

Letter to the Editor

Cow's milk allergy and the association between fatty acids and childhood asthma risk

To the Editor:

The increased prevalence of allergic diseases and asthma in Western societies during the past decades parallels an increase in the dietary intake of n-6 polyunsaturated fatty acids (PUFAs) and a decrease in the intake of n-3 PUFAs and saturated fatty acids (SAFAs).^{1,2} N-6 PUFAs are major precursors of proinflammatory eicosanoids and might play a role in the development of IgE-mediated allergic diseases, such as asthma.¹ The main link between n-6 PUFAs and inflammatory processes is through arachidonic acid (AA) and its metabolites. Because of their anti-inflammatory properties, n-3 PUFAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid, might prevent the development of asthma by antagonizing the effects of AA.¹

Serum fatty acid (FA) composition is modulated by diet, metabolic processes, and the atopic disease process itself.³ In early infancy higher serum levels of n-3 PUFAs have been associated with a decreased risk of atopy, but the evidence is inconsistent.³ Linoleic acid (LA) status has not been associated with the occurrence of atopic diseases, but there is evidence of lower serum proportions of its metabolites, dihomo- γ -linolenic acid, γ -linolenic acid, and AA, in children with atopic disease.³ This

might represent insufficient ability to convert LA to its longer-chain metabolites or increased use of these FAs in atopic children.

The objective here was to investigate the associations between longitudinal serum FA composition during childhood and the risk of childhood asthma by 5 years of age, taking into account the putative confounding role of cow's milk allergy (CMA).

This is a substudy of the Type 1 Diabetes Prediction and Prevention (DIPP) study, a prospective birth cohort study started in 1994, in which all infants born in 3 university hospitals in Finland (Turku, Tampere, and Oulu) were screened for HLA-conferred susceptibility to type 1 diabetes with the use of cord blood samples after parental informed consent. Infants with a high or moderate genetic risk were invited to participate.⁴ The DIPP Nutrition Study, which was carried out at the University Hospitals of Oulu and Tampere from 1996, investigated the associations between nutrition during pregnancy, lactation, and early childhood and the development of type 1 diabetes, asthma, allergic diseases, and obesity in childhood.⁵ Children still taking part in the dietary follow-up at the age of 5 years were invited to participate in the DIPP Allergy Study. The parents were requested to complete a modified validated version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. A blood sample was obtained for analysis of serum IgE levels. Asthma was defined as doctor-diagnosed asthma plus either any wheezing

TABLE I. Odds ratios (95% CIs) for the risk of asthma associated with serum FA composition analyzed longitudinally until asthma diagnosis

FA	All asthma (n = 142 cases and n = 284 control subjects), unadjusted		All asthma (n = 119 cases and n = 235 control subjects),* adjusted†		Atopic asthma (n = 63 cases and n = 124 control subjects), adjusted‡		Nonatopic asthma (n = 42 cases and n = 81 control subjects), adjusted‡	
		P value		P value		P value		P value
Myristic acid 14:0	0.88 (0.74-1.04)	.13	0.95 (0.75-1.22)	.71	0.95 (0.62-1.46)	.82	1.01 (0.68-1.50)	.96
Pentadecanoic acid 15:0	0.85 (0.70-1.02)	.08	1.05 (0.84-1.33)	.66	1.15 (0.78-1.70)	.49	1.85 (0.97-3.53)	.06
Palmitic acid 16:0	0.87 (0.73-1.04)	.13	0.84 (0.68-1.04)	.11	0.78 (0.60-1.03)	.08	1.08 (0.57-2.069)	.82
Palmitoleic acid 16:1n-9	0.94 (0.78-1.13)	.48	0.94 (0.71-1.26)	.69	0.73 (0.43-1.26)	.26	1.39 (0.81-2.40)	.23
Palmitoleic acid 16:1n-7	0.79 (0.66-0.94)	<.01	0.84 (0.70-1.02)	.08	0.75 (0.56-1.01)	.06	0.92 (0.61-1.39)	.71
Stearic acid 18:0	0.93 (0.78-1.11)	.43	0.99 (0.77-1.26)	.91	0.76 (0.58-1.00)	.05	1.83 (1.04-3.22)	.04
Oleic acid 18:1n-9	1.08 (0.90-1.30)	.42	0.97 (0.79-1.18)	.75	1.04 (0.76-1.41)	.81	0.72 (0.49-1.08)	.11
Vaccenic acid 18:1n-7	0.85 (0.71-1.01)	.07	0.95 (0.75-1.20)	.65	0.74 (0.49-1.12)	.16	0.89 (0.50-1.59)	.70
LA 18:2n-6	1.23 (1.04-1.44)	.02	1.19 (0.98-1.44)	.08	1.43 (1.08-1.89)	.01	1.16 (0.85-1.59)	.35
γ -Linolenic acid 18:3n-6	0.92 (0.76-1.11)	.38	0.88 (0.70-1.11)	.27	0.77 (0.52-1.13)	.18	0.86 (0.50-1.47)	.58
Conjugated LA 18:2CON	0.73 (0.60-0.89)	<.01	0.89 (0.70-1.14)	.35	0.94 (0.68-1.30)	.70	1.26 (0.78-2.02)	.34
Dihomo- γ -linolenic acid 20:3n-6	0.95 (0.76-1.19)	.65	1.12 (0.87-1.46)	.38	1.05 (0.80-1.38)	.71	0.94 (0.48-1.85)	.87
AA 20:4n-6	0.95 (0.79-1.16)	.63	1.05 (0.79-1.40)	.72	0.87 (0.53-1.43)	.59	1.12 (0.63-1.99)	.70
α -Linolenic acid 18:3n-3	1.01 (0.86-1.19)	.93	1.02 (0.81-1.29)	.87	1.22 (0.92-1.63)	.18	0.89 (0.56-1.41)	.62
Eicosapentaenoic acid 20:5n-3	0.77 (0.63-0.93)	<.01	0.79 (0.66-0.95)	.01	0.82 (0.59-1.15)	.25	0.66 (0.47-0.92)	.02
Docosapentaenoic acid 22:5n-3	0.85 (0.71-1.01)	.06	0.91 (0.72-1.16)	.45	0.76 (0.49-1.18)	.22	1.13 (0.75-1.70)	.57
Docosahexaenoic acid 22:6n-3	0.74 (0.61-0.91)	<.01	0.85 (0.64-1.13)	.25	0.86 (0.57-1.28)	.45	0.86 (0.54-1.37)	.53
Total n-6 PUFA	1.18 (1.00-1.39)	.06	1.19 (0.98-1.45)	.09	1.18 (1.00-1.39)	.06	1.23 (1.02-1.48)	.03
Total n-3 PUFA	0.75 (0.62-0.90)	<.01	0.82 (0.64-1.05)	.12	0.86 (0.57-1.28)	.45	0.76 (0.49-1.19)	.23
Marine PUFA	0.73 (0.60-0.90)	<.01	0.81 (0.64-1.03)	.08	0.83 (0.57-1.21)	.34	0.77 (0.51-1.16)	.21
Total n:6 to total n:3	1.41 (1.15-1.73)	<.01	1.20 (0.88-1.64)	.26	1.22 (0.72-2.08)	.46	1.11 (0.67-1.84)	.69

Odds ratios describe the change in risk when serum FA composition is changed by an amount corresponding to its SD. Numbers in boldface indicate statistical significance.

*Numbers of cases and control subjects are different in the adjusted model compared with the unadjusted model because not all the children have all information on the putative confounders available.

†Adjusted for duration of gestation, maternal age, maternal smoking during pregnancy, number of previous deliveries, maternal asthma or allergic rhinitis, paternal asthma or rhinitis, birth weight, mode of delivery, duration of breast-feeding, maternal vocational education, dogs at home during the first year of life, and CMA.

‡Associations that remained significant after controlling the false discovery rate.

symptom or use of asthma medication during the preceding 12 months.⁶ Atopic asthma was defined as IgE-positive asthma, and nonatopic asthma was defined as IgE-negative asthma. All these children still had asthma at age 5 years, indicating persistent asthma, and food allergy diagnoses and the age at asthma diagnosis came from the questionnaire and from registers of the Social Insurance Institution.

The present analysis is nested within the cohort of children born between 1996 and 2004 in Tampere (n = 3916) and Oulu (n = 3866), Finland, with completed ISAAC questionnaire and at least 1 serum sample available. For each case, 2 control subjects were randomly selected (free of asthma at least until the age when the patient was given a diagnosis of asthma and matched for sex, genetic risk group for type 1 diabetes, research area [Oulu or Tampere district], and time of birth [range, ± 3 months]). The control subject must have been followed up for asthma until the age of 5 years and could not come from the same family as the case. The control subjects were selected independently so that the same child could be a control subject for more than 1 case and a child who was already a control subject could become a case at the later time point. Altogether, 142 asthma cases and 284 matched control subjects formed the final sample for the present study. Eleven children served as control subjects for more than 1 case but were included only once in the total number of control subjects. Four of the control subjects became cases at a later date and were counted only as cases. Because of this, the final number of control subjects was 268.

Nonfasting serum samples were obtained annually at the ages of 1 to 5 years, and serum FA profiles were analyzed with gas chromatography.⁷ A generalized estimating equations analysis based on conditional logistic regression was used to analyze the associations between longitudinal serum FA proportions and the risk of asthma.^{8,9}

The median age at asthma diagnosis was 3 years (range, 1–5 years). Reported CMA and maternal and paternal asthma or allergic rhinitis were associated with an increased risk of childhood asthma by age 5 years (see Table E1 in this article's Online Repository at www.jacionline.org).

Serum FA proportions at the age of 1 year differed between children with reported CMA (n = 59) and others (n = 320). In children with reported CMA, the serum proportions of oleic acid, LA, α -linolenic acid, and total n-6 PUFAs were higher and all other serum FA proportions were lower compared with those seen in children without reported CMA (see Table E2 in this article's Online Repository at www.jacionline.org).

A higher proportion of EPA was associated with a decreased risk of asthma when CMA was taken into account as a putative confounder. When stratifying the results by atopic and nonatopic asthma, higher proportions of LA and total n-6 PUFAs were associated with an increased risk of atopic asthma. Also, higher proportions of stearic acid and total n-6 PUFAs were associated with an increased risk and higher proportions of EPA were associated with a decreased risk of nonatopic asthma (Table I).

To our knowledge, no earlier study has examined prospectively the associations between repeated serum FA measurements and the onset of asthma in children. Also, the previous analyses on the relationship between serum FA profiles and asthma were not controlled for food allergies. However, most of the recent studies investigating associations between food intake and childhood allergic diseases have taken the possible disease-related

modification of the diet into account by excluding children with food allergy or by using food allergy as a confounding variable.¹⁰ Changes in serum FA composition might predispose to CMA and subsequently to asthma because these diseases are within the same spectrum. Diagnosed CMA results in elimination of milk and dairy products from the diet and thus further changes in serum FA profiles. These changes might modify the immunologic reactions of the child already in early life. Clearly, as seen in the current study, the FA proportions of children with CMA differed from the FA proportions of those without CMA, as did asthma risk. In conclusion, of the 17 FAs studied, after adjusting for CMA, only EPA remained inversely associated with the risk of asthma, whereas other associations found before CMA adjustment lost their statistical significance.

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TABLE E1. Distributions of background characteristics and their associations with asthma

Background characteristic	Cases (n = 142), no. (%)	Control subjects (n = 268),* no. (%)	Odds ratio for asthma (95% CI)	P value†
Sex				
Boys	86 (60.6)	160 (59.7)		
Girls	56 (39.4)	108 (40.3)		
Maternal age (y)				.56
<25	21 (14.8)	36 (13.4)	1	
25-29	50 (35.2)	88 (32.8)	0.90 (0.47-1.72)	
30-34	46 (32.4)	80 (29.9)	0.92 (0.47-1.78)	
>34	25 (17.6)	64 (23.9)	0.64 (0.31-1.31)	
Mode of delivery				.85
Vaginal	121 (85.2)	227 (84.7)	1	
Cesarean section	21 (14.8)	37 (13.8)	1.06 (0.60-1.87)	
Missing information	0 (0)	4 (1.5)		
Gestational age (wk), in quarters				.16
First, <38.9	36 (25.4)	58 (21.6)	1	
Second, 38.9-39.9	43 (30.0)	60 (22.4)	1.16 (0.66-2.06)	
Third, 40.0-40.8	31 (21.8)	74 (27.6)	0.65 (0.34-1.23)	
Fourth, >40.8	32 (22.5)	72 (26.9)	0.70 (0.38-1.28)	
Missing information	0 (0)	4 (1.5)		
No. of previous deliveries				.39
0	56 (39.5)	113 (42.2)	1	
1	53 (37.3)	83 (31.0)	1.27 (0.78-2.06)	
2	25 (17.6)	44 (16.4)	1.18 (0.65-2.12)	
>2	6 (4.2)	23 (8.6)	0.59 (0.23-1.54)	
Missing information	2 (1.4)	5 (1.9)		
Maternal vocational education				.47
None	3 (2.1)	11 (4.1)	1	
Vocational school or course	39 (27.5)	71 (26.5)	2.81 (0.59-13.26)	
Secondary vocational	69 (48.6)	118 (44.0)	2.97 (0.65-13.61)	
University studies or degree	29 (20.4)	64 (23.8)	2.33 (0.49-11.01)	
Missing information	2 (1.4)	4 (1.5)		
Maternal smoking during pregnancy				.71
No	129 (90.9)	234 (87.3)	1	
Yes	11 (7.8)	23 (8.6)	0.86 (0.41-1.84)	
Missing information	2 (1.4)	11 (4.1)		
Maternal asthma or allergic rhinitis				<.01
No	45 (31.7)	140 (52.2)	1	
Yes	94 (66.2)	117 (43.7)	2.28 (1.49-3.48)	
Missing information	3 (2.1)	11 (4.1)		
Paternal asthma or allergic rhinitis				<.01
No	60 (42.3)	153 (57.1)	1	
Yes	74 (52.1)	94 (35.1)	2.04 (1.32-3.16)	
Missing information	8 (5.6)	21 (7.8)		
Reported CMA				<.01
No	104 (73.2)	239 (89.2)	1	
Yes	38 (26.8)	29 (10.8)	2.99 (1.71-5.22)	
Missing information	0 (0)	0 (0)		
Birth weight (g), in quarters				.09
First quarter: >3280	45 (31.7)	55 (20.5)	1	
Second quarter: 3280-3604	37 (26.1)	66 (24.6)	0.66 (0.37-1.17)	
Third quarter: 3605-3890	30 (21.1)	72 (26.9)	0.51 (0.29-0.92)	
Fourth quarter: >3890	30 (21.1)	71 (26.5)	0.52 (0.29-0.94)	
Missing information	0 (0)	4 (1.5)		
Dogs at home during the first year of life				.46
No	123 (86.6)	224 (83.6)	1	
Yes	19 (13.4)	44 (16.4)	0.80 (0.44-1.45)	
Missing information	0 (0)	0 (0)		

Values shown in boldface indicate statistical significance.

*Eleven children served as control subjects for more than 1 case but were included only once in the total number of control subjects. Four of the control subjects became cases at a later date and were counted only as cases.

†Conditional logistic regression was used to test associations between background characteristics and asthma.

TABLE E2. Median (range) proportions (percentages) of serum FAs at the age of 1 year in children without and with CMA

FA	FA proportions, no CMA (n = 320)	FA proportions, CMA (n = 59)	P value*
Myristic acid 14:0	1.00 (0.73-1.41)	0.77 (0.53-0.98)	<.01
Pentadecanoic acid 15:0	0.21 (0.17-0.25)	0.11 (0.08-0.16)	<.01
Palmitic acid 16:0	22.36 (21.36-23.18)	21.27 (20.26-22.08)	<.01
Palmitoleic acid 16:1n-9	0.42 (0.34-0.50)	0.37 (0.32-0.49)	.04
Palmitoleic acid 16:1n-7	1.59 (1.32-1.94)	1.20 (0.97-1.69)	<.01
Stearic acid 18:0	7.74 (7.22-8.37)	7.47 (6.87-8.01)	.03
Oleic acid 18:1n-9	26.62 (24.87-28.31)	28.38 (24.95-29.75)	.02
Vaccenic acid 18:1n-7	1.84 (1.70-2.01)	1.75 (1.61-1.98)	.07
LA 18:2n-6	27.60 (25.15-29.91)	29.26 (26.17-31.35)	<.01
γ-Linolenic acid 18:3n-6	0.25 (0.19-0.33)	0.26 (0.18-0.34)	.86
Conjugated LA 18:2CON	0.16 (0.12-0.22)	0.07 (0.04-0.13)	<.01
Dihomo-γ-linolenic acid 20:3n-6	1.33 (1.12-1.54)	1.20 (1.03-1.42)	.01
AA 20:4n-6	4.83 (3.92-5.64)	4.73 (4.01-6.14)	.93
α-Linolenic acid 18:3n-3	0.87 (0.71-1.07)	0.99 (0.76-1.46)	.03
EPA 20:5n-3	0.42 (0.29-0.63)	0.31 (0.23-0.41)	<.01
Docosapentaenoic acid 22:5n-3	0.49 (0.41-0.58)	0.42 (0.35-0.52)	<.01
Docosahexaenoic acid 22:6n-3	1.40 (1.01-2.10)	1.25 (0.90-1.75)	.13
Total n-6 PUFA	34.24 (31.41-36.42)	35.23 (32.41-38.20)	.01
Total n-3 PUFA	3.29 (2.75-4.16)	3.23 (2.58-3.96)	.16
Marine PUFA	1.83 (1.38-2.70)	1.64 (1.19-2.21)	.02

Values in boldface indicate statistical significance.

*The Mann-Whitney *U* test was used to examine differences in serum FA proportions.