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Role of maternal tryptophan metabolism in allergic diseases in the offspring

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Author Contributions

Lau HX and Yap QV analysed the data and wrote the manuscript. Chan YH provided statistical advice and intellectual input. El-Heis S and Tan CPT provided intellectual input and wrote the manuscript. Karnani N, Tan KML, Tham EH, Goh AEN, Teoh OH, Tan KH, Eriksson JG, Chong YS, Chong MF-F, Van Bever H, Lee BW, Shek LP contributed to the study design and provided intellectual input. Loo EXL and Godfrey KM conceptualized the study design, contributed to the analysis and wrote the manuscript. All authors critically reviewed the manuscript.

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Abstract

Background—Nicotinamide (vitamin B3) is metabolite of tryptophan and a dietary precursor of enzymes involved in many regulatory processes, which may be influence fetal immune development.

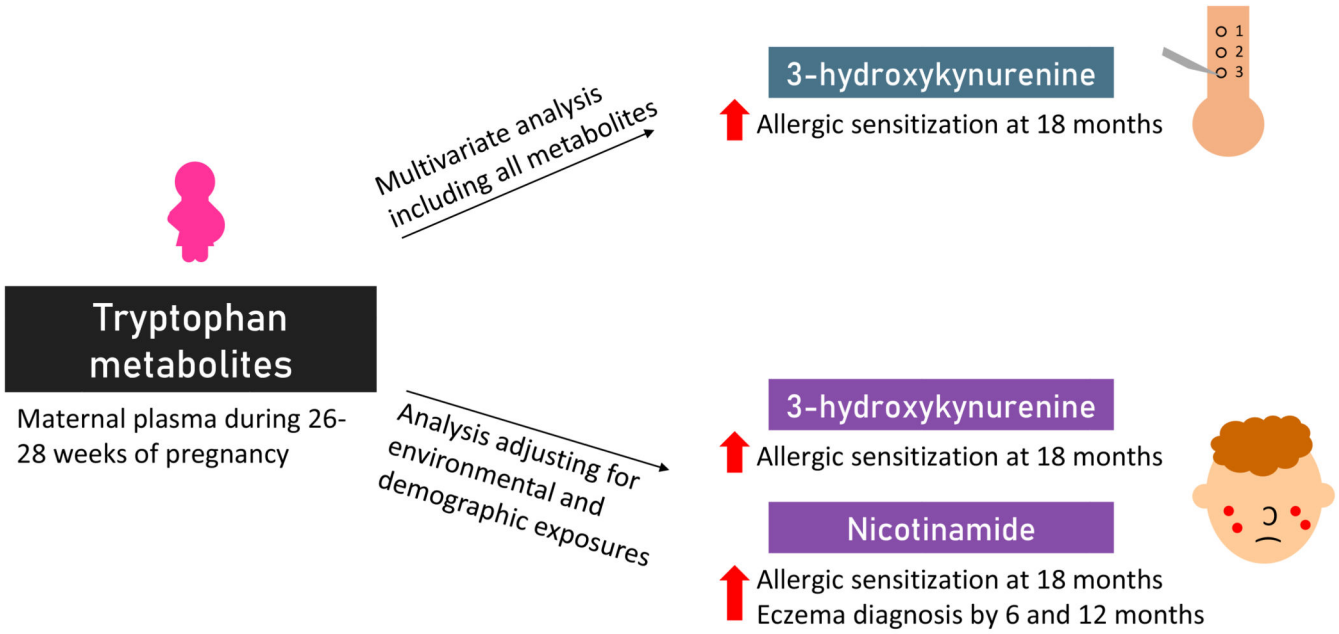
Objective—We examined whether maternal plasma concentrations of nicotinamide, tryptophan or nine related tryptophan metabolites during pregnancy were associated with risk of development of infant eczema, wheeze, rhinitis or allergic sensitization.

Methods—In the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study, we analysed the associations between maternal plasma levels of nicotinamide, tryptophan and tryptophan metabolites at 26-28 weeks gestation and allergic outcomes collected through interviewer-administered questionnaires at multiple timepoints and skin prick testing to egg, milk, peanut and mites at age 18 months. Multivariate analysis was undertaken adjusting for all metabolites measured, and separately adjusting for relevant demographic and environmental exposures. Analyses were also adjusted for multiple comparisons using the false discovery method.

Results—Tryptophan metabolites were evaluated in 976/1247 (78%) women enrolled in GUSTO. In multivariate analysis including all metabolites, maternal plasma 3-hydrokynurenine was associated with increased allergic sensitization at 18 months (AdjRR 2.6, 95% CI 1.3-5.2 for highest quartile) but the association with nicotinamide was not significant (AdjRR 1.8, 95% CI 0.9-3.6). In analysis adjusting for other exposures, both 3-hydrokynurenine and nicotinamide were associated with increased allergic sensitization (AdjRR 2.0, 95% CI 1.1-3.6 for both metabolites). High maternal plasma nicotinamide was associated with increased infant eczema diagnosis at 6 and 12 months, which was not significant when adjusting for all metabolites measured, but was significant when adjusting for relevant environmental and demographic exposures. Other metabolites measured were not associated with allergic sensitisation or eczema, and maternal tryptophan metabolites were not associated with offspring rhinitis and wheeze.

Conclusions and Clinical Relevance—Maternal tryptophan metabolism during pregnancy may influence the development of allergic sensitization and eczema in infants.

Abstract



Graphic abstract.

Keywords

Nicotinamide; Vitamin B3; Tryptophan metabolism; Kynurenine pathway; Eczema

Introduction

Worldwide, there is a high prevalence of allergic diseases in early life [1]. An estimated 22.7% of Singaporean children develop eczema in the first 2 years of life [2]. The Developmental Origins of Health and Disease (DOHaD) concept hypothesises that early stimuli, starting from preconception, throughout pregnancy and into early life, may contribute to the early onset of allergic diseases by influencing fetal and neonatal immune regulation [3].

Maternal health, diet and lifestyle during pregnancy have been shown to affect risk for major disease outcomes in the offspring, including eczema and allergic diseases [4-7]. Adequate levels of maternal nutrients are important for fetal health, as nutrients essential for the development of the fetal immune system, for instance, can be transferred from the mother to the fetus via the placenta [8,9].

A key nutrient in our diet is vitamin B3 (also known as nicotinamide), the precursor of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, enzymes that are involved in many regulatory processes [10]. Nicotinamide is obtained through diets rich in eggs, nuts, meat, grains and poultry and tryptophan metabolism via

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the kynurenine pathway [11-15]. Although the inflammatory response in allergic diseases is complex, Th2 responses are a major driver. Tryptophan metabolism is key in modulating Th1/Th2 immune responses through production of catabolites and cytokines [16]. For instance, 3-hydroxyanthranilic acid and quinolinic acid can alter Th1 cells [16] and tend to increase Th2 activity. The physiological state of an individual affects the tryptophan metabolism rate, where conversion of tryptophan to nicotinamide has been reported to increase from mid to late pregnancy [13]. Microbiome and tryptophan metabolites interaction can also play a role in affecting the skin barrier as well as the inflammatory responses [17]. High levels of nicotinamide beyond recommended daily intakes have also been linked to adverse outcomes including oxidative cell damage, alteration of DNA methylation and lower sirtuin 1 activity [18], an enzyme involved in skin barrier integrity [19]. Besides this, a high quartile of plasma tryptophan has been associated with higher risk of development of inflammatory diseases [20-23]. Hence we hypothesised that dysregulation of the tryptophan metabolism pathway and high levels of metabolites may lead to inflammation and allergic disease development.

The Nurses' Health Study 2 in United States reported an increased risk of eczema in women with the highest levels of total and supplemental nicotinamide consumption as compared to the lowest, and those effects were not continuous across the distribution [24]. However, only one study has investigated the association between maternal nicotinamide and allergy in offspring. El-Heis et al. reported that higher maternal plasma levels of nicotinamide and anthranilic acid were associated with a lower risk of eczema development in infants by age of 12 months in the UK Southampton Women's Survey cohort [25], suggesting involvement of metabolites in the tryptophan metabolism pathway in eczema development.

The relationship between maternal tryptophan metabolites on cord blood cytokines has also not been clearly elucidated although cytokines and chemokines present in blood play a role in the inflammatory pathways influencing allergic disease pathogenesis. In this study, we examined associations between maternal plasma concentrations of nicotinamide and related tryptophan metabolites in the tryptophan pathway during pregnancy and the offspring's cord blood immune profile and risk of allergic diseases. We focused on the chemokines, monocyte chemoattractant protein-1 (MCP-1) and monokine induced by gamma interferon (MIG) due to their chemoattractant properties as well as role in affecting the T-helper 1 (Th1) and T-helper 2 (Th2) balance. MCP-1 is a C-C chemokine and a strong monocyte chemotactic factor responsible for recruitment of monocytes, T cells and natural killer cells to inflammation sites [26]. MIG is an indicator of functional interferon gamma (IFN-γ) signalling pathway and bioactivity and is also key in T cell recruitment[27]. To the best of our knowledge, this is the first study examining the influences of maternal nicotinamide and tryptophan metabolites levels in pregnancy and their impact on offspring eczema, wheeze, rhinitis and allergic sensitization. Better understanding of their influences and impact on offspring allergy risk can help elucidate supporting evidence for recommendations during pregnancy to lower the risk of allergy development in the offspring.

Methods

Study design and questionnaires

The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study recruited 1247 healthy pregnant mothers. The detailed methodology for the GUSTO study was described by Soh et al. [28]. Trained interviewers gathered information on demographic characteristics, family history of allergy, social data and lifestyle factors. We used the modified ISAAC modified questionnaire at ages 3, 6, 9, 12, 15 and 18 months for evaluation of offspring allergic symptoms. Eczema was primarily defined as physician-diagnosed eczema was where the answer to the question: “Has your child ever been diagnosed with eczema?” was ‘yes’. We also used another secondary definition of eczema, defined by having an itchy rash that is coming and going, other than nappy rash and which affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, on the cheeks, or around the neck, ears or eyes. Wheeze with use of nebulizers/inhalers was defined by positive responses to the questions: “Has your child ever wheezed?” and “Has your child ever been prescribed with nebulizer/inhaler treatment?”. Rhinitis was defined by a positive response to the question: “Has your child had running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for two or more weeks duration?”. Cumulative allergy outcomes by ages 6, 12 and 18 months were classified as “yes” when a subject answered “yes” by the timepoint. Subjects were classified as “no” if the subject answered “no” at all timepoints. Skin prick testing (SPT) was conducted at 18 months for allergens cow’s milk, egg, peanut and house dust mites, *Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farina* (*Derp f*) (Greer Laboratories, Lenoir, NC, USA) and *Blomia tropicalis* (*Blo t*) (developed in-house) [29]. Maternal dietary intake during pregnancy was assessed at week 26-28 using 24-h recall food diaries. The detailed methodology was described by Chia et al. [30].

Ethical approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group (D/2009/021) and the Centralised Institutional Review Board of SingHealth (2018/2767). The conduct of this study was based on the guidelines in the Declaration of Helsinki. Informed consent was obtained from all participants.

Assessment of maternal plasma metabolite levels as well as cord blood cytokines, chemokines and antibodies

Maternal plasma metabolite levels of N1-methylnicotinamide, nicotinamide, trigonelline, 3-hydroxyanthranilic acid, 3-hydroxykynurenine, anthranilic acid, kynurenic acid, kynurenine, quinolic acid, tryptophan, xanthurenic acid at 26-28 weeks gestation were analysed by tandem mass spectrometry (API 4000, AB Sciex). Cord blood MIG, MCP-1 and IFN-γ levels were assayed in plasma using customised Human ProcartaPlex Panels (Thermo Fisher) which uses Luminex xMAP technology in combination with DropArray bead plates (Curiox Biosystems, Singapore). Interleukin-6 (IL-6) was measured using Single molecule array (SiMoA) assays on the SP-X platform (Quanterix Corp., USA). All values were corrected for plate effects using median centering.

Statistical analysis

All analyses were performed using SPSS for Windows version 26.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics for numerical variables were presented as mean (SD) when normality and homogeneity assumptions were satisfied, otherwise median (IQR) were presented and n (%) for categorical variables. Maternal plasma metabolite levels were divided into quartiles. A multivariate analysis was conducted where all metabolites were included in the model, noting that this reduced statistical power as not all participants had complete data. Predictors for infant eczema, rash, wheeze with use of nebulizers/inhalers and rhinitis by ages 6, 12 and 18 months and allergic sensitization at 18 months were assessed using univariate and multivariate Poisson regression. Further multivariate analyses were performed for each metabolite with $p<0.05$ in univariate Poisson regression, adjusting for demographic and relevant covariates. Differences in the cord blood immune profile between subjects with each allergic outcome and controls were evaluated using Mann Whitney U test. Pearson correlation coefficient was used to investigate the relationship between plasma nicotinamide and 3-hydroxykynurenine concentration with the mother's dietary, vitamin and supplement intake. Type 1 error for multiple comparisons were adjusted using Benjamini-Hochberg procedure with false discovery rate at 0.20.

Results

Population characteristics

We included in the study 976 mother-offspring pairs with maternal metabolites analysed. The mothers' median age at delivery was 30.9 years (IQR 27.4-34.6, Table 1). The majority of mothers were of Chinese ethnicity [532 (54.5%)], had at least 12 years of education [668 (69.4%)] and no history of allergy [580 (61.1%)]. Of the 976 infants; 507 (51.9%) were male and by 6, 12 and 18 months, 74 (9.1%), 107 (14.0%) and 157 (22.5%) developed eczema respectively; 197 (23.8%), 253 (32.3%) and 374 (50.1%) developed itchy rash respectively; 26 (3.1%), 69 (9.6%) and 97 (14.6%) developed wheeze with the use of nebulizers/inhalers respectively; 230 (27.5%), 329 (42.6%) and 390 (52.6%) developed rhinitis respectively and 105 (14.0%) developed allergic sensitization at 18 months.

Analysis of maternal plasma metabolites at 26-28 weeks pregnancy with allergic outcomes

In multivariate analysis where all metabolites were included (Tables 2-6), the highest quartile of 3-hydroxykynurenine was associated with increased risk of allergic sensitization at 18 months (AdjRR=2.6, 95% CI=1.3-5.2, p=0.008, Table 6) after adjusting for confounders. There was a trend of increasing risk of allergic sensitization development at 18 months with increasing quartiles of 3-hydroxykynurenine (p=0.003). There were no associations between metabolites and eczema, rash, wheeze with the use of nebulizers/inhalers and rhinitis outcomes in the first 18 months of life (Tables 2-5).

As inclusion of all metabolites in the same model reduced statistical power, we conducted further analysis by conducting multivariate analysis for each metabolite which was significant in univariate analyses. In multivariate analysis, the highest quartile of nicotinamide remained associated with increased risks of eczema development by ages 6 and 12 months (AdjRR=2.6, 95% CI=1.2-5.7, p=0.013 and AdjRR=2.3, 95% CI=1.2-4.3,

p=0.011, respectively) as compared to the lowest quartile. There was a trend of increasing risks of eczema development by ages 6 and 12 months with increasing quartiles of nicotinamide (p-trend=0.008 and 0.016, respectively, Supplementary Table 1 and 2). There were no associations between 3-hydroxyanthranilic acid, 3-hydroxykynurenine and tryptophan with eczema in the first 18 months of life after adjusting for confounders.

The highest quartile of nicotinamide remained significantly associated with increased risks of itchy rash development by age 6 months (AdjRR=1.8, 95% CI=1.2-2.7, p=0.008) as compared to the lowest quartile. There was a trend of increasing risk of itchy rash development by ages 6 and 12 months with increasing quartiles of nicotinamide (p-trend=0.003 and 0.011, respectively, Supplementary Table 3 and 4). There were no associations between trigonelline, 3-hydroxykynurenine and kynurenic acid with rash in the first 18 months of life after adjusting for confounders.

There were no associations between N1-methylnicotinamide and trigonelline with wheeze in the first 18 months of life after adjusting for confounders (Supplementary Table 5 and 6). There were also no associations between nicotinamide and kynurenic acid with rhinitis in the first 18 months of life after adjusting for confounders (Supplementary Table 7 and 8).

The highest quartile of nicotinamide and 3-hydroxykynurenine remained significantly associated with increased risks of allergic sensitization development at age 18 months (AdjRR=2.0, 95% CI=1.1-3.6, p=0.027 and AdjRR=2.0, 95% CI=1.1-3.6, p=0.022 respectively) as compared to the lowest quartile. There was a trend of increasing risks of allergic sensitization development at age 18 months with increasing quartiles of nicotinamide and 3-hydrokynurenine (p-trend=0.043 and 0.008, respectively, Supplementary Table 9 and 10).

Differences in cord blood cytokines and chemokines between subjects with allergic conditions and controls

We next analysed differences in MCP-1, MIG, IL-6 and IFN-γ levels in offspring with allergic conditions and controls. MIG levels were higher in offspring with wheeze by 18 months as compared to controls [median (IQR) 14.29 (10.08-20.2) vs 12.30 (7.89-17.32) pg/ml, p=0.016, Supplementary Table 13]. Similarly, MIG levels were higher in offspring with rhinitis by 12 [median 13.51 (9.02-18.70) vs 12.01 (7.81-16.61) pg/ml, p=0.006, Supplementary Table 14] and 18 months [median 13.45 (9.01-18.80) vs 12.00 (7.86-16.15) pg/ml, p=0.002]. In addition, MCP-1 levels were higher in offspring with rhinitis by 12 [median 108.14 (73.31-162.46) vs 93.23 (65.54-131.0) pg/ml, p=0.007) and 18 months [median 104.76 (74.44-152.18) vs 92.35 (64.33-136.91) pg/ml, p=0.014]. There were no significant differences in cord blood levels of these cytokines and chemokines between offspring with eczema, itchy rash and allergic sensitization with controls (Supplementary Tables 11, 12 and 15).

Correlation analysis between nicotinamide and 3-hydroxykynurenine with diet during pregnancy

To examine if nicotinamide and 3-hydroxykynurenine were associated with the mother's dietary, vitamin and supplement intake, we carried out correlation analyses between these

metabolites and each of the 38 food groups recorded in the 24-hour dietary recall, vitamin and supplement intake. There were positive correlations between nicotinamide levels and healthy red meat (r=0.075, p=0.020), porridge (r=0.095, p=0.003) and supplements (r=0.097, p=0.004, Supplementary Table 16). Positive correlation between 3-hydroxykynurenine and legumes (r=0.092, p=0.004) was observed.

Discussion

In this study, we observed that highest quartile of maternal plasma levels of 3-hydroxykynurenine at 26-28 weeks pregnancy was associated with increased risk of allergic sensitization at age 18 months as compared to the lowest quartile. In addition, high maternal plasma nicotinamide at 26-28 weeks pregnancy was associated with increased risks of eczema development in the offspring by 6 and 12 months of life. Increasing quartiles of nicotinamide were associated with increased risks of eczema by 6 and 12 months as well as allergic sensitization at 18 months. No associations were observed between tryptophan metabolites and risks of wheeze and rhinitis development in the offspring.

These results suggest that 3-hydroxykynurenine and nicotinamide may influence the risk of early life allergic sensitization and eczema, possibly through Th2 immune differentiation. Conversely, most instances of wheeze and rhinitis in early life are recognized to be non-allergic and result from viral infections in early life [31,32]; in the COAST cohort of high-risk children with a parental history of respiratory allergy, 90% of wheezing illness in the first 3 years of life were attributed to viral causes [33]. The GUSTO cohort also reported higher viral detection from children within a month of a rhinitis episode [34]. We also observed higher levels of MIG in the cord blood of offspring with wheeze and rhinitis compared to controls and cord blood MCP-1 levels were higher in offspring with rhinitis. These results suggest that MIG and MCP-1 may affect susceptibility to respiratory viral infections. Preterm infants with respiratory distress syndrome and/or chronic lung disease were reported to have higher cord blood MCP-1 levels as compared to controls [35]. Higher MCP-1 and MIG levels were also associated with higher mortality in patients with severe acute respiratory syndrome [36].

Tryptophan, a source of 3-hydrokynurenine and nicotinamide, is broken down by the enzymes tryptophan 2,3-dioxygenase in the liver and rate-limiting indolamine 2,3-dioxygenase-1 and -2 in other parts of the body to kynurenine derivatives (Figure 1) [13,37]. Perturbation to the tryptophan-kynurenine pathway is linked to inflammation and immune activation [38]. Tryptophan metabolites have been shown to preferentially induce Th1 cell apoptosis as compared to Th2 [16]. 3-hydroxykynurenine is a known generator of reactive oxidative species which can induce cell apoptosis [39]. Excess reactive oxidative species production and decreased antioxidant response are linked to higher susceptibility to allergic sensitization through altering dendritic cell functions and inducing Th2 differentiation [40]. 3-hydrokynurenine also reduced Th1 cytokine IFN-γ and promoted Th2 cytokine IL-4 and IL-13 production in stimulated invariant natural killer T cells [41].

In the tryptophan-kynurenine pathway, 3-hydrokynurenine is catabolised to 3-hydroxyanthranilic acid by kynureninase. We postulate that 3-hydrokynurenine may be an important point and bottleneck in the tryptophan metabolism pathway where high levels

of 3-hydrokynurenine drives the generation of 3-hydroxyanthranilic acid which is quickly broken down to subsequent metabolites and nicotinamide.

Nicotinamide has been shown to reduce Th1 cytokines such as IL-12, hence promoting a Th2 immune response [42]. While there are studies suggesting that topical nicotinamide application may protect against eczema through reduced transepidermal water loss [43], anti-inflammatory and antioxidant actions [44], effects of systemic nicotinamide on eczema development remain non-conclusive. Nicotinamide deficiency is commonly associated with pellagra, characterized by an eczema skin reaction [45], while data from the Nurses' Health Study 2 suggested that women in the highest quartile of total and supplemental nicotinamide consumption had higher risks of eczema [24]. Hence we postulate that the relationship between nicotinamide levels and allergic outcomes may be non-linear and follow a U-shaped curve. While small increases in nicotinamide levels may protect against eczema development and allergic sensitization, deficiency or excessive nicotinamide may exhibit an opposite effect. In our study, we observed that the highest quartile of maternal plasma nicotinamide was linked to higher risk of eczema development in early life, opposite to that reported by the UK Southampton Women Survey; this could be due to the higher plasma nicotinamide levels in the GUSTO study compared to the UK study [25] (median 184.0 nmol/l versus 140.2 nmol/l). This may also indicate dietary or microbiome differences or a greater dysregulation of the tryptophan metabolism pathway, resulting in higher levels of nicotinamide.

Besides Th2 immune responses ("inside out" hypothesis), skin barrier dysfunction has recently been proposed to lead to eczema development and allergic sensitization ("outside in" hypothesis). Filaggrin gene mutations may lead to compromised skin epithelium that results in eczema and allergic sensitization and subsequently result in the induction of Th2 responses [46,47] However, this may only explain the occurrence of eczema in a subset of patients as Cai et al. detected filaggrin gene mutations in 25% of Singaporean Chinese with eczema [48]. Filaggrin mutations were also not associated with allergic sensitization at age 4 years in the PIAMA cohort [49]. Hence it is likely that immune dysregulation plays a greater role in the pathogenesis of eczema and allergic sensitization.

A main source of nicotinamide in diet is meat, which is supported by the correlation between nicotinamide and red meat in this study. Evidence from other studies have demonstrated links between maternal consumption of meat and eczema development in offspring; for example, the Osaka Maternal and Child Health Study showed that higher maternal consumption of meat was associated with higher risk of eczema in infants aged 3 – 4 months [50]. Nicotinamide can also be obtained from supplements and we too observed a positive correlation between nicotinamide and use of supplement in our study. The positive association between 3-hydroxykynurenine and legumes is likely because legumes contain high amounts of tryptophan which is subsequently broken down to 3-hydroxykynurenine [51].

Strengths of the study include the objective assessment of maternal plasma metabolites and cord blood cytokines and chemokines profile by laboratory analysis. In addition, there was regular follow up of the offspring with interviewer administered questionnaires at multiple timepoints in early life. A limitation of the study is that the maternal metabolite

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and cord blood cytokine measurements were only undertaken at single time points and that a limited panel is tested. Hence, further investigation into the role of 3-hydroxykynurenine and nicotinamide in offspring eczema development and allergic sensitization is needed. A further limitation is that the dietary information obtained by 24-hour recall may not be representative of the general diet of the mothers during pregnancy; multiple exploratory analyses of the dietary data were undertaken and the weak associations found need to be interpreted with caution.

Conclusion

In this study, we demonstrated that high maternal plasma concentrations of nicotinamide in late gestation were associated with a higher risk of eczema development and allergic sensitization in infants in early life. Our results highlighted the importance of the tryptophan metabolism pathway on infant eczema development and allergic sensitization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abbreviations

GUSTO	Growing Up in Singapore Towards healthy Outcomes

IFN-γ	Interferon gamma
IL-6	Interleukin 6
MCP-1	Monocyte chemoattractant protein-1
MIG	Monokine induced by gamma interferon
Th	T-helper

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Key messages

- High maternal late pregnancy plasma 3-hydroxykynurenine and nicotinamide concentrations were associated with offspring allergic sensitization.
- High maternal late pregnancy plasma nicotinamide concentrations were also associated with offspring infantile eczema.
- Maternal plasma tryptophan metabolite concentrations were not associated with offspring rhinitis and wheeze.

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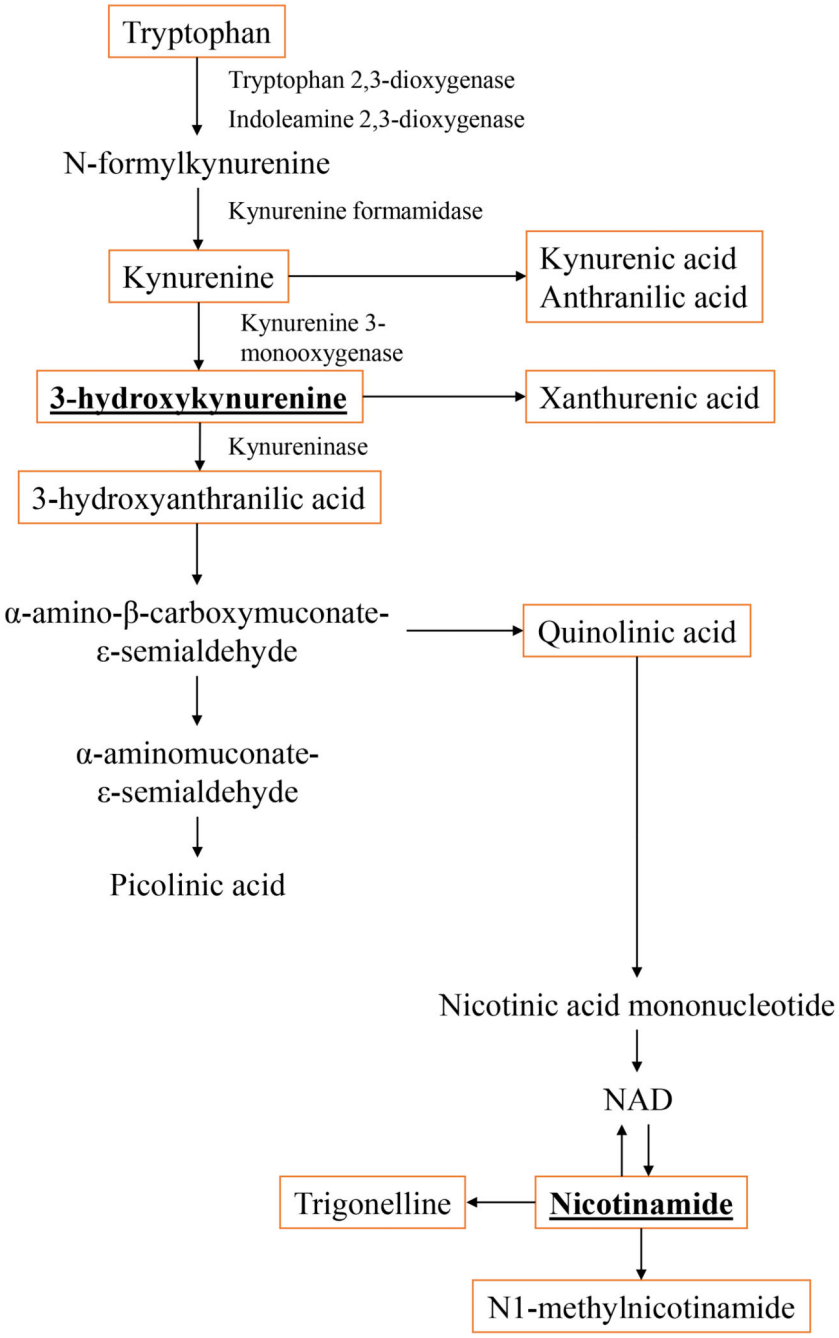

Figure 1.

Metabolism of tryptophan via the kynurenine pathway. Metabolites highlighted in orange boxes were analysed in this study. High levels of maternal plasma 3-hydroxykynurenine and nicotinamide were associated with increased risks of allergic sensitization and eczema in infants.

Table 1
Characteristics of the study population

	n	Median (IQR), Mean (SD) or *n* (%)
Maternal age at child's birth (years)	976	30.9(27.4-34.6)
Ethnicity	976	
Chinese	532	54.5%
Indian	183	18.8%
Malay	261	26.7%
Education	963	
≥ 12 years of education	668	69.4%
< 12 years of education	295	30.6%
Maternal history of allergy (eczema, rhinitis and/or asthma)	949	
Yes	369	38.9%
No	580	61.1%
Parity	976	
Parous	562	57.6%
Nulliparous	414	42.4%
Household income	913	
0-999	17	1.9%
1000-1999	127	13.9%
2000-3999	282	30.9%
4000-5999	231	25.3%
>=6000	256	28.0%
Smoking status	971	
Current or ever smoker	130	13.4%
Non smoker	841	86.6%
Caesarean delivery	976	
Yes	288	29.5%
No	688	70.5%
Supplements	879	2(1-3)
Maternal serum metabolite concentrations in late pregnancy		
N1-methylnicotinamide (nmol/L)	976	257.50(195.00-329.00)
Nicotinamide (nmol/L)	976	184.00 (124.00-252.00)
Trigonelline (μmol/L)	976	0.14(0.09-0.27)
3-Hydroxyanthranilic acid (nmol/L)	976	69.75(59.70-82.20)
3-Hydroxykynurenine (nmol/L)	976	46.15(36.73-58.90)
Anthranilic acid (nmol/L)	976	10.60(8.78-12.70)
Kynurenic acid (nmol/L)	976	16.90(13.70-21.60)
Kynurenine (μmol/L)	976	1.02 (0.87-1.16)
Quinolinic acid (nmol/L)	976	369.00 (316.00-431.75)
Tryptophan (μmol/L)	976	46.60(41.00-51.88)
Xanthurenic acid (nmol/L)	976	10.30(6.80-15.08)

	n	Median (IQR), Mean (SD) or *n* (%)
Infant Sex	976	
Male	507	51.9%
Female	469	48.1%
Birth weight (kg)	930	3.1 (0.4)
Use of antibiotics	727	
Yes	335	46.1%
No	392	53.9%
Type of milk feed	910	
Mainly formula feed	407	44.7%
Mixed feeding	394	43.3%
Mainly breastfeeding	109	12.0%
Eczema by 6 months	817	
Yes	74	9.1%
No	743	90.9%
Eczema by 12 months	765	
Yes	107	14.0%
No	658	86.0%
Eczema by 18 months	699	
Yes	157	22.5%
No	542	77.5%
Itchy rash by 6 months	829	
Yes	197	23.8%
No	632	76.2%
Itchy rash by 12 months	783	
Yes	253	32.3%
No	530	67.7%
Itchy rash by 18 months	747	
Yes	374	50.1%
No	373	49.9%
Wheeze by 6 months	828	
Yes	26	3.1%
No	802	96.9%
Wheeze by 12 months	720	
Yes	69	9.6%
No	651	90.4%
Wheeze by 18 months	666	
Yes	97	14.6%
No	569	85.4%
Rhinitis by 6 months	835	
Yes	230	27.5%
No	605	72.5%
Rhinitis by 12 months	772	

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	n	Median (IQR), Mean (SD) or *n* (%)
Yes	329	42.6%
No	443	57.4%
Rhinitis by 18 months	742	
Yes	390	52.6%
No	352	47.4%
SPT by 18 months	749	
Positive	105	14.0%
Negative	644	86.0%

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Table 2

Multivariate associations between all maternal plasma metabolites and eczema development by 6, 12 and 18 months in the offspring.

	6 months (n=782)		12 months (n=732)		18 months (n=667)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
N1-methylnicotinamide		*0.102*		*0.167*		*0.423*
Lowest	1.0		1.0		1.0	
2nd	0.88(0.44 – 1.76)	0.714	1.1(0.6 – 2.1)	0.704	1.1(0.7 – 1.8)	0.708
3rd	0.71(0.34 – 1.50)	0.370	0.92(0.49 – 1.73)	0.788	0.82(0.48 – 1.39)	0.451
Highest	0.58(0.25 – 1.34)	0.202	0.65(0.32 – 1.34)	0.245	0.88(0.50 – 1.57)	0.672
Nicotinamide		*0.004*		*0.019*		*0.136*
Lowest	1.0		1.0		1.0	
2nd	1.8(0.8 – 4.2)	0.192	1.7(0.9 – 3.4)	0.123	1.1(0.7 – 1.9)	0.683
3rd	2.3(1.0 – 5.4)	0.055	1.6(0.8 – 3.3)	0.177	1.1(0.6 – 1.9)	0.735
Highest	3.2(1.4 – 7.6)	0.008	2.2(1.1 – 4.6)	0.029	1.4(0.8 – 2.4)	0.244
Trigonelline		*0.858*		*0.352*		*0.649*
Lowest	1.0		1.0		1.0	
2nd	0.81(0.41 – 1.59)	0.532	0.92(0.53 – 1.61)	0.781	0.95(0.59 – 1.50)	0.812
3rd	0.80(0.40 – 1.58)	0.522	0.83(0.47 – 1.48)	0.525	1.0(0.6 – 1.6)	0.948
Highest	0.94(0.44 – 2.02)	0.880	0.82(0.43 – 1.58)	0.548	0.86(0.50 – 1.45)	0.565
3-Hydroxyanthranilic acid		*0.512*		*0.264*		*0.032*
Lowest	1.0		1.0		1.0	
2nd	1.2(0.5 – 2.5)	0.702	0.93(0.48 – 1.81)	0.822	1.2(0.7 – 2.0)	0.504
3rd	1.3(0.6 – 2.8)	0.489	1.6(0.8 – 3.0)	0.160	1.6(0.9 – 2.8)	0.086
Highest	1.4(0.6 – 3.4)	0.432	1.4(0.7 – 3.0)	0.358	1.9(1.1 – 3.6)	0.031
3-Hydroxykynurenine		*0.023*		*0.135*		*0.387*
Lowest	1.0		1.0		1.0	
2nd	1.8(0.8 – 4.0)	0.167	1.7(0.9 – 3.3)	0.094	1.6(1.0 – 2.7)	0.068
3rd	2.7(1.2 – 6.1)	0.017	1.9(0.9 – 3.8)	0.076	1.5(0.9 – 2.7)	0.118
Highest	2.9(1.2 – 7.0)	0.020	1.8(0.9 – 3.9)	0.123	1.5(0.8 – 2.7)	0.192
Anthranilic acid		*0.305*		*0.098*		*0.152*
Lowest	1.0		1.0		1.0	

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	6 months (n=782)		12 months (n=732)		18 months (n=667)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
2nd	0.71(0.36 – 1.41)	0.334	0.72(0.40 – 1.31)	0.285	0.72(0.45 – 1.16)	0.178
3rd	0.70(0.34 – 1.44)	0.333	0.71(0.38 – 1.31)	0.272	0.72(0.44 – 1.17)	0.179
Highest	0.72(0.33 – 1.56)	0.402	0.56(0.28 – 1.12)	0.103	0.68(0.39 – 1.16)	0.155
Kynurenic acid		*0.682*		*0.699*		*0.361*
Lowest	1.0		1.0		1.0	
2nd	1.2(0.5 – 2.6)	0.734	1.2(0.6 – 2.4)	0.628	0.94(0.55 – 1.64)	0.838
3rd	1.0(0.4 – 2.7)	0.956	1.2(0.6 – 2.8)	0.590	0.84(0.45 – 1.59)	0.595
Highest	0.81(0.27 – 2.42)	0.702	1.2(0.5 – 3.0)	0.702	0.79(0.38 – 1.64)	0.524
Kynurenine		*0.080*		*0.067*		*0.338*
Lowest	1.0		1.0		1.0	
2nd	0.87(0.42 – 1.80)	0.713	1.0(0.6 – 1.9)	0.891	0.96(0.58 – 1.58)	0.878
3rd	0.72(0.32 – 1.62)	0.423	0.87(0.44 – 1.70)	0.675	0.84(0.48 – 1.46)	0.530
Highest	0.36(0.13 – 1.01)	0.053	0.44(0.19 – 1.04)	0.061	0.71(0.36 – 1.40)	0.321
Quinolinic acid		*0.362*		*0.643*		*0.597*
Lowest	1.0		1.0		1.0	
2nd	0.59(0.27 – 1.29)	0.187	0.73(0.39 – 1.38)	0.329	0.63(0.38 – 1.07)	0.086
3rd	0.77(0.34 – 1.72)	0.518	0.76(0.39 – 1.49)	0.418	0.77(0.45 – 1.33)	0.352
Highest	1.3(0.6 – 3.2)	0.520	1.1(0.5 – 2.4)	0.741	0.70(0.37 – 1.33)	0.280
Tryptophan		*0.475*		*0.179*		*0.153*
Lowest	1.0		1.0		1.0	
2nd	1.2(0.5 – 2.6)	0.711	1.3(0.7 – 2.5)	0.468	1.6(0.9 – 2.8)	0.085
3rd	1.2(0.5 – 2.7)	0.642	1.5(0.8 – 3.0)	0.235	1.6(0.9 – 2.8)	0.107
Highest	1.3(0.6 – 3.0)	0.547	1.5(0.7 – 3.0)	0.325	1.6(0.9 – 3.0)	0.115
Xanthurenic acid		*0.680*		*0.602*		*0.894*
Lowest	1.0		1.0		1.0	
2nd	0.47(0.21 – 1.08)	0.075	0.62(0.31 – 1.26)	0.187	0.93(0.54 – 1.61)	0.803
3rd	0.60(0.25 – 1.44)	0.257	0.76(0.36 – 1.61)	0.474	0.91(0.49 – 1.71)	0.771
Highest	0.72(0.27 – 1.94)	0.514	0.70(0.29 – 1.66)	0.413	1.0(0.5 – 2.0)	0.997

RR = 1.0 is the reference category.
p values of trend of metabolites in italics

Clin Exp Allergy. Author manuscript; available in PMC 2022 April 01.

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Benjamini-Hochberg correction with false discovery rate at 0.20 and n=132 was applied. No associations were significant after correction.

* Adjusted for ethnicity, maternal education level, maternal history of allergy, parity, infant sex and type of milk feed

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Table 3

Multivariate associations between all maternal plasma metabolites and itchy rash by 6, 12 and 18 months in the offspring.

	6 months (n=792)		12 months (n=747)		18 months (n=707)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
N1-methylnicotinamide		*0.359*		*0.685*		*0.643*
Lowest	1.0		1.0		1.0	
2nd	0.88(0.57 – 1.36)	0.563	0.98(0.67 – 1.45)	0.926	1.1(0.8 – 1.5)	0.489
3rd	0.81(0.51 – 1.28)	0.369	0.92(0.62 – 1.38)	0.684	0.93(0.66 – 1.30)	0.660
Highest	0.79(0.48 – 1.30)	0.358	0.92(0.59 – 1.42)	0.693	0.94(0.65 – 1.36)	0.757
Nicotinamide		*0.002*		*0.011*		*0.042*
Lowest	1.0		1.0		1.0	
2nd	1.1(0.7 – 1.8)	0.605	0.94(0.63 – 1.43)	0.782	1.0(0.7 – 1.4)	0.985
3rd	1.5(0.9 – 2.4)	0.102	1.3(0.9 – 1.9)	0.199	1.1(0.8 – 1.5)	0.567
Highest	2.0(1.2 – 3.2)	0.006	1.6(1.0 – 2.4)	0.037	1.4(1.0 – 1.9)	0.074
Trigonelline		*0.433*		*0.684*		*0.587*
Lowest	1.0		1.0		1.0	
2nd	1.1(0.7 – 1.6)	0.725	1.2(0.8 – 1.7)	0.373	1.1(0.8 – 1.5)	0.627
3rd	1.0(0.7 – 1.5)	0.982	1.1(0.7 – 1.5)	0.784	1.1(0.8 – 1.5)	0.416
Highest	0.82(0.51 – 1.32)	0.414	0.94(0.62 – 1.43)	0.774	1.1(0.8 – 1.5)	0.577
3-Hydroxyanthranilic acid		*0.352*		*0.768*		*0.540*
Lowest	1.0		1.0		1.0	
2nd	0.79(0.50 – 1.24)	0.299	0.87(0.59 – 1.29)	0.490	0.94(0.68 – 1.29)	0.703
3rd	0.93(0.59 – 1.47)	0.761	0.99(0.66 – 1.49)	0.973	0.98(0.70 – 1.37)	0.913
Highest	0.72(0.43 – 1.23)	0.229	0.89(0.56 – 1.41)	0.606	0.89(0.61 – 1.30)	0.540
3-Hydroxykynurenine		*0.044*		*0.147*		*0.752*
Lowest	1.0		1.0		1.0	
2nd	1.4(0.9 – 2.2)	0.193	1.2(0.8 – 1.8)	0.308	1.1(0.8 – 1.5)	0.641
3rd	1.8(1.1 – 2.8)	0.017	1.5(1.0 – 2.2)	0.072	1.2(0.8 – 1.7)	0.330
Highest	1.6(1.0 – 2.7)	0.071	1.4(0.9 – 2.2)	0.190	1.1(0.8 – 1.6)	0.614
Anthranilic acid		*0.780*		*0.738*		*0.395*
Lowest	1.0		1.0		1.0	

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	6 months (n=792)		12 months (n=747)		18 months (n=707)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
2nd	0.86(0.55 – 1.32)	0.484	0.85(0.58 – 1.25)	0.407	0.76(0.55 – 1.04)	0.085
3rd	0.79(0.50 – 1.27)	0.333	0.76(0.50 – 1.14)	0.182	0.84(0.61 – 1.16)	0.302
Highest	0.95(0.59 – 1.52)	0.818	0.96(0.64 – 1.45)	0.849	0.85(0.60 – 1.19)	0.334
Kynurenic acid		*0.413*		*0.844*		*0.851*
Lowest	1.0		1.0		1.0	
2nd	1.1(0.7 – 1.8)	0.670	1.0(0.7 – 1.6)	0.849	0.86(0.61 – 1.22)	0.395
3rd	1.4(0.8 – 2.5)	0.209	1.2(0.7 – 1.9)	0.487	0.97(0.66 – 1.42)	0.861
Highest	1.4(0.7 – 2.6)	0.336	1.1(0.6 – 1.9)	0.728	0.99(0.63 – 1.55)	0.965
Kynurenine		*0.435*		*0.438*		*0.562*
Lowest	1.0		1.0		1.0	
2nd	0.92(0.58 – 1.45)	0.711	0.95(0.64 – 1.42)	0.803	0.86(0.62 – 1.19)	0.361
3rd	0.99(0.60 – 1.62)	0.951	1.0(0.7 – 1.6)	0.921	0.87(0.61 – 1.26)	0.466
Highest	0.75(0.41 – 1.36)	0.346	0.78(0.46 – 1.32)	0.348	0.83(0.54 – 1.28)	0.403
Quinolinic acid		*0.292*		*0.536*		*0.339*
Lowest	1.0		1.0		1.0	
2nd	0.93(0.58 – 1.48)	0.755	0.83(0.55 – 1.25)	0.368	0.89(0.64 – 1.25)	0.509
3rd	1.1(0.7 – 1.9)	0.682	0.97(0.62 – 1.52)	0.908	1.2(0.9 – 1.8)	0.269
Highest	1.3(0.7 – 2.2)	0.435	1.1(0.7 – 1.8)	0.743	1.1(0.7 – 1.7)	0.649
Tryptophan		*0.208*		*0.363*		*0.921*
Lowest	1.0		1.0		1.0	
2nd	1.0(0.6 – 1.5)	0.983	1.0(0.7 – 1.5)	0.992	1.2(0.9 – 1.7)	0.241
3rd	0.84(0.53 – 1.36)	0.480	0.94(0.62 – 1.42)	0.758	1.1(0.8 – 1.6)	0.571
Highest	0.74(0.45 – 1.22)	0.238	0.82(0.53 – 1.28)	0.381	1.1(0.7 – 1.5)	0.695
Xanthurenic acid		*0.776*		*0.881*		*0.709*
Lowest	1.0		1.0		1.0	
2nd	0.97(0.61 – 1.55)	0.896	0.93(0.62 – 1.40)	0.735	1.1(0.8 – 1.5)	0.609
3rd	0.83(0.49 – 1.42)	0.500	0.88(0.55 – 1.40)	0.578	1.0(0.7 – 1.5)	0.989
Highest	0.91(0.49 – 1.68)	0.759	0.95(0.55 – 1.64)	0.849	1.1(0.7 – 1.7)	0.762

RR = 1.0 is the reference category.
p values of trend of metabolites in italics

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Benjamini-Hochberg correction with false discovery rate at 0.20 and n=132 was applied. No associations were significant after correction.

* Adjusted for ethnicity, maternal history of allergy, parity and type of milk feed

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Table 4

Multivariate associations between all maternal plasma metabolites and wheeze by 6, 12 and 18 months in the offspring.

	6 months (n=694)		12 months (n=667)		18 months (n=646)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
N1-methylnicotinamide		*0.748*		*0.688*		*0.952*
Lowest	1.0		1.0		1.0	
2nd	0.37(0.08 – 1.78)	0.215	0.81(0.35 – 1.87)	0.627	0.92(0.46 – 1.84)	0.804
3rd	0.22(0.04 – 1.23)	0.085	0.60(0.25 – 1.41)	0.241	0.93(0.46 – 1.88)	0.839
Highest	0.88(0.18 – 4.27)	0.870	0.89(0.35 – 2.29)	0.813	0.94(0.42 – 2.11)	0.884
Nicotinamide		*0.783*		*0.459*		*0.398*
Lowest	1.0		1.0		1.0	
2nd	1.3(0.3 – 5.2)	0.748	0.70(0.33 – 1.53)	0.373	0.69(0.35 – 1.35)	0.279
3rd	0.48(0.09 – 2.66)	0.400	0.86(0.40 – 1.84)	0.691	0.68(0.35 – 1.33)	0.263
Highest	0.69(0.12 – 3.86)	0.670	0.69(0.28 – 1.68)	0.412	0.74(0.36 – 1.52)	0.411
Trigonelline		*0.161*		*0.417*		*0.251*
Lowest	1.0		1.0		1.0	
2nd	1.9(0.5 – 7.8)	0.350	0.91(0.43 – 1.93)	0.803	0.80(0.43 – 1.49)	0.482
3rd	1.0(0.2 – 4.4)	0.965	0.90(0.41 – 1.96)	0.793	0.79(0.41 – 1.52)	0.482
Highest	0.13(0.01 – 1.67)	0.118	0.53(0.20 – 1.39)	0.197	0.55(0.25 – 1.20)	0.131
3-Hydroxyanthranilic acid		*0.799*		*0.533*		*0.612*
Lowest	1.0		1.0		1.0	
2nd	1.5(0.3 – 7.7)	0.608	1.8(0.8 – 4.2)	0.162	1.7(0.8 – 3.5)	0.132
3rd	0.56(0.08 – 4.14)	0.572	1.1(0.4 – 2.9)	0.904	0.83(0.36 – 1.92)	0.663
Highest	2.6(0.4 – 16.6)	0.323	2.0(0.7 – 5.7)	0.212	1.7(0.7 – 4.0)	0.229
3-Hydroxykynurenine		*0.365*		*0.369*		*0.091*
Lowest	1.0		1.0		1.0	
2nd	1.4(0.3 – 7.3)	0.705	0.88(0.36 – 2.14)	0.783	1.1(0.5 – 2.2)	0.891
3rd	1.1(0.2 – 6.9)	0.938	1.6(0.7 – 3.8)	0.254	1.5(0.7 – 3.2)	0.243
Highest	2.1(0.4 – 11.7)	0.409	1.4(0.5 – 3.8)	0.467	1.9(0.9 – 4.2)	0.113
Anthranilic acid		*0.616*		*0.781*		*0.778*
Lowest	1.0		1.0		1.0	

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	6 months (n=694)		12 months (n=667)		18 months (n=646)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
2nd	1.1(0.3 – 4.7)	0.857	0.88(0.39 – 1.98)	0.755	0.81(0.39 – 1.66)	0.562
3rd	0.43(0.07 – 2.79)	0.378	1.0(0.4 – 2.4)	0.991	1.2(0.6 – 2.5)	0.556
Highest	0.57(0.11 – 3.00)	0.503	1.0(0.4 – 2.5)	0.924	0.97(0.46 – 2.06)	0.932
Kynurenic acid		*0.530*		*0.864*		*0.866*
Lowest	1.0		1.0		1.0	
2nd	0.43(0.06 – 2.96)	0.388	0.63(0.26 – 1.55)	0.317	0.68(0.32 – 1.45)	0.314
3rd	0.52(0.07 – 4.19)	0.542	0.53(0.19 – 1.44)	0.211	0.60(0.27 – 1.34)	0.212
Highest	1.2(0.2 – 9.9)	0.841	1.2(0.4 – 3.2)	0.781	0.91(0.38 – 2.19)	0.826
Kynurenine		*0.883*		*0.179*		*0.403*
Lowest	1.0		1.0		1.0	
2nd	0.83(0.14 – 4.87)	0.840	0.53(0.22 – 1.29)	0.161	0.75(0.36 – 1.55)	0.432
3rd	0.95(0.16 – 5.64)	0.956	0.51(0.21 – 1.28)	0.154	0.63(0.29 – 1.37)	0.244
Highest	1.3(0.1 – 11.4)	0.824	0.38(0.12 – 1.16)	0.089	0.66(0.26 – 1.65)	0.372
Quinolinic acid		*0.809*		*0.890*		*0.481*
Lowest	1.0		1.0		1.0	
2nd	0.37(0.06 – 2.40)	0.296	0.51(0.20 – 1.31)	0.163	0.75(0.36 – 1.56)	0.439
3rd	0.87(0.16 – 4.79)	0.872	0.99(0.40 – 2.44)	0.986	0.98(0.46 – 2.11)	0.963
Highest	0.44(0.06 – 3.46)	0.436	0.84(0.28 – 2.51)	0.753	0.69(0.27 – 1.77)	0.443
Tryptophan		*0.349*		*0.666*		*0.154*
Lowest	1.0		1.0		1.0	
2nd	1.1(0.2 – 6.2)	0.891	1.5(0.7 – 3.3)	0.340	1.3(0.6 – 2.6)	0.528
3rd	3.1(0.6 – 16.0)	0.181	1.5(0.6 – 3.7)	0.350	1.5(0.7 – 3.3)	0.281
Highest	2.0(0.3 – 12.5)	0.473	1.4(0.5 – 3.8)	0.532	2.0(0.9 – 4.5)	0.103
Xanthurenic acid		*0.779*		*0.886*		*0.904*
Lowest	1.0		1.0		1.0	
2nd	4.4(0.6 – 31.1)	0.142	1.8(0.8 – 4.4)	0.182	1.7(0.8 – 3.8)	0.158
3rd	4.0(0.5 – 32.2)	0.197	2.1(0.8 – 5.4)	0.146	2.0(0.8 – 4.7)	0.117
Highest	0.98(0.07 – 13.48)	0.985	0.90(0.27 – 3.03)	0.870	1.0(0.4 – 2.9)	0.934

RR = 1.0 is the reference category.
p values of trend of metabolites in italics

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Benjamini-Hochberg correction with false discovery rate at 0.20 and n=132 was applied. No associations were significant after correction.

* Adjusted for maternal age, ethnicity, antibiotic used and infant sex

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Table 5

Multivariate associations between all maternal plasma metabolites and rhinitis by 6, 12 and 18 months in the offspring.

	6 months (n=675)		12 months (n=659)		18 months (n=651)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
N1-methylnicotinamide		*0.305*		*0.561*		*0.943*
Lowest	1.0		1.0		1.0	
2nd	1.0(0.6 – 1.6)	0.989	1.1(0.8 – 1.6)	0.562	1.2(0.8 – 1.6)	0.396
3rd	1.1(0.7 – 1.7)	0.741	1.1(0.7 – 1.6)	0.679	1.1(0.8 – 1.5)	0.721
Highest	1.3(0.8 – 2.1)	0.356	1.2(0.7 – 1.8)	0.522	1.1(0.7 – 1.6)	0.749
Nicotinamide		*0.198*		*0.091*		*0.209*
Lowest	1.0		1.0		1.0	
2nd	0.83(0.55 – 1.24)	0.358	0.83(0.58 – 1.18)	0.303	0.83(0.60 – 1.15)	0.272
3rd	0.74(0.48 – 1.15)	0.182	0.82(0.57 – 1.18)	0.278	0.88(0.63 – 1.23)	0.456
Highest	0.77(0.48 – 1.23)	0.277	0.70(0.47 – 1.05)	0.088	0.76(0.52 – 1.11)	0.155
Trigonelline		*0.539*		*0.962*		*0.691*
Lowest	1.0		1.0		1.0	
2nd	1.0(0.7 – 1.5)	0.992	0.92(0.65 – 1.31)	0.650	0.92(0.67 – 1.27)	0.620
3rd	1.1(0.7 – 1.7)	0.725	1.0(0.7 – 1.5)	0.847	0.92(0.66 – 1.29)	0.640
Highest	1.2(0.8 – 2.0)	0.376	1.0(0.7 – 1.5)	0.980	0.97(0.68 – 1.39)	0.858
3-Hydroxyanthranilic acid		*0.562*		*0.796*		*0.791*
Lowest	1.0		1.0		1.0	
2nd	1.0(0.7 – 1.5)	0.987	1.1(0.8 – 1.6)	0.560	1.0(0.8 – 1.5)	0.785
3rd	0.83(0.51 – 1.34)	0.445	1.1(0.7 – 1.6)	0.725	0.97(0.67 – 1.41)	0.890
Highest	0.90(0.53 – 1.55)	0.706	1.1(0.7 – 1.7)	0.802	0.95(0.63 – 1.43)	0.797
3-Hydroxykynurenine		*0.529*		*0.757*		*0.357*
Lowest	1.0		1.0		1.0	
2nd	1.0(0.7 – 1.6)	0.923	1.0(0.7 – 1.5)	0.995	1.0(0.7 – 1.4)	0.933
3rd	1.0(0.6 – 1.6)	0.990	0.99(0.66 – 1.48)	0.955	1.1(0.8 – 1.6)	0.641
Highest	1.3(0.8 – 2.1)	0.357	1.2(0.8 – 1.8)	0.505	1.2(0.8 – 1.9)	0.294
Anthranilic acid		*0.872*		*0.092*		*0.276*
Lowest	1.0		1.0		1.0	

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	6 months (n=675)		12 months (n=659)		18 months (n=651)	
	RR (95% CI)	**p-value** *	**RR (95% CI)**	**p-value** *	**RR (95% CI)**	**p-value** *
2nd	0.97(0.63 – 1.50)	0.893	0.81(0.57 – 1.15)	0.242	0.94(0.68 – 1.29)	0.688
3rd	0.94(0.58 – 1.51)	0.789	0.69(0.47 – 1.02)	0.061	0.81(0.57 – 1.16)	0.250
Highest	1.1(0.7 – 1.8)	0.692	0.74(0.50 – 1.11)	0.143	0.85(0.59 – 1.23)	0.402
Kynurenic acid		*0.574*		*0.530*		*0.495*
Lowest	1.0		1.0		1.0	
2nd	0.76(0.47 – 1.22)	0.253	0.87(0.59 – 1.30)	0.506	0.93(0.64 – 1.33)	0.679
3rd	0.65(0.37 – 1.15)	0.142	0.80(0.50 – 1.27)	0.343	0.84(0.55 – 1.28)	0.420
Highest	1.2(0.7 – 2.3)	0.483	1.2(0.7 – 1.9)	0.585	1.2(0.7 – 1.9)	0.554
Kynurenine		*0.917*		*0.803*		*0.707*
Lowest	1.0		1.0		1.0	
2nd	0.87(0.54 – 1.42)	0.584	0.94(0.64 – 1.40)	0.763	0.84(0.59 – 1.20)	0.335
3rd	1.1(0.7 – 1.8)	0.763	0.95(0.63 – 1.45)	0.824	0.90(0.61 – 1.32)	0.576
Highest	0.88(0.48 – 1.64)	0.694	0.94(0.57 – 1.55)	0.822	0.91(0.57 – 1.45)	0.681
Quinolinic acid		*0.690*		*0.860*		*0.845*
Lowest	1.0		1.0		1.0	
2nd	0.82(0.51 – 1.31)	0.400	0.87(0.59 – 1.29)	0.492	0.88(0.61 – 1.26)	0.492
3rd	0.99(0.60 – 1.62)	0.952	0.99(0.65 – 1.51)	0.973	1.0(0.7 – 1.5)	0.831
Highest	0.84(0.47 – 1.50)	0.552	0.89(0.54 – 1.47)	0.645	0.90(0.57 – 1.43)	0.664
Tryptophan		*0.704*		*0.242*		*0.761*
Lowest	1.0		1.0		1.0	
2nd	1.1(0.7 – 1.7)	0.621	1.0(0.7 – 1.5)	0.904	0.97(0.69 – 1.37)	0.858
3rd	0.96(0.60 – 1.53)	0.847	1.3(0.9 – 1.9)	0.232	1.2(0.8 – 1.7)	0.339
Highest	0.97(0.58 – 1.65)	0.922	1.2(0.8 – 1.9)	0.360	1.0(0.7 – 1.5)	0.991
Xanthurenic acid		*0.699*		*0.488*		*0.641*
Lowest	1.0		1.0		1.0	
2nd	1.1(0.7 – 1.7)	0.781	1.1(0.8 – 1.7)	0.517	1.0(0.7 – 1.5)	0.791
3rd	1.0(0.6 – 1.8)	0.911	1.1(0.7 – 1.7)	0.787	1.1(0.7 – 1.7)	0.670
Highest	0.86(0.45 – 1.62)	0.635	0.86(0.50 – 1.48)	0.591	0.90(0.55 – 1.47)	0.667

RR = 1.0 is the reference category.
p values of trend of metabolites in italics

Clin Exp Allergy. Author manuscript; available in PMC 2022 April 01.

Benjamini-Hochberg correction with false discovery rate at 0.20 and n=132 was applied. No associations were significant after correction.

* Adjusted for maternal age, ethnicity, maternal history of allergy, antibiotic used and infant sex

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Table 6

Multivariate associations between all maternal plasma metabolites and positive SPT at 18 months in the offspring.

	18 months (n=716)	
	RR (95% CI)	**p-value** *
N1-methylnicotinamide		*0.878*
Lowest	1.0	
2nd	0.97(0.53 – 1.76)	0.913
3rd	0.85(0.44 – 1.64)	0.630
Highest	1.1(0.6 – 2.2)	0.715
Nicotinamide		*0.089*
Lowest	1.0	
2nd	1.6(0.8 – 3.0)	0.155
3rd	1.6(0.8 – 3.1)	0.162
Highest	1.8(0.9 – 3.6)	0.088
Trigonelline		*0.477*
Lowest	1.0	
2nd	1.1(0.7 – 2.0)	0.633
3rd	1.1(0.6 – 1.9)	0.801
Highest	0.81(0.41 – 1.58)	0.530
3-Hydroxyanthranilic acid		*0.183*
Lowest	1.0	
2nd	0.80(0.43 – 1.48)	0.477
3rd	0.96(0.52 – 1.75)	0.880
Highest	0.58(0.28 – 1.21)	0.147
3-Hydroxykynurenine		***0.003***
Lowest	1.0	
2nd	1.2(0.6 – 2.3)	0.625
3rd	2.0(1.0 – 3.7)	0.042
Highest	2.6(1.3 – 5.2)	**0.008**
Anthranilic acid		*0.713*
Lowest	1.0	

	18 months (n=716)	
	RR (95% CI)	**p-value** *
2nd	1.0(0.6 – 1.8)	0.990
3rd	0.61(0.31 – 1.19)	0.149
Highest	0.95(0.50 – 1.8)	0.873
Kynurenic acid		*0.774*
Lowest	1.0	
2nd	1.0(0.5 – 2.0)	0.921
3rd	1.0(0.5 – 2.2)	0.921
Highest	1.2(0.5 – 2.8)	0.693
Kynurenine		*0.936*
Lowest	1.0	
2nd	1.3(0.7 – 2.3)	0.448
3rd	1.1(0.5 – 2.2)	0.792
Highest	1.1(0.5 – 2.6)	0.744
Quinolinic acid		*0.270*
Lowest	1.0	
2nd	0.72(0.39 – 1.31)	0.276
3rd	0.68(0.35 – 1.32)	0.250
Highest	0.61(0.29 – 1.31)	0.207
Tryptophan		*0.895*
Lowest	1.0	
2nd	1.0(0.6 – 1.9)	0.882
3rd	1.0(0.5 – 1.9)	0.985
Highest	1.0(0.5 – 2.1)	0.905
Xanthurenic acid		*0.718*
Lowest	1.0	
2nd	0.89(0.45 – 1.78)	0.749
3rd	1.3(0.6 – 2.7)	0.502
Highest	1.1(0.4 – 2.6)	0.870

RR = 1.0 is the reference category.
p values of trend of metabolites in italics

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Significant p-value after Benjamini-Hochberg correction with false discovery rate at 0.20 and n=44 in bold

* Adjusted for ethnicity, smoking status, type of milk feed, caesarean delivery and infant sex