

ORIGINAL ARTICLE

Dietary fatty acid composition during pregnancy and the risk of asthma in the offspring

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Keywords

asthma; children; fatty acids; maternal diet; pregnancy; cohort study.

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Abstract

Background: Fatty acids (FA) modulate the immune system, and it has been proposed that they affect the incidence of IgE-mediated allergic diseases. We explored the association of maternal dietary FA composition during pregnancy with the risk of asthma in the offspring.

Methods: We analyzed data from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study. Maternal dietary intake during pregnancy (8th month) was assessed by a validated 181-item food frequency questionnaire. The occurrence of asthma was assessed at the age of 5 yr with a questionnaire modified from the International Study of Asthma and Allergies in Childhood (ISAAC). Cox proportional hazards regression was used for the statistical analyses.

Results: Low maternal intakes of α -linolenic acid (18:3n-3) [lowest quarter vs. mid-half HR 1.67 (95% CI 1.12–2.48)] and total n-3-polyunsaturated fatty acids (PUFA) [HR 1.66 (95% CI 1.11–2.48)] during pregnancy were associated with an increased risk of asthma in the offspring, while a low intake of arachidonic acid (20:4n-6) [HR 0.52 (95% CI 0.32–0.84)] and high intake of total saturated fatty acids [highest quarter vs. mid-half HR 0.55 (95% CI 0.34–0.90)] and palmitic acid (16:0) [HR 0.51 (95% CI 0.31–0.83)] were associated with a decreased risk of asthma. The ratios of n-6 to n-3-PUFA and 18:2n-6 to 18:3n-3, and the maternal intake of oils, fish and fish products, showed no association with the risk of asthma. The associations found were independent of several perinatal and clinical confounders.

Conclusion: Maternal intake of FA during pregnancy was associated with childhood asthma. Maternal α -linolenic acid, total n-3 PUFA and palmitic acid intake may decrease, while arachidonic acid intake may increase the risk of asthma in the offspring.

Abbreviations:

FA, fatty acid; SAFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; LA, linoleic acid; ALA, α -linolenic acid; ARA, arachidonic acid; EPA, eicosapentanoic acid; DHA, docosahexaenoic acid.

Epidemiological studies suggest that the increasing rate of asthma and allergic diseases in Western societies are partly related to the changes in dietary habits that have taken place over the recent decades. The increased consumption of margarines and vegetable oils that has coincided with the

decreased consumption of oily fish and fish products has together lead to an increased intake of n-6 polyunsaturated fatty acids (PUFA) and a decreased intake of n-3 PUFA (1). In Finland, the consumption of saturated fatty acids (SAFA) has decreased, while the consumption of PUFA has increased during the past 25 yr (2). These changes may be crucial in the development of asthma and allergic diseases as fatty acids (FA) modulate the immune system. The effects of FA, and PUFA in particular, on immune function, have been intensively studied during the past few decades. The n-6 PUFA arachidonic acid is a precursor for pro-inflammatory eicosanoids, while the n-3 PUFA are a precursor for less potent inflammatory eicosanoids as well as anti-inflammatory resolvins. Changes in dietary habits shift the T-helper balance from type 1 to type 2 and stimulate the production of immunoglobulin E (IgE), thus increasing the incidence of IgE-mediated allergic diseases such as asthma (3).

The intrauterine environment and antenatal exposures have an impact on the development of allergic diseases. Maternal diet during pregnancy can modulate the early immunologic reactions of the fetus and the infant, thus affecting the balance between inflammatory and anti-inflammatory reaction types. The mother's prenatal diet might influence the development of childhood asthma by affecting fetal airway development and by modulating interactions between allergens and the immune system (4, 5). In addition, it is possible that prenatal n-3 FA exposure alters the eicosanoid metabolism of a neonate (6).

Observational studies suggest that maternal fish or fish oil consumption during pregnancy is protective against childhood allergies and atopy. However, the results of these studies are inconsistent (7).

In a recent systematic review of double-blind placebo controlled randomized trials, no clear evidence was obtained for an association between supplementation of the child with n-3 PUFA and n-6 PUFA at any age and the risk of asthma, allergic rhinitis, atopic eczema or food allergy (8). However, intervention studies have reported that early maternal fish oil supplementation during pregnancy has a persistent, long-term protective effect against asthma until adolescence (7).

There are only a few studies investigating the impact of maternal fatty acid intake during pregnancy on the risk of asthma in the offspring. A Japanese group found that maternal intake of α -linolenic acid and docosahexaenoic acid during pregnancy may protect against infantile wheezing (9). The impact of maternal fatty acid status on childhood atopic diseases was studied in a recent cohort study (10). High ratio of n-6 to n-3 PUFA was associated with a lower risk of atopic eczema in infants during the first year of life. Also, they found that a high intake of arachidonic acid was associated with a decreased risk of atopic eczema. Further information is needed on to elucidate whether the incidence of asthma can be reduced by modulating the dietary fatty acid composition during pregnancy or early life.

The aim of this study was to explore the associations between maternal dietary FA composition during pregnancy and the offspring's risk of asthma by the age of 5 yr.

Subjects and methods

Subjects and study design

In the Type 1 Diabetes Prediction and Prevention (DIPP) Project, a population-based cohort study, infants at three university hospitals in Finland (Turku, Tampere and Oulu) were screened for HLA-conferred genetic susceptibility to type 1 diabetes (HLA-DQB1) with the use of cord blood samples after parental informed consent (11). Infants with a high or moderate genetic risk (HLA-DQB1*02/0302 heterozygous and DQB1*0302/x-positive subjects; x stands for homozygosity or neutral alleles) of type 1 diabetes were invited to participate in the study (15% of those screened). Infants with severe congenital malformations or diseases, parents of non-Caucasian origin or parents who did not have a working knowledge of Finnish, Swedish or English were excluded from the study.

The current report is part of the DIPP Nutrition Study (12), which was started within the framework of the larger DIPP in 1996. The focus of the Nutrition Study is to investigate the impact of maternal nutrition during pregnancy and lactation, and the child's diet, on the development of advanced beta cell autoimmunity, type 1 diabetes, asthma, allergic diseases and obesity in the offspring.

Altogether 7238 children were invited in the DIPP Nutrition Study during the time period when also maternal pregnant dietary data were collected. Of those, children who were still taking part in the dietary follow-up at the age of 5 yr ($n = 4065$) were invited to participate in the DIPP Allergy Study by completing a questionnaire on the child's history of allergic symptoms and asthma. Maternal dietary data during pregnancy were requested for children born between December 13, 1997, and October 31, 2004, in Oulu University Hospital and October 20, 1997, and September 5, 2004, in Tampere University Hospital. The end-point data were available for 2908 children. Of those children for whom maternal dietary data were available, 2680 had also information on their history of asthma. One case child was excluded because of missing data on the age of asthma diagnosis, which would have been required for statistical analyses, resulting in 2679 subjects available in the end-point analysis.

Dietary assessment

Dietary intakes during pregnancy were determined using a validated, self-administered, semi-quantitative 181-item food frequency questionnaire (FFQ) (13). The FFQ was designed to assess the total maternal diet over a period of 1 month. The frequency of food consumption (number of times per day, per week or per month) was assessed as common serving sizes (portion sizes based on natural units and commonly used portions identified in earlier Finnish dietary studies). The questionnaire was designed to reflect specifically the food use of pregnant Finnish women. The FFQ assessed the diet of the mother during the 8th month of pregnancy, the month just before maternity leave in Finland. The mothers were asked to supply information on the use of nutrient supplements over the whole duration of the pregnancy. The use of

nutrient supplements during the whole pregnancy was asked in a separate question from the mothers with brand names, manufacturers and the amount of use per day, week or month. Only 1.8% of the mothers used fish oil containing supplements.

The FFQ was returned to the study center and checked by a trained study nurse or doctor at the child's 3-month visit. All returned FFQ forms were further assessed by a trained nutritionist. FFQs with 10 or more food items with missing data were rejected. Food consumption data were analyzed using a software program, which is continuously being updated, developed at the National Institute of Health and Welfare, Helsinki, and converted into a daily food diary from which the mean daily use of foods and nutrients was calculated. Information on fats used in cooking and baking and oils used for salad dressing was inquired and included in the nutrient calculations. Detailed information on the content of the FFQ and data processing has been described earlier (13, 14).

Asthma diagnosis

When the child was 5 yr, the parents completed a modified, validated (15), ISAAC-based (16) allergy questionnaire, where the child's history of allergic diseases was inquired. The ISAAC-based questionnaire was validated against the anti-asthmatic medication reimbursement data of the Finnish Social Insurance Institution. Two combined questions (any wheezing symptom or use of asthma medication during the preceding 12 months plus doctor diagnosed asthma) were validated against a valid reimbursement with a purchase of at least one anti-asthmatic medication during a 12-month period (15). Based on the validation study, asthma was defined as doctor-diagnosed asthma plus any wheezing symptom or the use of asthma medication during the preceding 12 months before completion of the ISAAC-based questionnaire. The age at diagnosis was reported by the parents. We choose the age of 5 yr at the age at diagnosis to exclude younger children with wheezing associated with viral infections. All the children in our study population still had asthma at the age of 5 yr indicating persistent asthma. There were seven cases with missing age at diagnosis and three cases with the age at diagnosis 0 yr. For five of those, the age of first wheezing was set at the age at diagnosis. For one case, the age at diagnosis was defined from the Social Insurance Institution data on anti-asthmatic medication. The age at diagnosis was the age of the first reimbursement. One child missing all the information on age at diagnosis or first wheezing episode was excluded, as was one child with bronchopulmonary dysplasia.

Sociodemographic and perinatal characteristics

Information on the child's gender, maternal age at the time of child's birth, parental vocational education and the number of earlier deliveries was recorded in a structured questionnaire filled in by the parents after the delivery. Information on duration of gestation, the mode of delivery (vaginal delivery or cesarean section), birth weight, place of birth and

maternal smoking during pregnancy, as well as diagnoses of any infections of the mother during pregnancy and delivery, and infections and antibiotic treatment of the child during the first week of life, was received from the Medical Birth Register.

Statistical analysis

Logistic regression analysis was used to assess the associations between background characteristics and the risk of asthma. We applied Cox proportional hazards regression to assess the association between maternal intake of FAs and dietary fats during pregnancy and the risk of asthma in the children by the age of 5 yr. The dietary intake of FAs was energy adjusted by the Willett's residual method (17). When assessing associations with the food variables, energy was also included in the model. All dietary variables were divided into quarters. The lowest and highest quarters were compared with the combined mid-half as the reference category. The selection of confounding variables was based on their relations with the exposure and the outcome in the present study and also according to earlier findings. In the adjusted models, the following covariates were used: maternal age, mode of delivery, duration of gestation, number of earlier deliveries, birth weight, sex of the child, area of birth, maternal smoking during pregnancy, parental asthma or allergic rhinitis, maternal vocational education, pets at home, farming, contact with cow stable during the first year of life and the duration of total breastfeeding. The statistical significance of the dietary variables was tested with the Wald's chi-square test.

There were 27 twin-to-twin pairs and 283 other sibling pairs. When taking the sibling effect into account in the Cox regression, the results remained the same. Maternal sources of dietary FAs were calculated in grams or milligrams per day and in per cents of the total fatty acid intake. Analyses were computed using the SAS statistical package (Version 9.1.; SAS Institute Inc., Cary, NC, USA). The sibling effect was taken into account in the Co regression by clustering by family in STATA (Version 9.2.; College Station, TX, USA).

Ethical approval

The DIPP Nutrition study has been approved by the ethical committees of Oulu and Tampere University Hospitals, and a written informed consent was obtained from the parents.

Results

Among the children with end-point data, 175 (6%) were reported to have persistent asthma by the age of 5 yr (Table 1). Among the children with complete information on maternal diet and the end-point, 158 (5.9%) had asthma. There was evidence of associations between some of the background variables and asthma. Higher gestational age and female gender were associated with a reduced risk of asthma. Maternal as well as paternal asthma and allergic rhinitis, and antibiotic treatment of the child during the first

Table 1 Characteristics of the participating children with information on their history of asthma (N = 2908) and their mothers

	Distribution of children (%) N = 2908	Number of children with asthma (cumulative incidence %) N = 175 (6%)
Maternal age (yr)		
<25	429 (14.8)	32 (7.5)
25–29	1029 (35.4)	60 (5.8)
30–34	884 (30.4)	54 (6.1)
≥35	566 (19.5)	29 (5.1)
Missing data	–	–
Delivery		
Vaginal	2507 (86.2)	144 (5.7)
Cesarean section	379 (13.3)	30 (7.9)
Missing data	22 (0.8)	1 (4.6)
Gestational age (weeks)		
<37	176 (6.1)	19 (10.8)
37–42	2613 (89.9)	148 (5.7)
>42	88 (3.0)	7 (8.0)
Missing data	31 (1.1)	1 (3.2)
Number of previous deliveries		
0	1294 (44.5)	71 (5.5)
1–2	1320 (45.4)	94 (7.1)
>2	263 (9.0)	7 (2.7)
Missing data	31 (1.1)	3 (9.7)
Gender		
Girls	1391 (47.8)	68 (4.9)
Boys	1517 (52.2)	107 (7.1)
Area		
Northern Finland	1030 (35.4)	63 (6.1)
Southern Finland	1878 (64.6)	112 (6.0)
Missing data	–	–
Smoking during pregnancy		
No	2603 (89.5)	157 (6.0)
Yes	208 (7.2)	13 (6.3)
Missing data	97 (3.3)	5 (5.2)
Maternal asthma or allergic rhinitis		
No	1535 (52.8)	56 (3.7)
Yes	1270 (43.7)	114 (9.0)
Missing data	103 (3.5)	5 (4.9)
Paternal asthma or allergic rhinitis		
No	1651 (56.8)	78 (2.7)
Yes	1098 (37.8)	87 (7.9)
Missing data	159 (5.5)	10 (6.3)
Maternal vocational education		
None	139 (4.8)	6 (4.3)
Vocational school or course	762 (26.2)	49 (6.4)
Secondary vocational	1307 (44.9)	77 (5.9)
University studies or degree	653 (22.5)	36 (5.5)
Missing data	47 (1.6)	7 (14.9)
Birth weight in quarters		
780–3240 g	723 (24.9)	57 (7.9)
3241–3599 g	721 (24.8)	38 (5.3)
3600–3910 g	721 (24.8)	44 (6.1)
3911–5620 g	721 (24.8)	35 (4.9)

Table 1 (Continued)

	Distribution of children (%) N = 2908	Number of children with asthma (cumulative incidence %) N = 175 (6%)
Missing data	22 (0.8)	1 (4.6)
Antibiotic treatment of the child during 1st week of life		
No	2842 (97.7)	168 (5.9)
Yes	44 (1.5)	6 (13.6)
Missing data	22 (0.8)	1 (4.6)

week of life, were associated with an increased risk of asthma (Table 1).

Low maternal intake of α -linolenic acid (18:3n-3) (HR 1.67 [95% CI 1.12–2.48]) and total n-3 PUFA (HR 1.66 [95% CI 1.11–2.48]) during pregnancy were associated with an increased risk of asthma in the offspring, while a low intake of arachidonic acid (20:4n-6) (HR 0.52 [95% CI 0.32–0.84]) was associated with a decreased risk of asthma (Table 2). High intakes of total saturated fatty acids (HR 0.55 [95% CI 0.34–0.90]) and palmitic acid (16:0) (HR 0.51 [95% CI 0.31–0.83]) during pregnancy were associated with a decreased risk of asthma in the offspring. High intake of conjugated linoleic acid (18:2n-6, con) (HR 0.64 [95% CI 0.40–1.00]) was marginally associated with a decreased risk of asthma (Table 2). Conjugated linoleic acid (18:2n-6, con) includes all the isomers together, that is, both trans- and cis-isomers, and is same as 9-cis, 11-trans-CLA. The results remained the same when adjusted for vitamin D intake (data not shown). Associations between the main dietary sources of these fatty acids and childhood asthma could not be demonstrated (Table 3).

When the variables 18:3n-3 and 16:0 and 20:4n-6 were studied together in the same model with respect to the risk of asthma, they were all independently associated with the risk of asthma (data not shown).

We found no association between maternal intake of oils, oily fish and fish products and the risk of asthma in the offspring. High maternal consumption of butter and butter spreads during pregnancy was associated with an increased risk of asthma in the offspring (Table 3). This finding was not statistically significant after adjustments for putative confounders. The use of margarine was divided into two groups (users and non-users), not quarters, because <75% of the mothers used margarines. Use of margarines was not associated with the risk of asthma.

The main sources of n-6 PUFA and 18:2n-6 among pregnant Finnish women were oils, margarines and red meat and meat products, while the main sources of n-3 PUFA were oils, margarines and fish (Table 4). The main source of SAFA and conjugated linoleic acid was milk and milk products. The intakes of n-3 and n-6 PUFA were highly correlated with each other (Spearman correlation coefficient 0.86, $p < 0.0001$). The intakes of total SAFA, 16:0, n-6 PUFA,

Table 2 The risk of asthma (hazard ratios (HR) and 95% confidence interval (CI)) associated with maternal fatty acid intake during pregnancy (N = 2679, 158 children with asthma)

FAs in quarters (ranges)	Unadjusted HR (95% CI)	P-value*	Adjusted† HR (95% CI)	P-value*
SAFAs				
Lowest quarter (<32.93)	1.29 (0.90–1.86)	0.024	1.28 (0.86–1.90)	0.008
Mid-half (32.93–53.84)	1		1	
Highest quarter (>53.84)	0.68 (0.45–1.03)		0.55 (0.34–0.89)	
MUFAs				
Lowest quarter (<27.58)	1.11 (0.76–1.63)	0.364	1.14 (0.75–1.74)	0.173
Mid-half (27.58–42.97)	1		1	
Highest quarter (>42.97)	0.81 (0.55–1.19)		0.71 (0.45–1.10)	
PUFAs				
Lowest quarter (<10.71)	1.47 (1.03–2.11)	0.073	1.32 (0.89–1.97)	0.162
Mid-half (10.71–17.01)	1		1	
Highest quarter (>17.01)	1.00 (0.67–1.49)		0.84 (0.53–1.32)	
Palmitic acid				
16:0				
Lowest quarter (<15.53)	1.24 (0.86–1.79)	0.013	1.30 (0.87–1.94)	0.003
Mid-half (15.53–24.82)	1		1	
Highest quarter (>24.82)	0.61 (0.41–0.94)		0.50 (0.30–0.82)	
N-6 PUFAs				
Lowest quarter (<8.03)	1.62 (1.14–2.31)	0.011	1.41 (0.95–2.08)	0.039
Mid-half (8.03–12.75)	1		1	
Highest quarter (>12.75)	0.95 (0.63–1.43)		0.75 (0.47–1.20)	
LA				
18:2n-6				
Lowest quarter (<7.78)	1.52 (1.06–2.17)	0.03	1.30 (0.87–1.92)	0.067
Mid-half (7.78–12.36)	1		1	
Highest quarter (>12.36)	0.92 (0.61–1.38)		0.71 (0.45–1.13)	
LA, conjugated				
18:2n-6, con				
Lowest quarter (<0.13)	0.95 (0.64–1.39)	0.274	0.91 (0.60–1.39)	0.148
Mid-half (0.13–0.24)	1		1	
Highest quarter (>0.24)	0.72 (0.49–1.08)		0.64 (0.41–1.00)	
ARA				
20:4n-6				
Lowest quarter (<0.06)	0.60 (0.39–0.91)	0.052	0.52 (0.32–0.84)	0.025
Mid-half (0.06–0.11)	1		1	
Highest quarter (>0.11)	0.85 (0.58–1.24)		0.77 (0.51–1.17)	
N-3 PUFAs				
Lowest quarter (<2.24)	1.69 (1.17–2.42)	0.018	1.66 (1.11–2.48)	0.036
Mid-half (2.24–3.84)	1		1	
Highest quarter (>3.84)	1.19 (0.81–1.77)		1.09 (0.70–1.70)	
ALA				
18:3n-3				
Lowest quarter (<1.83)	1.78 (1.24–2.55)	0.005	1.70 (1.14–2.53)	0.022
Mid-half (1.83–3.18)	1		1	
Highest quarter (>3.18)	1.13 (0.76–1.68)		1.06 (0.68–1.65)	
EPA				
20:5n-3				
Lowest quarter (<0.04)	1.20 (0.83–1.74)	0.606	1.09 (0.72–1.65)	0.604
Mid-half (0.04–1.13)	1		1	
Highest quarter (>0.13)	0.97 (0.66–1.43)		0.84 (0.54–1.31)	
DHA				
22:6n-3				
Lowest quarter (<0.10)	0.89 (0.61–1.31)	0.605	0.80 (0.52–1.23)	0.467
Mid-half (0.10–0.32)	1		1	
Highest quarter (>0.32)	0.83 (0.56–1.22)		0.83 (0.53–1.29)	

Table 2 (Continued)

FAs in quarters (ranges)	Unadjusted HR (95% CI)	P-value*	Adjusted† HR (95% CI)	P-value*
Ratio of n-6 to n-3 FAs				
Lowest quarter (<3.07)	0.98 (0.67–1.43)	0.937	0.95 (0.62–1.46)	0.835
Mid-half (3.07–3.82)	1		1	
Highest quarter (>3.82)	1.06 (0.72–1.55)		1.10 (0.72–1.68)	
Ratio of LA to ALA				
Lowest quarter (<3.56)	1.04 (0.71–1.52)	0.523	0.99 (0.64–1.53)	0.191
Mid-half (3.56–4.47)	1		1	
Highest quarter (>4.47)	1.24 (0.85–1.80)		1.40 (0.93–2.09)	

*Test for trend (Wald's chi-square test)

†Adjusted for sex, area of birth, duration of gestation, maternal age, maternal vocational education, maternal smoking during pregnancy, number of previous deliveries, parental asthma, parental allergic rhinitis, birth weight, mode of delivery, pets at home, farming, contact with cow stable during the first year of life and the duration of total breastfeeding.

FA=fatty acid, SAFA=saturated fatty acid, MUFA=monounsaturated fatty acid, PUFA=polyunsaturated fatty acid, LA=linoleic acid, ALA= α -linolenic acid, ARA=arachidonic acid, EPA=eicosapentanoic acid, DHA=docosahexanoic acid**Table 3** The risk of asthma (hazard ratios (HR) and 95% confidence interval (CI)) associated with maternal dietary fat consumption during pregnancy (N = 2679, 158 cases with asthma)

Food variable (ranges)	Unadjusted* HR (95% CI)	P-value†	Adjusted‡ HR (95% CI)	P-value
Oils				
Lowest quarter (<7.32)	1.21 (0.83–1.77)	0.414	1.07 (0.69–1.65)	0.576
Mid-half (7.32–16.60)	1		1	
Highest quarter (>16.60)	1.26 (0.86–1.87)		1.26 (0.82–1.94)	
Margarines				
User (>15.00)	0.76 (0.55–1.04)	0.084	0.82 (0.58–1.17)	0.274
Non-user (0)	1		1	
Butter and butter oil mixes				
Lowest quarter (<4.63)	1.49 (1.00–2.22)	0.011	1.41 (0.91–2.19)	0.126
Mid-half (4.63–19.78)	1		1	
Highest quarter (>19.78)	1.73 (1.91–2.51)		1.47 (0.96–2.23)	
Industrial fats§				
Lowest quarter (<11.44)	1.50 (1.01–2.22)	0.068	1.40 (0.91–2.16)	0.309
Mid-half (11.44–29.70)	1		1	
Highest quarter (>29.70)	1.42 (0.96–2.09)		1.09 (0.70–1.70)	
Fish				
Lowest quarter (<10.67)	1.31 (0.90–1.89)	0.347	1.12 (0.74–1.70)	0.861
Mid-half (10.67–31.99)	1		1	
Highest quarter (>31.99)	1.19 (0.80–1.76)		1.06 (0.68–1.65)	
Red meat and meat products				
Lowest quarter (<88.49)	0.90 (0.60–1.36)	0.629	0.76 (0.47–1.22)	0.469
Mid-half (88.49–156.44)	1		1	
Highest quarter (>156.44)	1.16 (0.77–1.74)		1.06 (0.67–1.67)	
Milk and milk products				
Lowest quarter (<546.62)	1.27 (0.88–1.84)	0.069	1.17 (0.78–1.77)	0.282
Mid-half (546.62–1099.84)	1		1	
Highest quarter (>1099.84)	0.70 (0.45–1.09)		0.73 (0.44–1.21)	

*Energy included in the model.

†Test for trend (Wald's chi-square test)

‡Adjusted for sex, area of birth, duration of gestation, maternal age, maternal vocational education, maternal smoking during pregnancy, number of previous deliveries, parental asthma, parental allergic rhinitis, birth weight, mode of delivery, pets at home, farming, contact with cow stable during the first year of life and the duration of total breastfeeding.

§Industrial fat mixes and animal fats.

Table 4 Maternal sources of dietary fatty acids (g/day or mg/day (%*)) among pregnant Finnish women during 1997–2004

Ingredient	Saturated fatty acids g/d (%)	n-6 PUFA g/d (%)	Linoleic acid 18:2n-6 g/d (%)	Arachidonic acid 20:4n-6 mg/d (%)	n-3 PUFA g/d (%)	α -linolenic acid 18:3n-3 g/d (%)	EPA 20:5n-3 mg/d (%)	DHA 22:6n-3 mg/d (%)
Oils	1.3 (2.8)	3.3 (30.6)	3.3 (31.4)	0.2 (0.2)	1.0 (32.4)	1.0 (37.9)	0 (0)	0 (0)
Margarines	1.8 (4.1)	1.0 (9.3)	1.0 (9.4)	0 (0)	0.4 (12.7)	0.4 (14.9)	0 (0)	0 (0)
Butter and butter oil mixes	5.8 (13.0)	0.5 (4.7)	0.5 (4.7)	0 (0)	0.2 (6.6)	0.2 (7.8)	0 (0)	0 (0)
Industrial fat†	3.3 (7.5)	0.7 (6.4)	0.7 (6.6)	0.02 (0.02)	0.2 (5.9)	0.2 (7.3)	0 (0)	0 (0)
Fish	0.3 (0.7)	0.1 (1.3)	0.1 (1.2)	8 (8.2)	0.4 (11.4)	0.02 (0.9)	70 (75.6)	200 (79.1)
Red meat and meat products	7.1 (16.0)	2.1 (19.3)	1.8 (18.1)	72 (72.8)	0.3 (11.4)	0.2 (8.9)	22 (22.5)	40 (14.6)
Milk and milk products	9.2 (20.6)	0.2 (2.4)	0.2 (2.3)	4 (3.8)	0.06 (1.9)	0.06 (2.3)	0 (0)	0 (0)
Cheese	9.9 (22.3)	0.3 (2.6)	0.3 (2.7)	0.001 (0.8)	0.08 (2.5)	0.08 (2.8)	0.003 (0.003)	0 (0)
Total	44.5 (100)	10.7 (100)	10.4 (100)	90 (100)	3.1 (100)	2.6 (100)	92 (100)	300 (100)

*% of the total fatty acid intake.

†Industrial fat mixes and animal fats.

18:2n-6, 20:4n-6 and n-3 PUFA were correlated with each other (data not shown).

We also carried out all the analyses separately with allergic ($n = 1183$) and non-allergic ($n = 1403$) mothers, but the results remained the same in both groups (data not shown).

Discussion

Our results provide evidence that a low maternal intake of α -linolenic acid (18:3n-3) during pregnancy is associated with an increased risk of asthma in the offspring. We further found that a low intake of arachidonic acid (20:4n-6) and a high intake of SAFAs, especially palmitic acid (16:0), are associated with a decreased risk of asthma in the offspring at the age of 5 yr.

The strength of the present study is that the collection of dietary data before the development of asthma excludes the selection of subjects according to the end-point. The study population is comprehensive, and the end-point is based on a standardized, validated questionnaire designed specifically for epidemiological studies. We selected the age of 5 yr for asthma diagnosis to exclude those younger children from the end-point who have wheezing associated with viral infections. As an end-point, we selected persistent asthma.

A limitation of our study is the study population, which was selected on the basis of HLA-conferred susceptibility to type 1 diabetes (about 15% of all newborn infants in Finland). As children with type 1 diabetes have been reported to have a reduced incidence of asthma and allergic diseases compared with the general population, the genetic susceptibility to type 1 diabetes may decrease the applicability of our results to the general population. However, the evidence on the association between type 1 diabetes and asthma is inconsistent (18, 19). In the present study, the cumulative incidence of asthma (5.9%) is comparable to previous studies in Finnish children (20).

The FFQs usually overestimate the intake of foods and nutrients (13). The FFQ used in our study was validated and

found suitable to measure the food consumption of pregnant Finnish women. Three criteria of validity apply to epidemiological studies: Spearman correlation coefficient should be above 0.5, more than 50% of subjects should be correctly classified and <10% of subjects should be grossly misclassified into thirds. An average of 70% of the women in the validation study of the FFQ were classified into the same or adjacent quintiles according to food intake and an average of 69% according to nutrient intake (13). In terms of dietary fats and fatty acids, the greatest misclassifications were found in oils (52%) and monounsaturated fatty acids (58%). Nonetheless, the overall classification of dietary fatty acids was adequate.

In the present study, low maternal intakes of α -linolenic acid (18:3n-3) and total n-3 PUFA during pregnancy were associated with an increased risk of asthma in the offspring. 18:3n-3 is the most common plant-derived fatty acid and can be further metabolized to 20:5n-3 and to a lesser degree to 22:6n-3. Similar results were found in a Japanese report, which suggested that higher intake of α -linolenic acid in pregnancy protects against infantile wheeze (9).

Studies investigating the connection between maternal dietary fat composition during pregnancy and atopic diseases during childhood have generated conflicting results. Epidemiological studies on maternal fish intake during pregnancy have shown a protective association on atopic outcomes in the children. In a retrospective survey, maternal intake of oily fish during pregnancy was inversely associated with the incidence of childhood asthma, but only in asthmatic mothers (21). Furthermore, low fish consumption has also been associated with an increased risk of wheezing, asthma and other atopic outcomes in the offspring (7).

In intervention studies, early fish oil supplementation (during pregnancy, lactation, infancy and childhood) has been shown to lead to immunologic changes in cord blood and higher n-3 PUFA plasma concentrations in children. It has been suggested that these changes have a persistent protective effect against allergic diseases and asthma until adolescence

(7). In the present study, we found no association between maternal fish intake and the risk of asthma in the offspring. However, the amount of fish oils used in the above mentioned studies was considerably higher than the amounts consumed by the mothers in the current study.

The finding that a low intake of arachidonic acid (20: 4n-6), a precursor for many inflammatory eicosanoids, during pregnancy decreases the risk of asthma in the offspring supports the original lipid hypothesis. However, moderate amounts of arachidonic acid are required during perinatal time for growth, health and development (22).

In the present study, high intake of SAFA and palmitic acid (16:0) in particular was associated with a decreased risk of asthma even after adjustments for putative confounding factors. Also, a high intake of conjugated linoleic acid (18:2n-6, con) was marginally associated with a decreased risk of asthma in the offspring. Our results remained the same after adjusting for pets at home and farming and contact with cow stable during the first year of life. This finding is not supported by earlier pregnancy studies in which no association between SAFAs and the risk of asthma has been observed (23). SAFAs have neither inflammatory nor anti-inflammatory properties. The finding of a protective effect of SAFAs against asthma may be related to the overall composition of the diet and may hence act as a proxy for a certain dietary pattern. However, we could not demonstrate any inverse correlation between saturated fatty acids and n-6- and n-3-PUFA (data not shown). The main sources of saturated fats in the diet of pregnant Finnish women are milk and milk products. In a prospective cohort study from Japan, higher maternal intake of total dairy products during pregnancy was related to a decreased risk of infantile wheeze in the infants aged 16–24 months. However, the beneficial association with dairy foods was suggested to be attributable, at least to some extent, to calcium (24).

The inverse relationship between milk fat consumption and asthma observed in our study has also been reported in some earlier childhood studies. A prospective birth cohort study among pre-school children from the Netherlands reported that frequent consumption of high-fat milk and butter among 2-year-olds was associated with a decreased prevalence of asthma and wheezing at the age of 3 yr (25). Further, Von Ehrenstein et al. found an inverse association between consumption of high-fat milk and asthma in 5- to 7-year-old children living on a farm, as did Hijazi et al. in

12-year-old children in Saudi Arabia. In the current study, adjustments for farming, contact with cow stable and pets at home did not change the results. We found that a high intake of conjugated linoleic acid was marginally associated with a decreased risk of asthma in the offspring. In line with our results, a prospective cohort study from the Netherlands pointed out that higher concentrations of ruminant fats, vaccenic acid (17:0), trans-11-C18:1, and cis-9, trans-11-C18:2 conjugated linoleic acid, in breast milk, were associated with a decreased risk of atopic eczema and allergic sensitization in infancy (26). In an intervention study, treatment with conjugated linoleic acid alleviated asthma symptoms in mild asthmatics (27). In mice, conjugated linoleic acid has been shown to reduce allergic airway inflammation (28).

In addition to maternal diet, cord blood PUFA concentrations are affected by the transport processes and metabolic factors of the placenta and the fetus (29). Placenta prefers the transportation of n-3 PUFA compared with n-6 PUFA, and it is possible that the actual transport of these FAs to the fetus has been in favor of the n-3 series FA (30).

In conclusion, maternal intake of FA during pregnancy was associated with the risk of childhood asthma. High maternal α -linolenic acid, total n-3 PUFA and palmitic acid may decrease, while high arachidonic acid may increase the risk of asthma in the offspring.

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References

1. Calvani M, Alessandri C, Sopo SM, et al. Consumption of fish, butter and margarine during pregnancy and development of allergic sensitizations in the offspring: role of maternal atopy. *Pediatr Allergy Immunol* 2006; **17**: 94–102.
2. Valsta LM, Tapanainen H, Sundvall J, et al. Explaining the 25-year decline of serum cholesterol by dietary changes and use of lipid-lowering medication in Finland. *Public Health Nutr* 2010; **13**: 932–8.
3. Prescott SL, Calder PC. N-3 polyunsaturated fatty acids and allergic disease. *Curr Opin Clin Nutr Metab Care* 2004; **7**: 123–9.
4. Olsen SF, Osterdal ML, Salvig JD, et al. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr* 2008; **88**: 167–75.
5. Devereux G. The increase in the prevalence of asthma and allergy: food for thought. *Nat Rev Immunol* 2006; **6**: 869–74.
6. Blumer N, Renz H. Consumption of omega-3 fatty acids during perinatal life: role in immuno-modulation and allergy prevention. *J Perinat Med* 2007; **35** (Suppl 1): S12–8.
7. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy Risk in Infants and Children in Relation to Early Exposure to Fish, Oily Fish, or Long-

- Chain Omega-3 Fatty Acids: A Systematic Review. *Clin Rev Allergy Immunol* 2009; Epub ahead of print.
8. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy* 2009; **64**: 840–8.
 9. Miyake Y, Sasaki S, Tanaka K, Ohfuji S, Hirota Y. Maternal fat consumption during pregnancy and risk of wheeze and eczema in Japanese infants aged 16–24 months: the Osaka Maternal and Child Health Study. *Thorax* 2009; **64**: 815–21.
 10. Notenboom ML, Mommers M, Jansen EH, Penders J, Thijs C. Maternal fatty acid status in pregnancy and childhood atopic manifestations: KOALA Birth Cohort Study. *Clin Exp Allergy* 2011; **41**: 407–16.
 11. Kupila A, Muona P, Simell T, et al. Feasibility of genetic and immunological prediction of type 1 diabetes in a population-based birth cohort. *Diabetologia* 2001; **44**: 290–7.
 12. Virtanen SM, Kenward MG, Erkkola M, et al. Age at introduction of new foods and advanced beta cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes. *Diabetologia* 2006; **49**: 1512–21.
 13. Erkkola M, Karppinen M, Javanainen J, Rasanen L, Knip M, Virtanen SM. Validity and reproducibility of a food frequency questionnaire for pregnant Finnish women. *Am J Epidemiol* 2001; **154**: 466–76.
 14. Prasad M, Lumia M, Erkkola M, et al. Diet composition of pregnant Finnish women: changes over time and across seasons. *Public Health Nutr* 2010; **13**: 939–46.
 15. Nwaru BI, Lumia M, Kaila M, et al. Validation of the Finnish ISAAC questionnaire on asthma against anti-asthmatic medication reimbursement database in 5-year-old children. *Clin Respir J* 2010; Epub ahead of print.
 16. Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. *Clin Exp Allergy* 1998; **5**: 52–66. discussion 90–1.
 17. Willett WC. Nutritional Epidemiology. New York: Oxford University Press, 1998.
 18. Cardwell CR, Shields MD, Carson DJ, Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. *Diabetes Care* 2003; **26**: 2568–74.
 19. Caffarelli C, Cavagni G, Pierdomenico R, Chiari G, Spattini A, Vanelli M. Coexistence of IgE-mediated allergy and type 1 diabetes in childhood. *Int Arch Allergy Immunol* 2004; **134**: 288–94.
 20. Kaila M, Rautava P, Holmberg-Marttila D, Vahlberg T, Aromaa M, Sillanpaa M. Allergy from infancy to adolescence. A population-based 18-year follow-up cohort. *BMC Pediatr* 2009; **9**: 46.
 21. Salam MT, Li YF, Langholz B, Gilliland FD. Maternal fish consumption during pregnancy and risk of early childhood asthma. *J Asthma* 2005; **42**: 513–8.
 22. Calder PC. Dietary arachidonic acid: harmful, harmless or helpful? *Br J Nutr* 2007; **98**: 451–3.
 23. Miyake Y, Sasaki S, Tanaka K, et al. Fish and fat intake and prevalence of allergic rhinitis in Japanese females: the Osaka Maternal and Child Health Study. *J Am Coll Nutr* 2007; **26**: 279–87.
 24. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J* 2000; **35**: 1228–34.
 25. Wijga AH, Smit HA, Kerkhof M, et al. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. *Thorax* 2003; **58**: 567–72.
 26. Thijs C, Muller A, Rist L, et al. Fatty acids in breast milk and development of atopic eczema and allergic sensitisation in infancy. *Allergy* 2010; **66**: 58–67.
 27. MacRedmond R, Singhera G, Attridge S, et al. Conjugated linoleic acid improves airway hyper-reactivity in overweight mild asthmatics. *Clin Exp Allergy* 2010; **40**: 1071–8.
 28. Jaudszus A, Krokowski M, Mockel P, et al. Cis-9,trans-11-conjugated linoleic acid inhibits allergic sensitization and airway inflammation via a PPARgamma-related mechanism in mice. *J Nutr* 2008; **138**: 1336–42.
 29. Sala-Vila A, Miles EA, Calder PC. Fatty acid composition abnormalities in atopic disease: evidence explored and role in the disease process examined. *Clin Exp Allergy* 2008; **38**: 1432–50.
 30. Cunningham P, McDermott L. Long chain PUFA transport in human term placenta. *J Nutr* 2009; **139**: 636–9.