Received: 6 January 2023 | Revised: 25 January 2023 | Accepted: 27 January 2023

DOI: 10.1111/pai.13917

ORIGINAL ARTICLE

WILEY

Diet-associated vertically transferred metabolites and risk of asthma, allergy, eczema, and infections in early childhood

Nicklas Brustad[1] | Alessandra Olarini[2] | Min Kim[1] | Liang Chen[1] | Mina Ali[1] | Tingting Wang[1] | Arieh S. Cohen[3] | Madeleine Ernst[3] | David Hougaard[3] | Ann-Marie Schoos[1] | Jakob Stokholm[1,4] | Klaus Bønnelykke[1] | Jessica Lasky-Su[5] | Morten A. Rasmussen[1,2] | Bo Chawes[1]

[1]COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

[2]Section of Chemometrics and Analytical Technologies, Department of Food Science, University of Copenhagen, Copenhagen, Denmark

[3]Section for Clinical Mass Spectrometry, Danish Center for Neonatal Screening, Department of Congenital Disorders, Statens Serum Institute, Copenhagen, Denmark

[4]Department of Pediatrics, Naestved Hospital, Naestved, Denmark

[5]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence
Bo Chawes, COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark.
Email: chawes@copsac.com

Funding information
European Research Council, Grant/Award Number: 946228; National Heart and Lung Institute, Grant/Award Number: R01HL123915, R01HL141826 and R01HL155742; Region Hovedstaden, Grant/Award Number: A7187; COPSAC; The Lundbeck Foundation, Grant/Award Number: R16-A1694; Ministry of Health, Grant/Award Number: 903516; Danish Council for Strategic Research, Grant/Award Number: 0603-00280B

Editor: Ömer Kalayci

Abstract

Background: Evidence suggests maternal pregnancy dietary intake and nutrition in the early postnatal period to be of importance for the newborn child's health. However, studies investigating diet-related metabolites transferred from mother to child on disease risk in childhood are lacking. We sought to investigate the influence of vertically transferred metabolites on risk of atopic diseases and infections during preschool age.

Methods: In the Danish population-based $COPSAC_{2010}$ mother–child cohort, information on 10 diet-related vertically transferred metabolites from metabolomics profiles of dried blood spots (DBS) at age 2–3 days was analyzed in relation to the risk of childhood asthma, allergy, eczema, and infections using principal component and single metabolite analyses.

Results: In 678 children with DBS measurements, a coffee-related metabolite profile reflected by principal component 1 was inversely associated with risk of asthma (odds ratio (95% CI) 0.78 (0.64; 0.95), $p = .014$) and eczema at age 6 years (0.79 (0.65; 0.97), $p = .022$). Furthermore, increasing stachydrine (fruit-related), 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (fish-related), and ergothioneine (fruit-, green vegetables-, and fish-related) levels were all significantly associated with reduced risks of infections at age 0–3 years ($p < .05$).

Abbreviations: CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate; COPSAC, Copenhagen Prospective Studies on Asthma in Childhood; DBS, dried blood spots; FFQ, food frequency questionnaire; LC–MS, liquid chromatography–mass spectrometry; RCT, randomized clinical trial.

Jessica Lasky-Su, Morten A. Rasmussen and Bo Chawes are shared senior authors

This article is commented on by Beatriz Moya, et al. To view this editorial comment visit https://onlinelibrary.wiley.com/doi/10.1111/pai.13947.

Conclusion: This study demonstrates associations between pregnancy diet-related vertically transferred metabolites measured in children in early life and risk of atopic diseases and infections in childhood. The specific metabolites associated with a reduced disease risk in children may contribute to the characterization of a healthy nutritional profile in pregnancy using a metabolomics-based unbiased tool for predicting childhood health.

KEYWORDS
asthma, COPSAC, eczema, infections, metabolomics

1 | INTRODUCTION

An association between maternal dietary intake during pregnancy and the newborn child's health has been proposed from several observational studies.[1,2] In particular, pregnancy supplementation regimes have emphasized this mother–child link by demonstrating protective effects on the child's risk of developing asthma and infections from different micronutrients.[3–5] These effects are mainly hypothesized to be explained by optimizing the nutrient supply during the rapid growth period of the fetus where the organs and the immune system develop and mature, which has also been referred to as the first window of opportunity.[6] In addition, the following early postnatal period also referred to as the neonatal window of opportunity is now considered another critical time frame in a children's life for lifelong health and disease susceptibility. During this period, environmental factors such as nutritional intake seem highly important for immune and tissue maturation, which could influence the risk of later immune-mediated disease development.[6]

We have recently shown in the Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$) mother–child cohort that a total of 10 diet-related metabolites were transferred longitudinally from the mothers at week 24 of pregnancy to the children at birth (Pearson's correlation; $R > .3$), comprising a group of lipids, amino acids, and xenobiotics.[7] For most of these metabolites, the levels tracked until school age, suggesting long-term dietary habits. However, the potential effects on childhood health from metabolites reflecting maternal dietary intake during both the prenatal and postnatal periods are unknown. Therefore, we sought to investigate the relationship between 10 diet-related vertically transferred metabolites both as a principal component score and individually and the child's risk of developing atopic diseases and infections during preschool age in the $COPSAC_{2010}$ cohort. Finally, we sought to investigate the relationship between maternal dietary intake through a food frequency questionnaire and metabolite levels and the risk of diseases.

Key Message

This study identifies specific vertically transferred diet-associated metabolites, which are associated with risk of atopic diseases and infections in early life. The identification of associated metabolites with risk of disease may contribute to developing a healthy nutritional profile in pregnancy through a metabolomics-based unbiased approach.

2 | METHODS

2.1 | Study population

The Danish population-based $COPSAC_{2010}$ mother–child cohort has previously been described in detail including participant baseline characteristics and the enrollment procedure. In brief, 736 pregnant mothers were included at pregnancy week 24 and their children were followed longitudinally in the COPSAC clinic until age 6 years with 12 scheduled visits in addition to acute care visits focusing predominantly on infections and atopic diseases.[8–10] The women participated in a 2×2 factorial designed double-blinded RCT to receive either fish oil 2.4 g (55% eicosapentaenoic acid (EPA) and 37% docosahexaenoic (DHA)) of n-3 LCPUFA or placebo capsules NCT00798226.[3] Additionally, 623 women were included in a high-dose (2800 IU/day) versus standard-dose (400 IU/day) vitamin D (cholecalciferol) RCT NCT00856947.[10] The study was approved by the Danish Ethics Committee (H-B-2008-093) and the Danish Data Protection Agency (2008-41-2599).

2.2 | Metabolomics profiling

We collected information on metabolites from dried blood spot (DBS) samples routinely collected in Denmark from the baby's heel 2–3 days after birth as part of the national newborn screening program. A separate application to Statens Serum Institute was required and approved before obtaining biomaterial from the DBS samples for metabolomics profiling. The samples were stored at −20°C at Statens Serum Institute. The sample preparation and metabolomics profiling using liquid chromatography–mass spectrometry (LC–MS) have previously been described in detail.[7,11] Further information on metabolomics profiling is provided in the Data S1.

2.3 | Diet-related metabolites

We previously identified 10 diet-related vertically transferred metabolites between mother and child in the DBS samples:

N,N,N-trimethyl-5-aminovalerate, tryptophan betaine, stachydrine, paraxanthine, ergothioneine, homostachydrine, homoarginine, paraxanthine, caffeine, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF).[7]

2.4 | Food frequency questionnaire

Maternal dietary intake during pregnancy was obtained through a validated semiquantitative food frequency questionnaire (FFQ), which was filled out by the mothers at pregnancy week 24 covering the preceding 4 weeks.[12] The FFQ consisted of 360 items of food and beverages, which were divided into 43 different groups.

2.5 | Clinical outcomes

Persistent wheeze/asthma at age 0–6 years was diagnosed according to a previously validated algorithm[13] requiring: (1) recurrent wheeze, (2) typical asthma symptoms, (3) need for short-acting inhaled beta$_2$-agonist, and (4) response to a 3-month trial of inhaled corticosteroids with relapse upon cessation. The diagnosis "persistent wheeze" was used until the age of 3 years and "asthma" thereafter. T2-high asthma was characterized by having asthma at age 6 years and allergic sensitization against inhaled allergens or blood eosinophil count $>0.3\times10^{-9}$/L.

Allergic sensitization at age 6 years was assessed by skin prick tests (ALK-Abelló) and specific-IgE blood measurements (ImmunoCAP, Thermo Fischer Scientific) defined as a skin reaction ≥3 mm or any specific-IgE measurement ≥0.35 kU$_A$/L against a panel of food and inhaled allergens, including grass, birch, mugwort, cat, dog, horse, house dust mites, molds, egg, cow milk, wheat, and peanut.

Eczema at age 0–6 years was diagnosed according to the criteria of Hanifin and Rajka and required three of four major criteria (pruritus, typical morphologic features and distribution, chronic dermatitis, and personal or family history of atopy) and at least three of 23 minor criteria.

Number of infections were diagnosed from acute visits and daily diaries during age 0–3 years and included pneumonia, tonsilitis, otitis media, gastroenteritis, and croup. All infections were diagnosed or verified by the COPSAC physicians.

2.6 | Statistical analyses

Information on metabolite preprocessing, quality control, and correlation analyses has been described in detail previously.[7] In this follow-up analysis, we performed a principal component analysis (PCA) capturing the overall trend of the 10 vertically transferred metabolites visualized by a PCA biplot where units of change are standard deviations. We then analyzed potential associations between the principal component 1 (PC1) and the clinical outcomes. Furthermore, we analyzed the association between each diet-related metabolite and the clinical outcomes using logistic regression for asthma, allergic sensitization and eczema, and Quasi-Poisson for risk of infections. We also analyzed potential associations between the 10 vertically transferred metabolites and 10 related food groups from the pregnancy FFQ using a linear regression model and analyzed the association between the food groups and clinical outcomes. Using this approach, we could compare the predictiveness of maternal FFQ and child DBS metabolite measurements on childhood disease risk, respectively. Analyses were adjusted for covariates that were considered as potential confounders, which were pregnancy fish oil (2.4 g n-3 long-chain polyunsaturated fatty acids)[3] or high-dose vitamin D supplementation (2800 IU/day),[4] sex, social circumstances, smoking during pregnancy, gestational age, birthweight, delivery method, hospitalization at birth, antibiotics during pregnancy, maternal asthma, birth season, maternal age, maternal BMI, breastfeeding days, or siblings at home. All metabolite levels were log-transformed and scaled. Analyses are presented as crude unless stated otherwise and performed using R (version 4.1.1) with a p-value $<.05$ indicative of significance.

3 | RESULTS

In the COPSAC$_{2010}$ cohort, 678 (97%) of the 700 children had available metabolomics profiles from DBS samples at age 2–3 days where 348 (51%) of them were boys.

3.1 | Diet-related DBS metabolite score versus clinical outcomes

Primary outcomes (asthma, sensitization, and eczema at age 6 years): The PC1 score of the diet-related metabolites explaining 19.5% of the variation across the 10 diet-related metabolites was mainly driven by an increase in the coffee-related metabolites paraxanthine and caffeine (Figure 1). An increased PC1 was associated with a decreased risk of asthma at age 6 years: odds ratio (OR) (95% CI) 0.78 (0.64; 0.95), $p = .014$ ($n = 629$), which was significant in the adjusted analysis: 0.77 (0.60; 0.98), $p = .032$. Similarly, an increased PC1 was associated with a decreased risk of eczema at age 6 years: 0.79 (0.65; 0.97), $p = .022$ ($n = 631$) but not in the adjusted analysis: 0.84 (0.66; 1.06), $p = .140$. There was no significant association between PC1 and risk of allergic sensitization (Table 1).

Secondary outcomes (infections at age 0–3 years, persistent wheeze, and eczema at age 3 years and T2-high and T2-low asthma at age 6 years): An increased PC1 score was associated with an increased risk of infections in the adjusted analysis: adjusted incidence rate ratio (aIRR) 1.06 (1.00; 1.11) $p = .034$. There were no significant associations with T2-high or T2-low asthma at age 6 years although both estimates went in the same direction as asthma and showed a trend of reduced risk of T2-high asthma: aOR = 0.70 (0.47; 1.05) $p = .080$ (Table 1). There were no associations with persistent wheeze or eczema at age 3 years ($p > .05$).

3.2 | Individual diet-related DBS metabolites versus clinical outcomes

Higher paraxanthine levels (coffee intake biomarker in our FFQ data) were associated with a decreased risk of asthma at age 6 years both crude: OR 0.70 (0.54; 0.91), $p = .007$ and adjusted: 0.69 (0.50; 0.95), $p = .022$. Furthermore, higher caffeine (coffee intake biomarker) levels showed similar associations with both asthma: 0.71 (0.53; 0.94) $p = .017$ and eczema: 0.73 (0.55; 0.97) $p = .027$ at age 6 years, which remained significant for asthma after adjustments: 0.67 (0.48; 0.94), $p = .021$, but not eczema. There was no association between any of the metabolites and risk of sensitization at age 6 years ($p > .05$; Figure 2).

Higher CMPF (fish intake biomarker) levels were associated with a reduced risk of persistent wheeze at age 3 years, higher tryptophane betaine (nuts intake biomarker) and stachydrine (fruit intake biomarker) levels were associated with a reduced risk of eczema at age 3 years, higher paraxanthine (coffee intake biomarker) and homoarginine levels were associated with a reduced risk of T2-high asthma and higher homostachydrine (whole grain intake biomarker) levels were associated with an increased risk of T2-low asthma at age 6 years (Figure 3). After adjustments, only the association between stachydrine and eczema at age 3 years remained significant: 0.74 (0.58; 0.95), $p = .017$.

Finally, higher levels of three diet-related metabolites were associated with an overall reduced risk of infections by age 3 years: stachydrine (fruit intake biomarker): IRR 0.92 (0.87; 0.98) $p = .007$, CMPF (fish intake biomarker): 0.91 (0.85; 0.97) $p = .002$, and ergothioneine (fish intake biomarker): 0.94 (0.88; 0.99) $p = .040$. These metabolites were also associated with specific infections as illustrated in Figure 4. After adjustments, only stachydrine remained significant: 0.93 (0.86; 0.99), $p = .028$. However, after adjustments, paraxanthine and caffeine were both associated with increased risk of infections: 1.08 (1.00; 1.16), $p = .039$ and 1.08 (1.00; 1.15), $p = .043$.

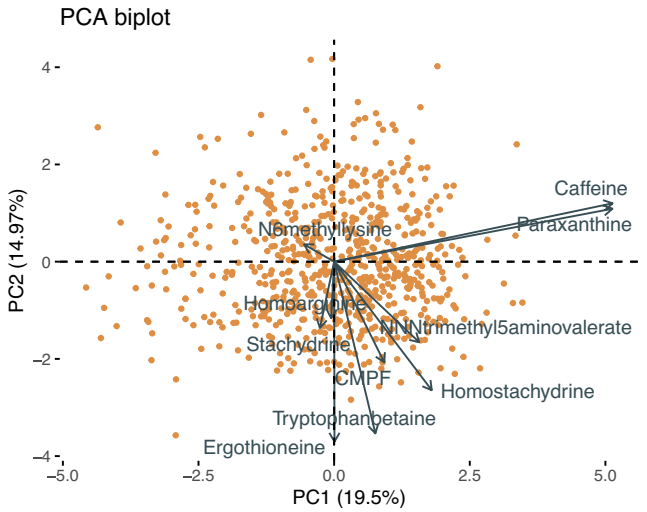


FIGURE 1 Biplot showing the overall trend of the 10 vertically transferred metabolites. CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate.

3.3 | Maternal FFQ versus DBS metabolites and clinical outcomes

In total, 626 (89%) of the 700 children had mothers with available FFQ data from pregnancy week 24. First, our analyses of the associations between the 10 dietary groups from the FFQ and DBS metabolite levels confirmed that paraxanthine and caffeine were strongly related to coffee intake and CMPF to fish intake as expected. We also found that ergothioneine and stachydrine, which were associated with risk of infections, were related to fish, green vegetables, and fruit intake, respectively (Table S1). When analyzing the associations between the 10 individual FFQ food groups and

TABLE 1 Associations between principal component score 1 (PC1) of vertically transferred diet-related metabolites and clinical outcomes of the children.

	Number of children (*n*)	Crude estimate (95% CI) *p*-value	Adjusted estimate (95% CI) *p*-value
Primary outcomes			
Asthma at age 6 years	629	OR: 0.78 (0.64; 0.95) $p = .014$	0.77 (0.60; 0.98) $p = .032$
Sensitization at age 6 years	479	OR: 1.13 (0.98; 1.31) $p = .089$	1.17 (0.99; 1.39) $p = .075$
Eczema at age 6 years	631	OR: 0.79 (0.65; 0.97) $p = .022$	0.84 (0.66; 1.06) $p = .140$
Secondary outcomes			
Persistent wheeze at age 3 years	651	OR: 1.01 (0.87; 1.17) $p = .917$	1.01 (0.86; 1.20) $p = .886$
Eczema at age 3 years	653	OR: 1.00 (0.87; 1.17) $p = .957$	1.11 (0.93; 1.33) $p = .273$
Asthma T2 high at age 6 years	421	OR: 0.73 (0.53; 1.02) $p = .055$	0.69 (0.46; 1.03) $p = .071$
Asthma T2 low at age 6 years	421	OR: 0.80 (0.61;1.08) $p = .131$	0.79 (0.52;1.22) $p = .277$
Infections by age 3 years	640	IRR: 1.03 (0.99;1.08) $p = .163$	1.06 (1.00;1.11) $p = .034$

Note: Adjusted analyses are adjusted for fish oil- and high-dose vitamin D interventions, sex, social circumstances, smoking during pregnancy, gestational age, birthweight, delivery method, hospitalization at birth, antibiotics during pregnancy, maternal asthma, birth season, maternal age, maternal BMI, breastfeeding days, and siblings at home.

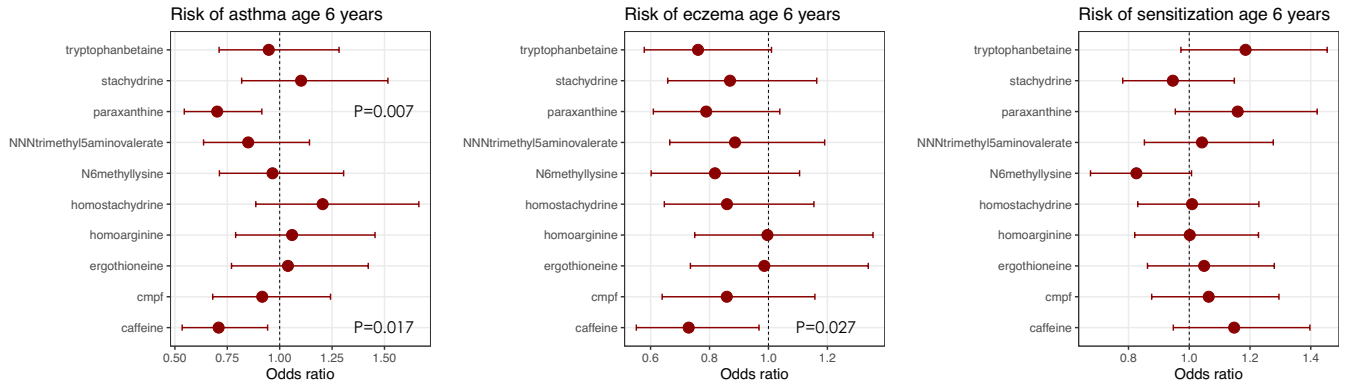
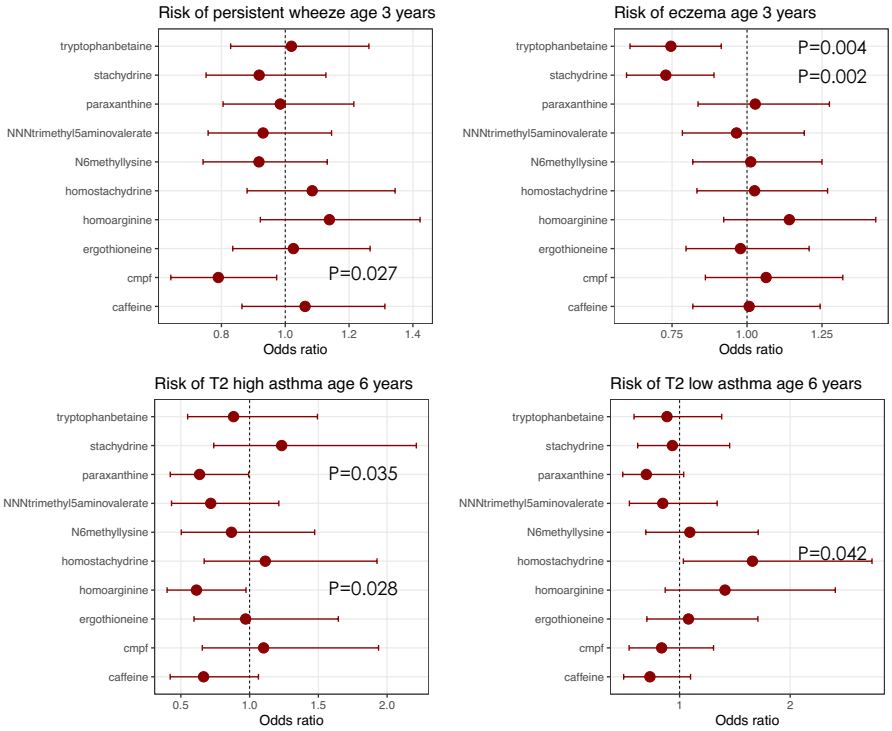


FIGURE 2 Forest plots showing the associations between the 10 vertically transferred metabolites from DBS and risk of asthma, eczema, and sensitization at age 6 years. CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate.

FIGURE 3 Forest plots showing the associations between the 10 vertically transferred metabolites from DBS on secondary clinical outcomes. CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate.



clinical outcomes, we found that low-fat- and high-fat dairy, nuts, fruit juice, and whole grain were related to the primary or secondary outcomes (Table S2).

4 | DISCUSSION

In the Danish $COPSAC_{2010}$ mother–child cohort, we found that a profile consisting of 10 diet-related vertically transferred metabolites derived from DBS samples collected shortly after birth was associated with later risk of atopic diseases and infections in childhood. Specifically, increased levels of coffee-related metabolites were associated with a decreased risk of asthma and eczema at age 6 years. Furthermore, higher ergothioneine levels, which were related to fish-, fruit, and vegetable intake in our study, were associated with an overall decreased risk of infections.

4.1 | Strengths and limitations

The overall strength of our study is the comprehensive amount of clinical data from our population-based cohort where the children have been followed from pregnancy until school age with deep clinical phenotyping allowing for thorough assessment of disease development. In addition, we had detailed information available on dietary intake of the mothers during pregnancy and blood metabolic profiles of the newborns. However, the observational study design with risk of residual lifestyle confounding does not allow for drawing any causal conclusions although we found significant associations both crude and after adjustment for potential confounders. Given the lack of a replication cohort and the explorative design of our study with several association analyses, the risk of chance findings exists from our results when investigating the individual metabolites in relation to clinical outcomes. As many of

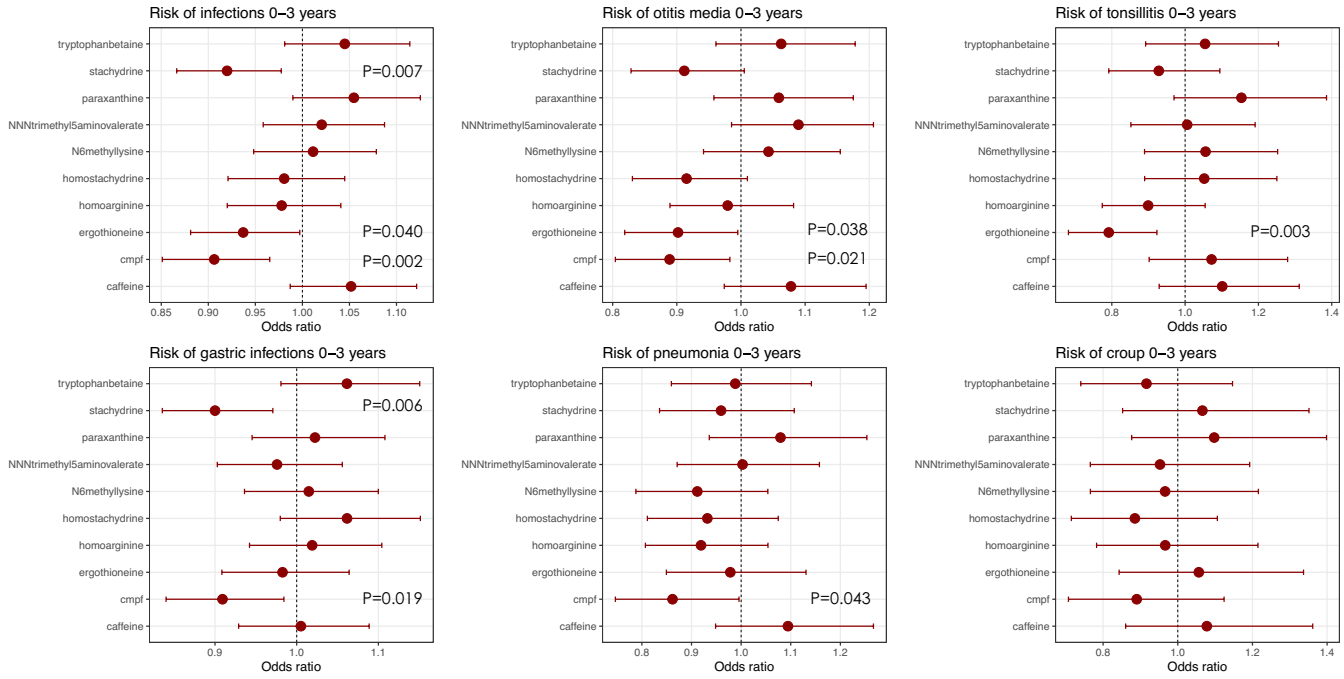


FIGURE 4 Forest plots showing the associations between the 10 vertically transferred metabolites from DBS on infection outcomes. "Risk of infections" is the overall risk of otitis media, tonsillitis, gastric infections, pneumonia, and croup. CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate.

our outcomes and metabolites are somehow correlated, it reduces the number of associations tested and the need for multiple correction adjustments. Although in such case, none of the individual metabolites measured would have a statistically significant association with the primary outcomes.

4.2 | Interpretation

Our finding of an inverse association between maternal coffee intake during pregnancy, reflected by the coffee-related metabolites in newborn DBS measurements, and risk of childhood asthma is in line with previous studies.[14,15] The protective effect might be due to the suggested anti-inflammatory and immunomodulatory abilities of caffeine or the fact that caffeine has shown to improve lung function measurements in children.[16-18] Interestingly, coffee intake as reported by the mothers in the semiquantitative FFQ did not show a significant association with any of the childhood clinical outcomes including asthma, which could reflect the limitations related to the questionnaire such as recall bias, health consciousness bias, and errors in nutrition estimation from food composition diets.[19] This might suggest that the objective measurement of metabolites is a superior unbiased strategy in the assessment of maternal nutritional intake. It could also reflect misclassification arising from the fact that caffeine intake also comes from tea, colas, and chocolate. On the contrary, this approach does not reflect long-term dietary patterns and is more invasive, but the latter should not be considered an issue when utilizing newborn DBS measurements collected as part of the screening for inborn errors of metabolism.

We found that higher ergothioneine levels (reflecting fish, fruit, and green vegetable intake) measured in the newborn DBS samples were associated with an overall decreased risk of infections. This relationship has previously been examined, and it has been speculated whether ergothioneine has a protective effect on risk of infections including coronavirus infectious disease 2019 (COVID-19) due to inhibition of viral replication, but the role in microbial physiology is still poorly understood.[20,21] We also found higher stachydrine and CMPF levels to be associated with an overall decreased risk of infections. Stachydrine was mostly correlated with fruit intake, whereas CMPF is known to be related to fish intake and fish oil supplementation as previously shown in our cohort,[22] which, together with green vegetables, was also confirmed in our analyses. As ergothioneine was also strongly correlated with both maternal fish, fruit, and green vegetables, increased intake of these dietary groups might be essential in a preventive nutritional strategy against risk of childhood infections. Interestingly, we have previously demonstrated in a randomized clinical trial that fish oil supplementation in pregnancy reduced the risk of respiratory infections in the children.[3] Moreover, a maternal diet rich in fruit and vegetables during pregnancy has been shown to be associated with an infant gut microbiome at age 2 months suggested to be protective against infections.[23]

The inverse associations between levels of specific diet-related vertically transferred metabolites measured around birth and risk of atopic diseases and infections in early childhood point toward a modifiable neonatal window of opportunity, where nutritional intake seems highly important for immune-mediated disease development.[6] As we previously demonstrated a tracking phenomenon of these metabolites from pregnancy week 24 until time of DBS

samples, it also points toward a prenatal nutrition-based programing effect.[7] This phenomenon has been investigated in relation to several diseases including asthma, allergy, and bone disorders[24,25] and could be key for promoting childhood health through optimization of maternal nutritional status during pregnancy. Interestingly, and in contrast to our findings, the World Health Organization recommends limited coffee (<300 mg/day) intake during pregnancy due to previous observed associations with increased risk of preterm birth and reduced birthweight.[26] However, this has recently been challenged by a null finding on associations between coffee intake and miscarriages, preterm birth, and birthweight in a large Mendelian randomization study[27] utilizing data from both the UK Biobank (n = 251,058) and ALSPAC (n = 14,541) cohorts, suggesting that the previous observational findings are driven by confounding factors such as smoking and alcohol. Again, this null finding on birthweight and gestational length was also demonstrated in a Danish RCT investigating caffeine supplementation (n = 1207).[28] Further research seems necessary to answer the question whether coffee intake during pregnancy has a protective or harmful effect on childhood health, although our findings point toward a beneficial effect of the coffee-related metabolites on risk of asthma and eczema.

4.3 | Conclusions

This study demonstrates associations between diet-related vertically transferred metabolites measured in early life and later risk of atopic diseases and infections in childhood. Specifically, increased coffee-related metabolites were associated with a decreased risk of asthma and eczema, and increased fruit-, green vegetables-, and fish-related metabolites were associated with an overall decreased risk of infections. These findings indicate that early nutritional intake may affect long-term health through transfer of specific metabolites from mother to child and that a DBS metabolomic-based approach holds promises for developing an unbiased strategy assessing maternal diet during pregnancy important for childhood health.

AUTHOR CONTRIBUTIONS

Nicklas Brustad: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; data curation; supervision. **Alessandra Olarini:** Methodology; investigation; writing – review and editing. **Min Kim:** Writing – review and editing. **Liang Chen:** Writing – review and editing. **Mina Ali:** Writing – review and editing. **Tingting Wang:** Writing – review and editing. **Arieh S. Cohen:** Writing – review and editing. **Madeleine Ernst:** Writing – review and editing. **David Hougaard:** Writing – review and editing. **Ann-Marie Schoos:** Writing – review and editing. **Jakob Stokholm:** Writing – review and editing. **Klaus Bønnelykke:** Writing – review and editing. **Jessica Lasky-Su:** Writing – review and editing; funding acquisition; methodology. **Morten A. Rasmussen:** Methodology; writing – review and editing. **Bo Chawes:** Writing – review and editing; funding acquisition; investigation; methodology; conceptualization; supervision.

ACKNOWLEDGMENTS

We express our deepest gratitude to the children and families of the $COPSAC_{2010}$ cohort study for all their support and commitment. We acknowledge and appreciate the unique efforts of the COPSAC research team.

FUNDING INFORMATION

All funding received by COPSAC is listed on www.copsac.com. The Lundbeck Foundation (Grant no. R16-A1694); The Ministry of Health (Grant no. 903516); Danish Council for Strategic Research (Grant no. 0603-00280B); and The Capital Region Research Foundation have provided core support to the COPSAC research center. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (Grant no. 946228). NB received funding from the Capital Region Research Foundation (Grant no. A7187). JL-S received funding from National Heart, Lung, and Blood Institute grants R01HL123915, R01HL141826, R01HL155742.

CONFLICT OF INTEREST STATEMENT

All authors declare no potential, perceived, or real conflict of interest regarding the content of this manuscript. JL-S is a scientific advisor for Precion, Inc.

ORCID

Nicklas Brustad https://orcid.org/0000-0001-6383-8845
Ann-Marie Schoos https://orcid.org/0000-0002-5827-0885
Jakob Stokholm https://orcid.org/0000-0003-4989-9769
Bo Chawes https://orcid.org/0000-0001-6846-6243

REFERENCES

1. Fleming TP, Watkins AJ, Velazquez MA, et al. Origins of lifetime health around the time of conception: causes and consequences. *Lancet*. 2018;391:1842-1852.
2. Vinding RK, Rago D, Kelly RS, et al. Delayed motor milestones achievement in infancy associates with perturbations of amino acids and lipid metabolic pathways. *Metabolites*. 2020;10:337.
3. Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med*. 2016;375:2530-2539.
4. Wolsk HM, Chawes BL, Litonjua AA, et al. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: a combined analysis of two randomized controlled trials. *PLoS ONE*. 2017;12:e0186657.
5. Brustad N, Yang L, Chawes BL, et al. Fish oil and vitamin D supplementations in pregnancy protect against childhood croup. *J Allergy Clin Immunol Pract*. 2022;11(1):315-321. doi:10.1016/j.jaip.2022.09.027
6. Renz H, Adkins BD, Bartfeld S, et al. The neonatal window of opportunity—early priming for life. *J Allergy Clin Immunol*. 2018;141:1212-1214.
7. Olarini A, Ernst M, Gürdeniz G, et al. Vertical transfer of metabolites detectable from Newborn's dried blood spot samples using UPLC-MS: a Chemometric study. *Metabolites*. 2022;12:94.
8. Bisgaard H, Vissing NH, Carson CG, et al. Deep phenotyping of the unselected COPSAC2010 birth cohort study. *Clin Exp Allergy*. 2013;43:1384-1394.
9. Brustad N, Garland J, Thorsen J, et al. Effect of high-dose vs standard-dose vitamin D supplementation in pregnancy on Bone

mineralization in offspring until age 6 years: a Prespecified secondary analysis of a double-blinded, randomized clinical trial. *JAMA Pediatr*. 2020;174:419-427.
10. Chawes BL, Bønnelykke K, Stokholm J, et al. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. *JAMA*. 2016;315:353-361.
11. Gürdeniz G, Ernst M, Rago D, et al. Neonatal metabolome of caesarean section and risk of childhood asthma. *Eur Respir J*. 2022;59:2102406.
12. Mikkelsen TB, Osler M, Olsen SF. Validity of protein, retinol, folic acid and n-3 fatty acid intakes estimated from the food-frequency questionnaire used in the Danish National Birth Cohort. *Public Health Nutr*. 2006;9:771-778.
13. Bisgaard H, Pipper CB, Bønnelykke K. Endotyping early childhood asthma by quantitative symptom assessment. *J Allergy Clin Immunol*. 2011;127:1155-1164.e2.
14. Huang M, Kelly RS, Chu SH, et al. Maternal metabolome in pregnancy and childhood asthma or recurrent wheeze in the vitamin D antenatal asthma reduction trial. *Metabolites*. 2021;11:65.
15. Liu X, Liew Z, Olsen J, et al. Association of prenatal exposure to acetaminophen and coffee with childhood asthma. *Pharmacoepidemiol Drug Saf*. 2016;25:188-195.
16. Weichelt U, Cay R, Schmitz T, et al. Prevention of hyperoxia-mediated pulmonary inflammation in neonatal rats by caffeine. *Eur Respir J*. 2013;41:966-973.
17. Dekker J, Hooper SB, van Vonderen JJ, Witlox RSGM, Lopriore E, te Pas AB. Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial. *Pediatr Res*. 2017;82:290-296.
18. Kassim Z, Greenough A, Rafferty GF. Effect of caffeine on respiratory muscle strength and lung function in prematurely born, ventilated infants. *Eur J Pediatr*. 2009;168:1491-1495.
19. Guasch-Ferré M, Bhupathiraju SN, Hu FB. Use of metabolomics in improving assessment of dietary intake. *Clin Chem*. 2018;64:82-98.
20. Cheah IK, Halliwell B. Could Ergothioneine aid in the treatment of coronavirus patients? *Antioxidants (Basel)*. 2020;9:E595.
21. Cumming BM, Chinta KC, Reddy VP, Steyn AJC. Role of Ergothioneine in microbial physiology and pathogenesis. *Antioxid Redox Signal*. 2018;28:431-444.
22. Gürdeniz G, Kim M, Brustad N, et al. Furan fatty acid metabolite in newborns predicts risk of asthma. *Allergy*. 2022;78:429-438. doi:10.1111/all.15554
23. Fan H-Y, Tung YT, Yang YCSH, et al. Maternal vegetable and fruit consumption during pregnancy and its effects on infant gut microbiome. *Nutrients*. 2021;13:1559.
24. Palmer AC. Nutritionally mediated programming of the developing immune system. *Adv Nutr*. 2011;2:377-395.
25. Cooper C, Walker-Bone K, Arden N, Dennison E. Novel insights into the pathogenesis of osteoporosis: the role of intrauterine programming. *Rheumatology (Oxford)*. 2000;39:1312-1315.
26. Chen L-W, Wu Y, Neelakantan N, Chong MFF, Pan A, van Dam RM. Maternal caffeine intake during pregnancy is associated with risk of low birth weight: a systematic review and dose-response meta-analysis. *BMC Med*. 2014;12:174.
27. Brito Nunes C, Huang P, Wang G, et al. Mendelian randomization study of maternal coffee consumption and its influence on birthweight, stillbirth, miscarriage, gestational age and pre-term birth. *Int J Epidemiol*. 2023;52:165-177. doi:10.1093/ije/dyac121
28. Bech BH, Obel C, Henriksen TB, Olsen J. Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial. *BMJ*. 2007;334:409.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Brustad N, Olarini A, Kim M, et al. Diet-associated vertically transferred metabolites and risk of asthma, allergy, eczema, and infections in early childhood. *Pediatr Allergy Immunol*. 2023;34:e13917. doi:10.1111/pai.13917