Dietary intake of fatty acids, antioxidants and selected food groups and asthma in adults

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Objective: Within a prospective study, we explored the associations between dietary intake of fatty acids, antioxidants and relevant food sources of these nutrients on the clinical manifestation of asthma in adulthood.
Method: A total of 105 newly physician-diagnosed cases of asthma from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg cohort were identified during follow-up and matched with 420 controls. Baseline dietary intake was obtained by means of validated food frequency questionnaires. The association of dietary intake variables and asthma risk was explored by unconditional logistic regression models.
Results: A high intake of oleic acid (C18:1 n-9) was positively associated with asthma (*P*-value for trend 0.035), while no significant associations were found for the other dietary fatty acids. Most prominently, a high margarine intake increased the risk of onset of asthma in adulthood (adjusted odds ratio (OR) 3rd tertile: 1.73 (95% confidence interval (95% CI): 1.05–2.87), *P* for trend = 0.050), the effect being stronger in men (2nd tertile: OR = 1.66, 3rd tertile: OR = 2.51) than in women (2nd tertile: OR = 0.91; 3rd tertile: OR = 1.47). The dietary intake of antioxidants and their main food sources had no effect on asthma risk.
Conclusions: In summary, the present results provide evidence that even in adulthood a high margarine intake increases the risk of clinical onset of asthma. Whether oleic acid may serve as a proxy for margarine-derived *trans*-fatty acids (C18:1 t9) remains to be clarified.

Introduction

Asthma is an inflammatory airway disease associated with increased airway responsiveness, inflammation and intermittent airway obstruction (Lemanske and Busse, 2003). It affects, with regional differences, 9.5–40.9% of the European population (ECRHS, 1996, Heinrich *et al*, 2002). In most developed countries, an increasing prevalence of asthma in children (von Mutius *et al*, 1998) and adults (ECRHS, 1996; Sunyer *et al*, 1999) has been reported. However, recent updates revealed no further increase of asthma prevalence in Switzerland and Italy (Verlato *et al*, 2003; Braun-Fahrlander *et al*, 2004). Genetic and environmental factors including air pollution, housing conditions and other lifestyle factors have been linked to its aetiology and triggering (Lemanske and Busse, 2003). Humbert *et al* (1999) found more similarities than differences between atopic and non-atopic asthma and hypothesized that immunologic factors play a significant role in both variants (Humbert *et al*, 1999).

Recent research focuses on crucial components of typical western lifestyle such as dietary factors, which might substantially contribute to allergic sensitization (Fogarty and Britton, 2000; Filipiak *et al*, 2001, Douwes and Pearce, 2002). Attention was assigned to the quantity and quality of dietary fat intake (Black and Sharpe, 1997; Kankaanpaa *et al*, 1999). In particular, differences in the consumption of n-3 and n-6 fatty acids have been discussed in relation to the prevalence of atopy (Hirsch and Kempe, 1999; Wakai *et al*, 2001). Further fatty acid-related effects may be based on the configuration of the double bounds, either *cis* or *trans*, mainly of octadecenoic acid (Connor, 2000).

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Contributors: G Nagel analysed the data and wrote the manuscript. J Linseisen provided consultation on the interpretation of the results and commented on the final version.

Epidemiological studies on children reported an association between elevated margarine consumption and atopy risk (von Mutius *et al*, 1998; Bolte *et al*, 2001). Margarine intake contributes to the intake of linoleic acid and is also a major source of *trans*-fatty acids (Willet and Ascherio, 1994), especially elaidic acid (C18:1 t9). Weiland *et al* (1999) observed in an ecological study that the dietary intake of *trans*-fatty acids is positively associated with allergic diseases.

According to the results of prospective (Troisi *et al*, 1995) and cross-sectional (Rubin *et al*, 2004) studies and a recent review (Caramori and Papi, 2004), dietary antioxidants, such as vitamin E, C, and β-carotene, are associated with asthma risk. Clinical studies reported that asthma patients may experience increased oxidative stress (Kelly *et al*, 1999) and that carotenoids, vitamin C, and E influence pulmonary function (Schunemann *et al*, 2002).

Therefore, the present evaluation aims to examine prospectively within the European Prospective Investigation into Cancer and nutrition (EPIC)-Heidelberg, the potential effect of dietary fatty acids and antioxidants as well as their main food sources on the risk of newly physician-diagnosed asthma cases among adults.

Material and methods

Data collection

The EPIC is a prospective multicentre study to further investigate the association between diet, lifestyle and chronic diseases with emphasis on cancer (Riboli and Kaaks, 1997). The EPIC cohort in Heidelberg comprises of about 25 500 subjects aged 35–65 y in women and 40–65 y in men, recruited from June 1994 until October 1998 (Boeing *et al*, 1999a, b). The baseline assessment of the cohort included a self-administered food frequency questionnaire (FFQ) (Boeing *et al*, 1997; Bohlscheid-Thomas *et al*, 1997) as a dietary assessment tool, a computerized lifestyle interview and standardized anthropometric measurements (Klipstein-Grobusch *et al*, 1997). The response rate of the first follow-up, which took place between 1998 and 2000, was 93.5%.

Outcome

During the median follow-up time of 2.1 y, 211 participants with new onset asthma were identified by comparison of self-reported baseline and follow-up data. In order to ask specifically for a diagnosis confirmed by a physician, the self-reported cases were contacted again by mail (Grassi *et al*, 2001). The participants identified by follow-up were asked to complete an additional questionnaire on the onset of asthma, diagnostic tests, symptoms and medication use.

Thus, 105 cases of newly physician diagnosed asthma cases were verified and characterized. The diagnosis is based on clinical examination ($n=86$, 81.9%), skin prick tests ($n=45$, 42.9%), lung function tests ($n=79$, 75.2%) and other tests ($n=5$, 4.8%). During the last 12 months, 73 (69.5%) participants experienced symptoms and 76 (72.4%) used asthma medication. The control group comprised of 420 randomly selected cohort members without self-reported prevalent asthma or other atopic diseases, matched (4:1) to the cases by sex and age group (5 y).

Variable definition

Dietary intake estimates for food groups, fatty acids and antioxidants were based on the results of the self-administered, semiquantitative food frequency questionnaire. Nutrient intake data were calculated from the food intake data by means of the German Food Composition Tables BLS, Version II.3 (Bundeslebensmittelschlüssel, Bg VV, Berlin, Germany, 1989).

The level of education was categorized as low (not more then 9 y of schooling without a specific vocational training), middle (high school degree (10 y) and/or vocational or technical training) and high (13 y of high school and/or a university degree). Participants were recategorized as non-smokers when less than 3 months of regular smoking was reported, as ex-smokers when smoking was stopped for at least 1 y before the baseline interview and as smokers when present smoking was reported or when smoking was quitted less than 1 year before the baseline interview. Body mass index (BMI) was calculated as weight in kg/height in m^2. Sports activity was classified as 'yes' when any sports activity was mentioned.

Statistical methods

A case–control evaluation, with frequency matching for sex and age, was conducted. The medians and tertiles were calculated using the SAS procedure UNIVARIATE. Associations between asthma and intake of dietary fatty acids, antioxidants and food groups were evaluated by the Wilcoxon test (SAS procedure NPAR1WAY).

The tertile cut points were based on consumption levels among controls corresponding to the values of the 33- and 66 percentiles. The associations between dietary intake and the risk of asthma were assessed fitting unconditional logistic regression models. Adjusted estimates of the models are presented. The total energy intake was subdivided into energy derived from fat intake and nonfat intake. Regression models with different energy adjustment (eg as total energy intake, energy divided into intake related to fatty acid families and nonfat energy) were calculated, across which the effect estimates appeared stable (Willet, 1998). The adjustment for sports did not influence the effect estimates and was therefore not included in the models. In the final model age, fat energy intake, nonfat energy intake, BMI, smoking status, gender and educational level remained as adjustment variables in the model.

As effect estimates, the odds ratios (OR) and corresponding 95% CI (95% CI) were calculated using the PROC LOGISTIC procedure of the statistical software package SAS release 8.2 (SAS Institute, Cary, NC, USA). Tests for linear trend with

two-sided *P*-values were calculated by using the median values of each category as continuous exposure score.

Results

Table 1 shows the basic characteristics of cases and controls. Except for the educational level, no differences between groups existed regarding BMI, smoking habits or the median follow-up time.

The median intake and the tertile cutpoints of dietary fatty acids, antioxidants and food group consumption among cases and controls are given in Table 2. There were no significant differences regarding the intake of total fat, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), n-6- and n-3-polyunsaturated fatty acids (PUFA) between cases and controls. Moreover, cases and controls did not differ distinctly in the intake of food groups, which can be regarded as the most important food sources for fatty acids and antioxidants. However, margarine intake ($P = 0.029$) was significantly higher in cases than in controls.

Table 3 shows the relationship between the intake of fatty acids and food groups and the risk of onset of clinical symptoms of asthma. An increasing intake of C18:1 (oleic acid) was positively associated with asthma with a $P = 0.035$ for trend. The OR in the highest *vs* lowest intake tertile was 2.32 (95% CI = 0.82–6.59). No evidence was found for the dietary intake of other fatty acids or the n6-/n3-PUFA ratio. Furthermore, the associations between the dietary intake of vitamins C, E, A and β-carotene and asthma risk were analysed but none of the results were significant (data not shown).

The results for the food groups, which substantially contribute to fat intake, are presented in Table 4. A high intake of margarine was associated with a significantly increased risk for the development of asthma symptoms in adults. The odds ratio in the 3rd tertile (*vs* 1st) was 1.73 (95% CI: 1.05–2.87) and with a borderline statistically significant trend ($P = 0.05$). The effect of margarine intake on asthma risk was stable in different adjustment models. In grouped analysis, the effects for margarine consumption were stronger in men (2nd tertile: OR = 1.66 (95% CI = 0.53–5.23); 3rd tertile: OR = 2.51 (95% CI = 1.01–6.23); all *vs* 1st tertile) than in women (2nd tertile: OR = 0.91 [95% CI = 0.44–1.89); 3rd tertile: OR = 1.47 (95% CI = 0.79–2.74)). The odds ratio in the highest (*vs* lowest) tertile of egg intake was distinctly increased but failed to reach statistical significance. Consumption of none of the other investigated food groups revealed a significant effect on asthma risk in this study sample.

Discussion

Within the frame of the EPIC-Heidelberg cohort, we investigated the relationship between dietary intake of fatty acids and antioxidants including their dietary food sources and newly diagnosed asthma at a relatively high age (> 35 y). On average, the time lag between the assessment of dietary habits and the asthma diagnosis was 2.1 y. We found significant associations between the dietary intake of oleic acid (C18:1) and margarine with the risk of asthma in adulthood.

Table 1 Sample characteristics of incident self-reported and verified asthma cases ($n = 105$) and matched controls ($n = 420$)

	Cases		*Controls*		
	N	%	N	%	P-*value*[a]
Age (matching variable)					
< 50 years	39		156		
50–59 years	46		183		
≥ 60 years	20		81		
Sex (matching variable)					
Male	37		148		
Female	68		272		
Educational level					0.034
High (University)	24	22.9	151	36.0	
Medium (Professional training)	67	63.8	229	54.5	
Low (no professional training)	14	13.3	40	9.5	
Smoking status					0.083
Never	39	37.1	187	44.5	
Ex	27	25.7	123	29.3	
Current	39	37.1	110	26.2	
	Median	*25–75%ile*	*Median*	*25–75%ile*	P-*value*[c]
Follow-up time (years after recruitment)[b]	2.1	1.8–2.5	2.1	1.6–2.6	0.212
BMI (kg/m^2)	25.1	22.6–28.5	25.4	22.9–28.6	0.881

[a]Chi^2-test.
[b]First Follow-up.
[c]Wilcoxon test.

Table 2 Dietary intake of energy, fatty acids, antioxidants and selected food groups in cases with asthma ($n=105$) and controls ($n=420$)

	Cases		*Controls*		
	Median	*33%–66%iles*	*Median*	*33%–66%iles*	P-*value*[a]
Total energy intake (kcal/day)	1842	1560–2054	1767	1565–2048	0.754
Total fat (g/day)	68.5	56.6–78.9	68.7	59.6–80.1	0.523
SFA (g/day)	28.5	23.6–32.6	29.1	24.3–34.2	0.404
C16:0 (g/day)	14.0	11.3–15.7	14.0	11.7–16.6	0.469
C18:0 (g/day)	5.7	4.9–7.2	5.9	5.0–7.1	0.545
MUFA (n-9) (g/day)	23.5	19.9–27.6	24.1	20.4–28.1	0.432
C16:1 (n-9) (g/day)	1.5	1.2–1.8	1.5	1.3–1.6	0.339
C18:1 (n-9) (g/day)	20.3	17.4–24.4	21.2	17.7–24.6	0.469
n-6 PUFA (g/day)	9.4	8.1–10.7	9.5	7.9–11.3	0.848
C18:2 (n-6) (g/day)	9.3	8.0–10.5	9.3	7.8–11.1	0.862
C20:4 (n-6) (mg/day)	140.1	110.6–169.2	149.7	118.2–174.7	0.192
n-3 PUFA (g/day)	1.3	1.2–1.6	1.4	1.2–1.6	0.594
C18:3 (n-3) (g/day)	1.1	1.0–1.3	1.2	1.0–1.3	0.653
C20:5 (n-3) (mg/day)	51.9	33.4–84.0	56.7	38.4–80.2	0.923
C22:6 (n-3) (mg/day)	130.6	91.6–168.4	139.4	103.2–176.7	0.485
n6/n3 PUFA ratio	6.9	6.2–7.4	7.0	6.3–7.4	0.845
Selected vitamins					
Retinol (mg/day)	0.6	0.5–0.8	0.6	0.5–0.8	0.930
β-Carotene (mg/day)	2.0	1.7–2.4	2.1	1.8–2.4	0.187
Vitamine C (mg/day)	91.2	73.9–114.4	93.8	77.3–113.2	0.498
Vitamine E (mg/day)	10.1	8.5–12	10.3	9.0–11.8	0.360
Vitamine D (μg/day)	2.6	1.9–3.4	2.6	2.0–3.3	0.935
Selected food groups					
Meat (g/day)	47.5	36.3–59.1	48.3	35.7–62.2	0.808
Meat products (g/day)	35.1	22.6–48.9	34.4	21.1–47.4	0.506
Cheese (g/day)	22.8	14.5–33.2	21.9	14.4–31.9	0.710
Milk (g/day)	6.2	0–53.4	12.3	0–42.8	0.580
Fish (g/day)	14.8	6.2–22.2	15.6	8.2–22.2	0.742
Eggs (g/day)	10.3	6.2–17.8	9.0	5.7–13.6	0.122
Margarine (g/day)	1.0	0–4.1	0.3	0–1.8	0.029
Vegetable oils (g/day)	3.6	3.1–5.0	4.3	3.0–5.6	0.338
Butter (g/day)	5.3	3.6–10	6.9	2.7–10	0.615
Vegetables (g/day)	105.3	83.2–119.2	111.2	89.5–130.6	0.163
Fruit (g/day)	91.9	77.5–101.8	95.8	76.2–121.1	0.234
Fruit juice (g/day)	65.9	28.5–121.5	76.1	34.4–150.8	0.676

[a]Wilcoxon test.
BMI = body mass index; SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids.

The finding of increased risk of adult onset asthma with dietary intake of the monounsaturated fatty acid oleic acid (C18:1) is consistent with the results of Heinrich *et al* (2001) who also reported in an ecological study that dietary intake of energy-adjusted MUFA was positively related to the prevalence of atopy. An increased risk was also observed for margarine consumption. This observation corroborates previous findings of a cross-sectional study regarding butter *vs* margarine consumption and the prevalence of hay fever and asthma among children (Bolte *et al*, 2001). In ecological studies, dietary factors, including high margarine consumption, were suggested to contribute to changes in prevalence rates of allergic disease in Eastern Germany after reunification (von Mutius *et al*, 1994, 1998; Hirsch and Kempe, 1999).

In the present study, individuals with asthma tended to have a lower educational level than the controls. However, the prevalence of asthma has often been linked to higher social classes, although the literature provides additional findings (Kogevinas *et al*, 1998; Eisner *et al*, 2001a). Regarding smoking status and asthma, our results are consistent with Eisner *et al* (2001b), who reported no association between asthma and current-smoking. In contrast to other findings, BMI was not associated with asthma (Huovinen *et al*, 2003; Romieu *et al*, 2003), which may be due to the predominant normal weight in our sample.

For the main dietary food sources of *cis*-C18:1 in the typical German diet, that is, meat, meat products, butter, milk, milk products and cheese, no associations with asthma were found. The intake of isoforms of *trans*-C18:1 is provided by ruminant fat (mainly C18:1 t11) and margarine (C18:1 t9, elaidic acid). Owing to the results found for margarine consumption, it may be speculated that a higher intake of C18:1 would accompany an increased intake of C18:1 t9. There is evidence that the configuration (*cis-, trans-*) of

Table 3 Adjusted[a] odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association between the dietary intake of fatty acids and asthma (105 verified cases, 420 controls)

Nutrient	*1st Tertile (lowest)*	*2nd Tertile*	*3nd Tertile (highest)*	P *for trend*
Total Fat[a]				0.237
Cases	37	36	32	
OR	1	1.27	1.43	
(95% CI)		0.66–2.45	0.48–4.22	
C16:0[a]				0.177
Cases	36	37	32	
OR	1	1.36	1.62	
(95% CI)		0.71–2.60	0.56–4.70	
C18:0[a]				0.099
Cases	36	37	32	
OR	1	1.16	1.77	
(95% CI)		0.62–2.18	0.69–4.58	
C16:1 (n-9)[a]				0.272
Cases	38	37	30	
OR	1	1.00	0.85	
(95% CI)		0.55–1.82	0.34–2.14	
C18:1 (n-9)[a]				0.035
Cases	35	35	35	
OR	1	1.47	2.32	
(95% CI)		0.76–2.84	0.82–6.59	
C18:2 (n-6)[a]				0.252
Cases	31	39	35	
OR	1	1.61	1.75	
(95% CI)		0.89–2.89	0.83–3.68	
C20:4 (n-6)[a]				0.838
Cases	41	30	34	
OR	1	0.70	0.85	
(95% CI)		0.39–1.23	0.44–1.68	
C18:3 (n-3)[a]				0.283
Cases	33	41	32	
OR	1	1.80	1.87	
(95% CI)		0.97–3.33	0.78–4.53	
C20:5 (n-3)[a]				0.774
Cases	39	30	39	
OR	1	0.78	0.92	
(95% CI)		0.45–1.33	0.54–1.57	
C22:6 (n-3)[a]				0.382
Cases	40	32	33	
OR	1	0.79	0.81	
(95% CI)		0.46–1.34	0.46–1.43	
n6/n3 PUFA ratio[a]				0.614
Cases	37	35	33	
OR	1	0.93	0.82	
(95% CI)		0.54–1.58	0.48–1.42	

[a]Estimate adjusted for age (<50, 50–59 and ≥60 y); fat energy intake (kcal/day, continuous); nonfat energy intake (kcal/day, continuous); body mass index (continuous); smoking status (never, ex, current); gender; educational level (high, middle, low).

Table 4 Adjusted[a] odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the association between the dietary intake of selected food groups and asthma (105 verified cases, 420 controls)

Food group	*1st Tertile (lowest)*	*2nd Tertile*	*3rd Tertile (highest)*	P *for trend*
Meat[a]				0.707
Cases	33	40	32	
OR	1	1.15	0.90	
(95% CI)		0.67–1.96	0.49–1.66	
Meat products[a]				0.099
Cases	31	36	38	
OR	1	1.13	1.37	
(95% CI)		0.65–1.97	0.75–2.50	
Cheese[a]				0.163
Cases	34	33	38	
OR	1	1.07	1.47	
(95% CI)		0.62–1.85	0.84–2.56	
Milk[a]				0.389
Cases	35	31	39	
OR	1	0.86	1.13	
(95% CI)		0.49–1.51	0.66–1.94	
Fish[a]				0.318
Cases	37	35	33	
OR	1	0.99	0.93	
(95% CI)		0.58–1.68	0.54–1.59	
Eggs[a]				0.226
Cases	33/160	32/131	40/129	
OR	1	1.13	1.65	
(95% CI)		0.65–1.97	0.95–2.85	
Margarine[a]				0.050
Cases	32/182	39/100	30/138	
OR	1	1.12	1.73	
(95% CI)		0.61–2.05	1.05–2.87	
Vegetable oils[a]				0.924
Cases	33	41	31	
OR	1	1.24	0.97	
(95% CI)		0.73–2.11	0.55–1.70	
Butter[a]				0.784
Cases	32	39	30	
OR	1	1.22	1.09	
(95% CI)		0.71–2.08	0.59–1.99	

[a]Estimate adjusted for age (<50, 50–59 and ≥60 y); fat energy intake (kcal/day, continuous); nonfat energy intake (kcal/day, continuous); body mass index (continuous); smoking status (never, ex, current); gender; educational level (high, middle, low).

monounsaturated fatty acids affects serum and cellular fatty acid composition with possible metabolic consequences (Colandre *et al*, 2003; Mensink *et al*, 2003). Weiland *et al* (1999) found in an ecological study that the intake of *trans*-fatty acids is associated with allergic disease. It was suggested that *trans*-fatty acids promotes an increase in IgE production, mediated by the modulation of the desaturation and chain elongation of n-6 and n-3 fatty acids, thereby influencing the prostaglandin and leukotrienes synthesis (Precht and Molkentin, 1995).

We did not find an association between asthma and dietary intake of the n-3 PUFA, α-linolenic acid (C18:3), eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6), whereas an inverse relationship between eicosapentaenoic acid (EPA, C20:5) intake and hay fever risk in adults in a recent study in the EPIC-Heidelberg cohort was observed (Nagel *et al*, 2003). Moreover, we found no association between n-6 PUFA intake and asthma risk. This is consistent with the prospective results of Troisi *et al* (1995) but in contrast to the findings of Wakai and co-workers (2001), who reported results from a cross-sectional study a positive association between allergic rhino-conjunctivitis

and the intake of n-6 PUFA in adults. However, they did not observe any significant association with the intake of SFA, MUFA and n-3 PUFA.

Prostaglandin E2 (PGE2), an n-6-derived product, shifts the Th1/Th2 balance in the direction of Th2-linked diseases such as allergies (Kankaanpaa *et al*, 1999). Conversely, EPA (n-3 PUFA) may be negatively associated with allergic diseases (James *et al*, 2000). However, not only in our study but also in an evaluation dealing with hay fever risk in adults (Nagel *et al*, 2003) no association between increasing n-6/n-3 PUFA ratio and asthma risk was found. This is consistent with the recent results of Woods *et al* (2004) who found no association between the risk of asthma in young adults and any plasma fatty acid level for the n-6/n-3 ratio, respectively. Contradictory effects of single fatty acids may have annihilated the effects of the fatty acid families. Furthermore, the allergic component in the present asthma cases might have been secondary (Schafer *et al*, 2003).

Heinrich *et al* (2001) observed an inverse association between fruit intake and allergic sensitization while no association with vegetable consumption was found. Troisi *et al* (1995) investigated the impact of diet on adult onset of asthma and found a risk reduction with high vitamin E intake from diet (but not from supplements). Owing to the oxidative stress situation, which may occur in asthma, an effect of antioxidant intake on asthma symptoms may be hypothesized (Dworski, 2000). In our sample, however, no effects of antioxidant (vitamins C, E, A, β-carotene) intake or of the consumption of antioxidant-providing food groups such as fruit (eg apples) intake, as potential dietary source of flavonoids, or meat intake, as potential source for selenium on asthma risk, were observed. This is consistent with observations of Woods *et al* (2003), whereas Shaheen *et al* (2001) observed an inverse association between apple consumption and selenium intake and asthma.

Our finding of a stronger effect of margarine consumption on asthma risk in men than in women is consistent with the results of Bolte *et al* (2001), who reported an association between margarine consumption and allergic sensitization in boys but not in girls. There is evidence that gender is an important factor in immunmodulation via sex hormones and glucocorticoids (Da Silva, 1999), which may lead to gender differences in immune reactions (Athreya *et al*, 1998; Whitacer *et al*, 1999).

Studies on the association between dietary factors and risk of atopic diseases must deal with two major problems: the case definition and the measurement error included in the dietary intake data. The identification of asthma 'cases' in epidemiological research is a cause of debate (Grassi *et al*, 2001; Peat *et al*, 2001). In the present evaluation, self-reported cases of asthma with first clinical onset after recruitment in the study were identified through active follow-up and verified by means of additional questioning leading to a lower number of cases and therefore statistical power of our study. Asthma cases refer to a diagnosis made by a physician. Furthermore, an investigation of self-reported prevalent hay fever of the same cohort revealed good agreement between reported hay fever and plasma IgE values (Nieters *et al*, 2004). In the control group it is unlikely that a misclassification other than random or nondifferential occurred, which would have biased the association towards the null. Owing to the low statistical power of the study and the large number of statistical tests, the results have to be interpreted with caution, since they may be observed by chance. Further follow-up of the cohort will contribute to clarify the present findings.

Secondly, dietary intake data may suffer from measurement error. The food frequency questionnaire used in this prospective study was validated by comparison with the results of twelve 24-h dietary recalls in the same individual. The adjusted correlation coefficients giving an indication for the goodness of fit between both instruments were in an acceptable range (Bohlscheid-Thomas *et al*, 1997). The same is true for food group consumption (Bohlscheid-Thomas *et al*, 1997). However, single fatty acids were not explored. In the 24 h data for the fatty acid intake, very good agreement with a valid biomarker, the plasma phospholipid fatty acid composition, was found (Linseisen *et al*, 2003).

However, the strength of the present study is the prospective and population-based study design of the EPIC-Heidelberg study with a major emphasis on diet, in which the case–control study is embedded.

In conclusion, the results of this prospective study provide evidence that dietary factors affect the risk of onset of asthma in adulthood. A high dietary intake of oleic acid (C18:1) and a high consumption level of margarine were found to increase asthma risk. The association of oleic acid intake with asthma may be explained by a concomitantly increased intake of *trans*-C18:1, which is relatively high in typical western diets and for one isomer, C18:1 t9 (elaidic acid), margarine is the most important dietary source. Further studies are needed to clarify these associations.

Acknowledgements

We thank the volunteers who participated in EPIC. Furthermore, we thank first of all the EPIC team, Jutta Schmitt and Yvonne Küster, for documentation and D Zoller for the calculation of the food and nutrient data. We thank Bettina Mock for her helpful comments on earlier versions of the manuscript. EPIC is supported by the Deutsches Krebsforschungszentrum and grants from the European Community (SI2.326938) and Deutsche Krebshilfe e.V. (70-2488), J Linseisen at the TU Munich is supported by the Kurt-Eberhard-Bode-Stiftung.

References

Athreya BH, Rettig P & Williams WV (1998): Hypophyseal-pituitary-adrenal axis in autoimmune and rheumatic diseases. *Immunol. Res.* **18**, 93–102.

Black PN & Sharpe S (1997): Dietary fat and asthma: Is there a connection? *Eur. Resp. J.* **10**, 6–12.

Boeing H, Bohlscheid-Thomas S, Voss S, Schneeweiss S & Wahrendorf J (1997): The relative validity of vitamin intakes derived from a food frequency questionnaire compared to 24h-hour recalls and biological measurements: results from the EPIC pilot study in Germany. European Prospective Investigation into Cancer and nutrition. *Int. J. Epidemiol.* **26** (Suppl), S82–S90.

Boeing H, Korfmann A & Bergmann MM (1999a): Recruitment procedures of EPIC-Germany. European Investigation into Cancer and Nutrition. *Ann. Nutr. Metab.* **43**, 205–215.

Boeing H, Wahrendorf J & Becker N (1999b): EPIC-Germany — a source for studies into diet and risk of chronic diseases. European Investigation into Cancer and Nutrition. *Ann. Nutr. Metab.* **43**, 195–204.

Bohlscheid-Thomas S, Hoting I, Boeing H & Wahrendorf J (1997): 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.* **26** (Suppl), S71–S81.

Bolte G, Frye C, Hoelscher B, Meyer I, Wjst M & Heinrich J (2001): Margarine consumption and allergy in children. *Am. J. Resp. Crit. Care Med.* **163**, 277–279.

Braun-Fahrlander C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T, Varonier HS, Wuthrich B & Sennhauser FH (2004): No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur. Resp. J.* **23**, 407–413.

Caramori G & Papi A (2004): Oxidants and asthma. *Thorax* **59**, 170–173.

Colandre ME, Diez RS & Bernal CA (2003): Metabolic effects of trans fatty acids on an experimental dietary model. *Br. J. Nutr.* **98**, 631–638.

Connor WE (2000): Importance of n-3 fatty acids in health and disease. *Am. J. Clin. Nutr.* **71** (Suppl), S171–S175.

Da Silva JA (1999): Sex hormones and glucocorticoids: Interactions with the immune ystem. *Ann. N. Y. Acad. Sci.* **876**, 102–117.

Douwes J & Pearce N (2002): Asthma and the westernisation 'package'. *Int. J. Epidemiol.* **31**, 1098–1102.

Dworski R (2000): Oxidative Stress in Asthma. *Thorax* **55** (Suppl), S51–S53.

Eisner MD, Katz PP, Yelin EH, Shiboski SC & Blanc PD (2001a): Risk factors for the hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. *Resp. Res.* **3**, 53–60.

Eisner MD, Yelin EH, Trupin L & Blanc PD (2001b): Asthma and smoking status in a population-based study of California adults. *Public Health Rep.* **116**, 148–157.

European Community Respiratory Health Survey (ECRHS) (1996): Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma mediators in the European Community Respiratory Health Survey (ECRHS). *Eur. Resp. J.* **9**, 687–695.

Filipiak B, Heinrich J, Nowak D & Wichman HE (2001): The distribution in specific IgE and the prevalence of allergic symptoms in the 25–64 years old inhabitants of an eastern and a western German city — results from Augsburg and Erfurt. *Eur. J. Epidemiol.* **17**, 77–84.

Fogarty A & Britton J (2000): The role of diet in the aetiology of asthma. *Clin. Exp. Allergy* **30**, 615–627.

Grassi M, Villani S, Marinoni & for the ECRHS Group (2001): Classification methods for the identification of 'case' in epidemiological diagnosis of asthma. *Eur. J. Epidemiol* **17**, 19–29.

Heinrich J, Hoelscher B, Bolte G & Winkler G (2001): Allergic sensitisation and diet: analysis in selected European cities. *Eur. Resp. J* **17**, 395–402.

Heinrich J, Richter K, Frye C, Meyer I, Wolke G, Wjst M, Nowak D, Magnussen H & Wichmann HE (2002): European Community Respiratory Health Survey in Adults (ECRHS). *Pneumologie* **56**, 297–303.

Hirsch T & Kempe G (1999): Consumption of omega-3 and omega -6 fatty acids in former East and West Germany and changes in East Germany after the reunification. *Resp. Med.* **93**, 213–216.

Humbert M, Menz G, Ying S, Corrigan CJ, Robinson DS, Durham SR & Kay AB (1999): The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. *Immunol. Today* **20**, 528–533.

Huovinen E, Kaprio J & Koskenvuo M (2003): Factors associated to lifestyle and risk of adult onset asthma. *Resp. Med.* **97**, 273–280.

James MJ, Gibson RA & Cleland LG (2000): Dietary polysaturated fatty acids and inflammatory mediator production. *Am. J. Clin. Nutr.* **71** (Suppl), S343–S348.

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

Kelly FJ, Mudway I, Blomberg A, Frew A & Sandstrom T (1999): Altered lung antioxidant status in patients with mild asthma. *Lancet* **354**, 482–483.

Klipstein-Grobusch K, Georg T & Boeing H (1997): Interviewer variability in anthropometric measurements and estimates of body composition. *Int. J. Epidemiol.* **26**, 174–180.

Kogevinas M, Anto JM, Sunyer J, Tobias A, Krumhout H & Burney P (1998): Respiratory symptoms, lung function and use of health services among unemployed young adults in Spain. Spanish group of the European Community Respiratory Health survey. *Eur. Resp. J.* **11**, 1363–1368.

Lemanske Jr RF & Busse WW (2003): Asthma. *J. Allergy Clin. Immunol.* **111** (Suppl), S502–S519.

Linseisen J, Schulze MB, Saadation-Elahi M, Kroke A, Miller AB & Boeing H (2003): Quantity and quality of dietary fat, carbohydrate and fibre intake in the EPIC-Germany cohorts. *Ann. Nutr. Metab.* **47**, 37–46.

Mensink RP, Zock PL, Kester AD & Katan MB (2003): Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am. J. Clin. Nutr.* **77**, 1146–1155.

Nagel G, Nieters A, Becker N & Linseisen J (2003): The influence of dietary intake of fatty acids and antioxidants on hay fever in adults. *Allergy* **58**, 1277–1284.

Nieters A, Linseisen J & Becker N (2004): The association of polymorphisms in Th1, Th2 cytokines with hay fever and serum IgE levels in EPIC Heidelberg. *Clin. Exp. Allergy* **34**, 346–353.

Peat JK, Toelle BG, Marks GB & Mellis CM (2001): Continuing the debate about measuring asthma in population studies. *Thorax* **56**, 406–411.

Precht D & Molkentin J (1995): Trans fatty acids: implications for health, analytical methods, incidence in edible fats and intake (a review). *Die Nahrung.* **39**, 343–374.

Riboli E & Kaaks R (1997): The EPIC project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int. J. Epidemiol.* **26** (Suppl), S6–S14.

Romieu I, Avenel V, Leynaert B, Kauffmann F & Clavel-Chapelon F (2003): Body mass index, change in body silhouette, and risk of asthma in the E3N cohort study. *Am. J. Epidemiol.* **158**, 165–174.

Rubin RN, Navon L & Cassano PA (2004): Relationship of serum antioxidants to asthma prevalence in youth. *Am. J. Resp. Crit. Care Med.* **169**, 393–398.

Schafer T, Ruhdorfer S, Weigl L, Wessner D, Heinrich J, Doring A, Wichmann HE & Ring J (2003): Intake of unsaturated fatty acids and HDL cholesterol levels are associated with manifestations of atopy in adults. *Clin. Exp. Allergy* **33**, 1360–1367.

Schunemann HJ, McCunn S, Grant BJ, Trevisan M, Muti P & Freudenheim JL (2002): Lung function in relation to intake of carotenoids and other antioxidant vitamins in a population based study. *Am. J. Epidemiol.* **155**, 463–471.

Shaheen SO, Sterne JA, Thompson RL, Songhurst CE, Margetts BM & Burney PG (2001): Dietary antioxidants and Asthma in adults. *Am. J. Resp. Crit. Care Med.* **164**, 1823–1828.

Sunyer J, Antó JM, Tobias A & Burney P (1999): Generational increase of self-reported first-attack of asthma in fifteen industrialized

countries. European Community Respiratory Health Study (ECRHS). *Eur. Resp. J.* **14**, 885–891.

Troisi RJ, Willett WC, Weiss ST, Trichopoulos D, Rosner B & Speizer FE (1995): A prospective study of diet and adult-onset asthma. A prospective cohort study. *Am. J. Resp. Crit. Care Med.* **151**, 1401–1408.

Verlato G, Corsico A, Villani S, Cerveri I, Migliore E, Accordini S, Carolei A, Piccioni P, Bugiani M, Lo Cascio V, Marinoni A, Poli A & de Marco R (2003): Is the prevalence of adult asthma and allergic rhinitis still increasing? Results of an Italian study. *J. Allergy Clin. Immunol.* **111**, 1232–1238.

von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G & Thiemann HH (1994): Prevalence of asthma and atopy in two areas of West and East Germany. *Am. J. Resp. Crit. Care Med.* **149**, 358–364.

von Mutius E, Weiland SK, Fritzsch C, Duhme H & Keil U (1998): Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* **351**, 862–866.

Wakai K, Okamoto K, Tamakoshi A, Lin Y, Nakayama T & Ohno Y (2001): Seasonal allergic rhinoconjunctivitis and fatty acid intake: a cross-sectional study in Japan. *Ann. Epidemiol.* **11**, 59–64.

Weiland SK, von Mutius E, Husing A & Asher MI (1999): Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. ISAAC Steering Committee. *Lancet* **353**, 2040–2041.

Willet WC & Ascherio A (1994): Trans fatty acids: are the effects only marginal? *Am. J. Public Health* **84**, 722–724.

Willet WC (1998): *Nutritional Epidemiology* 2nd ed. Oxford University Press: New York.

Whitacer CC, Reingold SC & O'Looney PA (1999): A gender gap in autoimmunity. *Science* **283**, 1277–1278.

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

Woods RK, Raven JM, Walters EH, Abramson MJ & Thien FC (2004): Fatty acid levels and risk of asthma in young adults. *Thorax* **59**, 105–110.