The influence of the dietary intake of fatty acids and antioxidants on hay fever in adults

Background: The objective of the investigation was to explore in a prospective study the associations between dietary intake of fatty acids, antioxidants and hay fever manifestation in adulthood.
Methods: Three hundred and thirty-four hay fever cases with adult onset of clinical symptoms from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg cohort were identified during follow-up and matched with 1336 controls. Dietary intake data were obtained by means of validated food frequency questionnaires. The influence of dietary fatty acid and vitamin intake on hay fever risk was estimated by means of unconditional logistic regression.
Results: High intake of oleic acid was positively associated with hay fever [odds ratio (OR): 2.86, 95% confidence intervals (95% CI): 1.22–6.70], whereas high intake of eicosapentaenoic acid was inversely related to hay fever (OR: 0.45, 95% CI: 0.22–0.93). Furthermore, high β-carotene intake increased the risk of hay fever (OR: 1.69, 95% CI: 1.09–2.63) while increasing intake of vitamin E was a protective factor (OR: 0.38, 95% CI: 0.17–0.85). In grouped analyses, the effects of β-carotene and vitamin E were mainly observed among women and ex-/current-smokers; in these subgroups, linoleic acid increased the risk of hay fever.
Conclusions: In conclusion, the present results provide further evidence that dietary factors might affect the risk of clinical manifestation of hay fever. However, the effects in smokers and women may suggest different biological mechanisms for the investigated nutrients, which need further research.

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Hay fever or seasonal allergic rhinitis is characterized by a prolonged immunoglobulin E (IgE) mediated inflammation after allergen exposure (1). It affects, with regional differences, 9.5–40.9% of the European population (2, 3). Genetic and environmental factors including air pollution, housing conditions and other lifestyle factors have been linked to its etiology. Findings have increasingly been interpreted in the conceptual framework of the 'hygiene hypothesis' which explains the increasing occurrence of atopic diseases by a shift to T-helper cell 2 (Th2) triggered immune responses because of decreased childhood contacts to infectious agents, important stimulants for the Th1reaction (4).

Recent research is led by the observation that a substantial contribution to increasing allergic sensitization might additionally arise from dietary factors, crucial components of the typical western lifestyle pattern (5). Special attention was assigned to dietary fat intake, after a study among children in former Eastern Germany linked elevated margarine consumption positively and butter consumption inversely with hay fever (6). A role of dietary fat intake in the etiology of atopic diseases would fit into the above cited hypothesis, since fat intake and specifically the composition of the ingested dietary fatty acids are known to modulate immune reactions (7). As potential mechanisms their influence on membrane composition, their impact on the production of immune mediators such as prostaglandins and leukotrienes (LTs), and their differential effects on the regulation of Th1and Th2 cytokines are discussed (8).

Particularly, differences in the consumption of n-3 and n-6 fatty acids have been related to the prevalence of allergic diseases (9, 10). In a typical western diet the proportion of n-6 polyunsaturated fatty acids (PUFA) is much higher than that of n-3 PUFA (11). The main dietary sources for eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6) as members of the n-3 PUFA family, are fish and other marine food, which are scarce in most western diets (12). Important sources for the main n-6 PUFAs, linoleic acid (C18:2) and arachidonic acid (AA) (C20:4), are vegetable and animal fat, respectively. By the competitive metabolism of EPA and AA via the cyclooxygenase and lipooxygenase pathways, specifically the ratio of n-6 and n-3 PUFAs may influence the production of immune mediators such as prostaglandins, LTs, thromboxanes, and epoxy-compounds. The

metabolism of the n-6 PUFAs and AA leads to the formation of prostaglandin E2 (PGE2), which is an important immune regulator known to suppress Th1 activation and enhance Th2 activation thereby accelerating the formation of IgE in B cells (13).

Under unbalanced (patho-)physiological conditions such as deficiency of antioxidants or chronic inflammation the enzymatic metabolism of PUFAs leads to an increased internal exposure to free radicals. Additionally, autoxidation of the double bonds may substantially contribute to an enhanced radical load. Recent work indicates that this 'oxidative stress' might regulate Th1and Th2 cytokines differentially in favor of a Th2 response (14). It can be hypothesized that, dietary antioxidants such as β-carotene, vitamins C and E, might contribute to the pathogenesis of allergies by their anti-oxidative properties thus decreasing the risk of hay fever. An inverse association between IgE plasma levels and a high intake of vitamin E is described (15, 16). Taken together there is evidence that dietary factors may influence the inflammatory response following allergen-specific challenge and thus have impact on the clinical onset of allergic disease.

Therefore, the present evaluation aims to examine prospectively within European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg the potential effect of dietary fatty acids and antioxidants on the risk of hay fever among adults.

Material and methods

Data collection

The EPIC is a prospective multicentre study that has been implemented to further the understanding of the association between diet and chronic diseases with emphasis on cancer (17). In Heidelberg from June 1994 until October 1998 about 25 500 subjects aged 35–65 years in women and 40–65 years in men were recruited (18, 19). The baseline assessment of the cohort comprised a dietary measurement by means of a self-administered food frequency questionnaire (FFQ) (20, 21), a computerized lifestyle interview and standardized anthropometric measurements (22). The response rate of the first follow-up, which took place between 1998 and 2000, was 93.5% .

During the median follow-up time of 2.1years, 334 hay fever cases with first manifestation of clinical symptoms were identified through comparison of baseline and follow-up data. Cases were based on the participants' responses on the lifestyle follow-up questionnaire asking specifically for a diagnosis confirmed by a physician. Of 344 persons 189 (54.9%) noted the year of hay fever diagnosis, which was in median 1.3 years after baseline assessment. Furthermore, of 143 cases information on the specific allergens was available. Most often pollens (45.8%) and house dust mites (23.6%) were mentioned. The control group comprised of 1336 randomly selected cohort members without self-reported prevalent hay fever or other atopic diseases, that were matched (4 : 1) to the cases by sex and age group (5 years).

Variable definition

The information on the consumption of fatty acids, antioxidants, and nutrients are based on the self-administered FFQ. The nutrient intake was calculated on the base of the national food tables BLS, Version II.3 (23). Based on the distributions among the controls, the quartiles for the dietary intake of food groups, fatty acids and antioxidants were calculated.

Education was categorized as low (no more then 9 years of schooling without a specific vocational training), middle (high school degree (10 years) and/or vocational or technical training) and high (13 years of high school and/or a university degree). Sports activity was classified as 'yes' when any sports activity was mentioned. Participants were re-categorized as nonsmokers when less than 3 months of regular smoking was reported, as ex-smokers when smoking was quitted for at least 1year before the baseline interview, and as smokers when present smoking was reported or when smoking was quitted < 1year before the baseline interview. Body mass index (BMI) was calculated as weight in kg/height in m^2.

Statistical methods

A case–control evaluation frequency matched for sex and age was conducted. Mean, standard deviation, minimum, and maximum as well as quartiles were calculated using the SAS procedure UNIVARIATE.

The quartile cut points were based on consumption levels among controls corresponding to the values of the 25, 50, and 75 percentiles. The associations between dietary intake and the risk of hay fever were assessed fitting unconditional logistic regression models. Analyses grouped by sex and smoking habits were performed.

For each dietary variable the relationship between hay fever was explored separately by logistic regression without involvement of other nutrient variables. A multivariate basic model to evaluate the influence of fatty acids and antioxidants simultaneously on the risk of hay fever was fitted. In further models the ratios of fatty acids were included separately replacing the corresponding dietary fatty acids. In additional models EPA and DHA as n-3 PUFAs and vitamins were replaced by their main dietary sources, i.e. fish as well as fruits, fruit juice and vegetables, respectively. Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were calculated using the PROC LOGISTIC procedure of the statistical software package SAS release 8.2 (SAS Institute, Cary, NC). Tests for trend with two-sided *P*-values were calculated by using the median values for each category as continuous exposure score.

Results

Table 1shows the basic characteristics of cases and controls. Between the groups no differences regarding BMI and median follow-up time existed. Significant differences can be seen for smoking habits ($P = 0.001$) and educational level ($P = 0.042$). No group differences were found for sports activities ($P = 0.692$).

Table 2 shows the relationship between the intake of fatty acids and antioxidants and the risk of hay fever in the adjusted model. An increasing intake of C18:1 (oleic acid) was positively associated with hay fever (*P*-value for trend 0.040). For the highest consumption group (4. quartile) the risk of hay fever was almost threefold (OR: 2.86, 95% CI: 1.22–6.70) compared with the lowest consumption group (1. quartile). With increasing intake of C20:5 (EPA) the risk of hay fever symptoms decreased. For the group with the highest intake (4. quartile) the

Table 1. Sample characteristics hay fever cases and matched controls

Variable	Cases $n = 334$		Controls $n = 1336$		
	n	%	*n*	%	*P*-value*
Age (matching variable)					
<50 years	173	51.8	692	51.8	
50–59 years	121	36.2	484	36.2	
≥60 years	40	12.0	160	12.0	
Sex (matching variable)					
Male	114	34.1	456	34.1	
Female	220	65.9	880	65.9	
Educational level					
High (university)	23	6.9	92	6.9	0.042
Medium (professional training)	176	52.7	800	59.9	
Low (no professional training)	135	40.4	444	33.2	
Sports acitivity					
Yes	190	56.9	776	58.1	0.692
No	144	43.1	560	41.9	
Smoking status					
Never	133	39.8	554	41.5	0.001
Ex	130	38.9	391	29.3	
Current	71	21.3	391	29.3	
	Median	25–75 percentile	Median	25–75 percentile	*P*-value†
Follow-up time (years after recruitment)‡	2.1	1.7–2.7	2.0	1.7–2.6	0.102
BMI (kg/m^2)	25.35	23.0–28.0	25.2	22.8–28.1	0.725

* Chi^2-test, † Wilcoxon test, ‡ First follow up.
BMI, body mass index.

relationship was significant (OR: 0.45, 95% CI: 0.22–0.93). For individuals with low intake (2. quartile) of C18:2 (linoleic acid) the risk of hay fever was higher than in the reference category (OR: 1.61; 95% CI: 1.01–2.58), an effect which did not extend to the upper quartiles. For the intake of other fatty acids no significant effects on hay fever risk were found. Surprisingly, an increasing ratio of n-6 to n-3 PUFA tended to decrease hay fever risk ($P = 0.031$for trend), an effect which remained after adjustment.

Furthermore, an increasing consumption of β-carotene was positively associated with hay fever (*P*-value for trend 0.116). For the highest intake group the association with hay fever reached statistical significance (OR: 1.69; 95% CI: 1.09–2.63). For increasing intake of vitamin E a trend towards a decreased risk was observed (*P*-value for trend 0.067). For individuals with high intake of vitamin E (3. and 4. quartile) the inverse effects were significant (OR: 0.46, 0.38, respectively). For the replacement of micronutrients by the corresponding food groups (fish or fruit, fruit juice and vegetable, butter and margarine, respectively) no association with hay fever risk was observed (data not shown).

Subsequently, the data was analyzed by sex (Table 3) and smoking status (Table 4). Among men no significant associations were seen, whereas among women the intake of C18:2 was associated with a higher risk of hay fever with OR of 1.82 and 2.09 in the second and third quartile. Moreover, an increasing intake of β-carotene (4. quartile) was positively associated with hay fever risk (*P*-value for trend 0.134). In the group of nonsmokers an increase in risk for high C18:1 intake (OR: 4.82; 95% CI: 1.05–22.19) and an inverse effect for higher C20:5 was observed (OR: 0.31; 95% CI: 0.10–0.99). Among ex- and current smokers significant effects on hay fever risk were seen for high intake of β-carotene (positive association, *P*-value for trend 0.060) and vitamin E (inverse association, *P*-value for trend 0.133). In this subgroup, linoleic acid intake in the third quartile was significantly associated with hay fever risk.

Discussion

We used the frame of the prospective EPIC cohort to investigate the relationship between dietary intake of fatty acids and vitamins and occurrence at a relatively older age of a first diagnosis of hay fever, i.e. clinical manifestation of hay fever. The time lag between the assessment of dietary habits and the hay fever diagnosis was in median 2.1years. We found associations between the intake of several fatty acids (C18:1, C18:2, C20:5) and vitamins (vitamin E, β-carotene) with the risk of hay fever. However, the association between linoleic acid (C18:2), β-carotene and vitamin E and hay fever was related to smoking habits and gender, whereas others (C18:1, C20:5) were found independently. As these nutrients act biologically differently, the consistency and mechanistic plausibility of these findings has to be examined carefully.

Table 2. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association between the dietary intake of fatty acids and vitamins and the clinical manifestation of hay fever in adults

Nutrient	1. Quartile (lowest)	2. Quartile		3. Quartile		4. Quartile (highest)		*P* for trend
SFA (no. of cases)	81	76		84		93		
SFA* (g/d)	<22.7	22.7–28.7		28.7–37.5		>37.5		
SFA† (OR/95% CI)	1	1.20	0.71–2.02	1.41	0.68–2.93	1.27	0.50–3.21	0.996
MUFA								
C16:1 (no. of cases)	87	76		80		90		
C16:1* (g/d)	<1.2	1.2–1.5		1.5–2.0		>2.0		
C16:1† (OR/95% CI)	1	0.67	0.39–1.17	0.55	0.25–1.20	0.53	0.20–1.43	0.160
C18:1 (no. of cases)	80	76		78		100		
C18:1* (g/d)	<16.8	16.3–20.8		20.8–26.6		>26.6		
C18:1† (OR /95%CI)	1	1.22	0.73–2.04	1.48	0.74–2.95	2.86	1.22–6.70	0.040
n-6 PUFA								
C18:2 (no. of cases)	76	88		87		83		
C18:2* (g/d)	<7.2	7.2–9.4		9.4–12.4		>12.4		
C18:2† (OR/95%CI)	1	1.61	1.01–2.58	1.70	0.92–3.16	1.60	0.72 –3.54	0.333
C20:4 (no. of cases)	85	86		83		80		
C20:4* (mg/d)	<100	100–140.7		140.7–202.5		>202.5		
C20:4† (OR/95%CI)	1	1.01	0.68–1.50	0.88	0.54–1.44	0.67	0.36–1.27	0.040
n-3 PUFA								
C18:3 (no. of cases)	82	73		87		92		
C18:3* (g/d)	<0.9	0.9–1.2		1.2–1.5		>1.5		
C18:3† (OR/95%CI)	1	0.83	0.51–1.34	0.99	0.54–1.84	1.05	0.50–2.23	0.526
C20:5 (no. of cases)	87	76		85		86		
C20:5 (mg/d)	<30.2	30.2–55.1		55.1–95.9		>95.9		
C20:5†(OR/95% CI)	1	0.71	0.46–1.10	0.66	0.38–1.15	0.45	0.22–0.93	0.071
C22:6 (no. of cases)	77	84		82		91		
C22:6* (mg/d)	<83.4	83.4–113.6		113.6–194.5		>194.5		
C22:6† (OR/95% CI)	1	1.47	0.89–2.42	1.72	0.84–3.52	2.34	0.91– 5.98	0.006
Vitamins								
Retinol (no. of cases)	79	93		85		77		
Retinol* (μg/d)	<417.8	417.8–596.4		596.4–873.5		>873.5		
Retinol† (OR/95% CI)	1	1.19	0.81–1.75	1.03	0.67–1.59	0.87	0.53–1.41	0.370
β-Carotene (no. of cases)	83	59		84		108		
β-Carotene* (mg/d)	<1.7	1.7–2.2		2.2–2.9		>2.9		
β-Carotene† (OR/95% CI)	1	0.77	0.51–1.15	1.18	0.78–1.77	1.69	1.09–2.63	0.116
Vit. C (no. of cases)	83	84		86		81		
Vit. C* (g/d)	<70.9	70.9–94.7		94.7–125.5		>125.5		
Vit. C† (OR/95% CI)	1	0.99	0.67–1.45	1.00	0.67–1.51	0.89	0.56–1.42	0.132
Vit. E (no. of cases)	85	82		80		87		
Vit. E* (g/d)	<8.3	8.3–10.3		10.3–13.1		>13.1		
Vit. E† (OR/95%CI)	1	0.71	0.44–1.14	0.46	0.25–0.86	0.38	0.17–0.85	0.067
Vit. D (no. of cases)	81	75		83		95		
Vit. D* (μg/d)	<1.7	1.7–2.5		2.5–3.6		>3.6		
Vit. D† (OR/95% CI)	1	0.90	0.57–1.44	1.07	0.57–2.03	1.41	0.62–3.20	0.113
n-6/n-3 ratio (no. of cases)	97	92		80		65		
n-6/n-3 ratio*	<5.8	5.8–6.9		6.9–8.1		>8.1		
n-6/n-3 ratio†‡ (OR/95% CI)	1	0.99	0.70–1.39	0.87	0.60–1.26	0.70	0.45–1.10	0.031

* Cut-points of the quartiles.

† Micronutrient variables were examined simultaneously in the model, multivariate adjusted for adjustment variables.

‡ Replaced the fatty acids C18:2, and C20:4, C18:3 C20:5, and C22:6, respectively in the basis model, multivariate adjusted.

The model included as adjustment variables: age (<50, 50–59 and ≥60 years), total energy intake (kcal/d, continuous), body mass index (continuous), smoking status (never, ex, current), sex, educational level (high, middle, low), sports activity (yes, no).

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Monounsaturated fatty acids

The present study found an increasing intake of the MUFA oleic acid (C18:1) significantly associated with an increasing hay fever risk. This observation is consistent with the results of Heinrich et al. who reported that dietary intake of energy adjusted MUFA was positively related to the prevalence of atopy (3). Among the main dietary sources of *cis*-C18:1 in the typical German diet are meat, meat products, butter, milk, milk products and cheese. As the intake of *trans*-C18:1 is provided by ruminant fat and margarine, it may be therefore speculated that

Table 3. Odds Ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association between the consumption of selected fatty acids and vitamins and the clinical manifestation of hay fever by gender

Nutrient	1. Quartile (lowest)	2. Quartile		3. Quartile		4. Quartile (highest)		*P* for trend
		OR	95% CI	OR	95% CI	OR	95% CI	
Male ($n = 570$)								
C18:1*	1	1.37	0.42–4.53	1.07	0.22–5.13	3.53	0.56–22.19	0.129
C18:2*	1	1.08	0.40–2.88	0.95	0.26–3.49	1.02	0.22–4.82	0.876
C20:5*	1	0.64	0.26–1.58	0.50	0.18–1.42	0.38	0.11–1.31	0.127
β-Carotene*	1	0.48	0.37–1.51	1.64	0.80–3.35	1.25	0.57–2.74	0.556
Vit. E*	1	0.92	0.35–2.42	0.59	0.17–2.03	0.47	0.11–2.08	0.045
Female ($n = 1100$)								
C18:1*	1	1.25	0.70–2.23	1.70	0.76–3.78	2.63	0.96–7.25	0.008
C18:2*	1	1.82	1.05–3.18	2.09	1.01–4.33	1.53	0.57–4.09	0.616
C20:5*	1	0.73	0.44–1.20	0.72	0.36–1.45	0.40	0.15–1.07	0.044
β-Carotene*	1	0.76	0.45–1.27	1.02	0.60–1.72	1.96	1.12–3.43	0.134
Vit. E*	1	0.66	0.38–1.16	0.40	0.19–0.84	0.38	0.14–1.02	0.110

* Micronutrients were examined simultaneously in the model, multivariate adjusted for adjustment variables.
The model included as adjustment variables: age (<50, 50–59 and ≥60 years), total energy intake (kcal/d, continuous), body mass index (continuous), smoking status (never, ex, current), sex, educational level (high, middle, low), sports activity (yes, no), C16:1, C18:3, C20:4, vitamins C, A, D.

Table 4. Odds Ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association between the consumption of selected fatty acids and vitamins and the clinical manifestation of hay fever by smoking status

Nutrient	1. Quartile (lowest)	2. Quartile		3. Quartile		4. Quartile (highest)		*P* for trend
Non-smokers ($n = 687$)								
C18:1*	1	1.33	0.57–3.13	2.90	0.88–9.51	4.82	1.05–22.19	0.014
C18:2*	1	1.28	0.58–2.81	1.00	0.35–2.83	1.07	0.29–3.94	0.913
C20:5*	1	0.61	0.31–1.22	0.67	0.27–1.64	0.31	0.10–0.99	0.092
β-Carotene*	1	0.58	0.30–1.11	0.93	0.49–1.77	1.15	0.57–2.35	0.486
Vit. E*	1	1.61	0.73–3.55	0.73	0.26–2.05	0.93	0.25–3.52	0.638
Ex or current smokers ($n = 983$)								
C18:1*	1	1.20	0.61–2.36	1.03	0.41–2.57	2.45	0.82–7.30	0.131
C18:2*	1	1.81	0.98–3.32	2.25	1.02–4.97	1.73	0.61–4.89	0.465
C20:5*	1	0.73	0.41–1.30	0.64	0.30–1.35	0.55	0.21–1.47	0.133
β-Carotene*	1	0.87	0.51–1.50	1.33	0.77–2.32	2.21	1.22–4.00	0.060
Vit. E*	1	0.47	0.25–0.88	0.38	0.17–0.85	0.26	0.09–0.74	0.133

* Micronutrients were examined simultaneously the model, multivariate adjusted for adjustment variables.
The models included as adjustment variables: age (<50, 50–59 and ≥60 years), total energy intake (kcal/d, continuous), body mass index (continuous), smoking status (never, ex, current), educational level (high, middle, low), sports activity (yes, no), C16:1, C18:3, C20:4, vitamins C, A, D, and sex in the model grouped by smoking habits.

a higher intake of C18:1 may correlate with an increasing intake of *trans*-C18:1. There is evidence that the configuration (*cis*-, *trans*-) of monounsaturated fatty acids influences immune modulation. Weiland et al. found that the intake of *trans*-fatty acids is associated with allergic disease (24). It was suggested that *trans*-fatty acids may promote an increase in IgE, mediated by the modulation of the desaturation and chain elongation of n-6 and n-3 fatty acids and thereby influences the prostaglandin and LT synthesis (25).

Polyunsaturated fatty acids

We found indications for an inverse association between dietary intake of the n-3 PUFA EPA (C20:5) and the incidence of allergic rhinitis with a significantly decreased OR in the highest intake quartile. No association was observed for α-linolenic acid (C18:3) and DHA (C22:6) or the overall intake of n-3 PUFA.

Among the n-6 PUFA, some indication for a relationship of the intake of linoleic acid (C18:2) could be observed. However, this finding was only statistically significant in specific intake quartiles (2. quartile for the whole study population and second and third quartile for ex or current smokers) and is not supported by the trend test.

The results found in smokers, particularly in smoking women, would fit with the oxidative stress hypothesis of allergic respiratory diseases as discussed in Bowler and Crapo (26). In a situation with a high radical load the

double bonds of the main dietary PUFA are autoxidized, but may be prevented by vitamin E. In women, there is some evidence that a high linoleic acid intake may increase lipid peroxidation products (in certain conditions) which may be mediated by redox cycling of hydroxyestradiol compounds (27).

The literature provides a report from Japan describing a positive association between allergic rhino conjunctivitis and the intake of n-6 PUFA. However, that study could not find any significant association with the intake of SFA, MUFA, and n-3 PUFA (10). We could not corroborate previous links between butter *vs* margarine consumption and the prevalence of hay fever and asthma among children which were suggested to explain higher rates in West compared with East Germany (6, 9, 28, 29).

The n-6 and n-3 PUFA are both substrates of cyclooxygenase and lipoxygenase enzymes, leading, however, to molecules with different effects on inflammatory processes. Prostaglandin E2, a n-6 derived product, is known to shift the Th1/Th2 balance in the Th2 direction, which favors Th2 determined diseases such as allergies (7). In contrast, an increasing availability of the EPA as a n-3 PUFA inhibits the conversion of AA to PGE2 and LT B4 and can be expected to be negatively associated with allergic rhinitis (30).

The described biological mechanism suggests that the risk of hay fever increases with an increasing ratio of n-6 *vs* n-3 intake. Unexpectedly, in our study this relationship tended to decrease. This result might be caused by counterbalancing effects of the fatty acids within the n-3 and n-6 PUFA families.

Vitamin E

Our study indicates a decreasing risk of hay fever with increasing vitamin E intake. Although the trend is not statistically significant a decreased risk is statistically confirmed in the two upper quartiles of vitamin intake.

Two other studies addressed vitamin E intake in relation to atopic diseases. Consistent with our result is the finding of Fogerty et al. (15) who reported an inverse relationship between vitamin E intake and risk of atopy. Though addressing asthma, a study by Troisi shall be mentioned who investigated the impact of diet on adult-onset of asthma and observed compared to the lowest quintile, a risk reduction for the highest quintile of vitamin E intake derived from diet but not from supplements (31).

Vitamin E is an oxidant scavenger crucial for the protection of cell membranes from damage by reactive oxygen species and is found in high concentrations in the membranes of immune cells (32). Vitamin E is an important factor for normal immune function and its supplementation in the elderly was shown to significantly enhance cell-mediated immunity (33). The anti-oxidant properties of vitamin E as well as its negative effect on the production of PGE2 may be contributing factors to the inverse association of increasing vitamin E intake and hay fever seen in this study.

β-Carotene

For β-carotene, we observed a strongly increasing risk with increasing level of vitamin intake. This relationship is largely because of a particular strong association among smokers, while the tendency is much weaker among nonsmokers.

Though addressing a quite different issue, it appears worth taking into consideration that a risk increasing effect of high intake of β-carotene, particularly in smokers, has also been found in vitamin intervention trials for lung cancer (34, 35). Oxidants in cigarette smoke appear to induce β-carotene autoxidation, that promotes carcinogenesis and – as suggested in this study – probably also processes linked to allergic rhinitis. Another possible mechanism for the risk-increasing effect among smokers may be related to a β-carotene induced production of the cytochrom P450 carcinogen-bioactivating enzymes in the lung (36). Their activation of tobacco-smoke compounds to reactive metabolites may also increase oxidative stress and thereby impact on allergy pathogenesis. It may be that β-carotene impacts in a similar fashion also on other enzyme activities and proteins involved in the etiology of hay fever, for example the secretion of cytokines. In an intervention study with prolonged tomato juice consumption increasing concentrations of plasma β-carotene and ascorbic acid were associated with an elevated secretion of interleukin (IL)-4 whereas the IL-2 production was reduced (37). Interleukin-4 promotes the Th2 clonal expansion and limits the proliferation of Th1cells (38). This Th1/Th2 imbalance towards Th2 function may underlie the association between high β-carotene intake and hay fever. This is also supported by recent *in vitro* data by Stephensen et al. who reported a strong enhancement of Th2 development in mice treated with vitamin A (39).

Sociodemographic factors

The analysis by gender revealed stronger effects of β-carotene and vitamin E intake on hay fever risk in women than in men. Bolte et al. observed in a gender stratified analysis among children, that the association between margarine consumption was associated with allergic sensation only among boys (29). Clinical and experimental evidence support the hypothesis of gender differences in immune reactions (40, 41). Gender emerges as an important factor in immunmodulation via sex hormones and glucocorticoids (42).

In the present study hay fever was associated with educational level and smoking habits. Among people with hay fever less current smokers but more ex-smokers were observed. Some persons may have changed their smoking habits because they felt smoking was exacerbating their

symptoms in an early stage. This observation is consistent with observations of Annesi-Maesano et al. (43) who reported an association between seasonal allergic rhinitis and ex-smoking.

Individuals with hay fever tended to have a lower level of education than the controls. However, when compared with the whole cohort, the distribution is not statistically significant (6.4% in the low 57.7% in the middle and 35.9% high educational level). The prevalence of hay fever has often been linked to higher social classes (44).

Limitations of the study

The present evaluation deals with self-reported cases of physician diagnosed hay fever, a fact which may limit the impact of the results. On one hand, the self-diagnosis might lead to over-reporting. On the other hand, hay fever is a seasonal heterogeneous disorder with a high prevalence that is often undiagnosed (45). The EPIC tried to limit over-reporting by asking not for a self-diagnosis, but exclusively for hay fever which was diagnosed by a physician. Furthermore, in an investigation of self-reported prevalent cases at baseline of the same cohort a good agreement between reported hay fever and plasma IgE values was found (46).

Questionnaire data on dietary habits may also be biased. However, for the EPIC cohorts in Germany the FFQ data for food groups and selected nutrients were validated by comparison with the results of twelve 24-h diet recalls (19). No evaluation of single fatty acids was performed; however, the results for total fat, SFA, MUFA, and PUFA were in an acceptable range with adjusted correlation coefficients of 0.62, 0.75, 0.51, and 0.43 (19). For dietary fatty acid intake results as assessed by means of 24-h diet recalls a good agreement with the plasma phospholipid fatty acid composition was found at the group level, which refers also to the n-6/n-3 ratio (47). Vitamins were not included in the above mentioned FFQ validation study.

Conclusion

In conclusion, the present results provide further evidence that dietary factors might affect the risk and onset of clinical symptoms of hay fever. The dietary intake of oleic acid (C18:1), linoleic acid (C18:2) and EPA (C20:5), β-carotene and vitamin E influences the hay fever risk in adults. For linoleic acid (C18:2), β-carotene and vitamin E the effects occurred particularly among ex or current smokers with high oxidative load which is in accordance with the oxidative stress hypothesis. Among women higher dietary intake of linoleic acid (C18:2) may increase lipid peroxidation via the estrogen metabolism. High intake of EPA (C20:5) decreases the risk of hay fever in both genders and indicating a common underlying mechanism such as the immune modulation. It is possible that the association of oleic acid (C18:1) intake with the clinical manifestation of hay fever in both genders is explained by a concomitantly increased intake of *trans*-C18:1. Typical western diets may increase oxidative stress and therefore contribute to the increasing prevalence of atopic diseases. Dietary intervention studies might provide a well-suited framework to examine whether a change in usual dietary habits towards a pattern with less fat (reactive metabolites) and more fruits and vegetables (antioxidants) leads to a decline in the onset of clinical symptoms of allergies in adults.

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