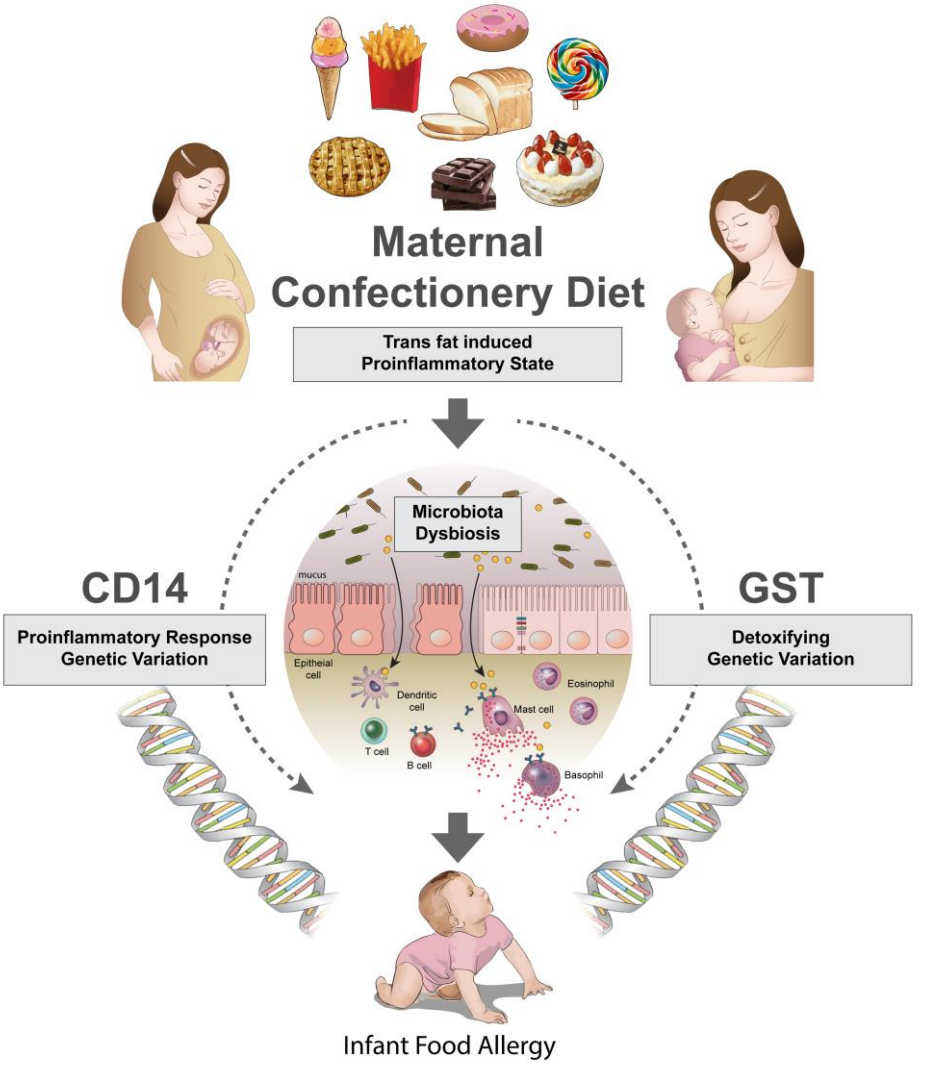

Figure 1. Summary figure

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I. INTRODUCTION

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 the programming of allergy.[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 also 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, and 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 (COCOA) 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.

II. MATERIALS AND METHODS

1. Subjects

The COCOA study[14] is an ongoing prospective longitudinal study involving women in the third 0trimester of pregnancy recruited from 5 tertiary hospitals and 8 public health centers for prenatal care in Seoul, Korea. Recruitment took place from November, 2007 to April, 2015. The institutional ethics committee of each institution approved this protocol. 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. Of the 2512

women who were recruited, 405 withdrew consent, and 57 were lost to follow-up. Another 119 were then excluded because the birth was preterm or the child had a congenital anomaly. Finally, 163 women with missing data on maternal diet during pregnancy and 140 babies with missing data on diagnosis of FA were excluded, leaving 1628 mother-baby pairs for diet analysis summarized in Figure 1.

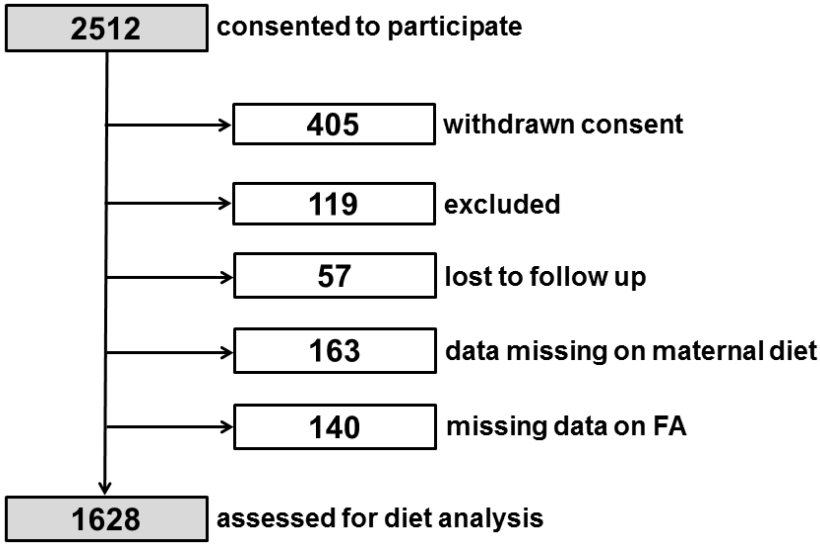

Figure 2. Flow chart of study subjects

2. Definition of food allergy

FA was diagnosed by pediatric allergy specialists based on detailed clinical histories and a questionnaire about food adverse reactions. 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 by a doctor and methods of diagnosis, 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 for the condition. All children and mothers visited an allergy clinic at

one of the institutions and were examined for the presence of FA by a pediatrician at 1 year of age. If there was a positive response, the diagnosis of FA was then confirmed by a pediatric allergy specialist during follow up at each hospital.

Finally, we defined FA 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 development, followed by repeated allergic symptoms from the same definitive causative food or the complete avoidance of the definitive causative food after the development of allergic symptoms.

3. Maternal dietary patterns during pregnancy

To assess maternal dietary intake, a semi-quantitative food frequency questionnaire (FFQ) was self-administered at 26 weeks of pregnancy. This questionnaire was validated previously and included 120 food items with nine non-overlapping intake frequencies (ranging from "rarely eaten" during the preceding year to "eaten more than three times per day") and three portion sizes (small, average, or large).[15,16] For clustering of dietary patterns, our analysis consisted of 35 food/food groups based on nutrient profiles of each food item (Table 1).

Table 1. Thirty-five food groups used in statistical analyses with factor analysis

Food/Food Group	Food
Alcohol	Wine, bear, 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 & 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, shrimps, 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 & 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

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). Since 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 (MFDS) 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 1), using daily intake frequency values per 1000 kcal, we performed factor analysis followed by varimax rotation to group dietary patterns. In accordance with the eigenvalue (> 1.0), scree plots, and interpretability of factors, eigenvalues ended in an abrupt slop down at 5 components point,[17] and therefore 5 dietary patterns were classified (Table 2). We calculated factor loadings for each food/food group across the five 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, then summing together.

Table 2. Factor-loading matrix for defining dietary patterns by factor analysis using 35 food/food group variables (n = 1628)

Food/Food Group	Traditional	Confectio-nery	Meat	Processed	Coffee & 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
Process fish	0.158	-0.034	0.453	0.169	-0.056
Process meat	-0.004	-0.045	0.432	0.286	0.071
Fast food	-0.079	0.016	0.14	0.584	0.02
Noodles & 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 & tea	0.098	0.03	0.064	0.081	0.799
Milk	0.102	0.057	0.081	-0.036	0.799

We named the five dietary patterns based on the food/food groups with the most positive factor loadings in the pattern (Table 3). The “traditional” pattern consisted of relatively higher intakes of vegetables, seaweeds, fruits, anchovies, beans and kimchi. The “confectionery” pattern was of higher intakes of bakes goods, including breads, rice-cakes, cereals and sweet breads, in addition to sugar confections like 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.

Table 3. Major food/food group according to maternal dietary patterns (N = 1628)

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

*Major food/food group defined as those ≥ 0.3 factor loading through factor analysis.

4. Assessment of genetic variations

For assessment 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 COCOA 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 genetic loci considered to be important in the development of allergic diseases.

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 with 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 with 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 (GSTP1**,** rs1695), which are related with antioxidant response.[18,19] Since the glutathione S-transferase (GST) superfamily has been known to play a role in gene-environment interaction, copy number variations (CNVs) of glutathione S-transferase mu 1(GSTM1) and glutathione S-transferase theta 1(GSTT1) were also screened;[20] accordingly genotypes of GSTM1 and GSTT1 were coded as categorical variables by these CNVs, i.e. 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 ($p > 0.1$).

5. Gut microbiota analysis

We analyzed gut microbiota in infants' stools which could be collected at 6 months. Fecal samples were collected and immediately stored at -80℃ before being processed for DNA extraction.

Metagenomic DNA was extracted from 250 mg of feces using the Power Microbiome RNA/DNA Isolation kit (Mo Bio/Qiagen, Carlsbad, CA, USA) according to the manufacturer's instructions, with additional glass bead-beating steps on a vortex adapter. The extracted DNA was quantified using a BioPhotometer D30 with a μCuvette G1.0 (Eppendrof, Hamburg, Germany) and stored at -80℃ until further processing.

For pyrosequencing, the extracted DNA was amplified using barcoded primers targeting the V1-V3 region of the 16S rRNA gene. The amplification was conducted using a C1000 thermal cycler (Bio-Rad, Hercules, CA, USA) as follows: denaturation at 94℃ for 5 min, followed by 30 cycles of denaturation at 94℃ for 30 sec, annealing at 55℃ for 30 sec, and extension at 72℃ for 30 sec, with a final extension step at 72℃ for 7 min. The amplified products were purified using an AMPure XP bead kit (Agencout Bioscience, Beverly, MA, USA) and quantified using the PicoGreen dsDNA assay kit (ThermoFisher Scientific, Waltham, MA, USA). Equimolar concentrations of samples were pooled and then amplified on sequencing beads by emulsion PCR. Beads recovered from the emulsion PCR were deposited on a 454 picotiter plate and sequenced on a Roche/454 FLX Titanium system following the manufacturer's

instructions.

The total amount of gut bacteria in fecal samples was determined by quantitative real-time PCR for 16S rRNA genes. The 16S rRNA gene was amplified with the primers 340F (5'-TCC TAC GGG AGG CAG CAG-3') and 518R (5-ATT ACC GCG GCT GCT GG-3') using a Thermal Cycle Dice Real-Time System Ⅲ (Takara Bio, Inc., Shiga, Japan). Each sample was measured triplicate in a 25 μL reaction containing 12.5 μL of SYBR Premix Ex Taq (Tli RNaseH Plus) (Takara, Japan), 2 μM of each primer, and 1 μL of DNA template (a ten-fold dilution series of sample DNA). The amplification conditions were as follows: 95℃ for 30 sec, followed by 40 cycles of denaturation at 95℃ for 30 sec and annealing at 60℃ for 30 sec. Standard curves were generated from a parallel reaction of serial dilutions (1×10^2–1×10^8) of the 16S rRNA gene from the Escherichia coli K12 w3110 strain. Regression coefficients (r^2) for all standard curves were ≥ 0.98. The measured rRNA gene copy numbers were divided by 4.2 (the average copy number of the 16S rRNA gene in bacteria) for estimation of the total cell number.[21] Differences between samples were analyzed by the Mann-Whitney test using R software (ver. 3.2.0). Results with P-values < .05 were considered statistically significant.

Pyrosequencing reads were analyzed as previously described.[22] The raw sequencing reads were de-multiplexed and low-quality sequences (average quality score < 25 or read length < 300 bp) were trimmed for further analysis. Chimeric sequences were removed using the UCHIME software.[23] The trimmed sequences were clustered, and representative sequences in each cluster were identified using a Basic Local Alignment Search Tool (BLAST) search of the EzTaxon-e database.[24] The sequence reads were clustered into operational taxonomic units (OTUs) based on a 97% nucleotide similarity. The diversity indices, Good's coverages, and rarefaction curves were calculated using MOTHUR after random subsampling.[25] Principal coordinate analysis (PCoA)

was performed to compare the microbiota among samples based on the Fast-UniFrac distance. The Mann-Whitney U-test was used to identify statistically significant differences using R software (Version 3.3.2).

6. Statistical analysis

Maternal and infant characteristics were compared between infants with FA and those 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 atopic dermatitis at 6 months) were used as potential confounding variables in multivariate analysis.

For assessing the influence of 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 multivariate analysis for the development of FA after adjusting with the confounders mentioned above. The amounts of energy and nutrients consumed, including trans fats, were compared amongst the different dietary patterns.

For identifying candidate SNPs that interact with maternal dietary patterns in the development of FA in infants, all homozygous and heterozygous SNP genotypes and copy number variations (CNVs) of more than one copy were evaluated using multiple logistic regression models with an added "interaction term". 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 (FDR) method.[26] To display the results graphically, 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. All *p*-values < .05 and interaction *p*-values < .10 were considered statistically significant.[27,28] SPSS version 23 statistical software (IBM Corp., Armonk, NY, USA) was used for all analyses.

III. RESULTS

1. Subjects' characteristics and incidences of infant food allergy (FA)

Among the 1628 infants, 147 (9.03%) infants were diagnosed with FA. Table 4 shows a comparison of maternal and infant characteristics between infants with FA and those without FA. Mothers of infants with FA are more likely to have a history of allergy, while other maternal characteristics show no difference between the two groups. Infants diagnosed with AD at 6 months are more likely to have FA at 1 year. Among 147 infants with FA, 40 (27.2%) infants also had AD at 1 year.

Table 4. Demographics and maternal dietary patterns during pregnancy between infants without FA and those with FA and multivariate analysis for development of FA (N=1628).

	Without FA (n=1481)	With FA (n=147)	ORs	95% CI
Maternal characteristics				
Age, year	33 (31-35)	33 (31-35)	0.981	0.933-1.034
History of allergic disease	421 (28.4)‡	58 (39.5)	1.652§	1.160-2.350
Smoking exposure*	840 (56.7)	80 (54.4)	0.872	0.618-1.232
Cesarean section	538 (36.3)	47 (32.0)	0.831	0.572-1.207
Birth season				
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
Infants' characteristics				
Male sex	696 (47.0)	69 (46.9)	0.968	0.685-1.367
Presence of siblings	608 (41.1)	58 (38.5)	0.906	0.632-1.300
Gestational age, week	39.1 (38.3-40.0)	39.4 (38.4-40.0)		
Birth weight (mg)	3190 (2920-3450)	3175 (2905-3490)		
Birth height (cm)	49.5 (48.0-51.0)	49.3 (48.0-50.2)		
Atopic dermatitis† at 6 month	213 (14.4)‡	34 (23.1)	1.849§	1.214-2.818
Atopic dermatitis† at 1 year	193 (13.0)‡	40 (27.2)		
Maternal dietary pattern during pregnancy				
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 & milk	738 (49.8)	76 (51.7)	1.026	0.726-1.449

FA, food allergy; OR, odds ratio; CI, confidential interval. Data expressed as mean ± SD or median (interquartile range) or number (percentages). * Smoking includes maternal and family members', who live together, smoking history during pregnancy, †Doctor diagnosed atopic dermatitis. Multivariate analysis adjusting with birth season, maternal allergic history, age, and smoking history, delivery method, presence of siblings, infants' sex, and atopic dermatitis at 6 months. ‡P < .05 between without and with FA. §P < .05 of ORs in multivariate analysis.

The most frequent causative foods were eggs (61 infants, 41.5%) and milk (43 infants, 29.3%). There were 34 infants with more than one causative food allergen, and one infant exhibited allergic symptoms in response to eggs, milk, and wheat concomitantly. The most common symptoms were skin rashes and weals, which were observed in 129 infants (88%), followed by facial swelling (35 infants, 24%) and gastrointestinal symptoms (17 cases, 12%). The causative

food allergens and allergic symptoms are shown in Figure 2, 3 and 4.

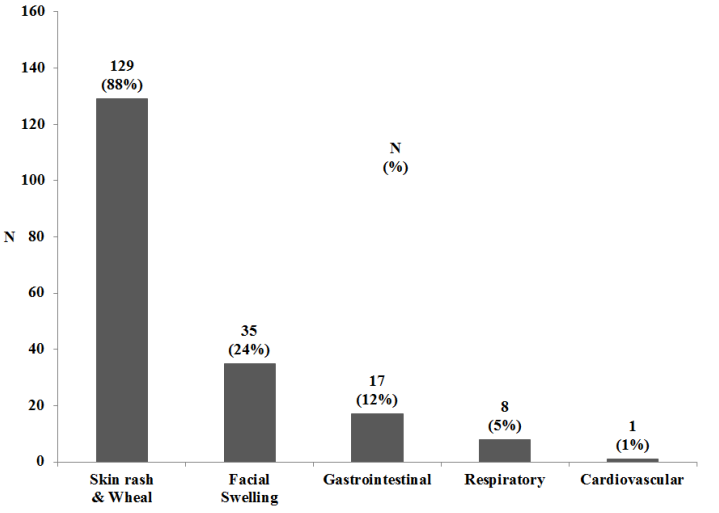

Figure 3. Food allergy symptoms infants

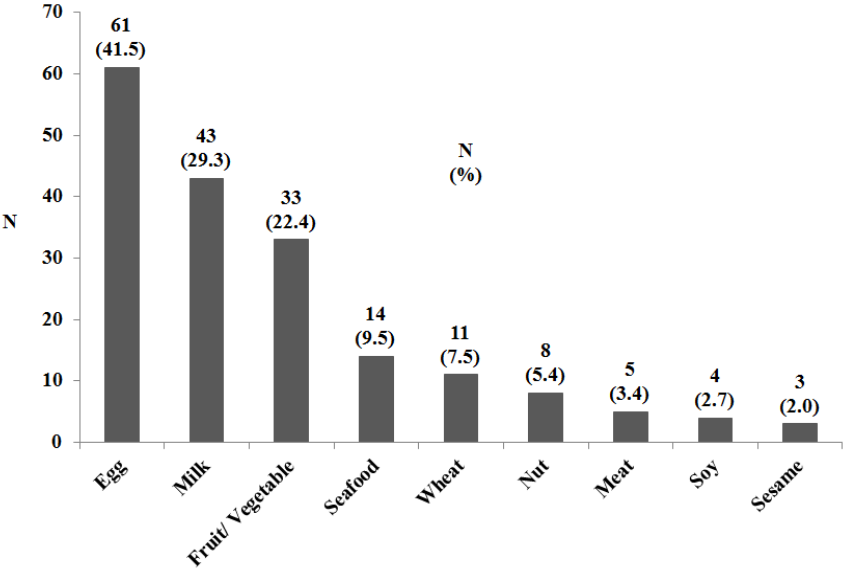

Figure 4. Causative food allergens in total infants with food allergy

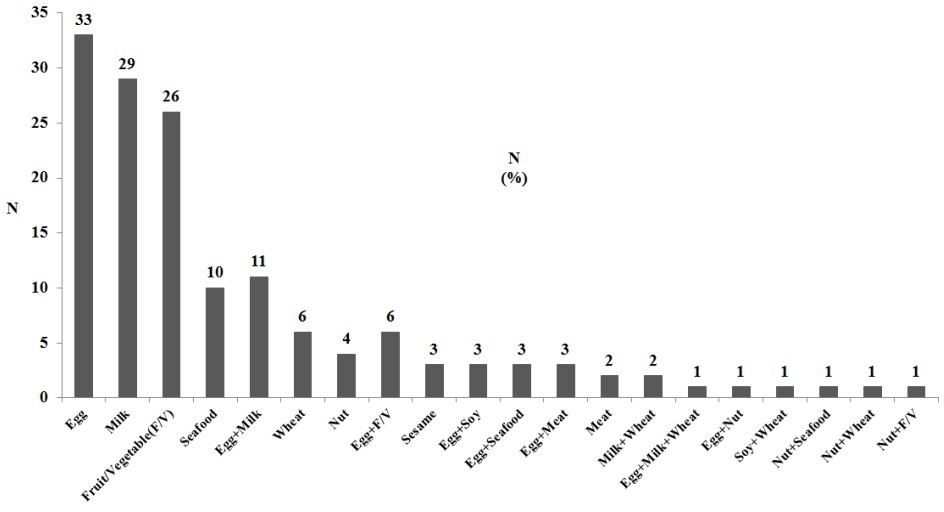

Figure 5. Causative food allergens in individual infants with food allergy

2. Maternal dietary patterns during pregnancy associated with infant FA

Table 4 shows the distribution of the five maternal diet patterns in infants with FA and those without FA, as well as the results of the multivariate analysis for the development of FA. For each dietary pattern, the percentage of individuals in the high intake group (Q3–Q4) was compared between infants with FA and those without FA. The percentage of individuals in the high intake group (Q3–Q4) for the maternal confectionery dietary pattern was higher among infants with FA than among those without FA, while the other dietary patterns showed no significant differences between groups. Upon multivariate 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 5). Since the confectionery diet was characterized by higher

intake of baked goods and sugary products, we also compared trans fat intake. 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 high [Q3-Q4] quartiles vs 39.8 g in low [Q1-Q2] quartiles). According to 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 low and high confectionery diet intake groups.

To assess correlations between the other dietary patterns and the trans fat intake, a correlation matrix was used (Figure 5). The meat dietary pattern factor score also showed a meaningful correlation with the minimal trans fat intake, while the factor scores of the traditional, processed, and coffee and milk patterns did not show any correlations with the trans fat intake.

Table 5. Daily nutrients and trans fat intakes according to 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	1839	21.2	18.8	13.8	14.5	445.9	91.2
	(10.0-16.0)	(1480-2191)	(17.4-24.9)	(16.9-20.7)	(11.3-16.8)	(12.1-17.0)	(357.3-558.6)	(69.6-119.1)
High (Q3-Q4)	12.8	1818	22.0	18.9	14.3	14.4	462.5	92.5
	(10.0-16.0)	(1422-2382)	(18.4-25.9)	(17.1-20.7)	(11.9-17.4)	(12.1-16.7)	(360.5-597.2)	(71.9-115.4)
P	0.630	0.196	0.001	0.621	0.030	0.842	0.036	0.600
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	0.440	0.956	0.120	0.005	0.849	0.853	0.040	0.023

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	284	10.2	7.0	7.4	5.8	39.8	0.64
	(46.4-75.0)	(248-334)	(8.7-11.7)	(5.5-8.6)	(6.1-8.8)	(4.8-6.9)	(30.0-56.2)	(0.41-0.86)
2146 (1594-2983)	61.8	294	10.4	7.2	7.6	5.9	56.6	0.65
	(46.6-78.1)	(247-345)	(8.8-11.9)	(5.8-8.7)	(6.3-9.1)	(4.9-7.2)	(37.2-82.3)	(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

Data expressed as mean ± SD or median (interquartile range).
GWG, gestational weight gain; SFA, saturated fatty acids; MFA, monounsaturated fatty acids; PUFA, polyounsaturated fatty acids; Trans fat (Max.), maximal intakes of trans fat; Trans fat (Min.), minimal intakes of trans fat.
All nutrients were adjusted with calorie intake except for the calorie variable. Correlation analysis was adjusted with calories and maternal age.

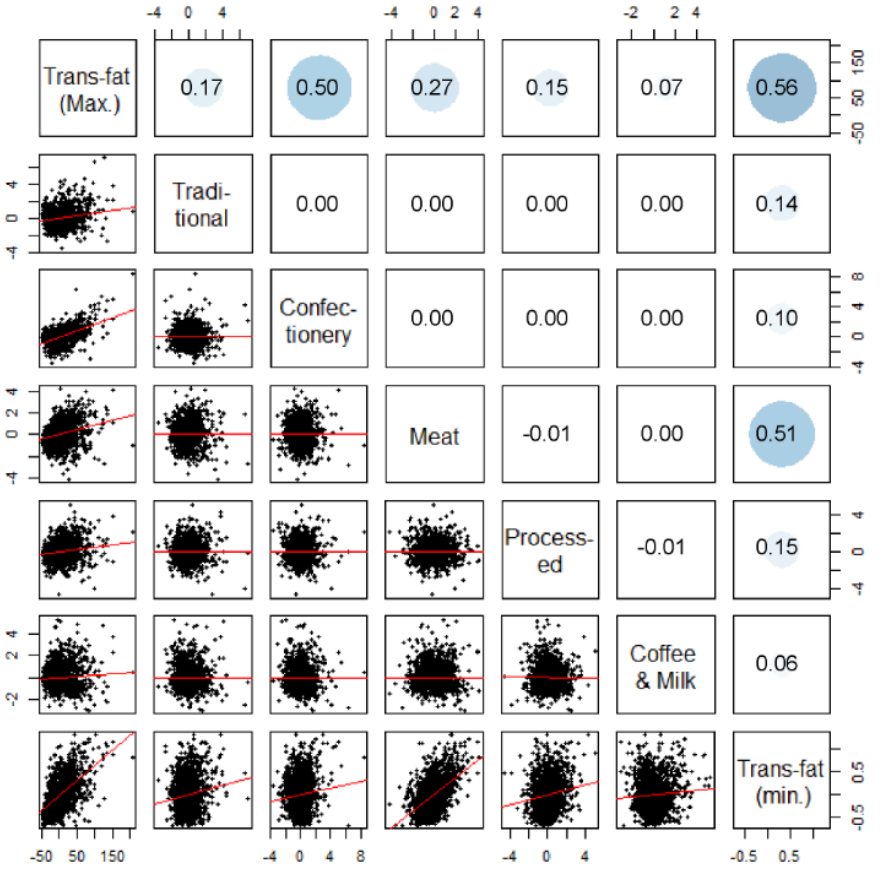

Figure 6. Correlation matrix between maximal and minimal trans fat intakes and five maternal dietary patterns

For assessment of correlation between the other diet patterns and the amount of trans-fat intakes, a correlation matrix was used (Figure 5). “Meat” diet pattern factor score also showed a meaningful correlation with the amount of trans-fat intakes while the factor scores of the other diet patterns including “traditional”, “processed” and “coffee and milk” did not show any correlation with the amount of trans-fat intakes.

3. Effect of breastfeeding

Since breastfeeding has been found to be an important factor in the development of allergy and as it also connects maternal diet to the nutrients 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 questions about the period of breastfeeding completely; 101 infants of the subjects were diagnosed with FA. 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 associated with the development of FA in the other infants with less than 6 months of breast feeding (OR = 1.219, *P* = .590), as shown in Table 6. However, the interaction between the breastfeeding period and the influence of the maternal dietary pattern on the development of FA was not statistically significant (interaction *P* = .374).

Table 6. 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 $P^\dagger$
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.

4. Genetic variations related with maternal dietary pattern for development of infant FA

Of the 1628 infants in the study, only 1508 samples of cord blood were eligible for genomic analysis of SNPs; of those infants 129 had FA. Interaction analysis between genetic variations and maternal confectionery dietary pattern for development of infant FA was significant only for SNPs of CD14 (rs2569190) (interaction p = 0.015); results of the analysis are shown in Table 7. In infants with the homozygous TT genotype of CD14 (rs2569190), maternal confectionery diet was significantly associated with development of infant FA (OR = 3.418, p = 0.001). This association was not conserved in infants with TC or CC genotype (OR = 1.133, p = 0.578).

Of the 1628 infants in the study, only 1031 samples of cord blood could be assessed for CNVs of GSTM1 and GSTT1; of those infants 77 had FA. Genotypes with more than one copy (CNV) of GSTM1 or GSTT1 were shown to have a significant interaction effect with maternal confectionery diet pattern on infant development of FA (interaction p = 0.048 in GSTM1, interaction p = 0.033 in GSTT1). For infants with CNV > 1 of GSTM1 or GSTT1, maternal confectionery dietary pattern was significantly associated with development of FA, whereas the association was not conserved for infants with CNV ≤ 1.

After correction for multiple testing, only CD14 and GSTT1 genetic variations showed a significant interaction with maternal confectionery dietary pattern (FDR p = 0.016 in CD14, FDR p = 0.036 in GSTT1). High maternal confectionery dietary pattern tended to increase the risk of development of FA in infants with the TT variant of CD14 (rs2569190) but not in infants with C-allele variants of CD14; this is shown in Figure 6. High maternal confectionery dietary pattern tended to increase the risk of development of FA in infants with more than one copy of GSTT1 or GSTM1, but not in infants of other genetic variation; this is shown in Figure 7 and 8.

Table 7. Screening of genetic variation having an interaction with maternal confectionary diet pattern for development of food allergy in infant.

ORs of Maternal confectionary diet		95% CI	P	Interaction P*	FDR P‡
Single nucleotide polymorphisms (SNPs), N(infants with FA/total subjects)†					
Total subjects (147/1628)	1.517	1.017-2.147	0.019		
IL 13, rs20541 (129/1512)					
CC (66/744)	1.891	1.106-3.234	0.020	0.345	0.376
TT+TC (63/768)	1.311	0.775-2.216	0.313		
TT (10/143)	1.242	0.283-5.454	0.774	0.719	
TC+CC (119/1369)	1.568	1.064-2.310	0.023		
CD14, rs2569190 (129/1508)					
TT (39/528)	3.418	1.608-7.266	0.001	0.015	0.016
CC+CT (90/980)	1.133	0.731-1.755	0.578		
CC(27/253)	1.364	0.595-3.128	0.463	0.874	
CT+TT(102/1255)	1.567	1.032-2.378	0.035		
TLR4, rs1927911 (130/1508)					
CC (48/555)	1.663	0.903-3.065	0.103	0.817	0.891
TT+TC (82/953)	1.465	0.919-2.337	0.109		
TT (21/228)	1.372	0.528-3.565	0.516	0.880	
TC+CC(107/1278)	1.540	1.024-2.317	0.038		
GSDMB, rs4794820 (126/1492)					
GG (66/784)	1.679	0.991-2.844	0.054	0.570	0.622
AA+AG(60/708)	1.381	0.801-2.380	0.245		
AA(11/138)	4.341	0.898-20.984	0.068	0.289	
AG+GG (115/1354)	1.447	0.979-2.137	0.064		
GSDMB, rs7216389 (128/1506)					
TT(72/830)	1.495	0.908-2.461	0.114	0.990	0.994
CC+CT(56/676)	1.526	0.867-2.687	0.143		
CC(12/127)	6.722	1.444-31.296	0.015	0.509	
CT+TT(115/1376)	1.375	0.933-2.029	0.108		
GR, rs41423247 (130/1511)					
GG(87/918)	1.530	0.972-2.409	0.066	0.898	0.979
CC+CG(43/593)	1.390	0.730-2.650	0.314		
CC(5/82)	26.943	0.140-5198.8	0.220	0.237	
CG+GG(0)	1.451	0.998-2.111	0.051		
BDNF, rs6265 (129/1512)					
GG(37/440)	2.235	1.075-4.647	0.031	0.185	0.202

AA+AG(92/1072)	1.314	0.850-2.030	0.219	0.426	
AA(24/338)	1.465	0.605-3.551	0.398		
AG+GG(105/1174)	1.570	1.040-2.373	0.032		
Nrf2, rs6726395 (129/1510)					
GG(52/562)	1.516	0.838-2.743	0.169	0.994	0.994
AA+AG(77/948)	1.620	1.000-2.625	0.050		
AA(19/223)	2.318	0.832-6.458	0.108	0.104	
AG+GG(110/1287)	1.501	1.003-2.245	0.048		
NAT2, rs4271002 (129/1505)					
GG(82/883)	1.496	0.941-2.380	0.089	0.691	0.754
CC+CG(47/622)	1.504	0.805-2.810	0.200		
CC(0/79)				0.998	
CG+GG(125/1422)	1.412	0.972-2.053	0.071		
GSTP1, rs1695 (130/1511)					
AA(93/1001)	1.295	0.839-2.000	0.243	0.153	0.167
GG+GA(37/510)	2.367	1.121-4.998	0.024		
GG(0/47)				0.998	
GA+AA(127/1460)	1.461	1.006-2.122	0.046		
Copy number variations (CNVs), N(infants with FA/total subjects)†					
GSTM1 (77/1031)					
CVN ≤ 1(53/836)	1.287	0.724-2.286	0.390	0.048	0.052
CVN > 1(23/191)	4.235	1.429-12.555	0.009		
GSTT1 (77/1031)					
CVN ≤ 1(51/820)	1.279	0.710-2.306	0.413	0.033	0.036
CVN > 1(25/209)	4.258	1.546-11.730	0.005		

IL 13, interleukin 13; CD14, cluster of differentiation 14; TLR4, Toll-like receptor 4; GSDMB, Gasdermin-B; GR, glucocorticoid receptor; BDNF; brain-derived neurotrophic factor; Nrf2, nuclear factor erythroid 2-related factor 2; NAT2, N-acetyltransferase 2; GSTP1, glutathione S-transferases pi; GSTM1, glutathione S-transferase mu; GSTT1, glutathione S-transferase theta

*interaction P < 0.05 in interaction between genetic variation and maternal confectionary diet pattern for development of food allergy in infant adjusting with birth season, maternal allergic history, age, and smoking history, delivery method, presence of siblings, infants' sex, and atopic dermatitis at 6 months.

‡ False Discovery Rate correction of interaction P.

†N(FA/subjects) is a number of infant with FA and a number of subjects whose cord blood could be assessed for a genetic variation.

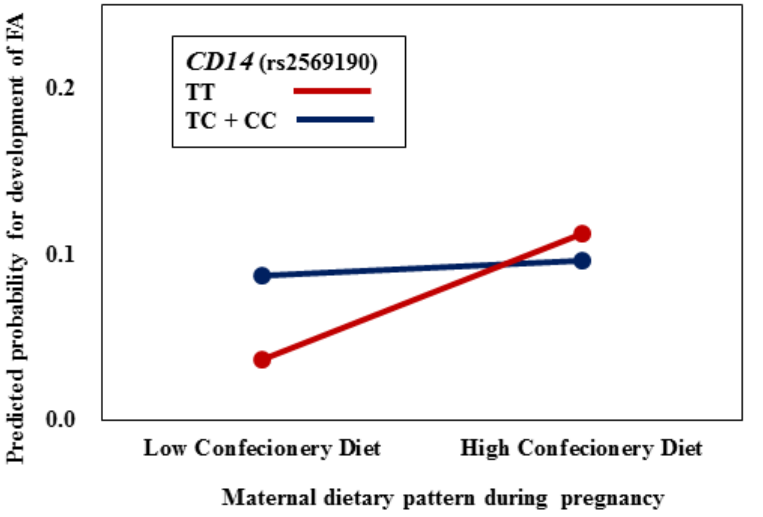

Figure 7. Fitted predicted probability plots for the development of food allergy in relation to maternal confectionery dietary pattern in infants with different genotypes at SNP rs2569190 in CD14

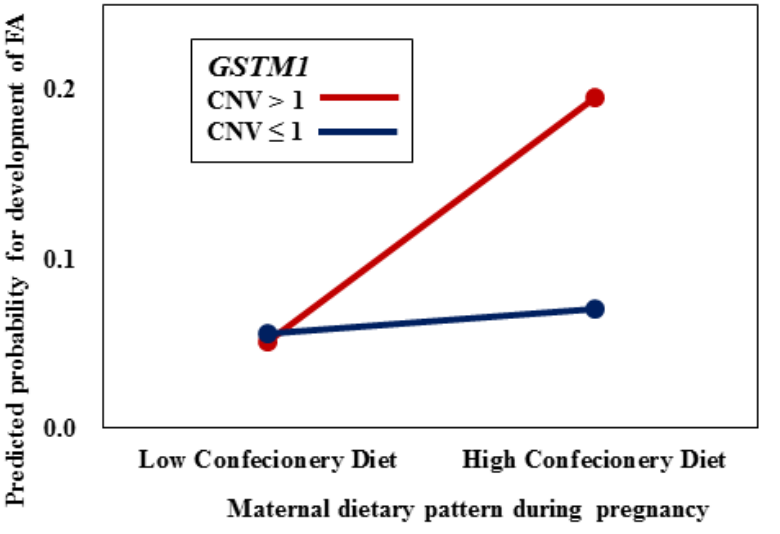

Figure 8. Fitted predicted probability plots for the development of food allergy in relation to maternal confectionery dietary pattern in infants with different genotypes at more than one copy of the *GSTM1 CNVs*

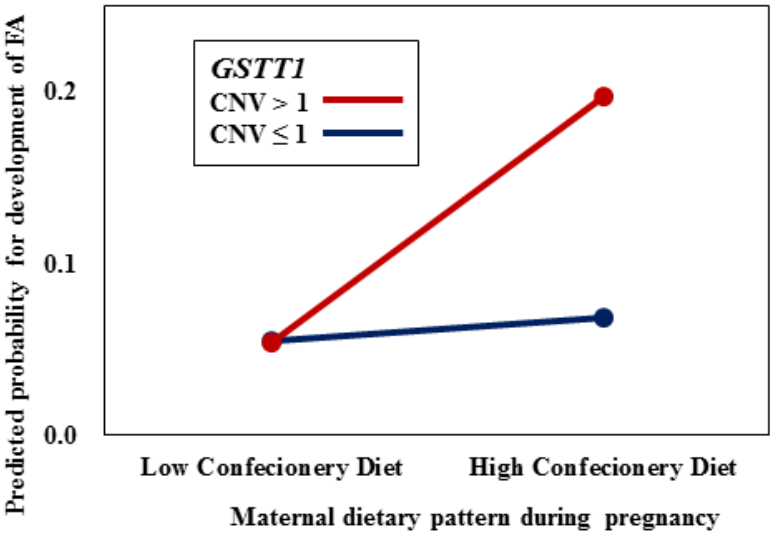

Figure 9. Fitted predicted probability plots for the development of food allergy in relation to maternal confectionery dietary pattern in infants with different genotypes at more than one copy of the GSTT1 CNVs

5. Gut microbiota analysis of infants at 6 months

We analyzed gut microbiota in infants' stools collected at 6 months. We compared the gut microbiota from infants of mothers with high confectionery dietary patterns against that from infants with mothers of low confectionery dietary patterns. For data on breastfeeding effects, we examined gut microbiota from infants who breastfed for longer than 6 months; we assumed that maternal dietary pattern might persist during perinatal periods and that maternal diet could affect infant microbiota through breastfeeding. We compared gut microbiota between infants diagnosed with FA and those without FA. Finally, to evaluate the relationship between maternal confectionery dietary pattern and infant development of FA, we compared gut microbiota from infants who were diagnosed with FA and whose mothers were grouped in the high confectionery dietary pattern quartiles against infants who were not diagnosed with FA and whose mothers were grouped in the low confectionery dietary pattern quartiles.

Since the interaction between maternal confectionery diet and SNPs of CD14, GSTM1, and GSTT1 for development of infant FA was shown to be significant above, we also compared the gut microbiota from infants of mothers with high confectionery dietary patterns and with the TT variant of CD14 (rs2569190) or more than one copy number of GSTM1 or GSTT1 against that from infants with mothers of low confectionery dietary patterns or with the CC + TC variant of CD14 (rs2569190) or one and zero copy number of GSTM1 or GSTT1. The numbers of infants' stools which were eligible are shown in Table 8.

Table 8. Numbers of eligible samples of gut microbiota of infants at 6 months

Selection condition	Comparison groups	Number of samples	Relevant figure
All infants	Maternal high confection diet	61	Figure 9
	Maternal low confection diet	58	
Infants breastfed > 6 month	Maternal high confection diet	31	Figure 10
	Maternal low confection diet	37	
All infants	Infants with FA	12	Figure 11
	Infants without FA	107	
All infants	Infants with FA & Maternal high confection diet	9	Figure 12
	Infants without FA & Maternal low confection diet	55	
All infants	Maternal high confection diet & TT of CD14	24	Figure 13
	Maternal low confection diet or CC + TC of CD14	92	
All infants	Maternal high confection diet & CNV > 1 of GSTM1	9	Figure 14
	Maternal low confection diet or CNV ≤ 1 of GSTM1	41	
All infants	Maternal high confection diet & CNV > 1 of GSTT1	11	Figure 15
	Maternal low confection diet or CNV ≤ 1 of GSTT1	39	

FA, food allergy.

Comparison between gut microbiota from infants of mothers with low confectionery dietary pattern (Q1-Q2) and gut microbiota from infants of mothers with high confectionery dietary pattern (Q3-Q4) showed no significant difference in alpha and beta diversities; and similar comparison at phylum and genus levels showed no significant difference in bacterial composition (Figure 9).

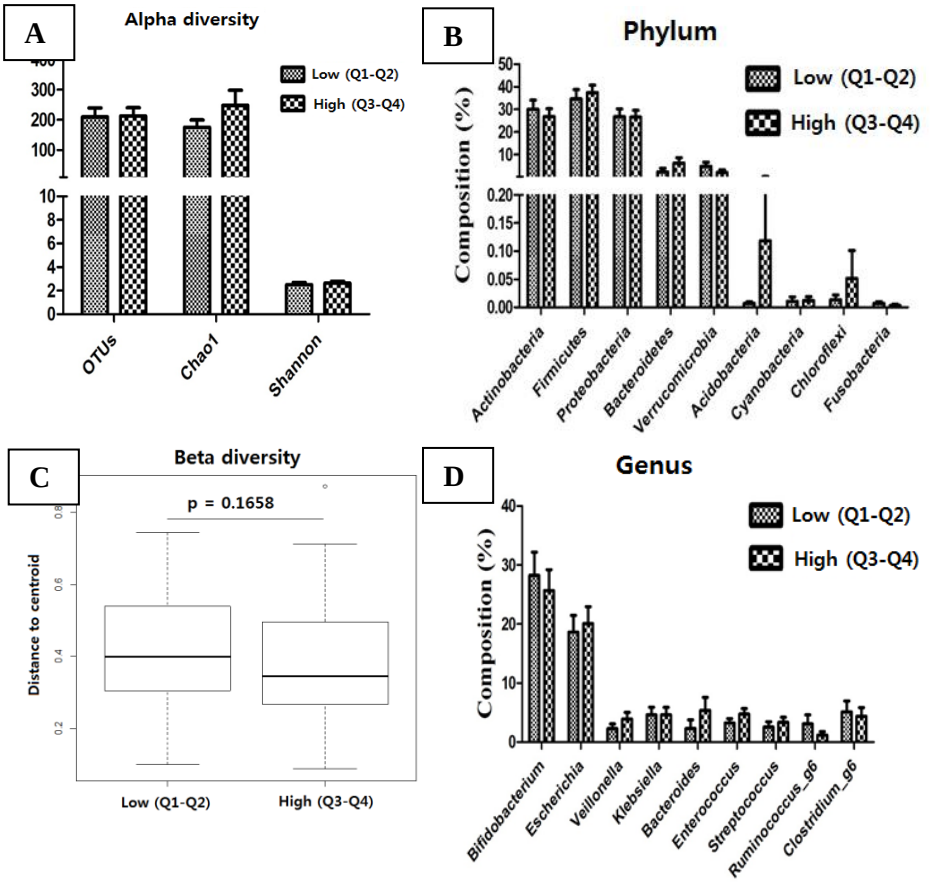

Figure 10. Gut microbiota analysis of 6 months-infants of mothers with low (Q1-Q2) and high (Q3-Q4) confectionery dietary patterns. (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus

Comparison between gut microbiota from infants who breastfed for 6 months or more and whose mothers were grouped into low confectionery dietary pattern quartiles (Q1-Q2) and infants who breastfed for 6 months or more and whose mothers were grouped into high confectionery dietary pattern quartiles (Q3-Q4) showed no significant difference in alpha and beta diversities; and similar comparison at phylum and genus levels showed no significant difference in bacterial composition (Figure 10).

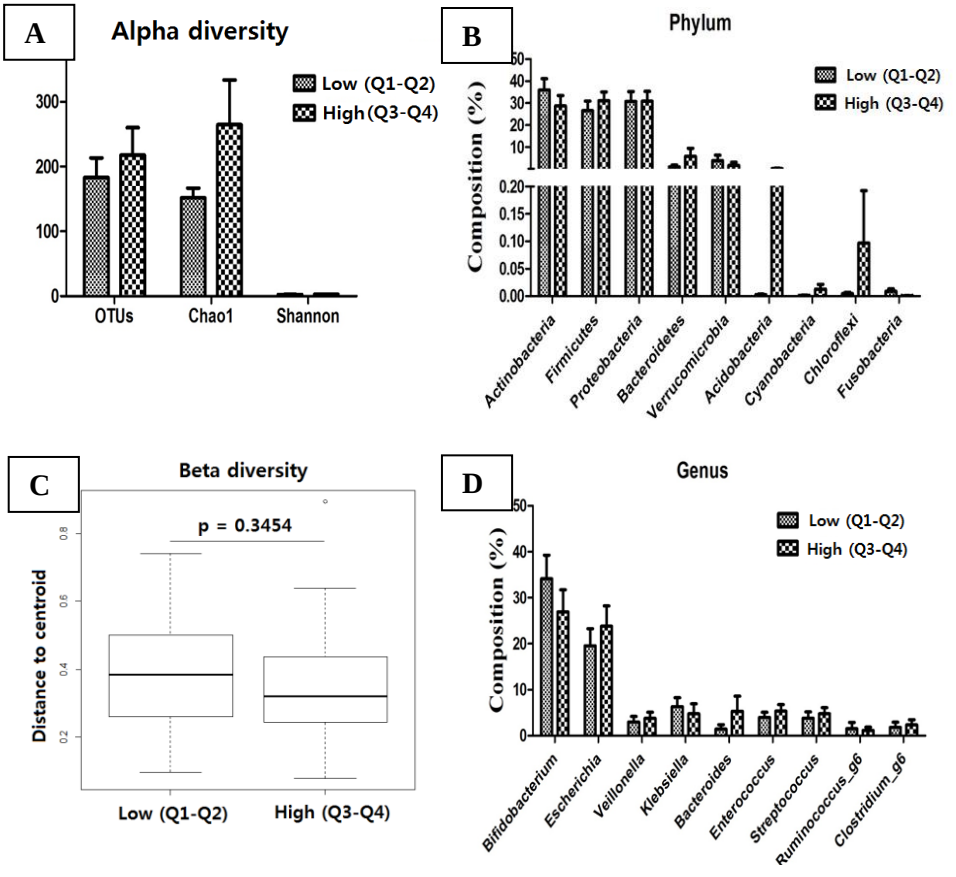

Figure 11. Gut microbiota analysis of 6 months-infants who were still breastfeeding grouped by low (Q1-Q2) and high (Q3-Q4) maternal confectionery dietary pattern. (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus

Comparison between gut microbiota from infants with FA and gut microbiota from infants without FA showed no significant difference in alpha and beta diversities; and similar comparison at phylum and genus levels showed no significant difference in bacterial composition (Figure 11).

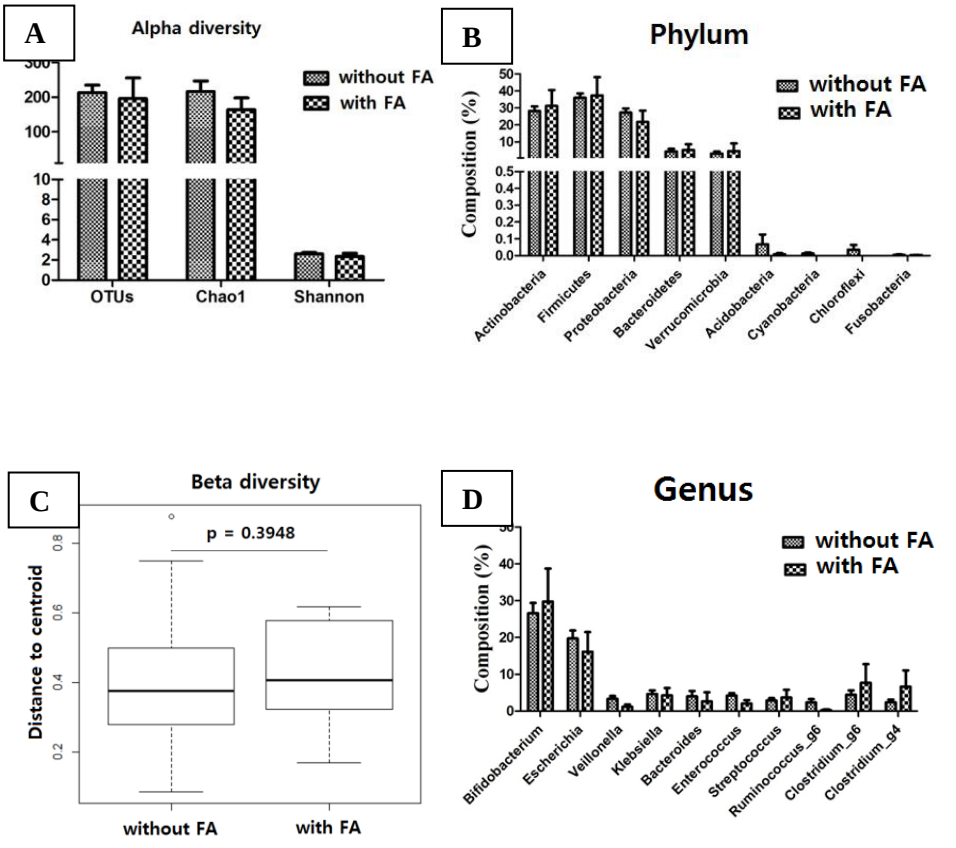

Figure 12. Gut microbiota analysis of 6 months-infants between those with and without FA. (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus

Comparison between gut microbiota from infants who were diagnosed with FA and whose mothers were grouped into high confectionery dietary pattern quartiles (Q3-Q4) and infants who were not diagnosed with FA and whose mothers were grouped into low confectionery dietary pattern quartiles (Q1-Q2) showed no significant difference in alpha and beta diversities; and similar comparison at phylum and genus levels showed no significant difference in bacterial composition (Figure 12).

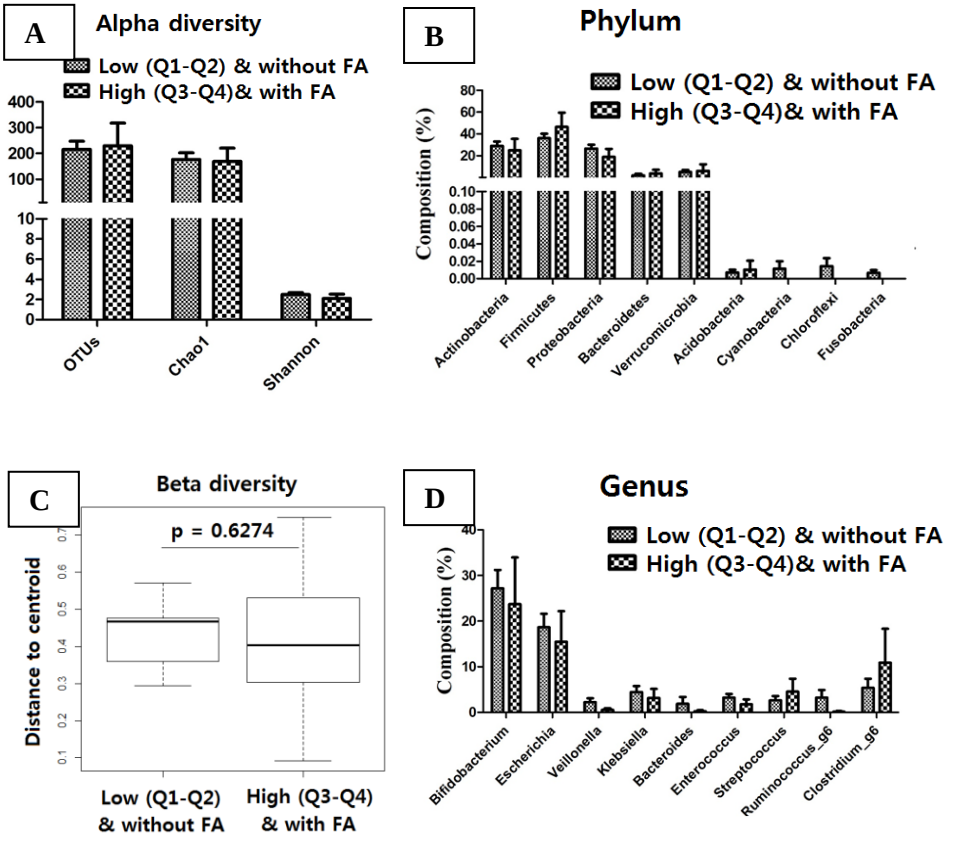

Figure 13. Gut microbiota analysis of infants with FA with mothers of high confectionery diet and infants without FA with mothers of low confectionery diet. (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus

Comparison between gut microbiota from infants of mothers with high confectionery dietary patterns and with the TT variant of CD14 (rs2569190) against that from infants with mothers of low confectionery dietary patterns or with the CC + TC variant of CD14 (rs2569190) showed no significant difference in alpha diversities; but beta diversity was lower and Firmicutes at phylum was more increased significantly in the former group (Figure 13).

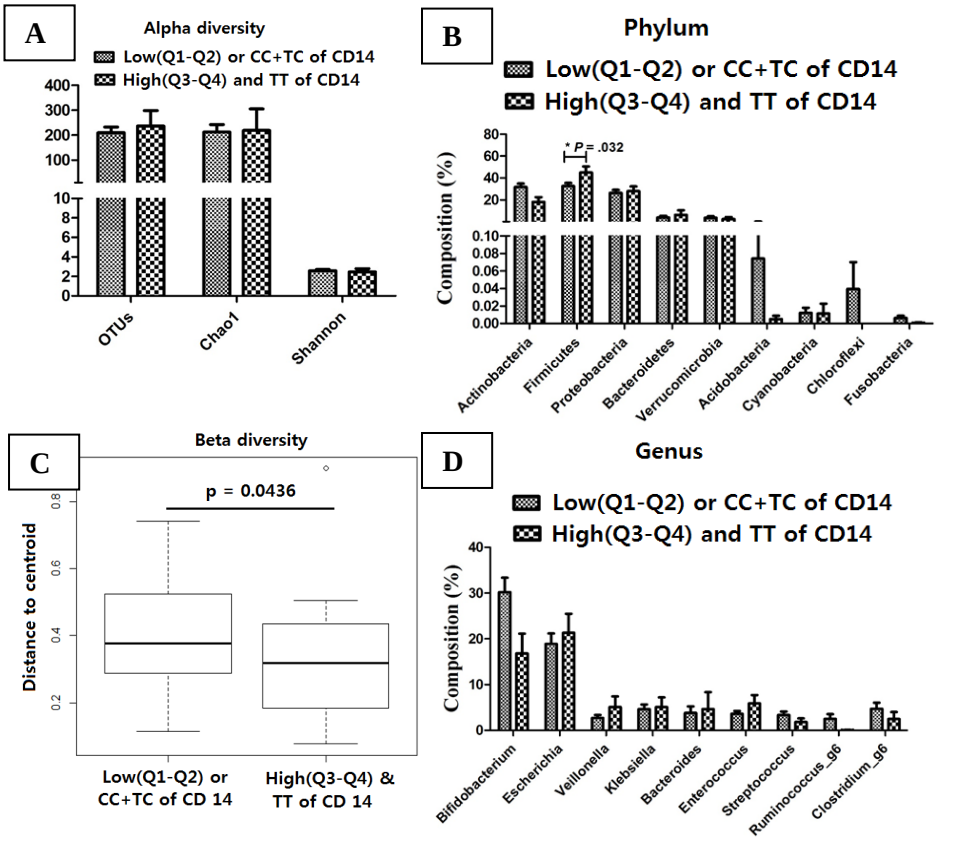

Figure 14. Gut microbiota analysis from infants of mothers with high confectionery dietary pattern and with the TT variant of CD14 (rs2569190) against that from infants of mothers with low confectionery dietary pattern or with the CC + TC variant of CD14 (rs2569190) (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus
*P < 0.05

Comparison between gut microbiota from infants of mothers with high confectionery dietary patterns and with more than one copy number of GSTM1 against that from infants with mothers of low confectionery dietary patterns or with one and zero copy number of GSTM1 showed that alpha diversity was lower and Verrucomicrobia at phylum level were more increased significantly in the former group (Figure 14).

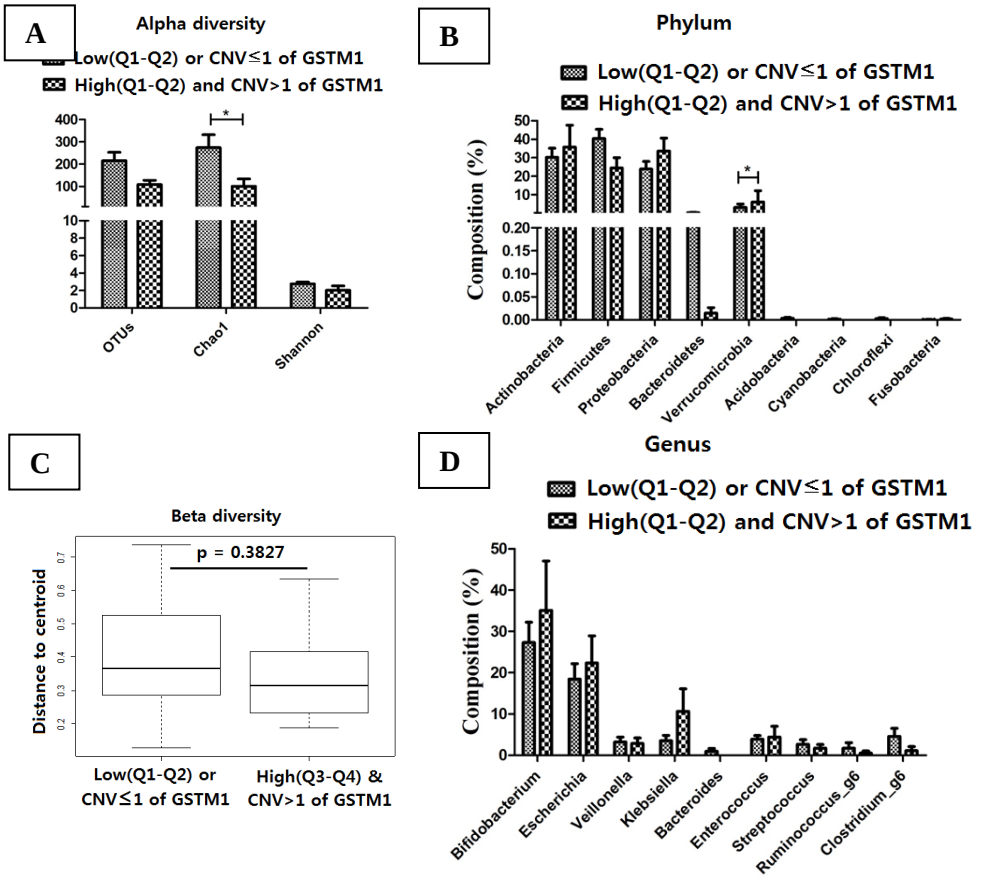

Figure 15. Gut microbiota analysis from infants of mothers with high confectionery dietary pattern and with more than one copy number of GSTM1 against that from infants with mothers of low confectionery dietary patterns or with one and zero copy number of GSTM1 (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus
*****P < 0.05

Comparison between gut microbiota from infants of mothers with high confectionery dietary patterns and with more than one copy number of GSTT1 against that from infants with mothers of low confectionery dietary patterns or with one and zero copy number of GSTT1 showed no significant difference in alpha and beta diversities; and similar comparison at phylum and genus levels showed no significant difference in bacterial composition (Figure 15).

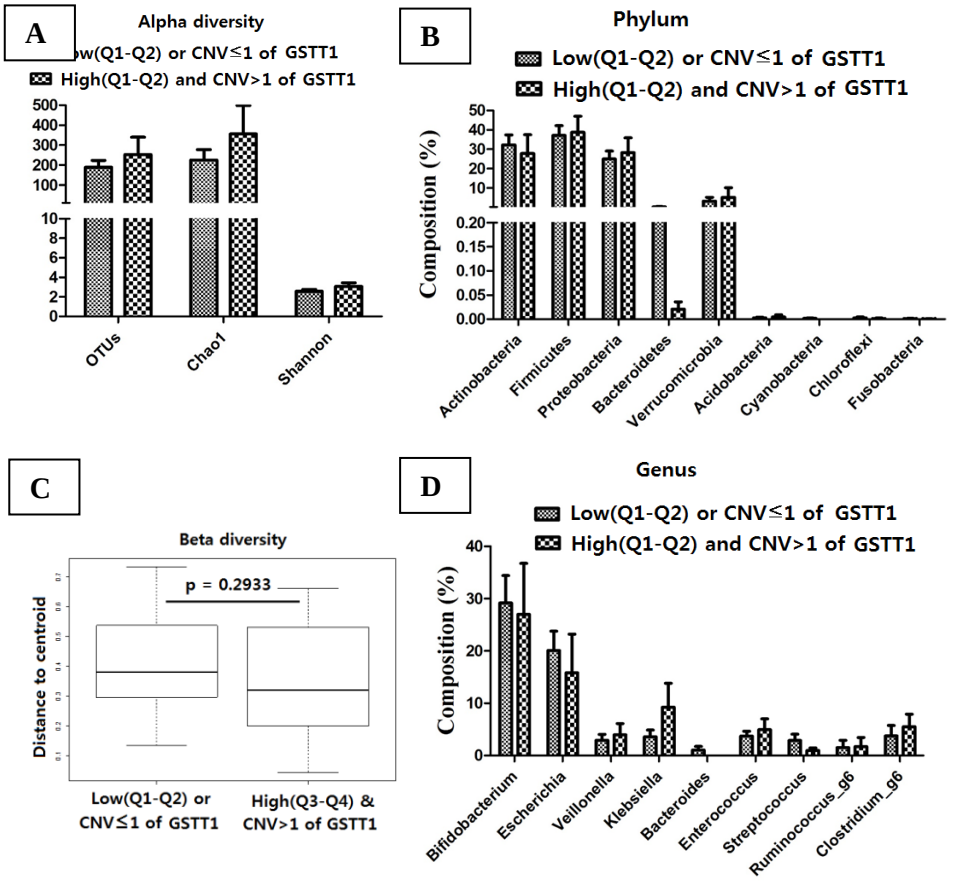

Figure 16. Gut microbiota analysis from infants of mothers with high confectionery dietary pattern and with more than one copy number of GSTT1 against that from infants with mothers of low confectionery dietary patterns or with one and zero copy number of GSTT1 (A) alpha diversity, (b) beta diversity (c) comparison of phylum (d) comparison of genus.

IV. DISCUSSION

During pregnancy a maternal dietary pattern that is high in baked and sugar confectionery products can be later linked to higher likelihood of 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), as well as infants with more than one CNVs of GSTM1 or GSTT1, maternal confectionery dietary pattern is more significantly related with development of FA.

1. Maternal confectionery dietary pattern and trans fat associated with infant 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.[28,29] 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.[9,30] Moreover, high trans fat intake, as a typical part of the “Western” diet, is 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.[31] 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.[32,33] In our study, 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 both direct effects related to inflammation and indirect effects related to gut microbiota dysbiosis, which is called the lipotoxicity of TFAs.[34,35] 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.[36,37] Since the importance of gut microbiota dysbiosis has been suggested in the development of FA, TFAs may be one of the triggering factors in the development of allergy through gut microbiota dysbiosis.[38-40] 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.[41,42] However, in our study, as shown in supplementary Table 5, mothers with high intake of a confectionery diet did not exhibit increased weight gain compared to the other mothers. This shows that the lipotoxicity of TFAs can influence human health without causing excess weight gain.[35]

The TFAs usually used in confections are industrial TFAs (iTFAs) produced during the partial hydrogenation of unsaturated fatty acids in vegetable oils, and concentrations of iTFAs can be as high as 60%.[34] In contrast, ruminant TFAs (rTFAs) are produced naturally from the bacterial metabolism of unsaturated fatty acids in the rumens of cows, sheep, and goats, and maximal concentrations of rTFAs may reach 6%.[34] This is why the meat dietary pattern was associated with minimal intake of trans fats, while the confectionery dietary pattern was associated with maximal intake of trans fats in the correlation matrix. However, 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 actually play a role in protecting against allergy development.[34,43,44]

2. Relationship between breastfeeding and maternal confectionery dietary pattern to infant FA

Breastfeeding is strongly recommended based on the assumption of various positive physical and psychological effects in both the infant and mother.[45] For the prevention of FA, exclusive breastfeeding is also recommended in high-risk infants.[46] In this study, however, 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 1 year, and it is commonly used in diet research under the assumption that individual dietary habits do not change easily or quickly.[47] 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.[29] It has been reported that mothers with high levels of TFAs in their milk consume higher amounts of baked confectioneries.[48]

3. Relationship between infant genetic polymorphisms and maternal confectionery dietary pattern to infant FA

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.[49] In addition to LPS, saturated fatty acids (SFAs) can be recognized by the CD14-TLR4 complex and trigger inflammatory pathways, exacerbating many chronic diseases.[50,51] The T allele at the CD14 rs2569190 polymorphism can induce higher expression of CD14 and increased monocyte cytokine production,[52,53] leading to an excessive inflammatory response.[54] Assuming that

TFAs result in a similar lipotoxic mechanism as SFAs,[35,51] 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 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.[55]

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.[56] 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.[35] A GSTM1 polymorphism has been reported to increase the potential protective role of the "Korean traditional healthy" diet against AD, and the CD14 polymorphism was also shown to influence the effect of prenatal antioxidant intake on infant respiratory infections in Korean children.[57,58] Thus, these CD14 and GST gene polymorphisms may be important in terms of the Korean population and diet.[59,60]

4. Microbiota dysbiosis

High fat diets have been shown to alter gut microbiota composition and cause obesity.[61] Other environmental factors such as cesarean section and early life exposure to antibiotics, as well as other dietary imbalances, can induce gut microbiota dysbiosis, which is critically related to food allergy.[1,61,62] Therefore, we hypothesized that maternal confectionery dietary patterns might change an infant's normal gut microbiota composition and prime the infant for development of FA. We evaluated this hypothesis with 4 comparisons of gut

microbiota across different groups of infants as follows: 1) all infants whose mothers had high confectionery dietary patterns vs all infants whose mothers had low confectionery dietary patterns; 2) infants who breastfed for at least 6 months and whose mothers had high confectionery dietary patterns vs infants who breastfed for at least 6 months and whose mothers had low confectionery dietary patterns; 3) all infants who were diagnosed with FA vs all infants who were not diagnosed with FA; 4) infants who were diagnosed with FA and whose mothers had high confectionery dietary patterns vs infants who were not diagnosed with FA and whose mothers had low confectionery dietary patterns. However, we did not find any statistical differences of alpha-, or beta-diversity, or of bacterial composition in phylum and genus levels. The critical limitation in these analyses of microbiota was the small sample size; not all infants' stools were collected. Another limitation was that the mothers' stools were not collected.

Although our analyses of microbiota could not be considered statistically significant, we nonetheless found some relationship between high maternal confectionery dietary patterns and infant development of FA. Ruminococcus bacteria were decreased in both infants with FA and mothers who had high confectionery dietary patterns; recently, it was reported that a poor colonization of mucin-degrading bacteria such as Ruminococcus could be associated with stunted immune development in infants with atopic dermatitis, and that such poor colonization could induce down-regulation of oxidative phosphorylation, PI3K-Akt signaling, estrogen signaling, NOD-like receptor signaling, and antigen processing.[63] In a similar vein, high maternal confectionery dietary patterns could decrease infant levels of helpful microbiotas such as Ruminococcus, and lead to infant development of FA.

We found also higher levels of Firmicutes and Clostridium bacteria in the gut microbiota of infants who were diagnosed with FA; Firmicutes bacteria were increased in mothers who had high confectionery dietary patterns, but

Clostridium bacteria were decreased. Enrichment of Firmicutes and Clostridium in the gut microbiome has been associated with an infant's later resolution of FA and tolerance of the causative food.[64] Clostridial taxa introduced to germ-free mice have been shown to protect against oral allergen sensitization by inducing innate lymphoid cell function at the intestinal mucosa.[65] A further study in this cohort on resolution of FA and development of tolerance might reveal additional roles of microbiota in infant FA.

Since the interaction between maternal confectionery diet and SNPs of CD14, GSTs for development of infant FA was significant, we also compared the gut microbiota from infants of mothers with high confectionery dietary patterns and with the TT variant of CD14 (rs2569190) or more than one copy number of GSTM1 or GSTT1 against that from infants with mothers of low confectionery dietary patterns or with the CC + TC variant of CD14 (rs2569190) or one and zero copy number of GSTM1 or GSTT1. The effect of high maternal confectionery dietary patterns for development of infant FA was synergetic in infant with the TT variant of CD14 and Firmicutes was more increased significantly in these infants. Beta diversity was different significantly in these infants compared with the other infants, which means that the synergic effects of high maternal confectionery dietary patterns and SNPs of CD14 could induce gut microbiota dysbiosis. The effect of maternal dietary patterns was also synergetic in infant with more than one copy number of GSTM1, and alpha diversity and Verrucomicrobia was more increased in these infants. Firmicutes was a risk candidate microbiota for development of infant FA relating with maternal high confectionery dietary pattern in our study because Firmicutes was increased in both infants with FA and mothers who had a high confectionery dietary pattern. Also, Firmicutes was more increased significantly in infants with the TT variant of CD14 and whose mothers had a high confectionery dietary pattern. Firmicutes might play a role in development of infant FA relating with pro-inflammatory response of gut. Firmicutes had been suggested

to be found higher in children with FA and associated with greater likelihood of out-growing milk allergy.[66-68] Decreased alpha diversity in human microbiota has been suggested to be one of the risk factors for development of allergic diseases.[67] Verrucomicrobia is one of the the dominant phyla and was reported to be decreased in infants with food allergy which was not consistent with our results.[69] This discrepancy should be addressed through further studies well designed with a large number of subjects and randomized controlled models or with mouse models about pathomechanism.

5. The strengths and limitations

There are some limitations of this study that should be considered. First, the diagnosis of FA was based on clinical symptoms and characteristics, not provocation tests. However, the definition of FA used here was not only based on self-reporting but was based on the existence of a definitive causative food and the time period to the development of symptoms as assessed by allergy specialists at each participating hospital. Moreover, it is difficult to perform food challenge tests in infants because of poor cooperation and the high risk of anaphylaxis. 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 subject to national regulations or labeled. Therefore, we thought there may be a large variation in trans fat amounts in domestic foods and that the minimal and maximal values would better reflect this reality. Third, 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.[57-59,70-72]

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. Many countries, including Korea, now recognize the deleterious effects of TFAs on human health and have begun regulating them in the food industry.

V. CONCLUSION

Maternal dietary patterns that involve high intake of confectionery products during periods of pregnancy and prolonged breastfeeding can lead to development of FA in the infant, and this type of FA may reflect the harmful effect of TFAs produced during industrial food processing. Polymorphisms of CD14 that play a role in increasing the proinflammatory response and 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 products. Maternal dietary interventions involving reducing the consumption of confectionery foods during the perinatal period should be implemented to prevent FA development, especially in genetically susceptible children.

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ABSTRACT (IN KOREAN)

영아 식품알레르기 발생에 대한 산모 식이패턴과 유전적 변이의 영향

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김윤희

소아 식품알레르기의 발병률과 유병률은 점점 증가하고 있으며, 이것은 유적전, 환경적 요인이 함께 관련된 것으로 여겨지고 있다. 하지만 어떤 유전적 요인과 환경적 요인이 영향을 미치는지는 아직 분명히 밝혀지지 않았다. 본 연구를 통하여 영아 식품알레르기의 발생에 영향을 미치는 산모의 식이 패턴과 그것과 의미있는 상호작용을 보이는 유전적 요인을 밝히고자 한다.

2007년부터 2015년까지 모집된 한국의 알레르기 질환 출생 코호트 (COCOA, COhort for Childhood Origin of Asthma and allergic diseases) 에서 1628명의 영아를 대상으로 하였다. 임

신 26주에 식품섭취빈도조사 (FFQ, food frequency questionnaire) 를 통하여 산모의 식이 패턴을 5가지로 분류하였다. 영아의 제대혈로 이전에 천식과 알레르기 질환에서 유의하다고 알려진 12가지 단일 핵산염기 다형성을 분석하였다. 6개월 대상군 영아의 분변에서 마이크로바이옴을 분석하였다.

총 1628명의 영아에서 147명 (9.0%)이 식품알레르기로 진단되었다. 임신 중 산모의 단 음식과 빵, 과자 등의 간식 섭취 패턴은 영아의 식품 알레르기 발생과 유의미한 관계를 보였다. (adjusted OR = 1.517, p = 0.019) 단 음식과 빵, 과자 등의 간식 섭취 빈도는 트랜스 지방 섭취와 의미있는 상관관계를 보였다. (r = 0.498, p=0.031) 산모의 간식 식이와 영아의 식품 알레르기 발생 관계는 6 개월이상 모유수유를 지속한 대상군에서 더 두드러졌다. (adjusted OR = 1.792, p = 0.031) 단일 핵산염기 다형성을 분석했을 때, CD 14 (rs2569190) 가 TT인 경우와 GSTM1 혹은 GSTT1에서 한 개 이상의 복제수 변이가 있는 경우 산모의 간식 식이와 영아의 식품 알레르기 발생 관계가 더 유의하였고 산모의 식이와 유전적 변이간에는 유의한 상호 관계를 보였다. CD14 혹은

GSTM1 유전적 변이를 보이는 영아에서 산모가 간식 식이 패턴을 보이는 경우 영아 분변의 마이크로바이오타 알파 다양성이 감소하거나, Firmicutes 혹은 Verrucomicrobia 가 감소하였다. 본 연구를 통하여 임신과 수유 중 산모의 단 음식과 빵, 과자 등의 간식 섭취 식이 패턴은 영아의 식품알레르기 발생에 영향을 미치며 이것은 식품내 트랜스 지방의 영향일 수 있는 가능성을 제시하였다. 또한 CD 14와 GST의 유전적 변이가 있는 경우 간식 섭취 빈도가 높은 식이 패턴을 갖는 산모의 영아는 식품알레르기 발생에 있어 더 취약할 수 있음을 보였고, 이런 산모의 식이 패턴과 영아의 유전적 변이간의 상호 작용은 영아의 장내 미생물 군집의 변화를 야기하여 영아 식품알레르기 발생에 영향을 미칠 수 있음을 보였다.

핵심되는 말 : CD14, 식이 패턴, 지방산, 식품알레르기, 유전, GST, 영아, 주산기, 마이크로바이옴