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Fish Consumption, Allergic Sensitisation and Allergic Diseases in Adults

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Key Words
Fish consumption · Allergic sensitization · Allergic diseases · Docosahexaenoic acid

Abstract
Background: Previous studies have suggested that fish intake plays a protective role in the development of allergic diseases because of its high content of n-3 very long chain polyunsaturated fatty acid (VLC-PUFA). However, it is not clear whether fish intake also has a beneficial effect in adulthood, when allergic diseases are thought to be predominantly manifested. ***Methods:*** Data from 388 adults from German study centres within the European Community Respiratory Health Study II were analysed. These subjects completed an extensive interviewer-administered questionnaire as well as a food frequency questionnaire, lung function measurement and blood drawing for specific IgE testing at the study centre. ***Results:*** Allergic sensitisation (RAST ≥2) was negatively associated with high fish consumption (adjusted OR 0.20, 95% CI 0.05–0.83) and high docosahexaenoic acid (DHA) intake (adjusted OR 0.26, 95% CI 0.07–0.95) in females but not in males when comparing the fourth quartile with the first quartile of intake. No other outcome was related to fish or DHA consumption. ***Conclusions:*** The findings of this study suggest that adult females with a high fish and DHA intake have a lower rate of allergic sensitisation. It is not understood why this association was only seen in females, but gender-related differences in metabolism of PUFAs could be a possible explanation.

Introduction

There is a wide consensus that the prevalence of allergic diseases has been increasing in countries with a Western lifestyle in recent decades [1, 2]. There is currently a debate on the aetiology of allergic diseases, with many hypotheses being proposed and discussed. As the genetic background has not changed substantially over this period, environmental factors are likely to contribute to this increase in prevalence rates. Furthermore, dietary factors may play a role in the development of allergic diseases. Recently, several studies have investigated the effect of prenatal and postnatal fatty acid intake on allergic outcomes and immunologic parameters by supplementation [3–5] and measurement of dietary intake [5–12].

The effect of dietary supplementation with fish oil, which is a major source of n-3 very long chain polyunsaturated fatty acid (VLC-PUFA) on allergic diseases and allergic sensitisation has been investigated in a number of studies [3, 4, 9, 13–17]. A high dietary intake of n-3 PUFAs has been associated with a decreased risk for allergic dis-

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eases, which is thought to be a result of their ability to inhibit the production of inflammatory mediators [18–20]. The n-3 hypothesis suggests that n-3 PUFAs, and especially those with very long chain lengths, modulate the immune response by shifting the immune system to a more anti-inflammatory state. Nevertheless, there are different and partly inconsistent results concerning the n-3 hypothesis. Some studies could find significant associations between PUFAs in the diet, allergic sensitisation and allergic symptoms [4, 8, 9, 11, 21], but other studies found no such effect [22–28]. Although the n-3 hypothesis is biologically plausible, it has not been confirmed by many epidemiological studies [29].

Different clinical manifestations, such as asthma, hay fever and atopic eczema, are generally referred to as allergic diseases although not all forms of asthma have an allergic background. This entity is considered as having a common immunological basis, but is manifest in different locations such as the lung, the gastrointestinal tract, the upper airway system or the skin [30]. We acknowledge the ongoing debate about whether these diseases have a common ground, form a common entity and whether they can be considered allergic in every case; nevertheless, below we refer to these 3 diseases as allergic diseases. Allergic sensitisation, which describes the presence of elevated serum levels of allergen-specific immunoglobulin E (IgE) antibodies, is thought to be fundamental to these disorders and is therefore considered as a potential risk factor for the development of allergic disorders [31–33].

There are only a few studies published that have looked at consumption of fish, allergic disease and sensitisation in adults [5, 28]. In the present study, the association between fish and docosahexaenoic acid (DHA) intake and allergic diseases and allergic sensitisation was analysed using data from the second European Community Respiratory Health Survey (ECRHS II). This should help to elucidate whether fish intake has beneficial effects in adulthood, when allergic diseases are thought to be predominantly manifested.

Methods

Due to the small number of observations in our study population, we were not able to restrict the analysis to subjects with IgE sensitisation, as would be appropriate when studying allergic diseases. We therefore cannot ensure that the outcomes studied are specific to the allergic states for asthma, hay fever and bronchial hyper-responsiveness.

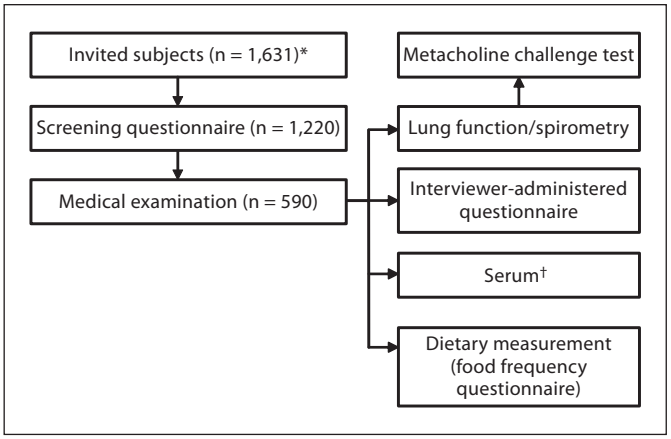

Fig. 1. Progression and composition of the study population in the ECRHS II of the German study centres at Hamburg and Erfurt. The group used in this analysis was the fraction that finished the interviewer-administered questionnaire, blood serum, lung function/provocation and dietary measurement. * 715 of the 731 participants who completed stage 2 in the ECRHS I in Erfurt who authorized the storage of their contact details were invited for ECRHS II. In Hamburg, a randomly selected representative subsample of 900 of the original 1,252 participants from the ECRHS I stage 2 were asked to take part in the second survey. † A blood sample of 27 ml was taken for analysis. Two serum Monovette® and 1 EDTA Monovette® were used. The aliquots were stored at –20°C until analysis.

Study Population

This analysis is based on the ECRHS II [34], follow-up of the ECRHS [35] (www.ecrhs.org). The data used for the present analyses were obtained from the 2 German study centres, Hamburg and Erfurt. In the German centres, the follow-up was conducted during 2000 and 2001. A total of 1,220 out of 1,631 invited subjects agreed to a follow-up examination. From these 1,220 subjects in the follow-up study, 590 underwent a medical examination including lung function measurement (including height and weight measurement), methacholine challenge, blood drawing at the study centre and an interviewer-administered questionnaire on symptoms, medical history, smoking, exposure to environmental tobacco smoke, occupation, home environment, air pollution, medication and use of medical services [35–37]. 390 subjects answered a food frequency questionnaire. The flow chart in figure 1 shows the complete procedure. A plausibility check of the intake data excluded 1 subject because of extremely high energy and fat intake. Another subject was excluded because of respiratory symptoms due to an accident, so the final data set consisted of 388 subjects.

The local ethics committees approved the study protocol.

Anthropometric Measurements

Anthropometric measurements were performed before lung function testing. Weight was measured by an electronic scale to the nearest kilogram. Height was measured, without shoes, to the

nearest centimetre using a scale fixed to a wall. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2).

Allergic Outcomes

Blood samples were collected for the measurement of total IgE and serum-specific IgE using the Pharmacia CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Samples were tested for specific IgE to house dust mite *(Dermatophagoides pteronyssinus)*, grass, cat, and *Cladosporium*. Allergic sensitisation was defined using RAST classes if one of the specific IgE levels was at least 0.35 kU/l (RAST 1) and 0.70 kU/l (RAST 2).

Questions on asthma were taken from the bronchial symptom questions of the International Union Against Tuberculosis and Lung Disease questionnaire [38, 39]. The definition for current asthma was based on a positive answer to 'During the past 12 months, have you had an asthma attack?' or to 'Are you currently taking asthma medication?'

Hay fever was assessed using the questions used for the International Study of Asthma and Allergies in Childhood. We classified subjects as having current hay fever if they answered 'yes' to the question 'Do you have allergic rhinitis, e.g. hay fever?'

Questions about eczema were based on the UK Working Party's diagnostic criteria for atopic dermatitis [40]. According to the position paper of the European Academy of Allergy and Clinical Immunology [41], atopic eczema was assumed if subjects gave a positive answer to the question 'Have you ever had eczema or skin allergy?' and if subjects had detectable IgE antibodies (RAST class 1 or above).

Bronchial hyperreactivity to methacholine was done with a standardised dosing schedule [37] (Provocholine®, Methapharm Inc., Brantford, Ont., Canada). Depending on whether individuals reported symptoms in the questionnaire or not, doubling or quadrupling doses of methacholine were inhaled until a 20% fall in post-diluent forced expiratory volume in 1 s (FEV_1) was observed or the maximum cumulative dose of 2 mg was reached. Bronchial hyperreactivity was then defined as a fall greater than 20% of FEV_1.

Dietary Intake

The food intake was surveyed by a validated food frequency questionnaire containing 148 food items, which was originally designed for the German part of the EPIC (European Investigation into Cancer and Nutrition) study [42–44]. For fish intake, 2 different groups were given. One group contained fish and fish products eaten cold or with bread, the other group asked for fish eaten warm or as a dish. The calculation of nutrient intake was based on the German Nutrient Data Base (BLS) version II.3 (Federal Research Centre for Nutrition and Food, Karlsruhe, Germany).

Statistical Analysis

In this analysis, descriptive statistics were used to describe the study population and to identify differences in fish and DHA intake between subjects with and subjects without allergic sensitisation and allergic diseases. Statistical significance of the differences was tested with the Wilcoxon 2-sample test (normal approximation, 2-sided).

For quantification of associations, simple logistic regression models were calculated. Furthermore, multiple logistic regression models were used to adjust for potential confounders [45]. For this purpose, the middle quartiles were combined (Q2 plus Q3) to contrast the fourth quartile (Q4) and Q2 plus Q3, with the lowest quartile (Q1). Crude and adjusted odds ratios with their corresponding 95% confidence intervals (95% CI) were calculated. Adjustment was performed for study centre, age, occupation, smoking status and BMI. Energy intake was not included in the final model because it did not show any change in the results in a preliminary analysis. All calculations were performed using the statistical analysis package SAS for Windows version 9.1 (SAS Institute, Cary, N.C., USA).

Table 1. Description of the study population

	Male (n = 193)		Female (n = 195)	
	n	%	n	%
Study centre				
Hamburg	97	50.3	104	53.3
Erfurt	96	49.7	91	46.7
Age[1]				
<40 years	68	35.2	66	33.8
40–49 years	82	42.5	86	44.1
50–54 years	43	22.3	43	22.1
Occupation				
Employed	137	71.0	148	75.9
Self-employed	33	17.1	8	4.1
Unemployed or job-seeking	13	6.7	14	7.2
Unable to work because of health	3	1.6	5	2.6
Househusband/housewife	0	0	14	7.2
Student	2	1.0	0	0
Retired	3	1.6	4	2.1
Miscellaneous	2	1.0	2	1.0
Smoking status				
Smoker	64	33.2	50	25.6
Ex-smoker	75	38.9	65	33.3
Never-smoker	54	28.0	80	41.0
BMI[2]				
<25	78	41	119	62.0
25–29.9	89	46.4	50	26.0
>30	25	13.0	23	12.0

[1] Age was calculated at date of screening.
[2] Data on height and weight were missing for 4 subjects.

Results

The basic characteristics of the study population are shown in table 1. Table 2 describes fish and DHA intake in the study population. The calculated fish intake for the 2 study centres was on average 10.6 g per day and person for Hamburg and 12.8 g per day and person for Erfurt (data not shown). DHA intake showed similar results, with on average 184 mg per day per person for Hamburg

Table 2. Fish and DHA intake in the study population described by location parameters

Intake	Male (n = 193)					Female (n = 195)				
	min.	Q1	median	Q3	max.	min.	Q1	median	Q3	max.
Fish, g/days	0.0	4.9	9.5	16.9	89.0	0.0	4.5	8.2	13.6	78.6
DHA, mg/days	47.1	118.3	195.1	291.5	1,091.4	31.1	98.6	157.9	204.8	1,387.6

Table 3. Prevalence of clinical and symptomatic outcomes examined in this study

Outcome	Total (n = 388)		Male (n = 193)		Female (n = 195)	
	n/N	%	n/N	%	n/N	%
Allergic sensitisation (RAST ≥2)	84/364	23.1	49/185	26.5	35/179	19.6
Current asthma (attacks or medication)	20/388	5.2	5/193	2.6	15/195	7.7
Hay fever (current)	96/388	24.7	40/193	20.7	56/195	28.7
Atopic eczema (with RAST ≥1)	54/364	14.8	20/185	10.8	34/179	19.0
Bronchial hyperreactivity	61/343	17.8	25/170	14.7	36/173	20.8

n = Number of patients with outcome; N = total number of patients in whom each outcome was possible.

and 236 mg per day per person for Erfurt. Table 3 shows the prevalence of allergic sensitisation (RAST ≥2), current asthma, hay fever, atopic eczema and bronchial hyperreactivity. There was a trend for a higher prevalence of allergic sensitisation (RAST ≥2), hay fever and atopic eczema in Hamburg, while males – but not females – showed a higher prevalence of asthma and bronchial hyperreactivity in Erfurt (data not shown).

In table 4 the median fish and DHA intake is compared between subjects with and subjects without allergic sensitisation, current asthma, hay fever, atopic eczema and bronchial hyperreactivity. Women but not men who were sensitised had a statistically significant lower intake of DHA ($p = 0.036$), while the difference was borderline significant for fish intake ($p = 0.052$). Similar results were found when 0.35 kU/l was used as the cut-off point, but associations were not statistically significant (data not shown). No significant differences were seen for the other outcomes.

The results of the logistic regression models for the association between fish and DHA intake and allergic outcomes are presented in table 5. All analyses were stratified by gender. High intake (fourth quartile) of fish (adjusted OR 0.20, 95% CI 0.05–0.83) and DHA (adjusted OR 0.26, 95% CI 0.07–0.95) were negatively associated with allergic sensitisation in women. Because of no significant associations the results for men are not shown. Further stratification did not show major differences between the study centres.

Discussion

The results of this study show that fish and DHA intake are inversely associated with allergic sensitisation in adult females, but not in males. Allergic diseases were not statistically significantly associated with fish or DHA intake.

Previous epidemiological studies investigating fish consumption in relation to allergic diseases and allergic sensitisation predominantly found protective effects. These studies were mainly performed during pregnancy or early childhood, suggesting a preventive role for fish intake in the development of allergic sensitisation and allergic diseases [8–10, 12, 22, 46]. One further interesting question is, however, whether fish intake and the beneficial fatty acid content in fish, respectively, have any effect in adulthood when allergy or allergic sensitisation are not developing, but have already manifested in most subjects. Only 1 study from Australia, conducted by Woods et al.

Table 4. Fish and DHA intake according to allergic sensitisation and allergic diseases in female and male study subjects

	Female					Male				
	n	Fish, g/day		DHA, mg/day		n	Fish, g/day		DHA, mg/day	
		median (Q1; Q3)	p	median (Q1; Q3)	p		median (Q1; Q3)	p	median (Q1; Q3)	p
Allergic sensitisation (RAST ≥ 2)										
No	144	8.22 (4.93; 14.43)	0.052	169.3 (99.3; 211.6)	0.036*	163	10.75 (4.52; 16.93)	0.863	205.9 (120.1; 300.3)	0.800
Yes	35	7.40 (4.11; 10.96)		135.2 (84.9; 175.9)		49	9.45 (4.93; 15.62)		194.0 (118.3; 293.9)	
Current asthma (attacks or medication)										
No	180	8.22 (4.52; 13.64)	0.828	159.2 (97.1; 205.5)	0.945	188	9.70 (4.93; 16.93)	0.431	195.0 (117.0; 292.7)	0.926
Yes	15	8.22 (4.93; 11.51)		150.3 (107.9; 190.6)		5	9.04 (2.30; 9.04)		198.9 (194.0; 240.0)	
Hay fever (current)										
No	139	8.22 (4.93; 13.84)	0.357	167.2 (97.0; 207.7)	0.529	153	9.45 (4.52; 16.93)	0.497	196.5 (115.8; 286.0)	0.697
Yes	56	8.22 (4.52; 12.16)		141.1 (107.1; 202.3)		40	10.48 (6.37; 23.08)		193.9 (127.1; 333.0)	
Atopic eczema (with RAST ≥ 1)										
No	145	8.22 (4.52; 14.38)	0.386	167.8 (97.3; 207.7)	0.349	165	9.70 (4.93; 16.93)	0.914	200.9 (124.5; 299.7)	0.364
Yes	34	7.88 (4.93; 11.51)		137.8 (110.3; 180.0)		20	9.86 (4.58; 15.89)		164.8 (104.5; 290.5)	
Bronchial hyperreactivity										
No	137	8.60 (4.93; 14.25)	0.118	167.8 (100.7; 212.4)	0.115	145	11.23 (5.04; 16.93)	0.965	199.7 (115.8; 299.7)	0.601
Yes	36	7.40 (4.25; 10.48)		128.0 (90.5; 175.4)		25	9.45 (4.93; 19.29)		225.1 (131.5; 300.9)	

Statistical significance was determined by Wilcoxon 2-sample test, normal approximation, 2-sided. * $p < 0.05$ (significant).

Table 5. Crude and adjusted odds ratios for the association between fish intake and different outcomes in females

	n	Fish intake, g/day					DHA intake, mg/day				
		Q1 (≤4.5)	Q2+Q3 (4.6–13.6)		Q4 (>13.6)		Q1 (≤98.6)	Q2+Q3 (98.6–204.8)		Q4 (>204.8)	
		OR	OR	95% CI	OR	95% CI	OR	OR	95% CI	OR	95% CI
Allergic sensitisation (RAST ≥2)											
OR	179	1	0.97	0.42–2.23	0.24*	0.06–0.93	1	0.90	0.39–2.08	0.30	0.09–1.03
aOR	179	1	0.99	0.39–2.45	0.20*	0.05–0.83	1	0.79	0.32–1.97	0.26*	0.07–0.95
Current asthma (attacks or medication)											
OR	195	1	1.74	0.46–6.63	0.73	0.12–4.57	1	2.97	0.63–13.97	1.02	0.14–7.56
aOR	195	1	1.62	0.40–6.54	0.62	0.10–4.10	1	2.57	0.53–12.54	0.79	0.10–6.15
Hay fever (current)											
OR	195	1	0.91	0.44–1.89	0.61	0.24–1.52	1	1.28	0.60–2.75	0.92	0.37–2.29
aOR	195	1	0.85	0.40–1.82	0.60	0.23–1.55	1	1.21	0.55–2.66	0.92	0.36–2.39
Atopic eczema (with RAST ≥1)											
OR	179	1	1.91	0.75–4.87	0.57	0.16–2.11	1	1.43	0.58–3.54	0.58	0.17–1.93
aOR	179	1	1.95	0.74–5.13	0.64	0.17–2.45	1	1.52	0.59–3.92	0.68	0.20–2.39
Bronchial hyperreactivity											
OR	173	1	0.77	0.33–1.80	0.47	0.16–1.42	1	0.66	0.28–1.54	0.39	0.13–1.14
aOR	173	1	0.82	0.33–2.03	0.56	0.18–1.81	1	0.62	0.25–1.53	0.41	0.13–1.30

aOR = Odds ratio adjusted for study centre, age, occupation, smoking status and BMI. * $p < 0.05$ (significant).

[28], has used data from a validated food frequency questionnaire to relate fish intake to doctor-diagnosed asthma, bronchial hyperreactivity and atopy in adulthood. They could not find any significant association, which is similar to our findings in terms of other allergic outcomes than allergic sensitisation. In contrast to our study, the study by Woods et al. [28] used a skin-prick test to define allergic sensitisation. Because different methods were applied to assess allergic sensitisation, a direct comparison with our findings is difficult.

Although we have found no associations with other allergic outcomes, the fact that only allergic sensitisation was negatively associated with fish and DHA intake fits to the hypothesis that n-3 fatty acids can affect the production of IgE. Allergic sensitisation to common allergens is often related to different allergic disorders [31, 33, 47], such as asthma and hay fever [48]. However, clinical or symptomatic allergic outcomes do not necessarily follow allergic sensitisation because other genetic or environmental factors are needed until allergies manifest clinically. It was found that about 50% of the subjects without hay fever or without asthma were sensitised (specific IgE $\geq$0.35 kU/l) [49].

Gender-specific effects as observed in the present study have been reported previously [50–52]. The reason for this difference is not clear, but it might be possible that it is due to gender-specific differences in the metabolism of n-3 fatty acids. In women, fractional conversion of α-linoleic acid to DHA appears to be greater compared to men, and because of the effect of oestrogen on D6-desaturase, up-regulation of the conversion of eicosapentaenoic acid to DHA has also been suggested [53, 54]. Although the effect of oestrogen on DHA concentration in women awaits confirmation, these 2 possible mechanisms could be responsible for the different effects in men and women at similar intake levels [55].

Some limitations should be considered when interpreting the findings of this study. First, as the ECRHS is a cross-sectional study, data on allergic outcomes and on food intake were assessed at the same time. Even if the food frequency questionnaire covers the last year of diet, it cannot provide any information about dietary habits at an earlier time. Allergies predominately develop before adulthood [56], and efforts to prevent and influence their onset seem to be more effective if administered in the pre- and postnatal periods and in childhood than if started in adulthood [57, 58]. However, it might be possible that fish intake during the 12 months prior to the blood measurement contributes to differences in serum IgE concentrations between study participants, possibly as a short-term effect. This is indirectly supported by longitudinal studies demonstrating changes in specific IgE antibody levels over time [59].

One might also speculate that atopic subjects alter their diet and avoid fish because of its allergenic potential. However, as sensitised subjects were probably not aware of the fact that they have an allergic reaction to inhalant allergens, it seems unlikely that the results can be explained by reverse causation.

The possibility that significant associations occurred by chance as a result of multiple testing should also be kept in mind, but as the observed significant effects correspond with the biological hypothesis, it is unlikely that the results might be explained by chance alone.

Furthermore, the validated food frequency questionnaire used in this study did not incorporate supplements like fish oil capsules. Therefore, it was not possible to consider additional intake by supplementation in the nutrient calculation, which might have led to some misclassification bias.

Beside these weaknesses, this study also has several strengths. The main advantage of this study is the use of a validated food frequency questionnaire and standardised interviews and identical laboratory methods. The high quality of the ECRHS using standard operating procedures for all study centres made sure that all outcomes were assessed identically.

Conclusion

The findings of this study suggest that adults with a high fish and DHA intake have a lower rate of allergic sensitisation. It is not understood why this association was only seen in females, but gender-related differences in metabolism of PUFAs could be a possible explanation.

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References

1 Warner JO, Kaliner MA, Crisci CD, Del Giacco S, Frew AJ, Liu GH, Maspero J, Moon HB, Nakagawa T, Potter PC, Rosenwasser LJ, Singh AB, Valovirta E, Van Cauwenberge P: Allergy practice worldwide: a report by the World Allergy Organization Specialty and Training Council. Int Arch Allergy Immunol 2006;139:166–174.

2 Eder W, Ege MJ, von Mutius E: The asthma epidemic. N Engl J Med 2006;355:2226–2235.

3 Denburg J, Hatfield H, Cyr M, Hayes L, Holt P, Sehmi R, Dunstan J, Prescott S: Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. Pediatr Res 2005;57:276–281.

4 Dunstan JA, Prescott SL: Does fish oil supplementation in pregnancy reduce the risk of allergic disease in infants? Curr Opin Allergy Clin Immunol 2003;5:215–221.

5 Sausenthaler S, Koletzko B, Heinrich J: Dietary fat intake and allergic diseases. Curr Nutr Food Sci 2006;2:351–359.

6 Calder PC, Krauss-Etschmann S: Early nutrition and immunity – progress and perspectives. Br J Nutr 2006;96:774–790.

7 Salam MT, Yu-Fen L, Langholz B, Gilliland FD: Maternal fish consumption during pregnancy and risk of early childhood asthma. J Asthma 2005;42:513–518.

8 Calvani M, Alessandri C, Sopo SM, Panetta V, Pingitore G, Tripodi S, Zappalà D, Zicari AM: 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.

9 Sausenthaler S, Koletzko S, Schaaf B, Lehmann I, Borte M, Herbarth O, von Berg A, Wichmann HE, Heinrich J; for the LISA Study Group: Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 years of age. Am J Clin Nutr 2007;85:530–537.

10 Romieu I, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fito N, Anto JM, Sunyer J: Maternal fish intake during pregnancy and atopy and asthma in infancy. Clin Exp Allergy 2007;37:518–525.

11 Nafstad P, Nystad W, Magnus P, Jaakkola JJK: Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. J Asthma 2003;40:343–348.

12 Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M: Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy 2006;61:1009–1015.

13 Nagakura T, Matsuda S, Shichijyo K, Sugimoto H, Hata K: Dietary supplementation with fish oil rich in omega-3 polyunsaturated fatty acids in children with bronchial asthma. Eur Respir J 2000;16:861–865.

14 Thien F, De Luca S, Woods R, Abramson M: Dietary marine fatty acids (fish oil) for asthma in adults and children. Cochrane Database Syst Rev. DOI: 10.1002/14651858.CD001283.

15 Van Gool CJAW, Zeegers MPA, Thijs C: Oral essential fatty acid supplementation in atopic dermatitis: a meta-analysis of placebo-controlled trials. Br J Dermatol 2004;150:728–740.

16 Reisman J, Schachter HM, Dales RE, Tran K, Kourad K, Barnes D, Sampson M, Morrison A, Gaboury I, Blackman J: Treating asthma with omega-3 fatty acids: where is the evidence? A systematic review. BMC Complement Altern Med 2006;6:26–33.

17 Soyland E, Funk J, Rajka G, Sandberg M, Thune P, Rustad L, Helland S, Middelfart K, Odu S, Falk ES, Solvoll K, Bjorneboe GEA, Drevon CA: Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis. A double-blind, multicentre study. Br J Dermatol 1994;130:757–764.

18 Kankaanpaa P, Sutas Y, Salminen S, Lichtenstein A, Isolauri E: Dietary fatty acids and allergy. Ann Med 1999;31:282–287.

19 Hoff S, Seiler H, Heinrich J, Kompauer I, Nieters A, Becker N, Nagel G, Gedrich K, Karg G, Wolfram G, Linseisen J: Allergic sensitisation and allergic rhinitis are associated with n-3 polyunsaturated fatty acids in the diet and in red blood cell membranes. Eur J Clin Nutr 2005;59:1071–1080.

20 Prescott SL, Calder PC: n-3 polyunsaturated fatty acids and allergic disease. Curr Opin Clin Nutr Metab Care 2004;7:123–129.

21 Bjorneboe A, Soyland E, Bjorneboe G, Rajka G, Drevon C: Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. Br J Dermatol 1987;117:463–469.

22 Andreasyan K, Ponsonby AL, Dwyer T, Kemp A, Dear K, Cochrane J, Carmichael A: A differing pattern of association between dietary fish and allergen-specific subgroups of atopy. Allergy 2005;60:671–677.

23 Berth-Jones J, Graham-Brown RAC: Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. Lancet 1993;341:1557–1560.

24 Farchi S, Forastiere F, Agabiti N, Corbo G, Pistelli R, Fortes C, Dell'Orco V, Perucci CA: Dietary factors associated with wheezing and allergic rhinitis in children. Eur Respir J 2003;22:772–780.

25 Fluge O, Omenaas E, Eide GE, Gulsvik A: Fish consumption and respiratory symptoms among young adults in a Norwegian community. Eur Respir J 1998;12:336–340.

26 Nagel G, Linseisen J: Dietary intake of fatty acids, antioxidants and selected food groups and asthma in adults. Eur J Clin Nutr 2005;59:8–15.

27 Thien F, Mencia-Huerta J, Lee T: Dietary fish oil effects on seasonal hay fever and asthma in pollen-sensitive subjects. Am Rev Respir Dis 1993;147:1138–1143.

28 Woods RK, Walters EH, Raven JM, Wolfe R, Ireland PD, Thien FC, Abramson MJ: Food and nutrient intakes and asthma risk in young adults. Am J Clin Nutr 2003;78:414–421.

29 Kompauer I: n6/n3 hypothesis and allergies: biologically plausible, but not confirmed. Eur J Med Res 2004;9:378–382.

30 Leung DYM, Sampson HA, Geha RS, Szefler SJ (eds): Pediatric Allergy: Principles and Practice. St Louis, Mosby, 2003.

31 Arshad SH, Tariq SM, Matthews S, Hakim E: Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. Pediatrics 2001;108:33–40.

32 Illi S, von Mutius E, Lau S, Nickel R, Niggemann B, Sommerfeld C, Wahn U: The pattern of atopic sensitization is associated with the development of asthma in childhood. J Allergy Clin Immunol 2001;108:709–714.

33 Laan MP, Baerta MRM, Bijl AMH, Vredendaal AECM, De Waard-Van Der Spek FB, Oranje AP, Savelkoul HF, Neijens HJ: Markers for early sensitization and inflammation in relation to clinical manifestations of atopic disease up to 2 years of age in 133 high-risk children. Clin Exp Allergy 2000;30:944–953.

34 Protocol for the European Community Respiratory Health Survey II. London, King's College, 2002. www.ecrhs.org/Quests/ECRHSIIprotocol.pdf (accessed January 28, 2009).

35 Burney PG, Luczynska C, Chinn S, Jarvis D: The European Community Respiratory Health Survey. Eur Respir J 1994;7:954–960.

36 Mayer I, Hölscher G, Frye C, Wölke G, Kött S, Pitz M, Cyrys J, Manuwald O, Tumat C, Manuwald B, Schlegelmich C, Mücke M, Richter K, Heinrich J: LUFU-Studie/ECRHS II – Studienmanual. 2000.

37 The European Community Respiratory Health Survey II Steering Committee: The European Community Respiratory Health Survey II. Eur Respir J 2002;20:1071–1079.

38 Abramson MJ, Hensley MJ, Saunders NA, Wlodarczyk JH: Evaluation of a new asthma questionnaire. J Asthma 1991;28:129–139.

39 Burney P, Chinn S: Developing a new questionnaire for measuring the prevalence and distribution of asthma. Chest 1987;91:79S–83S.

40 Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, Bingham EA, Finlay AY, Pembroke AC, Graham-Brown RA: The UK Working Party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 1994;131:383–396.

41 Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, van Cauwenberge P, Williams HC: Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832–836.
42 Boeing H, Bohlscheid-Thomas S, Voss S, Schneeweiss S, Wahrendorf J: The relative validity of vitamin intakes derived from a food frequency questionnaire compared to 24-hour recalls and biological measurements: results from the EPIC pilot study in Germany. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26:S82–S90.
43 Bohlscheid-Thomas S, Hoting I, Boeing H, Wahrendorf J: Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the German part of the EPIC project. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26:S59–S70.
44 Bohlscheid-Thomas S, Hoting I, Boeing H, Wahrendorf J: Reproducibility and relative validity of energy and macronutrient intake of a food frequency questionnaire developed for the German part of the EPIC project. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26:S71–S81.
45 Hosmer DW, Lemeshow S: Applied Logistic Regression. Hoboken, Wiley, 1989.
46 Kim JL, Elfman L, Mi Y, Johansson M, Smedje G, Norback D: Current asthma and respiratory symptoms among pupils in relation to dietary factors and allergens in the school environment. Indoor Air 2005;15:170–182.
47 Kurukulaaratchy RJ, Matthews S, Arshad SH: Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. Allergy 2005;60:1280–1286.
48 Boulay ME, Boulet LP: The relationships between atopy, rhinitis and asthma: pathophysiological considerations. Curr Opin Allergy Clin Immunol 2003;3:51–55.
49 Abraham CM, Ownby DR, Peterson EL, Wegienka G, Zoratti EM, Williams LK, Joseph CLM, Johnson CC: The relationship between seroatopy and symptoms of either allergic rhinitis or asthma. J Allergy Clin Immunol 2007;119:1099–1104.
50 Miyake Y, Sasaki S, Tanaka K, Ohya Y, Miyamoto S, Matsunaga I, Yoshida T, Hirota Y, Oda H; the Osaka Maternal and Child Health Study Group: Fish and fat intake and prevalence of allergic rhinitis in Japanese females: the Osaka Maternal and Child Health Study. J Am Coll Nutr 2007;26:279–287.
51 Osman M: Therapeutic implications of sex differences in asthma and atopy. Arch Dis Child 2003;88:587–590.
52 Trak-Fellermeier MA, Brasche S, Winkler G, Koletzko B, Heinrich J: Food and fatty acid intake and atopic disease in adults. Eur Respir J 2004;23:575–582.
53 Burdge GC, Wootton SA: Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr 2002;88:411–421.
54 Giltay EJ, Gooren LJ, Toorians AW, Katan MB, Zock PL: Docosahexaenoic acid concentrations are higher in women than in men because of estrogenic effects. Am J Clin Nutr 2004;80:1167–1174.
55 Williams CM, Burdge G: Long-chain n-3 PUFA plant vs. marine sources. Proc Nutr Soc 2006;65:42–50.
56 Turner SW, Devereux G: Early life influences on the development of allergy and asthma – how early is early? Clin Exp Allergy 2007;37:163–165.
57 Gold M, Kemp A: Atopic disease in childhood. Med J Aust 2005;182:298–304.
58 Halken S: Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. Pediatr Allergy Immunol 2004;15:9–32.
59 Odijk J, Bengtsson U, Borres MP, Hulthen L, Ahlstedt S: Specific immunoglobulin E antibodies to peanut over time in relation to peanut intake, symptoms and age. Pediatr Allergy Immunol 2004;15:442–448.