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Fetal lipidome and incident risk of food allergy: A prospective birth cohort study

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Abstract

Background: Lipids are proposed to be important in developing adaptive immunity and allergy. However, studies to date reported inconsistent findings.

Objective: To examine newborn lipidome (a comprehensive profiling of circulating lipid metabolites) on child's risk of developing food allergy (FA). The maternal-cord joint effects of lipid metabolites on FA development were also investigated.

Methods: This study included 647 mother-child pairs from the Boston Birth Cohort and analyzed 202 lipid metabolites in cord plasma profiled by liquid chromatography tandem mass spectrometry. FA was defined based on standard clinical criteria. Logistic regression was applied to examine the relationships between individual metabolites and risk of FA.

Results: Of the 647 children, 61 developed FA. Cord triacylglycerols of long carbon chains and multiple double bonds were significantly associated with decreased risk of FA. These associations were comparable across strata of pertinent maternal and child covariates, and were independent of maternal triacylglycerols when assessed simultaneously. Besides, cord and maternal triacylglycerols had an additive effect in association with risk of FA: Children having high ($\geq$ Median) C56:8 triacylglycerol levels in both cord and maternal plasma were at the lowest risk of developing FA (OR = 0.24,

Abbreviations: BBC, Boston Birth Cohort; BMC, Boston Medical Center; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; DBPCFC, double-blind, placebo-controlled food challenge; EMR, electronic medical record; FA, food allergy; FDR, false discovery rate; FS, food sensitization; fs-IgE, food-specific immunoglobulin E; LC-MS, liquid chromatography tandem mass spectrometry; OR, odds ratios; OWO, overweight or obesity; PUFA, polyunsaturated fatty acid; SD, standard deviation; TAG, triacylglycerol; TH₂, T helper type 2; WGCNA, weighted-gene coexpression network analysis.

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95% CI = 0.10–0.56, $p = .001$), compared to those having low levels in both cord and maternal plasma.

Conclusion: This is the first birth cohort study to link altered cord plasma lipidome with future risk of development FA during childhood. It calls for further investigation on triacylglycerols of long carbon chains and multiple double bonds as potential novel predictive biomarkers and therapeutic targets for FA.

KEYWORDS

food allergy, food sensitization, lipidome, mother-child pairs, triacylglycerol

1 | INTRODUCTION

Food allergy (FA) has emerged as a major clinical and public health problem worldwide due to its enormous adverse medical, psychosocial, and economic consequences.^{1–3} Its prevalence in infants and toddlers has been rising worldwide, and the increase has been greatest among non-Hispanic black children,⁴ which underscores the critical need for biomarkers to identify at-risk children in multi-ethnic populations during the earliest possible developmental windows, including the less-studied in utero period.

Lipids and metabolic pathways are intricately associated with immune cell physiology, not only via providing energy and substrate for growth and survival, but also instructing effector functions, differentiation, and gene expression.⁵ Gideon Lack's dietary fat hypothesis,⁶ which argues that reduction in consumption of animal fats and corresponding increase in the use of margarine and vegetable oils may lead to the increase in allergies, also holds that lipids play a role in allergy development. However, epidemiological studies to date have reported inconsistent findings.^{7–11} Most of these studies applied the standard clinical measurement of a lipid panel, which cannot capture the functionally and chemically diverse molecular components.¹² Recently, limited metabolomic or lipidomic studies were conducted in FA, which identified lower levels of plasma sphingolipids¹³ and diacylglycerols¹⁴ in FA cases than non-allergic controls. Both studies, however, were cross-sectional in design and had limited sample size. In the Boston Birth Cohort (BBC), we previously reported maternal triacylglycerol signature for FA development in the offspring.¹⁵ Given that the lipidomic profile in that study was measured in maternal plasma collected 1–3 days after delivery and that delivery of the placenta may cause a dramatic drop in estrogen levels, it is likely that the measured maternal lipidomic profiles do not fully reflect the prenatal exposure. Further prospective studies are needed to identify early-life lipidomic signature to predict FA development.

As a natural extension of our previous work in maternal lipidome, the current study examined lipidomic profiles in cord plasma (reflecting fetal circulation) from children in the BBC, a U.S. multi-ethnic prospective birth cohort, with the aim to 1) identify cord lipidomic profiles that were associated with risk of food sensitization (FS) and FA during childhood and 2) test the independent, joint, and interactive associations of maternal and cord lipid metabolites in predicting child FA risk. We were also interested in whether the

Key Message

With lipidomic profiling in cord plasma, this study identified that cord triacylglycerols of long carbon chains and multiple double bonds, individually and jointly with triacylglycerols in maternal plasma, may protect against the development of food allergy during childhood. These findings indicate that triacylglycerol signature at birth may serve as early-life biomarkers to identify high-risk children for food allergy.

identified associations may be modified by other early-life factors such as sex, race, prenatal exposure, infant feeding, and by different types of FAs.

2 | METHODS

2.1 | Study participants

Study participants were enrolled from the BBC, a well-established ongoing low-income, high-risk minority urban birth cohort, as we reported previously.¹⁶ Detailed information on participant enrollment and data collection has been reported previously.¹⁶ Briefly, available mother-child pairs were recruited 24–72 h after delivery since 1998 at the Boston Medical center (BMC), Massachusetts. After obtaining written informed consent, mothers were interviewed using a standardized questionnaire. Since 2004, children were followed prospectively since birth up to age 21 years. The study protocol was approved by the Institutional Review Boards of Boston University Medical Center and Johns Hopkins Bloomberg School of Public Health.

As of July 2020, 3,394 mother-child pairs have been followed in the BBC. The target populations of this study were those 1,796 children born during year 1999–2013 with measurements of food-specific IgE (fs-IgE). The current study focused on 647 children with available data on fs-IgE and cord lipidome, whose maternal and early-life characteristics were largely comparable to those of the target population (Table S1).

2.2 | Lipidome profiling in cord plasma

Lipidomic assessment in cord plasma was conducted at the Broad Institute Metabolite Profiling Laboratory using LC-MS techniques.^{17,18} Details of the laboratory protocols and quality control steps were similar to what we reported previously in maternal samples (collected within 1–3 days after delivery).¹⁵ As a quality control step, a pooled study reference sample, comprised from all of the studied cord plasma, was repeatedly measured together with the study samples (per 20–30 study samples). Coefficient of variation (CV) for each metabolite was calculated by analyzing repeated measures of the pooled study sample. About 202 lipid metabolites were measured, and 8 metabolites with CV >20% were removed. About 194 metabolites from multiple lipid classes were available for subsequent analyses, which were annotated as “C[number of total acyl chain carbon atoms]:[number of double bonds in fatty acid moieties] [lipid class].”

2.3 | Definition of FA outcomes and covariates

Plasma fs-IgE for the eight allergens (egg white, cow's milk, peanut, soy, shrimp, walnut, wheat, and cod) in early childhood was measured using ImmunoCAP® (Thermo Fisher/Phadia) at Quest Diagnostics. FS was defined as having an fs-IgE ≥ 0.35 kU_A/L.

At each follow-up visit, mothers were interviewed about a history of physician-diagnosed FA for the index child, and clinical allergic symptoms ever experienced by the child upon ingestion of each allergenic food, the timing and treatment of these reactions (if there were any), and dietary history for which mothers were asked if, and how often, the child consumed the allergenic foods. IgE-mediated FA was then defined as meeting the following criteria, as we reported recently^{15,19}: 1) evidence of FS as defined above; and 2) clinical manifestations: within 2 h of food ingestion, having a convincing clinical history of allergic symptoms in skin, pharynx, oral cavity, lower respiratory, and/or gastrointestinal tract.

Other covariates were collected via maternal interview at enrollment and follow-up visits. Briefly, maternal history of atopy was defined if the mother ever had any of the physician-diagnosed allergic conditions including FA, eczema, atopic rhinitis, or asthma. During the follow-up visit, each mother was interviewed about breastfeeding history and timing of first solid food introduction. Physician-diagnosed eczema during the 1st year of life was defined based on ICD codes using the archived electronic medical records.

2.4 | Statistical analysis

For each lipid metabolite, non-detectable values were imputed with one-half of the limit of detection. Rank-based inverse normal transformation was performed to render the distribution of each metabolite approximately Gaussian, which was scaled to per standard deviation (SD). Multiple logistic regression models were used to investigate the associations between each cord lipid metabolite and

FA outcomes, with the adjustment of known or suspected confounders, including maternal age at delivery, maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI, child's sex, eczema diagnosed during the 1st year of life, and child's age when fs-IgE was measured (with FS as the outcome) or child's age when FA was diagnosed (with FA as the outcome; for non-FA controls, child's age was coded as age at the last questionnaire interview). We applied the Benjamini-Hochberg false discovery rate (FDR <0.05) to adjust for multiple testing.

To minimize issues of metabolite collinearity, we performed weighted-gene coexpression network analysis (WGCNA),²⁰ which utilizes an unsupervised network-based approach to group metabolites into “modules” based on their correlation patterns. For each established module, principal component analysis was applied on metabolites within the module and the first principal component was calculated to represent the module score. Each module score was then analyzed for its association with risk of FA outcomes using multiple logistic regression models as described above.

For the identified metabolites that were significantly associated with FA outcomes, we performed stratified analyses by each stratum of covariates for the lipid metabolite-FA association, using the logistic regression models with the adjustment of other covariates as described above. We then investigated whether the specific metabolite level in cord plasma and in maternal plasma was independently associated with risk of FA outcomes by adding both into the same logistic regression models. We further tested their interactive effects by adding their product item into the same model. All analyses were performed in R 3.6 version.

3 | RESULTS

Among the 647 children, there were 237 (36.6%) children with FS, and 61 (9.4%) with FA to at least one of the eight major food allergens tested. As expected, children with FS or with FA included a higher proportion of males and were more likely to have eczema during the 1st year of life, compared to those without (Table 1, $p < .05$). Children with FS were more likely to be born to older mothers ($p = .046$) and have their fs-IgE measured at an older age ($p = .017$) compared to those without. Children with FA were more likely born to Black mothers compared to those without ($p = .035$) (Table 1).

3.1 | Associations between cord lipid metabolites and risk of FA outcomes, and subgroup analyses

Figure 1 presents the associations between the 194 lipid metabolites and the risk of having FS and FA in childhood. Table 2 summarizes those associations with FDR <0.05, and Table S2 summarizes the rest associations with $p < .05$. At FDR < 0.05, 9 cord TAGs (C54:7, C54:8, C56:8, C56:9, C56:10, C58:9, C58:10, C58:11, and C60:12), all with relatively long carbon chains and multiple double bonds, were

TABLE 1 Characteristics of 647 mother-child pairs from the Boston Birth Cohort, stratified by FS and FA status

Variable ^a	FS (n = 647)		FA (n = 549) ^b	
	No	Yes	No ^c	Yes
N	410	237	488	61
Maternal age (year), Mean $\pm$ SD	28.1 $\pm$ 6.5	29.2 $\pm$ 6.6 [*]	28.4 $\pm$ 6.5	29.5 $\pm$ 6.9
Maternal race/ethnicity				
Black	217 (52.9)	148 (62.5)	264 (54.1)	45 (73.8) [*]
White	29 (7.1)	10 (4.2)	30 (6.1)	2 (3.3)
Hispanic	98 (23.9)	50 (21.1)	121 (24.8)	8 (13.1)
Others	66 (16.1)	29 (12.2)	73 (15.0)	6 (9.8)
Maternal history of atopy				
No	261 (63.7)	129 (54.4)	310 (63.5)	31 (50.8)
Yes	106 (25.8)	77 (32.5)	129 (26.4)	20 (32.8)
Unknown	43 (10.5)	31 (13.1)	49 (10.1)	10 (16.4)
Maternal smoking during pregnancy				
Never	334 (81.5)	199 (84.0)	398 (81.6)	52 (85.2)
Quitting	32 (7.8)	14 (5.9)	37 (7.6)	3 (5.0)
Continuous	44 (10.7)	24 (10.1)	53 (10.8)	6 (9.8)
Maternal pre-pregnancy BMI (kg/m ²)				
<25	191 (46.6)	102 (43.0)	228 (46.7)	23 (37.7)
25–29.9	114 (27.8)	66 (27.9)	137 (28.1)	16 (26.2)
≥ 30	82 (20.0)	58 (24.5)	95 (19.5)	18 (29.5)
Unknown	23 (5.6)	11 (4.6)	28 (5.7)	4 (6.6)
Maternal highest education, college, or above	136 (33.2)	79 (33.3)	162 (33.2)	16 (26.2)
Maternal diabetes/gestational diabetes	51 (12.5)	34 (14.4)	61 (12.5)	12 (19.7)
Child's sex, male	209 (51.0)	141 (59.5) [*]	254 (52.0)	44 (72.1) ^{**}
Preterm birth	63 (15.4)	39 (16.5)	74 (15.2)	13 (21.3)
Delivery type: Cesarean delivery	141 (34.4)	80 (33.8)	161 (33.0)	23 (37.7)
Child's age at fs-IgE measurement (year)	2.2 $\pm$ 2.0	2.7 $\pm$ 2.4 [*]	2.4 $\pm$ 2.1	2.4 $\pm$ 2.6
Child's age when FA was diagnosed (year) ^d	5.2 $\pm$ 3.3	5.0 $\pm$ 3.1	5.3 $\pm$ 3.4	4.0 $\pm$ 2.9 ^{**}
Never breastfed ^e	110 (26.8)	52 (21.9)	127 (26.0)	16 (26.2)
Delayed solid food introduction (≥ 7 months)	48 (11.7)	28 (11.8)	55 (11.3)	10 (16.4)
Eczema diagnosed during the 1 st year of life ^f	51 (12.4)	57 (24.1) ^{**}	64 (13.1)	21 (34.4) ^{**}

Note: ***,The differences in population characteristics between FS and non-FS children and between FA and non-FA children were tested using the t-test and chi-square test for continuous and categorical variables, respectively. * $p < .05$; ** $p < .01$.

^aMean $\pm$ SD and n (%) are shown for continuous and categorical variables, respectively.

^bAbout 98 children who had some clinical symptom on food exposure but did not meet the criteria of FA were removed from the analysis for FA.

^cThe FA control group included 114 children with asymptomatic FS.

^dFor non-FA children, child's age was coded as age at the last questionnaire interview.

^eAbout 7 children had missing data on this variable.

^fAbout 8 children had missing data on this variable.

inversely associated with risk of FA (Table 2). Cord C56:8 TAG had the most significant association with risk of FA: Per 1 SD increase in this metabolite was associated with 43% reduction in FA risk ($p = .0003$). Furthermore, 10 sphingomyelins tended to be associated with a lower risk of FS or FA at $p < .05$ (Table S2), although these associations were no longer significant after FDR correction.

In WGCNA analyses, 180 out of 194 metabolites were attributed into 5 metabolite modules (Table S3). All the identified 9

FA-associated TAGs were assigned into the "Brown" module. The score for the "Brown" module was significantly and inversely associated with risk of FA at $p = .002$, which remained significant after Bonferroni correction for multiple tests on the 5 different modules (Table S4). No significant associations were found for the rest 4 modules (Table S4).

We then focused on C56:8 TAG for the subsequent analyses, since it had the most significant association with risk of FA and was

highly correlated with all the other 8 FA-associated TAGs ($r > .71$, Figure S1) and with the score of the “Brown” module ($r = .93$). As shown in Figure 2, subgroup analyses showed consistent associations between cord C56:8 TAG and risk of FA across strata of each potential confounder, including sex, maternal ethnicity, maternal history of atopy, maternal pre-pregnancy overweight or obesity (OWO), breastfeeding, and solid food introduction. Although a relatively larger difference in the point estimate of the ORs for FA was observed across strata of preterm birth and strata of eczema during the 1st year of life, tests of interactions between each of these covariates and cord C56:8 TAG did not produce significant findings.

The association between cord C56:8 and risk of FA remained comparable when more stringent FA definitions were applied, or when allergy to egg, cow's milk and peanut allergy were analyzed separately (Table 3).

3.2 | Maternal-cord joint effects in associations with risk of FA

Among the 559 mother-child pairs with lipidomic profiles measured in both cord and maternal plasma, the maternal-cord correlation for 9 FA-associated TAGs varied from modest to moderate ($r = .03$ – $.39$; Figure S1). Using C56:8 TAG as the example (maternal-cord correlation $r = .20$), we found that both cord and maternal C56:8 TAG were independently associated with a lower risk of FA, after adjusting for each other in the regression model (Table 4). The maternal-cord joint association of this metabolite is also shown in Table 4. Compared to

those with low C56:8 TAG (defined as $<$ median) in both maternal and cord plasma, children with a high level (defined as $\geq$ Median) only in maternal (OR = 0.33, 95% CI = 0.14–0.80) or only in cord plasma (OR = 0.39, 95% CI = 0.16–0.98) were at a lower risk of having FA; in contrast, children with high levels in both maternal and cord plasma were at the lowest risk of developing FA (OR = 0.24, 95% CI = 0.10–0.56). However, no significant maternal-cord TAG interactions were observed.

4 | DISCUSSION

To our knowledge, this is the first comprehensive lipidomic study in a prospective birth cohort to examine the link between lipidomic signature as early as at birth and subsequent risk of FA development during childhood. This study has made following novel contributions. First, we found that cord plasma TAGs with long carbon chains and multiple double bonds (with C56:8 TAG as the top metabolite) were inversely associated with FA development during childhood; that is, they were protective against FA. Second, the inverse associations between cord TAGs and risk of FA remained robust across strata of pertinent covariates such as maternal metabolic and atopic status (pre-pregnancy OWO and history of atopy), race/ethnicity, child's sex, and infant feeding (breastfeeding and timing of solid food introduction). Third, the inverse associations between cord TAGs and risk of FA were independent of the effect of maternal TAGs. Our data further suggest that cord TAGs (reflecting fetal circulation) and maternal TAGs (reflecting in utero exposure) may have an

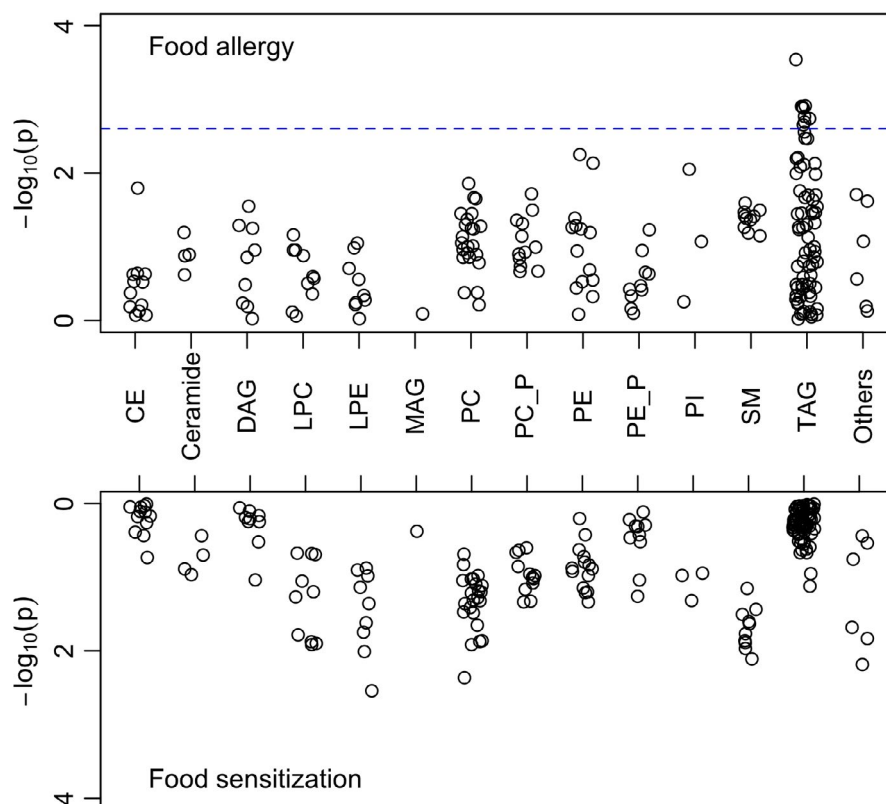


FIGURE 1 Mirror scatter plots for associations of 194 lipid metabolites in cord blood with risk of FA and FS from the Boston Birth Cohort. The gray dotted line represents the significance cutoff with FDR < 0.05 . CE, cholesterol ester; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PC_P, PC plasmalogen; PE, phosphatidylethanolamine; PE_P, PE plasmalogen; PI, phosphatidylinositol; SM, sphingomyelin; TAG, Triacylglycerol

Metabolite	FS			FA		
	OR ^a	95% CI	p	OR ^a	95% CI	p ^b
C54:7 TAG	0.93	0.78–1.10	.380	0.60	0.44–0.82	.001
C54:8 TAG	0.93	0.79–1.10	.414	0.60	0.44–0.82	.001
C56:8 TAG	0.94	0.80–1.11	.475	0.57	0.42–0.77	.0003
C56:9 TAG	0.93	0.79–1.11	.432	0.60	0.44–0.82	.001
C56:10 TAG	0.95	0.80–1.12	.519	0.61	0.45–0.83	.002
C58:9 TAG	0.96	0.81–1.13	.634	0.62	0.46–0.84	.002
C58:10 TAG	0.93	0.79–1.10	.392	0.62	0.45–0.84	.002
C58:11 TAG	0.94	0.80–1.12	.495	0.61	0.45–0.84	.002
C60:12 TAG	0.94	0.79–1.11	.451	0.60	0.44–0.82	.001

Abbreviations: CI, confidence interval; OR, odds ratio; TAG, triacylglycerol.

^aAdjusted for maternal age at delivery, maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI, child's sex, eczema diagnosed during the 1st year of life, and child's age when fs-IgE was measured (with FS as the outcome) or child's age when FA was diagnosed (with FA as the outcome).

^bAll FDR <0.05.

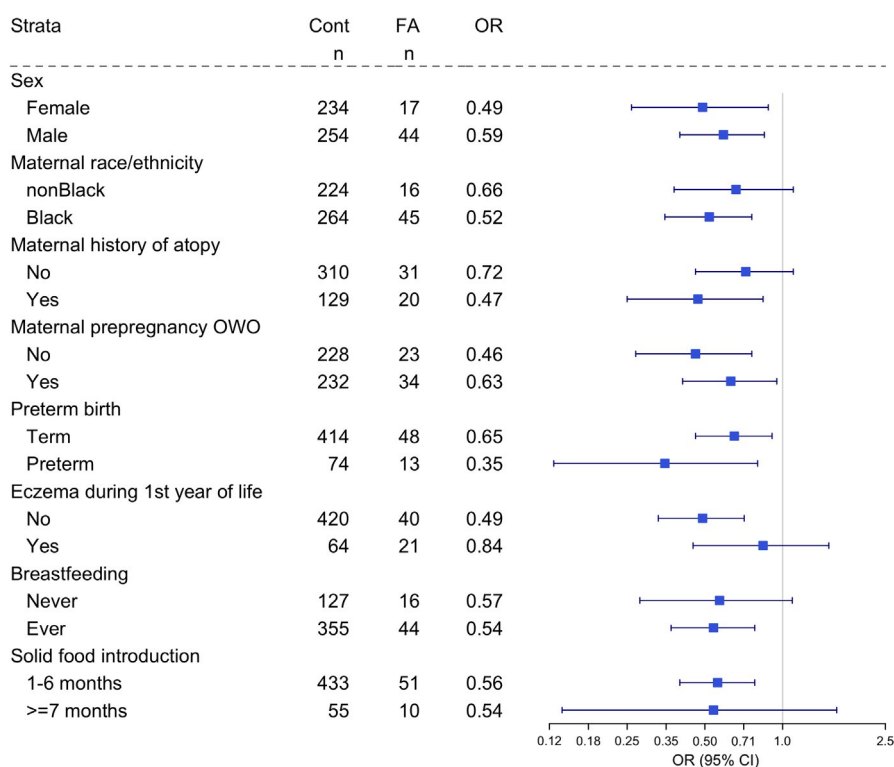


TABLE 2 Associations of cord lipid metabolites with the risk of FS and FA in 647 children from the Boston Birth Cohort

FIGURE 2 Forest plots summarizing the subgroup analyses of the association between cord C56:8 TAG levels and risk of FA, stratified by each pertinent covariate. In the figure, squares represent the ORs, with whiskers indicating 95% confident interval. The analyses adjusted for maternal age at delivery, maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI, child's sex, eczema diagnosed during the 1st year of life, and child's age when FA was diagnosed after excluding the variable applied for stratification. OWO, overweight/obesity

additive effect in predicting risk of FA: Children having high C56:8 TAG levels in both cord and maternal plasma were at the lowest risk of developing FA, with a 76% risk reduction, than those having low levels in both cord and maternal plasma. Fourth, we observed similar association trends between cord TAGs and each of the three common types of FA (egg allergy, cow's milk allergy, and peanut allergy), suggesting a shared etiology of allergy development. In comparison, TAGs showed no associations with FS. These findings may indicate that the FA-associated TAGs, either in maternal or cord plasma, may influence the manifestation of clinical symptoms, or oral tolerance in sensitized children, rather than affect IgE production. Whether and

how TAGs contribute to protection against FA will still be the subject of future studies.

Although a few such studies have been conducted, here we highlight some relevant previous studies to put in context on similarities and differences between prior studies and ours. In a pilot study, Crestani et al¹³ reported that patients with FA exhibited a disease-specific metabolomic signature compared with both control subjects and asthmatic subjects, including a marked decrease in sphingolipids levels (both ceramides and sphingomyelins). Bao et al, in 18 twin pairs, identified that multiple diacylglycerols were lower in allergic twins compared to their non-allergic siblings.¹⁴ Both studies were of

TABLE 3 Associations of cord TAG C56:8 with risk of FA in children based on various FA definitions, as well as with risk of allergy to egg, milk, and peanut separately

FA outcomes	N _{control/case}	TAG 56:8-FA association ^c		
		OR	95% CI	p
Various definitions of FA and controls				
Confirmed or convincing FA ^a	488/38	0.58	0.40–0.84	.004
FA plus fs-IgE measured at ≥2 years	488/27	0.54	0.36–0.83	.004
FA plus fs-IgE ≥95%PPV	488/36	0.69	0.49–0.98	.036
FA compared to non-allergic and non-sensitized controls ^b	374/61	0.68	0.51–0.90	.007
Type of FA				
Egg allergy	488/34	0.65	0.44–0.97	.033
Milk allergy	488/16	0.37	0.20–0.68	.001
Peanut allergy	488/27	0.54	0.33–0.86	.009

Abbreviations: CI, confidence interval; OR, odds ratio; PPV, positive predictive value; TAG, triacylglycerol.

^aConfirmed or convincing FA was defined if the child met all the following criteria: 1) fs-IgE ≥0.35 kU_A/L to a specific food; 2) having convincing clinical allergic symptoms within 2 h upon ingestion of that food; and 3) avoidance of the food based on the food frequency questionnaire.

^bAbout 114 children with asymptomatic FS were removed from the control group.

^cAdjusted for maternal age at delivery, maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI, child's sex, eczema diagnosed during the 1st year of life, and child's age when FA was diagnosed.

TABLE 4 Joint associations between maternal and cord C56:8 TAG on risk of FA in children from the Boston Birth Cohort

Cord TAGs	Maternal TAGs	FS			FA			
		N (%case)	OR (95% CI) ^b	<i>p</i>	N (%case)	OR (95% CI) ^b	<i>p</i>	
C56:8								
Per SD		-	0.91 (0.76–1.09)	.312	-	0.59 (0.42–0.82)	.002	
	Per SD	-	0.92 (0.74–1.14)	.439	-	0.66 (0.45–0.97)	.035	
Low ^a	Low ^a	159 (39.6)	Ref	Ref	141 (17.0)	Ref	Ref	
Low	High	120 (33.3)	0.64 (0.37–1.09)	.101	104 (9.6)	0.33 (0.14–0.80)	.014	
High	Low	120 (35.0)	0.82 (0.49–1.37)	.448	100 (8.0)	0.39 (0.16–0.98)	.045	
High	High	160 (36.3)	0.76 (0.46–1.25)	.273	136 (8.1)	0.24 (0.10–0.56)	.001	
<i>p</i> for interaction				.071				.760

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

^aLow vs high C56:8 TAG was defined as C56:8 TAG <Median and C56:8 TAG ≥Median, respectively.

^bAdjusted for maternal age at delivery, maternal race/ethnicity, maternal history of atopy, maternal pre-pregnancy BMI, child's sex, eczema diagnosed during the 1st year of life, and child's age when fs-IgE was measured (with FS as the outcome) or child's age when FA was diagnosed (with FA as the outcome).

cross-sectional case-control study designs, and thus, the temporal relationship was unclear. There was a possibility that the identified changes in metabolites may be the consequence of FA, which await further replication in a larger prospective study cohort. With lipidomic profiling in maternal blood, we recently reported a significant maternal TAG signature for offspring risk of FA.¹⁵ As a natural extension of that previous work, the current study further demonstrated that cord plasma TAGs of long carbon chains and multiple double bonds (reflecting fetal circulation) may protect against FA development during childhood, which is consistent with the findings we observed in maternal plasma. In comparison, multiple sphingomyelins

also showed marginally inversed associations with risk of FS and FA at $p < .05$ in this study, which were consistent with the finding by Crestani et al.¹³

Our identified inverse associations between TAGs of long carbon chains and multiple double bonds and risk of FA are biologically plausible.^{21–24} Besides their involvement in chronic inflammation,²⁵ lipids can regulate T helper type 2 (TH₂) response^{21,22} and/or skin barrier function.²³ In particular, TAGs constitute the largest source of different types of dietary fatty acids, which potentially have different impacts on the immune system. TAGs with long carbon chains and multiple double bonds are predominantly composed of

polyunsaturated fatty acids (PUFAs). PUFAs, especially *n*-3 PUFAs, may regulate functions of the fetal immune system through several anti-inflammatory mechanisms leading to a reduced TH₂ response, protecting against allergy.^{21,22,26} Alternatively, the identified TAG-FA associations may be indirectly caused by shared genetic susceptibility, maternal diet, or other exposure during pregnancy. In this study, we observed that cord blood C56:8 TAG level was significantly associated with maternal C56:8 TAG levels as well as other maternal or fetal factors (Table S5), including race/ethnicity, fish intake during pregnancy,²⁷ and Cesarean delivery²⁸ that have been reported to be associated with allergy phenotypes. Further studies in a larger population are needed to investigate whether this TAG may mediate the impact of such maternal or fetal factors on FA development.

A key strength of this study is its prospective birth cohort study design. With TAGs measured at birth, our finding has a clear temporal relationship and unaffected by reverse causation. Another strength is the recruitment and longitudinal follow-up of well-phenotyped mother-child pairs from birth to childhood, with available standard clinical diagnosis of FA in an under-represented, high-risk multi-ethnic birth cohort. As such, the findings will have direct relevance to understanding and preventing FA in high-risk minority population. Besides, a simultaneous assessment of maternal and fetal lipidome in this study offers a rare opportunity to examine joint influence of maternal and fetal lipid metabolism on child future risk of FA.

However, caution is needed when generalizing our finding to other populations with different ethnicities. Some other limitations should also be acknowledged. First, FA cases enrolled in this study were defined based on the robust clinical, dietary, and serologic information,¹⁵ rather than using a double-blind, placebo-controlled food challenge (DBPCFC), and FS was defined based on fs-IgE ≥ 0.35 kU/L given that the skin prick test was not available in this study. Our sensitivity analyses showed that the cord TAG-FA associations remained similar when more stringent FA definition (Table 3) was applied, indicating that our findings would not be substantially affected by potential misclassification of FA. Second, our current sample size limited our ability to further investigate whether cord TAGs may mediate the associations between early-life exposure and FA development. Third, lipidome in this study was measured using the LC-MS technology, which reported relative rather than absolute quantitation.

In summary, our study demonstrated that maternal and cord TAG signature may individually and jointly predict child risk of FA development. Specifically, maternal and/or cord TAGs of long carbon chains and multiple double bonds may protect against FA development during childhood. These findings, if further validated by future studies, suggest that lipidomic profiling at birth can be a powerful approach to advance our knowledge on early life origins of FA and underlying molecular pathways. New knowledge gained from such type of studies may improve our ability to identify newborns at high risk of FA.

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CONFLICT OF INTEREST

The authors declare no relevant conflicts of interest.

AUTHOR CONTRIBUTION

Xiumei Hong: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Funding acquisition (equal); Investigation (equal); Visualization (lead); Writing – original draft (lead). **Liming Liang:** Conceptualization (supporting); Formal analysis (supporting); Methodology (supporting); Writing – review & editing (equal). **Hongkai Ji:** Formal analysis (supporting); Methodology (supporting); Writing – review & editing (supporting). **Pamela Guerrero:** Visualization (supporting); Writing – review & editing (equal). **Guoying Wang:** Data curation (equal); Investigation (supporting); Writing – review & editing (supporting). **Colleen Pearson:** Data curation (equal); Investigation (equal); Writing – review & editing (supporting). **MJ Stampfer:** Writing – review & editing (equal). **Frank Hu:** Conceptualization (supporting); Writing – review & editing (supporting). **Xiaobin Wang:** Conceptualization (supporting); Data curation (equal); Funding acquisition (lead); Investigation (equal); Project administration (equal); Supervision (lead); Writing – review & editing (supporting).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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