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Maternal energy-adjusted fatty acid intake during pregnancy and the development of cows' milk allergy in the offspring

Anni Lamminsalo[1,2]*, Johanna Metsälä[3], Hanna-Mari Takkinen[1,3], Heli Tapanainen[3], Mari Åkerlund[1,2,3], Sari Niinistö[3], Jorma Toppari[4], Jorma Ilonen[5,6], Riitta Veijola[7], Mikael Knip[8,9,10], Minna Kaila[11,12]† and Suvi M. Virtanen[1,2,3,10]†

[1]*Faculty of Social Sciences, Unit of Health Sciences, Tampere University, Tampere 33014, Finland*
[2]*Research, Development, and Innovation Center, Tampere University Hospital, Tampere, Finland*
[3]*Health and Well-Being Promotion Unit, Finnish Institute for Health and Welfare, Helsinki 00271, Finland*
[4]*Department of Pediatrics, University of Turku, Turku 20014, Finland*
[5]*Department of Clinical Microbiology, University of Eastern Finland, Kuopio 70211, Finland*
[6]*Immunogenetics Laboratory, University of Turku, Turku 20014, Finland*
[7]*Department of Paediatrics, University of Oulu, Oulu 90014, Finland*
[8]*Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki 00290, Finland*
[9]*Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki 00014, Finland*
[10]*Center for Child Health Research, Tampere University, Tampere University Hospital, Tampere 33521, Finland*
[11]*Public Health Medicine, University of Helsinki, Helsinki 00014, Finland*
[12]*Department of Paediatrics, Tampere University Hospital Tampere 33521, Finland*

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Abstract

Cows' milk allergy (CMA) is one of the earliest manifestations of allergic diseases. Early dietary factors, like maternal diet during pregnancy, may play a role in the development of allergic diseases in the offspring. We aimed to investigate the association between maternal intake of fatty acids during pregnancy and the risk of CMA in the offspring. Our study was conducted in a population-based cohort, the Finnish Type 1 Diabetes Prediction and Prevention study. We collected the maternal dietary data by a validated FFQ. We obtained the information on CMA in the study participants (*n* 448) from registers and from the parents. Dietary data and information on CMA were available for 4921 children. We used logistic regression in the analyses, and fatty acid intakes were energy adjusted. The maternal intake of SFA, MUFA, PUFA, *n*-3 PUFA, *n*-6 PUFA, trans fatty acids, ratio of *n*-3 PUFA to *n*-6 PUFA or ratio of linoleic acid to *α*-linolenic acid was not associated with the risk of CMA in the offspring when adjusted for perinatal factors, background factors, parental history of asthma or allergic rhinitis and infant animal contacts. The intake of *α*-linolenic acid was associated with a decreased risk (OR 0·72; 95 % CI 0·56, 0·93) of CMA in the offspring of mothers without a history of allergic rhinitis or asthma. In conclusion, the maternal intake of fatty acids during pregnancy is not associated with the risk of CMA in the offspring.

Key words: **Milk hypersensitivity: Pregnancy: Diet: Fatty acid**

Allergic diseases are among the most common chronic diseases, especially in developed countries[1]. One of the earliest manifestations of allergic diseases is cows' milk allergy (CMA), which affects 2–6 % of children in Finland[2,3].

In developed countries, the dietary intake of *n*-6 PUFA has increased, and simultaneously, the intake of *n*-3 PUFA has decreased[4]. This changed ratio of intake of *n*-6/*n*-3 PUFA has led to a more pro-inflammatory environment, as the *n*-6 PUFA are observed to promote allergic inflammation by releasing allergy promoting eicosanoids from the cells, whereas *n*-3 PUFA reduce the allergic inflammation by damping the release of pro-inflammatory factors from the cells[5]. Because the fatty acid status of the fetus and the newborn infant may be modulated by maternal fatty acids, and that the development

Abbreviations: CMA, Cows' milk allergy; DIPP, Diabetes Prediction and Prevention; RCT, randomised controlled trial.

* **Corresponding author:** Anni Lamminsalo, email anni.lamminsalo@tuni.fi

† These authors contributed equally to this work

of the immune system starts already *in utero*, it has been implicated that maternal fatty acid intake may affect the risk of development of allergic diseases in children[6].

A systematic review of epidemiological studies and meta-analysis of randomised controlled trials (RCT) has suggested a protective role of higher intake of *n*-3 PUFA and fish during pregnancy for allergic diseases, especially for eczema, wheeze and asthma[7]. However, some null results have also been reported[8–11], and one of the studies had used sensitisation for cows' milk protein as an outcome[10]. The RCT of the role of maternal supplementation of *n*-3 PUFA in pregnancy have reported both inverse[12] and null results[13,14] in relation to the risk of food allergy in the offspring. However, none of these RCT used CMA as an outcome. Thus, the role of maternal fatty acid intake during pregnancy for the development of CMA in the offspring remains unclear.

The aim of our study was to examine the maternal intake of different fatty acids during pregnancy and the development of CMA in the offspring. To our knowledge, this is the first study to assess this association. We hypothesised that maternal higher intake of *n*-3 PUFA decreases and higher intake of *n*-6 PUFA increases the risk of CMA in the offspring.

Methods

Study population

We obtained the data from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) nutrition study, which is a multidisciplinary prospective population-based birth cohort study done in a framework of the ongoing DIPP study. The DIPP study carried out in Finland in the area of Turku, Tampere and Oulu University Hospitals aimed at generating novel insights into the pathogenesis of type 1 diabetes[15]. All newborn infants in these areas have been invited for screening of their human leucocyte antigen -conferred susceptibility for type 1 diabetes. Children carrying genotypes conferring high or moderate disease risk (14 % of the infants) are invited to enrol in the follow-up study. Children with severe congenital abnormalities or diseases, whose parents were of non-Caucasian origin, or did not understand Finnish, English or Swedish, were excluded from the DIPP study.

The DIPP nutrition study is conducted among children born in the area of Oulu and Tampere University Hospitals. The present study comprises children born between August 1997 and September 2004 (*n* 6288), with available personal identity code. Altogether, 4921 children had information on maternal diet during pregnancy and child's CMA by the age of 3 years (Fig. 1, Tables 1–3). In addition to the dietary data, we collected information on parental history of allergic rhinitis or asthma from the Asthma and Allergy sub-study, where all children still in follow-up at the age of 5 years (*n* 4075) were invited to participate (*n* 3781). Altogether, 2327 children had information on maternal diet during pregnancy, basic background factors, child's CMA by the age of 3 years and parental history of allergic rhinitis or asthma (Table 3:2. Adjustment column).

The present study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving patients were approved by the respective ethical committees of the hospital districts of Oulu and Tampere. Written informed consent was obtained from all parents, and they were informed that they can withdraw from the study at any time without further explanations.

Dietary data

The mothers completed a validated 181-item semi-quantitative FFQ , which was designed to reflect the diet during the 8th month of pregnancy (1 month preceding the start of the Finnish maternity leave). The FFQ was validated against 10-d food records[16]. The FFQ was mailed to the mothers after delivery and returned at the child's 3-month study visit. The use of food ingredients and dishes was reported as common serving sizes and the frequency of use as no use, daily, weekly or monthly use. The individual variation of used fats in cooking, baking and salad dressings was also queried. Further, the information about the vitamin and mineral supplements used during the whole pregnancy, including supplement's brand name and the amount of used supplements (tablets, drops, spoonfuls or millilitres), was collected. The FFQ that were filled in inadequately or contained more than ten missing values were excluded (*n* 53, 1·1 %). The data processing of the FFQ has been described earlier[16]. Briefly, we double entered the dietary data into the database. We used Finnish Food Composition Database 'Fineli'[17] and in-house software of the Finnish Institute of Health and Welfare to calculate the estimate of the daily average of the studied fatty acids for each mother.

The fatty acids investigated in the present study were SFA, MUFA, PUFA, *n*-3 PUFA, *n*-6 PUFA and trans fatty acids. In addition, we investigated the ratios of *n*-3 PUFA to *n*-6 PUFA and linoleic acid to *α*-linolenic acid. In the validation of the FFQ against two 5-d food records, the Pearson correlations were SFA (0·55), MUFA (0·34), PUFA (0·47), *n*-3 PUFA (0·39) and *n*-6 PUFA (0·49)[16].

Confounding factors

At the time of enrolment, we asked from the parents their age, occupation, education level and the place of residence. We collected the information on the child's sex, delivery type, gestational age, pregnancy and delivery complications, birth weight and height, mother's earlier deliveries and maternal smoking during pregnancy from the Medical Birth Registers of Tampere and Oulu University Hospitals. We asked about breast-feeding from parents at study visits at the child's age of 6 months, 1, 2 and 3 years. Among children who participated in the Asthma and Allergy sub-study, we collected the information of maternal and paternal history of allergic rhinitis or asthma, pet keeping and contacts to the farm animals during the child's first year of life by the parental questionnaire completed at the 5-year study visit.

Endpoints

Our definition of CMA was based on information obtained from the special reimbursement register maintained by the Social Insurance Institution of Finland and linked using personal

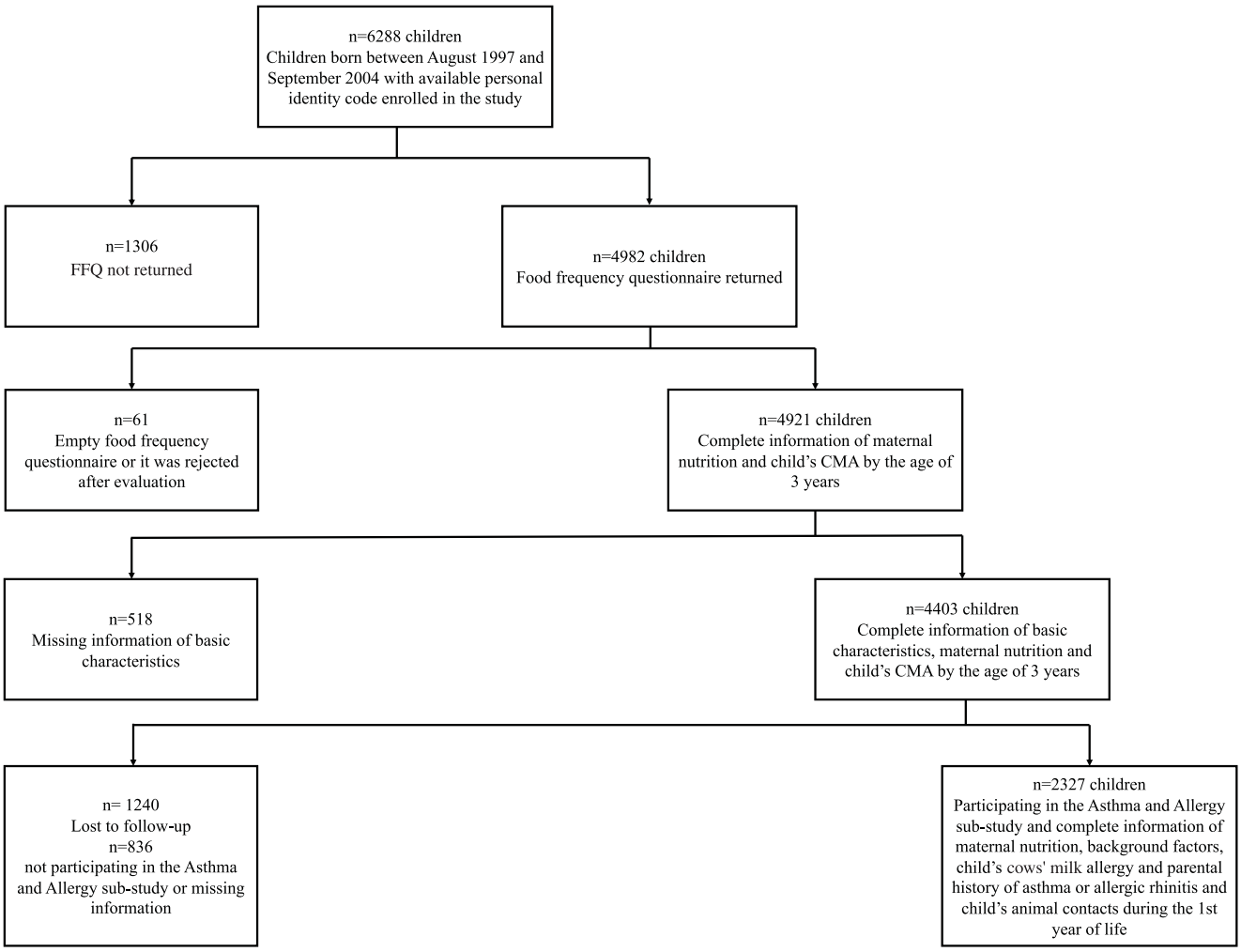

Fig. 1. Flow chart of the participants. CMA, cows' milk allergy.

identity codes[18]. We complemented the register data with a parental report on CMA queried by the validated questionnaire, which was filled in at study visits, when the child was 6 and 12 months old and annually thereafter, until the age of 9 years[19,20].

From the register, we obtained the information about a valid special reimbursement for the costs of special infant formula needed in the treatment of diagnosed CMA (ICD-10 codes L27.2 or K52.2). In Finland, every child with CMA, diagnosed by a paediatrician, is entitled for this reimbursement up to the age of 2 years, irrespective of the family's socio-economic status or place of residence. At the time of the present study, the CMA diagnosis in Finland was usually based on an open oral food challenge[21].

Statistical methods

We analysed the difference in background factors between children with and without CMA by the χ^2 test. We selected the variables used in the adjusted models based on previous knowledge[22–24] and their association with CMA in the present study. We analysed the association between maternal fatty acid intake and the risk of CMA in the offspring by logistic regression. The possible reliance among siblings was accounted for using the generalised estimating equations with the sandwich estimator of variance to estimate regression coefficients in logistic regression.

After the logarithmic transformation, we adjusted the nutrients for energy intake by the residual method[25] and we used standardised scores in the analyses. We also divided the energy-adjusted dietary intake into quartiles, and the first and last quartiles were compared with the combined mid quartiles in our analysis. We analysed fatty acid intakes from food and from food and supplements, if the supplemental intake was meaningful. Our first adjusted model included study centre, sex, birth weight, maternal age and education, maternal smoking during pregnancy, duration of gestation, mode of delivery, season of birth, number of older siblings, length of breast-feeding and urbanity of the living environment as covariates. We made the unadjusted and the first adjusted model among children with information on maternal diet during pregnancy, child's CMA status and basic background characteristics (n 4921). We made the second adjusted analysis among children participating in the Asthma and Allergy sub-study (n 2327). The variables used in the second adjusted model were all those in the first adjusted model in

Table 1. Distribution of background characteristics among the whole study population (*n* 4921) and cases with cows' milk allergy (Numbers and percentages, *n* 448)

	All participants *n* 4921		Cows' milk allergy Cases *n* 448		
	%	*n*	%	*n*	*P**
Sex					0·001
Boys	52·6	2590	60·3	270	
Girls	47·4	2331	39·7	178	
Season of birth					0·256
Spring (April–May)	18·4	904	16·3	73	
Summer (June–August)	26·6	1310	25·0	112	
Fall (September–November)	22·2	1091	21·9	98	
Winter (December–March)	32·8	1616	36·8	165	
Age of the mother at delivery (years)					0·017
< 25	18·8	927	13·6	61	
25–29	34·8	1714	35·5	159	
30–34	29·1	1433	33·3	149	
> 35	17·2	847	17·6	79	
Maternal vocational education					<0·001
No professional education	6·2	296	4·5	20	
Vocational school or course	27·1	1300	18·9	83	
Upper secondary vocational education	43·4	2082	50·0	220	
Academic education	23·2	1114	26·6	117	
Missing information		129		8	
Maternal smoking status during pregnancy					0·010
No	90·0	4278	93·5	406	
Yes	10·0	474	6·5	28	
Missing information		169		14	
Mode of delivery					0·520
Caesarean section	13·0	633	13·9	62	
Vaginal	87·0	4253	86·1	383	
Missing information		35		3	
Urbanity of the place of living					0·162
Rural	12·5	609	10·1	45	
Semi-urban	9·6	467	11·2	50	
Urban	78·0	3809	78·7	350	
Missing information		36		3	
Duration of breast-feeding (months)					0·103
< 3	21·2	991	17·2	74	
3·0–6	18·8	879	20·5	88	
> 6	60·1	2813	62·2	267	
Missing information		238		19	
Duration of gestation (weeks)					0·070
≤ 38·9	25·0	1219	26·1	116	
39–39·9	23·9	1165	22·5	100	
40–40·8	24·8	1210	29·1	129	
≥ 40·9	26·2	1279	22·3	99	
Missing information		48			
Birth weight in quartiles (g)					0·112
780–3219	24·5	1198	21·8	97	
3220–3571	25·5	1245	23·4	104	
3572–3889	24·5	1195	24·9	111	
3890–5620	25·5	1248	29·9	133	
Missing information		35			
Number of previous pregnancies					0·282
0	46·9	2286	44·5	198	
1–2	44·9	2186	48·3	215	
> 2	8·2	400	7·2	32	
Missing information		49			
Maternal asthma or allergic rhinitis†					<0·001
No	54·2	1410	43·1	112	
Yes	45·8	1190	56·9	148	
Missing information		2321		188	
Paternal asthma or allergic rhinitis†					0·001
No	60·5	1546	50·8	129	
Yes	39·5	1008	49·2	125	
Missing information		2367		194	

Table 1. (*Continued*)

	All participants *n* 4921		Cows' milk allergy Cases *n* 448		
	%	*n*	%	*n*	*P**
Pets inside home during the first year of life†					0·004
No	67·7	1817	75·6	201	
Yes	32·3	865	24·4	65	
Missing information		2239		182	
Visits to stable during the first year of life†					0·348
No	81·9	2183	84·0	221	
Yes	18·1	482	16·0	42	
Missing information		2256		185	

* Comparison done with χ^2 test, comparing the distribution of the cows' milk allergy across the categories.
† Information collected only from the children participating in the Asthma and Allergy sub-study at the age of 5 years.

Table 2. Maternal daily intake of fatty acids during pregnancy from diet and supplements together
(Mean values and standard deviations, *n* 4921)

Fatty acid	Mean	SD
SFA, g	43·7	16·9
Myristic acid 14:0, g	4·7	2·0
Palmitic acid 16:0, g	20·7	7·7
Stearic acid 18:0, g	10·5	4·3
MUFA, g	35·7	12·6
Sum of 18:1 isomers, g	32·9	11·7
PUFA, g	13·8	5·1
n-3 PUFA, g	2·9	1·2
α-Linolenic acid (18:3*n*-3),g	2·5	1·0
EPA (20:5*n*-3), mg	82·3	63·9
DHA (22:6*n*-3), mg	223·9	152·7
n-6 PUFA, g	10·6	4·0
Linoleic acid (18:2*n*-6), g	10·3	3·9
Arachidonic acid (20:4*n*-6), mg	128·2	53·6
γ-Linolenic acid (18:3*n*-6), mg	56·8	31·7
Conjugated linoleic acid (18:2*n*-6), mg	180·9	80·6
Trans fatty acids, g	1·7	0·87
Ratios:		
n-6:*n*-3	3·7	0·84
Linoleic acid (18:2*n*-6): α-linolenic acid (18:3*n*-3)	4·3	1·0
Energy, kJ	11 700	3440

addition to maternal and paternal history of allergic rhinitis or asthma, and both visits to a stable and pets inside the home during the study participant's first year of life. We tested the interaction of maternal history of allergic rhinitis or asthma and fatty acids among the population participating in the Asthma and Allergy sub-study. If the interaction was significant (*P*-value < 0·05), we studied the association separately among mothers with and without a history of allergic rhinitis or asthma using the fully adjusted model. Missing data were addressed using complete case analysis. SAS version 9.3 (SAS Institute Inc.) and IBM SPSS Statistics for Windows, version 27 (IBM corp.) were used in the analysis.

Results

We identified 448 children with CMA (9·1 %). Children with CMA were more often male, had less often pets inside the home during the first year of life, and their mothers were more often non-smokers during pregnancy and had higher vocational education. Further, their mothers and fathers were more often affected by asthma or allergic rhinitis (Table 1). Children who participated in the Asthma and Allergy sub-study had older, more educated and less frequently smoking mothers when compared with non-participants[26].

The maternal intake of studied fatty acids is shown in Table 2. Maternal total intake of SFA, MUFA, PUFA, *n*-3 PUFA, *n*-6 PUFA, trans fatty acids, ratio of *n*-3 PUFA to *n*-6 PUFA or ratio of linoleic acid to α-linolenic acid was not associated with the risk of CMA in the offspring (Table 3). When fatty acid intakes and ratios were analysed as quartiles, we did not observe significant associations between either the lower or the higher quartile as compared with the mid-half and CMA (data not shown).

We observed an interaction between maternal history of allergic rhinitis or asthma and the maternal intake of α-linolenic acid (*P*-value = 0·012). For mothers without a history of allergic rhinitis or asthma (*n* 1265), α-linolenic acid was associated with a decreased risk (OR 0·72; 95 % CI 0·56, 0·93) of CMA in the offspring (*n* 237), but not in mothers with a history of allergic rhinitis or asthma (*n* 1062, OR 1·05; 95 % CI 0·88, 1·26).

Discussion

We did not observe an association between maternal intake of fatty acids and the development of CMA in the offspring. When we took the maternal history of allergic rhinitis or asthma into account, the maternal intake of α-linolenic acid was inversely associated with the risk of CMA in the offspring of the mothers without a history of allergic rhinitis and asthma, but not in mothers with such a history.

To our knowledge, this is the first study to report the association between maternal intake of fatty acids during pregnancy and the development of CMA in the offspring. The associations between maternal intake of fatty acids during pregnancy and development of allergic rhinitis, asthma, eczema and wheeze in the offspring have been previously reported from the same cohort as in the present study[11,27]. Higher maternal intake of α-linolenic acid during pregnancy was associated with a decreased risk of asthma[27] and allergic rhinitis in the

Table 3. Associations between maternal daily intake of energy-adjusted fatty acids during pregnancy with the risk of cows' milk allergy in the offspring by the age of 3 years. The OR are presented per 1 standard deviation increment of the particular fatty acid. Both the dietary intake and total intake (dietary + supplement) of each fatty acid were analysed if the supplemental intake was meaningful
(Odd ratios and 95 % confidence intervals)

	Unadjusted *n* 448*/4921†		Adjustment 1‡ *n* 409*/4403†		Adjustment 2§ *n* 234*/2327†
Fatty acid	OR	95 % CI	OR	95 % CI	OR	95 % CI
SFA total	0·88	0·79, 0·98	0·94	0·84, 1·05	0·96	0·82, 1·13
Myristic acid 14:0 total	0·89	0·80, 0·99	0·94	0·85, 1·06	1·00	0·86, 1·16
Palmitic acid 16:0, total	0·89	0·80, 0·99	0·95	0·84, 1·06	0·95	0·81, 1·12
Stearic acid 18:0, total	0·89	0·81, 0·99	0·94	0·84, 1·06	0·94	0·80, 1·10
MUFA, total,	0·94	0·85, 1·05	0·96	0·85, 1·07	0·91	0·78, 1·08
Sum of 18:1 isomers, total	0·95	0·85, 1·05	0·96	0·85, 1·07	0·91	0·77, 1·07
PUFA, total	1·03	0·93, 1·14	1·01	0·90, 1·13	0·95	0·82, 1·12
n-3 PUFA, food	0·98	0·89, 1·09	0·96	0·86, 1·07	0·92	0·79, 1·06
n-3 PUFA, total	0·98	0·89, 1·09	0·96	0·86, 1·08	0·92	0·79, 1·07
α-Linolenic acid (18:3*n*-3), total	0·99	0·89, 1·09	0·97	0·87, 1·08	0·93	0·80, 1·07
EPA (20:5*n*-3), food	0·97	0·88, 1·08	0·95	0·85, 1·06	0·95	0·80, 1·11
EPA (20:5*n*-3), total	0·96	0·87, 1·07	0·94	0·83, 1·06	0·95	0·79, 1·13
DHA (22:6*n*-3), food	0·98	0·88, 1·08	0·95	0·85, 1·07	0·94	0·79, 1·12
DHA (22:6*n*-3),total	0·97	0·87, 1·08	0·95	0·84, 1·07	0·94	0·79, 1·13
n-6 PUFA, total	1·04	0·94, 1·15	1·02	0·91, 1·14	0·97	0·82, 1·14
Linoleic acid (18:2*n*-6), total	1·04	0·94, 1·15	1·02	0·91, 1·14	0·97	0·82, 1·14
Arachidonic acid (20:4*n*-6), food	1·07	0·97, 1·18	1·06	0·96, 1·18	0·97	0·83, 1·14
Arachidonic acid (20:4*n*-6), total	1·07	0·97, 1·18	1·06	0·96, 1·18	0·97	0·83, 1·14
γ-Linolenic acid (18:3*n*-6), food	0·96	0·86, 1·06	0·99	0·89, 1·11	1·03	0·90, 1·19
γ-Linolenic acid (18:3*n*-6), total	0·97	0·88, 1·07	1·01	0·91, 1·12	1·04	0·91, 1·20
Conjugated linoleic acid (18:2*n*-6), total	0·92	0·83, 1·02	0·98	0·88, 1·10	1·03	0·89, 1·19
Trans fatty acids, total	0·92	0·84, 1·02	0·96	0·86, 1·07	0·94	0·81, 1·09
Ratios:						
n-6 PUFA:*n*-3 PUFA, food	1·06	0·97, 1·17	1·07	0·97, 1·18	1·11	0·96, 1·27
n-6 PUFA:*n*-3 PUFA, total	1·06	0·97, 1·17	1·07	0·97, 1·18	1·10	0·96, 1·27
Linoleic acid (18:2*n*-6): α-linolenic acid (18:3*n*-3)	1·05	0·96, 1·16	1·05	0·95, 1·17	1·09	0·95, 1·25

* Number of children with cows' milk allergy.
† Number of children in the analysis.
‡ Adjusted for study centre, sex, birth weight, maternal age and education, maternal smoking during pregnancy, duration of gestation, mode of delivery, season of birth, number of mother's previous deliveries, length of breast-feeding and urbanity of the living environment.
§ Adjusted additionally for the parental history of allergic rhinitis and asthma, pets inside home during the child's first year of life and visits to the stable during the child's first year of life. This additional information was collected when the child was 5 years old.

offspring[11], but for other fatty acids the findings were more inconsistent.

Our results are supported by the RCT where no associations were observed between maternal supplementation of *n*-3 PUFA during pregnancy and the risk of food allergy in the offspring[13,14]. However, a protective effect has been observed in one RCT[12]. The inconsistent results might be explained by the methodological differences between the studies. The dosage of *n*-3 PUFA supplementation has varied, and it is possible that there exists a dose-dependent association. In addition, the variable timing of the supplementation may have resulted in inconsistencies, as the crucial timing of the immune development in infants is yet to be determined.

Our results are in apparent contrast to the recent systematic review concluding that maternal fish oil supplementation during pregnancy may reduce the risk of sensitisation for egg and peanut in the offspring[28]. However, in epidemiological studies null results have been observed when studying the association between maternal dietary intake of fatty acids and food sensitisation in the offspring[29,30], one study reporting the sensitisation to cows' milk proteins[10]. As egg and peanuts are consumed only in small quantities, and maybe not as early in life as cows' milk products, the maternal intake of fatty acids may have a greater role in the prevention of egg and peanut allergy. Further, the association between sensitisation and food allergy varies, and it is possible to have sensitisation without clinical food allergy, as well as food allergy without sensitisation[31].

Our result that α-linolenic acid was inversely associated with the development of CMA only in mothers without a history of allergic rhinitis or asthma may be explained by the possibility that mothers transfer the risk of allergy to their offspring[32]. Thus, it is possible that the maternal history of allergy overpowers the protective effect of α-linolenic acid.

The major strength of our study is prospectively collected data from a relatively large sample size, which minimise the selection bias. Our endpoint was based on register-based information and complemented with a parental questionnaire which is validated to represent exceptionally well the physician diagnosed CMA[19,20]. Further, our food consumption data had good coverage and were collected by validated FFQ, specifically designed for the present study. In addition, the FFQ took into account the individual habit of used fats, which increases the accuracy of the intake of specific fatty acids.

The major limitation of our study is the restriction of the participants to those with human leucocyte antigen conferred susceptibility to type 1 diabetes. As previously reported, these

infants may have increased intestinal permeability[33]; also, the knowledge of the risk of type 1 diabetes may alter the behaviour of the family, and the parents may seek medical advice more eagerly leading to receiving the diagnosis of CMA more often. These factors may explain the higher incidence of CMA in our study population compared with what is previously reported in Finland[2,3]. Therefore, the generalisability of our results to the general paediatric populations may be limited. In addition, we did not have data on the duration between the onset of symptoms of CMA and the date of diagnosis or start of the elimination diet, even though these should be coincidental. The FFQ was designed to represent the total diet during the 8th month of pregnancy and thus presents an estimate of the diet during the whole pregnancy. In the validation study, the FFQ was observed to slightly overestimate the nutrient intake; this should be ameliorated by the usage of energy-adjusted nutrient intakes. As the FFQ was mailed to the participants after the delivery, it is open for recall bias. However, the FFQ was validated in the same design as the present study was performed and was found to be suitable to measure the maternal diet during pregnancy and has shown acceptable reproducibility and validity[16]; thus, the risk of recall bias should be minor. The use of food supplements was not taken into account in the validation study. As our results were substantially similar for the fatty acid intakes from food and from food and supplements together, this should not have major relevance in our study. The fact that we did not have data on the child's dietary intake may result in some residual confounding.

In conclusion, the present study provides novel information about the association between maternal intake of fatty acids during pregnancy and the development of CMA in the offspring. We did not observe an association between the maternal intake of fatty acids and the development of CMA in the offspring, except the maternal intake of α-linolenic acid which was associated with decreased risk of CMA in the offspring of mothers without a history of allergic rhinitis or asthma. Thus, additional benefits may not be expected for the prevention of CMA in the offspring by advising the pregnant women to use supplements containing fatty acids in addition to a healthy and balanced diet.

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S. M. V., M. K., A. L. and J. M. were responsible for formulating the research questions. J. I., M. K., J. T. and R. V. are members of the steering committee of the DIPP study. S. M. V. designed the DIPP nutrition study and within the DIPP nutrition study the allergy study was designed by S. M. V. and M. K. S. M. V. and M. K. were responsible for carrying out the study. R. V. was responsible for the clinical work in Oulu, M. K. was responsible for the clinical work in Tampere. A. L. and H.-M. T. were responsible for analysing the data. A. L. wrote the first version of the article. J. M., M. K., and S. M. V. participated in the writing process. S. M. V. and M. K. had the primary responsibility for the final work with equal contribution. All the authors participated in the critical revision of the manuscript and have accepted the final version.

All authors declare that there are no conflicts of interest.

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