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PRENATAL POLYUNSATURATED FATTY ACIDS AND ATOPIC DERMATITIS AND FOOD ALLERGY IN CHILDREN FROM POLISH MOTHER AND CHILD COHORT STUDY

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Abstract
Objectives: Polyunsaturated fatty acids (PUFAs) are involved both in immune system regulation and inflammation. The aim of this prospective study was to evaluate the association between maternal dietary intake of PUFAs during pregnancy and atopic dermatitis (AD) and food allergy (FA) in their children up to 7–9 years of age. **Material and Methods:** The study population consists of 557 mother–child pairs from the Polish Mother and Child Cohort (REPRO_PL). Based on the *Food Frequency Questionnaire* completed between the 20–24th weeks of pregnancy, n-3 and n-6 PUFAs as well as n-6:n-3 fatty acid ratio were estimated using food composition tables. Children's health examinations at the age of 1, 2, and 7–9 years were performed by an allergist. Generalized estimating equations were performed in order to assess the prevalence of AD and FA at 3 time points. Independent variables in the equation were n-3, n-6 PUFAs and n-6:n-3 PUFAs ratio. In addition multivariate models were performed to assess the association of PUFAs with AD and FA. **Results:** The prevalence of AD was 37%, 26% and 21% and FA 26%, 22% and 22% at age of 1, 2 and 7–9 years, respectively. Higher n-6:n-3 fatty acid ratio correlated with higher prevalence of AD at age of 7–9 years ($p < 0.07$). In multivariate model n-6 PUFAs were significantly associated with increased risk of persistent FA (OR = 1.5, 95% CI: 1.1–2.1). **Conclusions:** These results may contribute to the existing knowledge on the impact of maternal diet during pregnancy on children's optimal health, however further studies are needed before drawing conclusions and creating clinical practice guidelines. Int J Occup Med Environ Health. 2023;36(3):428–36

Key words:
polyunsaturated fatty acids, omega-6, omega-3, food allergy, atopic dermatitis, prospective cohort

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INTRODUCTION

The increase in the prevalence of allergic diseases, such as atopic dermatitis (AD) and food allergy (FA) in children and adults, observed in recent decades represents a public health and clinical challenge [1]. The AD is a chronic, recurrent inflammatory skin disease that manifests itself with intense itching and eczematous lesions [2]. Its underlying mechanisms include a complex interaction between a dysfunctional skin barrier, dysregulation of the immune system, skin microbiome dysbiosis, genetic predispositions and environmental factors [1]. The AD might progress to FA and respiratory allergy. Moreover, food allergens are indicated as one of the triggers of AD exacerbations.

Environmental factors, microbiome and epigenetic mechanisms acting during immune programming may play an important role in the development of allergic diseases in childhood or later in life [2–4]. Recently it has been suggested that polyunsaturated fatty acids (PUFAs), may determine the development of AD and FA [4–8]. The PUFAs are fatty acids with a structure characterized by >1 double bond, where n-3 PUFAs share a terminal carbon-carbon double bond at the omega 3 position, while n-6 PUFAs have it at the omega 6 position [8]. Among n-3 PUFAs, the main sources of α-linolenic acid (ALA) (C18:3n-3) are linseeds, chia seeds, vegetable oils (i.e. soybean, linseed, wheat germ or rapeseed oils) and nuts. Eicosapentaenoic acid (EPA) (C20:5n-3) and docosahexaenoic acid (DHA) (C22:6n-3) are present in oily fish and fish oil. The PUFA n-6, such as linoleic acid (LA) (C18:2n-6) can be found in vegetable oils (i.e., sunflower, soybean, corn, wheat germ and sesame) whereas arachidonic acid (AA) (C20:4n-6) mainly in meat and meat products or egg yolks.

Given that n-6 PUFAs are linked to a pro-inflammatory response and n-3 PUFAs (mostly EPA and DHA) promote an anti-inflammatory response, observed dietary changes such as an increase of plant-based n-6 PUFAs intake and a decrease in n-3 PUFAs intake (mainly oily fish) may contribute to the increased incidence of allergic diseases in childhood [9–14].

The review papers that focus on the studies evaluating the association of maternal fish or supplements intake, dietary PUFAs intake (based on questionnaires data) during pregnancy, prenatal or cord blood PUFAs concentrations with offspring AD or FA do not give clear results [2,4,7,8,15]. Findings include negative associations between n-3 PUFAs or fish consumption and positive ones of n-6 PUFAs or n-6:n-3 PUFAs ratio and childhood allergy yet some are inconclusive or suggest no relationship.

The aim of this prospective cohort was to evaluate the association between dietary intake of PUFAs in pregnancy and AD and FA in their offspring up to early school age.

MATERIAL AND METHODS

Study design and population

The data used in the current analysis came from a prospective Polish Mother and Child Cohort study (REPRO_PL) – with the following inclusion criteria: no *in vitro* fertilization, no maternal chronic diseases and pregnancy complications, single pregnancy and recruitment up to the 12th week of pregnancy [16–18]. The analysis covered mother-child pairs with exposure data available from prenatal period (phase I, N = 557) and outcome data available from at least 1 time point after birth:

- early childhood period (phase II – assessments at 1 and 2 years of age, N = 340 and N = 216, respectively),
- early school age period (phase III – assessments at 7–9 years of age, N = 336).

The number of children assessed at each visit does not add up to the total number of mother–child pairs (N = 557), which is due to the fact that children could have been assessed at all 3 time points and also at 2 time points or at only 1 time point.

Ethical Committee of the Nofer Institute of Occupational Medicine, Łódź, Poland granted the approval for each phase

of the study (phase I – decision No. 7/2007, phase II – decision No. 3/2008, and phase III – decision No. 22/2014).

Maternal diet in pregnancy

Maternal dietary assessment was based on modified version of *Food Frequency Questionnaire* (FFQ) filled in the second trimester of pregnancy [19–21]. For each of the food items indicated in FFQ, women reported the frequency of average consumption (never, less than once a month, 1–3 times a month, 1–3 times a week, 4–6 times a week, daily). The size of an average portion was considered. Nutrient intake of ALA, stearidonic acid (SDA) (C18:4n-3), EPA, omega-3 docosapentaenoic acid (DPA) (C22:5n-3), DHA, n-3 (as the sum of the listed PUFAs), LA, dihomo-gamma-linolenic acid (DGLA) (20:3n-6), AA and n-6 (as the sum of the listed PUFAs) was estimated in g/day using the Polish food composition tables [22]. In addition, the ratio of n6:n3 fatty acids was calculated to assess the balance of n-6 and n-3 PUFA intake in the mother's diet.

Atopic dermatitis and food allergy

The assessment of children's health was done for each time point of the study (at 1, 2 and 7–9 year of age) using the several procedures: questionnaires filled in by the mothers (based on the International Study of Asthma and Allergies in Childhood [ISAAC] recommendations), information from medical chart and examination performed by an allergist. Details ware published previously [17,18,23].

Covariates

The authors have considered the following covariate variables (based on analyses from this and other cohorts): mother's age and education level, family economic situation, previous pregnancies, pre-pregnancy body mass index (BMI), maternal saliva cotinine level, child's sex, child's urine cotinine level, child's breastfeeding and diet, pets at home, dampness/mold at home, and parental atopy or asthma. Details have been published previously [17–19,24].

Statistical analyses

Maternal/parental or home characteristics are presented as percentages or means (M) and standard deviations (SD). Generalized estimating equations were performed in order to assess the prevalence of AD and FA at 3 time points. Independent variables in the equation were n-3, n-6 PUFAs and n-6:n-3 PUFAs ratio. In addition, multivariate models were run to assess the association of PUFAs with AD and FA. The results were presented as odds ratios (OR), 95% confidence intervals (CI) and p-value.

RESULTS

The parental, home and child characteristics are shown in Table 1. On average, women were 29 years old at delivery. The majority of women had higher education level attainment and were of high socio-economic status (SES). About 10% of the women smoked in pregnancy whereas 50% of the toddlers and 30% of early school age children were exposed to passive smoking. More than 50% of the population owned pets. Dampness at home was declared by 10% of the mothers.

Summary of the PUFAs intake are presented in Table 2. In the entire population the n-3 PUFAs was M±SD 1.2±0.4 g/day, n-6 PUFAs was 7.7±2.2 g/day and n-6:n-3 fatty acid ratio was 6.8±1.1. The prevalence of AD was 37%, 26% and 21% and FA 26%, 22% and 22% at age of 1, 2 and 7–9 years, respectively (Table 1). In multivariate model n-6 PUFAs were significantly associated with increased risk of persistent FA (OR = 1.5, 95% CI: 1.1–2.1) (Table 3). No other statistically significant associations for multivariate models were observed. Based on generalized estimating equations higher n-6:n-3 fatty acid ratio correlated, of borderline significance, with higher prevalence of AD at age of 7–9 years ($p < 0.07$).

Table 1. Characteristics of the study population in the prospective study on the association between maternal dietary intake of PUFAs during pregnancy and atopic dermatitis (AD) and food allergy (FA) in children up to 7–9 years of age, Poland, 2007–2019

Variable[a]	Participants (N = 557)		
	examined at age of 1 year (N = 340)	examined at age of 2 years (N = 216)	examined at age of 7–9 years (N = 336)
Maternal/parental or home characteristics			
maternal age [years] (M±SD)	29.5±4.3	29.7±4.3	29.5±3.8
maternal education [%]			
≤12 years	34.4	31.9	29.5
>12 years	65.6	68.1	70.5
socio-economic status [%]			
low/medium	22.8	24.4	27.2
high	77.2	75.6	72.8
missing data[b]	0.9	1.4	1.5
parity [%]			
0	41.7	42.1	43.2
≥1	58.3	57.9	56.8
missing data[b]	0.6	0.9	0.0
maternal pre-pregnancy BMI [kg/m^2] (M±SD)	22.5±3.6	22.7±3.9	22.4±3.8
missing data[b] [%]	1.2	1.9	0.6
cotinine level in maternal saliva during pregnancy (GM±SD) [ng/ml]	1.3±4.6	1.3±4.2	1.2±3.7
missing data[b] [%]	9.1	6.9	5.1
parental atopy or asthma [%]			
yes	21.3	19.2	18.8
no	78.7	80.8	81.2
missing data[b]	0.6	0.9	0.0
dampness at home [%]			
yes	13.2	8.8	11.2
no	86.8	91.2	88.8
missing data[b]	1.8	0.5	4.5
pets at home [%]			
yes	52.2	60.5	60.7
no	47.8	39.5	39.3
missing data[b]	6.5	12.0	3.0
Child characteristics			
sex [%]			
female	51.5	50.0	50.0
male	48.5	50.0	50.0
cotinine level in urine (GM±SD) [ng/ml]	2.0±3.5	2.0±3.9	1.1±3.5
missing data[b] [%]	0.6	1.4	4.8

Table 1. Characteristics of the study population in the prospective study on the association between maternal dietary intake of PUFAs during pregnancy and atopic dermatitis (AD) and food allergy (FA) in children up to 7–9 years of age, Poland, 2007–2019 – cont.

Variable[a]	Participants (N = 557)		
	examined at age of 1 year (N = 340)	examined at age of 2 years (N = 216)	examined at age of 7–9 years (N = 336)
Child characteristics– cont.			
breastfeeding [%]			
yes	91.8	93.1	n.a.
no	8.2	6.9	n.a.
atopic dermatitis [%]			
yes	37.2	25.6	20.9
no	62.8	74.4	79.1
missing data[b]	0.3	0.5	9.2
food allergy [%]			
yes	25.5	22.3	22.3
no	74.5	77.7	77.7
missing data[b]	1.2	1.4	6.5

[a] Characteristics (percentages or means) calculated for observed values.
[b] Percentages of total number of subjects.
n.a. – not applicable.

DISCUSSION

The existing studies indicate that prenatal PUFAs, through inflammation, can impact development of the immune system of the fetus, which may increase the risk of development of allergic diseases later in life. The long-term consequences of maternal diet during pregnancy, specifically n-6 PUFAs and n-6:n-3 fatty acids ratio, on FA and AD were observed in our prospective REPRO_PL cohort.

The studies in this field focused on the assessment of maternal PUFAs intake, fish consumption, PUFAs supplementation as well as the assessment of prenatal or cord blood fatty acids and offspring FA and AD, however the results are not consistent [4,7,8,15]. For instance, studies conducted in Singapore or Germany found no association between prenatal intake of PUFAs and development of childhood AD [14,25]. In the Dutch cohort negative association was observed between plasma n-6:n-3 PUFAs in the last trimester of pregnancy and AD at age of 6–7 years, in a Spanish study higher plasma PUFAs concentrations during pregnancy and higher PUFA n-3 concentrations in cord blood protected against AD in early childhood [26,27]. In Dutch and U.S. cohorts n-6 PUFAs were associated with increased risk of AD [28,29]. First, it needs to be underlined that PUFAs can cross placenta. Moreover, the inconsistency in existing studies may be due to several aspects, including the accuracy of PUFAs intake or content assessment, the age of the child, and tools/methods used to assess their health and control for confounding factors.

In the sample, the average dietary n-6:n-3 fatty acid ratio during pregnancy was M±SD 6.8±1.1. Accord-

Table 2. Polyunsaturated fatty acids (PUFAs) from maternal diet during pregnancy in the prospective study on the association between maternal dietary intake of PUFAs during pregnancy and atopic dermatitis (AD) and food allergy (FA) in children up to 7–9 years of age based on data from Polish Mother and Child Cohort (REPRO_PL) (557 mother–child pairs)

PUFAs	Age at examination		
	1 year	2 years	7–9 years
Total [g/day]			
M±SD	8.83±2.33	8.73±2.27	8.91±2.64
min.–max	2.37–20.04	2.37–19.25	1.52–20.04
n-3 [g/day]			
M±SD	1.17±0.34	1.16±0.32	1.16±0.38
min.–max	0.32–2.78	0.32–2.51	0.21–3.22
n-6 [g/day]			
M±SD	7.67±2.06	7.58±2.00	7.74±2.33
min.–max	2.06–17.28	2.06–17.74	1.31–17.28
n-6:n-3 fatty acid ratio			
M±SD	6.72±1.08	6.65±1.00	6.77±1.08
min.–max	2.30–9.36	3.54–9.36	2.92–9.01

AA – arachidonic acid (C20:4n-6); ALA – alpha-linolenic acid (C18:3n-3); DGLA – dihomo-gamma-linolenic acid (20:3n-6); DHA – docosahexaenoic acid (C22:6n-3); DPA – docosapentaenoic acid (C22:5n-3); EPA – eicosapentaenoic acid (C20:5n-3); LA – linoleic acid (C18:2n-6); SDA – stearidonic acid (C18:4n-3).
PUFAs – sum of n-3 and n-6.
n-3 = ALA + SDA + EPA + DPA+ DHA; n-6 = LA + DGLA + AA.

ing to the current recommendations n-6:n-3 fatty acid ratio should be <5. In the sample only 6.5% of the mothers followed that recommendation and almost half had the ratio >7. In the EDEN cohort (established in France at a similar period as REPRO_PL) average maternal dietary n-6:n-3 fatty acid ratio was even higher (M±SD 8.5±2.4) [30]. A high amount of n-6 PUFAs may reduce n-3 PUFAs since the metabolic pathways of both PUFAs compete for the same enzymes (d-5 and d-6 desaturases – encoded by fatty acid desaturase 1 (FADS1) and FADS2) [31]. As mentioned previously n-3 PUFAs have anti-inflammatory properties, reduce circulating inflammatory markers and oxidative stress, whereas n-6 PUFAs generally have a pro-inflammatory effect. It is suggested that n-3 PUFAs (EPA and DHA) by inhibiting IκB phosphorylation inhibit nuclearfactor-κappa B (NF-κB) signaling pathway, thereby reducing the expression of inflammation-related genes.

The prospective nature of this study is undoubtedly its strength. The assessment of maternal PUFAs intake (based on FFQ) allowed the authors to consider such nutrients from variety of sources. Moreover, child allergy was assessed based on ISAAC recommendations as well as allergist examination. Finally, in the analyses a wide spectrum of covariates has been taken into account.

The limitation of this study is the accuracy of the evaluation of PUFAs intake during pregnancy. The authors used FFQ for dietary assessment. Thus, the under or over reporting of nutrients intake could have occurred. Considering its practicality FFQ seems to be the tool of choice in population studies. The estimates based on FFQ are less accurate compared to 24-h recalls, however PUFAs intake assessed from FFQ correlates well with biological markers [32]. In addition, in the REPRO_PL study, dietary data were not collected at several time points, making it impossible to determine changes in dietary patterns occurring through pregnancy. It should

Table 3. Polyunsaturated fatty acids (PUFAs) from maternal diet during pregnancy and offspring atopic dermatitis and food allergy – multivariable models – the prospective study on the association between maternal dietary intake of PUFAs during pregnancy and atopic dermatitis (AD) and food allergy (FA) in children up to 7–9 years of age based on data from Polish Mother and Child Cohort (REPRO_PL) (557 mother–child pairs)

PUFAs	At age of 1 year			At age of 2 years			At age of 7–9 year			Persistent		
	AOR	95% CI	p	AOR	95% CI	p	AOR	95% CI	p	AOR	95% CI	p
Atopic dermatitis												
n-3	0.91	0.43–1.94	0.85	1.14	0.63–2.07	0.65	1.14	0.63–2.07	0.65	0.50	0.10–2.53	0.40
n-6	0.98	0.87–1.12	0.85	1.00	0.93–1.08	0.96	1.00	0.93–1.08	0.96	0.81	0.62–1.07	0.14
n-6:n-3 fatty acid ratio	1.05	0.83–1.32	0.71	0.85	0.64–1.12	0.24	0.85	0.64–1.12	0.24	0.65	0.34–1.24	0.19
Food allergy												
n-3	1.21	0.51–2.86	0.66	0.86	0.29–2.59	0.79	1.66	0.51–5.41	0.40	4.99	0.73–34.21	0.10
n-6	1.05	0.91–1.20	0.53	1.00	0.84–1.19	0.97	1.10	0.91–1.32	0.32	**1.49**	**1.06–2.10**	**0.02**
n-6:n-3 fatty acid ratio	1.08	0.83–1.40	0.58	1.11	0.78–1.59	0.56	1.03	0.71–1.50	0.86	1.20	0.71–2.04	0.50

aOR – adjusted odds ratio: adjusted for covariates listed in methods section.
Bolded are p-values <0.05.

be noted, that the existing analyses do not report significant changes in eating patterns during pregnancy. The estimates of nutrients were based on the food composition tables, which do not consider all their variations depending on food origin, its quality as well as cooking processes. The effect of children's diet (partially considered in this study) on AD or FA cannot be ruled out. It is of note that the observed associations can also be due to other nutrients associated with PUFAs consumption. Finally, although a wide range of potential covariates have been evaluated, some could have been missed. Taking this into account confounding due to unmeasured factors (i.e., socio-demographic or lifestyle-related) may have occurred.

CONCLUSIONS

The authors' results may contribute to the existing knowledge on the impact of maternal diet during pregnancy on children's optimal health. More precisely, the authors noted that n-6 PUFAs and the ratio between maternal dietary n-6 and n-3 PUFAs are associated with a higher risk of persistent FA and AD respectively. However, given the lack of consistent associations in the studies to date, further research is needed before developing public health recommendations and guidelines for clinical practice.

Author contributions

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