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Childhood diet and asthma and atopy at 8 years of age: the PIAMA birth cohort study

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ABSTRACT (200 words)

Diet may affect the development of asthma. We investigated if asthma or atopy outcomes at 8 years of age were associated with long-term dietary exposure, and whether associations were different for consumption at early or later age.

The PIAMA birth cohort at baseline enrolled 4,146 participants, who were followed up to 8 years of age. Dietary intakes of interest were fruit, vegetables, brown/wholemeal bread, fish, milk, butter and margarine. Associations between food intake at early (2-3 years) and later (7-8 years) age, and long-term intake and asthma and atopy at 8 years were calculated by logistic regression.

Complete longitudinal dietary data for at least one of the food groups were available for 2,870 children. Fruit consumption at early age was associated with reduced asthma symptoms (OR per 1 consumption-day/week increase 0.93 95% CI 0.85-1.00). Long-term fruit intake was inversely associated with asthma symptoms (OR 0.90; 95% CI 0.82-0.99) and sensitization to inhalant allergens (OR 0.90; 95% CI 0.82-0.99). We found no consistent associations between diet and outcomes for other foods.

This study indicates no consistent effects of increased early or late consumption, or long-term intake of certain foods on asthma and atopy in 8-year-olds, with a possible exception for fruit.

Key words: asthma, atopy, children, diet
Word count: 3500

INTRODUCTION

Prosperity associated changes in diet, and more specifically the reduced consumption of antioxidant rich foods and change in dietary fat intake, have been linked to the increase in asthma and allergic disease in the last decades.[1,2] Previous studies have reported beneficial associations between a higher consumption of fruit,[3-5] vegetables,[4] fish,[5,6] full fat dairy products,[7] and wholegrain products,[7,8] and symptoms of asthma or allergy in children, while harmful associations have been reported for margarine and salt intake.[9,10] It has been hypothesized that dietary exposure in early life (from conception to 2 years) might be particularly important in the development of childhood asthma, because the airways and immune system are developing during this period.[11] Most of the previous studies that assessed the effect of diet on asthma in children, relate dietary data that is obtained at one point in time to asthma and/or allergy outcomes at the same point in time or a (few) year(s) later. Results of these studies do not give information about the effects of long-term dietary exposure or differences in effects of dietary habits at early or later age. The use of longitudinal dietary data would give more insight in these effects, which may be crucial for (the timing of) dietary preventive strategies for childhood asthma and allergy.
The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study has annual follow-up dietary data from birth to 8 years of age. The aim of the present study was to investigate the effects of long-term dietary exposure from 2 to 8 years of age, and dietary habits at early and later age on symptoms and clinical outcomes of asthma and atopy at 8 years of age.

METHODS

Study population and study design

In 1996, a large birth cohort study was set up to investigate the Prevention and Incidence of Asthma and Mite Allergy (PIAMA). Details of the design of the PIAMA study have been published previously.[12] Briefly, 10,232 pregnant women were screened for atopy while visiting their prenatal health clinic.[13] Based on this screening, 2,779 atopic and 5,083 non-atopic women were invited to participate in the study, of whom 1,327 atopic and 2,819 non-atopic women agreed. In the intervention part of PIAMA, which was designed to study the effect of mite-allergen avoidance by means of mite-impermeable mattress- and pillow covers, only children born to atopic mothers (‘high-risk’ children) were enrolled. In the observational natural history part, children of atopic as well as children of non-atopic mothers (‘low-risk’ children) were enrolled. 183 mothers (~4.5%) were lost to follow-up before any data on the child had been collected, so 3,963 children continued in the study. A flow chart of the recruitment and response of the study population is shown in figures E1 in the online supplement.

Questionnaires contained the ISAAC core questions on asthma, rhinitis and eczema[14] as well as various questions on lifestyle factors (nutrition, pets, home characteristics etc.) and were sent to the participants at 3 months of age, and annually from 1 to 8 years of age. The Medical Ethical Committees of the participating institutes approved the study, and all participants gave written informed consent.

Assessment of the child's diet from 2 to 8 years of age

Longitudinal data on the child's diet were derived from the annual questionnaires from 2 to 8 years of age. These questionnaires enquired about the frequency of consumption of approximately 30 to 35 different foods or food groups in the preceding month. The foods and food groups of interest were the ones high in antioxidants (fruit, vegetables and brown/wholemeal bread), n-3 fatty acids (fish), n-6 fatty acids (margarine) and milk fat (full cream milk, semi-skimmed milk and butter). Answer options for the frequency of consumption were: (1) never, (2) less than once a week, (3) one to two days a week, (4) three to five days a week, and (5) six to seven days a week. These answer options were translated in continuous variables in consumption-days per week: option 1 = 0, option 2 = 0.5, option 3 = 1.5, option 4 = 4, and option 5 = 6.5 consumption-days per week. The original data of the frequency of consumption of the different foods and food groups from 2 to 8 years of age is presented in table E1a-c in the online supplement.

Definition of early and late consumption and long-term intake

Consumption at early age was defined as the mean consumption frequency (in consumption-days per week) of the questionnaires at both 2 and 3 years of age, while consumption at later age was defined as the mean consumption frequency of the questionnaires at both 7 and 8 years of age.

Long-term intake was defined as the mean consumption frequency (in consumption-days per week) of all questionnaires from 2 to 8 years of age.

Children's health outcomes

The child's health outcomes of interest were wheeze, dyspnea, inhaled steroid use and the composite variable asthma at 8 years of age derived from the questionnaire, and sensitization against inhalant and food allergens, and bronchial hyperresponsiveness (BHR) at 8 years of age assessed by medical examination. Besides these specific health outcomes, a composite variable 'asthma symptoms' is used within the PIAMA study. A child was defined as having 'asthma symptoms' when the parents reported one or more attacks of wheeze, and/or one or more events of dyspnea and/or prescription of inhaled steroids for respiratory problems in the last 12 months. A child who had none of these characteristics was defined as not having 'asthma symptoms'. This composite variable 'asthma symptoms' has been designed

to include children with prevalent wheeze or dyspnea symptoms, but also children who might not have had these symptoms because they used asthma medication (inhaled steroids) during the last 12 months. In this way, symptomatic children can be compared with a 'clean' reference group of children that had neither wheeze nor dyspnea nor used inhaled steroids for respiratory problems.

At 8 years of age, children from the intervention part, the 'high-risk' natural history part, and a random sample of the 'low-risk' natural history part, drawn at the beginning of the PIAMA study, were invited for the hospital-based medical examination. Participants who were not able to come to the hospital clinic and the remaining group of 'low-risk' natural history children were invited for a community-based medical examination either at a local community health centre or at home. Both the hospital-based and the community-based medical examination included blood sampling for the assessment of total and specific IgE levels. Children were considered to be sensitized against inhalant allergens if one or more allergen specific IgE levels to house dust mite (*Dermatophagoides pteronyssinus*), cat, dog, birch (*Betula verrucosa*), grass (*Dactylis glomerata*) and fungus (*Alternaria alternata*) were equal to or higher than 0.35 IU/ml. Sensitization to food allergens was defined as a high level of allergen specific IgE to milk or egg (also ≥0.35 IU/ml). A metacholine provocation test as indicator for bronchial hyperresponsiveness (BHR) was only conducted within the hospital-based medical examination. Children were defined as having BHR when the cumulative dose of metacholine bromide causing a 20% decrease in FEV_1 (PD20) was ≤0.61 mg.

Statistical analyses

Univariate and multivariate logistic regression analyses were used to assess associations between 1 consumption-day per week increase in consumption of the different foods and food groups during childhood and asthma and allergy outcomes at 8 years of age. This was done for average consumption at early age (2 and 3 years of age), later age (7 and 8 year of age) and average long-term intake from 2 to 8 years of age. Given the often skewed distribution of the food consumption categories, an analysis by tertiles or quartiles was not usually possible, so a more continuous representation of exposure gave more easily interpretable results, similar for all investigated foods and food groups.

The analyses for consumption at early age were performed on children with the respective food intake data at both 2 and 3 years of age as well as the respective outcome at 8 years of age and all confounders. For consumption at later age, food data was present at both 7 and 8 years of age, while for long-term consumption, food data was present at all ages from 2 to 8 years.

Covariates included as potential confounding factors in the multivariate model were: sex, parental atopy, maternal education (low, intermediate, high), maternal smoking during pregnancy, smoking in the home by the mother, father or others at 8 years of age, breast feeding (yes/no), presence of older siblings, birth

weight (≤3000 g, 3001 to 3999 g, ≥4000 g), overweight mother (maternal BMI ≥25 kg/m^2 assessed at 1 year follow-up), overweight of the child at 8 years of age (BMI was calculated and overweight was defined according to age and gender specific international standards, that use cut-off points equivalent to the 25 kg/m^2 cut-off that is commonly used for adults[15]), region (north, central, south-west) and study arm (intervention study, 'high-risk' or 'low-risk' natural history study). All analyses were carried out using SAS for Windows version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

At 8 year follow-up, questionnaire information was obtained for 3,269 children. 1,554 participants were invited for the hospital-based medical examination while 1,964 participants were invited for the community-based medical examination, of whom 1,133 and 1,081 children participated. The metacholine provocation test, which was included in the hospital-based examination, was successful for 938 children. IgE levels in blood samples were analysed for 1,713 children. Complete dietary data from 2 to 8 years of age for at least one of the investigated food groups were obtained for 2,870 children.
The characteristics of respondents at baseline compared to complete cases at 8 years of age (complete dietary data from 2 to 8 for at least one of the investigated food groups, 8-year questionnaire and all confounders) and complete cases with IgE data at 8 years of age are shown in table 1.

Table 1. Characteristics of the study population at baseline and complete cases at 8 years of age

Characteristic	Respondents at baseline N=3,963		Subjects with complete data at 8 yrs N=2,145		Subjects with complete data and IgE data at 8 yrs N=1,140	
	n	(%)	n	(%)	n	(%)
Female child	1911	(48.2)	1060	(49.4)	562	(49.3)
Atopic mother	821	(20.7)	381	(17.8)*	259	(22.7)
Atopic father	801	(20.2)	453	(21.1)	226	(19.8)
Both parents atopic	416	(10.5)	183	(8.5)*	128	(11.2)
Allergic sibling	756	(19.2)	409	(19.1)	235	(20.6)
Maternal education low	894	(23.5)	416	(19.4)*	214	(18.8)
Maternal education intermediate	1582	(41.5)	918	(42.8)	485	(42.5)
Maternal education high	1331	(35.0)	811	(37.8)*	441	(38.7)
Maternal smoking during pregnancy	696	(17.8)	306	(14.3)*	154	(13.5)
Smoking in the home at 8 yrs	-		284	(13.2)	146	(12.8)
Ever breastfed	3200	(82.1)	1795	(83.7)*	966	(84.7)
Presence of older siblings	1994	(50.7)	1068	(49.8)	585	(51.3)
Birth weight low (≤ 3000 g)	353	(13.8)	271	(12.6)*	133	(11.7)
Birth weight normal (3001-3999 g)	2677	(68.2)	1459	(68.0)	781	(68.5)
Birth weight high (≥ 4000 g)	702	(18.0)	415	(19.4)*	226	(19.8)
Maternal overweight (BMI ≥ 25 kg/m^2)	886	(25.1)	535	(24.9)	278	(24.4)
Child overweight at 8 yrs	-		237	(11.1)	117	(10.3)
Region north	1231	(31.1)	693	(32.3)	288	(25.3)**
Region central	1586	(40.0)	903	(42.1)	551	(48.3)
Region south-west	1146	(28.9)	549	(25.6)*	301	(26.4)
Intervention study	781	(19.7)	307	(14.3)*	227	(19.9)
'High-risk' Natural History study	456	(11.5)	257	(12.0)	160	(14.0)
'Low-risk' Natural History study	2726	(68.8)	1581	(73.7)	753	(66.1)

* $p<0.05$: complete cases included in the analyses are compared with non-complete cases.
** $p<0.05$: complete cases with IgE data are compared with complete cases without IgE data.

Children with complete data at 8 years of age were less likely to have an atopic mother, a mother who smoked during pregnancy, or to be from region south-west compared to the children at baseline. Furthermore, these children were more likely to have a mother with a higher educational level, and to have a higher mean birth weight compared to the children at baseline. Children with IgE data at 8 years of age were less likely to be from region north. Yet, the magnitude of the differences between populations was small.

Table 2 shows the mean and median consumption of the investigated foods and food groups in consumption-days per week.

Table 2. Mean and median early, late and long-term food consumption in days per week

	Early consumption			Late consumption			Long-term intake		
	N	Mean (SD)	Med (IQR)	N	Mean (SD)	Med (IQR)	N	Mean (SD)	Med (IQR)
Fresh fruit	3574	5.3 (1.6)	6.5 (2.5)	3088	5.1 (1.7)	5.3 (2.5)	2815	5.3 (1.4)	5.8 (2.1)
Cooked vegetables	3571	5.0 (1.5)	5.3 (2.5)	3094	4.7 (1.4)	4.0 (2.5)	2793	4.8 (1.2)	4.7 (1.8)
Brown/wholemeal bread	3584	5.9 (1.3)	6.5 (0.0)	3107	5.8 (1.5)	6.5 (1.3)	2839	5.9 (1.2)	6.5 (0.7)
Fish	3540	0.8 (0.7)	0.5 (0.5)	3073	0.9 (0.7)	0.5 (1.0)	2716	0.8 (0.6)	0.7 (0.6)
Full cream milk	3545	1.9 (2.5)	0.0 (3.3)	3086	0.4 (1.4)	0.0 (0.0)	2756	1.0 (1.6)	0.1 (0.7)
Semi-skimmed milk	3565	3.9 (2.6)	4.0 (5.8)	3089	4.1 (2.7)	5.3 (5.5)	2778	4.1 (2.2)	4.7 (3.9)
Butter	3567	0.6 (1.6)	0.0 (0.3)	3088	0.5 (1.4)	0.0 (0.3)	2818	0.6 (1.3)	0.1 (0.4)
Margarine	3556	5.1 (2.0)	6.5 (2.5)	3082	5.2 (2.2)	6.5 (2.5)	2794	5.3 (1.7)	6.1 (1.6)

At early age, most children daily consumed fruit, brown/wholemeal bread and margarine. Cooked vegetables and semi-skimmed milk were generally consumed on 5 and 4 days per week respectively, while fish, full cream milk and butter were generally consumed less than once a week. At later age, consumption of fish, semi-skimmed milk and margarine increased, while consumption of fruit, vegetables and full cream milk decreased. Average long-term intake was highest for brown/wholemeal bread, fruit and margarine, while it was lowest for butter and fish.

Prevalence of health outcomes at 8 years of age are shown in table 3.

Table 3. Prevalence of health outcome variables at 8 years of age

Health outcome	N*	n (%)
Wheeze in the last 12 months	3269	213 (6.5)
Dyspnea in the last 12 months	3269	293 (9.0)
Use of inhaled steroids in the last 12 months	3269	208 (6.4)
Asthma symptoms**	3269	425 (13.0)
Sensitization to inhalant allergens¤	1713	550 (32.1)
Sensitization to food allergens§	1713	285 (16.6)
Bronchial hyperresponsiveness	938	402 (42.9)

* Number of children with questionnaire information, IgE data or conducted metacholine provocation test respectively.
** Composite variable of wheeze, dyspnea or inhaled steroid use.
¤ House dust mite, cat dog, grass, birch or fungus.
§ Milk or egg.

Among the 8-year-olds with questionnaire data, dyspnea was the most often reported symptom (9.0%). Of the children with IgE data, 32.1% was sensitized to inhalant allergens while 16.6% was sensitized to milk or egg. The metacholine provocation test was positive in 42.9% of the children. However, the subgroup of children that performed a metacholine provocation test contained a larger proportion of 'high-risk' children than the total study population.

Adjusted associations between average long-term intake of the different foods and food groups from 2 to 8 years of age and the different asthma and atopy outcomes at 8 years of age are shown in table 4. There were no consistent associations between increased long-term intake of fish, full cream milk, semi-skimmed milk, butter or margarine on symptoms of asthma, atopy or BHR at 8 years of age. Long-term intake of fresh fruit was significantly inversely associated with asthma symptoms (OR per 1 consumption-day per week increase 0.90; 95% confidence interval 0.82-0.99) and sensitization to inhalant allergens (OR 0.90; 95% CI 0.82-0.99). Long-term intake of cooked vegetables and brown/wholemeal bread consumption were significantly positively associated with respectively wheeze and sensitization to food allergens (OR 1.22; 95% CI 1.04-1.44 and OR 1.30; 95% CI 1.06-1.60, respectively). The effects of inclusion of potential confounding factors in the different models were minimal. After additionally adjusting for sensitization to pollen or hay fever at 8 years of age the association between long-term fruit intake and asthma symptoms changed to borderline significant (OR 0.92; 95% CI 0.83-1.01).

Table 4. Adjusted* associations between 1 day increase in average long-term intake from 2 to 8 years of age and health outcomes at 8 years of age

	Wheeze	Dyspnea	Inhaled steroid use	Asthma symptoms**	Sensitization to inhalant allergens	Sensitization to food allergens	BHR
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Fresh fruit	0.98 (0.86-1.13)	0.94 (0.84-1.06)	0.94 (0.82-1.08)	**0.90 (0.82-0.99)**	**0.90 (0.82-0.99)**	0.96 (0.84-1.08)	1.09 (0.95-1.24)
Cooked vegetables	**1.22 (1.04-1.44)**	1.08 (0.95-1.24)	1.06 (0.90-1.25)	1.10 (0.98-1.24)	1.00 (0.89-1.12)	1.03 (0.89-1.19)	1.01 (0.87-1.17)
Brown/wholemeal bread	0.91 (0.78-1.06)	0.96 (0.83-1.11)	0.97 (0.83-1.15)	0.95 (0.84-1.07)	0.98 (0.87-1.11)	**1.30 (1.06-1.60)**	0.89 (0.76-1.06)
Fish	1.32 (0.97-1.80)	1.01 (0.75-1.35)	1.36 (0.98-1.88)	1.23 (0.97-1.57)	0.98 (0.78-1.24)	1.09 (0.82-1.45)	0.79 (0.58-1.09)
Full cream milk	1.10 (0.99-1.24)	1.03 (0.92-1.15)	1.08 (0.96-1.22)	1.03 (0.94-1.12)	0.94 (0.86-1.03)	0.99 (0.89-1.11)	0.96 (0.86-1.09)
Semi-skimmed milk	0.95 (0.87-1.03)	0.96 (0.90-1.04)	0.97 (0.89-1.05)	0.98 (0.92-1.04)	0.98 (0.92-1.04)	1.06 (0.98-1.15)	0.99 (0.92-1.06)
Butter	1.05 (0.92-1.19)	0.99 (0.88-1.12)	1.00 (0.87-1.16)	0.99 (0.89-1.10)	0.97 (0.88-1.07)	0.89 (0.78-1.02)	1.03 (0.92-1.16)
Margarine	1.00 (0.90-1.11)	1.01 (0.92-1.11)	0.99 (0.89-1.11)	1.00 (0.92-1.08)	1.00 (0.92-1.07)	1.05 (0.96-1.16)	0.94 (0.85-1.03)

* Multivariate model is adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, overweight child at 8 years, region and study arm (intervention or natural history).

** Wheeze and/or dyspnea and/or inhaled steroid use in the last 12 months.

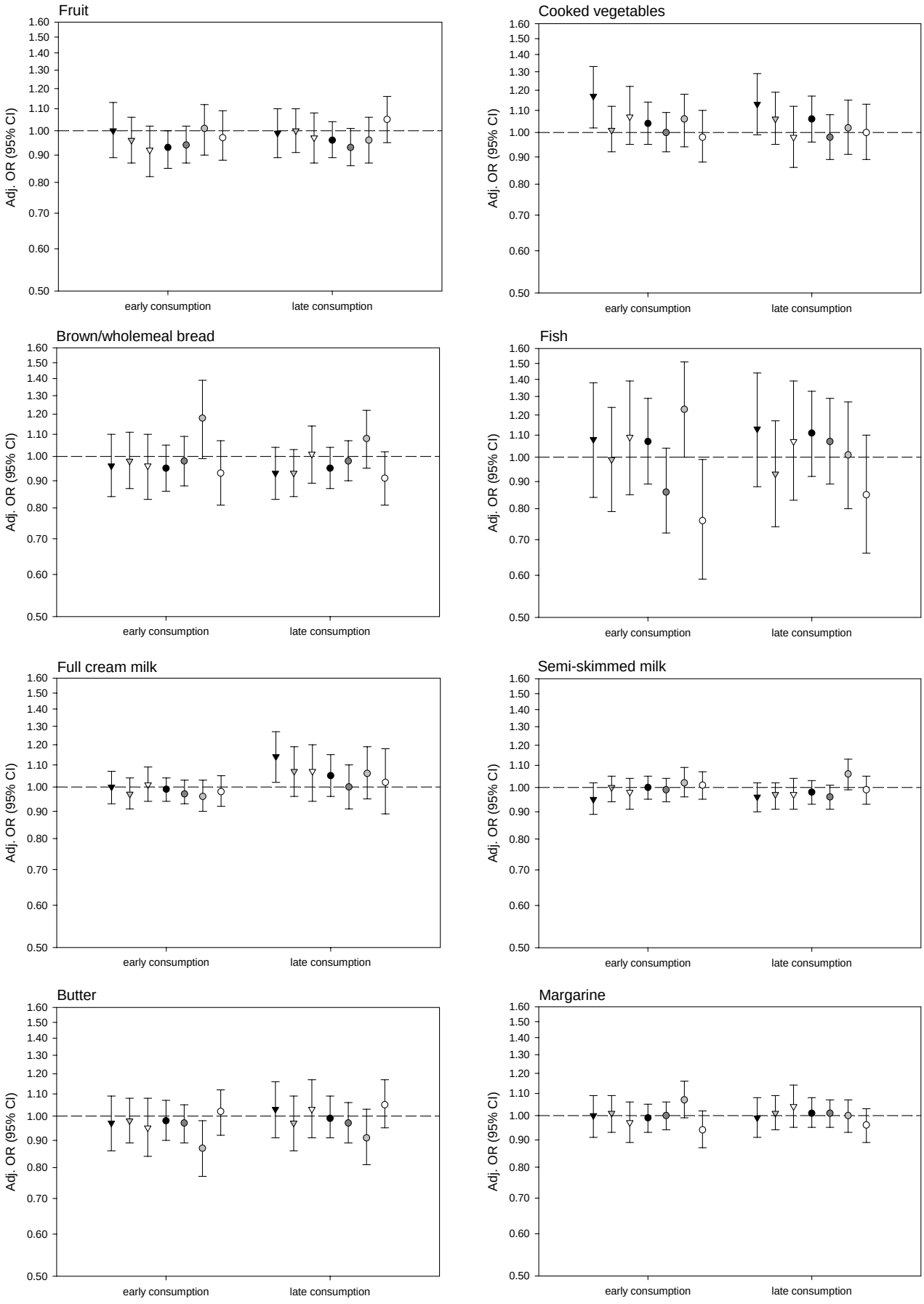
Fruit
Cooked vegetables
Brown/wholemeal bread
Fish
Full cream milk
Semi-skimmed milk
Butter
Margarine
Adj. OR (95% CI)
1.60
1.50
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
early consumption
late consumption

Figure 2. Adjusted* associations between early and late consumption of fruit, cooked vegetables, brown/wholemeal bread, fish, full cream milk, semi-skimmed milk, butter and margarine and wheeze (▼), dyspnea (▼), inhaled steroid use (v), asthma (●), sensitization to inhalant allergens (●), sensitization to food allergens (●), and BHR (○) at 8 years of age. OR's are shown for 1 consumption-day per week increase in intake.
* Multivariate model is adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breast feeding, presence of older siblings, birth weight, overweight mother, overweight child at 8 years, region and study arm (intervention or natural history).

Figure 2 shows the adjusted associations between 1 consumption-day increase in the investigated foods and food groups at early age and later age and symptoms of asthma, atopy and BHR at 8 years of age.

There were no associations between increased consumption of brown/wholemeal bread, semi-skimmed milk, or margarine, at either early or later age, on symptoms of asthma, atopy or BHR. The results did show an inverse association between increased fruit consumption at early age and asthma symptoms (OR 0.93; 95% CI 0.85-1.00). Increased fish consumption at early age was significantly inversely associated with BHR (OR 0.76; 95% CI 0.59-0.99), while borderline significantly positively associated with sensitization to food allergens at 8 years of age (OR 1.23; 95% CI 1.00-1.51). Furthermore, we found significantly positive associations between increased consumption of cooked vegetables at early age and full cream milk at later age and wheeze at 8 years of age (OR 1.17; 95% CI 1.02-1.33 and OR 1.14; 95% CI 1.02-1.27, respectively) and a significantly inverse association between increased consumption of butter at early age and sensitization to food allergens at 8 years of age (OR 0.87; 95% CI 0.77-0.98).

DISCUSSION

We have investigated associations between long-term dietary intake, and dietary intake in early and later childhood and symptoms and clinical outcomes of asthma and atopy at 8 years of age. No consistent associations were found for long-term dietary consumption or consumption at early or later age on outcomes at 8 years of age, except for fruit. Increased fruit consumption at early age was beneficially associated with inhaled steroid use, asthma symptoms and sensitization to inhalant allergens, however these associations were only borderline statistically significant. Increased long-term fruit intake was significantly inversely associated with asthma symptoms and sensitization to inhalant allergens.

The associations between fruit consumption and childhood asthma and atopy we observed in this study were not very strong. Results from previous studies in children are ambiguous as well. Some studies have found beneficial associations between fruit consumption and lung function,[16] wheeze,[17] cough,[4,5] or rhinitis,[18] whereas other studies did not find associations between fruit consumption and lung function,[19] asthma or wheeze,[7,20-22] or only found associations with specific types of fruit, especially the ones high in vitamin C.[3,8,23] High fruit consumption probably leads to a higher

antioxidant status in the body, which provides more protection against oxidative damage through infections, passive smoking and air pollution.[24,25]

The inverse relations between increased fruit consumption and asthma symptoms and sensitization to inhalant allergens are potentially attributable to allergen cross reactivity between pollen and specific types of fruit.[26] This would lead to reverse causation: asthmatic children allergic to pollen might be more likely to avoid certain fruits due to food allergic reactions. However, additional adjustment of the analyses for hay fever and (in those with sensitization data) for pollen sensitization did not substantially change the results.

Maintenance of high fruit consumption over a longer period of time may reflect a more healthy diet or more healthy lifestyle in general. However, adjustment for socioeconomic and lifestyle factors like maternal education, maternal smoking during pregnancy, smoking in the home and breast feeding did not materially alter the results. Neither did we find consistent effects of increased long-term intake of vegetables and fish, other foods that may reflect a healthy diet or lifestyle. However, since both socioeconomic status and a healthy lifestyle are complex concepts, residual confounding cannot be ruled out.

In 1997, Black and Sharpe[2] have proposed that changes in dietary fat intake during the last decades may have contributed to the increase in asthma and atopic disease in children. They argued that the decrease in intake of n-3 polyunsaturated fatty acids from fish and saturated fats from butter and lard, and the increased intake of n-6 PUFAs from margarine and vegetable oils has led to an increased ratio of n-6 to n-3 fatty acid intake. This can result in increased production of arachidonic acid and prostaglandin E2 (PGE2) with a consequent increase in the likelihood of atopic Th2 sensitization, asthma and atopic disease.[2] Several studies have reported beneficial associations of dietary fish intake,[5,6,8,22,23,27-29] or harmful associations of margarine and vegetable oil intake[4,9,23,27,29] with asthma and atopic disease in children, whereas other studies did not find effects of n-3 PUFAs[4,7,20] or n-6 rich foods.[18] In this study, increased fish consumption at early age appeared to be protective for sensitization to inhaled allergens and BHR, but seemed to increase the risk of sensitization to food allergens at 8 years of age. We did not find any consistent effects for increased margarine consumption. The lack of clear findings for increased fish and margarine consumption might be due to the fact that the FFQ questions were not detailed enough to estimate the intake of n-3 or n-6 fatty acids or the ratio of these two. The effect mechanisms of dietary PUFA intake on inflammatory mediators and Th-cell differentiation are very complex, which makes it more likely that epidemiological studies produce conflicting results.[30] An earlier study of the same cohort has reported beneficial associations of daily consumption of full cream milk and butter at two years of age on wheeze and asthma at three years of age.[7] The present study shows that this association did not persist to 8 years of age.

The overall results of this study did not indicate strong differences between consumption at early or later age. The hypothesis that nutrients which exert effects on airway development or Th-cell

differentiation are especially important during early life[30] could not be confirmed in this study. Probably, the time window of exposure relevant for effects on the developing airways and immune system is even earlier in life, before the age of two or during pregnancy. Previous analyses in this cohort on the longitudinal effects of maternal fruit consumption during pregnancy revealed an overall beneficial effect on wheeze. However, the association lost statistical significance after adjustment for potentially confounding factors.[31]

Weaknesses of our study design were the lack of data on consumption of specific types of fruit, vegetables and fish. To understand more of the biological mechanisms underlying the associations between nutrition and asthma or allergy, more information about the intake of specific foods and nutrients is needed. If the effects observed in this study are caused by specific nutrients, estimating the intake of total food groups may have attenuated the effects on the asthma and allergy outcomes. Furthermore, the use of self-reported dietary data could have led to misclassification of dietary exposure. However, it is unlikely that this has happened non-randomly. The food frequency questions in our questionnaire were not validated in our study population. However, food frequency questionnaire data are widely used in epidemiological studies and provide reasonably valid and reproducible estimates to rank individuals according to food group.[32] We have chosen a limited number of foods and food groups based on reported associations with asthma or atopy in previous studies. However, analyses of associations between several food groups and several outcomes could have led to chance findings due to multiple testing. Incidental associations for dietary consumption of a certain food and only one of the investigated outcomes must therefore be interpreted with caution.

Our study population contained an intervention arm to investigate the effect of mite-allergen avoidance by means of mite-impermeable mattress- and pillow covers. This intervention arm only contained children born to atopic mothers, while the in natural history arm of the study children born to non-atopic mothers were overrepresented. However, the proportion of atopic mothers in the total baseline study population was similar to the proportion of atopic mothers in the screened population (~30%). Furthermore, the intervention was shown to have no clinical effects at age 1, 2 and 4[33] and 8 (results not published yet), so we do not expect any consequences regarding the generalizability of the present results. Nevertheless, all analyses were adjusted for study arm, and we checked for effect modification by maternal atopy, which was not the case. Table E2a-c in the online depository show results excluding the intervention study population. These results were similar to those in the total study population although some associations lost statistical significance due to the loss of power.

The strength of our study was the use of longitudinal dietary data. Dietary exposure during childhood changes over time, which might change associations with symptoms of asthma or atopy as well. Longitudinal dietary data can be used to investigate differences of consumption at early or later age, providing more evidence on possible mechanisms of effects.

In conclusion, the results of this study indicate no consistent effects of increased early or late consumption, or increased long-term intake of certain foods or food groups on asthma and allergy

outcomes in 8-year-old children, with a possible exception for fruit. Future prospective studies should use more detailed dietary data to better assess nutrient or food specific effects.

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COMPETING INTERESTS

The authors declare to have no competing interests.

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