Thorax Online First, published on October 21, 2005 as 10.1136/thx.2005.043034

Diet and asthma in Dutch school children (ISAAC-2)

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keywords: diet, asthma, children, fish, whole grains

ABSTRACT

Background: The rise in asthma prevalence in western societies may be related to changed dietary habits. Epidemiological studies in children have shown inverse associations of asthma related outcomes with intake of fruits, vegetables, dairy and whole grain products, and fish. In contrast to most of these studies, we used both questionnaire and clinical data to define asthma.

Methods: Intake of the mentioned foods was studied in relation to asthma in 598 Dutch children aged 8-13 years. Dietary intake was estimated using a parent-completed semi-quantitative food frequency questionnaire. Current wheeze and current asthma were defined based on questionnaire data. Subsequently, more complex end-points were defined using information on bronchial hyperresponsiveness (BHR) and atopic sensitization as well. Linear associations were studied using logistic regression analysis and odds ratio's presented for the highest vs. the lowest tertile of intake. In the final models adjustments were made for maternal educational level, foreign descent and total energy intake.

Results: Intake of whole grain products and of fish was inversely associated with asthma. Adjusted odds ratio's for the independent associations with whole grains and fish were 0.46 (95%CI=0.19-1.10) and 0.34 (95%CI=0.13-0.85) for current asthma and 0.28 (95%CI=0.08-0.99) and 0.12 (95%CI=0.02-0.66) for atopic asthma with BHR. For current wheeze and atopic wheeze with BHR, respectively, similar results were observed. Intake of (citrus) fruits, vegetables and dairy products showed no clear associations with asthma end-points.

Conclusions:

Our findings support a potential protective effect of a high intake of whole grain products and fish against asthma in children.

INTRODUCTION

It has been postulated that the rise in asthma prevalence in western societies may be related to changed dietary habits since the 1950's, namely decreased intake of fruits, vegetables and fish.[1] Also the fact that the current western diet is rich in n-6 fatty acids, as a result of recommendations to substitute saturated fatty acids with n-6 fatty acids to reduce serum cholesterol concentrations, may be involved.[2] The biological mechanisms through which these dietary changes may affect asthma all seem to include airway inflammation.

Antioxidants are thought to reduce airway inflammation by protecting the airways against oxidants from both endogenous (activated inflammatory cells) and exogenous (e.g. cigarette smoke) sources.[3] Fruits, vegetables and also whole grain products are rich in antioxidant vitamins (i.e. vitamin C, vitamin E, ß-carotene) and other substances with antioxidant capacity (including phenolic acids and phytic acid in whole grains[4][5]). Fish oils are rich sources of n-3 fatty acids. Both n-6 and n-3 fatty acids are precursors for the production of pro-inflammatory mediators called eicosanoids, including prostaglandins and leukotrienes. Increasing the intake of n-3 fatty acids shifts the balance towards eicosanoids derived from n-3 fatty acids, which are thought to be biologically less active.[2] As a result the present western diet may promote airway inflammation, a major characteristic of asthma.

Epidemiological studies in children have indeed shown inverse associations with asthma and related outcomes for (citrus) fruits[6][7][8], vegetables[8][9][10][11], whole grain products[12] and fish[6] [9] [13][14][15][16]. Furthermore inverse associations with asthma in children were observed for butter[13] [17] and (whole or farm) milk[10] [12] [18][19]. A high intake of the latter products, being rich in saturated fatty acids, may reduce the relative contribution of unsaturated fatty acids, including n-6 fatty acids, to total fat intake.

We studied intake of fruits, vegetables, dairy and whole grain products, and fish in relation to asthma in 598 Dutch children aged 8-13 years, also considering independent and combined effects of foods associated with asthma. Main asthma end-points studied were current wheeze and current asthma based on questionnaire data. Information from tests on bronchial hyperresponsiveness (BHR) and of sensitization to common allergens (i.e. skin prick testing) available for these children, allowed us to define more complex asthma end-points based on both questionnaire and clinical data (atopic wheeze with BHR and atopic asthma with BHR).

METHODS

Study population

As part of ISAAC-2 ('International Study on Allergy and Asthma in Childhood-2'), in the period 1997-1998 respiratory health was studied in relation to living close to freeways in Dutch children aged 7-13 years.[20] Parents of all children were asked to complete the ISAAC questionnaire on respiratory and allergic symptoms, completed with questions on pets and passive smoking. Children aged 8 to 13 years were invited to participate in tests of bronchial hyperresponsiveness (BHR) and of sensitization to common allergens (including skin prick testing). Additionally, a dietary questionnaire was sent to the parents of all children that participated in the BHR testing.

Adequate dietary information was collected in 812 children aged 8-13 years. Information on atopic sensitization from the skin prick tests and on BHR, as well as questionnaire data used to define asthma end-points (see data analysis), was available for 609 of these children. An additional 11 children had missing values on one or more potential confounders considered in the final analysis. Therefore, the final study population consisted of 598 children.

Medical ethical approval was obtained from the Ethical Board of the Wageningen University, the Netherlands. Parents gave written informed consent for each test separately.

Diet

Dietary intake was estimated using a semi-quantitative food frequency questionnaire (FFQ), developed and validated for the Dutch EPIC (European Prospective Investigation into Cancer and Nutrition) cohort of adults.[21] The EPIC-FFQ contained questions on the absolute frequency of consumption of 79 main food items (possible answers: times per day/week/month/year or never) and for several food items additional questions on the relative consumption frequency of subitems (possible answers: always or mostly/often/sometimes/ seldom or never). For 21 main foods the questionnaire contained colour photographs of 2 to 4 differently sized portions (possible answers: one of the amounts shown, less than the smallest or more than the largest amount shown). From the obtained information the habitual consumption of 178 food items during the past year can be estimated. We used the 1996 Dutch food composition table[22] to calculate energy intake.

Parents were asked to fill in the EPIC-FFQ for their child participating in ISAAC-2. Standard procedures for cleaning and processing of the data, as developed for the Dutch adult cohort, were evaluated for use in children. Since in children portion sizes may depend on both gender and age, we imputated not the gender-specific mean value, but the age- (8-9, 10-11, 12-13 years) and gender-specific mean value of the respondents if the portion size of a food was missing (n= 0 to 39 of 598 for different foods). If a cross instead of a number was placed in one of the four boxes (per day/week/month/year) of questions into absolute food consumption frequencies, we imputated the average number responded into that box. If this average was based on less than 5 children, the lowest possible number (=1) was imputated.

Fruit intake did not include consumption of fruit juices. Vegetable intake did not include consumption of potatoes, legumes and vegetable juices. Intake of 'dairy other than low-fat' was defined as intake of dairy products with a total fat content of 1.5 g or more per 100 g product and intake of whole grain products as intake of wholemeal bread and of unrefined grains (e.g. brown rice).

Asthma

The ISAAC questionnaire provided information on among other things: respiratory symptoms, current use of asthma medication and a large range of potential confounders.[23] Current

wheeze was defined as wheeze in the past 12 months and ever asthma as a positive response to the question 'did your child ever have asthma?' Children were defined as having current asthma if they fulfilled at least one of three criteria: a. ever asthma in combination with current wheeze, b. ever asthma in combination with current use of a bronchodilator (ß-agonists or anti-cholinergics), c. current use of specific asthma medication (corticosteroids, cromoglycate, nedocromil, or xanthines). Atopic wheeze with BHR was defined as current wheeze in combination with both atopy and BHR. Atopic asthma with BHR was defined as current asthma in combination with both atopy and BHR.

BHR tests were performed according to the ISAAC protocol.[24][25] Children with a baseline FEV_1 < 75% predicted were excluded from BHR testing. Parents were asked to stop their children's use of salbutamol 6 hr, and that of antihistaminics 48 hr, before the test. In short, the challenge protocol consisted of inhalation of a hypertonic (4.5%) saline aerosol for 0.5, 1, 2, 4 and 8 minutes. After each inhalation step two reproducible measurements of FEV_1 were achieved of which the higher was selected. The test stopped after completing all inhalation steps, or when a fall in FEV_1 of more than 15% of baseline was observed. A positive test (BHR) was defined as a fall in FEV_1 ≥15% after inhalation of maximal 23 mL hypertonic saline. All lung function tests were performed according to ERS guidelines.[26]

Skin Prick Tests for atopic sensitization were performed according to the standardized ISAAC-II protocol.[27] Standardized allergen extracts and controls were provided by the ALK Company (Horsholm, Denmark). Allergens tested were D. Farinae, D. pteronyssinus, cat, dog, Alterinaira tenuis, mixed tree pollen and mixed grass pollen. The test was performed on the volar side of the left forearm. A mean weal diameter of 3 mm or more was regarded as a positive reaction.[28]

Data analysis

All statistical analyses were performed using the SAS statistical package version 8.02 (Cary, USA). To estimate the (adjusted) prevalence of the studied asthma end-points for levels of categorised dietary variables, PROC GLM (option LSMEANS) was used with the asthma outcome (yes/no) as independent variable. Since this method may at low estimated prevalences give invalid SE's, logistic regression analysis was used to test for differences between categories (using dummy variables).

Logistic regression analysis was furthermore used to study linear associations between dietary variables and asthma end-points. The presented odds ratio's are calculated by multiplying the estimated regression coefficient (ß) with the difference between the mean intake of the studied food in the third vs. the first tertile of intake (DIF in either g/day or natural log (g/day): OR = exp(ß*DIFF)). To evaluate the independent effects of foods associated with asthma, the representing dietary variables were entered simultaneously as independent variables in a single logistic regression model. To study the combined 'effect' of whole grain products and fish, the prevalences of current wheeze and current asthma were compared between children with an intake of both foods in the highest food-specific tertile and children with an intake of both foods in the lowest food-specific tertile.

In the final analyses adjustments were made for educational level of the mother, foreign descent and total energy intake. Preliminary analyses showed no confounding effects of age, gender, number of siblings, ever asthma in siblings, ever asthma in parents, smoking of the mother during pregnancy, being breastfed, passive smoking, the presence of pets in the home or body mass index. The term statistically significant refers to p-values lower than 0.05 (two-sided tests).

RESULTS

Table 1 gives a description of the study population (n=598). The studied children were on average 10 years old and almost equally distributed according to gender. Of the 53 children with current wheeze (prevalence=8.9%), 37 were atopic and in 24 both atopy and bronchial hyperreactivity was observed. In the 39 children with current asthma (prevalence=6.5%) this was the case for 30 and 19 children, respectively. The average daily intake was relatively high for fruits (171 g) and dairy products (644 g), while fish intake was low with an average intake of only 7 grams daily (table 1).

Table 1: Description of the study population (ISAAC-2: n=598)

Variable	Unit	Mean	SD
Age	years	10.4	1.2
Height	m	1.48	0.09
Weight	kg	39.5	8.3
Energy intake, total	MJ/day	9.4	2.2
Fruits, total	g/day	171	108
Citrus fruits	g/day	43	37
Vegetables, total	g/day	94	42
Dairy products, total	g/day	644	301
Dairy other than low-fat	g/day	470	253
Whole grain products, total	g/day	45	59
Fish, total	g/day	7	7
Variable	**Category**	**%**	
Current wheeze*	yes	8.9	
Current asthma†	yes	6.5	
Atopy‡	yes	29.4	
BHR§	yes	21.9	
Gender	boys	52.7	
Educational level mother	low¶	41.6	
Foreign descent**	yes	16.1	
Ever asthma: parents††	yes	13.2	
Ever asthma: siblings‡‡	yes	15.2	

*,†,‡, § see methods
¶ intermediate secondary education or less
** defined as: child and/or one of the parents not born in the Netherlands
†† n=552
‡‡ n=500

Table 2 gives the average intake and the crude prevalence of current wheeze and current asthma for tertiles of intake of the studied foods. A high intake of whole grain products and of fish was inversely associated with the prevalence of both outcomes. The observed prevalences were 2 to 3 times lower in the highest vs. the lowest tertiles of intake. Furthermore, for current asthma a borderline significant ($p<0.10$) difference in prevalence between the highest and lowest tertile of intake of citrus fruits and of vegetables was observed (table 2).

Table 2: Average intake and the crude prevalence of current wheeze and current asthma per tertile of intake of selected dietary factors in children (ISAAC-2)

Dietary intake			Prevalence (%) of:	
Selected foods	Ter-Tiles*	Mean intake per tertile (g/day)	Current wheeze†	Current asthma‡
Fruits, total	T1	79	8.5	6.0
	T2	148	9.5	8.0
	T3	287	8.5	5.5
Citrus fruits	T1	13	9.5	10.1
	T2	34	8.5	4.0§
	T3	81	8.5	5.5¶
Vegetables, total	T1	53	9.0	8.0
	T2	88	10.0	8.0
	T3	140	7.5	3.5¶
Dairy products, total	T1	347	8.0	6.5
	T2	611	8.5	6.0
	T3	973	10.1	7.0
Dairy, other than low-fat	T1	206	10.1	7.5
	T2	458	7.5	7.5
	T3	746	9.0	4.5
Whole grain products, total	T1	1	13.1	10.6
	T2	15	7.0§	4.5§
	T3	118	6.5§	4.5§
Fish, total	T1	1	13.1	10.6
	T2	6	8.6	6.1
	T3	15	5.0**	3.0**

* T1=low, T2=medium, T3=high
†,‡ see methods
¶ $p<0.10$, § $p<0.05$, ** $p<0.01$, with T1 as reference

In table 3, linear associations of intake of citrus fruits, vegetables, whole grain products and fish with the asthma endpoints are given. Food intake was entered as a continuous variable into the logistic model and odds ratio's are presented for the difference in intake (in g/day) between the highest and lowest tertile of intake (for average food intake per tertile, see table 2). In the univariate analyses, fish intake showed an inverse linear association with both end-points. A trend towards an inverse linear association ($p<0.10$) was observed for intake of citrus fruits with current asthma and for intake of whole grain products with both end-points. After adjustment for potential confounders, fish intake remained inversely associated with both current wheeze and current asthma and for whole grain intake a trend towards an inverse association with both end-points could still be observed (table 3). Smoothing techniques showed that the curve of the

association with fish intake was fairly linear for both end-points, while the strongest decline in prevalence of both end-points were observed at whole grain intakes higher than 150 grams daily.

When intake of whole grain products and of fish was studied simultaneously in a single model, the associations of the foods with either end-point were observed to be largely independent of each other (table 3). The associations of the two foods with current asthma remained essentially unchanged after additional adjustment for intake of citrus fruits and vegetables. To gain some insight into the combined 'effect' of whole grain and fish intake, children with a high intake (= in highest tertile) of both foods were compared to those with a low intake (= in lowest tertile) of both foods (table 4). The crude prevalence of current wheeze was observed to be 19.4% in children with a low vs. 4.2% in children with a high intake of both foods. For current asthma this was 16.7 vs. 2.8%. These results may be compared with those in table 2 to evaluate additivity (see discussion).The association of the combined intake of whole grain products and fish with the two end-points remained essentially unchanged after adjustment for potential confounders (table 4).

Table 3: Linear association of intake of selected foods with current wheeze and current asthma in children (ISAAC-2)

		Current wheeze*	**Current asthma†**
Selected foods		OR‡ (95%CI)	OR‡ (95%CI)
		individual associations	
Citrus fruits§	crude	0.88 (0.52-1.48)	0.61 (0.35-1.05)
	adjusted¶	0.96 (0.56-1.66)	0.65 (0.37-1.14)
Vegetables, total	crude	1.15 (0.66-2.00)	0.67 (0.32-1.38)
	adjusted¶	1.24 (0.69-2.23)	0.69 (0.33-1.45)
Whole grain products, total§	crude	0.53 (0.26-1.08)	0.44 (0.19-1.00)
	adjusted¶	0.51 (0.24-1.08)	0.43 (0.18-1.02)
Fish, total	crude	0.40 (0.19-0.84)	0.31 (0.13-0.78)
	adjusted¶	0.42 (0.20-0.89)	0.32 (0.13-0.81)
		Independent associations (adjusted¶)**	
Whole grains§		0.55 (0.26-1.15)	0.46 (0.19-1.10)
Fish		0.44 (0.21-0.93)	0.34 (0.13-0.85)

*,† see methods
‡ regression-coefficient estimated modelling food intake as a continuous variable (g/day or natural log of g/day), and OR presented for the difference in average intake (in g/day) between the highest and lowest tertile of intake (for average food intake per tertile see table 2).
§ dietary variable modelled as natural log of g/day
¶ adjusted for educational level of the mother, foreign descent and total energy intake
** the variables representing whole grain intake and fish intake were entered simultaneously in a single logistic model

Table 4: Combined intake of whole grain products and fish in relation to current wheeze and current asthma in children (ISAAC-2)

	Whole grain products and fish:	
end-points studied	intake of both foods in lowest tertile	intake of both foods in highest tertile
	n=72	*n=71*
current wheeze*		
prevalence (%), crude	19.4	4.2†
prevalence (%), adjusted‡	18.9	4.8†
current asthma§		
prevalence (%), crude	16.7	2.8†
prevalence (%), adjusted‡	16.1	3.4†

*,§ see methods
† $p<0.05$
‡ adjusted for educational level of the mother, foreign descent and total energy intake

The analyses in table 3 were repeated for the end-points; atopic wheeze with BHR and atopic asthma with BHR (for definitions: see methods section). Similar results to those for current wheeze and current asthma were observed. The adjusted odds ratio (ORa) for the independent association with atopic wheeze with BHR was 0.31 (95%CI=0.10-0.95) for whole grain intake and 0.15 (95%CI=0.03-0.63) for fish intake. For the independent association with atopic asthma with BHR, the resulting ORa's were 0.28 (95%CI=0.08-0.99) for whole grain intake and 0.12 (95%CI=0.02-0.66) for fish intake.

Finally, the independent associations of the two foods with atopy and with BHR were studied. The ORa's for the association with atopy were 1.42 (95%CI=0.89-2.24) for whole grains and 1.28 (95%CI=0.89-1.83) for fish. With regard to BHR the ORa's were 1.48 (95%CI=1.01-2.16) for whole grains and 0.87 (95%CI=0.58-1.32) for fish. For the other studied foods no association with atopy or BHR was observed.

DISCUSSION

We observed an inverse association of intake of whole grain products and of fish with current wheeze and current asthma in children. Intake of these foods was furthermore inversely associated with more complex asthma end-points based on both questionnaire and clinical data (atopic wheeze with BHR and atopic asthma with BHR). The associations of whole grain and fish intake with these asthma end-points were observed to be largely independent of each other, and indications for additivity were observed. No clear associations with asthma were observed for intake of (citrus) fruits, vegetables and dairy products.

With regard to fish intake and asthma in children, a substantial number of epidemiological studies have been published showing conflicting results. Potential protective effects of fish were observed for asthma symptoms[6] [9], BHR alone[15] or in combination with wheeze[14], and atopic disease[13] [16]. However, in other studies no association was observed with asthma symptoms[10] [12], recent asthma[12], lung function[8], atopy[11] or atopic disease[13]. In one study ever asthma confirmed by a physician was observed to be positively associated with fish intake.[29] Also within studies seemingly conflictive results were reported. Hodge, et al.[14], for instance, observed a potential protective effect for oily fresh fish, but not for non-oily fresh fish or for canned or processed fish.

Fish oils, or more specifically the n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid, are thought to have anti-inflammatory effects through their influence on arachidonic acid metabolism.[2] Despite the plausible biological mechanism, an important concern is the low level of fish intake at which potential effects are observed. The high fish group consumed, for instance, any (vs. no) fish in the study by Hodge et al.[14] and consumed fish more than once a week or more than once a month in the studies by Peat et al.[15] and Antova et al.[6], respectively. In our study children in the highest tertile of fish intake consumed on average 15 grams of fish daily. It has been questioned whether fish intake at this level can have a substantial physiological effect on inflammatory processes in the airways.[30] In placebo-controlled trials in asthma patients, supplementation with high doses of fish oils has been observed to have inhibitory effects on neutrophils.[31][32] However, in asthma other inflammatory cells, like eosinophils and mast cells, seem to play a more predominant role.[30] Fact is that in the mentioned trials no clinical benefit of fish oil suppletion was observed.

Our findings regarding whole grain intake are in line with those reported by Wijga et al.[12] and suggest a protective effect of whole grain intake against asthma in children. COPD in adults has also been observed to be inversely associated with whole grain intake.[33] Whole grains are rich in antioxidant compounds (including vitamin E, phenolic acids and phytic acid)[4][5] and a high intake of whole grain products may therefore help to protect the airways against oxidant damage.

In the literature, inverse associations with asthma-related outcomes in children were reported for intake of (citrus) fruits[6][7] and of vegetables[8][9][10][11], foods also rich in antioxidant compounds. Absence of an association between vegetable intake and asthma-related outcomes in children was reported in one study.[12] With regard to fruit intake, however, the majority of published epidemiological studies on the subject observed no association.[8] [10][11][12] [34] In our study, total fruit intake showed no association with the studied outcomes (including atopy and BHR individually). Also for intake of citrus fruits and of vegetables no statistically significant associations with the studied outcomes were observed. The results regarding current asthma, however, do suggest a potential inverse association with both foods.

In contrast to a number of other epidemiological studies[10] [12] [18][19], we did not observe an inverse association between intake of (other than low-fat) dairy products and asthma. Intake of these foods can be seen as a marker for intake of saturated fatty acids. Collected data did not allow us to study intake of the different types of fatty acids (e.g. n-6, n-3 and saturated fatty acids) in relation to asthma.

The associations of intake of whole grain products and fish with asthma were observed to be largely independent of each other. The fact that in children with a high vs. low intake of either food (see table 2) the observed difference in prevalence of current wheeze and of current asthma was smaller than in children with a high vs. low intake of both foods (see table 4), suggests that the effects of the two foods may be (partly) additive. Our attempts to study this aspect were limited by the fact that the size of the study population did not allow for more detailed stratification.

When intake of the selected foods was studied in relation to atopy and to BHR, a positive association between whole grain intake and BHR was observed. Furthermore, atopy tended to be positively associated with intake of both whole grain products and fish. To our knowledge similar findings have not been reported earlier. It needs to be established whether these are mere chance findings or whether they can be confirmed in other epidemiological studies.

A high intake of whole grain products and of fish may reflect a more healthy diet and even a more healthy lifestyle in general. We, however, observed no clear confounding effects of other health related lifestyle factors on observed associations of whole grain and fish intake with asthma outcomes. Adjustment for intake of fruits or vegetables, generally considered to be healthy, did not cause a relevant change in these associations (results not shown). The same was observed when adjusting for an indicator of socio-economic status of the family (educational level of the mother), which is generally considered to be associated with healthy lifestyle. Furthermore, in preliminary analyses no strong confounding effects were observed for smoking of the mother during pregnancy, being breastfed, passive smoking or body mass index. However, since both healthy lifestyle and socio-economic status are complex concepts residual confounding can not be excluded.

A validated questionnaire for assessing dietary intake in children is and was, to the very best of our knowledge, not available in the Netherlands. We used the EPIC- FFQ, validated in Dutch adults[21], and asked parents to fill in this questionnaire with regard to their child's diet. This allowed us to study the habitual intake, the exposure of interest in relation to disease, of a broad range of dietary factors. The answer categories of all questions, into relative or absolute frequencies of food consumption and into portion sizes, encompassed the whole range of intake. Potentially relatively smaller (frequencies of) intakes in children could therefore be entered without problem. FFQ's are widely used in epidemiological research and have been observed to be reasonably valid for ranking individuals according to food group, as was also observed for the EPIC-FFQ with regard to adults[21]. However, since the EPIC-FFQ was not validated for use in children, our results have to be interpreted with additional caution. In most studies on diet and asthma in children published sofar, unvalidated questions and questionnaires have been used to assess dietary intake. The development and validation of dietary questionnaires for children seems to be an important area for future research.

Conclusion:
Our findings support a potential protective effect of a high intake of whole grain products and fish against asthma in children. Based on our study causal inferences can not be made. Prospective studies in which dietary factors (intake of fish and whole grains but preferably also

fruits and vegetables) and asthma are monitored and trials into the effect of dietary modifications on e.g. airway inflammation are needed to clarify this issue.

Sponsor details

The study was financially supported by the Ministry of the Environment of The Netherlands and by the Netherlands Asthma Foundation.

Competing interest statement:

All authors declare not to have any competing interests.

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