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RESEARCH LETTER

WILEY

Diet diversity in pregnancy and early allergic manifestations in the offspring

To the editor,

The aetiology behind food allergy (FA) and eczema is multifactorial and involves both environmental and genetic factors. Patterns of immune dysregulation are apparent already at birth, and there is emerging evidence that maternal diet in pregnancy may influence neonatal immune responses.[1] Pregnancy is thus considered a window of opportunity for allergy prevention.[2]

Diet diversity in early childhood may reduce the risk of FA[3] and has been implicated in the development of other allergic manifestations but with inconsistent results.[1] So far, little is known about the impact of gestational diet diversity on the fetus, but recently, a healthy diet diversity score was in pregnancy associated with lower risk of any allergy excluding wheeze until the age of 4 years in a U.S. population.[4] The time from conception up to 1 year of age is an especially critical period in the child's immune system development[5] and an important period to study for allergy prevention. Hence, we performed this study with the objective to investigate whether a more diverse diet during pregnancy was associated with decreased risk of offspring eczema, wheeze, FA, asthma and IgE sensitization until 18 months of age.

We used data from the large population-based NorthPop Birth Cohort Study in Northern Sweden, which follows families longitudinally to study the early life environment in relation to subsequent disease and health status.[6] Pregnant women in Västerbotten, Sweden, are invited to participate in the study at their routine ultrasound examination at gestational weeks 17–20, and families are prospectively followed until the child is 7 years old with repeated web-based questionnaires and collection of biological samples. For the present study, dietary data were collected from the pregnant women through a self-reported food frequency questionnaire (FFQ) at around pregnancy week 35. A total of 40 food items were included to calculate a diet diversity (DD) score based on the EAACI (The European Academy of Allergy and Clinical Immunology) taskforce recommendations for measuring diet diversity in the context of allergy[1] and on the present dietary guidelines for pregnant women in Sweden[7] which in summary recommend eating plenty of fruits and vegetables, fibre-rich foods, to consume a certain amount of dairy foods, to eat fish and seafood regularly, and to keep a high variety in the diet. Briefly described, each pregnant woman was assigned 1 point if she had reported to eat the food item 1–3 times/week or more and 0 points if less was reported. For red and white meat, 1 point was assigned if reported to be eaten between 1–3 times/week and 4–6 times/week. If fibre-rich soft bread and fibre-rich crisp bread, respectively, were reported as the most common bread type consumed (ranked as number 1 or 2 of 6 bread types), 1 point was assigned. If a total consumption of ≥2 dL cow's milk or milk replacement per day was reported, 1 point was assigned. Finally, if consumption of unpasteurized cow's milk was reported regularly, 1 point was assigned. The DD score could potentially range from 0 to 40 points for an individual and was adjusted for total energy intake in kcal per day during pregnancy using the residual method. Detailed information about the DD score can be found here: https://zenodo.org/record/7908503#.

The specific outcomes were parentally reported eczema, wheeze, physician-diagnosed asthma, and physician-diagnosed FA in the offspring until 18 months of age. Eczema severity was assessed according to the Patient-Oriented Eczema Measurement (POEM) score. At 18 months of age, the families were invited to an allergy screening. The screening included an inhalation mix (Phadiatop) and a food mix (fx5) with cod, peanut, soybean, cow's milk, egg white, and wheat. Sensitization was defined as positive if IgE levels ≥0.35 PAU (Phadiatop) and ≥0.35 kUA/L (fx5).

Covariates collected through self-reported questionnaires and register data were included as potential confounding factors and analysed using logistic regression and multinomial logistic regression models. In addition to a crude model in which only the energy-adjusted DD score was included as the main exposure, a multivariable model was conducted additionally adjusted for maternal history of allergy, maternal BMI at pregnancy registration, maternal education level, gestational supplementation, delivery mode, and child sex. All statistical analyses were performed using the IBM SPSS Statistics v. 28.0 (IBM, New York, NY, USA), and a *p*-value of .05 was regarded as statistically significant.

A comprehensive and detailed description of the study methods can be found here: https://zenodo.org/record/7908503#.

Participant characteristics of all the 3200 mother–child dyads are presented for all participants and according to quartiles of the DD score in Table 1. Cumulative incidence of eczema was reported for 35.8% of the children, wheeze for 20.2%, physician-diagnosed asthma for 3.9% and physician-diagnosed FA for 5.6%.

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We found a modest but statistically significant association between higher DD score in pregnancy and decreased risk of FA (Odds ratio [OR] per 1 unit increase in multivariable-adjusted DD scores 0.96, 95% confidence interval [CI] 0.92–0.99, *p .022*) (Figure 1A). When participants were classified into quartiles of the DD score, results demonstrated that for children whose mothers reported to eat the most diverse diet (Q4) during pregnancy, there was an association to a significant 43% decreased risk of FA compared with children whose mothers reported the lowest DD score (Q1) (multivariable OR 0.57, 95% CI 0.35–0.94, *p =.027*; Figure 1B). There was an indication of an association between energy-adjusted DD score in pregnancy and a modestly decreased risk of infant wheeze in the crude model (crude OR 0.97, 95% CI 0.96–0.99, *p= .009*), but the association did not remain statistically significant after further adjustments (multivariable OR 0.98, 95% CI 0.96–1.00, *p= .115*; Figure 1A).

Key messages

- Diet diversity in pregnancy was associated with reduced risk of food allergy in early life.
- Diet diversity in pregnancy was not associated with other early allergic manifestations.
- More studies should investigate robust measurements of diet diversity and early allergy risk.

For the other allergic manifestations, there were no clear signs of associations to risk but results per quartile indicated a possible positive relation between the DD score and overall eczema and lower POEM scores (0–7) with crude ORs above 1.0 for quartile 2 and 3,

TABLE 1 Study participant characteristics of 3200 mother–child dyads based on quartiles of the energy-adjusted diet diversity (DD) score in pregnancy and the cumulative incidence of allergic manifestations until the age of 18 months.

	All	DD Q1	DD Q2	DDQ3	DD Q4	Missing
	3200	800	800	800	800	
n		*n* (%)/mean (SD)	*n* (%)/mean (SD)	*n* (%)/mean (SD)	*n* (%)/mean (SD)	*n* (%)
DD score unadjusted (0–40), mean (SD)	20.79 (5.13)	14.91 (3.44)	19.42 (2.74)	22.42 (2.52)	26.42 (2.95)	0 (0)
Early allergic manifestations, *n* (%)						
Eczema	1144 (35.8)	271 (34.0)	290 (36.4)	310 (38.8)	273 (34.2)	8 (0.2)
Clear-to-mild eczema[a]	974 (30.5)	227 (28.4)	247 (31.0)	266 (33.3)	234 (29.3)	
Moderate-to-severe eczema[b]	170 (5.3)	44 (5.5)	43 (5.4)	44 (5.5)	39 (4.9)	
Wheeze	620 (20.2)	170 (22.0)	157 (20.5)	147 (19.0)	146 (19.1)	125 (3.9)
Physician-diagnosed asthma	120 (3.9)	35 (4.5)	24 (3.1)	34 (4.4)	27 (3.5)	125 (3.9)
Physician-diagnosed food allergy	168 (5.6)	50 (6.6)	42 (5.6)	45 (6.0)	31 (4.1)	194 (6.1)
Positive to foodmix at allergy screening 18 months[c]	338 (17.6)	92 (18.7)	94 (18.8)	68 (14.8)	84 (17.9)	
Positive to inhalants at allergy screening 18 months[c]	88 (4.6)	22 (4.5)	24 (4.8)	19 (4.1)	23 (4.9)	
BMI at pregnancy registration, mean (SD)	24.66 (4.42)	25.25 (4.79)	24.93 (4.63)	24.31 (4.24)	24.15 (3.89)	79 (2.5)
Gestational total energy intake in kcal, mean (SD)	2347 (706)	2333 (794)	2348 (727)	2338 (676)	2366 (615)	0 (0)
Gestational age at delivery, mean (SD)	30.9 (4.3)	30.1 (4.5)	30.9 (4.2)	31.0 (4.3)	31.7 (4.2)	0 (0)
Maternal education level, *n* (%)						
University education	2185 (69.7)	445 (56.5)	532 (68.7)	594 (76.0)	614 (77.8)	67 (2.1)
Maternal history of asthma and allergy, *n* (%)						
Food allergy	537 (17.2)	135 (17.2)	134 (17.4)	125 (16.0)	142 (18.0)	75 (2.3)
Asthma	571 (18.3)	169 (21.6)	140 (18.1)	125 (16.0)	137 (17.4)	
Pollen allergy	832 (26.6)	216 (27.6)	200 (25.8)	194 (24.8)	222 (28.2)	
Furred animal allergy	655 (21.0)	175 (22.3)	159 (20.5)	143 (18.3)	178 (22.6)	
Atopic eczema	515 (16.5)	130 (16.6)	127 (16.4)	120 (15.4)	138 (17.5)	

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TABLE 1 (Continued)

	All	DD Q1	DD Q2	DDQ3	DD Q4	Missing
	3200	800	800	800	800	
n		*n* (%)/mean (SD)	*n* (%)/mean (SD)	*n* (%)/mean (SD)	*n* (%)/mean (SD)	*n* (%)
Gestational supplementation, *n* (%)						
Probiotics	66 (2.2)	8 (1.0)	14 (1.8)	18 (2.4)	26 (3.5)	177 (5.5)
Omega-3	647 (21.4)	173 (22.7)	171 (22.5)	147 (19.5)	156 (20.9)	
Vitamin D	353 (11.7)	77 (10.1)	83 (10.9)	91 (12.1)	102 (13.6)	
Multivitamin	1703 (56.3)	399 (52.4)	419 (55.1)	429 (57.0)	456 (61.0)	
Folic acid	1158 (38.3)	290 (38.1)	306 (40.2)	276 (36.7)	286 (38.2)	
Gestational exercise min/week, *n* (%)						
No exercise	1491 (49.4)	483 (63.6)	382 (50.3)	336 (44.7)	290 (38.8)	180 (5.6)
<60 min/week	1027 (34.0)	208 (27.4)	263 (34.6)	276 (36.7)	280 (37.4)	
>60 min/week	502 (16.6)	69 (9.1)	115 (15.1)	140 (18.6)	178 (23.8)	
Breastfeeding duration until 18 months, *n* (%)						
Never breastfed	83 (2.8)	30 (4.0)	18 (2.4)	17 (2.3)	18 (2.4)	209 (6.5)
0–3 months	381 (12.7)	137 (18.3)	88 (12.0)	91 (12.1)	65 (8.6)	
4–6 months	449 (15.0)	117 (15.6)	118 (16.0)	98 (13.0)	116 (15.3)	
7–9 months	886 (29.6)	209 (27.9)	224 (30.4)	231 (30.8)	222 (29.4)	
10–12 months	632 (21.1)	127 (17.0)	152 (20.7)	178 (23.7)	175 (23.1)	
>12 months	560 (18.7)	128 (17.1)	136 (18.5)	136 (18.1)	160 (21.2)	

Abbreviations: BMI, body mass index; DD, diet diversity; min, minutes; POEM, Patient Oriented Eczema Measurement; Q, quartile; SD, standard deviation.

[a]According to POEM score 0–7.

[b]According to POEM score 8–28.

[c]% of $n = 1922$ that participated in screening testing.

although not significant in adjusted models (Figure 1B). A sensitivity analysis with the addition of post-natal confounders can be found here: https://zenodo.org/record/7908503#.

Data on sensitization were available from $n = 1922$ children (60.1%), and of these, $n = 338$ (17.6%) were positive in the Food mix fx5 test and $n = 88$ (4.6%) were positive in the Phadiatop test (Table 1). There were no associations between diet diversity in pregnancy and positive sensitization (≥0.35 PAU/kUA/L) to either Phadiatop or foodmix fx5, (Figure 1A). The 18-month-old children positive to the foodmix ($n = 338$) were further tested for each specific food allergen of which none associated with diet diversity in the pregnant mothers (Figure 1A).

The aetiology for eczema, FA and also asthma involves both the state of the epidermal barrier and the mucosal immune system, commensal bacteria but also diet diversity and timing of introduction to solid foods in infancy.[3] Hence, it is a complex task to clarify the role of each contributing factor. The found possible link to FA in this study may however be essential also for the prevention of other allergic diseases due to the confirmed higher risk of subsequent respiratory allergies among children with early FAs.[8]

Our results stand in contrast to findings from the Healthy Start study which found that diet diversity scores in pregnancy were not associated with FA until 4 years of age, but with atopic dermatitis, asthma and wheeze instead.[4] There is still inconsistency in the concept and terminology of diet diversity in the literature, and we agree with The European Academy of Allergy and Clinical Immunology (EAACI) taskforce that there is a major knowledge gap regarding diet diversity and allergy prevention that needs to be further investigated.[1]

Major strengths with this large cohort study were its prospective population-based design which implicated enough power to the main analyses and enabled quartile analyses. Further, the detailed information collected from the families at repeated time-points from early pregnancy until the age of 18 months in the child, enabled investigation of a considerable number of important covariates. However, the study was limited by self-reported data although number of self-reported outcomes was not considered overestimated in relation to national figures of FA prevalence and asthma. The use of physician-diagnosed FA and asthma may lead to an underestimation of the true prevalence but reduces the risk of detection bias. Further, a substantial proportion of the mothers in the present study was highly educated, (69.5% had university education), and hence, the result may not be generalizable.[9] We want to emphasize that these novel results require further investigation, preferably in both well-designed observational studies and in randomized control trials in different populations.

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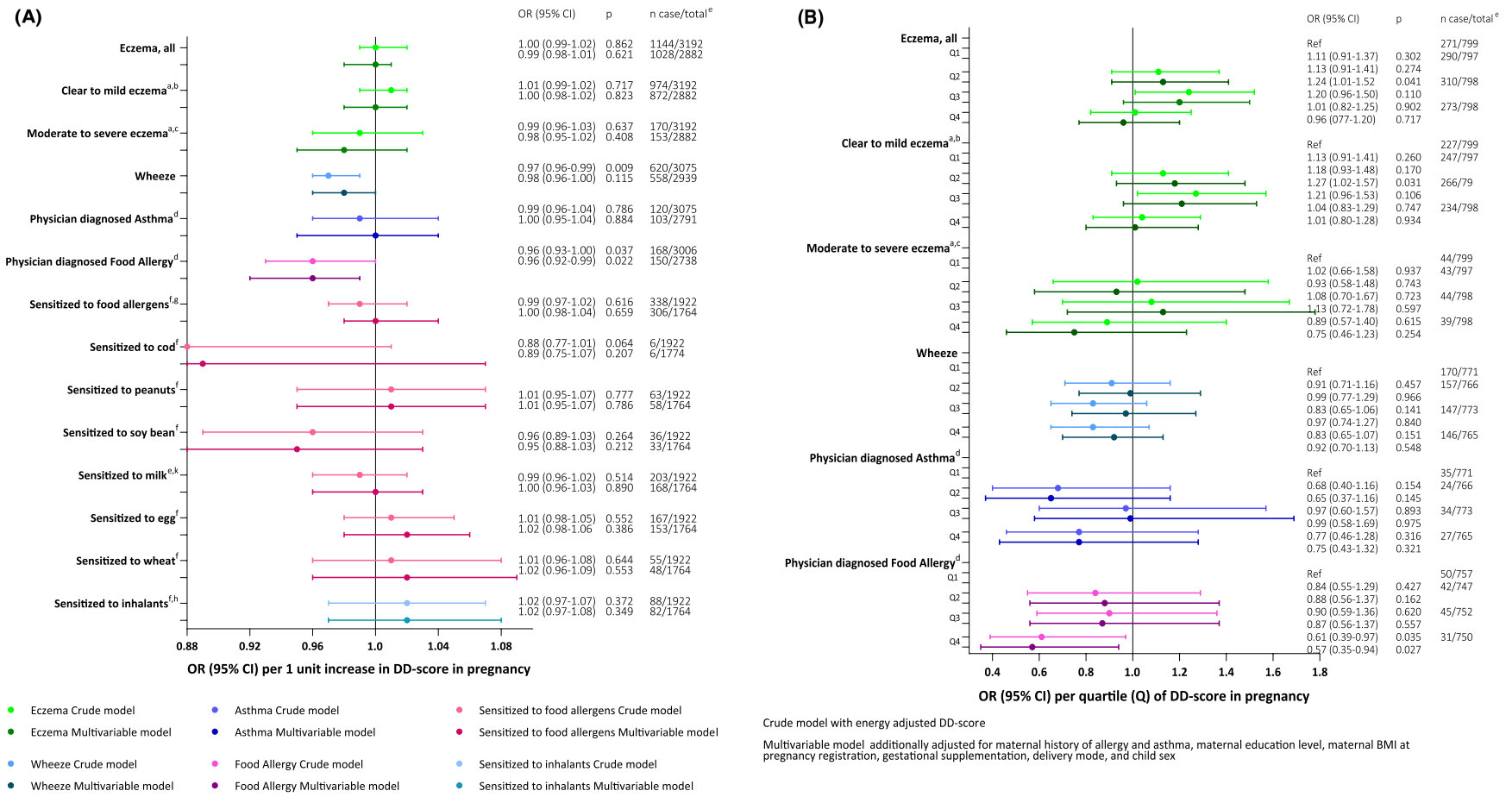

FIGURE 1 Association between DD score in pregnancy and cumulative incidence of allergic manifestations until the age of 18 months ($n = 3200$) in crude and multivariable models. Coloured dots represent the odds ratio per 1 unit increase in DD score in (A), and the odds ratio per quartile of DD score in (B), and coloured lines represents the 95% confidence intervals. [a]ORs produced with multinomial logistic regression with 'no eczema' as reference. [b]According to POEM score 0–7. [c]According to POEM score 8–28. [d]Physician-diagnosed, reported by the parent. [e]Number of cases and total participants in crude model. [f]Sensitization was defined as positive if IgE levels ≥0.35 kU/L. [g]Sensitized to food mix (fx5) with cod, peanut, soybean, cow's milk, egg white, and wheat. [h]Sensitized to inhalation mix (Phadiatop). BMI, body mass index; CI, confidence interval; DD, diet diversity; OR, odds ratio; POEM, Patient Oriented Eczema Measurement.

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In conclusion, a diverse diet during pregnancy, including frequent intake of fruit, vegetables, dairy products, fibre-rich foods, fatty fish and moderate intake of meat, may be associated with reduced early childhood FA incidence and associated individual and healthcare burden. As we will collect data prospectively from these investigated children within the ongoing NorthPop Birth Cohort Study, it will be interesting to see whether these novel results will persist during childhood until the age of 7 years.

AUTHOR CONTRIBUTIONS

Stina Bodén and Christina E. West contributed to study design; Stina Bodén, Christina E. West and Carina Venter contributed to conceptualization; Stina Bodén, Anna Lindam, Christina E. West and Carina Venter contributed to methodology; Christina E. West and Magnus Domellöf contributed to ethics approval; Stina Bodén, Christina E. West and Magnus Domellöf contributed to funding acquisition Stina Bodén, Christina E. West, Anna Lindam, Carina Venter and Magnus Domellöf contributed to interpretation of data; Stina Bodén contributed to statistical analysis and data visualization and wrote the first draft of the manuscript. All authors revised the manuscript and approved the final version.

KEYWORDS

allergy prevention, diet diversity, food allergy, offspring, pregnancy

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CONFLICT OF INTEREST STATEMENT

Dr. Venter reports grants from Reckitt Benckiser Food Allergy Research and Education, National Peanut Board; personal fees from Reckitt Benckiser, Nestle Nutrition Institute, Danone, Abbott Nutrition, Else Nutrition, Before Brands and Owen outside the submitted work. Dr. West has received research funding from Thermo Fisher Scientific and Arla, which was directly paid to the institution, and speaker honorarium from Thermo Fisher Scientific and Aimmune Therapeutics, a Nestlé Health Science company, outside the submitted work. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data generated in this study are not publicly available due to Swedish Authority for Privacy Protection regulations (the national supervisory authority under the European General Data Protection Regulation, GDPR). Data may be available upon reasonable request to the corresponding author.

ETHICAL APPROVAL

The study protocol for the present investigation was approved by the Regional Ethical Review Board, Umeå, Sweden, 2014/224–31. All participants (mother and partner) provided a written informed consent to use the collected data from both parent and child. All data handling complies with the European Union General Data Protection Regulation, and the study conforms with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964).

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