

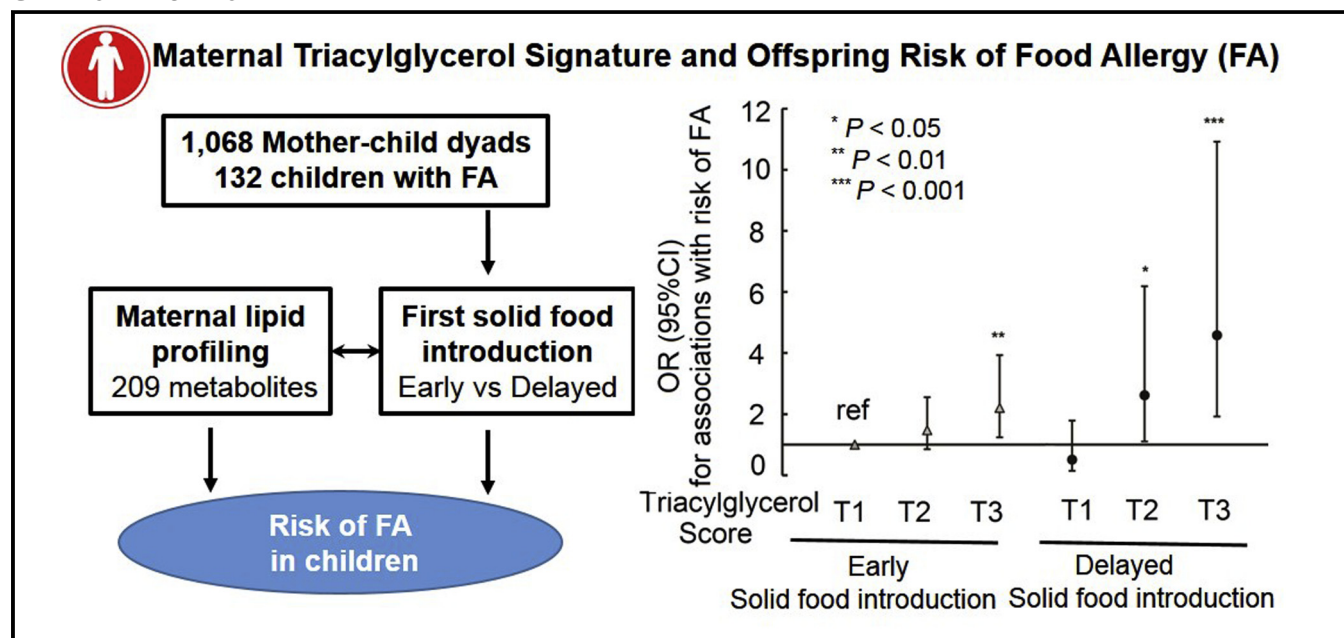
Maternal triacylglycerol signature and risk of food allergy in offspring



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GRAPHICAL ABSTRACT



Background: The prevalence of IgE-mediated food allergy (FA) is increasing worldwide, but the underlying mechanisms are poorly understood.

Objective: We sought to examine the role of maternal lipidomic profiles in risk of FA development in offspring and to investigate the potential modification effects by timing of first solid-food introduction.

Methods: This report included 1068 mother-child dyads from the Boston Birth Cohort. Maternal lipid metabolites in plasma were assessed by using liquid chromatography tandem mass spectrometry. Food sensitization (FS) was defined as a specific IgE level of 0.35 kU/L or greater to any of the 8 common food allergens determined by using ImmunoCAP. FA was defined based on FS, clinical symptoms, and food avoidance. Logistic

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regression was applied to analyze associations between maternal metabolites and risk of FS and FA in offspring and to explore potential effect modifications.

Results: Of the 1068 children, 411 had FS, and 132 had FA. Among the 209 metabolites, maternal triacylglycerols (TAGs) of shorter carbon chains and fewer double bonds were associated with greater risk of FA, whereas TAGs of longer carbon chains and more double bonds were significantly associated with lower risk of FA in offspring. These associations were stronger in children with delayed solid-food introduction (≥ 7 months of age) than those with earlier solid-food introduction ($P = .010$ for interaction between the maternal TAG score and timing of solid-food introduction). No significant association was found for FS. **Conclusion:** This is the first study to demonstrate a link between maternal TAGs and risk of FA in offspring and potential risk modification by timing of solid-food introduction. (J Allergy Clin Immunol 2019;144:729-37.)

Key words: Food allergy, lipidomics, triacylglycerol, timing of first solid-food introduction

Food allergy (FA), a condition arising from a specific adverse immune response that occurs reproducibly on exposure to a given food, has emerged as a major clinical and public health problem worldwide, given its increasing prevalence¹⁻³ and the adverse medical, psychosocial, and economic consequences of this potentially life-threatening condition.⁴⁻⁶ Current treatment for FA relies heavily on food avoidance and emergency preparedness.⁷ Unfortunately, accidental food ingestions are common,⁸ and allergic reactions can be severe and even fatal.⁹ Thus identification of early-life modifiable factors is crucial for early prediction and intervention for FA.

Many hypotheses have been proposed for the recent increase in FA prevalence, including Gideon Lack's dietary fat hypothesis.¹⁰ One intriguing observation is the parallel increase in the prevalence of FA and metabolic diseases, such as obesity, diabetes, and metabolic syndrome, across all age groups, including pregnant women. This raises a question about whether maternal metabolic disorders can increase risk of FA in offspring. Indeed, there is increasing interest in exploring the role of lipids and related metabolic factors in affecting allergy development, with some plausible evidence.¹¹⁻¹⁷ Previous studies, including ours in Chinese twin cohorts, have demonstrated that dyslipidemia might be associated with an increased risk of allergy development.^{14,16} However, some other studies have reported conflicting results.^{18,19}

Plasma lipids are composed of dozens of distinct molecules that can have varying influence on disease development. A recent study in mice reported that medium-chain but not long-chain triglycerides can promote allergic sensitization and anaphylaxis to peanut protein by affecting antigen absorption and by stimulating T_H2 -skewing cytokines.¹⁴ This animal study not only provides insight into mechanical pathways through which dietary medium-chain triglycerides affect FA risk, it also indicates that the standard clinical measurement of a lipid panel might be insufficient to capture the influence of different lipid molecules on FA risk. This notion has been further supported by findings from the Framingham Heart Study, in which hundreds of plasma lipid molecules from distinct classes were quantified by using the newly developed liquid chromatography tandem mass spectrometry (LC-MS) technologies but with diabetes as the

Abbreviations used

BBC:	Boston Birth Cohort
BMC:	Boston Medical Center
BMI:	Body mass index
FA:	Food allergy
FS:	Food sensitization
LC-MS:	Liquid chromatography tandem mass spectrometry
OR:	Odds ratio
PUFA:	Polyunsaturated fatty acid
sIgE:	Specific IgE
TAG:	Triacylglycerol

end point.²⁰ To our knowledge, no such study has been conducted to systematically investigate the role of maternal lipid molecules in FA development.

By leveraging cutting-edge biological technology, this study aimed to examine whether maternal lipid metabolites (that reflect fetal intrauterine exposure) are associated with risk of food sensitization (FS) and FA in offspring in the Boston Birth Cohort (BBC), a US urban, low-income, minority population with a high prevalence of maternal metabolic disorders and child atopic diseases, including FA. We were also interested in identifying early-life nutritional factors (including breast-feeding and timing of solid-food introduction) that can modulate the associations between maternal lipid metabolites and FA development in offspring.

METHODS

Study population

Study participants were enrolled from the BBC, an ongoing prospective urban, low-income minority birth cohort enrolled and followed at the Boston Medical Center (BMC), Boston, Massachusetts, as described previously.²¹ All eligible mothers were enrolled within 1 to 3 days after delivery, were interviewed by using a standard questionnaire, and underwent a blood draw.

Starting in 2004, infants who sought primary or specialist care at BMC were invited to participate in a follow-up study. Follow-up visits were scheduled at 6 to 12 months, 2 years, 4 years, and 6 years of age, consistent with the child's pediatric primary care visit schedule. At each visit, mothers were interviewed by using postnatal health questionnaires. Electronic medical records of the study children were abstracted annually. The study protocol was approved by the Institutional Review Boards of BMC and Johns Hopkins Bloomberg School of Public Health.

As of July 2018, 3163 mother-child dyads have been enrolled and followed in the BBC, and with data being entered into the database. Among them, 2830 dyads enrolled from 1998-2012 were the target population of the current study. After removing 1040 mother-child dyads with no IgE measurement to food allergens and 728 dyads with no data on maternal plasma lipid metabolites, the current study was focused on 1068 mother-child dyads.

Assessments of maternal plasma lipidomics

Lipidomic assessment in maternal plasma (collected within 1-3 days after delivery) was conducted at the Broad Institute Metabolomics Platform by using LC-MS techniques.²²⁻²⁴ Details of laboratory protocols, sample processing, and quality control steps have been reported previously.^{25,26} Briefly, maternal plasma specimens were sent to the laboratory in a blinded fashion. A pooled study reference sample composed of all of the study plasma samples was randomly distributed throughout the study samples (per 20-30 study samples). Coefficients of variation for each metabolite were calculated

by analyzing the study reference sample, which was repeatedly measured 77 times.

Using high-resolution full-scan mass spectrometric data acquisition, 216 lipid metabolites from multiple classes (including cholesterol esters, diacylglycerols, lysophosphatidylcholine, lysophosphatidylethanolamines, phosphatidylcholine, phosphatidylethanolamines, and triacylglycerol [TAGs]) were identified in maternal plasma. These metabolites were further classified based on the number of total acyl chain carbon atoms and double-bond contents and annotated as follows: [Lipid class] [Number of acyl chain carbon atoms]:[Number of double bonds in fatty acid moieties]. After removing 6 metabolites with coefficients of variation of greater than 20% and 1 metabolite that was unquantifiable in more than 10% of samples, 209 metabolites were available for next-step analyses.

Definition of outcomes

Plasma specific IgE (sIgE) levels for the 8 common food allergens (including egg white, cow's milk, peanut, soy, shrimp, walnut, wheat and cod) in early childhood were measured by using ImmunoCAP (Thermo Fisher/Phadia, Waltham, Mass) at Quest Diagnostics, according to the manufacturer's prescribed protocol. FS was defined as having an sIgE level of 0.35 kU_A/L or greater to any of the 8 food allergens, which is similar to other publications.^{27,28}

At each follow-up visit, mothers were interviewed about a history of physician-diagnosed FA in the index child, clinical allergic symptoms (and/or anaphylaxis) that the child ever experienced on ingestion of each of the 8 allergenic foods, and the timing and treatment of these reactions (if any). In addition, a dietary history was recorded at each visit, in which parents were asked whether and how often the child consumed these allergenic foods. Based on these available data, we categorized children into 5 groups for each visit.

Group 5 (confirmed/convincing FA) was defined as a child meeting all the following criteria: (1) having an sIgE level of 0.35 kU_A/L or greater to a specific food; (2) having convincing clinical allergic symptoms within 2 hours on ingestion of that food; and (3) avoidance of the food based on the food frequency questionnaire. Group 4 (probable FA) was defined as follows: (1) having an sIgE level of 0.35 kU_A/L or greater to a specific food and convincing clinical allergic symptoms on ingestion of that food but without information on food avoidance or (2) having an sIgE level of 95% or greater positive predictive values. Group 3 (possible FA) was defined as follows: (1) having an sIgE level of within 0.35 kU_A/L and 95% positive predictive values to a specific food and food avoidance without reported clinical allergic symptoms on food ingestion or (2) having a parental report of clinical allergic symptoms or physician-diagnosed FA but with an sIgE level of less than 0.35 kU_A/L to the specific food. Group 2 (asymptomatic) was defined as follows: having an sIgE level of 0.35 kU_A/L or greater but reported consumption of the specific food without clinical allergic symptoms. Group 1 (not sensitized and not allergic) was defined as follows: (1) having levels of all sIgEs of less than 0.35 kU/L; (2) having no reported clinical allergic symptoms on food ingestion; and (3) having no history of parent-reported physician-diagnosed FA.

For the purposes of analyses, each child was placed in the highest FA category he or she attained over the period of postnatal follow-up. Those who were grouped into the "convincing or confirmed FA" or "probable FA" categories were defined as having FA, and those who were either "asymptomatic" or "not sensitized and not allergic" were defined as nonallergic control subjects. Those with possible FA were removed from the analyses when FA was analyzed as the outcome.

Other allergic diseases, including allergic dermatitis, allergic rhinitis, and asthma, were defined if the child had 1 or more physicians' diagnoses of the relevant disease, respectively, based on archived International Classification of Diseases–ninth revision and International Classification of Diseases–tenth revision codes from the electronic medical record.

Major covariates

At enrollment, each mother was interviewed by using a health questionnaire to collect health characteristics and exposures during

pregnancy. Maternal prepregnancy body mass index (BMI) was calculated as self-reported prepregnancy weight in kilograms divided by self-reported height in meters squared. Maternal diabetes status was classified as nondiabetic, preexisting, and gestational diabetes.²¹ Maternal history of atopy was defined if the mother ever had any of the physician-diagnosed conditions, including FA, allergic dermatitis, allergic rhinitis, or asthma. Information regarding delivery mode was abstracted from the electronic medical record.

During the follow-up visit at less than 2 years of age, each mother was asked the following: "At what age did you first introduce solid food to your child?" The options were "not yet," "never," "unsure," or detailed years and months when the common solid foods were first introduced. Timing of first solid-food introduction was then classified as "early" (within the first 3 months of age), "suggested" (within 4–6 months of age), or "delayed" (7 months of age or later). Infant breast-feeding history ("bottle-fed exclusively," "both bottle-fed and breast-fed," or "breast-fed exclusively") was also assessed at follow-up visits and grouped into "ever" versus "never" breast-feeding, as reported previously.²⁹

Statistical analysis

For each lipid metabolite (with a missing rate <10%), we first imputed any missing values with one half of the limit of detection and then performed inverse normal transformation (which were scaled to per SD) to render the distributions approximately Gaussian. Pearson correlations were applied to examine intercorrelations among lipid metabolites. Multiple logistic regression models were used to investigate associations between each lipid metabolite and FA outcomes by estimating odds ratios (ORs) with 95% CIs, with adjustment of known or suspected confounders, including maternal race/ethnicity, maternal history of atopy, delivery mode, and infant's sex. We also adjusted for maternal prepregnancy BMI, which is significantly associated with maternal lipid profiles.^{30,31} Lipid metabolites were analyzed both as continuous and categorical (by using tertiles) variables. We applied the Benjamini-Hochberg false discovery rate (FDR)³² to adjust for multiple testing, with FDRs of less than 0.05 as the significance threshold. For identified associations with FA, a sensitivity test was performed on FA definitions by using more stringent criteria to define FA cases. We further performed stratified analyses based on the timing of food sIgE measurement (<2 vs ≥2 years).

To estimate the combined effects of multiple TAG metabolites that were individually associated with FA outcomes, the maternal weighted TAG score was calculated as follows:

$$\text{Score} = \sum_{k=1}^n \beta_k \times \text{TAG}_k,$$

where n is the total number of selected TAGs to be analyzed ($n = 2$ in this study, representing TAGs 48:1 and 58:10) and β_k is the corresponding regression coefficient for TAG _{k} in association with FA risk, as estimated from the individually fitted regression models. The weighted TAG score did not include the interaction term between the TAGs (or TAG 48:1 and 58:10 in this study), which was not statistically significant. Associations between the weighted TAG score (or tertiles) and FA outcomes were then tested by using logistic regression models.

To minimize residual confounding effects, we performed propensity score–matched sensitivity analyses³³ to investigate the effect of high (or the third tertile) versus low (or the first tertile) maternal TAG scores on FA risk. The propensity score for exposure to a high maternal TAG score was first calculated by using the multivariate logistic regression model, with maternal ethnicity, maternal history of atopy, maternal prepregnancy BMI, delivery mode, and infant's sex as the covariates. One-to-one pair matching on the propensity score was applied. By using the "nearest neighbor" technique with a caliper value of 0.1 in the R package *MatchIt*, 177 (of 311) children with a high maternal TAG score were successfully matched to 177 children with a low maternal TAG score. Next, between these 177 pairs of children, risk of FA was compared by using both the χ^2 test and logistic regression.

TABLE I. Population characteristics of the 1068 study mother-child dyads stratified by FS and FA status

Variable	FS (n = 1068)			FA (n = 913)*		
	No	Yes	P value†	No	Yes	P value†
No.	657	411		781	132	
Maternal age (y)	28.4 ± 6.5	28.8 ± 6.8	.407	28.5 ± 6.5	28.9 ± 6.9	.499
Maternal race						
Black	400 (60.9)	272 (66.2)	.062	483 (61.8)	95 (72.0)	.113
White	39 (5.9)	11 (2.7)		37 (4.7)	3 (2.3)	
Hispanic	130 (19.8)	79 (19.2)		158 (20.2)	23 (17.4)	
Other	88 (13.4)	49 (11.9)		103 (13.2)	11 (8.3)	
Maternal history of atopy						
No	415 (63.2)	231 (56.2)	.075	495 (63.4)	70 (53.0)	.075
Yes	168 (25.6)	123 (29.9)		199 (25.5)	44 (33.3)	
Unknown	74 (11.2)	57 (13.9)		87 (11.1)	18 (13.7)	
Maternal education						
College or greater	231 (35.2)	139 (33.8)	.547	269 (34.4)	39 (29.5)	.478
Maternal BMI (kg/m ²)						
<25	288 (43.8)	190 (46.2)	.630	345 (44.2)	65 (49.2)	.423
25-29.9	189 (28.8)	104 (25.3)		225 (28.8)	29 (22.0)	
≥30	152 (23.1)	101 (24.6)		177 (22.7)	31 (23.5)	
Unknown	28 (4.3)	16 (3.9)		34 (4.3)	7 (5.3)	
Smoking during pregnancy	55 (8.4)	26 (6.3)	.290	60 (7.7)	11 (8.3)	.923
Cesarean delivery	232 (35.3)	149 (36.3)	.796	267 (34.2)	58 (43.9)	.057
Maternal diabetes						
No	580 (88.3)	363 (88.3)	.977	695 (89.0)	111 (84.1)	.234
Gestational diabetes	48 (7.3)	29 (7.1)		54 (6.9)	12 (9.1)	
Pre-existing diabetes	29 (4.4)	19 (4.6)		32 (4.1)	9 (6.8)	
Child's sex, male	301 (45.8)	230 (56.0)	.001	378 (48.4)	81 (61.4)	.006
Preterm birth	166 (25.3)	102 (24.8)	.869	189 (24.2)	36 (27.3)	.449
Child's age at sIgE measurement (y)	2.4 ± 2.2	2.7 ± 2.4	.031	2.4 ± 2.2	2.7 ± 2.7	.255
Child's age at the last visit (y)	5.6 ± 3.4	5.7 ± 3.3	.447	5.5 ± 3.3	5.9 ± 3.8	.295
Never breast-fed	164 (25.0)	92 (22.4)	.463	196 (25.1)	31 (23.5)	.926
Timing of solid-food introduction						
Early (1-3 mo)	137 (20.9)	81 (19.7)	.903	165 (21.1)	15 (11.4)	.011
Suggested (4-6 mo)	435 (61.2)	276 (67.2)		518 (66.3)	92 (69.7)	
Delayed (≥7 mo)	85 (12.9)	54 (13.1)		98 (12.6)	25 (18.9)	

Means ± SDs and numbers (percentages) are shown for continuous and categorical variables, respectively.

*Approximately 155 children were classified as having "possible FA" but did not meet the criteria for FA and thus were removed from analysis for FA.

†Difference in each population's characteristics between children with and without FS or between children with FA and nonallergic children was assessed based on *t* tests and χ^2 tests for continuous and categorical variables, respectively.

To explore potential effect modification by timing of solid-food introduction, we first analyzed associations between the maternal weighted TAG score and FA risk stratified by timing of solid-food introduction. Specifically, we observed that the identified associations were comparable in children with solid food introduced within 3 months of age and in children with solid food introduced at 4 to 6 months of age, and thus we reclassified timing of solid-food introduction to "0-6 months of age" (or early) versus "≥7 months of age" (or delayed) in subsequent analyses. Joint effects between the maternal weighted TAG score (analyzed as tertiles) and timing of solid-food introduction were analyzed in the logistic regression models, with adjustment of confounders, as described above. Interaction effects between the maternal weighted TAG score and timing of solid-food introduction were then estimated by adding their interaction term into logistic regression models. Similar analyses were performed to explore the modification effect of breast-feeding status. All analyses were performed in R software, 3.5.1 version.

RESULTS

As shown in Table E1 in this article's Online Repository at www.jacionline.org, demographic characteristics of the 1068 mother-child dyads enrolled in this study were largely comparable with those of the total target population. Among the 1068 children, food sIgE levels were measured at an average of

2.5 ± 2.3 years of age, and about 44.7% of the children had sIgE levels measured at more than 2 years of age. There were 411 (38.5%) children with FS and 132 (12.4%) with FA to at least 1 of the 8 major food allergens tested. As expected, children with FS were more likely to be male (*P* = .001) than those without FS (Table I). A similar sex difference was also observed for FA. In addition, children with FA were more likely to have delayed solid-food introduction (≥7 months) than those without (*P* = .011, Table I).

Lipidomic profiles identified a significant lipid signature for FA

Table E2 in this article's Online Repository at www.jacionline.org summarizes the 209 maternal metabolites studied in this study, among which 23 metabolites had missing values (18 with a missing rate of <1.0% and 5 with a missing rate of 1.0% to 4.0%) that were imputed by using one half of the limit of detection for next-step analyses. Fig E1 in this article's Online Repository at www.jacionline.org and Fig 1 illustrate associations between the 209 maternal lipid metabolites and risk of having FS or FA in offspring, respectively. With FDRs of less than 0.05 as the cutoff, 6 of the

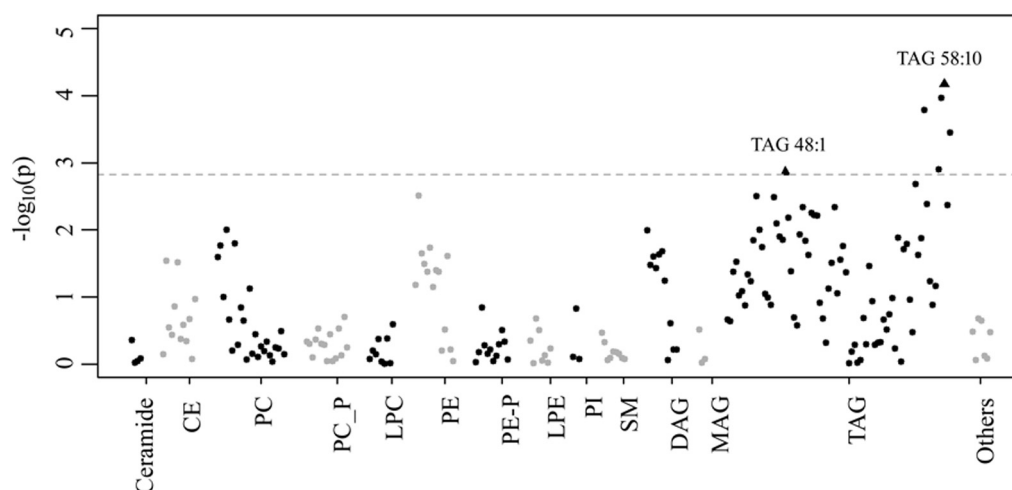


FIG 1. Manhattan plot for associations of 209 maternal lipid metabolites with risk of FA in offspring in 1068 mother-child dyads from the BBC adjusted for maternal ethnicity, maternal history of atopy, maternal prepregnancy BMI category, delivery mode, and sex. Each dot represents a lipid metabolite in a specific class. The dotted line represents the FDR significance cutoff. Triangles represent the 2 metabolites of interest in this study. CE, Cholesterol esters; DAG, diacylglycerol; MAG, monoacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PC_P, phosphatidylcholine plasmalogen; PE, phosphatidylethanolamine; PE_P, phosphatidylethanolamine plasmalogen; PI, phosphatidylinositol; SM, sphingomyelin.

78 TAG metabolites, including TAG 48:1 ($P = .001$), 56:8 ($P = 1.6 \times 10^{-4}$), 58:8 ($P = .001$), 58:9 ($P = 1.1 \times 10^{-4}$), 58:10 ($P = 6.8 \times 10^{-5}$), and 60:12 ($P = 3.6 \times 10^{-4}$), were significantly associated with an altered risk of FA, which was independent of other maternal metabolic factors (maternal overweight/obesity and maternal preexisting/gestational diabetes, data not shown). As for the metabolites in the other lipid classes, only maternal phosphatidylethanolamine 32:1 showed a borderline significant association with risk of FA in offspring ($P = .003$, FDR = 0.067). In comparison, no significant associations were found for FS (see Fig E1).

Maternal TAG profile and risk of FA outcomes in offspring

Fig E2 in this article's Online Repository at www.jacionline.org presents the correlation matrix for all 78 maternal TAG metabolites analyzed in this study. TAGs of shorter carbon chains (ie, 41-52 carbons) with relatively fewer double bonds (ie, 0-4) were positively correlated with each other, and TAGs of longer carbon chains (ie, 56-60 carbons) with relatively more double bonds (5-12) were also positively correlated with each other; however, these 2 groups of TAGs were inversely correlated. Associations between maternal TAGs and risk of FA in offspring also varied by the number of acyl chain carbons and double bonds (Fig 2): TAGs of shorter carbon chains and fewer bonds (TAG 48:1 as the top significant metabolite of this group) were associated with an increased risk for FA with an OR of greater than 1. In comparison, TAGs of longer carbon chains and more double bonds (TAG 58:10 as the top significant metabolite of this group) were associated with a decreased risk for FA with an OR of less than 1.

Given the significant correlations between the top metabolites (TAGs 48:1 and 58:10) and other FA-associated TAGs, we

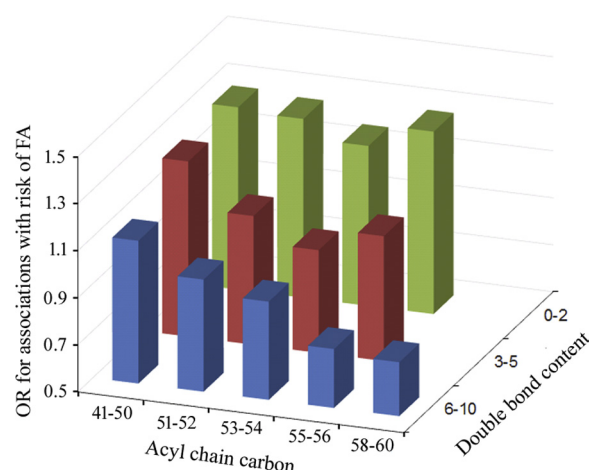


FIG 2. Average ORs for maternal TAG – risk of FA in offspring associations according to the number of total acyl chain carbon atoms (41-50, 51-52, 53-54, 55-56, and 58-60) and double-bond content (0-1, 2-4, and ≥ 5). The y-axis is the OR for having FA per SD increment of each type of TAG, the x-axis is the number of acyl chain carbon atoms, and the z-axis is the number of double bonds.

focused on TAGs 48:1 and 58:10 in the subsequent analyses (Table II). Each SD increment of maternal TAG 48:1 was associated with a 1.4-fold (95% CI, 1.2-1.8; $P = .001$) increased risk of FA in offspring, whereas each SD increment of maternal TAG 58:10 was associated with a reduction in FA risk by 36% (OR, 0.6; 95% CI, 0.5-0.8; $P = 6.8 \times 10^{-5}$). In the sensitivity tests we observed that the estimated ORs for TAG 48:1 and TAG 58:10 remained comparable when more stringent FA definitions were applied (see Table E3 in this article's Online Repository at www.jacionline.org), and these associations did not significantly vary by child's age when food sIge levels were

TABLE II. Associations of maternal lipid metabolites with risk of FS and FA in offspring in 1068 mother-child dyads from the BBC

Metabolite*	FS				FA			
	FS (%)	OR	95% CI	P value†	FA (%)	OR	95% CI	P value†
Maternal TAG 48:1								
Continuous (Per SD increment)	1068 (38.5)	1.08	0.94-1.24	.294	913 (14.5)	1.42	1.15-1.76	.001
Low (T1)	353 (34.8)	1.00	Reference	Reference	301 (10.3)	1.00	Reference	Reference
Medium (T2)	362 (41.4)	1.41	1.02-1.94	.036	309 (17.2)	2.34	1.42-3.88	9.1×10^{-4}
High (T3)	353 (39.1)	1.41	1.00-1.99	.049	303 (15.8)	2.68	1.55-4.63	4.3×10^{-4}
Maternal TAG 58:10								
Continuous (Per SD increment)	1068 (38.5)	0.94	0.82-1.09	.402	913 (14.5)	0.64	0.51-0.80	6.8×10^{-5}
Low (T1)	353 (38.5)	1.00	Reference	Reference	312 (17.6)	1.00	Reference	Reference
Medium (T2)	362 (39.2)	0.97	0.71-1.33	.870	301 (15.6)	0.77	0.49-1.21	.254
High (T3)	353 (37.7)	0.92	0.65-1.29	.616	300 (10.0)	0.40	0.23-0.67	6.0×10^{-4}
Maternal weighted TAG score								
Continuous (Per SD increment)	1068 (38.5)	1.12	0.91-1.37	.285	913 (14.5)	1.92	1.41-2.61	3.6×10^{-5}
Low (T1)	353 (35.4)	1.00	Reference	Reference	304 (10.5)	1.00	Reference	Reference
Medium (T2)	362 (40.3)	1.28	0.93-1.77	.123	302 (14.9)	1.88	1.13-3.13	.016
High (T3)	353 (39.7)	1.38	0.97-1.95	.073	307 (17.9)	2.94	1.71-5.05	9.4×10^{-5}

T1, First tertile; T2, second tertile; T3, third tertile.

*Two individual metabolites that were significantly associated with FA, one (TAG 48:1) having the strongest positive association and the other (TAG 58:10) having the strongest negative association, are shown in Table II as examples.

†Adjusted for maternal race/ethnicity, maternal history of atopy, maternal prepregnancy BMI category, delivery mode, and infants' sex.

measured (see Table E4 in this article's Online Repository at www.jacionline.org).

The weighted score for the maternal TAGs (referred to as "the maternal TAG score," which correlated positively with TAG 48:1 but inversely with 58:10) was then analyzed to reflect the combined effect, for which each SD increment was associated with a 1.9-fold (95% CI, 1.4-2.6; $P = 3.6 \times 10^{-5}$) increased risk of having FA in offspring. Similarly, children in the third tertile of the maternal TAG score were at a 2.9 (95% CI, 1.7-5.1; $P = 9.4 \times 10^{-5}$) times greater risk of having FA than children in the first tertile (Table II).

In propensity score-matched sensitivity analyses, there were 177 pairs of matched children with comparable covariates (see Table E5 in this article's Online Repository at www.jacionline.org). Among these 177 pairs, we further observed that children in the third tertile of the maternal TAG score were at a 2.4-fold increased risk (95% CI, 1.4-4.4; $P = .008$) of having FA compared with those in the first tertile of the maternal TAG score.

When other allergic phenotypes were analyzed, similar trends were observed between maternal TAG 58:10 and risk of asthma in offspring (or hay fever), which were no longer significant after FDR correction for multiple testing (see Table E6 in this article's Online Repository at www.jacionline.org).

Modification effects by timing of solid-food introduction in infancy

In this cohort children with delayed solid-food introduction were more likely to have FA ($P = .011$, Table I) than children with early solid-food introduction, although their maternal TAG levels were comparable ($P = .24$). Joint associations between the maternal TAG score and the timing of solid-food introduction ("early: 0-6 months" vs "delayed: ≥ 7 months of age"; see the Methods section for details) on the risk of FA are presented in Fig 3. By using children in the first tertile of the maternal TAG score and with early solid-food introduction as the reference group, the risks of having FA were 1.5 (95% CI, 0.9-2.6;

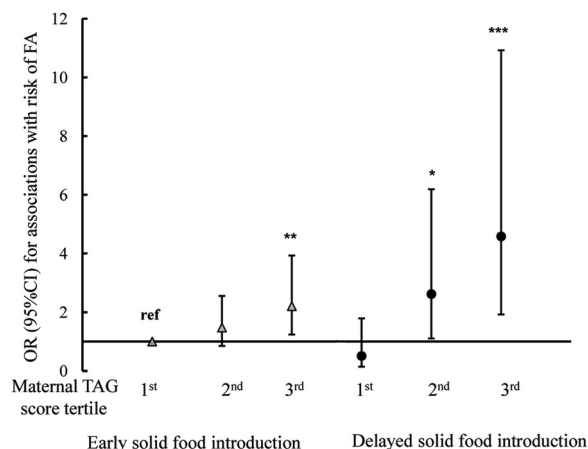


FIG 3. Joint associations between tertiles of the maternal weighted TAG score and timing of first solid-food introduction on risk of FA in 913 mother-child dyads from the BBC. The y-axis reflects the OR and 95% CI of FA risk for each subgroup stratified by tertiles of the maternal weighted TAG score and timing of first solid-food introduction, by using children in the first tertile of maternal TAG score and with early solid-food introduction as the reference group. * $P < .05$, ** $P < .01$, and *** $P < .001$ compared with the reference group.

$P = .166$) and 2.2 (95% CI, 1.2-3.9; $P = .007$) times greater in their counterparts exposed to the second and third tertiles of maternal TAG scores, respectively; the risk was greatest (OR, 4.6; 95% CI, 1.9-10.9; $P = .0006$) in children in the third tertile of the maternal TAG score and with delayed solid-food introduction. There was a significant interaction ($P = .011$) between the maternal TAG score (analyzed as a continuous variable) and timing of solid-food introduction. In comparison, no significant interaction was observed between maternal TAGs and breast-feeding status (data not shown).

DISCUSSION

This is the first study to link high-throughput snapshots of maternal lipidomics with FA development in offspring in a

prospective minority birth cohort. We showed that maternal TAG levels of longer carbon chains and more double bonds might protect against FA development in the offspring, whereas maternal TAG levels of shorter carbon chains and fewer double bonds were associated with an increased risk of FA. These identified associations can be modified by the timing of first solid-food introduction, for which effect sizes were stronger if the children had delayed introduction of solid foods. These findings, if validated in another independent cohort, might facilitate the identification of high-risk children and suggest that early solid-food introduction can alleviate the risk for FA in this high-risk group.

Dyslipidemia was reported as a risk factor for allergy development by our study in a Chinese twin cohort¹⁶ and by others,^{15,34} although some other studies have reported inconsistent findings.^{18,19} Because most of these studies used a cross-sectional study design, the temporal relationship was unclear. Also, among the existing studies, plasma lipid levels were measured by using standard clinical measurement, which might have obscured the diversity of lipid molecules from distinct classes. In comparison, by analyzing 209 maternal lipid molecules from different classes, we clearly demonstrated that the maternal TAG profile (rather than other lipid classes) was associated with risk of FA in offspring, and its association directions varied by numbers of acyl chain carbons and double bonds of the specific TAGs. Integrating the positive risk captured by a TAG of relatively shorter carbon chains and fewer double bonds (TAG 48:1) with the negative risk captured by a TAG of relatively longer carbon chains and more double bonds (TAG 58:10) might slightly improve FA prediction.

Several lines of evidence demonstrate that the identified associations between maternal TAGs and FA risk in offspring are biologically plausible. An animal study has suggested that medium-chain triglycerides but not long-chain triglycerides can increase intestinal-epithelial mRNA expression of 3 T_H2-biasing cytokines, including thymic stromal lymphopoietin, IL-25, and IL-33, providing a potential pathway for FA development.¹⁴ Consistently, our study supported that maternal TAGs of shorter acyl carbon chains were associated with an increased FA risk in offspring.

TAGs constitute the largest source of different types of dietary fatty acids, which potentially have different effects on the immune system. TAGs with shorter carbon chains and fewer double bonds are predominantly composed of saturated (ie, 16:0 palmitic acid and 18:0 stearic acid) and monounsaturated (eg, 18:1 oleic acid) fatty acids.²⁰ Saturated fatty acids, such as palmitic acids, might induce proinflammatory signaling through activation of Toll-like receptor 4^{35,36} and thus might promote allergy development. In comparison, TAGs with longer carbon chains and more double bonds, which can protect against development of FA in the offspring, as observed in this study, are predominantly composed of polyunsaturated fatty acids (PUFAs; ie, 18:2 linoleic acid, 18:3 α -linolenic acid, and 22:5 docosahexaenoic acid). Maternal PUFAs, especially n-3 PUFAs, can regulate the functions of the fetal immune system through several anti-inflammatory mechanisms and/or result in a reduced T_H2 response, thus protecting against allergy.³⁷⁻³⁹ In addition, our findings are also consistent with a recent study that demonstrated that epidermal PUFAs and saturated short-chain fatty acids can affect allergy development differently through altering skin barrier function.¹⁷ Alternatively, another plausible

explanation for the identified associations is that there is a common cause (eg, maternal diets/environmental exposures during pregnancy and genetic factors) shared by maternal TAG levels and FA development in offspring that leads to indirect associations between these 2 traits, which is worth further investigation.

Of note, these identified FA-associated TAGs showed no significant associations with risk of FS in offspring (see Table II) after adjusting for multiple testing. FS and FA are known to be 2 different phenotypes. Although immediate-type FAs are mediated by IgE, the presence of IgE is insufficient for developing clinical allergic reaction on exposure. For example, in our cohort only one third of sensitized children had allergic symptoms on food exposure. We hypothesized that the FA-associated TAGs identified in this study might influence the manifestation of clinical symptoms and/or oral tolerance in sensitized children rather than affect IgE production, which awaits further validation.

Previous studies⁴⁰⁻⁴² have reported that early solid-food introduction was associated with decreased FA risk. This finding indicates that dietary factors during infancy can modulate a child's risk of FA, although the underlying mechanism is unclear. Given the potential role of maternal dietary and/or metabolic factors in regulating the fetal immune system¹⁴ and on FA development,^{11,17} we were motivated to test potential interactions between maternal TAGs (a prenatal nutritional factor) and timing of solid food-introduction (a postnatal nutritional factor) and observed that the adverse effect of maternal TAGs on risk of FA in offspring was much stronger if the children had delayed solid-food introduction. Alternatively, early solid-food introduction might partly reduce the risk of FA in high-risk children exposed to a higher maternal TAG score, although the mechanisms are still unclear. Our findings, if proved true, will provide new insight into the biological pathways of FA and a new avenue for early risk assessment and interventions for FA.

This birth cohort study design allowed us to clearly assess the temporal relationship between the *in utero* metabolic environment and FA development. Compared with most available studies, which have primarily focused on European populations, this study was conducted in high-risk but far less-studied inner-city minority (black and Hispanic) populations. We expect that our findings have direct relevance to understanding and reducing FA in minority populations.

Meanwhile, several limitations of this study also warrant discussion. First, the enrolled children did not undergo double-blind, placebo-controlled food challenges (the gold standard for FA diagnosis), and food sIgE levels were measured only at 1 time point. Our FA definition, similar to that in other published studies,²⁷ is based on available robust clinical, serologic, and dietary information. We further showed that the identified associations between maternal TAGs and risk of FA were robust when more stringent FA definitions were applied. It is likely that if misclassification of FA existed in this study, it was random and did not substantially influence our findings. Taken together, our findings might be regarded as hypothesis generating, and replication studies in other independent cohorts, especially with FA defined by food challenge testing, are warranted.

Second, our study population was comprised of predominantly urban, low-income minorities living in the United States, an

understudied population. However, caution is needed when generalizing our findings to other populations.

Third, the LC-MS technology applied in this study does not provide absolute quantitation of lipid metabolites, nor can it identify the specific fatty acids that constitute the TAG metabolites of interest.

Fourth, we focused on the timing of introduction of any solid food as opposed to allergenic food introduction. We did not have sufficient data to further investigate whether our findings remained consistent when the timing of allergenic solid food introduction was analyzed, which awaits future studies. We also cannot fully exclude the possibility that the identified interaction between maternal TAGs and timing of solid-food introduction on FA risk was a chance finding, which calls for further replication in other independent cohorts.

In conclusion, we are the first to link maternal lipidomics with FA development in offspring and demonstrate that the identified associations between maternal TAG profiles and FA risk in offspring could be modified by the timing of solid-food introduction, which, if further validated in other cohorts, will have important clinical implications for personalized FA prevention and intervention. Overall, our analyses provide novel evidence revealing the role of maternal TAGs (but not other lipid classes) and the underlying biology they represent in FA development. Future studies of this kind are needed to validate and extend our findings.

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Key messages

- Maternal lipids of different classes can have different associations with risk of FA in offspring.
- Maternal TAGs of shorter carbon chains and fewer double bonds were associated with an increased risk of FA, whereas TAGs of longer carbon chains and more double bonds can protect against FA development in offspring.
- There was a significant interaction between maternal TAG levels and timing of solid-food introduction in predicting risk of FA in offspring.

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Supplementary Tables and Figures

Table E1. Population characteristics of the total 2,830 mother-child dyads followed in the BBC and of the 1,068 dyads enrolled in this study

Variables	Total mother-child dyads	Enrolled dyads	P ^a
n	2,830	1,068	
Maternal age (years), Mean±SD	28.6±6.5	28.6±6.6	0.983
Maternal race, n (%)			
Black	1,690 (59.7)	672 (62.9)	0.012
White	206 (7.3)	50 (4.7)	
Hispanic	601 (21.2)	209 (19.6)	
Other	333 (11.8)	137 (12.8)	
Maternal history of atopy, n(%)	652 (27.9)	291 (31.1)	0.068
Maternal education, n(%)			
College or above	974 (34.4)	369 (34.6)	0.959
Maternal BMI (kg/m ²), n(%)			
< 25	1,302 (46.0)	478 (44.8)	0.401
25-29.9	741 (26.2)	293 (27.4)	
≥ 30	640 (22.6)	253 (23.7)	
Unknown	147 (5.2)	44 (4.1)	
Smoking during pregnancy, n(%)	304 (10.7)	96 (9.0)	0.255
Cesarean-section delivery, n(%)	1,020 (36.2)	381 (35.9)	0.859
Maternal diabetes, n(%)			
No	2,479 (88.6)	942 (88.3)	0.814
Gestational diabetes	186 (6.7)	77 (7.2)	
Diabetes	130 (4.7)	48 (4.5)	
Male sex, n(%)	1,433 (50.6)	531 (49.7)	0.610
Preterm birth, n(%)	804 (28.4)	268 (25.1)	0.039
Never breastfed, n(%)	733 (26.2)	256 (24.2)	0.389
Timing of solid food introduction, n(%)			
Early (0-3 months)	592 (20.9)	218 (20.4)	0.770
Suggested (4-6 months)	1,838 (64.9)	711 (66.6)	
Delayed (≥7 months)	364 (12.9)	127 (11.9)	
Unknown	36 (1.3)	12 (1.1)	

Mean±SD and n (%) are shown for continuous and categorical variables, respectively.

^aThe difference of each population characteristic factor between the total number of mother-child dyads enrolled in the BBC and the dyads enrolled in the current study was assessed based on t-test and chi-square test, respectively, for continuous and categorical variables.

Table E2. The 209 lipid metabolites investigated in the current study and their corresponding coefficients of variance and missing rates.

Metabolites	CV (%)	Missing(%) ^a	Metabolites	CV (%)	missing (%) ^a
Ceramide					
Ceramide 16:0	5.0	0.0	Ceramide 22:0	4.0	0.0
Ceramide 24:0	3.3	0.0	Ceramide 24:1	3.5	0.0
Cholesterol ester (CE)					
CE 14:0	7.6	0.0	CE 16:0	2.7	0.0
CE 16:1	3.2	0.0	CE 18:0	2.1	0.0
CE 18:1	1.7	0.0	CE 18:2	2.1	0.0
CE 18:3	1.7	0.0	CE 20:3	3.9	0.0
CE 20:4	2.2	0.0	CE 20:5	1.7	0.0
CE 22:4	8.9	0.2	CE 22:6	2.3	0.0
Phosphatidylcholine (PC)					
PC 30:0	3.2	0.0	PC 30:1	3.3	0.0
PC 32:0	3.0	0.0	PC 32:1	3.1	0.0
PC 32:2	3.5	0.0	PC 34:0	3.4	0.0
PC 34:1	2.6	0.0	PC 34:2	2.5	0.0
PC 34:3	3.2	0.0	PC 34:4	3.2	0.0
PC 36:0	5.0	0.0	PC 36:1	3.2	0.0
PC 36:2	2.7	0.0	PC 36:3	2.9	0.0
hydroxy-PC 36:4	4.1	0.0	PC-A 36:4	3.8	0.0
PC-B 36:4	2.3	0.0	PC 38:2	3.2	0.0
PC 38:3	3.3	0.0	PC 38:4	2.9	0.0
PC 38:6	2.4	0.0	PC 40:10	5.3	0.0
PC 40:6	3.5	0.0	PC 40:9	1.8	0.0
PC plasmalogen					
PC plasmalogen-A 34:1	3.2	0.0	PC plasmalogen-B 34:1	10.0	0.0
PC plasmalogen 34:2	3.3	0.0	PC plasmalogen 34:3	2.6	0.0
PC plasmalogen 34:5	16.0	0.3	PC plasmalogen 36:1	4.0	0.0
PC plasmalogen 36:2	3.4	0.0	PC plasmalogen 36:3	3.2	0.0
PC plasmalogen 36:4	6.2	0.0	PC plasmalogen-A 36:5	6.5	0.0
PC plasmalogen-B 36:5	2.7	0.0	PC plasmalogen 38:4	3.4	0.0
PC plasmalogen 38:6	3.2	0.0	PC plasmalogen 38:7	3.2	0.0
PC plasmalogen 40:7	3.2	0.0			
Lysophosphatidylcholine (LPC)					
LPC 14:0	2.8	0.0	LPC 16:0	3.4	0.0
LPC 16:1	2.9	0.0	LPC 18:0	3.0	0.0
LPC 18:1	3.1	0.0	LPC 18:2	3.1	0.0
LPC 20:4	3.1	0.0	LPC 20:5	3.2	0.0
LPC 22:6	3.4	0.0			
Phosphatidylethanolamine (PE)					
PE 32:0	6.2	0.0	PE 32:1	8.5	0.1
PE 34:0	3.9	0.0	PE 34:2	3.7	0.0

PE 36:0	4.2	0.0	PE 36:1	3.8	0.0
PE 36:2	2.9	0.0	PE 36:3	4.1	0.0
PE 36:4	4.2	0.0	PE 38:2	2.9	0.0
PE 38:4	3.5	0.0	PE 38:5	4.4	0.0
PE 38:6	3.6	0.0	PE 40:6	4.8	0.0
Phosphatidylethanolamine (PE) plasmalogen					
PE plasmalogen 34:2	6.3	0.0	PE plasmalogen 34:3	7.4	0.4
PE plasmalogen 36:1	10.3	0.0	PE plasmalogen 36:2	4.2	0.0
PE plasmalogen 36:3	3.4	0.0	PE plasmalogen 36:4	7.0	0.1
PE plasmalogen 36:5	4.1	0.0	PE plasmalogen 38:3	8.5	0.1
PE plasmalogen 38:5	3.2	0.0	PE plasmalogen 38:6	3.6	0.0
PE plasmalogen 38:7	4.5	0.0	PE plasmalogen 40:7	3.9	0.0
Lysophosphatidylethanolamine (LPE)					
LPE 16:0	4.3	0.0	LPE 18:0	3.6	0.0
LPE 18:1	3.4	0.0	LPE 18:2	3.2	0.0
LPE 20:0	2.8	0.0	LPE 20:4	3.4	0.0
LPE 22:0	5.9	0.0	LPE 22:6	4.1	0.0
Phosphatidylinositol (PI)					
PI 36:2	11.7	0.0	PI 36:4	12.2	0.0
PI 38:4	7.0	0.0			
Sphingomyelin (SM)					
SM 14:0	3.5	0.0	SM 16:0	3.3	0.0
SM 16:1	3.2	0.0	SM 18:0	3.0	0.0
SM 18:1	3.3	0.0	SM 20:0	3.3	0.0
SM 22:0	3.1	0.0	SM 24:0	3.2	0.0
SM 24:1	3.1	0.0			
Diacylglycerol (DAG)					
DAG 38:5	2.7	0.0	DAG 32:0	2.6	0.0
DAG 32:1	10.5	1.8	DAG 34:0	2.6	0.0
DAG 34:1	1.8	0.0	DAG 34:2	3.0	0.0
DAG 36:1	2.0	0.0	DAG 36:2	1.5	0.0
DAG 36:3	1.5	0.0	DAG 36:4	5.8	0.4
DAG 38:4	4.8	0.0			
Monoacylglycerol					
MAG 14:1	4.6	0.0	MAG 16:1	5.8	0.0
MAG 18:0	1.8	0.0			
Triacylglycerol (TAG)					
TAG 42:0	2.7	0.0	TAG 43:0	6.1	0.2
TAG 43:1	4.4	0.8	TAG 43:2	6.9	3.5
TAG 44:0	2.5	0.0	TAG 44:1	2.3	0.0
TAG 44:2	2.4	0.0	TAG 45:0	5.0	0.0
TAG 45:1	5.1	0.0	TAG 45:2	3.6	0.0
TAG 45:3	5.1	0.4	TAG 46:0	5.1	0.1
TAG 46:1	1.9	0.0	TAG 46:2	2.1	0.0
TAG 46:3	2.4	0.0	TAG 46:4	2.8	0.1

TAG 47:0	6.3	0.1	TAG 47:1	9.9	1.3
TAG 47:2	3.2	0.0	TAG 48:0	4.5	0.0
TAG 48:1	3.3	0.0	TAG 48:2	1.9	0.0
TAG 48:3	1.9	0.0	TAG 48:4	2.4	0.0
TAG 48:5	2.7	0.0	TAG 49:0	4.2	0.0
TAG 49:2	6.9	0.0	TAG 49:3	3.1	0.0
TAG 50:0	2.4	0.0	TAG 50:1	3.1	0.0
TAG 50:2	3.1	0.0	TAG 50:3	2.5	0.0
TAG 50:4	1.8	0.0	TAG 50:5	2.2	0.0
TAG 50:6	2.7	0.0	TAG 51:0	6.3	0.1
TAG 51:1	4.5	0.0	TAG 51:2	4.7	0.0
TAG 51:3	5.2	0.0	TAG 52:0	2.5	0.0
TAG 52:1	1.8	0.0	TAG 52:2	2.2	0.0
TAG 52:3	2.8	0.0	TAG 52:4	2.5	0.0
TAG 52:5	1.4	0.0	TAG 52:6	2.0	0.0
TAG 52:7	2.4	0.0	TAG 53:2	2.4	0.0
TAG 53:3	5.3	0.0	TAG 54:1	2.3	0.0
TAG 54:2	1.8	0.0	TAG 54:3	1.8	0.0
TAG 54:4	2.7	0.0	TAG 54:5	3.6	0.0
TAG 54:6	5.7	0.0	TAG 54:7	1.6	0.0
TAG 54:8	2.5	0.0	TAG 54:9	6.6	0.1
TAG 54:10	10.1	1.0	TAG 55:2	3.0	0.0
TAG 55:3	3.6	0.0	TAG 56:1	3.2	0.0
TAG 56:2	2.5	0.0	TAG 56:3	2.5	0.0
TAG 56:4	2.2	0.0	TAG 56:5	2.6	0.0
TAG 56:6	3.0	0.0	TAG 56:7	3.5	0.0
TAG 56:8	2.3	0.0	TAG 56:9	2.6	0.0
TAG 56:10	3.2	0.0	TAG 58:6	4.2	0.0
TAG 58:7	10.5	0.0	TAG 58:8	11.8	0.1
TAG 58:9	4.7	0.0	TAG 58:10	2.2	0.0
TAG 58:11	2.7	0.0	TAG 60:12	3.7	0.3
Others					
Campesterol	6.8	0.0	N-oleoylethanolamine	14.6	3.6
Palmitoylethanolamide	3.6	0.0	Piperine	3.5	2.0
Sphingosine	9.4	0.0	PS 34:0	6.0	0.0
Cholesterol	3.7	0.0			

CV: Coefficients of variance

^a For each metabolite, any missing value was imputed using one-half of the limit of detection in next-step data analyses.

Table E3. Associations of maternal TAGs with offspring risk of food allergy based on various food allergy definitions in the Boston Birth Cohort.

FA definition	N _{cont/case}	TAG 48:1			TAG 58:10		
		OR ^e	95%CI	P	OR ^e	95%CI	P
Confirmed FA ^a	781/85	1.57	1.20-2.04	0.0009	0.62	0.47-0.81	0.0005
Confirmed FA + physician diagnosis ^b	781/50	1.83	1.28-2.60	0.0008	0.56	0.39-0.80	0.001
Confirmed FA + sIgE ≥ 95%PPV ^c	781/35	1.52	1.03-2.25	0.036	0.60	0.40-0.89	0.012
Confirmed FA + sIgE ≥ 95%PPV + physician diagnosis ^d	781/26	1.64	1.03-2.64	0.038	0.55	0.34-0.89	0.016

Abbreviation: CI: confidence interval; FA: food allergy; OR: odds ratio; PPV: positive predictive value; TAG: Triacylglycerol.

^a Children in the “confirmed or convincing FA” category as defined in the Methods.

^b Children having confirmed or convincing FA and having physician-diagnosed FA based on the EMR (with ICD code of V15.0, V15.01-V15.05, 995.60-995.69, Z91.010-Z91.013, Z91.018, T78.00-T78.05, T78.07-T78.09, T78.00XA-T78.05XA, T78.07XA-T78.09XA, T78.00XD-T78.05XD, or T78.07XD-T78.09XD).

^c Children having confirmed or convincing FA, and with sIgE ≥ 95% positive predictive value (PPV) to the specific food allergen.

^d Children having confirmed or convincing FA, and having physician-diagnosed FA based on the EMR, and with sIgE ≥ 95% PPV to the specific food allergen.

^e Adjusted for maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI category, delivery mode, and infants’ sex.

Table E4. Associations of maternal TAGs with offspring risk of food sensitization and food allergy, stratified by the timing of food sIgE measurement

Outcome	N _{cont/case}	TAG 48:1			TAG 58:10		
		OR ^a	95%CI	P	OR ^a	95%CI	P
Children with sIgE measured at age < 2 years							
FS	376 / 217	1.05	0.87-1.28	0.583	1.01	0.82-1.24	0.938
FA	444 / 75	1.54	1.15-2.06	0.004	0.63	0.46-0.85	0.003
Children with sIgE measured at age ≥ 2 years							
FS	281 / 194	1.11	0.89-1.38	0.345	0.88	0.72-1.09	0.244
FA	337 / 57	1.30	0.93-1.83	0.124	0.63	0.45-0.88	0.007

Abbreviation: CI: confidence interval; FA: food allergy; FS: food sensitization; OR: odds ratio; TAG: Triacylglycerol.

^a Adjusted for maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI category, delivery mode, and infants' sex.

Table E5. Propensity score-based sensitivity analysis for the association between high vs. low maternal TAG score and risk of FA, in 177 matched pairs from the Boston Birth Cohort (BBC)

Variables	Low maternal TAG score ^a (n=177)	High maternal TAG score ^a (n=177)	P ^b
Covariates			
Maternal race, n(%)			0.405
Black	122 (68.9)	116 (65.5)	
White	3 (1.7)	8 (4.5)	
Hispanic	30 (16.9)	27 (15.3)	
Other	22 (12.4)	26 (14.7)	
Pre-pregnancy BMI category (kg/m ²)			0.788
< 25.0	85 (48.0)	81 (45.8)	
25-29.9	49 (27.7)	54 (30.5)	
≥ 30	35 (19.8)	31 (17.5)	
Unknown	8 (4.5)	11 (6.2)	
Maternal history of atopy			0.475
No	108 (61.0)	112 (63.3)	
Yes	47 (26.6)	50 (28.2)	
Unknown	22 (12.4)	15 (8.5)	
Delivery type			0.726
Vaginal	127 (71.8)	124 (70.1)	
Cesarean Section	50 (28.2)	53 (29.9)	
Child's sex			0.671
Boy	89 (50.3)	93 (52.5)	
Girl	88 (49.7)	84 (47.5)	
Outcomes			
Food sensitization	53 (29.9)	64 (36.2)	0.214
Food allergy	15 (8.5)	32 (18.1)	0.008

^a The low maternal TAG score was defined as having a maternal TAG score in the 1st tertile and the high maternal TAG score was defined as having a maternal TAG score in the 3rd tertile of the studied population.

^b The difference in each variable between children with high maternal TAG score and children with low maternal TAG score was assessed based on t-test and chi-square test, respectively, for continuous and categorical variables.

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Table E6. Associations of maternal TAG 48:1 and TAG 58:10 and offspring risk of other allergic disease in the 1,068 mother-child dyads of the BBC

Metabolite	TAG 48:1				TAG 58:10			
	N (%)	OR	95%CI	P	N (%)	OR	95%CI	P
Allergic dermatitis								
Continuous (1SD)	1068(39.2)	1.08	0.94-1.25	0.258	1068 (39.2)	0.98	0.85-1.13	0.746
Low (T1)	353 (36.8)	1.00	1.00-1.00	1.000	353 (38.0)	1.00	1.00-1.00	1.000
Medium (T2)	362 (42.8)	1.46	1.06-2.00	0.020	362 (39.5)	0.95	0.70-1.31	0.769
High (T3)	353 (38.0)	1.33	0.94-1.86	0.111	353 (40.2)	0.92	0.66-1.29	0.630
Asthma								
Continuous(1SD)	1068(30.7)	1.00	0.86-1.16	0.993	1068 (30.7)	0.84	0.72-0.98	0.028
Low (T1)	353 (30.3)	1.00	1.00-1.00	1.000	353 (32.9)	1.00	1.00-1.00	1.000
Medium (T2)	362 (32.9)	1.23	0.88-1.73	0.231	362 (31.2)	0.89	0.63-1.24	0.486
High (T3)	353 (28.9)	1.19	0.82-1.72	0.366	353 (28.0)	0.75	0.52-1.08	0.125
Hay fever								
Continuous (1SD)	1068(29.9)	1.18	1.01-1.37	0.036	1068 (29.9)	0.86	0.74-1.01	0.059
Low (T1)	353 (27.8)	1.00	1.00-1.00	1.000	353 (32.3)	1.00	1.00-1.00	1.000
Medium (T2)	362 (31.2)	1.35	0.96-1.91	0.085	362 (27.6)	0.77	0.55-1.08	0.131
High (T3)	353 (30.6)	1.59	1.10-2.30	0.014	353 (29.7)	0.82	0.57-1.17	0.279

Abbreviation: CI: confidence interval; OR: odds ratio; SD: standard deviation; T1:1st tertile; T2: 2nd tertile; T3: 3rd tertile.

^a Adjusted for maternal ethnicity, maternal history of atopy, maternal pre-pregnancy BMI category, delivery mode, and infants' sex.

Online Repository Figure Legends

Figure E1. Manhattan plot for associations of 209 maternal lipid metabolites with offspring risk of food sensitization in the Boston Birth Cohort, adjusted for maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI category, delivery mode, and infants' sex. Each dot represents a lipid metabolite in a specific lipid class.

Figure E2. Pairwise correlation coefficients of maternal TAG metabolites in the Boston Birth Cohort

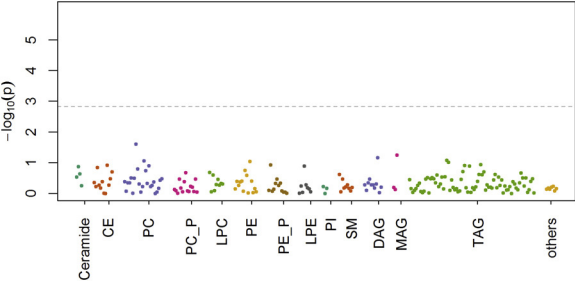


Figure 1E

