

The role of antioxidants and 25-hydroxyvitamin D during pregnancy in the development of allergic diseases in early school-age children – Polish Mother and Child Cohort Study

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ABSTRACT

Purpose: Based on the available data, alterations of the antioxidant defense as well as the vitamin status in mothers may affect the prenatal process of lung and immune system development as a pathophysiological background of increased prevalence of allergic diseases. The primary aim of the current study was to assess the associations among cord blood concentrations of zinc (Zn); copper (Cu); selenium (Se); β -carotene; and vitamin A, E, and D, and the occurrence of atopic dermatitis, food allergy, allergic rhinitis, and asthma in early school-age children.

Methods: We evaluated 211 children, 7–9 years old, from the Polish Mother and Child Cohort Study. The women were interviewed during pregnancy to collect demographic and socioeconomic data, and the medical and reproductive history. At delivery, umbilical cord blood plasma was sampled. Seven to nine years after the birth, the child's exposure and health status (including skin-prick test and spirometry for allergy assessment and urine sample for cotinine level) were examined. In the analyses, a multivariable model was applied.

Results: Statistically significant relationships were found among Zn; Cu; Se; and vitamin A, E, and D concentrations in cord blood; and the prevalence of food allergy, allergic rhinitis, atopic dermatitis, and asthma in children ages 7–9 years after adjustment for several confounders.

Conclusion: We showed an imbalance in the antioxidant defense system in cord blood, which may lead to the occurrence of allergic diseases later in life. The maternal diet may have substantial potential to modify immune tolerance and, consequently, the development of allergic disease in the offspring.

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Allergic diseases have seen a rise worldwide, with children having the highest burden. A number of factors, including the maternal diet, have been investigated for the prevention of allergic diseases. As a supply of all nutrients, the maternal diet has significant potential to modify the success or failure of immune tolerance and, consequently, the development of allergic disease in the offspring.¹ Pregnancy is potentially associated with an increased risk of oxidative stress. Deficiencies of the nutrients selenium (Se); zinc (Zn); and vitamins A, C, D, and E may be associated with

the development of asthma and allergic disorders. A limited number of other studies, including birth cohort studies have suggested an inverse association between higher maternal intakes of antioxidants such as vitamin E^{2–4} and Zn² and the development of early childhood wheeze and asthma⁵ as well as other allergic manifestations.^{3,4,6} There are few studies that suggest that cigarette smoking during pregnancy is an additional source of oxidative stress for mothers and children.⁷ There is evidence that allergic and inflammatory skin diseases are mediated by oxidative stress and that the development of allergy is associated with the generation of oxidative stress.⁷

Based on our previous analysis of the data from Polish Mother and Child Cohort (REPRO_PL cohort),^{7–13} higher Zn and copper (Cu) concentrations in cord blood are associated with an increased likelihood of wheezing in 1-year-old children, mainly among children exposed to tobacco smoke at home¹¹; the effect of Se on the risk of atopy was not significant after adjustment for confounding factors.¹² Cord plasma 25-hydroxyvitamin D levels were inversely associated with the risk of multi-triggered wheezing and espe-

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cially viral-induced wheezing by the age of 2 years, but no association was found with food allergy, atopic dermatitis, and frequency of infections.¹³ Also, the relationship between plasma concentration of vitamins A and E, and the risk of allergy in their young children has not been demonstrated.⁷

It is of interest to evaluate if the consequences observed within the first 2 years of life still persist until school age or they are compensated by other factors. What is more, the consequences of prenatal exposures may not be observed or reliably diagnosed within the first years of life but can appear at a later age. The primary aim of current analyses was to determine the associations between cord blood concentrations of Zn; Cu; Se; β -carotene (a precursor of vitamin A); and vitamin A, E, and D and the occurrence of atopic dermatitis, food allergy, allergic rhinitis, and asthma in early school-age children. As confounders, we gathered data about parental smoking, education level, and parental atopy based on the results from our previous reports.^{7,11–16}

METHODS

Study Design and Population

The REPRO_PL cohort was established in 2007.⁸ A complete description of the methodological assumptions has been published elsewhere.^{8–10} Briefly, the women were recruited during their first trimester of pregnancy at maternity units or clinics if they fulfilled the following inclusion criteria: single pregnancy up to 12 weeks of gestation, no assisted conception, no pregnancy complications, and no chronic diseases as specified in the study protocol.⁸ They were interviewed during pregnancy to collect sociodemographic data and medical history as well as information about environmental, occupational, and lifestyle factors. During pregnancy and at delivery, biologic samples (saliva and umbilical cord blood) were collected.

Between 7 and 9 years after the child's birth, an invitation letter was sent to the mothers with an offer to participate in follow-up examinations that cover exposure (including questionnaire data) and child's health status assessment.⁷ The current analysis was restricted to 211 children at ages 7–9 years. All the mothers of the patients gave their written consent for the participation in the study. The study was approved by the ethics committee of the Nofer Institute of Occupational Medicine, Łódź, Poland (Decisions 7/2007 and 22/2014), for the primary study and follow-up of the children at age 7 years, and by the medical ethics committee of the Medical University of Lodz (Decision RNN/388/17/KE) for the follow-up study at age 9 years.

Child Health Assessment

Children's health status was assessed at ages 7 and 9 years. For the appropriate recognition of the children's

health status, a questionnaire was administered to the mothers and was supplemented with information from the medical chart of each child. This part of the questionnaire was developed by an allergist (MBK), based on recommendations from the International Study of Asthma and Allergies in Childhood and has previously been applied.^{10,17} The patients were defined as having food allergy, asthma, allergic rhinitis, or atopic dermatitis if they had ever been diagnosed by a physician; asthma was diagnosed based on Global Initiative for Asthma guidelines.¹⁸

The clinical examination was performed by a pediatrician/allergist (MBK, JJ) in the presence of the mother or a relative. Patients underwent spirometry and skin-prick tests. Detailed information on the methods used is available in our previous articles.^{10,19} Skin-prick testing to standard allergen extracts was performed by using Allergopharma, Reinbek, Germany. Reactions > 3 mm in diameter above the negative control recorded at 15 minutes were considered positive. The occurrence of allergy among the family members was noted and considered in the analysis.

Plasma Cu and Zn Concentrations

Plasma Cu and Zn concentrations in cord blood were analyzed by the flame atomic absorption technique.^{11,20} This method was validated by using the reference material (lyophilized human reference serum samples of Seronorm from Nycomed Pharma AS, Oslo, Norway), and through participation in the inter-laboratory comparisons trials.

Plasma Se Concentrations

The measurements of plasma Se concentration in cord blood were performed by graphite furnace atomic absorption spectrometry on an Unicam Solar 989 QZ (Pye Unicam, US) apparatus according to the modified method of Nève *et al.*^{12,21} The accuracy of the method was verified by using internal quality control of the certified reference material BCR-637 (The Institute for Reference Materials and Measurements (IRMM), Geel, Belgium), in which the reference value and measured concentration were 81.0 $\mu\text{g/L}$ (range, 74–88 $\mu\text{g/L}$) and $82.5 \pm 0.7 \mu\text{g/L}$, respectively.

Vitamins A, D, and E, and β -Carotene Levels

Vitamin A, D, and E, and β -carotene levels were determined in cord plasma by using the high-performance liquid chromatography (HPLC) system integrated with Ultraviolet-visible spectroscopy (UV-VIS) detector range of 190–800 nm.^{7,22}

Assessment of Mother and Children Exposure to Tobacco

Prenatal exposure to tobacco constituents was assessed based on questionnaire data and cotinine

levels in saliva collected from the women during pregnancy.⁸ If the women reported quitting smoking during pregnancy, then the following procedure was applied: such information was first verified based on the cotinine level in the saliva, and the durations of the smoking and non-smoking statuses were then taken into account in an exposure calculation. Child exposure to environmental tobacco smoke was assessed based on questionnaire data and cotinine levels in urine collected at 7–9 years of age. The cotinine levels in saliva and urine were analyzed by using high-performance liquid chromatography coupled with tandem mass spectrometry/positive electrospray ionization (high-performance liquid chromatography coupled with tandem mass spectrometry/positive electrospray ionization (LC-MS/MS-ESI+)) and the isotope dilution method. A description of the methodological assumptions has been published elsewhere.^{8,10}

Statistical Analysis

Variables were described by way of measures of location (arithmetic or geometric mean) and measures of dispersion (standard deviation, 95% confidence interval, and minimum and maximum values). The categorical variables were depicted by using absolute values and percentages. A multifactor analysis of variance was carried out to test the significance of differences between the two study groups after having estimated the normality of distribution and homogeneity of variances of the numerical traits. When dealing with non-normally distributed variables and/or heterogeneous variances, generalized linear models along with robust standard errors (*i.e.*, sandwich estimators) were applied. A level of $p < 0.05$ was considered statistically significant. All the statistical computations were carried out by means of Stata/Special Edition, release 14.2 (StataCorp LP, College Station, TX).

RESULTS

Description of the Study Population

A description of the study population is given in Table 1. The lifetime prevalence of the selected outcomes is given. More than 29% of the children had a positive parental history of atopy. More than 28% of children were exposed to tobacco smoke at home (cotinine level in child urine: mean $\pm$ standard deviation 1.76 ± 0.99 ng/mL).

Zn, Cu, and Se, and Child Allergy and Asthma

We observed significantly lower Zn concentrations in umbilical cord blood plasma of the children with allergic rhinitis at ages 7–9 years compared with children who did not have that condition ($p = 0.009$) (Table 2). In addition, significantly lower Cu concentrations in umbilical cord blood plasma of the children with

asthma at ages 7–9 years compared with children who did not have asthma were observed ($p = 0.017$). Also, significantly higher Cu concentrations in umbilical cord blood plasma of children with allergic rhinitis ($p = 0.048$) and atopic dermatitis ($p = 0.015$) at ages 7–9 years compared with children who did not have allergic rhinitis and atopic dermatitis was noted (Table 2).

Vitamins A, D, and E, and β -Carotene Levels and Child Allergy and Asthma

There were no significant associations between vitamin A, E, and D, and β -carotene concentrations in cord blood and the prevalence of atopic dermatitis in children ages 7–9 years ($p > 0.05$) (Table 2). However, we observed significantly lower vitamin E and β -carotene concentrations in umbilical cord blood plasma of children who developed food allergy ($p = 0.025$ and $p = 0.001$, respectively). A lower β -carotene concentration was also observed in the case of children with asthma ($p = 0.049$). Also, significantly higher 25-hydroxyvitamin D concentrations in umbilical cord blood of children who developed food allergy at ages 7–9 years compared with children who did not was identified ($p = 0.006$) (Table 2).

Confounding Effects

All of the above-mentioned relationships with regard to the investigated concentrations in umbilical cord blood plasma of the studied children, were controlled for the co-occurrence of food allergy, atopic dermatitis, asthma, or allergic rhinitis and/or rhinoconjunctivitis. Statistical models performed were also checked for potential confounders, such as parental atopy, parental education level, and parental smoking. We did not find any interferences with observed associations.

DISCUSSION

This study investigated the levels of antioxidants and 25-hydroxyvitamin D at delivery in relation to development of allergic diseases in early school-age children. After inclusion of a variety of confounding factors, such as exposure to tobacco constituents, parents' education level, parental atopy, some statistically significant associations between Zn, Cu, and Se concentrations as well as vitamins A, E, and D concentrations in umbilical cord blood plasma, and the prevalence of food allergy, allergic rhinitis, atopic dermatitis, and asthma in children ages 7–9 years were revealed. The interaction between smoking during pregnancy and studied antioxidants and vitamins levels on the risk of allergy was not statistically meaningful.

Our results with concern to Zn, Cu and Se effects on children's health revealed some significant results. However, it seemed that, in our population, higher

Table 1 Descriptive characteristics of the study cohort (N = 211)*

Variable	Statistical Parameters
Girls, no. (%)	117 (55.45)
Clinical profile (children ages 7–9 y), no. (%)	
Food allergy	39 (18.57)
Allergic rhinitis	31 (14.76)
Atopic dermatitis	50 (23.81)
Asthma	17 (8.10)
Comorbidity, no. (%)	
One condition	33 (15.4)
Two conditions	23 (10.7)
Three conditions	18 (8.4)
Four conditions	2 (0.9)
Skin-prick test result (children ages, 7–9 y), no. (%)	
Negative	121 (60.50)
One allergen only	7 (3.5)
House-dust mites only	13 (6.50)
Animal dander only	2 (1.00)
Seasonal allergens only	23 (11.50)
Mites and other allergens only	34 (17.00)
Family status	
Mother's age, mean $\pm$ SD, y	29,18 $\pm$ 4.57
Mother's education, no. (%)	
Primary school	7 (3.32)
Secondary school	70 (33.17)
University	134 (63.51)
Father's age, mean $\pm$ SD, y	31.13 $\pm$ 5.89
Father's education, no. (%)	
Primary school	13 (6.22)
Secondary school	107 (51.20)
University	89 (42.58)
Parental atopy	63 (29.86)
Parental smoking, no. (%)	60 (28.57)
Concentration of cotinine in mother's saliva during pregnancy, mean $\pm$ SD, ng/mL [#]	3,66 $\pm$ 1.19
Concentration of cotinine in children's urine (in children ages 7–9 y), mean $\pm$ SD, ng/mL [#]	1,76 $\pm$ 0.99
Spirometry in children ages 7–9 y, mean $\pm$ SD	
FEV ₁ , mean $\pm$ SD, best/pred. %	99.17 $\pm$ 11.06
FVC, mean $\pm$ SD, best/pred. %	99.57 $\pm$ 10.54
Concentration in umbilical blood, mean $\pm$ SD	
Zinc, mg/L	1.05 $\pm$ 0.032
Selenium, μ g/L	29.27 $\pm$ 7.88
Copper, mg/L [#]	0.50 $\pm$ 0.72
β -Carotene, μ g/mL [#]	0.046 $\pm$ 0.053
Vitamin A, μ g/mL	0.57 $\pm$ 0.19
Vitamin D, ng/mL [#]	6.24 $\pm$ 0.56
Vitamin E, μ g/mL	3.47 $\pm$ 1.76

SD = Standard deviation; FEV₁ = forced expiratory volume in the first second of expiration; FVC = forced vital capacity; best/pred. = best/predicted value.

*Missing data were case-wise deleted.

[#]Geometric means were provided.

Table 2 Descriptive statistics for the blood concentrations of Zn, Se, Cu, β -carotene, vitamin A vitamin E ($n = 211$) and vitamin D ($n = 188$) in the case of food allergy, allergic rhinitis, atopic dermatitis, and asthma at ages 7–9 y

Investigated Trait	Condition in Question Present			Condition in Question Absent			<i>p</i> *
	Mean ± SD	95% CI	Min.-Max.	Mean ± SD	95% CI	Min.-Max.	
Food allergy							
Zn, mg/L	1.02 ± 0.30	0.87–1.18	0.50–1.68	1.06 ± 0.33	0.98–1.13	0.53–2.70	0.974
Se, µg/L	30.48 ± 6.19	27.50–33.47	21.47–41.35	29.03 ± 8.33	27.01–31.04	0.03–49.76	0.467
Cu, mg/L [#]	0.53 ± 0.52	0.41–0.70	0.24–1.72	0.49 ± 0.76	0.41–0.59	0.15–34.33	0.051
β-Carotene, µg/mL [#]	0.040 ± 0.038	0.029–0.055	0.012–0.182	0.048 ± 0.057	0.040–0.057	0.012–0.300	0.001
Vitamin A, µg/mL	0.55 ± 0.21	0.44–0.65	0.26–1.03	0.57 ± 0.20	0.53–0.61	0.26–1.04	0.520
Vitamin D, ng/mL [#]	8.45 ± 0.72	5.05–14.13	1.97–27.81	5.93 ± 0.52	5.18–6.79	1.65–20.34	0.006
Vitamin E, µg/mL	3.019 ± 1.689	2.205–3.833	0.617–6.560	3.594 ± 1.761	3.212–3.977	0.122–8.747	0.025
Allergic rhinitis							
Zn, mg/L	0.92 ± 0.24	0.80–1.04	0.50–1.36	1.08 ± 0.33	1.00–1.16	0.63–2.70	0.009
Se, µg/L	28.69 ± 10.31	23.38–33.99	0.03–43.32	29.51 ± 7.28	27.77–31.24	1.25–49.76	0.573
Cu, mg/L [#]	0.66 ± 1.12	0.37–1.17	0.24–34.33	0.47 ± 0.58	0.41–0.54	0.15–3.73	0.048
β-Carotene, µg/mL [#]	0.061 ± 0.042	0.044–0.084	0.018–0.182	0.043 ± 0.056	0.036–0.051	0.012–0.300	0.001
Vitamin A, µg/mL	0.59 ± 0.22	0.49–0.69	0.26–1.03	0.56 ± 0.19	0.52–0.60	0.26–1.04	0.245
Vitamin D, ng/mL [#]	5.88 ± 0.71	3.55–9.73	1.65–13.48	6.31 ± 0.54	5.48–7.26	1.86–27.81	0.856
Vitamin E, µg/mL	3.303 ± 1.626	2.519–4.086	0.617–6.560	3.530 ± 1.789	3.142–3.918	0.122–8.747	0.504
Atopic dermatitis							
Zn, mg/L	1.05 ± 0.31	0.92–1.17	0.50–1.68	1.05 ± 0.33	0.97–1.13	0.63–2.70	0.329
Se, µg/L	29.79 ± 8.83	26.22–33.35	0.03–44.8	29.16 ± 7.54	27.23–31.09	1.25–49.76	0.862
Cu, mg/L [#]	0.57 ± 0.96	0.39–0.84	0.24–34.33	0.47 ± 0.59	0.40–0.55	0.15–3.73	0.015
β-Carotene, µg/mL [#]	0.044 ± 0.024	0.036–0.055	0.012–0.100	0.047 ± 0.062	0.038–0.057	0.012–0.300	0.447
Vitamin A, µg/mL	0.56 ± 0.17	0.50–0.63	0.29–1.03	0.57 ± 0.21	0.52–0.61	0.26–1.04	0.488
Vitamin D, ng/mL [#]	5.66 ± 0.74	3.69–8.68	1.65–27.81	6.40 ± 0.51	5.58–7.35	1.86–20.34	0.370
Vitamin E, µg/mL	3.344 ± 1.788	2.664–4.024	0.122–8.747	3.544 ± 1.750	3.139–3.950	0.600–8.256	0.310
Asthma							
Zn, mg/L	1.05 ± 0.36	0.72–1.38	0.66–1.54	1.05 ± 0.32	0.98–1.12	0.50–2.70	0.861
Se, µg/L	30.56 ± 9.27	21.99–39.13	21.47–49.76	29.24 ± 7.83	27.50–30.98	0.03–44.80	0.868
Cu, mg/L [#]	0.38 ± 0.38	0.27–0.54	0.27–0.67	0.51 ± 0.74	0.43–0.60	0.15–34.33	0.017
β-Carotene, µg/mL [#]	0.031 ± 0.018	0.18–0.52	0.012–0.068	0.048 ± 0.055	0.041–0.56	0.012–0.300	0.049
Vitamin A, µg/mL	0.54 ± 0.28	0.24–0.84	0.26–1.03	0.57 ± 0.19	0.53–0.61	0.26–1.04	0.936
Vitamin D, ng/mL [#]	6.35 ± 0.26	4.16–9.69	4.35–8.02	6.24 ± 0.57	5.41–7.19	1.65–27.81	0.714
Vitamin E, µg/mL	3.596 ± 1.719	1.792–5.400	0.732–5.400	3.481 ± 1.765	3.126–3.837	0.122–8.747	0.809

Zn = Zinc; Se = selenium; Cu = copper; SD = standard deviation; CI = confidence interval; Min. = minimum; Max. = maximum; n = number of analyzed patients; p = p value statistical significance.

*Multivariate analyses were fitted, i.e., all regression models were controlled for sociodemographic determinants and environmental conditions as confounders.

[#]Geometric means were provided.

levels of Cu and lower levels of Zn in cord blood predisposed children ages 7–9 years to allergic rhinitis and higher Cu only to atopic dermatitis. In addition, we noticed lower concentrations of Cu in umbilical cord blood in patients with asthma. In summary, high levels of Cu in cord blood were associated with an increased risk of atopic dermatitis and allergic rhinitis but with a reduced risk of asthma. Lower levels of Zn in cord blood were associated with a reduced risk of allergic rhinitis. These findings were opposite to the results

of studies that showed that, in children with asthma, moderate levels of Zn and Cu plasma (not cord blood) were similar or even higher than in healthy children.^{23–25}

Although there are no available studies to our knowledge that examined Cu in cord blood in the context of allergy, there are observations that support a role for this element in immunomodulation. Cu requirements are increased in pregnancy, and a suboptimal supply may have adverse effects on developing tissues and organ systems, including the lung, skin, and

immune system.²⁵ No significant associations were found in our data between Se concentrations in umbilical cord blood plasma and the prevalence of food allergy, allergic rhinitis, atopic dermatitis, and asthma in children ages 7–9 years. In a multicenter case-control study of the Global Allergy and Asthma European Network (GA2LEN) project, there were big differences between the multiple centers with concern to the protective effect of Se in asthma.²⁶

Devereux *et al.*,²⁷ in a birth cohort study of almost 2000 mothers and their newborns, proved that low levels of Se in maternal serum in the first trimester of gestation and in the newborns' umbilical cord blood were associated with an increased risk of wheezing at 2 years of age but not with asthma at 5 years. In the Avon Longitudinal Study of Parents and Children based on the observation of 2044 mothers and their offspring, the researchers revealed a negative association between the umbilical cord serum concentration of Se and persisting childhood wheezing between 0–6 months and 36–42 months.²⁸ As presented in this study, the mean concentration of Se was approximately 30 µg/L in the cord blood.²⁸

In the current study, we observed significantly lower vitamin E concentrations in umbilical cord blood plasma of children with food allergy and significantly lower β -carotene concentrations of children with asthma and food allergy, and higher concentrations with allergic rhinitis. Data on 44,594 mother-child pairs from the Danish National Birth Cohort presented weak inverse associations for maternal vitamin A intake during pregnancy with child allergic rhinitis.^{29–32} Few studies have examined the association between prenatal vitamin D status with offspring's risk of asthma and related conditions. Wei *et al.*³⁰ meta-analysis found that lower maternal vitamin D during pregnancy was associated with an increased risk of childhood eczema but was not associated with childhood asthma or wheeze.

In the current study, we noticed significantly higher concentrations of vitamin D in umbilical cord blood of children with food allergy. Rosendahl *et al.*³³ suggested, that high-dose vitamin D supplementation did not prevent allergic sensitization, allergic diseases, or wheezing during the first year of life. They observed an increased risk of milk allergy in infants with higher vitamin D supplementation and an increased risk of allergic sensitization in infants with high cord blood vitamin D status, which indicated a possible adverse effect of high concentrations of vitamin D.³³ There is evidence that vitamin D is even more complex and may act through modulating susceptibility to early allergic sensitization, upper respiratory tract colonization with bacterial pathogens, or both,³⁴ and lower levels of vitamin D were associated with reduced asthma control.³¹

Nurmatov *et al.*³² published a systematic review and meta-analysis with regard to the influence of nutrients and foods for the primary prevention of asthma and allergy. The researchers assessed actual trials and revealed that maternal dietary vitamin D intakes during pregnancy were protective for the development of wheezing outcomes; serum vitamin A was lower in children with asthma compared with controls.³² They concluded that the available epidemiologic evidence is weak but, nonetheless, supportive with respect to vitamins A, D, and E; Zn; fruit; and vegetable intake for the prevention of asthma.³² Our study revealed similar results, including for Cu, for the prevention of allergic diseases. For β -carotene, we revealed that low levels seemed to be associated with an increased risk of food allergy and asthma but with a decreased risk of allergic rhinitis. High levels of vitamin D in the cord blood were associated with an increased risk of food allergy. Low levels of vitamin E in cord blood are associated with a reduced risk of food allergy. The majority of children with asthma also have allergic rhinitis and some with atopic dermatitis also have both asthma and rhinitis, therefore, our observations need to be confirmed in another trials.

The prospective design of our study limited the risk of recall bias and the diagnosis of allergic disease relies on both clinical assessment and evidence of allergic sensitization. In addition, the smoking status of pregnant women and children were assessed based on a biomarker of exposure. Another strength of the present study was the assessment of skin-prick tests and spirometry, which allowed objective outcome evaluation. The main limitation of our study was that we only looked at prenatal exposure and were not able to evaluate antioxidants and vitamins levels in children ages 7–9 years.

CONCLUSION

According to our previous and current observations of the REPRO-PL cohort, we concluded that maternal diet may have substantial potential to modify immune tolerance and, consequently, the development of allergic disease in the offspring.^{11,12} Unfortunately, available data are not sufficient to formulate dietary recommendations for pregnant women. Further studies are needed.

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